frontiers | Research Topics

Equity in cancer care

Edited by
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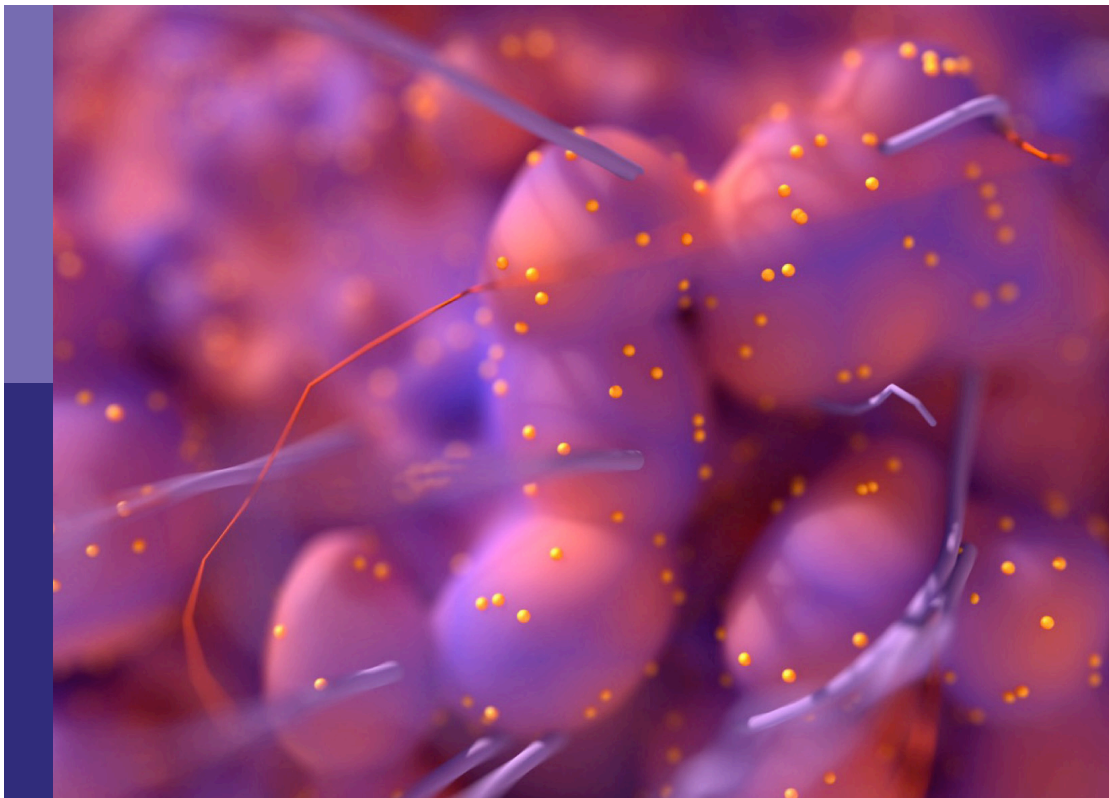
Published in
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-8325-4301-6
DOI 10.3389/978-2-8325-4301-6

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Equity in cancer care

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Citation

Nieva, J. J., Ahmed, H. G., eds. (2024). *Equity in cancer care*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-4301-6

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frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 05 January 2024
DOI 10.3389/fonc.2023.1346785

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 29 November 2023
ACCEPTED 26 December 2023
PUBLISHED 05 January 2024

CITATION
Nieva JJ (2024) Editorial: Equity in cancer care.
Front. Oncol. 13:1346785.
doi: 10.3389/fonc.2023.1346785

Editorial: Equity in cancer care

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KEYWORDS

health equity, cancer care, cancer biology, global health, Social determinants of health

Editorial on the Research Topic
Equity in cancer care

Different patient populations will experience different average outcomes from their cancer. This experience is not unique to any one nation or healthcare system but is seen worldwide and can result from population differences in economic factors, disease comorbidities, educational differences, and exposure to economic and political crises. Each of the manuscripts in this Research Topic represents an opportunity for improvement. After all, if we can see one group doing worse than another regarding cancer outcomes, it is relatively easy to imagine a solution that simply gives what the advantaged group has to those who lack it. In this Research Topic of Frontiers in Oncology dedicated to Equity in Cancer Care, we are presented with experiences worldwide that address these difficult problems. While seeing a solution may be easy, finding the resources to correct them is often where the challenge lies.

Sometimes the solution is simply to improve health literacy among women to improve rates of screening mammography (Poon et al.). But such interventions may be difficult to implement across populations where local effects of neighborhoods create heterogeneity in the population that call for unique approaches that may need to vary from block to block (Layne et al.). A better approach may be to alter the criteria for screening in the first place, to ensure that the indications for screening do not leave out minority groups (Olazagasti et al.). Meanwhile, segregation of populations can impact other health behaviors besides screening and ending such segregation may be a potential solution (Pichardo et al.), as targeted interventions aimed at minority populations have been notoriously difficult to conduct (Pichardo et al.). Simple solutions, such as making screening easier on patients, by covering sedation along with screening colonoscopy for example, may go a long way to improving screening rates among the poor (Zhuo et al.).

Other solutions may need to be rooted in biological differences between groups. A comorbidity such as diabetes and all its impacts on cancer care is not evenly distributed in patient populations and might make care for some groups inferior (Ashing et al.), though another study in this Research Topic found that for small cell lung cancer at least, those effects did not lead to inferior outcomes in minority populations at higher risk for diabetes (Olateju et al.). Cardiac disease is also unevenly distributed as a comorbidity in cancer patients and optimal outcomes for cancer will not be achieved if this disparity is not addressed (Patel et al.).

Biology matters. The cancer itself may also have different biology and there is much we can learn from studying differences among ethnic groups. Of course, if our cell lines come from only one segment of the population, we are missing a tremendous opportunity to have laboratory models that apply to the whole population of affected patients (Leon et al.). Cancer mediators such as miRNAs are differentially expressed among different ethnic groups and their study can offer insights into biology of neoplasia (Gobin et al.). The same can be said of genomic, epigenomic and transcriptomic signatures (Stevens et al.).

Sadly, regional, and national economic and political factors make the outcome of cancer worse. We have seen worsening of breast cancer mortality in South Africa despite the end of apartheid even as much of the rest of the world sees improvement (Olorunfemi et al.). In Lebanon, economic and policy factors have created an environment of drug shortages that have been devastating for cancer patients (Kattan and Kattan). Greater wisdom among leaders is badly needed and sometimes is in short supply. I hope that the insights from the excellent authors in this journal bring much wisdom to the readers and working together, we can make cancer outcomes better for everyone, starting with those who need it most.

Author contributions

JN: Conceptualization, Project administration, Writing – original draft.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 01 November 2022
DOI 10.3389/fonc.2022.995408

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cancer Epidemiology and Prevention, a section of the journal Frontiers in Oncology

RECEIVED 15 July 2022
ACCEPTED 06 October 2022
PUBLISHED 01 November 2022

CITATION
Olazagasti C, Ehrlich M and Seetharamu N (2022) One size does not fit all: Evaluating disparities in lung cancer screening eligibility amongst the Hispanic population.
Front. Oncol. 12:995408.
doi: 10.3389/fonc.2022.995408

One size does not fit all: Evaluating disparities in lung cancer screening eligibility amongst the Hispanic population

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Lung cancer (LC) is the leading cause of cancer death among Hispanic men. We assessed the tendencies for screening eligibility amongst Hispanic prior to LC diagnosis according to the NCCN and The USPSTF guidelines available at the time of diagnosis. We conducted an observational study in patients diagnosed with LC from 2016 to 2019. Charts were reviewed to assess their screening eligibility prior to LC. The chi-square test was used to examine the association between race and ethnicity with each screening criteria. A total of 530 subjects were reviewed, of which 432 were included in the analysis. One hundred fifty-three and 245 subjects were ineligible for screening under NCCN and USPSTF criteria prior to their LC diagnosis. Twenty-eight of the subjects who did not fulfill NCCN criteria identified as AA and 12 as Hispanics. Forty and 20 of the USPSTF screening ineligible subjects identified as AA and Hispanics. There was a significant association between screening eligibility criteria in Hispanics, with 52% Hispanic subjects meeting NCCN criteria compared to only 20% who met USPSTF (p=0.0184). There was also a significant association between ethnicity and USPSTF eligibility criteria (p=0.0166), as 80% of Hispanic subjects were screening ineligible under USPSTF criteria compared to 56% of non-Hispanic or other. In our study, Hispanics had significantly lower tendencies of meeting the USPSTF LC screening eligibility criteria than non-Hispanics or other. Interestingly, a proportionally higher number of Hispanics who were ineligible under USPSTF criteria met NCCN criteria. These findings suggest that leniency in the screening criteria can possibly lead to earlier detection of LC in high-risk individuals. Recently, USPSTF has modified their criteria which may benefit more of these individuals. To improve rates of screening and overall mortality of minorities, organizations should continue to re-evaluate and liberalize their screening guidelines.

KEYWORDS

lung cancer, screening, tobacco, early detection, disparities

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, accounting for almost 25% of all cancer deaths (1). The five-year overall survival for lung cancer remains less than 20% (2). Its incidence and mortality rate are even more pronounced within certain subgroups, where racial disparities are particularly predominant (1). African Americans have the highest rates of LC mortality in the United States and the second-highest LC incidence. African Americans are also more likely to develop LC at an earlier age and present with advanced-stage disease (3). While the incidence is not as high amongst Hispanics, LC is the leading cause of mortality in Hispanic men and the second-leading cause of cancer mortality in Hispanic women. The survival rates for Hispanics are lower than those for Non-Hispanic Whites (NHW), mainly due to lower rates of early diagnosis and screening. Compared to non-Hispanic Whites, Hispanics have higher rates of being diagnosed at advanced stages of lung cancer, discarding their candidacy for surgical resection and curative intent (4).

In the last two decades, two landmark prospective randomized-controlled studies – the National Lung Screening Trial (NLST) and the Dutch–Belgian Lung Cancer Screening Trial (NELSON) – demonstrated that screening with annual low-dose computed tomography (LDCT) reduces lung cancer mortality among high-risk individuals (5, 6). On the other hand, the Multicentric Italian Lung Detection (MILD) trial assessed the mortality rates from lung cancer by comparing annual and biannual screening with LDCT. However, the study revealed a similar overall mortality between both arms (7). Organizations such as the National Comprehensive Cancer Network (NCCN) and U.S. Preventative Services Task Force (USPSTF) extrapolated the findings of the aforementioned trials to create lung cancer screening guidelines in 2011 and 2013, respectively, recommending annual LDCT among high-risk adults. The NCCN11 classified high-risk patients as those ages 55-74 with ≥ 30 pack-year history of smoking with <15 years since smoking cessation; or ≥20 pack-year history of smoking, and additional risk factors that increase the risk of lung cancer to >1.3%, which include: family history of lung cancer, personal history of other malignancy, history of COPD or pulmonary fibrosis, radon exposure, occupational exposure, and/or second hand-smoking exposure (8). The USPSTF13, on the other hand, recommended annual screening for lung cancer in adults aged 55-80 years with ≥ 30 pack-year smoking history, current smokers or those that had quit within 15 years (8, 9) Unfortunately, however, subsequent analysis found that certain minority populations were underrepresented in these trials. The participants in the NLST were predominantly white (95%), and only 1.8% of the participants were Hispanics – likely leading to some of the racial and ethnic disparities in lung cancer screening that we see today (5).

Many studies have published data citing lower rates of screening eligibility and low dose CT implementation in the African American population. There was a secondary analysis of the NLST that demonstrated an even greater reduction in lung cancer and all-cause mortality in African Americans compared to White, despite low participation (4.4% black vs 90.9% white) (10). Additionally, African Americans have been shown to have lower lung cancer screening eligibility rates despite having greater incidences of lung cancer (11, 12). Regretfully, the efforts have focused mainly on this minority group and limited data exists understanding the eligibility patterns and screening uptake in the Hispanic population. In efforts to understand the patterns and the factors that contribute to these inequities, we conducted a secondary analysis of an observational study (13) to evaluate the tendencies for screening eligibility among the Hispanics population prior to their lung cancer diagnosis. To our knowledge, no previous studies have been published that highlight a potential for missed opportunities in high-risk, underserved groups such as the Hispanic populations that are eventually diagnosed with lung cancer.

Methods

Study description

We conducted a secondary analysis from a single-center observational study in an outpatient Academic Center that originally sought to retrospectively assess the rates of lung cancer screening uptake in subjects with lung cancer, prior to their diagnosis The study protocol was reviewed by institutional review board and the need for approval was waived by Northwell Health Institutional Review Board (IRB #190580)We reviewed the charts of consecutive patients with an established diagnosis of LC at the Northwell Health Cancer Institute between 2016 and 2019. Charts were reviewed for demographics, detailed smoking history at the time or prior to screening, family history, history of previous malignancy, radon exposure, occupational exposure and/or second hand-smoking exposure to assess lung cancer screening eligibility prior to the diagnosis of lung cancer.

In this *ad-hoc* analysis, we aimed to assess the patterns of lung cancer screening eligibility according to NCCN11 and/or USPSTF13 criteria in patients prior to their diagnosis of cancer. Our primary endpoint was to compare the NCCN11 and USPSTF13 rates of screening eligibility according to race and ethnicity. We also sought to understand potential disparities in LDCT uptake according to sex, race, and ethnicity.

Statistical methods

Subjects were considered to have fulfilled LC screening criteria if they met eligibility according to NCCN11 and/or USPSTF13 LC screening guidelines. Those who did not meet either of the criteria were considered screening ineligible. Subjects who had missing information that was required for determining eligibility for either or both criteria were not categorized and excluded from analysis. All analyses were carried out separately for each screening criteria (NCCN11 and USPSTF13). The association between each categorical demographic and clinical factor and referred for screening (yes/no) was examined using the chi-square test or Fisher's exact test. The association between screening eligibility with race and ethnicity was examined using the chi- square.

Results

Charts of 530 subjects were reviewed, of whom 432 were current or former smokers and 98 had no history of smoking. Baseline characteristics are shown in Table 1.

Out of the patients with a smoking history, 55% were male and 45% female. White was the most prevalent race, with 68.5% participants self-identifying as White, whereas 15.1%, 10.4% and 6.0% self-identified as AA, other, and Asian. In terms of ethnicity, up to 91% of participants identified as Non-Hispanic, 5.8% identified as Hispanic, and 3.2% as other. English was the primary language for 93% of participants.

Screening eligibility

Table 2 depicts the Screening criteria eligibility per race and ethnicity. A total of 245 of participants with a history of smoking were ineligible for lung cancer screening according to NCCN11 prior to their lung cancer diagnosis. When assessing the relationship between NCCN11 eligibility and race, 43% of the self-identified African American subjects and 34% of Whites, Asian, or other subjects were ineligible for lung cancer screening per NCCN11 criteria (p=0.206). When comparing NCCN11 eligibility and ethnicity, 48% of the self-identified Hispanic subjects and 35% of non-Hispanicsor others did not fulfill NCCN11 eligibility criteria (p=0.201).

Out of the patients with a smoking history, 153 did not fulfill USPSTF13 eligibility criteria prior to their diagnosis of lung cancer. When assessing the relationship between USPSTF13 eligibility and race, 62% of the self-identified African American subjects and 56% of Whites, Asian, or other did not fulfill USPSTF13 eligibility criteria (p=0.496). When comparing USPSTF13 eligibility and ethnicity, 80% of the self-identified Hispanic subjects were ineligible for screening, compared to 56% of non-Hispanics or others (p=0.017).

TABLE 1 Baseline characteristics and characteristics at diagnosis.

	Smokers N (%)	Never Smokers N (%)
Frequency	432 (82.0)	98 (18.0)
Baseline Characteristics		
Gender*		
Male	231 (55.1)	27 (27.6)
Female	188 (44.9)	71 (72.4)
Race**		
African American	65 (15.1)	18 (18.4)
White	295 (68.5)	40 (40.8)
Asian	26 (6.0)	29 (29.6)
Other	45 (10.4)	11 (11.2)
Ethnicity**		
Hispanic	25 (5.8)	6 (6.1)
Non-Hispanic	392 (91.0)	87 (88.8)
Other	14 (3.2)	5 (5.1)
Primary Language**		
English	399 (92.6)	78 (79.6)
Other	32 (7.4)	20 (20.4)

*Missing data for 13 subjects with smoking history.
**Missing data for 1 subject with smoking history.

TABLE 2 Screening criteria eligibility per race and ethnicity.

	NCCN Eligible		p-value	UPSSTF Eligible		p-value
	Yes(%)	No(%)		Yes(%)	No(%)	
Race	56.9	43.1	**0.206**	38.5	61.5	**0.496**
African American	65.6	34.4		43.8	56.2	
White, Asian, other						
Ethnicity	52.0	48.0	**0.201**	20.0	80.0	**0.017**
Hispanic Non-Hispanic or other	65.0	35.0		44.4	55.6	

There was a significant association between screening eligibility criteria (NCCN11 and USPSTF13) in Hispanics, where 52% of HispanicX subjects were eligible according to NCCN11 criteria compared to only 20% Hispanics who fulfilled USPSTF13 eligibility criteria (chi-square 5.555; p=0.0184).

Screening uptake

As published in our original study (13), only 4.0% and 4.8% of the subjects that fulfilled NCCN and USPSTF eligibility criteria, respectively, underwent LDCT (95% exact CI: 2.0, 7.0 and 2.2, 9.0). Ninety one percent of the subjects that had LDCT uptake in the NCCN eligible group were men (Figure 1). Similarly, 100% of the subjects that underwent screening in the USPSTF eligible group were men (Figure 1). Of the NCCN eligible individuals that underwent screening, 54.5% self-identified as White, 18.2% as African American, 18.2% as Asian, and 9.1% as other (Figure 2). None of the subjects that had LDCT in this group self-identified their ethnicity as Hispanic (Figure 3). Comparably, in the USPSTF eligible group that underwent LDCT, 55.6% of the subjects self-identified as White, whereas 11.1% identified as African American, 22.2% as Asian, and 11.1% other (Figure 2). No subjects self-identified as Hispanic (Figure 3). An association between screening and age, gender, race, and ethnicity could not be evaluated due to the low sample size of individuals that underwent LDCT screening.

For additional information regarding screening according to smoking status and staging at diagnosis, please refer to original study (13).

Discussion

Vast literature exists to support the disparities in lung cancer screening eligibility and implementation in the African American population (11, 14, 15). However, to our knowledge, our study is the first one to evaluate the rates of screening eligibility according to race and ethnicity amongst the different criteria, set forth by the NCCN11 and USPSTF13. Contrary to other studies which analyzed subjects eligible for screening, our cohort of patients was individuals with lung cancer that were retrospectively assessed for NCCN11 and USPSTF13 lung cancer screening eligibility and LDCT uptake prior to their diagnosis of lung cancer. We found significantly lower rates of

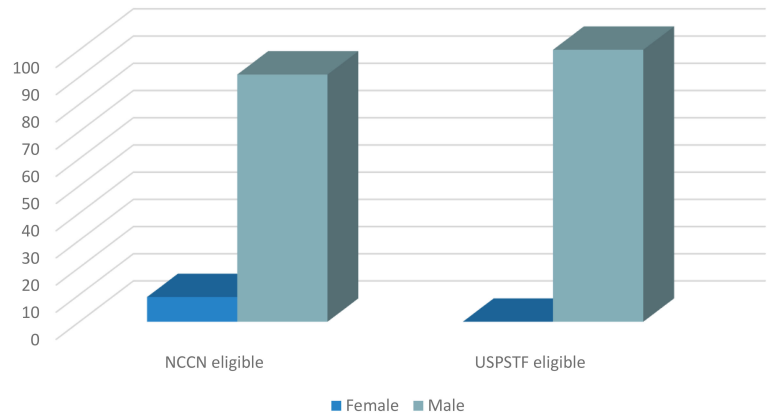

FIGURE 1
Sex of eligible subjects that underwent LDCT.

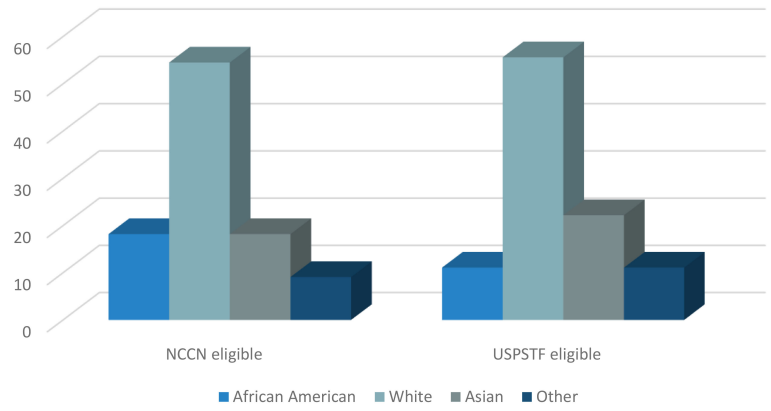

FIGURE 2
Race of eligible subjects that underwent LDCT.

USPSTF13 eligibility for Hispanics compared to non-Hispanic or others. Our study suggested that the differences in the screening criteria between NCCN11 and USPSTF13 influenced eligibility amongst Hispanics, who were noted to have higher tendencies to fulfill NCCN11 than USPSTF13 criteria.

Evidence has suggested that underrepresented groups tend to have a higher risk of LC at a younger age and with less smoking exposure (16). Findings such as these provided the impetus for the latest changes in the screening guidelines, the most important of which decreased the age and pack-year requirements. In March of 2021, the USPSTF updated their lung cancer screening recommendations to include adults aged 50 (formerly 55) to 80 years who have a ≥20 (formerly 30) pack-year smoking history and currently smoke or have quit within the past 15 years (17). The 2020 guidelines set forth by the NCCN identify high-risk individuals as those aged 55-77 (formerly 74) with a ≥30 pack-year history of smoking who are current smokers or have quit within 15 years, or age ≥50 with a ≥20 pack-year history and one additional risk factor (9). In a recent study which retrospectively observed these changes in eligibility under the updated USPSTF guidelines, the proportion eligible for screening among current and former smokers increased by 76.7% for African American and 78.1% for Hispanic populations. However, compared with white individuals, African American and Hispanic individuals still had lower odds of eligibility (18). Clearly, even with updated guidelines, disparities exist in LC screening among underrepresented populations. Another cross-sectional

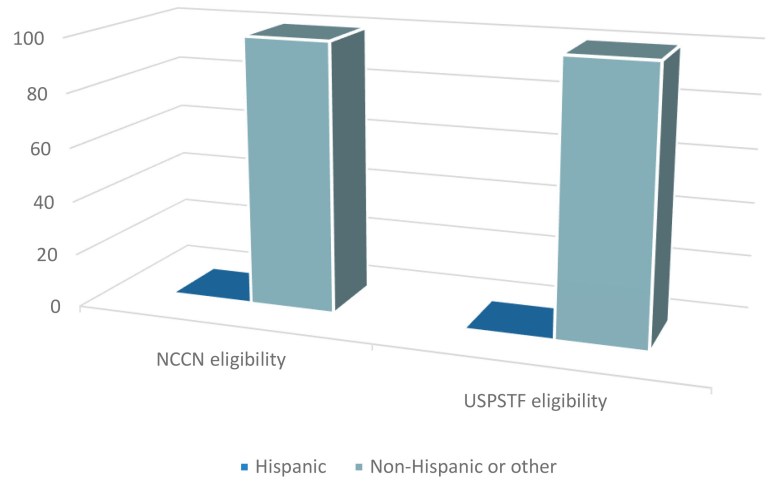

FIGURE 3
Ethnicity of eligible subjects that underwent LDCT.

retrospective survey study evaluated the association between race and ethnicity and lung cancer screening eligibility in subjects from 20 states. The rates for screening eligibility increased from 12%, 4%, and 7% to 15%, 5%, and 9% in White, Hispanic, and African Americans, respectively, under the new screening guidelines. Nevertheless, African American ($p<0.001$) and Hispanic ($p<0.001$) respondents were still less likely to fulfill lung cancer screening eligibility than Whites. Additionally, the study found no statistical association in the rates of screening eligibility for racial and ethnic minorities under the revised USPSTF21 guidelines ($p=0.76$) (19). Lastly, one study evaluated whether the updated USPSTF21 lung cancer screening recommendations would ameliorate racial disparities in screening eligibility. It found that although the revised guidelines increased the eligibility of minorities compared to the USPSTF13 guidelines, racial and ethnic disparities may inadvertently increase (20).

While this study primarily focused on screening eligibility of Hispanic patients, a retrospective objective analysis of the data from our previous study revealed potential disparities in screening implementation and LDCT uptake according to sex, race, and ethnicity. Despite 52% and 20% of the self-identified Hispanic subjects with lung cancer in our study being eligible under NCCN and USPSTF criteria, respectively, none underwent screening prior to their diagnosis of lung cancer. Additionally, White and male subjects had higher rates of screening uptake. While, liberalizing and loosening the lung cancer screening guidelines is the first step to increase the rates of screening eligibility for high-risk individuals, it comes at the risk of perpetuating pre-existing disparities that exist for underrepresented groups. Disparities in screening will continue to widen if factors including sex, race, and ethnicity are not taken into consideration. Additionally, assessing and weighing the individuals' social determinants of health such as socioeconomic status, living environment, and health insurance to understand the risk of lung cancer and ability to undergo LDCT is of paramount importance to increase the rates of lung cancer screening and early diagnosis for all groups.

Despite sharing some common characteristics, one size does not fit all when it comes to sex, race, and ethnicities - and we must take into account the different risk factors and characteristics each group possesses in order to seek health equity for our most vulnerable populations. Possible ways to mitigate these disparities include making active efforts to improve inclusivity in clinical trials and continuing to revise and expand the inclusion criteria for LDCT, incorporating social determinants of health Ongoing prospective studies to understand how these factors affect the risk of lung cancer and create guidelines to integrate these will be of need to optimally close the gap in lung cancer screening disparities.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

ME assisted in data collection and the writing of the manuscript. NS overlooked the study and assisted with manuscript proofread. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. American Cancer Association. *Key statistics for lung cancer*. (2022). Available at: https://www.cancer.org/cancer/lung-cancer.

2. U.S. National Institute of Health and National Cancer Institute. *SEER Cancer Statistics Review, 1975-2015*. Available at: http://www.seer.cancer.gov.

3. Haddad DN, Sandler KL, Henderson LM, Rivera MP, Aldrich MC. Disparities in lung cancer screening: A review. *Ann Am Thorac Soc* (2020) 17 (4):399–405. doi: 10.1513/annalsats.201907-556cme

4. *Cancer Stat Facts: Cancer Disparities*. Bethesda, MD: National Cancer Institute (2009). Available at: http://www.seer.cancer.gov.

5. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* (2011) 365(5):395–409. doi: 10.1056/NEJMoa1102873

6. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *N Engl J Med* (2020) 382(6):503–13. doi: 10.1056/NEJMoa1911793

7. Pastorino U., Rossi M., Rosato V., Marchiano A., Sverzellati N., Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year

results of the MILD trial. *Eur J Cancer Prev* (2012) 21:308–15. doi: 10.1097/CEJ.0b013e328351e1b6

8. U.S. Preventive Services Task Force. *Lung cancer: Screening*. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening.

9. National Comprehensive Cancer Network, Inc.. *Lung cancer screening* (2020). Available at: http://www.nccn.org/patients/guidelines/content/PDF/lung_screening-patient.pdf.

10. Tanner NT, Gebregziabher M, Hughes Halbert C, Payne E, Egede LE, Silvestri GA. Racial differences in outcomes within the national lung screening trial. implications for widespread implementation. *Am J Respir Crit Care Med* (2015) 192(2):200–8. doi: 10.1164/rccm.201502-0259oc

11. Aldrich MC, Mercaldo SF, Sandler KL, Blot WJ, Grogan EL, Blume JD. Evaluation of USPSTF lung cancer screening guidelines among African American adult smokers. *JAMA Oncol* (2019) 5(9):1318–24. doi: 10.1001/jamaoncol.2019.1402

12. Ryan BM. Differential eligibility of African American and European American lung cancer cases using LDCT screening guidelines. *BMJ Open Respir Res* (2016) 3:e000166. doi: 10.1136/bmjresp-2016-000166

13. Olazagasti C, Kohn N, Aviles K, Ehrlich M, Hoilett A, Seetharamu N. Missed opportunities? A retrospective analysis of lung cancer screening utilization among patients with lung cancer. *Cancer Control* (2022) 29:1–8. doi: 10.1177/10732748221077959

14. Narayan AK, Chowdhry DN, Fintelmann FJ, Little BP, Shepard JO, Flores EJ. Racial and ethnic disparities in lung cancer screening eligibility. *Radiology* (2021) 301(3):712–20. doi: 10.1148/radiol.2021204691

15. Prosper A, Brown K, Schussel B, Aberle D. Lung cancer screening in African Americans: The time to act is now. *Radiology* (2020). doi: 10.1148/rycan.2020200107

16. Li CC, Matthews AK, Rywant MM, Hallgren E, Shah RC. Racial disparities in eligibility for low-dose computed tomography lung cancer screening among older adults with a history of smoking. *Cancer Causes & Control: CCC* (2019) 30(3):235–40. doi: 10.1007/s10552-018-1092-2

17. US Preventive Services Task Force. Screening for lung cancer: US preventive services task force recommendation statement. *JAMA* (2021) 325(10):962–70. doi: 10.1001/jama.2021.1117

18. Reese TJ, Schlechter CR, Potter LN, Kawamoto K, Del Fiol G, Lam CY, et al. Evaluation of revised US preventive services task force lung cancer screening guideline among women and Racial/Ethnic minority populations. *JAMA Netw Open* (2021) 4(1):e2033769. doi: 10.1001/jamanetworkopen.2020.33769

19. Narayan AK, Chowdhry DN, Fintelmann FJ, Little BP, Shepard J-AO, Flores EJ. Race and ethnic disparities in lung cancer screening eligibility. *Radiology* doi: 10.1148/radiol.2021204691

20. Landy R, Young CD, Skarzynski M, Cheung L, Berg CD, Rivera MP, et al. Using prediction models to reduce persistent racial and ethnic disparities in the draft 2020 USPSTF lung cancer screening guidelines. *J Natl Cancer Inst* (2021) 113(11):1590–4. doi: 10.1093/jnci/djaa211

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 19 December 2022
DOI 10.3389/fonc.2022.1024572

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cancer Epidemiology and Prevention, a section of the journal Frontiers in Oncology

RECEIVED 21 August 2022
ACCEPTED 26 October 2022
PUBLISHED 19 December 2022

CITATION
Pichardo MS, Pichardo CM, Talavera GA, Gallo LC, Castañeda SF, Sotres-Alvarez D, Molina Y, Evenson KR, Daviglus ML, Hou L, Joyce B, Aviles-Santa L and Plascak J (2022) Neighborhood segregation and cancer prevention guideline adherence in US Hispanic/Latino adults: Results from the HCHS/SOL. *Front. Oncol.* 12:1024572. doi: 10.3389/fonc.2022.1024572

Neighborhood segregation and cancer prevention guideline adherence in US Hispanic/Latino adults: Results from the HCHS/SOL

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Background: Adherence to the American Cancer Society (ACS) guidelines for cancer prevention is associated with a lower risk of cancer and mortality. The role of neighborhood segregation on adherence to the guidelines among Hispanic/Latino adults is relatively unexplored.

Materials and methods: The Hispanic Community Health Study/Study of Latinos is a community-based prospective cohort of 16,462 Hispanic/Latino adults, ages 18-74 years enrolled in 2008-2011 from the Bronx, Chicago, Miami and San Diego. Dimensions of neighborhood segregation were measured using 2010 United States' census tracts:—evenness (the physical separation of a group), exposure (the propensity for contact between groups), and their joint effect (hypersegregation). ACS guideline adherence levels – low, moderate, high – were created from accelerometry-measured physical activity, dietary intake, alcohol intake, and body mass index. Weighted multinominal logistic regressions estimated relative risk ratios (RRR) and 95% confidence intervals (CI) for guideline adherence levels and its components.

Results: Hispanic/Latino adults were classified as low (13.7%), moderate (58.8%) or highly (27.5%) adherent to ACS guidelines. We found no evidence of an association between segregation and overall guideline adherence. Exposure

segregation associated with lower likelihood of moderate adherence to alcohol recommendations ($RRR_{moderate\ vs.\ low}$:0.86, 95%CI:0.75-0.98) but higher likelihood for diet recommendations ($RRR_{moderate\ vs.\ low}$:1.07, 95% CI:1.01-1.14). Evenness segregation associated with lower likelihood of high adherence to the physical activity recommendations ($RRR_{high\ vs.\ low}$:0.73, 95% CI:0.57-0.94). Hypersegregation was associated with individual guideline components.

Conclusion: We found evidence of a cross-sectional relationship between neighborhood segregation and ACS cancer prevention guideline components, but not with overall ACS guideline adherence.

KEYWORDS

neighborhood segregation, obesity, diet, alcohol intake, physical activity, cancer prevention guidelines, Hispanic/Latino

Introduction

Prevalence of obesity, a disease identified in the etiology of at least 13 cancers and cancer sites (known as obesity-related cancers), remains high among U.S. Hispanic/Latino adults (1, 2). Adherence to the American Cancer Society (ACS) Guidelines on Nutrition and Physical Activity for Cancer Prevention (3, 4), which include maintaining a healthy weight throughout life, engaging in at least 150-300 minutes of moderate to vigorous physical activity every week, increasing intake of fruits, vegetables, whole grains, and reducing intake of red and processed meats, refined grains and alcohol, may reduce the risk of many obesity-related cancers (5, 6). Yet, adherence levels remain low among Hispanic/Latino adults (7, 8). For Hispanic/Latinos, the manifestation of structural racism —the intersection of low socioeconomic status and high race- and economic-based residential segregation—may contribute to poor energy balance and increase risk of developing obesity-related cancers (9–12), perpetuating cancer inequities (13).

The construct of structural racism is often operationalized as neighborhood racial-ethnic segregation and poverty; and evidence suggest that racial and ethnic segregation is particularly exacerbated by neighborhood poverty (14, 15). Segregation is formally measured using five dimensions as developed by Massey and Denton (16): evenness (the spatial distribution of a group), exposure (the propensity for contact between groups), clustering (groups of interest located in close proximity or neighboring areas), centralization (the extent to which a group resides in or near the center of an urban area), concentration (the relative amount of physical space a group occupies). High levels across more than one dimension is known as hypersegregation.

The literature on segregation using these formal, well-established measures of segregation among Hispanic/Latinos is limited. Systematic reviews of segregation and obesity (17) and segregation and cancer (18) note an overreliance of the literature on informal and non-valid, measures of segregation such as racial/ethnic density/composition, which does not reflect the distribution of racial and ethnic groups across space nor compares racial/ethnic composition between the neighborhood of interest to surrounding areas. The literature that incorporates formal segregation measures has predominantly focused on only the exposure dimension—measured by the isolation index—and its link to obesity (19–25). While majority of studies do not distinguish 'segregation' from 'ethnic enclave' methologically; conceptually the literature attempts to identify 'ethnic enclave' as a health promoting factor linked to social capital. Herein, we operationalize and conceptualize segregation in the context of health disparities according to White and Borrell; and we consider only segregation measures developed by Massey and Denton as 'formal' and other measures as 'informal' (26).

Regardless of the segregation measure used, studies have shown that neighborhoods with high Hispanic/Latino segregation (i.e., commonly referred to as ethnic enclave) have more obesogenic features (e.g., reduced opportunities and infrastructures for physical activity, lack of safety, low walkability, and fewer recreational resources) (27–31) and lower access to markets or stores with affordable healthy foods (30, 32), and fresh fruits and vegetables (33). These features in turn may increase risk of obesity (12, 34) among the population.

Beyond obesity, few segregation studies have examined other lifestyle behaviors related to cancer [e.g, diet quality, physical activity, and alcohol intake (33, 35)]. Moreover, none have examined segregation in relation to overall lifestyle patterns. Hispanic/Latino adults residing in segregated areas (i.e., ethnic enclaves) may have fewer opportunities to engage in the full range of healthful behaviors to prevent cancer, in concordance with ACS guidelines.

10.3389/fonc.2022.1024572

To better understand the potential mechanisms that contribute to poor energy balance and ultimately, cancer health inequities seen for Hispanic/Latino communities, we examined cross-sectional associations between neighborhood segregation and adherence to the ACS lifestyle guidelines in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).

Materials and methods

Study population

The HCHS/SOL is a longitudinal community-based cohort study that recruited between 2008 and 2011 (36). A total of 16,415 non-institutionalized Hispanic/Latino adults (aged 18–74 years) were enrolled in Miami, FL; San Diego, CA; Chicago, IL; and the Bronx, NY from areas with high concentrations of Hispanic/Latino residents and low residential mobility to maximize retention rates (36). Participants self-identified heritage as Cuban (n = 2,348), Puerto Rican (n = 2,728), Dominican (n = 1,473), Mexican (n = 6,472), Central American, (n = 1,732), and South American (n = 1,702). At baseline, participants completed questionnaires with trained bilingual interviewers to assess lifestyle, anthropometric, and sociodemographic characteristics. Baseline home addresses were geocoded at the census tract and linked to 2010 U.S. Census tract neighborhood indicators from the IPUMS National Historical Geographic Information System (NHGIS) (37).

Neighborhood segregation: Formal measures

For our primary analysis, neighborhood segregation was examined using two formal dimensions—evenness and exposure—using 2010 decennial census tract data at the State level (16, 38, 39). The joint effect of evenness and exposure captured hypersegregation. We measured evenness segregation through Gini coefficient of Hispanic/Latino (Figure 1) (16, 38). The Gini coefficient measures the variability of Hispanic/Latino residents within the census tract, ranging from 0 to 1 (i.e., with 1 indicating greater segregation). We measured exposure segregation through the isolation index (Figure 2) (39). The isolation index ranges from 0 to 1 with higher values suggesting increased probability of interacting with a Hispanic/Latino resident (i.e., greater isolation/segregation). Census-tract level segregation values were calculated based on ethnicity proportions at the block-level according to previous methods (16).

Neighborhood segregation: Informal/proxy measures

For our secondary analyses, in an effort to compare with prior studies, informal or proxy measures of segregation were examined—Hispanic/Latino density (proportion of adults in a census tract) and racialized economic segregation.

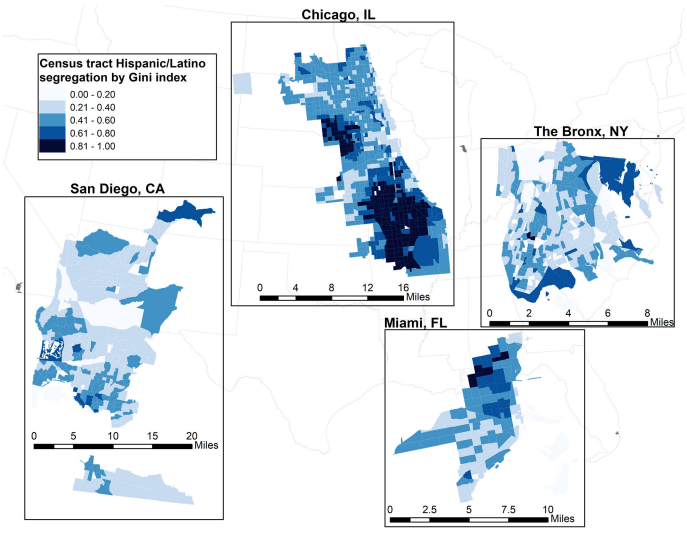

FIGURE 1
Evenness segregation of Hispanic/Latino census tracts, measured by the Gini index for each study site in the Hispanic Health Community Study/Study of Latinos.

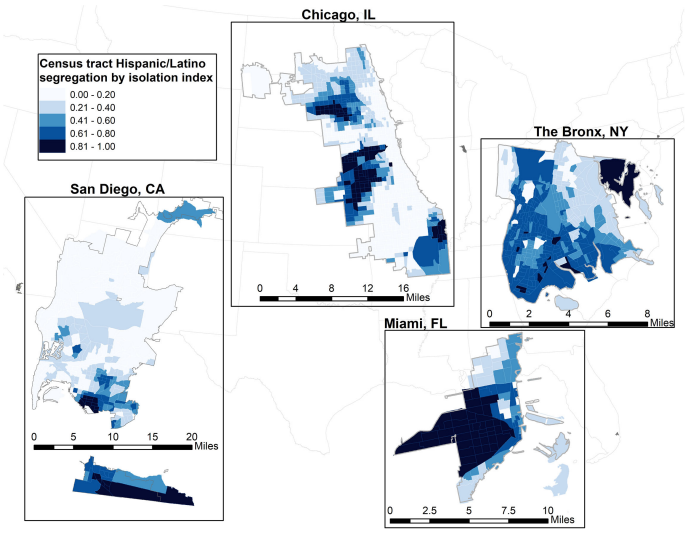

FIGURE 2
Exposure segregation of Hispanic/Latino census tracts, measured by the Isolation index for each study site in the Hispanic Health Community Study/Study of Latinos.

Hispanic/Latino density

A widely used proxy for neighborhood segregation is Hispanic/Latino density. For comparability with existing literature and with other formal measures of segregation, we operationalized Hispanic/Latino density using the 2006-2010 American Community Survey data. Higher values indicate higher proportion of Hispanic/Latino residents in the neighborhood.

Racialized economic segregation

Using data from the 2006-2010 5-year estimates of the American Community Survey, we calculated the proportional imbalance between affluence and poverty to obtain an Index of Concetration at the Extremes (ICE), which can range from -1 (low racial/ethnic or economic privilege) to 1 (most racial/ethnic or economic privileged). This measure allows us to examine the combined (i.e., racialized economic segregation) and separate influence of concentration of income as well as race/ethnicity. As such, three different types of ICE indices were calculated based on work by Krieger et al., utilizing income data alone, race/ethnicity data alone, and an integration of both income and race/ethnicity data (40, 41). Based on the 20th and 80th percentiles of the national household income distribution of the 2010 Census data, deprived groups were defined as those earning ≥ U.S $25,000 and advantaged groups were those earning ≥ U.S. $100,000.

ACS guideline adherence score

For comparability with the existing body of literature on adherence, the 2012 ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention, outlined in Table 1, were operationalized as a composite score based on previous studies (7, 8).

Diet

Diet data came from two 24-hour dietary recalls that assessed intake of specific foods and food groups during the past 12

TABLE 1 The 2012 American cancer society guidelines on nutrition and physical activity for cancer prevention[1].

1. Achieve and maintain a healthy weight throughout life.

2. Be physically active. Get at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week (or a combination of these), preferably spread throughout the week.

3. Eat a healthy diet, with an emphasis on plant foods.

3a. Limit how much processed meat and red meat you eat.

3b. Eat at least 21/2 cups of vegetables and fruits each day.

3c. Choose whole grains instead of refined grain products.

3d. If you drink alcohol, limit your intake. Drink no more than 1 drinker day for women or 2 per day for men.

[1]Kushi et al. (3). "American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity." CA Cancer J Clin 62(1): 30-67.

months (42). The diet components were scored as follows: (1) fruits and vegetables - 1 point for consuming ≥5 servings/day and 0 otherwise; (2) total carotenoids - 0, 1 or 2 points for being in the first, second or third tertile of carotenoid intake; (3) red and processed meat – log transformed, divided into quartiles and assigned scores of 0-3 (lowest quartile = 3); and (4) whole grains, defined as percentage of whole grains consumed (whole grains/ total grains x 100) then divided into quartiles and assigned a score of 0-3 (lowest quartile = 0). A final diet score (ranged 0-9) was obtained by summing across the four diet components.

Alcohol

Alcohol intake as grams per day, derived from the dietary recall and described in detail previously (43), was considered separately from the diet score. One drink was defined as 14 grams of pure alcohol.

Physical activity

Accelerometer-assessed moderate to vigorous physical activity (MVPA) was captured using an Actical accelerometer that participants wore for 7 days to assess frequency, duration, and intensity of their physical activity during that period. Further details of the accelerometry protocol, data cleaning, and derivation are available elsewhere (44).

Body mass index

Anthropometric measures (height and weight) were obtained during the baseline visit at each study site. Self-reported weight and height at age 21 years were also collected. Body mass index at enrollment and at age 21 were calculated using the formula kg/m^2 and categorized as: normal weight (BMI 18.5 to < 25.0 kg/m^2), overweight (25.0 to < 30.0 kg/m^2) and with obesity (≥ 30.0-50 kg/m^2). To capture the ACS guideline of maintenance of a healthy weight throughout life, the BMI scoring incorporated BMI at age 21 when available.

Composite adherence score

We categorized the diet score, alcohol intake, physical activity, and BMI into three levels. Behaviors most consistent with criteria received a score of "2" (7-9 diet points; nondrinker; ≥150 mins/week moderate activity or ≥75 mins/week of vigorous; and BMI < 25.0 kg/m^2 at enrollment *and* at age 21. Behaviors with mid-level concordance received a score of "1" (3-6 diet points; > 0 - ≤1 drink/day for women or 0- ≤2 drink/day for men; >0 to <150 mins/week of moderate activity or >0 to <75 mins/week of vigorous activity; and BMI of 25.0 to <30.0 at enrollment or at age 21). Behaviors with least consistency to guidelines received a score of "0" (0-2 diet points; >1 drink/day for women or >2 drink/day for men; 0 mins/week for physical activity; and BMI ≥ 30 kg/m^2 at study entry or at age 21). For participants with missing BMI at age 21, only BMI at study entry was used.

Components were summed with possible range of "0" (does not meet recommendations) to "8" (meets all recommendations), and further categorized based on *a priori* cut points used in other studies that included Hispanic/Latino adults (7, 8) as low (0-3), moderate (4-5), and high (6-8) adherence.

Covariates

We identified potential *a priori* individual and neighborhood level confounders including age categories (18-44, 45-65, >65), education (<high school, high school, some college, ≥college), sex (male, female), employment status (employed, unemployed), marital status (married, otherwise), household income (<$30,000, ≥$30,000, missing), acculturation level (language preference (Spanish, English), birthplace and duration of residence in the U.S. mainland (US born, foreign/US territory born <10 years, foreign/US territory born ≥10 years, missing), Hispanic/Latino heritage, and study site (Miami, San Diego, the Bronx, Chicago). Missing data was coded as the highest level in each categorical covariate.

Neighborhood level confounders included the neighborhood immigrant composition (percent of foreign-born residents in the tract) and the neighborhood deprivation index. The neighborhood deprivation index was calculated according to the approach originally described by Messer et al. (45). Using principal component analysis, we extracted a single factor that represented the shared variance from the following variables: percent of residents with less than a high school diploma, percent of residents with household incomes below 100% of the federal poverty level, percent of residents who are unemployed, and median household income. The index was standardized; increasing values indicated higher neighborhood deprivation.

Statistical analysis

Weights and missing data

We conducted complex survey analysis that accounted for sample weights and a two-stage sampling design from the HCHS/SOL study (46). Models included inverse probability weighting (IPW), due to missing accelerometry data as described previously (47, 48). Briefly, 92.3% (n=15,153) of participants had partial accelerometer data and 77% (N=12,750) had complete data (i.e., = 3 adherent days with > 10 hours of wear time (44). The product of the IPW weight and HCHS/SOL sampling weights were used in models of guideline adherence using accelerometry-measured physical activity which allowed for inferences to the target Hispanic/Latino population. Complex survey designed was accounted for using overall sampling weights; inverse probability weights accounted for missing accelerometer data. We excluded participants with missing data on variables of interest (not mutually exclusive): home addresses (n=316);

residing outside of counties of interest (n = 70); accelerometry data (n = 3,933); body mass index at study entry (n = 428); and intake of meat (n = 1,086), grains (n = 1,086), fruits (n = 1,086), vegetables (n = 1,086), nuts and legumes (n= 223), and carotenoids (n = 434). The final analytic sample was 11,957 adults.

Model building

Using design-based weighted analyses, we described participant characteristics by ACS guideline adherence. We examined correlations between segregation exposures. We fit weighted multinominal logistic regressions of ACS guideline adherence to estimate relative risk ratios (RRR) and 95% confidence intervals (CI) for a 1-unit increase in neighborhood segregation. Sequential multivariable analyses to control for potential confounders were performed. Model 1 adjusted for individual-level (e.g., age, sex, education, household income, self-identified heritage, study site) covariates. To evaluate the role of segregation, beyond neighborhood deprivation, model 2 additionally included the neighborhood deprivation index. Hypersegregation was examined using joint effects model that examined additive and multiplicative interactions between the dimensions of segregation and guideline adherence outcomes. The proportional odds/parallel lines assumptions were examined in each independent model and because of contradictory results between model fit indices (i.e., Akaike information criterion (AIC) and Bayesian information criterion (BIC)), results from ordinal models (Odds ratio, OR and 95% CI) are also shown. Sensitivity analysis examined associations among never smokers and among participants with complete data for BMI at age 21 at study entry (data not shown). All analysis was conducted in STATA and two-sided tests were considered statistically significant at $p<0.05$.

Results

Descriptive statistics

Differences in sociodemographic characteristics were found by ACS guideline adherence levels (Table 2). Overall, 28% of Hispanic/Latino adults were classified as highly adherent to the 2012 ACS guidelines. The majority of Hispanic/Latino adults were ages 18-44 (60%), female (52%), had less than a high school education (32%), had a Spanish-language preference (75%), were US/territory born ≥ 10 years (49%), had health insurance (50%), and had never smoked cigarettes. Overall, the mean BMI at study entry and age 21 were 29.4 and 24.0 kg/m^2, respectively. Participants engaged in about 150 and 24 minutes/week of

TABLE 2 Characteristics of U.S. Hispanic/Latinos by ACS guidelines on nutrition and physical activity for cancer prevention categories.

ACS Guideline Adherence Categories[1]		Total	Low Adherence	Moderate Adherence	High Adherence	P[3]
	No. of Participants	**11, 957**	**1,710, 13.7%**	**7,156, 58.8%**	**3, 091. 27.5%**	
Demographics		**Weighted column %**				
Age, %						<0.001
18-44	4,553	60.2%	51.4%	57.4%	70.6%	
45-65	6,384	31.5%	38.2%	33.0%	25.0%	
>65	1,020	8.3%	10.7%	9.6%	4.4%	
Sex						<0.001
Male	4,765	47.8%	41.0%	46.0%	55.2%	
Female	7,192	52.2%	59.0%	54.0%	44.8%	
Education						0.0305
< High school	4,621	32.2%	33.0%	33.0%	30.0%	
High School	3,014	28.3%	27.5%	27.1%	31.0%	
Some college	1,476	12.1%	13.7%	12.5%	10.4%	
≥ College	2,824	27.4%	25.7%	27.2%	28.5%	
Missing	22	0.1%	0.2%	0.1%	0.0%	
Employment status						
Unemployed	5,644	48.0%	54.8%	48.9%	42.8%	<0.001
Employed	6,181	50.6%	44.2%	50.0%	55.2%	
Missing	132	1.4%	1.0%	1.2%	2.1%	

(Continued)

TABLE 2 Continued

ACS Guideline Adherence Categories[1]		Total	Low Adherence	Moderate Adherence	High Adherence	P[3]
	No. of Participants	**11, 957**	**1,710, 13.7%**	**7,156, 58.8%**	**3, 091. 27.5%**	
Marital status						
Single, divorced, widowed	8,961	65.7%	69.2%	68.4%	58.0%	<0.001
Married or partnered	2,996	34.3%	30.8%	31.6%	42.0%	
Acculturation						
Language preference						0.3251
English	2,179	24.8%	26.0%	23.9%	26.3%	
Spanish	9,778	75.2%	74.0%	76.1%	73.7%	
Place of birth						<0.001
Foreign born in US <10 years	2,759	28.1%	25.9%	27.1%	31.6%	
Foreign born in US >=10 years	7,253	49.2%	53.2%	51.7%	41.8%	
US Born	1,897	22.2%	20.3%	20.7%	26.3%	
Missing	48	0.5%	0.6%	0.5%	0.3%	
Health-related characteristics						
Health Insurance						0.0017
Not insured	5,896	50.2%	44.0%	50.7%	52.3%	
Insured	6,061	49.8%	56.0%	49.3%	47.7%	
Smoking status						<0.001
Current	2,116	20.3%	25.3%	19.7%	19.2%	
Former	2,462	17.4%	19.6%	18.9%	13.2%	
Never	7,362	61.9%	55.0%	60.8%	67.6%	
Missing	17	0.4%	0.0%	0.7%	0.1%	
Cancer history						0.0014
No	11,467	96.5%	94.4%	96.5%	97.5%	
Yes	490	3.5%	5.6%	3.5%	2.5%	
Lifestyle behaviors, mean ± standard error						
Body size, kg/m2						
Body mass index at age 21 years, n = 9, 614	11,957	24.0 ± 0.1	24.7 ± 0.4	24.2 ± 0.1	23.1 ± 0.1	<0.001
Body mass index at study entry	9,614	29.4 ± 0.11	33.8 ± 0.3	30.3 ± 0.2	25.3 ± 0.1	<0.001
Physical Activity						
Self-reported Leisure time (min/week)						
Moderate	11,897	89.8 ± 4.1	70.0 ± 6.7	85.5 ± 5.7	108.8 ± 7.2	0.001
Vigorous	11,1902	81.4 ± 4.0	46.8 ± 10.4	69.4 ± 4.4	124.2 ± 7.3	<0.001
Self-reported Total (min/week)						
Moderate	11,915	670.1 ± 16.6	482.5 ± 27.6	647.1 ± 20.7	812.5 ± 31.7	<0.001
Vigorous	11,913	291.0 ± 11.0	239.7 ± 38.0	259.1 ± 11.6	384.9 ± 20.6	<0.001
Accelerometry-measured (min/week)						
Moderate	11,957	149.8 ± 2.9	70.1 ± 3.7	132.4 ± 3.1	226.4 ± 5.0	<0.001
Vigorous	11,957	24.1 ± 1.4	4.3 ± 0.6	19.4 ± 1.7	44.0 ± 2.7	<0.001
Diet						
Total energy, kcal/d	11,957	2,065.3 ± 14.7	1,979.7 ± 35.6	1,995.5 ± 18.2	2,257.2 ± 27.2	<0.001
Fruit and vegetables, servings/d	11,957	4.9 ± 0.1	4.0 ± 0.1	4.8 ± 0.1	5.6 ± 0.1	<0.001
Total carotenoids, mg/d	11,957	33.7 ± 0.4	27.2 ± 0.8	32.2 ± 0.4	40.0 ± 0.8	<0.001

(Continued)

TABLE 2 Continued

ACS Guideline Adherence Categories[1]		Total	Low Adherence	Moderate Adherence	High Adherence	P[3]
	No. of Participants	**11, 957**	**1,710, 13.7%**	**7,156, 58.8%**	**3, 091. 27.5%**	
Red and processed meat, servings/d	11,957	2.1 ± 0.1	2.11 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	0.487
Whole grains, servings/d	11,957	1.6 ± 0.1	0.5 ± 0.0	1.5 ± 0.1	2.4 ± 0.1	<0.001
Proportion of grains consumed as whole grains	11,957	21.9 ± 0.6	7.5 ± 0.6	21.4 ± 0.7	30.1 ± 1.0	<0.001
Alcohol intake among drinkers (servings/day)	11,957	0.3 ± 0.02	1.1 ± 0.1	0.2 ± 0.02	0.03 ± 0.01	<0.001
Alcohol intake among drinkers (servings/week)	11,957	1.9 ± 0.1	8.0 ± 0.7	1.3 ± 0.1	0.2 ± 0.04	<0.001
Neighborhood segregation measure[2]						
Formal measures of segregation						
Evenness dimension	11,957	0.39 ± .004	0.40 ± .006	0.39 ± 0.05	0.39 ± 0.005	0.138
Exposure dimension	11,957	0.76 ± 0.007	0.79 ± 0.01	0.76 ± 0.007	0.75 ± 0.008	<0.001
Proxy measure of segregation						
Economic Segregation	11,957	-0.28 ± 0.01	-0.32 ± 0.02	-0.29 ± 0.01	-0.25 ± 0.02	<0.001
Racial Segregation	11,957	-0.64 ± 0.01	-0.69 ± 0.01	-0.64 ± 0.01	-0.61 ± 0.01	<0.001
Racialized Economic Segregation	11,957	-0.26 ± 0.01	-0.31 ± 0.01	-0.27 ± 0.01	-0.24 ± 0.01	<0.001
Hispanic/Latino Density	11,957	0.74 ± 0.01	0.77 ± 0.01	0.74 ± 0.01	0.72 ± 0.01	<0.001

ACS, American Cancer Society.
[1]The ACS guideline adherence score ranged from 0-8. Data from baseline assessments were used in this analysis.
[2]The evenness dimension of segregation was measured with the Gini coefficient (1 indicates higher segregation); the exposure dimension was measured with the Isolation index (higher values indicate higher segregation); economic segregation measured via Index of Concentration at the Extremes (ICE) for income; racial segregation measured via ICE for race; Racialized economic segregation measured via ICE for income and race (-1 indicates low privilege, +1 indicates higher privilege).
[3]P values derived from Designed-based F tests.

moderate and vigorous activity respectively, consumed 4.9 servings/day of fruits and vegetables, 2.1 servings/day of red and processed meats, 22% of whole grains out of total grains consumed per day, and 1.9 servings/week of alcohol.

Correlations between neighborhood segregation measures are shown in Table 3. Overall, Hispanic/Latino adults lived in low segregated environments based on the evenness dimension (0.39, Figure 1) and highly isolated neighborhoods based on the exposure dimension (0.76, Figure 2). Hispanic/Latinos tended to reside in neighborhood environments with lower economic and racial privilege (economic segregation = -0.28, racial segregation = -0.64, racialized economic segregation = -0.26).

On average, adults more adherent to ACS guidelines were younger (age 18-44 at 71%), male (55%), had lower education (31% high school or 30% less than high school), were employed (55%), single (58%), enrolled at the San Diego site (30%), less acculturated (preferred Spanish (74%), foreign born in US <10 years (32%), or in US/territory born >=10 years (42%), of Mexican heritage (46%), not insured (52%), and were never smokers (68%).

TABLE 3 Correlations between neighborhood segregation measures in analytical sample.

	(1)	(2)	(3)	(4)	(5)	(6)
(1) Evenness dimension of segregation	1					
(2) Exposure dimension of segregation	0.274	1				
(3) Economic segregation	-0.080	-0.394	1			
(4) Racial segregation	-0.107	-0.853	0.574	1		
(5) Racialized economic segregation	-0.051	-0.585	0.897	0.763	1	
(6) Hispanic/Latino (HL) Density	0.168	0.942	-0.435	-0.933	-0.650	1
(7) Neighborhood deprivation index	0.111	0.194	-0.828	-0.390	-0.671	0.219

TABLE 4 Proportion of adults meeting the ACS nutrition and physical activity cancer prevention guidelines, by self-reported Hispanic/Latino Heritage, N = 11, 957.

		All Heritage	Dominican	Central American	Cuban	Mexican	Puerto Rican	South American	>1 One Heritage	Missing Heritage	P[8]
	No. of Participants	**11,957**	**1,103**	**1,230**	**1,588**	**4,902**	**1,958**	**822**	**333**	**214**	
Adherence to Guideline Components											
Alcohol[1,6]											<0.001
Low	528	4.6%	4.0%	3.7%	4.1%	4.9%	4.8%	4.4%	7.1%	16.8%	
Moderate	1,240	11.8%	10.8%	10.9%	21.5%	7.4%	12.6%	9.2%	11.7%	0.0%	
High	10,179	83.6%	85.2%	85.4%	74.4%	87.7%	82.7%	86.3%	81.2%	83.3%	
Dietary[2,6]											
Low	3,856	34.5%	51.7%	35.5%	41.7%	20.2%	46.6%	37.6%	39.9%	65.6%	<0.001
Moderate	7,359	59.9%	47.3%	59.3%	55.4%	70.0%	49.7%	60.0%	57.7%	33.4%	
High	742	83.6%	1.0%	5.2%	2.8%	9.8%	3.7%	2.4%	2.4%	1.0%	
Body Mass Index[3,6]											0.002
Low	3,857	29.7%	33.4%	27.6%	31.2%	27.4%	33.2%	22.6%	35.5%	11.4%	
Moderate	5,609	48.0%	45.7%	48.9%	45.6%	51.0%	45.5%	49.9%	41.5%	45.0%	
High	2,329	22.3%	20.9%	23.5%	23.2%	21.6%	21.3%	27.5%	23.0%	43.7%	
Physical Activity[4,7]											
Low	231	1.73%	1.2%	1.3%	2.9%	1.2%	2.4%	1.8%	0.4%	0.0%	
Moderate	7,548	60.0%	47.8%	58.8%	77.3%	59.6%	50.3%	55.2%	54.7%	38.0%	<0.001
High	4,178	38.3%	51.0%	39.9%	19.9%	39.2%	47.3%	43.0%	44.8%	62.0%	
Guideline Adherence score[5,7]											<0.001
Low	1,710	13.7%	13.5%	12.1%	21.5%	8.6%	17.4%	8.4%	17.5%	9.7%	
Moderate	7,156	58.8%	62.3%	60.3%	60.3%	57.6%	57.2%	58.9%	58.1%	34.9%	
High	3,091	27.5%	23.2%	27.4%	18.3%	33.9%	25.4%	32.7%	24.5%	55.5%	

ACS, American Cancer Society. Data from baseline assessments were used in this analysis.
[1]The alcohol recommendation was operationalized as 2 points for non-drinkers (high adherence) and 1 point for consuming up to 1 or 2 drinks per day for women and men (moderate adherence), respectively, and 0 points if exceeding the alcohol recommendations (low adherence).
[2]The dietary recommendations were operationalized as a summation score, ranging from 0-9 points, across 4 diet components: (1) servings of red and processed meats per day divided into quartiles (Q) and assigned a score of 0-3 (lowest Q = 3); (2) 1 point for consuming ≥5 fruits and vegetables (including nuts and legumes), (3) 1 or 2 points for being in the second or third tertile of total carotenoids, respectively; (4) percentage of whole grains over total grains consumed divided into quartiles and assigned a score of 0-3 (lowest Q =0). Dietary adherence was then classified as low (0-2 diet points), moderate (3-6 diet points) and high (7-9 diet points) adherence.
[3]The body mass index (BMI) recommendation was operationalized as 2 points for maintaining a BMI <25kg/m^2 at age 21 and at study entry (high adherence), 1 point for maintaining a BMI between 25-30 kg/m^2 at either time (moderate adherence), and 0 points for BMI ≥30kg/m^2 at either point (low adherence).
[4]The physical activity recommendations were operationalized using accelerometer measured MVPA where 2 points were given for engaging in ≥150 minutes/week of moderate or ≥75 minutes/week of vigorous activity per week (high adherence), 1 point for MVPA below recommended levels (moderate adherence), 0 points for 0 MVPA (low adherence).
[5]A summation across representing overall guideline adherence across scores for diet, alcohol, BMI and MVPA was calculated and ranged from 0-8. A priori cut offs for guideline adherence were low (score 0-3), moderate (score 4-5), and high (score 6-8) adherence.
Models accounted for [6]overall complex survey weights or [7]inverse probability weights for missing accelerometry data.
[8]P values derived from Designed-based F tests.

Adherence to the ACS guideline and its components varied by Hispanic/Latino heritage (Table 4) and study site (Table 5). Adults of Mexican heritage and adults enrolled in San Diego had the highest proportion of overall adherence to the ACS guidelines as well as high adherence to the alcohol recommendations. Adults of Mexican heritage and those enrolled in Chicago had the highest proportions of high adherence to the dietary recommendations. Adults of South American heritage and enrolled in Miami had the highest proportion of high adherence to the BMI recommendations. Adults of Puerto Rican heritage and enrolled in the Bronx had the highest proportion of adherence to the physical activity recommendations.

Associations for dimensions of segregation and guideline adherence

In fully adjusted multinominal regression, we found no association between the evenness dimension or exposure dimension of segregation and ACS guideline adherence category

TABLE 5 Proportion of adults meeting the ACS guidelines on nutrition and physical activity for cancer prevention guidelines, by Study Site, N = 11, 957.

	No. of Participants	Bronx, NY 2,966	Chicago, IL 3,283	Miami, FL 2,752	San Diego, CA 2,956	P[8]
Adherence to Guideline Components						
Alcohol[1,6]						<0.001
Low	528	3.7%	6.1%	4.0%	5.4%	
Moderate	1,240	9.6%	10.8%	19.3%	6.7%	
High	10,179	86.7%	83.2%	76.7%	87.9%	
Dietary[2,6]						<0.001
Low	3,856	51.1%	20.6%	39.0%	20.2%	
Moderate	7,359	46.4%	70.0%	58.0%	70.6%	
High	742	2.5%	9.4%	3.0%	9.3%	
Body Mass Index[3,6]						<0.001
Low	3,857	33.2%	28.6%	29.6%	26.5%	
Moderate	5,609	46.7%	49.2%	46.0%	50.8%	
High	2,329	20.1%	22.2%	24.3%	22.7%	
Physical Activity[4,7]						<0.001
Low	231	1.4%	1.6%	2.4%	1.4%	
Moderate	7,548	44.1%	60.4%	73.2%	62.7%	
High	4,178	54.6%	38.0%	24.3%	35.9%	
Guideline Adherence Score[5,7]						<0.001
Low	1,710	14.2%	11.3%	18.6%	8.9%	
Moderate	7,156	59.4%	56.5%	60.0%	58.2%	
High	3,091	26.4%	32.2%	21.5%	33.0%	

ACS, American Cancer Society. Data from baseline assessments were used in this analysis.
[1]The alcohol recommendation was operationalized as 2 points for non-drinkers (high adherence) and 1 point for consuming up to 1 or 2 drinks per day for women and men (moderate adherence), respectively, and 0 points if exceeding the alcohol recommendations (low adherence).
[2]The dietary recommendations were operationalized as a summation score, ranging from 0-9 points, across 4 diet components: (1) servings of red and processed meats per day divided into quartiles (Q) and assigned a score of 0-3 (lowest Q = 3); (2) 1 point for consuming ≥5 fruits and vegetables (including nuts and legumes), (3) 1 or 2 points for being in the second or third tertile of total carotenoids, respectively; (4) percentage of whole grains over total grains consumed divided into quartiles and assigned a score of 0-3 (lowest Q = 0). Dietary adherence was then classified as low (0-2 diet points), moderate (3-6 diet points) and high (7-9 diet points) adherence.
[3]The body mass index (BMI) recommendation was operationalized as 2 points for maintaining a BMI <25kg/m^2 at age 21 and at study entry (high adherence), 1 point for maintaining a BMI between 25-30 kg/m^2 at either time (moderate adherence), and 0 points for BMI ≥30kg/m^2 at either point (low adherence).
[4]The physical activity recommendations were operationalized using accelerometer measured MVPA where 2 points were given for engaging in ≥150 minutes/week of moderate or ≥75 minutes/week of vigorous activity per week (high adherence), 1 point for MVPA below recommended levels (moderate adherence), 0 points for 0 MVPA (low adherence).
[5]A summation across representing overall guideline adherence across scores for diet, alcohol, BMI and MVPA was calculated and ranged from 0-8. A priori cut offs for guideline adherence were low (score 0-3), moderate (score 4-5), and high (score 6-8) adherence.
Models accounted for [6]overall complex survey weights or [7]inverse probability weights for accelerometer data.
[8]P values derived from Designed-based F tests.

(Table 6). Furthermore, no associations were found after including both evenness and exposure dimensions in the joint effects models.

Associations for dimensions of segregation and individual components of the guidelines

In fully adjusted multinominal regression models, there was evidence of an association between exposure segregation (i.e., higher residential isolation) and lower likelihood of having moderate vs. low adherence to the alcohol recommendations (Table 6). Evenness segregation associated with lower likelihood of having high vs. low adherence to the physical activity guidelines. In a series of multinominal regression models examining joint effects (additive and multiplicative, Table 7), we found evidence that residence in hypersegregated neighborhoods associated with moderate vs. low adherence to the alcohol, dietary and BMI recommendations and with both moderate and high vs. low adherence to the physical activity recommendations.

TABLE 6 Multinomial logistic regression models for the association between neighborhood segregation measures and adherence to the ACS guidelines[1] on nutrition and physical activity for cancer prevention.

	Model 1[3,5] Relative Risk Ratio (95% CI)				Model 2[4,5] Relative Risk Ratio (95% CI)			
	Low	Moderate	High	P	Low	Moderate	High	P[6]
Formal measures of segregation[2]								
Main effects								
Evenness dimension	1.00	0.94 (0.86, 1.03)	0.93 (0.85, 1.03)		1.00	0.94 (0.86, 1.04)	0.96 (0.86, 1.06)	
Exposure dimension	1.00	0.95 (0.88, 1.04)	0.95 (0.86, 1.03)		1.00	0.95 (0.88, 1.04)	0.98 (0.89, 1.09)	
Joint Effects								
Evenness, while controlling for Exposure	1.00	0.95 (0.87, 1.05)	0.94 (0.85, 1.05)		1.00	0.95 (0.86, 1.05)	0.96 (0.86, 1.07)	
Exposure, while controlling for Evenness	1.00	0.96 (0.88, 1.04)	0.96 (0.87, 1.05)		1.00	0.96 (0.88, 1.04)	0.99 (0.89, 1.09)	
Evenness x Exposure, while controlling for main effects	1.00	1.02 (0.99, 1.05)	1.02 (0.98, 1.05)	0.552	1.00	1.02 (0.99, 1.05)	1.02 (0.98, 1.05)	0.583
Evenness x Exposure, without main effects	1.00	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)	0.764	1.00	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)	0.862
Proxy measures of segregation[2]								
Economic Segregation	1.00	1.08 (0.69, 1.70)	1.47 (0.86, 2.49)		1.00	1.00 (0.60, 1.66)	1.24 (0.71, 2.19)	
Racial Segregation	1.00	1.31 (0.84, 2.05)	1.49 (0.92, 2.41)		1.00	1.30 (0.82, 2.06)	1.23 (0.72, 2.08)	
Racialized Economic Segregation	1.00	1.35 (0.81, 2.24)	1.94 (1.01, 3.70)		1.00	NA	NA	
Hispanic/Latino Density	1.00	0.60 (0.28, 1.26)	0.54 (0.25, 1.17)		1.00	0.60 (0.28, 1.29)	0.72 (0.31, 1.68)	

ACS, American Cancer Society; CI, Confidence Interval, NA, Not Applicable.
[1]The ACS guideline adherence score ranged from 0-8. A priori cut offs for guideline adherence were low (score 0-3), moderate (score 4-5), and high (score 6-8). Data from baseline assessments were used in this analysis.
[2]The evenness dimension of segregation was measured with the Gini coefficient; the exposure dimension was measured with the Isolation index; economic segregation measured via Index of Concentration at the Extremes (ICE) for income; racial segregation measured via ICE for race; Racialized economic segregation measured via ICE for income and race.
[3]Model 1 was adjusted for individual level covariates: age (<45, 45-65, >65), sex (male, female), education (<HS, HS, Some College, College, Missing), income (less than $30,000, $30,000 or more, missing), marital status (married, otherwise), insurance status (yes, no), place of with combined with years in the US (US born, Foreign born and <10 years in US, Foreign born and 10 + years in US, Missing), Language preference (Spanish, English), Hispanic/Latino heritage (Mexican, Dominican, Puerto Rican, Cuban, Central American, South American, Other or More than 1 heritage, Missing), study site (the Bronx, Chicago, Miami, San Diego).
[4]Model 2 also adjusted for neighborhood level covariates as follows: models for evenness, racial segregation, and HL density included neighborhood deprivation index, while models for evenness, exposure, and economic segregation adjusted for neighborhood immigrant concentration).
[5]All models accounted for complex survey design using inverse probability weights.
[6]P values for multiplicative models were calculated using loglikelihood ratio tests comparing nested models with and without interaction effects.

Secondary analyses: Associations for proxies of neighborhood segregation and guideline adherence

Racialized economic segregation was associated with higher likelihood of having high vs. low overall guideline adherence (Table 6). Residence in areas with either higher economic segregation or higher racialized economic segregation was associated positively with the likelihood of having moderate or high vs. low adherence to the BMI recommendations. Other proxies of segregation (racial segregation or Hispanic/Latino density) did not associate with overall guideline adherence or its components.

Results from ordered logistic regression models are shown in Table 8.

Discussion

In this large and diverse population of U.S. Hispanic/Latino adults, we examined whether formal and proxy measures of neighborhood segregation were associated with adherence to the 2012 ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention. In our analysis, formal (e.g., evenness and exposure) measures of segregation were suggestive of a 2-7% lower odds of guideline adherence for every 1 unit increase in segregation. Segregation was also associated with several ACS guideline components. In multiplicative models, there was evidence of an association between hypersegration and BMI. Based on our proxy measures, individuals living in more affluent areas (economic segregation) were 28%-47% more likely to meet the BMI recommendations, whereas Hispanic/Latino adults residing in areas with both greater racial and economic privilege (i.e. more residents identifying with the White race and affluence) were almost 2 times more likely to meet them.

Our study expands a growing body of evidence that attempts to understand the role of neighborhood segregation on energy balance and cancer related inequities. Extant cancer research has focused on the role of neighborhood deprivation on cancer preventive behaviors (49) and cancer risk and outcomes (50), fewer studies have examined segregation, and among these, most relied on proxy measures of segregation (18).

TABLE 7 Multinomial logistic regression models for the association between neighborhood segregation measures and adherence to the individual components of the ACS guidelines[1] on nutrition and physical activity for cancer prevention.

	Alcohol[3,4]				Diet[3,4]			Body Mass Index[3,4]			Physical Activity[3,5]		
	Low	Moderate	High	P[6]	Moderate	High	P[6]	Moderate	High	P[6]	Moderate	High	P[6]
		Odds Ratio and (95% CI)											
Formal measures of segregation[2]													
Main effects													
Evenness dimension	1.00	1.05 (0.89, 1.24)	0.99 (0.85, 1.15)		1.02 (0.95, 1.09)	1.00 (0.88, 1.14)		1.01 (0.94, 1.08)	1.05 (0.96, 1.15)		0.80 (0.63, 1.01)	0.73 (0.57, 0.94)	
Exposure dimension	1.00	0.86 (0.75, 0.98)	0.90 (0.78, 1.04)		1.07 (1.01, 1.14)	1.08 (0.97, 1.20)		1.00 (0.94, 1.07)	1.03 (0.95, 1.12)		0.97 (0.82, 1.15)	0.92 (0.77, 1.10)	
Joint Effects													
Evenness, while controlling for Exposure	1.00	1.07 (0.91, 1.26)	1.01 (0.87, 1.17)		1.01 (0.94, 1.09)	0.99 (0.86, 1.13)		1.01 (0.95, 1.08)	1.05 (0.96, 1.15)		0.80 (0.64, 1.00)	0.74 (0.58, 0.94)	
Exposure, while controlling for Evenness	1.00	0.85 (0.74, 0.98)	0.90 (0.78, 1.05)		1.07 (1.01, 1.14)	1.08 (0.97, 1.21)		1.00 (0.94, 1.07)	1.03 (0.95, 1.11)		0.98 (0.84, 1.15)	0.94 (0.80, 1.12)	
Evenness x Exposure, while controlling for main effects	1.00	1.01 (0.95, 1.07)	1.00 (0.95, 1.05)	0.776	1.01 (0.98, 1.03)	0.99 (0.94, 1.04)	0.672	1.03 (1.01, 1.06)	1.02 (0.99, 1.05)	0.030	1.03 (0.95, 1.12)	1.02 (0.94, 1.11)	0.415
Evenness x Exposure, without main effects	1.00	1.00 (0.98, 1.01)	1.00 (0.99, 1.01)	0.148	1.00 (1.00, 1.01)	0.99 (0.98, 1.00)	0.712	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)	0.234	.99 (0.98, 1.01)	0.99 (0.97, 1.00)	0.727
Proxy measures of segregation													
Economic Segregation	1.00	1.78 (0.89, 3.59)	0.99 (0.46, 2.13)		1.22 (0.85, 1.76)	1.13 (0.61, 2.10)		1.53 (1.07, 2.19)	1.72 (1.08, 2.73)		0.47 (0.11, 1.97)	0.43 (0.09, 2.01)	
Racial Segregation	1.00	1.89 (0.90, 3.96)	1.44 (0.69, 2.99)		0.76 (0.56, 1.04)	1.09 (0.56, 1.80)		1.15 (0.84, 1.58)	1.02 (0.68, 1.51)		1.22 (0.47, 3.16)	1.41 (0.51, 3.87)	
Racialized Economic Segregation	1.00	2.34 (0.89, 6.11)	1.32 (0.48, 3.62)		1.10 (0.72, 1.68)	1.29 (0.53, 3.17)		1.75 (1.14, 2.71)	2.08 (1.18, 3.67)		0.67 (0.20, 2.30)	0.59 (0.15, 2.36)	
Hispanic/Latino Density	1.00	0.40 (0.13, 1.25)	0.66 (0.22, 2.03)		1.57 (0.97, 2.55)	1.25 (0.52, 3.01)		0.81 (0.49, 1.34)	1.06 (0.57, 1.98)		0.68 (0.19, 2.40)	0.51 (0.13, 1.99)	

ACS, American Cancer Society; CI, Confidence Interval.

[1]The ACS guideline adherence score ranged from 0-8. A priori cut offs for guideline adherence were low (score 0-3), moderate (score 4-5), and high (score 6-8). Data from baseline assessments were used in this analysis.

[2]The evenness dimension of segregation was measured with the Gini coefficient; the exposure dimension was measured with the Isolation index; economic segregation measured via Index of Concentration at the Extremes (ICE) for income; racial segregation measured via ICE for race; Racialized economic segregation measured via ICE for income and race.

[3]All models were adjusted for individual level covariates: age (<45, 45-65, >65), sex (male, female), education (<HS, HS, Some College, College, Missing), income (less than $30,000, $30,000 or more, missing), marital status (married, otherwise), insurance status (yes, no), place of with combined with years in the US (US born, Foreign born and <10 years in US, Foreign born and 10+ years in US, Missing), Language preference (Spanish, English), Hispanic/Latino heritage (Mexican, Dominican, Puerto Rican, Cuban, Central American, South American, Other or More than 1 heritage, Missing), study site (the Bronx, Chicago, Miami, San Diego); and neighborhood level covariates as follows: models for evenness, racial segregation, and HL density included neighborhood deprivation index, while models for evenness, exposure, and economic segregation adjusted for neighborhood immigrant concentration).

[4]Models accounted for complex survey design using overall sampling or [5]inverse probability weights for missing accelerometer data.

[6]P values for multiplicative models were calculated using loglikelihood ratio tests comparing nested models with and without interaction effects.

10.3389/fonc.2022.1024572

TABLE 8 Ordered logistic regression models for the association between neighborhood segregation measures and adherence to the individual components of the ACS[1] guidelines on nutrition and physical activity for cancer prevention, N = 11, 957.

	Model 1[3], Odds Ratio (95% CI)	P[5]	Model 2[4] Odds Ratio (95% CI)	P[5]
Formal measures of segregation[2]				
Main effects				
Evenness dimension	0.97 (0.91, 1.02)		0.98 (0.93, 1.04)	
Exposure dimension	0.97 (0.93, 1.03)		1.00 (0.94, 1.06)	
Joint Effects				
Evenness, while controlling for Exposure	0.97 (0.92, 1.03)		0.98 (0.92, 1.05)	
Exposure, while controlling for Evenness	0.98 (0.93, 1.03)		1.00 (0.95, 1.06)	
Evenness x Exposure, while controlling for main effects	1.01 (0.99, 1.03)	0.441	1.01 (0.99, 1.03)	0.469
Evenness x Exposure, without main effects	1.00 (0.99, 1.00)	0.489	1.00 (0.99, 1.00)	0.622
Proxy measures of segregation[2]				
Economic Segregation	1.31 (0.96, 1.78)		1.19 (0.87, 1.63)	
Racial Segregation	1.23 (0.93, 1.63)		1.08 (0.80, 1.46)	
Racialized Economic Segregation	1.50 (1.00, 2.26)			
Hispanic/Latino Density	0.73 (0.48, 1.13)		0.89 (0.56,1.43)	

ACS, American Cancer Society; CI, Confidence Interval.
[1]The ACS guideline adherence score ranged from 0-8. A priori cut offs for guideline adherence were low (score 0-3), moderate (score 4-5), and high (score 6-8). Data from baseline assessments were used in this analysis.
[2]The evenness dimension of segregation was measured with the Gini coefficient; the exposure dimension was measured with the Isolation index; economic segregation measured via Index of Concentration at the Extremes (ICE) for income; racial segregation measured via ICE for race; Racialized economic segregation measured via ICE for income and race.
[3]Model 1 was adjusted for individual level covariates: age (<45, 45-65, >65), sex (male, female), education (<HS, HS, Some College, College, Missing), income (less than $30,000, $30,000 or more, missing), marital status (married, otherwise), insurance status (yes, no), place of with combined with years in the US (US born, Foreign born and <10 years in US, Foreign born and 10 + years in US, Missing), Language preference (Spanish, English), Hispanic/Latino heritage (Mexican, Dominican, Puerto Rican, Cuban, Central American, South American, Other or More than 1 heritage, Missing), study site (the Bronx, Chicago, Miami, San Diego).
[4]Model 2 also adjusted for neighborhood level covariates as follows: models for evenness, racial segregation, and HL density included neighborhood deprivation index, while models for evenness, exposure, and economic segregation adjusted for neighborhood immigrant concentration). All models accounted for complex survey design using inverse probability weights.
[5]P values for multiplicative models were calculated using loglikelihood ratio tests comparing nested models with and without interaction effects.

Exposure dimension and ACS guideline adherence

The literature on segregation and cancer-related outcomes (examined with formal measures) is mixed (51, 52), focusses on multiple sequential and interacting segregation mechanisms as well as possible moderating effects of segregation not captured in our work. For example, our cross-sectional analysis is suggestive of possible mediating effects of neighborhood poverty given the large observed change in direction and attenuated magnitude of some estimates after we adjusted for the neighborhood deprivation index, consistent with the body of literature showing that neighborhood segregation leads to concentrated poverty (53–56). Our study also adds to a large but mixed body of literature on the role of neighborhood segregation or ethnic enclave on dietary patterns (33, 57, 58). Our findings are consistent with a body of literature showing that segregated poor communities are more likely to have increased exposure to alcohol and tobacco outlets and advertisements. Segregation, regardless of neighborhood racial/ethnic composition, has been associated with higher number of alcohol (59, 60) outlets.

The exposure dimension of segregation measures the probability of interaction with other members of the same racial/ethnic group. In our study, Hispanic/Latino adults resided in highly segregated neighborhoods (isolation index of 0.78, with >0.6 indicative of high segregation). High exposure to members of racial/ethnic groups that exhibit poor lifestyle behaviors and outcomes (i.e., limited exposure to healthier groups) may lead to poor lifestyle behaviors and health at the individual level (61). For example, Hispanic/Latinos are at high risk of sedentary behaviors (62, 63), and barriers include discouragement from peers and cultural norms (27). We found that only evenness segregation, after adjusting for isolation, was associated with a lower likelihood of meeting the physical activity guidelines. Although, it is important to note that other individual (e.g., fatigue, limited time), environmental (e.g., safety, lack of resources), and financial (e.g., cost) level factors related to segregation are strong barriers to physical activity among Hispanic/Latino adults (27, 64, 65).

Evenness and adherence to ACS guidelines

When racial/ethnic groups are unevenly distributed, thereby becoming isolated into smaller pockets across a given geographic space, access to health promoting resources become concentrated in neighboring concentrated White communities and health inequities arise. Studies suggest that evenness

segregation may not be associated with adverse health unless it is accompanied by isolation (i.e., hypersegregation) (66–68). Our findings counter this, in that evenness segregation alone was negatively associated with lower odds of meeting physical activity guidelines and when considered simultaneously, evenness segregation remained negatively associated with higher levels of physical activity.

Racialized economic concentration at the extremes

Our findings on racialized economic segregation are, in part, consistent with literature showing that Hispanic/Latino adults residing in segregated communities were more likely to be economically disadvantaged compared to those residing in non-segregated communities (54, 69, 70). In turn, they experienced decreased access to resources that enabled adoption and maintenance of cancer preventive behaviors (physical activity, walkable, open spaces, affordable quality foods) (61, 71).

We found that racialized economic concentration was not associated with overall guideline adherence but was associated with meeting the BMI recommendations. While we are unaware of any other study linking ICE indices to health behaviors, our findings align with prior studies demonstrating a link between racialized economic segregation and adverse health outcomes (41, 72). In these studies, economic and race-based segregation was associated with higher BMI among Hispanic/Latino adults of Mexican heritage (72) and worse cancer outcomes (50, 73, 74). Similarly, we found that Hispanic/Latinos residing in neighborhoods with greater racialized economic segregation (i.e., higher economic and/or racial privilege) were more likely to meet the recommendations for BMI and alcohol intake, but less likely to meet them for diet. Our findings suggest that both race/ethnicity and socioeconomic standing have a significant role in place-based stratification (75). Among Hispanic/Latino adults, socioeconomic gains or increased assimilation do not always translate to spatial assimilation; as residential gains for Hispanic/Latino of diverse heritage (i.e., adults reporting mixed-race and ethnicity, Black Hispanic adults) are achieved at a higher cost compared to their White counterparts (70, 76, 77). Additionally, among Hispanic/Latinos adults, the poverty rates of non-White neighbors are a major driver of poverty concentration, which explains the importance of capturing the interaction of class- and race- based segregation (78) at the neighborhood level.

Strengths and limitations

Our study has notable strengths and some limitations. We used data from a large and diverse sample of US. Hispanic/Latino adults (46), generalizable to Hispanic/Latino adults in Chicago, IL; San Diego, CA; Miami, FL and the Bronx, NY. We conceptualized segregation using multiple formal measures as well as novel proxies that integrate both dimensions of structural racism (segregation and poverty). We used objective measures of physical activity, and dietary data were derived from questionnaires designed and validated in our study population to capture traditional and culturally specific foods. Lastly, we adjusted for a range of important confounders (e.g., acculturation, heritage) for Hispanic/Latino populations that are known to contribute to variations in lifestyle behaviors.

Limitations of our study include the cross-sectional nature of the data that limits causal inferences due to temporality of the measures, the possibility of unmeasured confounders such as skin color (20) and lack of residential history (75, 79). Future studies could examine time varying associations, account for changes in participant's residential mobility, and explore the role of segregation at other known important neighborhood levels (e.g. county or block) (66).

This analysis evaluated the adherence to ACS guidelines using data collected between 2008-2011 and prior to the 2012 publication of the ACS guidelines. While our study does not evaluate guideline adherence over time as the guidelines became more widely recognized and implemented, our findings suggest that adoption and long-term maintenance of the guidelines has likely faced significant challenges in segregated neighborhood environments. Consideration of social and structural environments will be critical to the successful adoption of cancer preventive behaviors among Hispanic/Latino adults who reside in segregated neighborhoods or ethnic enclaves. Future studies should examine whether guideline adherence among Hispanic/Latinos has changed over time in light of the revised ACS recommendations published in June 2020.

Conclusion

Hispanic/Latino adults live in neighborhoods with high concentrations of racial/ethnic and economic segregation (33). Therefore, the lack of resources to engage in healthful behaviors in these neighborhoods translates to fewer opportunities to adopt and maintain healthful lifestyles and meet the guidelines on nutrition and physical activity for cancer prevention. Public

health policies and interventions that specifically focus on segregated neighborhoods has the potential to improve the adoption and maintenance of cancer preventive behaviors among Hispanic/Latino adults.

Data availability statement

Data are maintained by the individual Hispanic Health Community Study/Study of Latinos study centers and collaborative studies coordinating center at the University of North Carolina Chapel Hill and are available upon submitting a proposal to be approved by the HCHS/SOL publications committee. Requests to access the datasets should be directed to https://sites.cscc.unc.edu/hchs/New%20Investigator%20Opportunities.

Ethics statement

The studies involving human participants were reviewed and approved by The Hispanic Community Health Study/Study of Latinos, San Diego State University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, MSP, SFC, YM, and JP; Methodology, MSP, CMP, LCG, and JP; Coding, MSP, CMP, and JP; Formal Analysis, MSP and CMP; Resources, GAT, JP; Writing – Original Draft Preparation, MSP, CMP, and JP; Writing – Review and Editing, MSP, CMP, SFC, YM, GT, LCG, KRE, MLD, LH, DS-A, BJ, LA-S, and JP; Supervision, GAT, JP; Funding Acquisition, JP. All authors contributed to the article and approved the submitted version.

Funding

The Hispanic Community Health Study/Study of Latinos is a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (HHSN268201300001I/N01-HC-65233), University of Miami (HHSN268201300004I/N01-HC-65234), Albert Einstein College of Medicine (HHSN268201300002I/N01-HC-65235), University of Illinois at Chicago (HHSN268201300003I/N01- HC-65236 Northwestern Univ), and San Diego State University (HHSN268201300005I/N01-HC-65237). The following Institutes/Centers/Offices have contributed to the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, NIH Institution-Office of Dietary Supplements. BJ is partially supported by an American Heart Association Career Development Award (grant No. 19CDA34630050). DS-A is supported by the National Institutes of Health Award #N01-HC65233. LG is supported in part by the National Institutes of Health Award # 5P30DK111022 and 5 U54 TR002550. The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Acknowledgments

The authors thank the staff and participants of HCHS/SOL for their important contributions. Investigators website - http://www.cscc.unc.edu/hchs/.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Liu B, Du Y, Wu Y, Snetselaar LG, Wallace RB, Bao W. Trends in obesity and adiposity measures by race or ethnicity among adults in the united states 2011-18: Population based study. *BMJ* (2021) 372:n365. doi: 10.1136/bmj.n365

2. Petersen R, Pan L, Blanck HM. Racial and ethnic disparities in adult obesity in the united states: Cdc's tracking to inform state and local action. *Prev Chronic Dis* (2019) 16(E46):1–6. doi: 10.5888/pcd16.180579

3. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, et al. American Cancer society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* (2012) 62(1):30–67. doi: 10.3322/caac.20140

4. American Cancer Society. *Acs nutrition and physical activity cancer prevention guidelines* (2017). Available at: https://www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activity-cancer-prevention/guidelines.html#written_by.

5. Kabat GC, Matthews CE, Kamensky V, Hollenbeck AR, Rohan TE. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: A prospective cohort study. *Am J Clin Nutr* (2015) 101(3):558–69. doi: 10.3945/ajcn.114.094854

6. Kohler LN, Garcia DO, Harris RB, Oren E, Roe DJ, Jacobs ET. Adherence to diet and physical activity cancer prevention guidelines and cancer outcomes: A systematic review. *Cancer Epidemiol Biomarkers Prev* (2016) 25(7):1018–28. doi: 10.1158/1055-9965.EPI-16-0121

7. Pichardo MS, Esserman D, Ferrucci LM, Molina Y, Chlebowski RT, Pan K, et al. Adherence to the American cancer society guidelines on nutrition and physical activity for cancer prevention and obesity-related cancer risk and mortality in black and latina women's health initiative participants. *Cancer* (2022) 128(20):3630–40. doi: 10.1002/cncr.34428

8. Pichardo MS, Irwin ML, Esserman D, Molina Y, Ferrucci LM. A competing risk analysis of adherence to the American cancer society guidelines on nutrition and physical activity for cancer prevention and obesity-related cancer risk in Hispanic/Latino adults in the nih-aarp diet and health study. *Int J Cancer* (2022) 151(11):1902–12. doi: 10.1002/ijc.34200

9. Kershaw KN, Albrecht SS, Carnethon MR. Racial and ethnic residential segregation, the neighborhood socioeconomic environment, and obesity among blacks and Mexican americans. *Am J Epidemiol* (2013) 177(4):299–309. doi: 10.1093/aje/kws372

10. Fang CY, Tseng M. Ethnic density and cancer: A review of the evidence. *Cancer* (2018) 124(9):1877–903. doi: 10.1002/cncr.31177

11. Moore JX, Royston KJ, Langston ME, Griffin R, Hidalgo B, Wang HE, et al. Mapping hot spots of breast cancer mortality in the united states: Place matters for blacks and hispanics. *Cancer Causes Control* (2018) 29(8):737–50. doi: 10.1007/s10552-018-1051-y

12. Corral I, Landrine H, Zhao L. Residential segregation and obesity among a national sample of Hispanic adults. *J Health Psychol* (2014) 19(4):503–8. doi: 10.1177/1359105312474912

13. Alcaraz KI, Wiedt TL, Daniels EC, Yabroff KR, Guerra CE, Wender RC. Understanding and addressing social determinants to advance cancer health equity in the united states: A blueprint for practice, research, and policy. *CA Cancer J Clin* (2020) 70(1):31–46. doi: 10.3322/caac.21586

14. Sangaramoorthy M, Yang J, Guan A, DeRouen MC, Tana MM, Somsouk M, et al. Asian American/Pacific islander and Hispanic ethnic enclaves, neighborhood socioeconomic status, and hepatocellular carcinoma incidence in California: An update. *Cancer Epidemiol Biomarkers Prev* (2022) 31(2):382–92. doi: 10.1158/1055-9965.EPI-21-1035

15. Coughlin SS. Social determinants of breast cancer risk, stage, and survival. *Breast Cancer Res Treat* (2019) 177(3):537–48. doi: 10.1007/s10549-019-05340-7

16. Massey DS, Denton NA. The dimensions of residential segregation. *Soc Forces* (1988) 67(2):281–315. doi: 10.2307/2579183

17. Kershaw KN, Pender AE. Racial/Ethnic residential segregation, obesity, and diabetes mellitus. *Curr Diabetes Rep* (2016) 16(11):108–27. doi: 10.1007/s11892-016-0800-0

18. Landrine H, Corral I, Lee JGL, Efird JT, Hall MB, Bess JJ. Residential segregation and racial cancer disparities: A systematic review. *J Racial Ethn Health Disparities* (2017) 4(6):1195–205. doi: 10.1007/s40615-016-0326-9

19. Anderson KF, Fullerton AS. Residential segregation, health, and health care: Answering the Latino question. *Race Soc Problems* (2014) 6(3):262–79. doi: 10.1007/s12552-014-9125-2

20. Kershaw KN, Albrecht SS. Metropolitan-level ethnic residential segregation, racial identity, and body mass index among U.S. Hispanic adults: A multilevel cross-sectional study. *BMC Public Health* (2014) 14(1):283–93. doi: 10.1186/1471-2458-14-283

21. Lee MA, Ferraro KF. Neighborhood residential segregation and physical health among Hispanic americans: Good, bad, or benign? *J Health Soc Behav* (2007) 48(2):131–48. doi: 10.1177/002214650704800203

22. Nelson KA. Does residential segregation help or hurt? exploring differences in the relationship between segregation and health among U.S. hispanics by nativity and ethnic subgroup. *Soc Sci J* (2019) 50(4):646–57. doi: 10.1016/j.soscij.2013.09.010

23. Plascak JJ, Molina Y, Wu-Georges S, Idris A, Thompson B. Latino Residential segregation and self-rated health among latinos: Washington state behavioral risk factor surveillance system, 2012-2014. *Soc Sci Med* (2016) 159:38–47. doi: 10.1016/j.socscimed.2016.04.035

24. Yang GS, Kim HJ, Griffith KA, Zhu S, Dorsey SG, Renn CL. Interventions for the treatment of aromatase inhibitor-associated arthralgia in breast cancer survivors: A systematic review and meta-analysis. *Cancer Nurs* (2017) 40(4):E26–41. doi: 10.1097/NCC.0000000000000409

25. Yu CY, Woo A, Hawkins C, Iman S. The impacts of residential segregation on obesity. *J Phys Act Health* (2018) 15(11):834–9. doi: 10.1123/jpah.2017-0352

26. White K, Borrell LN. Racial/Ethnic residential segregation: Framing the context of health risk and health disparities. *Health Place* (2011) 17(2):438–48. doi: 10.1016/j.healthplace.2010.12.002

27. Keller C, Fleury J. Factors related to physical activity in Hispanic women. *J Cardiovasc Nurs* (2006) 21(2):142–5. doi: 10.1097/00005082-200603000-00012

28. Wen M, Maloney TN. Latino Residential isolation and the risk of obesity in Utah: The role of neighborhood socioeconomic, built-environmental, and subcultural context. *J Immigr Minor Health* (2011) 13(6):1134–41. doi: 10.1007/s10903-011-9439-8

29. Lee RE, Cubbin C. Neighborhood context and youth cardiovascular health behaviors. *Am J Public Health* (2002) 92(3):428–36. doi: 10.2105/ajph.92.3.428

30. Osypuk TL, Diez Roux AV, Hadley C, Kandula NR. Are immigrant enclaves healthy places to live? the multi-ethnic study of atherosclerosis. *Soc Sci Med* (2009) 69(1):110–20. doi: 10.1016/j.socscimed.2009.04.010

31. Mellerson J, Landrine H, Hao Y, Corral I, Zhao L, Cooper DL. Residential segregation and exercise among a national sample of Hispanic adults. *Health Place* (2010) 16(3):613–5. doi: 10.1016/j.healthplace.2009.12.013

32. Gouri Suresh SS, Schauder SA. Income segregation and access to healthy food. *Am J Prev Med* (2020) 59(2):e31–e8. doi: 10.1016/j.amepre.2020.02.009

33. Yi SS, Ruff RR, Jung M, Waddell EN. Racial/Ethnic residential segregation, neighborhood poverty and urinary biomarkers of diet in new York city adults. *Soc Sci Med* (2014) 122:122–9. doi: 10.1016/j.socscimed.2014.10.030

34. Yu C-Y, Woo A, Hawkins C, Iman S. The impacts of residential segregation on obesity. *J Phys Activity Health* (2018) 15(11):834–9. doi: 10.1123/jpah.2017-0352

35. Ryabov I. Examining the role of residential segregation in explaining Racial/Ethnic gaps in spending on fruit and vegetables. *Appetite* (2016) 98:74–9. doi: 10.1016/j.appet.2015.12.024

36. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, et al. Design and implementation of the Hispanic community health Study/Study of latinos. *Ann Epidemiol* (2010) 20(8):629–41. doi: 10.1016/j.annepidem.2010.03.015

37. Manson S, Schroeder J, Van Riper D, Ruggles S. *Ipums national historical geographic information system: Version 14.0 0* (2019). Available at: https://www.ipums.org.

38. James DR, Taeuber KE. Measures of segregation. *Sociological Method* (1985) 15. doi: 10.2307/270845

39. Iceland J, Weinberg DH, Steinmetz EU.S. Census Bureau. . Washington, DC: U.S. Governement Printing Office (2002). p. 1–151.

40. Krieger N. *J urban Health Bull New York Acad Med* (2006) 83(3):355–61. doi: 10.1007/s11524-006-9040-y

41. Krieger N, Feldman JM, Waterman PD, Chen JT, Coull BA, Hemenway D. Local residential segregation matters: Stronger association of census tract compared to conventional city-level measures with fatal and non-fatal assaults (Total and firearm related), using the index of concentration at the extremes (Ice) for racial, economic, and racialized economic segregation, Massachusetts (Us), 1995-2010. *J urban Health Bull New York Acad Med* (2017) 94(2):244–58. doi: 10.1007/s11524-016-0116-z

42. Daviglus ML, Talavera GA, Aviles-Santa ML, Allison M, Cai J, Criqui MH, et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the united states. *JAMA* (2012) 308(17):1775–84. doi: 10.1001/jama.2012.14517

43. Castaneda SF, Garcia ML, Lopez-Gurrola M, Stoutenberg M, Emory K, Daviglus ML, et al. Alcohol use, acculturation and socioeconomic status among Hispanic/Latino men and women: The Hispanic community health Study/Study of latinos. *PloS One* (2019) 14(4):e0214906. doi: 10.1371/journal.pone.0214906

44. Evenson KR, Sotres-Alvarez D, Deng YU, Marshall SJ, Isasi CR, Esliger DW, et al. Accelerometer adherence and performance in a cohort study of us Hispanic adults. *Med Sci Sports Exerc* (2015) 47(4):725–34. doi: 10.1249/MSS.0000000000000478

45. Messer LC, Laraia BA, Kaufman JS, Eyster J, Holzman C, Culhane J, et al. The development of a standardized neighborhood deprivation index. *J urban Health Bull New York Acad Med* (2006) 83(6):1041–62. doi: 10.1007/s11524-006-9094-x

46. Lavange LM, Kalsbeek WD, Sorlie PD, Aviles-Santa LM, Kaplan RC, Barnhart J, et al. Sample design and cohort selection in the Hispanic community

health Study/Study of latinos. *Ann Epidemiol* (2010) 20(8):642–9. doi: 10.1016/j.annepidem.2010.05.006

47. Gallo LC, Penedo FJ, Carnethon M, Isasi CR, Sotres-Alvarez D, Malcarne VL, et al. The Hispanic community health Study/Study of latinos sociocultural ancillary study: Sample, design, and procedures. *Ethn Dis* (2014) 24(1):77–83.

48. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* (2013) 22(3):278–95. doi: 10.1177/0962280210395740

49. Algren MH, Bak CK, Berg-Beckhoff G, Andersen PT. Health-risk behaviour in deprived neighbourhoods compared with non-deprived neighbourhoods: A systematic literature review of quantitative observational studies. *PloS One* (2015) 10(10):e0139297. doi: 10.1371/journal.pone.0139297

50. Krieger N, Feldman JM, Kim R, Waterman PD. Cancer incidence and multilevel measures of residential economic and racial segregation for cancer registries. *JNCI Cancer Spectr* (2018) 2(1):pky009. doi: 10.1093/jncics/pky009

51. Kershaw KN, Albrecht SS, Carnethon MR. Racial and ethnic residential segregation, the neighborhood socioeconomic environment, and obesity among blacks and Mexican americans. *Am J Epidemiol* (2013) 177(4):299–309. doi: 10.1093/aje/kws372

52. Shariff-Marco S, Gomez SL, Canchola AJ, Fullington H, Hughes AE, Zhu H, et al. Nativity, ethnic enclave residence, and breast cancer survival among latinas: Variations between California and Texas. *Cancer* (2020) 126(12):2849–58. doi: 10.1002/cncr.32845

53. Rothwell J, Massey DS. Geographic effects on intergenerational income mobility. *Econ Geogr* (2015) 91(1):83–106. doi: 10.1111/ecge.12072

54. Massey DS, Fischer MJ. How segregation concentrates poverty. *Ethnic Racial Stud* (2000) 23(4):670–91. doi: 10.1080/01419870050033676

55. Rugh JS, Albright L, Massey DS. Race, space, and cumulative disadvantage: A case study of the subprime lending collapse. *Soc Probl* (2015) 62(2):186–218. doi: 10.1093/socpro/spv002

56. Porter SR, Jones MR, Hendren N, Chetty R. Race and economic opportunity in the united states: An intergenerational perspective*. *Q J Economics* (2020) 135 (2):711–83. doi: 10.1093/qje/qjz042

57. Jack D, Neckerman K, Schwartz-Soicher O, Lovasi GS, Quinn J, Richards C, et al. Socio-economic status, neighbourhood food environments and consumption of fruits and vegetables in new York city. *Public Health Nutr* (2013) 16(7):1197–205. doi: 10.1017/S1368980012005642

58. Park Y, Neckerman K, Quinn J, Weiss C, Jacobson J, Rundle A. Neighbourhood immigrant acculturation and diet among Hispanic female residents of new York city. *Public Health Nutr* (2011) 14(9):1593–600. doi: 10.1017/S136898001100019X

59. Trangenstein PJ, Gray C, Rossheim ME, Sadler R, Jernigan DH. Alcohol outlet clusters and population disparities. *J urban Health Bull New York Acad Med* (2020) 97(1):123–36. doi: 10.1007/s11524-019-00372-2

60. Light M, Iceland J. The social context of racial boundary negotiations: Segregation, hate crime, and Hispanic racial identification in metropolitan America. *Sociological Sci* (2016) 3(4):61–84. doi: 10.15195/v3.a4

61. Yang TC, Park K, Matthews SA. Racial/Ethnic segregation and health disparities: Future directions and opportunities. *Sociol Compass* (2020) 14(6): e12794. doi: 10.1111/soc4.12794

62. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, et al. Amount of time spent in sedentary behaviors in the united states, 2003-2004. *Am J Epidemiol* (2008) 167(7):875–81. doi: 10.1093/aje/kwm390

63. Merchant G, Buelna C, Castaneda SF, Arredondo EM, Marshall SJ, Strizich G, et al. Accelerometer-measured sedentary time among Hispanic adults: Results from the Hispanic community health Study/Study of latinos (Hchs/Sol). *Prev Med Rep* (2015) 2:845–53. doi: 10.1016/j.pmedr.2015.09.019

64. Evenson KR, Sarmiento OL, Tawney KW, Macon ML, Ammerman AS. Personal, social, and environmental correlates of physical activity in north Carolina latina immigrants. *Am J Prev Med* (2003) 25(3 Suppl 1):77–85. doi: 10.1016/s0749-3797(03)00168-5

65. Evenson KR, Sarmiento OL, Macon ML, Tawney KW, Ammerman AS. Environmental, policy, and cultural factors related to physical activity among latina immigrants. *Women Health* (2002) 36(2):43–57. doi: 10.1300/J013v36n02_04

66. Acevedo-Garcia D, Lochner KA, Osypuk TL, Subramanian SV. Future directions in residential segregation and health research: A multilevel approach. *Am J Public Health* (2003) 93(2):215–21. doi: 10.2105/ajph.93.2.215

67. Denton N. Are African americans still hypersegregated? *Residential Apartheid: Am Legacy* (1994) . p:49–81.

68. Kramer MR, Hogue CR. Is segregation bad for your health? *Epidemiol Rev* (2009) 31(1):178–94. doi: 10.1093/epirev/mxp001

69. Riley AR. Neighborhood disadvantage, residential segregation, and beyond-lessons for studying structural racism and health. *J Racial Ethn Health Disparities* (2018) 5(2):357–65. doi: 10.1007/s40615-017-0378-5

70. Massey DS, Denton NA. Hypersegregation in U.S. metropolitan areas: Black and Hispanic segregation along five dimensions. *Demography* (1989) 26(3):373–91. doi: 10.2307/2061599

71. Schnake-Mahl AS, Jahn JL, Subramanian SV, Waters MC, Arcaya M. Gentrification, neighborhood change, and population health: A systematic review. *J urban Health Bull New York Acad Med* (2020) 97(1):1–25. doi: 10.1007/s11524-019-00400-1

72. Do DP, Dubowitz T, Bird CE, Lurie N, Escarce JJ, Finch BK. Neighborhood context and ethnicity differences in body mass index: A multilevel analysis using the nhanes iii survey (1988–1994). *Economics Hum Biol* (2007) 5(2):179–203.

73. Scally BJ, Krieger N, Chen JT. Racialized economic segregation and stage at diagnosis of colorectal cancer in the united states. *Cancer Causes Control* (2018) 29 (6):527–37. doi: 10.1007/s10552-018-1027-y

74. Krieger N, Wright E, Chen JT, Waterman PD, Huntley ER, Arcaya M. Cancer stage at diagnosis, historical redlining, and current neighborhood characteristics: Breast, cervical, lung, and colorectal cancers, Massachusetts, 2001-2015. *Am J Epidemiol* (2020) 189(10):1065–75. doi: 10.1093/aje/kwaa045

75. Sampson RJ, Sharkey P. Neighborhood selection and the social reproduction of concentrated racial inequality. *Demography* (2008) 45(1):1–29. doi: 10.1353/dem.2008.0012

76. Alba RD, Logan JR. Minority proximity to whites in suburbs: An individual-level analysis of segregation. *Am J Sociology* (1993) 98(6):1388–427. doi: 10.1086/230193

77. Charles CZ. The dynamics of racial residential segregation. *Annu Rev Sociology* (2003) 29(1):167–207. doi: 10.1146/annurev.soc.29.010202.100002

78. Quillian L. Segregation and poverty concentration: The role of three segregations. *Am Sociol Rev* (2012) 77(3):354–79. doi: 10.1177/0003122412447793

79. Oakes JM, Andrade KE, Biyoow IM, Cowan LT. Twenty years of neighborhood effect research: An assessment. *Curr Epidemiol Rep* (2015) 2 (1):80–7. doi: 10.1007/s40471-015-0035-7

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TYPE Original Research
PUBLISHED 05 January 2023
DOI 10.3389/fonc.2022.1053698

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Cancer Epidemiology and Prevention, a section of the journal Frontiers in Oncology

RECEIVED 26 September 2022
ACCEPTED 02 December 2022
PUBLISHED 05 January 2023

CITATION
Poon PKM, Tam KW, Lam T, Luk AKC, Chu WCW, Cheung P, Wong SYS and Sung JJY (2023) Poor health literacy associated with stronger perceived barriers to breast cancer screening and overestimated breast cancer risk. *Front. Oncol.* 12:1053698. doi: 10.3389/fonc.2022.1053698

Poor health literacy associated with stronger perceived barriers to breast cancer screening and overestimated breast cancer risk

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Background: Low health literacy (HL) is negatively associated with mammography screening uptake. However, evidence of the links between poor HL and low mammography screening participation is scarce.

Methods: We conducted a cross-sectional questionnaire survey among participants of a cancer screening program. We measured HL using a validated Chinese instrument. We assessed breast cancer screening-related beliefs using the Health Belief Model and the accuracy of risk perception. We used multivariable regression models to estimate the relationship between HL and the outcomes.

Results: A total of 821 females were included. 264 (32.2%) had excellent or sufficient, 353 (43.0%) had problematic, and 204 (24.8%) had inadequate health literacy (IHL). Women with IHL were more likely to agree that high price (β = -0.211, 95% CI -0.354 to -0.069), lack of time (β = -0.219, 95% CI -0.351 to -0.088), inconvenient service time (β = -0.291, 95% CI -0.421 to -0.160), long waiting time (β = -0.305, 95% CI -0.447 to -0.164), fear of positive results (β = -0.200, 95% CI -0.342 to -0.058), embarrassment (β = -0.225, 95% CI -0.364 to -0.086), fear of pain (β = -0.154, 95% CI -0.298 to -0.010), fear of radiation (β = -0.177, 95% CI -0.298 to -0.056), lack of knowledge on service location (β = -0.475, 95% CI -0.615 to -0.335), and lack of knowledge on mammography (β = -0.360, 95% CI -0.492 to -0.228) were barriers. They were also less likely to have an accurate breast cancer risk perception (aOR 0.572, 95% CI 0.341 to 0.956).

10.3389/fonc.2022.1053698

Conclusion: Women with lower HL could have stronger perceived barriers to BC screening and an over-estimation of their breast cancer risk. Tackling emotional and knowledge barriers, financial and logistical assistance, and guidance on risk perception are needed to increase their breast cancer screening uptake.

KEYWORDS

health literacy, cancer screening (MeSH), barrier, risk perception, overestimate

1 Introduction

Breast cancer (BC) is the world's most prevalent cancer among females with 2.26 million new cases and over 680,000 deaths in 2020 (1). BC screening is an important public health intervention to lessen the disease burden. Evidence showed that mammography screening could effectively reduce BC mortality (2, 3). Annual or biennial mammography screening has been widely adopted in cancer screening guidelines worldwide (4). However, the low uptake of BC screening remains a major concern; for instance, studies showed a screening rate of 32.1% in the United States (5) and 8-43% adherence to breast, colorectal and cervical cancer screening guidelines in Canada (6).

Having an adequate level of health literacy (HL) was shown in a recent meta-analysis to increase participation in BC screening (7). A study in the United States investigated HL and sociodemographic variables including ethnicity, language, education, smoking status, insurance, employment, income, and family history of BC. It found that, among all the factors considered, HL had the strongest association with adherence to mammography screening (8). Low HL was also shown to be negatively associated with up-to-date BC screening adhering to official guidelines (9). Indeed, the World Health Organization advocates empowering communities and improving HL as the first step for effective strategies for the promotion of early diagnosis (10). However, evidence on the links between poor HL and low BC screening participation is scarce. It is important to identify specific barriers or facilitators among people with poor HL to inform BC screening strategies catering for the needs of different people along the HL continuum.

On the other hand, most recommendations on BC screening are risk-based (4). Besides, evidence also showed that HL affected participation in non-recommended BC screening (11) which could be fuelled by an inaccurate risk perception. To further understand the association between BC screening behaviors and HL, investigating the role of perceived BC risk is of great importance. The association between HL and the perceived BC risk has not been widely researched and the available evidence is limited or inconclusive. For instance, a study in Ireland concluded that people with low HL tended to have an inaccurate perception of BC risk (12), while another study in Iran showed that HL level was not associated with perceived BC risk (13).

We hypothesized that women having a lower HL level would have more perceived barriers and less perceived facilitators for BC screening, and have less accurate BC risk perception.

Abbreviations: BC, Breast cancer; HL, Health literacy; IHL, Inadequate health literacy; PHL, Problematic health literacy.

2 Materials and methods

2.1 Study design and setting

This is a cross-sectional study including females who enrolled for mammography screening in the Multiple Cancer Screening Center (MCSC). This service is under a community-based multiple-cancer screening project, which was sponsored by the Hong Kong Jockey Club Charities Trust, a charitable organization, and run by the Faculty of Medicine of the Chinese University of Hong Kong. Further details of the project were described in a previous publication (14). Women registered online and were then contacted by trained staff by phone to confirm eligibility. Eligible individuals were females aged 50-75 years who did not have any of the following: a personal history of BC; swelling of all or part of the breast(s); breast skin irritation or dimpling; breast pain; nipple pain or the nipple turning inward; redness, scaliness or thickening of the nipple or breast skin; nipple discharge other than breast milk; lump(s) in the underarm area; or having received any BC screening test in the past 5 years. The screening service was free of charge.

Eligible women were invited to visit the MCSC to complete a structured self-administered questionnaire. Trained staff would provide on-site assistance if participants had difficulty understanding the questions. We measured HL using a validated Chinese instrument (HLS-SF12) (15). HLS-SF12 was derived from the 47-item European Health Literacy

Questionnaire (HLS-EU-Q47) which was developed based on a comprehensive definition and a conceptual model of HL (16). The HLS-SF12 has been shown to retain the conceptual framework of HLS-EU-Q47 and have adequate psychometric properties including high reliability (Cronbach's alpha = 0.85), good criterion-related validity and satisfactory item-scale convergent validity when used in different Asian countries (15). The components of HLS-SF12 include 12 health-related tasks representing the 12 dimensions of the conceptual model constructed from the four steps of information processing (finding health information, understanding health information, judging health information, and applying health information) (16). The women were asked to rate their perceived difficulty of each task on a 4-point Likert scale (1 = very difficult, 2 = difficult, 3 = easy, and 4 = very easy). The calculated HL scores ranged from 0 to 50 using the formula [(mean – 1) × (50/3)], where the mean was the mean of all the 12 items. The HL score of HLS-SF12 was shown to have a satisfactory correlation with the HL scores of HLS-EU-Q47 in multiple Asian countries, and the HLS-SF12 scores could explain 91-95% of the variance of the HL scores of HLS-EU-Q47 (15). Based on the HL scores, the HL levels were categorized as 'inadequate' (0–25), 'problematic' (>25–33), 'sufficient' (>33–42) and 'excellent' (>42–50) (17, 18). The 'sufficient' and 'excellent' levels were combined to a single level (>33–50) in the analysis to enhance statistical power. The required sample size was derived from the general rule of thumb for logistic regression by Bujang et al. (19) and calculated by the formula (n = 100 + 50i). With a total of 12 independent variables in our multivariable regression models, the recommended sample size was 700 (100 + 50*12).

2.2 Primary outcomes

The primary outcomes were BC screening-related beliefs or perceptions including BC risk perception. The 22 questions were developed based on the Health Belief Model and findings from previous studies on the health beliefs and behaviors of Chinese women on BC screening (20–22). The questions were then vetted by an expert panel consisting of public health specialists, family medicine doctors and experts in behavioral research. Several rounds of discussions were undertaken until a consensus was reached. To ensure clarity and comprehensibility, the questionnaire was pilot tested on 15 female MCSC participants, and face-to-face cognitive debriefings were conducted to verify that the translations of all the items on the questionnaire were understood in the same way by the target participants. Questions on perceived susceptibility to BC (1 question); perceived severity of BC (1 question); perceived benefits of BC screening (1 question); perceived barriers to BC screening (12 questions); and cues to action for undergoing BC screening (7 questions) were included. The women were asked to rate on a 4-point Likert scale (1 = strongly agree/very important, 2 = agree/important, 3 = disagree/unimportant, and 4 = strongly disagree/very unimportant) regarding the extent to which they agreed with the statements about their perceived susceptibility, perceived severity, perceived benefits, perceived importance of different barriers, and cues to action for BC screening. In the current study, Cronbach's alpha was 0.8 for perceived barriers and 0.76 for cues to action, showing an acceptable level of internal reliability.

We also assessed the accuracy of BC risk perception based on the family history of BC. Family history is one of the strongest known risk factors for BC (23–25). According to the Hong Kong government recommendations on BC risk stratification of local females (26), women were classified as having an increased BC risk, as compared to the general public, if they have one first-degree female relative with BC diagnosed at ≤50 years of age; or two first-degree female relatives diagnosed with BC after the age of 50 years. The risk perception was regarded as concordant if a woman with increased risk answered "strongly agree" or "agree" to the statement "I have a very high chance of having breast cancer"; or a woman without an increased risk answered "disagree" or "strongly disagree". Otherwise, the risk perception was regarded as discordant.

2.3 Covariates

Covariates included sociodemographic variables including age, place of birth, marital status, education level, personal and household income, and employment status. Data on self-rated health, history of common metabolic, gastrointestinal and pulmonary diseases including hypertension, diabetes, dyslipidemias, angina/ischaemic heart disease, stroke, fatty liver disease, chronic obstructive pulmonary diseases, gastroesophageal reflux disease, and history of any type of cancer (other than BC) were collected.

2.4 Statistical analyses

To test for any group differences across the three HL levels, the Chi-squared test was performed on categorical/dichotomous variables, and one-way ANOVA (analysis of variance) was performed on numerical variables. We used simple linear regression to estimate the relationship between HL and the primary outcomes. The dichotomous outcome of whether their BC risk perception was concordant with their family history was estimated using simple logistic regression. Further, multivariable linear and logistic regression models were used to adjust for potential confounders. The R software version 4.2.0 was used to perform the statistical analysis (27).

3 Results

A total of 821 females with a mean age near 58 years were included in the analysis. A total of 823 women who attended the mammography screening were recruited and 2 refused to join the study (response rate 99.8%). Over two-thirds were married or cohabitating and over half were employed. The mean HL level was 29.79 out of 50 with around one-third having excellent/sufficient HL and one-fourth having problematic HL. Education level and self-rated health were different among women with different HL levels. A minority (1.2%) reported a history of cancer (other than breast cancer) (Table 1).

Simple linear regression showed that perceived susceptibility and perceived severity of BC were higher in women with a lower HL level. Multiple perceived barriers to BC screening were stronger in women with lower HL levels. Perceptions of cues to action for undergoing BC screening were different by HL levels. Women with IHL were less likely to have a concordant BC risk perception (Table 2).

Multivariable linear regression showed that, compared to excellent and sufficient HL, women with IHL were more likely to have higher perceived susceptibility and higher perceived severity of BC. They were more likely to agree that high price, a lack of time, inconvenient service time, long waiting time, a fear of positive results, embarrassment, a fear of pain, a fear of radiation, a lack of knowledge on service location, and a lack of knowledge on mammography were barriers to BC screening. Compared to excellent and sufficient HL, women with PHL were more likely to agree that a lack of time, inconvenient service time, long waiting time, a fear of positive results, a lack of knowledge on service location, and a lack of knowledge on mammography were barriers to BC screening. Women with IHL did not show a statistically significant difference in terms of perception of cues to action compared to those with excellent and sufficient HL, but women with PHL were less likely to agree that media information was an important cue to action. Regarding cue to action, compared to college/university or above education level, women with lower education level were more likely to agree that recommendations from healthcare professionals or friends/relatives or media information were important cues to action. Women with IHL were less likely to have a concordant BC risk perception (aOR 0.572). Lower likelihoods of concordant BC risk perception were also seen in women with positive family history of BC (aOR 0.302) and lower education level (lower secondary education aOR 0.372, primary school or below aOR 0.291) (Table 3 is an abridged table, please refer to the Supplementary Table S1 for the full results). Among women participating in BC screening, education level was the strongest determinant among all covariates on HL level (Table S2).

4 Discussions

In our study, over two-thirds of the female participants had PHL or IHL (Table 1). The proportion is high when compared to the 47% found in a study using the HLS-EU-Q47 scale in the European region (17). Regarding perceived barriers to BC screening, women with IHL held a stronger belief than those with excellent or sufficient HL that financial (high price), logistical (time constraint, inconvenient service time, long waiting time), emotional (fear of positive results, fear of radiation, embarrassment) and knowledge (lack of knowledge on service location and mammography) factors were barriers to BC screening (Table 3). Women with PHL also had a stronger belief that the lack of knowledge on mammography and fear of positive results were barriers to BC screening. These findings are consistent with a study in the United States, which showed that women with lower HL reported more emotional and knowledge barriers to BC screening (28). However, the same study also indicated that these women reported fewer logistical barriers, which is not consistent with our findings. This inconsistency could be multifactorial including cultural differences (29), differences in access to health care (30), or socioeconomic status (31), that would require further research to investigate the effects of these factors on the relationship between HL and BC screening. Nevertheless, our results showed that women with low HL would perceive stronger barriers to BC screening in several dimensions, and provided evidence of the links between low HL and low BC screening participation. Unlike barriers, we found that cues to action or facilitators for BC screening were less affected by HL levels. Apart from women with PHL who accorded lower importance to “media information”, we did not see statistically significant differences across the HL continuum in terms of the importance of BC screening facilitators (Table 3). Intriguingly, independent of HL level, women with different education levels apparently would accord different importance to facilitators like recommendations from healthcare professionals, friends/relatives, and media information on screening. It may warrant further studies to explore the differential effects of HL and education level on cues to BC screening.

Various HL-based interventions have been developed aiming to improve BC screening uptake in people with low HL. These interventions mainly focus on building HL skills (32) or providing educational materials (33). However, studies have shown that materials or counselling techniques adopted in these interventions might not be responsive to the needs of the recipients (34, 35). Our study helps inform the development of such interventions that can tackle the stronger emotional and knowledge barriers to BC screening among people with lower HL. In addition to education and empowerment, our results indicated that addressing external factors such as price, service

10.3389/fonc.2022.1053698

TABLE 1 Characteristics of individuals by health literacy level.

	Level	Overall	Inadequate HL	Problematic HL	Sufficient/Excellent HL	p
N		821	204	353	264	
Health literacy	Mean score (SD)	29.79 (6.70)	21.31 (3.97)	29.39 (1.98)	36.89 (3.98)	<0.001
Age	Mean (SD)	57.96 (5.19)	59.36 (5.42)	57.60 (5.12)	57.35 (4.90)	<0.001
	50-54	265 (32.3)	46 (22.5)	122 (34.6)	97 (36.7)	0.01
	55-59	260 (31.7)	64 (31.4)	110 (31.2)	86 (32.6)	
	60-64	183 (22.3)	54 (26.5)	77 (21.8)	52 (19.7)	
	65+	113 (13.8)	40 (19.6)	44 (12.5)	29 (11.0)	
Waist circumference	Mean (SD)	90.46 (8.44)	91.63 (8.33)	90.18 (8.34)	89.95 (8.59)	0.07
BMI	Mean (SD)	25.99 (3.72)	26.17 (3.60)	26.03 (3.84)	25.79 (3.65)	0.53
Education	Primary school or below	113 (13.8)	57 (27.9)	40 (11.3)	16 (6.1)	<0.001
	Secondary 1-3	136 (16.6)	43 (21.1)	67 (19.0)	26 (9.8)	
	Secondary 4-7	370 (45.1)	74 (36.3)	173 (49.0)	123 (46.6)	
	College/ university or above	202 (24.6)	30 (14.7)	73 (20.7)	99 (37.5)	
Marital status	Married/ cohabitating	578 (70.4)	134 (65.7)	252 (71.4)	192 (72.7)	0.13
	Unmarried	112 (13.6)	28 (13.7)	49 (13.9)	35 (13.3)	
	Separated/ divorced	86 (10.5)	23 (11.3)	34 (9.6)	29 (11.0)	
	Widowed	45 (5.5)	19 (9.3)	18 (5.1)	8 (3.0)	
Employment status	Full-time	325 (40.0)	74 (37.2)	144 (40.8)	107 (41.2)	0.24
	Part-time	103 (12.7)	32 (16.1)	43 (12.2)	28 (10.8)	
	Retired	126 (15.5)	36 (18.1)	48 (13.6)	42 (16.2)	
	Housewife	210 (25.9)	45 (22.6)	98 (27.8)	67 (25.8)	
	Unemployed	29 (3.6)	10 (5.0)	13 (3.7)	6 (2.3)	
	Self-employed	19 (2.3)	2 (1.0)	7 (2.0)	10 (3.8)	
Born in Hong Kong	Yes	640 (78.0)	139 (68.1)	276 (78.2)	225 (85.2)	<0.001
	No	181 (22.0)	65 (31.9)	77 (21.8)	39 (14.8)	
Personal income (HKD)	5,000 or below	148 (21.1)	43 (25.1)	67 (22.0)	38 (16.9)	0.02
	5,001-10,000	120 (17.1)	38 (22.2)	50 (16.4)	32 (14.2)	
	10,001-15,000	137 (19.5)	40 (23.4)	54 (17.7)	43 (19.1)	
	15,001-20,000	98 (14.0)	20 (11.7)	45 (14.8)	33 (14.7)	
	20,001-30,000	89 (12.7)	14 (8.2)	44 (14.4)	31 (13.8)	
	30,001-40,000	50 (7.1)	8 (4.7)	23 (7.5)	19 (8.4)	
	40,000 or above	59 (8.4)	8 (4.7)	22 (7.2)	29 (12.9)	
Household income (HKD)	10,000 or below	66 (11.0)	22 (16.4)	29 (11.0)	15 (7.5)	<0.01

(Continued)

TABLE 1 Continued

	Level	Overall	Inadequate HL	Problematic HL	Sufficient/Excellent HL	p
	10,001-20,000	144 (24.1)	41 (30.6)	66 (25.0)	37 (18.5)	
	20,001-30,000	121 (20.2)	24 (17.9)	55 (20.8)	42 (21.0)	
	30,001-40,000	105 (17.6)	24 (17.9)	47 (17.8)	34 (17.0)	
	40,001 or above	162 (27.1)	23 (17.2)	67 (25.4)	72 (36.0)	
Self-reported health	Excellent	23 (2.8)	5 (2.5)	6 (1.7)	12 (4.5)	<0.001
	Good	233 (28.4)	38 (18.6)	90 (25.5)	105 (39.8)	
	Fair	520 (63.3)	142 (69.6)	238 (67.4)	140 (53.0)	
	Poor	43 (5.2)	18 (8.8)	18 (5.1)	7 (2.7)	
	Very poor	2 (0.2)	1 (0.5)	1 (0.3)	0 (0.0)	
Number of chronic conditions	Mean (SD)	1.02 (1.14)	1.16 (1.23)	0.97 (1.12)	0.97 (1.08)	0.12
Diabetes	Yes	93 (11.3)	25 (12.3)	36 (10.2)	32 (12.1)	0.67
	No	728 (88.7)	179 (87.7)	317 (89.8)	232 (87.9)	
Liver disease	Yes	79 (9.6)	24 (11.8)	35 (9.9)	20 (7.6)	0.30
	No	742 (90.4)	180 (88.2)	318 (90.1)	244 (92.4)	
Hypertension	Yes	230 (28.0)	67 (32.8)	85 (24.1)	78 (29.5)	0.07
	No	591 (72.0)	137 (67.2)	268 (75.9)	186 (70.5)	
Hyper- lipidemia	Yes	186 (22.7)	53 (26.0)	82 (23.2)	51 (19.3)	0.22
	No	635 (77.3)	151 (74.0)	271 (76.8)	213 (80.7)	
Ischemic heart disease	Yes	6 (0.7)	2 (1.0)	3 (0.8)	1 (0.4)	0.71
	No	815 (99.3)	202 (99.0)	350 (99.2)	263 (99.6)	
Chronic obstructive pulmonary disease	Yes	8 (1.0)	1 (0.5)	5 (1.4)	2 (0.8)	0.51
	No	813 (99.0)	203 (99.5)	348 (98.6)	262 (99.2)	
Stroke	Yes	15 (1.8)	2 (1.0)	10 (2.8)	3 (1.1)	0.17
	No	806 (98.2)	202 (99.0)	343 (97.2)	261 (98.9)	
Cirrhosis	Yes	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	0.35
	No	820 (99.9)	204 (100.0)	353 (100.0)	263 (99.6)	
Gastroesophageal reflux disease	Yes	66 (8.0)	24 (11.8)	28 (7.9)	14 (5.3)	0.04
	No	755 (92.0)	180 (88.2)	325 (92.1)	250 (94.7)	
Other co-morbidities	Yes	142 (17.3)	38 (18.6)	53 (15.0)	51 (19.3)	0.32
	No	679 (82.7)	166 (81.4)	300 (85.0)	213 (80.7)	
Cancer (any type other than breast cancer)	Yes	10 (1.2)	1 (0.5)	5 (1.4)	4 (1.5)	0.55

(Continued)

TABLE 1 Continued

	Level	Overall	Inadequate HL	Problematic HL	Sufficient/Excellent HL	p
	No	811 (98.8)	203 (99.5)	348 (98.6)	260 (98.5)	
Family history of breast cancer	Yes	55 (6.7)	16 (7.8)	20 (5.7)	19 (7.2)	0.57
	No	766 (93.3)	188 (92.2)	333 (94.3)	245 (92.8)	

HL, health literacy; SD, standard deviation; N, the number of observations. The p-values indicate the level of significance of chi-squared tests on categorical/dichotomous variables, and that of one-way ANOVA on numerical variables. Percentages (or standard deviation where specified) are in parenthesis.

TABLE 2 Associations between screening-related perceptions and health literary (N=821).

Reference level: Sufficient/Excellent HL		Inadequate HL	Problematic HL
Type	Outcome	Coefficient	Coefficient
Perceived susceptibility			
	"I have a very high chance of having breast cancer"	-0.283*** (-0.389, -0.177)	-0.096* (-0.189, -0.003)
Perceived severity			
	"I will die in 1-2 years if I have breast cancer"	-0.247*** (-0.346, -0.147)	-0.045 (-0.132, 0.042)
Perceived benefit			
	"Mammography can detect breast cancer that I am not aware of."	0.086 (-0.010, 0.182)	0.045 (-0.039, 0.129)
Financial barrier			
	"High price"	-0.192** (-0.313, -0.071)	-0.055 (-0.161, 0.050)
Logistical barriers			
	"Lack of time to do breast cancer screening"	-0.149** (-0.261, -0.038)	-0.147** (-0.244, -0.050)
	"Inconvenient service time"	-0.224*** (-0.334, -0.114)	-0.111* (-0.207, -0.015)
	"Long waiting time"	-0.299*** (-0.421, -0.177)	-0.135* (-0.242, -0.029)
Emotional barriers			
	"Fear of positive result"	-0.193** (-0.314, -0.073)	-0.139** (-0.244, -0.033)
	"Embarrassment"	-0.194** (-0.314, -0.074)	-0.083 (-0.187, 0.022)
	"Fear of pain"	-0.114 (-0.238, 0.011)	-0.027 (-0.135, 0.082)
	"Fear of radiation"	-0.136** (-0.240, -0.033)	0.017 (-0.073, 0.108)
Knowledge barriers			
	"No need to screen because of good health"	0.027 (-0.086, 0.140)	0.041 (-0.057, 0.139)
	"No recommendation from my doctor"	0.078 (-0.044, 0.199)	0.060 (-0.046, 0.166)
	"Lack of knowledge on service location"	-0.504*** (-0.625, -0.383)	-0.238*** (-0.344, -0.132)
	"Lack of knowledge on mammography"	-0.392*** (-0.505, -0.279)	-0.155** (-0.253, -0.056)
Cues to action			
	"One-stop multiple cancer screening service"	0.040 (-0.060, 0.139)	0.038 (-0.049, 0.125)
	"Fear of having breast cancer"	-0.176** (-0.281, -0.071)	-0.060 (-0.151, 0.032)
	"Healthcare professional recommendation"	-0.146** (-0.241, -0.050)	0.017 (-0.066, 0.100)
	"Relative/friend recommendation"	-0.055 (-0.151, 0.041)	0.000 (-0.084, 0.084)

(Continued)

TABLE 2 Continued

Reference level: Sufficient/Excellent HL		Inadequate HL	Problematic HL
Type	Outcome	Coefficient	Coefficient
	"Media information"	0.018 (-0.086, 0.122)	0.159*** (0.068, 0.249)
	"Free-of-charge service"	-0.051 (-0.159, 0.056)	0.055 (-0.039, 0.149)
	"Benefits of breast cancer screening"	0.013 (-0.083, 0.110)	0.073 (-0.011, 0.158)
Risk concordance			
	Concordant breast cancer risk perception	0.409*** (0.267, 0.622)	0.921 (0.612, 1.379)

HL; health literacy. 95% confidence intervals are in parenthesis. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Simple linear regression was used to estimate the coefficients, except for risk concordance whose coefficients are odds ratios estimated by simple logistic regression.

hours and capacity are also important in reducing barriers to BC screening for people with low HL.

Moreover, women with lower HL in our study had poorer self-rated health than those with higher HL regardless of the number of chronic illnesses that they had (Table 1). This finding is consistent with a previous study among Chinese adults showing higher HL was positively associated with better self-rated health (36). Our subjects with PHL or IHL also agreed more strongly with a high own BC risk and a high severity of BC than women with excellent or sufficient HL (Table 3). Similar findings of higher perceived BC risk among women with low HL were also seen in another study (37). Furthermore, we also found an association between low HL and inaccuracy of BC risk perception. Compared to women with excellent or sufficient HL, those with IHL had a nearly two-fold increase in the odds of having BC risk perception discordant with their BC family history (Table 3). Since most national and international recommendations on BC screening are risk-based (4, 26), a shared and informed decision on BC screening should ideally be made by a woman after a discussion with her healthcare provider on her own risk level. Family history of BC is an important risk indicator (26) and is not rare (6.7% among our subjects, Table 1). Besides, our results also showed that women with a positive family history were more likely to have a higher perceived susceptibility to BC that were less likely to be accurate (Table 3). It indicates that guidance for these women is needed for a correct interpretation of their positive family history. Decision aids have been developed to assist women to come up with a more accurate risk perception (38). An overestimation of risk could lead to over-utilization of mammography screening or other healthcare services as shown in a study in the United States (39). This could be a possible link to the observed suboptimal including overutilization of healthcare resources by people with low HL (40). Age-based screening recommendations are widely adopted internationally (4) that women aged 50 or above are recommended for regular mammography screening. While this is a risk-based and pragmatic approach for a public health policy, our results implied that women with low HL would require more guidance on BC risk perception. Besides screening decisions, correcting an overestimation of risk would reduce the associated unnecessary worries and psychological distress (41, 42), which could be equally important to an individual's well-being.

Limitations

First, the cross-sectional design of this study could not directly infer a causal relationship between HL levels and BC screening-related beliefs. A longitudinal study would provide further insights. Second, only mammography screening was assessed. That said, mammography is the most widely adopted BC screening method in population-based BC screening (4, 26). Third, we studied participants of a cancer screening program who could be more health conscious and might have a higher HL than the general population. We might not be able to assess if there was an over-representation of women with higher HL in our sample as data on the overall HL picture of the Hong Kong general population were not available. Nevertheless, the percentage of recruited subjects from the three regions of Hong Kong was 13.5%, 26.8%, 58.8% and 1.3% for Hong Kong Island, Kowloon, and New Territories and Islands respectively, that closely resembled the data from Hong Kong population census on population distribution (43). Moreover, this study did not aim to provide an estimate of the general HL level of the local population but aimed to investigate associations between HL and BC screening-related beliefs. The possible under-representation of people with low HL in our sample might affect the power of our study but should not have a marked impact on the direction of associations. Fourth, all subjects had already participated in BC screening in this study that did not provide a comparison unscreened group for further analysis (e.g. mediation analysis) of the mechanism among HL,

10.3389/fonc.2022.1053698

TABLE 3 Associations between screening-related perceptions and health literacy adjusted for covariates[#] (N=701).

		Health literacy level		Family history of breast cancer
		Ref: Sufficient/Excellent		
		Inadequate	Problematic	
Type	Outcome	Coef.	Coef.	Coef.
Perceived susceptibility				
	"I have a very high chance of having breast cancer"	-0.164** (-0.285, -0.044)	-0.060 (-0.160, 0.040)	-0.454*** (-0.623, -0.284)
Perceived severity				
	"I will die in 1-2 years if I have breast cancer"	-0.200*** (-0.317, -0.083)	-0.033 (-0.130, 0.064)	0.061 (-0.103, 0.225)
Perceived benefit				
	"Mammography can detect breast cancer that I am not aware of."	0.048 (-0.064, 0.160)	0.023 (-0.069, 0.116)	-0.055 (-0.213, 0.102)
Financial barrier				
	"High price"	-0.211** (-0.354, -0.069)	-0.074 (-0.193, 0.044)	0.069 (-0.131, 0.269)
Logistical barriers				
	"Lack of time to do breast cancer screening"	-0.219** (-0.351, -0.088)	-0.195*** (-0.304, -0.086)	-0.132 (-0.317, 0.053)
	"Inconvenient service time"	-0.291*** (-0.421, -0.160)	-0.136* (-0.244, -0.028)	-0.128 (-0.311, 0.055)
	"Long waiting time"	-0.305*** (-0.447, -0.164)	-0.165** (-0.282, -0.048)	-0.144 (-0.342, 0.055)
Emotional barriers				
	"Fear of positive result"	-0.200** (-0.342, -0.058)	-0.152* (-0.269, -0.034)	-0.231* (-0.430, -0.032)
	"Embarrassment"	-0.225** (-0.364, -0.086)	-0.067 (-0.182, 0.048)	-0.144 (-0.338, 0.051)
	"Fear of pain"	-0.154* (-0.298, -0.010)	0.004 (-0.115, 0.123)	-0.072 (-0.274, 0.130)
	"Fear of radiation"	-0.177** (-0.298, -0.056)	0.020 (-0.080, 0.120)	-0.099 (-0.269, 0.071)
Knowledge barriers				
	"No need to screen because of good health"	-0.017 (-0.151, 0.116)	0.036 (-0.075, 0.146)	-0.081 (-0.269, 0.106)
	"No recommendation from my doctor"	-0.027 (-0.169, 0.115)	0.045 (-0.073, 0.163)	0.055 (-0.145, 0.254)
	"Lack of knowledge on service location"	-0.475*** (-0.615, -0.335)	-0.206*** (-0.322, -0.090)	0.097 (-0.099, 0.294)
	"Lack of knowledge on mammography"	-0.360*** (-0.492, -0.228)	-0.113* (-0.222, -0.003)	-0.026 (-0.211, 0.160)
Cues to action				
	"One-stop multiple cancer screening service"	0.053 (-0.064, 0.170)	0.035 (-0.062, 0.132)	-0.036 (-0.200, 0.128)
	"Fear of having breast cancer"	-0.079 (-0.200, 0.041)	-0.014 (-0.114, 0.086)	0.051 (-0.118, 0.221)
	"Healthcare professional recommendation"	-0.059 (-0.172, 0.053)	0.065 (-0.029, 0.158)	0.151 (-0.008, 0.309)
	"Relative/friend recommendation"	0.072 (-0.042, 0.185)	0.037 (-0.056, 0.131)	-0.001 (-0.160, 0.158)
	"Media information"	0.113 (-0.010, 0.236)	0.231*** (0.129, 0.332)	0.170 (-0.003, 0.343)
	"Free-of-charge service"	-0.088 (-0.212, 0.037)	0.037 (-0.066, 0.141)	0.056 (-0.119, 0.232)
	"Benefits of breast cancer screening"	0.017 (-0.097, 0.131)	0.088 (-0.006, 0.183)	0.049 (-0.111, 0.209)

(Continued)

TABLE 3 Continued

		Health literacy level		Family history of breast cancer
		Ref: Sufficient/Excellent		
		Inadequate	Problematic	
Type	Outcome	OR	OR	OR
Risk concordance				
	Concordant cancer screening risk perception	0.572* (0.341, 0.956)	1.034 (0.648, 1.640)	0.302*** (0.157, 0.584)

Coef.; coefficients. OR; odds ratio. 95% confidence intervals are in parenthesis. #Adjusted for age, number of chronic diseases, history of other cancers, family history of breast cancer, waist circumference, body mass index, education level, marital status, employment status, birthplace, and household income. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Multiple linear regression was used to estimate the coefficients, except for risk concordance whose coefficients are odds ratios estimated by logistic regression. Each row represents a separate regression model. 120 were excluded from the model due to missing data on household income (N=120) and employment status (N=9). # Please refer to the Supplementary Table S1 for the full results.

screening beliefs and risk perception, and screening uptake. Further studies including both screened and unscreened subjects are needed to investigate the mechanism. Nevertheless, even only among screening participants, our study results supported the hypothesis that women with low HL would have more perceived barriers to BC screening and a less accurate BC risk perception.

5 Conclusion

Compared to women with excellent or sufficient HL, women with lower HL could have stronger perceived barriers to BC screening on multiple aspects including financial, logistical, emotional, and knowledge barriers. They also had an overestimation of their own BC risk. Besides addressing emotional and knowledge barriers in BC screening promotion strategies, providing financial and logistical assistance is also needed to increase BC screening uptake for women with low HL. They also require guidance on BC risk perception.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CRE-2018.165). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, investigation, methodology by PP, KT, AL, JS, and SW; data curation and analysis by PP and KT; funding acquisition by JS; writing - original draft by PP, KT, and SW; writing - review and editing by TL, AL, WC, PC, and JS; supervision by SW and JS. All authors contributed to the article and approved the submitted version.

Funding

The multi-cancer screening program is funded by the Hong Kong Jockey Club Charities Trust.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1053698/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, et al. Benefits and harms of breast cancer screening: A systematic review. *JAMA* (2015) 314(15):1615–34. doi: 10.1001/jama.2015.13183

3. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, et al. Breast-cancer screening–viewpoint of the IARC working group. *N Engl J Med* (2015) 372(24):2353–8. doi: 10.1056/NEJMsr1504363

4. Ebell MH, Thai TN, Royalty KJ. Cancer screening recommendations: an international comparison of high income countries. *Public Health Rev* (2018) 39:7. doi: 10.1186/s40985-018-0080-0

5. Katz ML, Reiter PL, Young GS, Pennell ML, Tatum CM, Paskett ED. Adherence to multiple cancer screening tests among women living in Appalachia Ohio. *Cancer Epidemiol Biomarkers Prev* (2015) 24(10):1489–94. doi: 10.1158/1055-9965.EPI-15-0369

6. Mema SC, Yang H, Vaska M, Elnitsky S, Jiang Z. Integrated cancer screening performance indicators: A systematic review. *PloS One* (2016) 11(8):e0161187. doi: 10.1371/journal.pone.0161187

7. Baccolini V, Isonne C, Salerno C, Giffi M, Migliara G, Mazzalai E, et al. The association between adherence to cancer screening programs and health literacy: A systematic review and meta-analysis. *Prev Med* (2022) 155:106927. doi: 10.1016/j.ypmed.2021.106927

8. Komenaka IK, Nodora JN, Hsu CH, Martinez ME, Gandhi SG, Bouton ME, et al. Association of health literacy with adherence to screening mammography guidelines. *Obstet Gynecol* (2015) 125(4):852–9. doi: 10.1097/AOG.0000000000000708

9. Sentell TL, Tsoh JY, Davis T, Davis J, Braun KL. Low health literacy and cancer screening among Chinese americans in California: a cross-sectional analysis. *BMJ Open* (2015) 5(1):e006104. doi: 10.1136/bmjopen-2014-006104

10. World Health Organization. *WHO report on cancer - setting priorities, investing wisely and providing care for all*. (2020) (Switzerland: World Health Organization).

11. Rutan MC, Sammon JD, Nguyen DD, Kilbridge KL, Herzog P, Trinh QD. The relationship between health literacy and nonrecommended cancer screening. *Am J Prev Med* (2021) 60(2):e69–72. doi: 10.1016/j.amepre.2020.08.018

12. Rutherford EJ, Kelly J, Lehane EA, Livingstone V, Cotter B, Butt A, et al. Health literacy and the perception of risk in a breast cancer family history clinic. *Surgeon* (2018) 16(2):82–8. doi: 10.1016/j.surge.2016.06.003

13. Rakhshkhorshid M, Navaee M, Nouri N, Safarzaii F. The association of health literacy with breast cancer knowledge, perception and screening behavior. *Eur J Breast Health* (2018) 14(3):144–7. doi: 10.5152/ejbh.2018.3757

14. Sung JJY, Luk AKC, Ng SSM, Ng ACF, Chiu PKF, Chan EYY, et al. Effectiveness of one-stop screening for colorectal, breast, and prostate cancers: A population-based feasibility study. *Front Oncol* (2021) 11:631666. doi: 10.3389/fonc.2021.631666

15. Duong TV, Aringazina A, Kayupova G, Nurjanah, Pham TV, Pham KM, et al. Development and validation of a new short-form health literacy instrument (HLS-SF12) for the general public in six Asian countries. *Health Lit Res Pract* (2019) 3(2):e91–e102. doi: 10.3928/24748307-20190225-01

16. Sorensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: a systematic review and integration of definitions and models. *BMC Public Health* (2012) 12:80. doi: 10.1186/1471-2458-12-80

17. Sorensen K, Pelikan JM, Rothlin F, Ganahl K, Slonska Z, Doyle G, et al. Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU). *Eur J Public Health* (2015) 25(6):1053–8. doi: 10.1093/eurpub/ckv043

18. HLS-EU Consortium. Comparative report of health literacy in eight EU member states. In: *The European health literacy survey HLS-EU (Second revised and extended version)* (2012 (Netherlands: The International Consortium of the HLS-EU Project).

19. Bujang MA, Sa'at N, Sidik T, Joo LC. Sample size guidelines for logistic regression from observational studies with Large population: Emphasis on the accuracy between statistics and parameters based on real life clinical data. *Malays J Med Sci* (2018) 25(4):122–30. doi: 10.21315/mjms2018.25.4.12

20. Fong DY, Kwok C, White K. Psychometric properties of the Chinese breast cancer screening beliefs questionnaire. *Eur J Oncol Nurs* (2012) 16(5):505–11. doi: 10.1016/j.ejon.2012.01.001

21. Wang X, Chen D, Xie T, Zhang W. Predicting women's intentions to screen for breast cancer based on the health belief model and the theory of planned behavior. *J Obstet Gynaecol Res* (2019) 45(12):2440–51. doi: 10.1111/jog.14109

22. Wu TY, Yu MY. Reliability and validity of the mammography screening beliefs questionnaire among Chinese American women. *Cancer Nurs* (2003) 26 (2):131–42. doi: 10.1097/00002820-200304000-00007

23. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* (1997) 71 (5):800–9. doi: 10.1002/(SICI)1097-0215(19970529)71:5<800::AID-IJC18>3.0.CO;2-B

24. Collaborative Group on Hormonal Factors in Breast C. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* (2001) 358(9291):1389–99. doi: 10.1016/S0140-6736(01)06524-2

25. Kharazmi E, Chen T, Narod S, Sundquist K, Hemminki K. Effect of multiplicity, laterality, and age at onset of breast cancer on familial risk of breast cancer: a nationwide prospective cohort study. *Breast Cancer Res Treat* (2014) 144 (1):185–92. doi: 10.1007/s10549-014-2848-3

26. Cancer Expert Working Group on Cancer Prevention and Screening (CEWG). Recommendations on prevention and screening for breast cancer for health professionals. In: *Centre for health protection DoH*. Hong Kong: HKSAR Government (2021).

27. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing (2022).

28. O'Hara J, McPhee C, Dodson S, Cooper A, Wildey C, Hawkins M, et al. Barriers to breast cancer screening among diverse cultural groups in Melbourne, Australia. *Int J Environ Res Public Health* (2018) 15(8):1677. doi: 10.3390/ijerph15081677

29. Kadivar H, Kenzik KM, Dewalt DA, Huang IC. The association of English functional health literacy and the receipt of mammography among Hispanic women compared to non-Hispanic U.S.-born white women. *PloS One* (2016) 11 (10):e0164307. doi: 10.1371/journal.pone.0164307

30. Kino S, Kawachi I. Can health literacy boost health services utilization in the context of expanded access to health insurance? *Health Educ Behav* (2020) 47 (1):134–42. doi: 10.1177/1090198119875998

31. Czwikla J, Urbschat I, Kieschke J, Schussler F, Langner I, Hoffmann F. Assessing and explaining geographic variations in mammography screening participation and breast cancer incidence. *Front Oncol* (2019) 9:909. doi: 10.3389/fonc.2019.00909

32. Han HR, Song Y, Kim M, Hedlin HK, Kim K, Ben Lee H, et al. Breast and cervical cancer screening literacy among Korean American women: A community health worker-led intervention. *Am J Public Health* (2017) 107(1):159–65. doi: 10.2105/AJPH.2016.303522

33. Davis TC, Rademaker A, Bennett CL, Wolf MS, Carias E, Reynolds C, et al. Improving mammography screening among the medically underserved. *J Gen Intern Med* (2014) 29(4):628–35. doi: 10.1007/s11606-013-2743-3

34. Maschke A, Paasche-Orlow MK, Kressin NR, Schonberg MA, Battaglia TA, Gunn CM. Discussions of potential mammography benefits and harms among patients with limited health literacy and providers: "Oh, there are harms?". *J Health Commun* (2020) 25(12):951–61. doi: 10.1080/10810730.2020.1845256

35. Gunn CM, Maschke A, Paasche-Orlow MK, Housten AJ, Kressin NR, Schonberg MA, et al. Using mixed methods with multiple stakeholders to inform development of a breast cancer screening decision aid for women with limited health literacy. *MDM Policy Pract* (2021) 6(2):23814683211033249. doi: 10.1177/23814683211033249

36. Nie X, Li Y, Li C, Wu J, Li L. The association between health literacy and self-rated health among residents of China aged 15-69 years. *Am J Prev Med* (2021) 60(4):569–78. doi: 10.1016/j.amepre.2020.05.032

37. Brewer NT, Tzeng JP, Lillie SE, Edwards AS, Peppercorn JM, Rimer BK. Health literacy and cancer risk perception: implications for genomic risk communication. *Med Decis Making* (2009) 29(2):157–66. doi: 10.1177/0272989X08327111

38. Stacey D, Legare F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* (2017) 4:CD001431. doi: 10.1002/14651858.CD001431.pub5

39. Haber G, Ahmed NU, Pekovic V. Family history of cancer and its association with breast cancer risk perception and repeat mammography. *Am J Public Health* (2012) 102(12):2322–9. doi: 10.2105/AJPH.2012.300786

40. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med* (2011) 155(2):97–107. doi: 10.7326/0003-4819-155-2-201107190-00005

41. Lipkus IM, Kuchibhatla M, McBride CM, Bosworth HB, Pollak KI, Siegler IC, et al. Relationships among breast cancer perceived absolute risk, comparative risk, and worries. *Cancer Epidemiol Biomarkers Prev* (2000) 9(9):973–5.

42. Metcalfe KA, Quan ML, Eisen A, Cil T, Sun P, Narod SA. The impact of having a sister diagnosed with breast cancer on cancer-related distress and breast cancer risk perception. *Cancer* (2013) 119(9):1722–8. doi: 10.1002/cncr.27924

43. Census and Statistics Department. 2021 Population Census: Domestic Households by District Council District and Year. In: *HKSAR Government* (2022) Hong Kong.

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 09 January 2023
DOI 10.3389/fonc.2022.1092355

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Cancer Epidemiology and Prevention,
a section of the journal
Frontiers in Oncology

RECEIVED 08 November 2022
ACCEPTED 12 December 2022
PUBLISHED 09 January 2023

CITATION
Olateju OA, Zeng Z, Adenaiye OO,
Varisco TJ, Zakeri M and Sujit SS
(2023) Investigation of racial
differences in survival from non-small
cell lung cancer with immunotherapy
use: A Texas study.
Front. Oncol. 12:1092355.
doi: 10.3389/fonc.2022.1092355

Investigation of racial differences in survival from non-small cell lung cancer with immunotherapy use: A Texas study

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Background: The use of immunotherapy is associated with improved survival among patients with Non-Small Cell Lung Cancer (NSCLC) and has gained widespread use in its management. However, there is limited information on whether the survival benefits associated with immunotherapy differ among races and ethnicities.

Objective: This study aimed to investigate racial differences in survival amongst patients with NSCLC who received immunotherapy as the first-line treatment in Texas.

Methods: Patients with NSCLC who received immunotherapy between October 2015 to December 2018 were identified from the Texas Cancer Registry (TCR). Disease-specific survival was evaluated and compared among patients across racial/ethnic categories using the Kaplan-Meier survival analysis, log-rank test, and a multivariable Cox proportional hazard regression model following an inverse probability treatment weighting (IPTW) propensity score analysis.

Results: A total of 1453 patients were included in the analysis. Median survival (in months) was longest among Asians (34, 95% CI: 15-Not Estimable), followed by African Americans (AAs) (23, 95% CI: 15-34), Hispanics (22, 95% CI: 16-26), and Whites (19, 95% CI: 17-22). The adjusted regression estimates had no statistically significant differences in survival among AAs (aHR = 0.97; 95% CI = 0.78-1.20; P =0.77) and Hispanics (aHR = 0.96; 95% CI = 0.77-1.19, P =0.73) when compared to White patients. Asians on the other hand, had 40% reduction in mortality risk compared to Whites (aHR = 0.60; 95% CI = 0.39-0.94, P = 0.03).

Conclusions: Our study indicated that African Americans and Hispanics do not have poorer survival compared to White patients when receiving immunotherapy as first-line treatment. Asians however had longer survival compared to Whites. Our findings suggest that existing racial disparity in NSCLC survival might be mitigated with the use of immunotherapy and should be considered in providing care to these minority groups.

KEYWORDS

immunotherapy, non-small cell lung cancer, racial disparity, retrospective study, survival analysis

1 Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer in the United States (US) and accounts for about 85% of all lung cancer cases (1, 2). Lung cancer is the leading cause of cancer-related deaths in the U.S (3). Fortunately, lung cancer-related mortality is on the decline, largely due to advances in treatment options (4, 5). Immunotherapy is an innovative therapy that has been well documented to improve survival in patients with NSCLC; these drugs act by activating immune cells and enhancing their antitumor responses (6). In the past decade, the U.S. Food and Drug Administration (FDA) has approved immunotherapeutic agents including immune checkpoint inhibitors (ICIs) and cytotoxic T-lymphocyte–associated protein 4 receptor (CTL4-A) inhibitors (7) as first- and second-line agents for NSCLC (7, 8).

Many studies have reported that racial disparity exists in lung cancer (8–13). For instance, across racial groups in the U.S., AAs have the highest incidence of lung cancer and mortality rates despite having lower smoking prevalence compared to Whites (14, 15). The American Lung Association (ALA) reports on racial differences among Asians, African Americans, Hispanics, and Whites with regards to prevalence, access to treatment and survival; ALA's statistics have shown poorer survival among African Americans and Hispanics compared to their White counterparts even when there is access to treatment (16). Further complicating this issue is the underrepresentation of minority racial groups in clinical trials targeting cancers (17). Many trials that have led to the approval of several immunotherapy drugs for NSCLC did not consider national representation of racial groups or racial differences in the burden of the disease in their study samples (18–22). These trials did not consider oversampling the minority groups to support subgroup analyses. In these trials, African American patients comprised only 1-4% of the treatment and control samples, despite the fact that 13.6% of the US population are AAs (23). Just as concerningly, Hispanics were not considered as a distinct category despite their increasing representation, currently at 18.9% of the U.S. population (23). Only few observational studies have evaluated immunotherapy for NSCLC in diverse patient samples found in real-world, clinical settings (7, 24–26) and although these studies provided valuable insights into whether racial disparity occurs with immunotherapy utilization, they were limited by sample size, insufficient representation of minority races or ethnic groups, and low generalizability. To our knowledge, no state-specific study has been done as the majority of previous studies were retrospective reviews of patients receiving treatments in a single treatment center (7, 27). Based on the ALA statistics, the state of Texas is below the national average in achieving racial equity for Lung cancer and White patients often have higher survival rates (28). As such, we hypothesized that White patients with NSCLC have longer survival compared to minority races when immunotherapy is received as the first course of therapy in Texas. Therefore, the objective of this study was to examine if there are racial differences in survival from NSCLC when immunotherapy is administered as the first course of treatment among patients receiving treatment in Texas.

2 Methods

2.1 Study design and data source

Our study was a retrospective cohort study of patients with histologically confirmed NSCLC who received immunotherapy as their first-line of treatment. Patient data were obtained from the Texas Cancer Registry (TCR) database. The TCR is a statewide population-based cancer registry with gold certification by the North American Association of Central Cancer Registries and is recognized as one of the largest cancer registries in the United States (29). The database provides information on cancer patients' sociodemographic, tumor, and other clinical characteristics as well as the general class of treatments received as the first-line of treatment (30). All

study procedures were approved by the University of Houston Institutional Review Board (IRB) with a waiver of informed consent as this was secondary research that used de-identified data. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (31).

2.2 Identification of study population and variables

We identified patients with NSCLC, aged 18 years and above, who received immunotherapy as the first-line of treatment from October 2015 to December 2018. Patients were retrospectively followed till December 2020. Patients were excluded if they had any missing values for race, ethnicity, or any other study variables (Figure 1). The third edition of the International Classification of Diseases for Oncology (ICD-O) codes was used to identify cases of NSCLC, based on the primary site of the cancer, its morphology, and behavior (Table S1) (30, 32).

The primary independent variable was race and ethnicity, referred to simply as race henceforth in the study. The use of immunotherapy was defined as whether patients received an immunotherapy agent as the first-line of treatment. The cancer stage was classified as localized, regional, and distant, according to the classification by the Commission on Cancer (CoC) (31, 33). The primary exposure was the receipt of immunotherapy, defined as being treated with immunotherapy as first-line of treatment. The unexposed group did not receive immunotherapy as first-line agents but received other treatments such as chemotherapy. The primary outcome was disease-specific survival and was defined as the time from initiation of immunotherapy to death or censoring at end of the follow-up period. Censored patients were those who were alive or died of other causes during the study period (34).

Covariates evaluated were demographic and socioeconomic characteristics such as age, sex, insurance type, county-level poverty index, and geographical location. Patient's smoking history and clinical characteristics such as cancer stage were also identified and defined at baseline. Immunotherapy is commonly administered with other agents, especially chemotherapy (29, 32), so receipt of other treatment modalities as first-line agents such as chemotherapy, radiotherapy, hormone therapy, and surgery were also measured.

2.3 Statistical analysis

Data management and statistical analyses were performed using SAS v9.4 software (SAS Institute Inc., Cary, NC, USA). Two-sided statistical significance was used to test hypotheses and was defined as $P<0.05$.

2.4 Descriptive statistics

To describe the baseline characteristics of the study cohort, continuous variables were presented as means with standard deviations, while categorical variables were presented as frequency and percentages, and comparisons were made using the Chi-square test. Comparisons across racial categories were performed using the analysis of variance (ANOVA) test.

2.5 Survival analysis

Crude survival differences across racial categories were obtained using unadjusted Kaplan-Meier (K-M) analysis and a

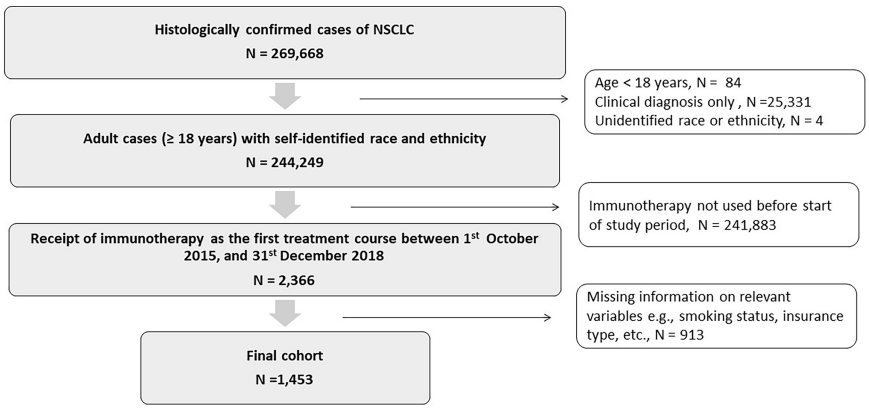

FIGURE 1
Consort diagram showing cohort selection: Patients 18 years and older with histologically confirmed cases of non-small cell lung cancer who received immunotherapy as the first treatment course between October 1, 2015, and December 31, 2018.

bivariate Cox proportional hazards (PH) regression model. K-M curves were used to depict the monthly survival probabilities of patients per racial category and statistical differences in these survival probabilities across the study period were determined using the log-rank test. Pairwise analysis of the K-M analysis was done to evaluate survival differences in each minority group versus Whites alone while adjusting for multiplicity hence inflation of Type 1 error using the Sidak test (35). Sidak adjustment assumes that each comparison is independent of the others and has more power than the more conservative Bonferroni adjustment (36). Median survival times obtained from the K-M analysis were compared across races. As a secondary analysis to obtain survival time, the restricted mean survival time (RMST) was obtained for all races. The RMST is not commonly used in survival analysis but is generally considered a more reliable estimate than the median survival time estimated using the K-M curve due to its ability to circumvent skewness and challenges associated with censoring in survival data (37, 38). In addition, it provides a summary of the survival time in the entire period of observation, as opposed to obtaining the survival rate at a specified time as with the K-M curve (38).

A multivariable Cox proportional hazards regression model was fitted to compare mortality risk among the different racial categories while adjusting for baseline covariates. Cancer stage and smoking status of the patients were introduced as interaction terms in the Cox proportional hazard model to examine if the survival of patients across racial categories varied according to the spread of cancer or smoking history (2, 39).

2.6 Propensity score analysis

The difference in mortality risk between patients across racial and ethnic groups was further examined after balancing differences in treatment (racial) groups by inverse probability treatment weighting (IPTW). IPTW has the advantage of yielding marginal treatment estimates while conserving sample size of all propensity score (PS) methods (40). Multiple PS technique which controls for bias by comparing more than two treatment groups was used in this study as there were four racial groups (41). The IPTW is the probability of assignment to each treatment category (41). Pairwise PS analysis when dealing with more than two groups i.e., comparing two groups at a time, is not recommended because the probability of choosing all treatment groups will be greater than one, and the model fits are less efficient leading to variance inflation (41, 42) hence our opting for the multiple propensity score technique. To carry out our PS analysis, PS (probability of each patient of a particular race belonging to another racial group) was obtained using a multinomial logistic regression analysis (41, 43). The generalized logit function was specified in the link option to contrast minority races to White as the reference group. All identified potential confounders, including interaction terms, were added to the logistics model. Overlap of generated PS across the racial groups was assessed. The inverse of the propensity scores was then used to generate the IPTW, also known as the propensity score weights (28, 29). The weights were stabilized to prevent undue influence of extreme weights which can bias the result (40). The balance of the baseline characteristics across treatment groups was assessed using Absolute Standardized Mean Differences (ASMD) (40, 44). Finally, a weighted multivariable Cox proportional hazard model was fitted with race as the only predictor and White patients as the reference group.

2.7 Sensitivity analysis

Sensitivity analysis was performed to examine the possible impact of informative censoring on the results obtained (44, 45). First, the risk of mortality was evaluated with censored patients assumed to have been observed for the entire follow-up period, i.e., the entire period of observation. This analysis tests the hypothesis that censored cases are at low mortality risk and thus have more extended times of death from NSCLC than other cases (45). A second analysis was done whereby patients who died of causes other than NSCLC were not censored. This analysis tests the hypothesis that people who died of other causes (and thus censored) would have experienced this if they had not died and were thus at high risk of mortality from NSCLC (45). The sensitivity analysis was repeated using the IPTWs and race as the only covariate.

3 Results

3.1 Characteristics of the study cohort

A total of 244,249 adult patients with NSCLC diagnosis and self-reported race and ethnicities were identified in the TCR database. The racial categories were defined as non-Hispanic White, non-Hispanic African American or African American, non-Hispanic Asian and Hispanic. These are henceforth referred to as White, AA, Asian, and Hispanic respectively. Of the identified patients with NSCLC, 2366 received immunotherapy as the first-line of therapy between October 2015 and December 2018. After excluding patients with missing information, the final cohort consisted of 1,453 patients. An attrition flowchart detailing inclusion and exclusion criteria is provided in Figure 1.

Among the study population, 1,044 (71.8%) were White, 185 (12.7%) were African American, 172 (11.8%) were Hispanic, and 72 (3.6%) were Asian. The median age for all patients was 68 years (Interquartile range, IQR: 61 – 74 years) [White: 69 (IQR: 27 - 98) years, African American: 66 (IQR: 40 - 90) years, Hispanic: 65 (IQR: 21 - 89) years, and Asian: 63 (IQR: 36 - 89) years]. All patients had immunotherapy initiation within two months of NSCLC diagnosis. More than half of the study population were females (52.6%). A larger

proportion of all patients had government-type insurance (66.8%), lived in metropolitan or urban areas (85.1%), were current or former smokers (80.3%), had metastatic cancer (75.6%), and received chemotherapy (as adjunct therapy or second-line treatment; 64.6%). Asians were the youngest population, with 44.2% of them being younger than 65 years of age at the diagnosis. Hispanics had the highest proportion (11.1%) of uninsured patients. African Americans (43.2%) and Hispanics (40.7%) had the highest proportion of patients at the highest percentile of the census tract poverty level category (20 – 100%), considered as the most extreme level of poverty. Almost all the Asian population lived in metropolitan areas (98.1%). The rate of smoking was highest among African Americans (86.5%) and Whites (83.0%) followed by Hispanics (64.0%) and Asians (59.6%).

3.2 Unadjusted survival characteristics of patients across racial groups

A larger proportion of White patients (N = 588; 56.3%) died during the observation period (Table S1). This was followed by Hispanics [N = 95; 55.2%], African Americans [N= 89; 48.2%] and Asians [N= 52; 42.3%]. While Asians maintained a slightly higher survival across the follow-up period, the overall Kaplan-Meier estimates (Figure 2) did not show any significant differences across all racial groups (P = 0.18). The pairwise tests showed that Asians had a higher survival probability compared to Whites (P = 0.05) (Figure 2E). The cohort's overall median disease-specific survival (DSS) was 19 months (95% CI = 17 - 22 months) and Asians had the longest median survival time (34 months, lower bound 95% CI = 15 months), followed by African Americans (23 months, 95% CI = 15 - 34), Hispanics (22 months, 95% CI = 16 - 26), and Whites (19 months, 95% CI = 17 - 22). The upper confidence interval limit of the median DSS for Asians was inestimable due to high rate of censoring in this population (30). The RMST values [(mean (SD)] obtained were 25.4 (0.68) months for Whites, 27.3 (1.64) months for African Americans, 26.3 (1.64) months for Hispanics, and 30.8 (3.14) months for Asians. (Figure S1). As with the K-M analysis, there was no statistically significant difference in survival among the racial categories (P = 0.29). No pairwise analysis was performed for the RMST analysis.

3.3 Adjusted association between race and survival using conventional Cox proportional hazard regression

The multivariable Cox proportional hazard regression results (Figure 3) indicated no significant differences in survival of African American (aHR = 0.84; 95% CI = 0.68-1.04, P =0.113) patients, and Hispanic patients (aHR = 0.98; 95% CI = 0.78-1.22, P =0.862) in comparison with White patients when immunotherapy was administered as the first-line of treatment. Asians on the other hand, had about 35% reduction in risk compared to White patients but the upper confidence level shows evidence of probability of similar survival chances as White patients (aHR = 0.65, 95% CI = 0.42-1.00, P =0.05) (52,53). Although cancer stage and smoking status were independently associated with survival in the adjusted regression model (P<0.05), their interaction terms were not statistically significant (P>0.05), indicating that the influence of race on survival does not differ by the stage of cancer or smoking status when immunotherapy is received.

The results of the first sensitivity analysis which assumed that censored observations had the longest follow-up period provided similar results with the main analysis (African Americans: aHR = 0.86, 95% CI = 0.69 -1.07, P =0.18, Hispanics: aHR = 1.01, 95% CI = 0.81 - 1.26, P =0.97; Asians: aHR = 0.64, 95% CI = 0.42 – 0.99, P =0.04). The second analysis which assumed that patients who died from other causes had similar mortality risk as those who died from cancer, did not show any significant difference among the racial groups regarding the mortality risk.

3.4 Propensity score estimation

The baseline characteristics among all races were comparable after adjustment using IPTW. There was considerable overlap among the treatment groups (Figure 4). The distribution of propensity scores was similar between all racial groups and the groups were thus comparable (31). The maximum ASMD for all covariates after IPTW was 11% and 90% of the measured covariates after IPTW had ASMD values below 0.1, as shown in (Table 1; Figure S2). This value was much less than the 25% recommended value (33, 34) confirming a good balance across the racial groups. ASMD below 0.1 indicated an acceptable balance between treatment (racial) groups (35). Figure 5 shows the regression estimates for the PS analysis. The propensity-score-weighted Cox proportional hazards model showed similar results with Cox analysis using regression adjustment (Figure 5). African Americans and Hispanics had comparable mortality risk as White patients (African Americans: aHR = 0.97, 95% CI = 0.78-1.20, P = 0.77, Hispanics: aHR = 0.96, 95% CI = 0.77-1.19, P = 0.73) while Asians had lower mortality risk compared to White patients (aHR = 0.60, 95% CI = 0.39 - 0.94, P = 0.03). The results of the sensitivity analyses using IPTW was similar to the results obtained from the adjusted regression model.

4 Discussion

This retrospective cohort study examined if differences in survival exist amongst NSCLC patients of different races who

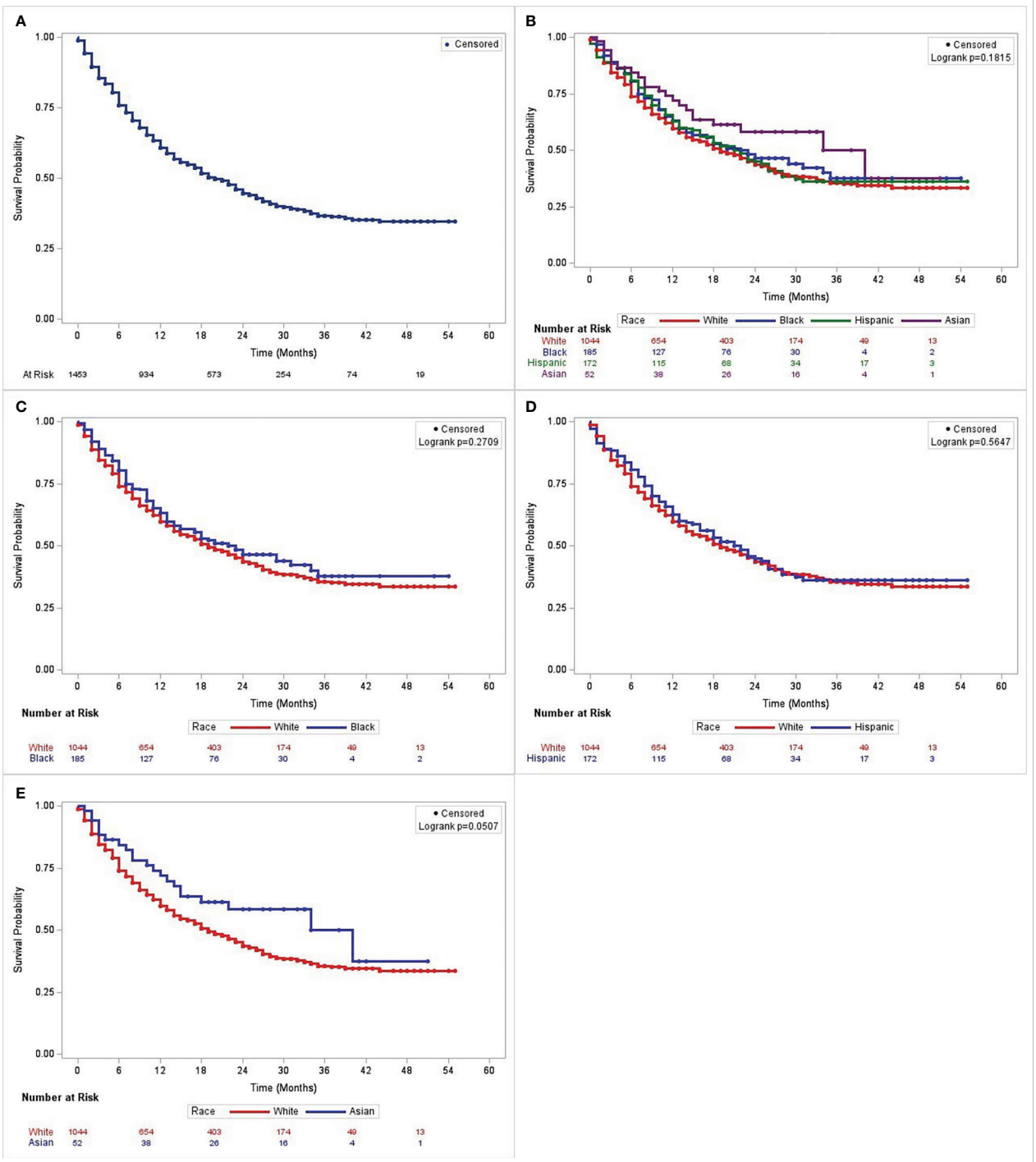

FIGURE 2
Kaplan-Meier curves showing disease-specific survival in patients with non-small cell lung cancer who received immunotherapy as the first course of treatment in Texas from 2009 to 2018. From L to R: **(A)** the entire cohort; **(B)** patients stratified by race and ethnicity; and comparisons between **(C)** African American and White patients, **(D)** Hispanic and White patients, and **(E)** Asian and White patients.

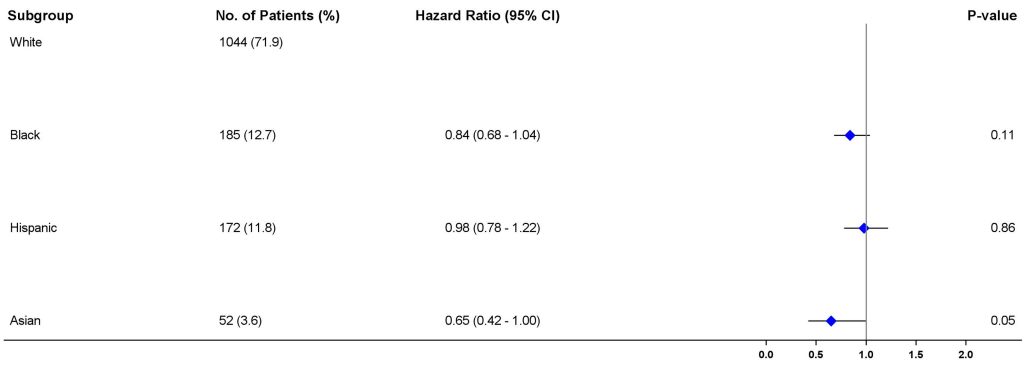

FIGURE 3
Forest plot of multivariable Cox proportional hazard regression analysis showing the association between patient characteristics and disease-specific survival using regression adjustment.

receive immunotherapy as the first-line of treatment in Texas. Our findings revealed no differences in survival among Whites, African Americans, and Hispanics (P>0.05), while Asians had a 40% decreased risk of mortality. We adjusted for patient baseline characteristics using regression adjustment and propensity score analysis, and there was no qualitative difference in the results obtained *via* both methods, as both methods gave the same interpretation of mortality risk across the racial groups. We demonstrated that the propensity score analysis reduced bias from measured confounders based on ASMD values, improving the reliability of our estimates.

Our findings are similar to those reported in previous studies.A retrospective cohort study using data collected from over 260 community cancer clinics in the U.S (25). reported a longer median overall survival (OS) among Asians [9.7 (IQR: 6.8 –13.2)] followed by African Americans [9.0 months (IQR: 4.8-12.7)], and Whites [8.0 months (IQR: 7.3 -9.2)]. This pattern was observed in our study, but they could not make further comparisons because their study did not include the Hispanic population, and race-stratified multivariable analysis was not done. Another study evaluated differences in survival between White and African American patients receiving treatment at a single institution in Georgia state (27) and reported similar OS (aHR = 0.90, 95% CI = 0.59 - 1.37, P = 0.13) and progression-free survival, PFS (aHR = 2.70, 95% CI = 1.08 – 6.74, P = 0.08) among the groups. This is also similar to our finding in which there was no significant difference in DSS between African American and White patients, but again other minority races were not considered in their study. Ayers et al. (7) oversampled African American patients (30.1% of the racial cohort) and included Asian (9.6%) and Hispanic populations (14.1%) in their study. Similar to our finding, their multivariable Cox analysis found no significant difference in survival of African Americans (aHR = 0.60, 95% CI = 0.34-1.03, P = 0.06) and Hispanics (aHR = 0.69, 95% CI = 0.37-1.27, P = 0.23) when compared to Whites, while their Asian population had improved overall survival (aHR =

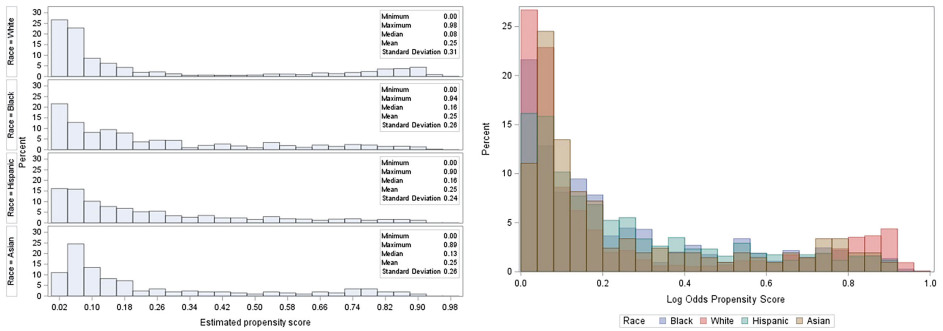

FIGURE 4
Histogram showing the distribution of propensity scores by treatment (racial) group. From L to R: stacked histogram showing individual propensity scores for treatment groups, the overlap of propensity scores among treatment groups.

TABLE 1 Descriptive characteristics of 1453 Patients with Non-Small Cell Lung Cancer Identified in the Texas Cancer Registry from October 2015 to December 2018 and Absolute Standardized Mean Differences (ASMD) Before and After Propensity Score Analysis using the Inverse Probability Treatment Weighting (IPTW) Method.

		Race					ASMD	
	Total	White	African American	Hispanic	Asian			
Characteristic	(N =1453)	(N =1044)	(N=185)	(N=172)	(N=52)	P-value	Before IPTW	After IPTW
Time to treatment initiation, Median (Q1-Q3), month	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.6	0.09	0.04
Age group								
18-64	532 (36.6)	344 (32.9)	80 (43.2)	79 (45.9)	29 (55.8)	<0.0001*	0.27	0.06
≥65	921 (63.4)	700 (67.1)	105 (56.8)	93 (54.1)	23 (44.2)			0.07
Sex								
Male	689 (47.4)	506 (48.5)	87 (47.0)	74 (43.0)	22 (42.3)	0.50	0.10	0.08
Female	764 (52.6)	538 (51.5)	98 (53.0)	98 (57.0)	30 (57.7)			0.09
Insurance								
Private	401 (27.6)	280 (26.8)	44 (23.8)	53 (30.8)	24 (46.2)	<0.0001*	0.10	0.06
Government	971 (66.8)	716 (68.6)	132 (71.3)	100 (58.1)	23 (44.2)		0.21	0.07
Uninsured	81 (5.6)	48 (4.6)	9 (4.9)	19 (11.1)	5 (9.6)		0.23	0.08
Poverty Index								
0-<5	272 (18.7)	231 (22.1)	15 (8.1)	12 (7.0)	14 (26.9)	<0.0001*	0.40	0.06
5-9.9	352 (24.2)	292 (28.0)	22 (11.9)	27 (15.7)	11 (21.2)		0.37	0.07
10-19.9	507 (34.9)	357 (34.2)	68 (36.8)	63 (36.6)	19 (36.5)		0.05	0.06
20-100	322 (22.2)	164 (15.7)	80 (43.2)	70 (40.7)	8 (15.4)		0.54	0.03
Location								
Metro	1236 (85.1)	866 (83.0)	162 (87.6)	157 (91.3)	51 (98.1)	0.0008*	0.23	0.11
Non-metro	217 (14.9)	178 (17.1)	23 (12.4)	15 (8.7)	1 (1.9)			0.10
Smoking status								
Never smoked	286 (19.7)	178 (17.0)	25 (13.5)	62 (36.0)	21 (40.4)	<0.0001*	0.43	0.08
Current/former smoker	1167 (80.3)	866 (83.0)	160 (86.5)	110 (64.0)	31 (59.6)			0.06
Stage								
Localized	82 (5.6)	58 (5.6)	9 (4.9)	14 (8.1)	1 (1.9)	0.17	0.06	0.06
Regional	273 (18.8)	205 (19.6)	33 (17.8)	31 (18.1)	4 (7.7)		0.08	0.09
Distant	1098 (75.6)	781 (74.8)	143 (77.3)	127 (73.8)	47 (90.4)		0.11	0.07
Histopathology								
Non-squamous cell	1184 (81.5)	833 (79.8)	154 (83.2)	150 (87.2)	47 (90.4)	0.03*	0.23	0.05
Squamous cell	269 (18.5)	211 (20.2)	31 (16.8)	22 (12.8)	5 (9.6)			0.05
Surgery								
No	1373 (94.5)	982 (94.1)	174 (94.0)	165 (95.9)	52 (100.0)	0.24	0.08	0.07

(Continued)

TABLE 1 Continued

		Race					ASMD	
	Total	White	African American	Hispanic	Asian			
Characteristic	(N =1453)	(N =1044)	(N=185)	(N=172)	(N=52)	P-value	Before IPTW	After IPTW
Yes	80 (5.5)	62 (5.9)	11 (6.0)	7 (4.1)	0 (0.0)			0.08
Radiotherapy								
No	908 (62.5)	640 (61.3)	119 (64.3)	118 (68.6)	31 (59.6)	0.28	0.15	0.11
Yes	545 (37.5)	404 (38.7)	66 (35.7)	54 (31.4)	21 (40.4)			0.10
Hormone therapy†								
No	1426 (98.1)	1026 (98.3)	183 (98.9)	167 (97.1)	50 (96.1)		0.08	0.05
Yes	27 (1.9)	18 (1.7)	2 (1.1)	5 (2.9)	2 (3.9)			0.07
Chemotherapy								
No	514 (35.4)	383 (36.7)	57 (30.8)	55 (32.0)	19 (36.5)	0.34	0.11	0.06
Yes	939 (64.6)	661 (63.3)	128 (69.2)	117 (68.0)	33 (63.5)			0.05

Number and percentages are reported except stated otherwise.
†Hormone therapy did not meet the Chi-square assumption that the expected value of cells in the contingency table should be 5 or greater in at least 80% of cells.
*Statistically significant at a significance level of 5%.
ASD means absolute standardized difference, the largest ASD among treated groups is reported.

0.32, 95% CI = 0.12-0.85, P = 0.02). After PS analysis with White and African American patients, African Americans showed improved survival, but the strength of the association was weak (aHR = 0.53, 95% CI = 0.28-1.01, P = 0.054). Our study findings are in line with previous studies, therefore, suggest that minority races can equally benefit from immunotherapy if they have access to immunotherapy. This is a positive finding since many studies have reported longer survival among only White population using conventional therapies like chemotherapy and surgery (9, 36).

In our analyses, the cancer stage, and patients 'smoking history were considered as potential moderators of the effect of race on survival. This is because these variables are known independent predictors of survival from lung cancers, individual responses to immunotherapy may therefore differ based on these factors' asides from racial status (37–39). In addition, race mediated through genetics may influence the aggressiveness of a cancer, hence, the stage (40) and behavioral factors such as smoking habits may differ across races. For instance, in our study population, there were more White and

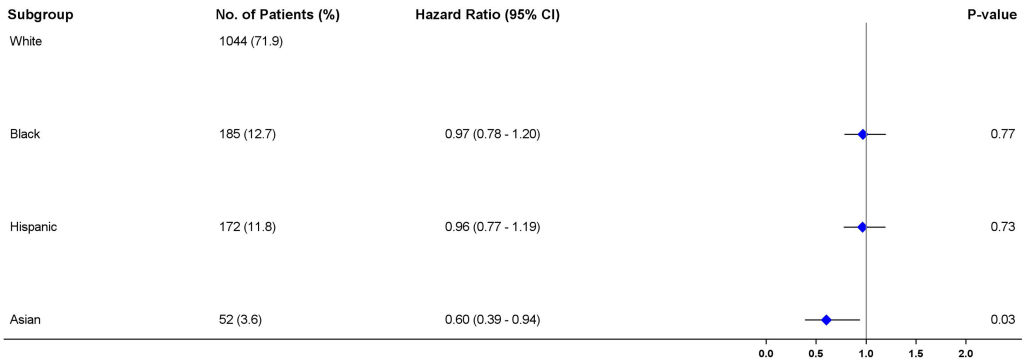

FIGURE 5
Forest plot of multivariable Cox proportional hazard regression analysis showing the association between patient characteristics and disease-specific survival using the inverse probability treatment weighting (IPTW) method.

African American smokers than Hispanics and Asians who smoked. Our analysis however indicated no interaction between race and cancer stage, or between race and smoking status. Therefore, we did not proceed with subgroup analysis for these variables to prevent inflation of type 1 error rates (31). Our analysis also included an evaluation of how sensitive our Cox regression estimates were to possible informative censoring, and the results showed that our study findings were moderately robust to informative censoring. The fact that Asians lost their "superior" survival in the second sensitivity analysis may suggest that Asians who died of other causes were systematically different from those who died of lung cancer. Also, high censoring percentage which was observed with Asians (57.7%) can increase bias if patients who provided most of the information, were censored (41). Overall, this result still shows that patients of all races may equally benefit from immunotherapy for treatment of NSCLC (37, 62–64)

The strength of our study is in its ability to corroborate existing but limited knowledge about racial variations in survival that may exist with immunotherapy utilization. To further improve on these studies, we used more rigorous analytic techniques and included more populations utilizing this therapy in real-world. For the first time in related studies, we used multiple propensity score techniques to effectively reduce potential confounding bias through its pseudo-randomization (31, 44) and increased the reliability of our estimates. PS methods have been mainly used for two treatment groups. Another strength of our study was balancing pre-treatment characteristics for more than two groups, which is not very common. Other studies did not conduct sensitivity analysis and to our knowledge, our study has the largest sample size (N =1,453) and explored the most heterogeneous patient population due to utilization of a registry database collecting information from all cancer institutes in Texas (8–12, 36). The distribution of racial categories in our study was more representative of national estimates than previous studies and clinical trials. The implication of our overall study finding is that the efficacy of immunotherapy as observed in clinical trials is likely realized in the heterogenous patient population in real world, especially across an important social and or biologic construct such as race. Access to immunotherapy should be increased for minority races since disparity in access to treatment has been reported by NSCLC (42, 43).

Our study has limitations. Firstly, we did not have information on some parameters such as the specific immunotherapeutic agents used by the patients, their dosing regimen, and duration of therapy. Response markers to immunotherapy and tumor mutations that could have been used for prediction of a patient's response to immunotherapy, were also not available (6). Second, Race and ethnicity were self-reported; information on ancestry and genetic data may provide more accurate information on the survival characteristics (46). The database we used lacked genetic data which may also drive differential survival characteristics observed in our study, for instance, being Asian has been reported to be a favorable prognostic factor for overall survival in NSCLC irrespective of smoking status (44). Our Asian population was small, similar to previous studies. This might be due to the low incidence of lung cancer among Asian population (16, 45). Third, unmeasured baseline characteristics which may act as confounders e.g., comorbidities were largely missing and were not considered in our analysis. Also, we excluded patients with missing information, which might have resulted in biased findings. Lastly, given that this study only focused on Texans, a more robust study in a nationally representative population is needed to confirm existing findings.

5 Conclusion

This retrospective cohort study showed no differences in survival between African American, Hispanic, and White patients in Texas when immunotherapy was used as the first-line of treatment for NSCLC. These results corroborate findings in previous studies and demonstrated similar outcomes for immunotherapy across races, thus reinforcing the value of observational studies in contributing to evidence-based knowledge and clinical decisions. It is recommended that access to immunotherapy is maintained across minority groups and nationally representative studies being conducted to generalize the finding across U.S. populations.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The TCR dataset is available upon request at no cost. Requests to access these datasets should be directed to https://www.dshs.texas.gov/tcr/data/requests.aspx.

Ethics statement

All study procedures were approved by the University of Houston Institutional Review Board (IRB) with a waiver of informed consent as this was secondary research that used de-identified data. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Author contributions

OO, ZZ, and SS conceptualized and designed the study. OO did the methodology, data analysis, data visualization and wrote initial draft of the manuscript. OA supported the study design

and analysis. OO, OA, and SS interpreted the results. TV and MZ were involved in manuscript drafts. SS was involved in study supervision, review, and editing of the draft. All authors conducted a critical revision of the manuscript for important intellectual content and approved the submitted version.

Acknowledgments

The data used in this study was collected by the Texas Cancer Registry (TCR), a statewide cancer registry funded by the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program and the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The views expressed in this study are solely those of the authors and do not necessarily reflect those of the TCR, SEER, or NPCR.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1092355/full#supplementary-material

References

1. Zhou K, Shi H, Chen R, Cochuyt JJ, Hodge DO, Manochakian R, et al. Association of race, socioeconomic factors, and treatment characteristics with overall survival in patients with limited-stage small cell lung cancer. *JAMA Netw Open* (2021) 4:e2032276. doi: 10.1001/JAMANETWORKOPEN.2020.32276

2. Raphael J, Batra A, Boldt G, Shah PS, Blanchette P, Rodrigues G. Predictors of survival benefit from immune checkpoint inhibitors in patients with advanced non-small-cell lung cancer: A systematic review and meta-analysis. *Clin Lung Cancer* (2020) 21:106–113.e5. doi: 10.1016/J.CLLC.2019.11.004

3. Hirsch FR, Scagliotti G v, Mulshine JL, Kwon R, Curran WJ, Wu Y-L, et al. Lung cancer: current therapies and new targeted treatments. *Lancet* (2017) 389:299–311. doi: 10.1016/S0140-6736(16)30958-8

4. Giaquinto AN, Miller KD, Tossas KY, Winn RA, Jemal A, Siegel RL. Cancer statistics for African American/Black people 2022. *CA Cancer J Clin* (2022) 72 (3):220–9. doi: 10.3322/CAAC.21718

5. Lung Cancer Statistics. *How common is lung cancer?* Available at: https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html (Accessed March 17, 2022).

6. Steven A, Fisher SA, Robinson BW. Immunotherapy for lung cancer. *Respirology* (2016) 21:821–33. doi: 10.1111/RESP.12789

7. Ayers KL, Mullaney T, Zhou X, Liu JJ, Lee K, Ma M, et al. Analysis of real-world data to investigate the impact of race and ethnicity on response to programmed cell death-1 and programmed cell death-ligand 1 inhibitors in advanced non-small cell lung cancers. *Oncologist* (2021) 26:e1226–39. doi: 10.1002/ONCO.13780

8. Wolf A, Alpert N, Tran Bv, Liu B, Flores R, Taioli E. Persistence of racial disparities in early-stage lung cancer treatment. *J Thorac Cardiovasc Surg* (2019) 157:1670–1679.e4. doi: 10.1016/J.JTCVS.2018.11.108

9. Harrison S, Judd J, Chin S, Ragin C. Disparities in lung cancer treatment. *Curr Oncol Rep* (2022) 24:241–8. doi: 10.1007/S11912-022-01193-4/FIGURES/1

10. Singh GK, Williams SD, Siahpush M, Mulhollen A. Socioeconomic, rural-urban, and racial inequalities in US cancer mortality: Part I-All cancers and lung cancer and part II-colorectal, prostate, breast, and cervical cancers. *J Cancer Epidemiol* (2011) 2011:27. doi: 10.1155/2011/107497

11. Jones CC, Mercaldo SF, Blume JD, Wenzlaff AS, Schwartz AG, Chen H, et al. Racial disparities in lung cancer survival: The contribution of stage, treatment, and ancestry. *J Thorac Oncol* (2018) 13:1464–73. doi: 10.1016/J.JTHO.2018.05.032

12. Hardy D, Xia R, Liu CC, Cormier JN, Nurgalieva Z, Du XL. Racial disparities and survival for nonsmall-cell lung cancer in a large cohort of black and white elderly patients. *Cancer* (2009) 115:4807–18. doi: 10.1002/CNCR.24521

13. Gadgeel SM, Kalemkerian GP. Racial differences in lung cancer. *Cancer Metastasis Rev* (2003) 22:39–46. doi: 10.1023/A:1022207917249

14. Mitchell KA, Zingone A, Toulabi L, Boeckelman J, Ryan BM. Comparative transcriptome profiling reveals coding and noncoding RNA differences in NSCLC from African americans and European americans. *Clin Cancer Res* (2017) 23:7412–25. doi: 10.1158/1078-0432.CCR-17-0527

15. Desantis CE, Siegel RL, Sauer AG, Miller KD, Fedewa SA, Alcaraz KI, et al. Cancer statistics for African americans, 2016: Progress and opportunities in reducing racial disparities. *CA Cancer J Clin* (2016) 66:290–308. doi: 10.3322/CAAC.21340

16. State of Lung Cancer. *Racial and ethnic disparities*. American Lung Association. Available at: https://www.lung.org/research/state-of-lung-cancer/racial-and-ethnic-disparities (Accessed June 3, 2022).

17. Loree JM, Anand S, Dasari A, Unger JM, Gothwal A, Ellis LM, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. *JAMA Oncol* (2019) 5(10):e191870. doi: 10.1001/JAMAONCOL.2019.1870

18. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-Small-Cell lung cancer. *N Engl J Med* (2015) 373:1627–39. doi: 10.1056/NEJMOA1507643

19. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-Small-Cell lung cancer. *N Engl J Med* (2015) 373:123–35. doi: 10.1056/NEJMOA1504627

20. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* (2015) 372:2018–28. doi: 10.1056/NEJMOA1501824

21. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* (2017) 389:255–65. doi: 10.1016/S0140-6736(16)32517-X

22. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* (2018) 378:2288–301. doi: 10.1056/NEJMOA1716948

23. *U.S. census bureau QuickFacts*. United States. Available at: https://www.census.gov/quickfacts/fact//US/RHI725219 (Accessed December 7, 2021).

24. Nazha B, Mishra M, Pentz R, Owonikoko TK. Enrollment of racial minorities in clinical trials: Old problem assumes new urgency in the age of immunotherapy. *Am Soc Clin Oncol Educ Book* (2019) 39:3–10. doi: 10.1200/EDBK_100021

25. Khozin S, Carson KR, Zhi J, Tucker M, Lee SE, Light DE, et al. Real-world outcomes of patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors in the year following U.S. regulatory approval. *Oncologist* (2019) 24:648–56. doi: 10.1634/THEONCOLOGIST.2018-0307

26. Florez MA, Kemnade JO, Chen N, Du W, Sabichi AL, Wang DY, et al. Persistent racial/ethnic associated disparity in anti-tumor effectiveness of immune checkpoint inhibitors despite equal access. *Cancer Res Commun* (2022). doi: 10.1158/2767-9764.CRC-21-0143

27. Nazha B, Goyal S, Chen Z, Engelhart A, Carlisle JW, Beardslee TJ, et al. Efficacy and safety of immune checkpoint blockade in self-identified blacks with advanced non-small cell lung cancer (NSCLC). *Cancer* (2020) 126(23):5040–9. doi: 10.1002/cncr.33141

28. *State data* . Texas: American Lung Association. Available at: https://www.lung.org/research/state-of-lung-cancer/states/texas (Accessed September 25, 2021).

29. Hofman P. The power of immunotherapy plus platinum–based chemotherapy for locally advanced or early stage non-small cell lung cancer. *Ann Transl Med* (2020) 8:151–1. doi: 10.21037/ATM.2020.01.91

30. Rao SR, Schoenfeld DA. Survival methods. *Circulation* (2007) 115:109–13. doi: 10.1161/CIRCULATIONAHA.106.614859

31. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. *Regression methods. In Biostatistics: Linear, logistic, survival, and repeated measures models. 2nd ed.* Springer-Verlag, Inc. (2012). doi: 10.1007/978-1-4614-1353-0

32. Ning X, Yu Y, Shao S, Deng R, Yu J, Wang X, et al. The prospect of immunotherapy combined with chemotherapy in patients with advanced non-small cell lung cancer: a narrative review. *Ann Transl Med* (2021) 9:1703–3. doi: 10.21037/ATM-21-4878

33. McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. *Psychol Methods* (2004) 9:403–25. doi: 10.1037/1082-989X.9.4.403

34. Coffman DL, Zhou J, Cai X. Comparison of methods for handling covariate missingness in propensity score estimation with a binary exposure. *BMC Med Res Methodol* (2020) 20:168. doi: 10.1186/S12874-020-01053-4//7

35. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* (2011) 46:399–424. doi: 10.1080/00273171.2011.568786

36. Farjah F, Wood DE, Yanez ND, Vaughan TL, Symons RG, Krishnadasan B, et al. Racial disparities among patients with lung cancer who were recommended operative therapy. *Arch Surg* (2009) 144:14–8. doi: 10.1001/ARCHSURG.2008.519

37. Chen VW, Ruiz BA, Hsieh MC, Wu XC, Ries LAG, Lewis DR. Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. *Cancer* (2014) 120:3781–92. doi: 10.1002/CNCR.29045

38. Tsao AS, Liu D, Lee JJ, Spitz M, Hong WK. Smoking affects treatment outcome in patients with advanced nonsmall cell lung cancer. *Cancer* (2006) 106:2428–36. doi: 10.1002/CNCR.21884

39. Janjigian YY, McDonnell K, Kris MG, Shen R, Sima CS, Bach PB, et al. Pack-years of cigarette smoking as a prognostic factor in patients with stage IIIB/IV nonsmall cell lung cancer. *Cancer* (2010) 116:670–5. doi: 10.1002/CNCR.24813

40. Kehm RD, Spector LG, Poynter JN, Vock DM, Altekruse SF, Osypuk TL. Does socioeconomic status account for racial and ethnic disparities in childhood cancer survival? *Cancer* (2018) 124:4090–7. doi: 10.1002/CNCR.31560

41. Lin NX, Logan S, Henley WE. Bias and sensitivity analysis when estimating treatment effects from the cox model with omitted covariates. *Biometrics* (2013) 69:850. doi: 10.1111/BIOM.12096

42. Osarogiagbon RU, Sineshaw HM, Unger JM, Acuña-Villaorduña A, Goel S. Immune-based cancer treatment: addressing disparities in access and outcomes. *Am Soc Clin Oncol Educ Book* (2021) 41:1–13. doi: 10.1200/EDBK_323523

43. Mulligan CR, Meram AD, Proctor CD, Wu H, Zhu K, Marrogi AJ. Unlimited access to care: Effect on racial disparity and prognostic factors in lung cancer. *Cancer Epidemiology Biomarkers Prev* (2006) 15:25–31. doi: 10.1158/1055-9965.EPI-05-0537

44. Ou SHI, Ziogas A, Zell JA. Asian Ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. *J Thorac Oncol* (2009) 4:1083–93. doi: 10.1097/JTO.0B013E3181B27B15

45. Raz DJ, Gomez SL, Chang ET, Kim JY, Keegan THM, Pham J, et al. Epidemiology of non-small cell lung cancer in Asian americans: Incidence patterns among six subgroups by nativity. *J Thorac Oncol* (2008) 3:1391–7. doi: 10.1097/JTO.0B013E31818DDFF7

46. Jorde LB, Wooding SP. Genetic variation, classification and "race." *Nat Genet* (2004) 36:S28–33. doi: 10.1038/ng1435

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 13 January 2023
DOI 10.3389/fonc.2022.1099566

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Cancer Epidemiology and Prevention,
a section of the journal
Frontiers in Oncology

RECEIVED 15 November 2022
ACCEPTED 30 December 2022
PUBLISHED 13 January 2023

CITATION
Ashing KT, Song G, Jones V, Brenner C and
Samoa R (2023) Racial disparities in
diabetes prevalence among
cancer patients.
Front. Oncol. 12:1099566.
doi: 10.3389/fonc.2022.1099566

Racial disparities in diabetes prevalence among cancer patients

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Introduction: Cancer inequity is one of the most critical public health issues faced by ethnic minorities and people of lower socioeconomic status. The disparate burden of cancer is caused by poor access to care and inadequate delivery of cancer treatment, as well as comorbid and co-occurring conditions. Diabetes is a common and serious comorbid condition of cancer.

Methods: To better understand diabetes prevalence among diverse cancer patients, this study analyzed and described characteristics of cancer patients with diabetes from local-level Service Planning Area (SPA) data using City of Hope Comprehensive Cancer Center data, and United States national-level data from The National Health Interview Survey.

Results: Findings from national level data showed that patients in racial/ethnic minority groups had a higher occurrence of being diagnosed with diabetes, especially for non-Hispanic Blacks (OR=1.76, 95% CI=1.51, 2.03) and Hispanic/Latino individuals (OR=1.34, 95% CI=1.18, 1.52). Cancer patients who are older, ethnic minority, overweight/obese and with lower educational levels were more likely to have co-occurring diabetes. SPA-level patient data found similar results.

Discussion: In response to our findings and other reports, clinicians and health system including health coverage organizations should routinely assess cancer patients for cooccurring chronic illnesses, in particular diabetes. Interventions improving coordinated care that integrates oncology, endocrinology and primary care, targeting cancer patients –especially racial/ethnic minorities, overweight/obese, and older patients who are at increased risk for diabetes – ought to be considered as best practice Whole Person care. With coordinated care management, ethnic disparities in cancer may be better addressed and reduced. Additionally, policymakers can contribute by enacting policies improving access to and coverage of integrated oncology, chronic disease prevention, and associated specialty care i.e., endocrinology to equalize quality care for ethnic minority, lower educated, overweight/obese and older cancer patients who are more likely to suffer greater comorbidity, and inadequate oncology and coordinated care to reduce disparities.

KEYWORDS

racial disparities, health disparities, diabetes, cancer, healthcare

Introduction

Cancer is a critical public health issue. In the United States, it is estimated that 1.9 million new cancer cases will be diagnosed and 609,360 deaths will be caused by cancer in 2022 (1).. As the second leading cause of death in this country, the direct medical costs and indirect costs of cancer are huge. In 2015, the medical costs related to cancer were $183 billion and would increase to $246 billion by 2030 (2). For cancer patients, the burden is increased with co-occurring comorbid illnesses. Comorbidity can be defined as "the existence of a long-term health condition in the presence of a major disease of interest" (3). Evidence suggested the prevalence of comorbidities would increase with the years of survivorship increasing (4). The development of comorbidities is also relevant to the type of cancer: patients with lung cancer, kidney cancer, and stomach cancer are more likely to have other comorbid conditions (4). Comorbid conditions can complicate the treatment and outcome of cancer that negatively impact health-related quality of life and survival (4).

Diabetes is one of the most common and serious comorbid conditions. Cancer and diabetes, especially Type 2 diabetes, have many risk factors in common, including age, race/ethnicity, overweight/obesity, physical inactivity, smoking, etc. (5). These risk factors make patients with cancer more vulnerable to diabetes and the effects of diabetes. Additionally, some cancer treatments, such as certain targeted therapy treatments and chemotherapy drugs, can accelerate the development of diabetes or aggravate the process of diabetes (6). Diabetes becomes an important factor for patients and providers to choose the proper cancer treatment (6). Previous research indicated the mortality of cancer patients with diabetes was higher than cancer patients without any comorbid conditions (7). Social vulnerability index (SVI) characterizes non-medical factors that can impact a patient's cancer outcome. In the cohort of patients who underwent stem cell transplantation, Hispanic and Asian patients showed an association with SVI and 1-year non-relapse mortality (NRM), while non-Hispanic whites showed no association with SVI and 1-year NRM. These findings highlight the important social-environmental factors play in health outcomes following hematopoietic cell transplantation (HCT), specifically among different racial and ethnic groups (8). For cancer patients with diabetes, more comprehensive healthcare services, including other medical specialties i.e., endocrinology, are necessary to meet patients' special needs.

Since race/ethnicity is a major risk factor for both cancer and diabetes, some racial/ethnic groups have a higher risk of developing both diseases. For example, compared to other racial/ethnic groups, non-Hispanic Blacks have higher mortality for many types of cancer (9). Non-Hispanic Black and Hispanic/Latino women also have a higher prevalence of cervical cancer than women of other racial/ethnic groups (9). Meanwhile, the rates of diagnosed diabetes among American Indians/Alaskan Natives (14.5%), non-Hispanic Blacks (12.1%), and Hispanics (12.1%) are higher than other racial/ethnic groups (10). Previous research has indicated Latina breast cancer survivors had a higher risk of developing Type 2 Diabetes than the general population and diabetes was most prevalent among Latina survivors aged over 65 years old (11, 12).

Although high-quality healthcare is critical for all patients, many patients with cancer have various barriers to accessing healthcare services, especially racial/ethnic minority patients. The 2019 National Healthcare Quality and Disparities Report found that compared to non-Hispanic Whites, all other racial/ethnic groups reported receiving poorer healthcare quality (13). Even given comparable backgrounds such as income level, educational level, and insurance coverage status, racial/ethnic minority groups were reported to have disparities due to language barriers, provider bias, etc. (2). Therefore, more efforts are needed to improve the health of the minority patients with cancer, which is also an important component of improving the overall public health.

Because of the number of minority patients residing there, Los Angeles (LA) County serves as an ideal setting to develop and test measures to improve overall public health Based on 2020 U.S. Census Estimates, 48.32% of the total population of Los Angeles County was Hispanic or Latino, 14.83% was Asian, and 8.07% was Black (14). In addition, previous research highlighted racial/ethnic disparities in cancer prevalence and diabetes prevalence in Los Angeles County (15, 16). With a highly diverse population, it is important for Los Angeles County to ensure health equality among racial/ethnic minority populations and help them access high-quality healthcare. However, limited studies focused on the racial/ethnic disparity of the development of comorbid conditions among cancer patients. Cancer patients in racial/ethnic groups, especially those with comorbid conditions, should have a higher quality of care.

To have a better understanding of current diabetes prevalence among cancer patients, this study analyzed and described the diabetes prevalence among cancer patients from Service Planning Area (SPA) level and the national level. A SPA is a specific geographic area divided by the Department of Public Health of LA County to help provide better public health and clinical services tailored to the specific health needs of the residents in those different areas (17). Results of this study can provide insights into the outcomes of cancer patients who also had diabetes as a comorbid condition. It will address the severity of disparities in Los Angeles County. With the awareness of disparities in prevalence, policymakers can develop tailored policies to improve the quality of care for minority patients.

Methods

Data Source

This study is a secondary data analysis study. For national-level data, we used The National Health Interview Survey (NHIS), which is a cross-sectional household face-to-face interview survey program (18). NHIS collected health-related information among civilian noninstitutionalized populations residing within the 50 states and the District of Columbia in the United States (18). The most recent one-year NHIS data 2021 was used in this research (19). In 2021 NHIS, totally, 30,673 households had been interviewed including 29,482 sample adults and 8,261 sample children; the total household response rate was 52.8% (20).

For SPA-level data, we used patient data collected from the City of Hope Comprehensive Cancer Center (COH) from January 2020 to September 2022. COH is a private, not-for-profit clinical research center, hospital and graduate school to provide treatment and care services for patients with cancer, diabetes, and other life-threatening

illnesses (21). Currently, COH's cancer clinics cover more than 35 locations across Southern California, the United States, and provide care services for giving thousands of patients (22). Patient data were collected by clinicians and organized by the Research Informatics team. Due to a different design from the national-level survey program, patient records of COH only provided limited information. Thus, not all variables used from patient record data were the same as those from the national-level dataset.

Measures

NHIS covers important health topics such as chronic diseases, health behaviors, health care status, use of preventive services, etc. The study population in this research is adults who have been diagnosed with cancer (any type). The dependent variable is the diagnosis of diabetes (any type) and the independent variable is self-reported race/ethnicity. Covariates included demographic characteristics (age, gender, marital status, educational attainment), healthcare coverage, BMI, and health behavior (tobacco use). NHIS questionnaire interviews the race and origin of participants and divides as *Hispanic/Latino, Non-Hispanic White only, Non-Hispanic Black/African American only, Non-Hispanic Asian only, Non-Hispanic American Indian and Alaska Native (AIAN) only, Non-Hispanic AIAN and any other group*, and *Other single and multiple races*. Though distinct groups that deserve focused attention, *Non-Hispanic AIAN only, Non-Hispanic AIAN and any other group, and Other single and multiple races* were merged into one category as *Other Single and Multiple Races* for statistical purposes only due to the small sample size. Cancer and diabetes diagnoses were self-reported on the survey questions: "Have you EVER been told by a doctor or other health professional that you had cancer?" and "Have you EVER been told by a doctor or other health professional that you had diabetes (Not including (gestational diabetes, prediabetes))" (23). Other covariate variables were recoded as age groups (18-34, 35-44, 45-54, 55-65, ≥65), marital status (married or live with a partner, other), educational attainment (did not graduate high school, graduated high school, attended college or technical school, and graduated from college or technical school), BMI (underweight, normal weight, overweight, and obese), tobacco use (current smoker, former smoker, and never smoker).

For SPA patient data, cancer diagnosis (any type) and diabetes diagnosis (any type) were reported by health professionals. Racial/ethnic information was self-reported and categorized as Hispanic/Latino, Non-Hispanic White only, Non-Hispanic Black/African American only, Non-Hispanic Asian only, and Other Single and Multiple Races. Covariate variables included in the patient record were age group (18-34, 35-44, 45-54, 55-65, ≥65), gender (female, male), healthcare insurance coverage (yes, no), BMI (overweight/obese, normal weight/underweight).

Data analysis

For national-level analysis, since descriptive estimates in this research were obtained from a subpopulation (patients with cancer), descriptive analyses were conducted using methods for analyzing complex sample design data (24). Second-order (Satterthwaite) Rao-Scott chi-square tests were conducted to explore associations between the diagnosis of diabetes and race/ethnicity. Weighted multivariable logistic regression models were conducted using PROC SURVEYLOGISTIC to test associations between dependent and independent variables after controlling for covariates (24). All analyses were conducted using Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc., Cary, NC).

Since only limited information was included in patient records, for SAP-level analysis, descriptive analysis was conducted to show the percentage in different categories.

Results

National level

There were 3,654 adults diagnosed with cancer in the 2021 NHIS survey program. Among them, 603 also reported that they were diagnosed with diabetes. Table 1A presents demographic characteristics (age, gender, marital status, and educational

TABLE 1A Cancer Patients with/without Diabetes Characteristics by Racial and Ethnic Category, NHIS 2021[a,b].

Characteristics	Non-Hispanic White N = 461 Weighted %	Non-Hispanic Black N = 67 Weighted %	Non-Hispanic Asian American N = 16 Weighted %	Hispanic/ Latino N = 43 Weighted %	Other Single and Multiple Races N = 16 Weighted %
Age					
45-54	*7.7*	10.3	3.2	20.1	17.2
55-64	*19.1*	17.5	9.0	24.5	18.1
≥ 65	71.4	68.8	85.1	48.0	48.0
Gender					
Male	49.8	45.8	44.3	51.9	44.0
Female	50.2	54.2	55.7	48.1	56.9

(Continued)

10.3389/fonc.2022.1099566

TABLE 1A Continued

Characteristics	Non-Hispanic White N = 461 Weighted %	Non-Hispanic Black N = 67 Weighted %	Non-Hispanic Asian American N = 16 Weighted %	Hispanic/ Latino N = 43 Weighted %	Other Single and Multiple Races N = 16 Weighted %
Marital Status					
Married or living with a partner	63.2	38.5	77.8	50.4	38.7
Other	36.8	61.5	22.2	49.6	61.3
Educational Attainment					
Did not graduate high school	15.8	19.9	7.1	32.8	21.3
Graduated high school	28.6	25.3	33.4	26.0	18.3
Attended college or technical school	30.2	33.2	11.6	36.7	43.0
Graduated from college or technical school	25.5	21.7	47.8	4.5	17.5
Healthcare Insurance Coverage					
Yes	98.7	97.5	100.0	93.1	83.3
BMI					
Overweight	32.9	33.7	33.5	50.2	11.1
Obese	47.9	47.2	35.1	31.2	41.5
Tobacco Use					
Current smoker	**13.0**	**4.3**	**0**	**4.9**	**31.1**

[a]Numbers of all race/ethnicity do not add up to the total number of patients due to missing cases.
[b]Percentages may not add up equal to 100% due to rounding.

TABLE 1B Cancer Patients without Diabetes Characteristics by Racial and Ethnic Category, NHIS 2021[a,b]

Characteristics	Non-Hispanic White N = 2,638 Weighted %	Non-Hispanic Black N = 268 Weighted %	Non-Hispanic Asian American N = 53 Weighted %	Hispanic/ Latino N = 137 Weighted %	Other Single and Multiple Races N = 53 Weighted %
Age					
45-54	10.4	7.9	21.9	16.1	10.2
55-64	21.2	19.4	13.2	20.7	7.6
≥ 65	58.6	57.4	48.8	36.9	54.1
Gender					
Male	44.4	43.3	20.4	42.2	33.1
Female	55.6	56.7	79.6	57.8	66.9
Marital Status					
Married or living with a partner	67.6	44.5	83.1	58.9	43.0
Other	32.4	55.5	16.9	41.1	57.0
Educational Attainment					
Did not graduate high school	7.0	14.1	7.1	25.9	7.3
Graduated high school	22.6	23.0	14.4	22.9	22.2
Attended college or technical school	26.0	33.4	19.3	31.6	40.7

(Continued)

TABLE 1B Continued

Characteristics	Non-Hispanic White N = 2,638 Weighted %	Non-Hispanic Black N = 268 Weighted %	Non-Hispanic Asian American N = 53 Weighted %	Hispanic/ Latino N = 137 Weighted %	Other Single and Multiple Races N = 53 Weighted %
Graduated from college or technical school	44.4	29.5	59.2	19.6	30.0
Healthcare Insurance Coverage					
Yes	97.7	96.8	100.0	93.0	95.1
BMI					
Overweight	35.4	36.7	20.8	42.9	21.8
Obese	27.9	38.5	6.5	30.3	33.2
Tobacco Use					
Current smoker	10.8	9.6	0	8.7	24.9

[a]Numbers of all race/ethnicity do not add up to the total number of patients due to missing cases.
[b]Percentages may not add up equal to 100% due to rounding.

attainment), healthcare coverage, and health behaviors (tobacco use, alcohol consumption, physical activity) among cancer patients with diabetes by racial and ethnic category. Table 1B presents characteristics among cancer patients without diabetes by racial and ethnic category. Based on the results, at the national level, more cancer patients with diabetes were aged over 65, especially patients in the non-Hispanic Asian group, with a percentage of 85%. Non-Hispanic Asian patients had higher educational levels than patients in other racial/ethnic groups, approximately 48% of them graduated from college or technical school. On the other hand, Hispanic/Latino patients had lower educational levels than others, about 33% of them did not graduate from high school; only 4.5% of them reported graduating from college or technical school. Over 80% of patients in all racial/ethnic groups had healthcare insurance coverage; however, Hispanic/Latino patients reported the lowest proportions of health insurance coverage which was 93.1%. Abnormal BMI was an important character for patients: more than half of all patients were overweight or obese; participatory, about 80% of patients in non-Hispanic White, non-Hispanic-Black, and Hispanic/Latino groups were overweight or obese.

Table 2 shows the results of the multivariable logistic regression model assessing diabetes status as a co-occurring condition, which

TABLE 2 Results of Multivariable Analyses Predicting Prevalence of Diabetes among Cancer Patients by Racial and Ethnic Category, 2021 NHIS [a].

	Prevalence of Diabetes among Cancer Patients Unweighted N= 603			
	β	Adjusted OR	95% CI	*P*
Age (Years)				<.0001
≥ 65 (Ref)				
45-54	-0.87	0.42	(0.36, 0.50)	<.0001
55-64	-0.34	0.71	(0.63, 0.82)	
Race/ethnicity				<.0001
Non-Hispanic White (Ref)				
Non-Hispanic Black	0.62	1.86	(1.58, 2.18)	
Non-Hispanic Asian American	0.82	2.27	(1.79, 2.89)	
Hispanic/Latino	0.51	1.67	(1.43, 1.95)	
Other	0.74	2.09	(1.46, 2.98)	
Educational Attainment				<.0001
Did not graduate high school (Ref)				
Graduated from college or technical school	-0.80	0.45	(0.37, 0.54)	
Attended college or technical school	-0.32	0.72	(0.61, 0.86)	

(Continued)

TABLE 2 Continued

	Prevalence of Diabetes among Cancer Patients Unweighted N= 603			
	β	Adjusted OR	95% CI	*P*
Graduated high school	-0.22	0.80	(0.67, 0.95)	
Health Insurance Coverage				0.01
No (Ref)				
Yes	0.34	1.40	(1.10, 1.79)	
Gender				0.00
Female (Ref)				
Male	0.22	1.25	(1.11, 1.40)	
BMI				<.0001
Normal weight (Ref)				
Overweight	0.70	2.01	(1.70, 2.39)	
Obese	1.36	3.89	(3.31, 4.58)	
Tobacco Use				0.01
Non-smoker (Ref)				
Current smoker	-0.03	0.97	(0.82, 1.15)	
Former smoker	0.19	1.20	(1.06, 1.36)	

[a]Adjusted ORs were obtained after controlling for other predictor variables in the model.

only included variables that were significantly associated with diabetes comorbidity. The overall Wald test suggested that all possible factors in the final model had statistically significant relations to diabetes comorbidity among cancer patients (F= 70.18, p<0.0001). Based on the results, age, race, gender, educational level, healthcare insurance coverage, BMI, and tobacco use were associated with diabetes comorbidity among cancer patients. Patients who are older, in minority groups, with lower educational levels would be more likely to be diagnosed with both cancer and diabetes at a statistical significance level. In addition, male patients were more likely to be diagnosed with cancer and diabetes (OR=1.25, 95% CI=1.11, 1.40). Cancer patients with abnormal BMI had significantly higher odds to co-occur with diabetes (overweight OR=2.01, 95% CI=1.70, 2.39; obese OR=3.89, 95% CI=3.31, 4.58). In terms of tobacco use, former smokers were more likely to develop diabetes (OR=1.20, 95% CI=1.06, 1.36). All ORs were adjusted.

Table 3 presents the unadjusted odds ratio of diabetes diagnosis by racial/ethnic groups. Compared to non-Hispanic White cancer patients, patients in racial/ethnic minority groups had higher odds of being diagnosed with diabetes, especially for non-Hispanic Black patients (OR=1.76, 95% CI=1.51, 2.03) and Hispanic/Latino patients (OR=1.34, 95% CI=1.18, 1.52) with statistically significant higher odds.

SPA level

Totally, there were 41,692 patients with cancer from 2020 to 2022. Among them, 3,644 patients were also diagnosed with diabetes. Table 4 presents the result of the descriptive analysis. Based on the results, the majority of cancer patients (86%) with diabetes were aged over 55 years old. There were more non-Hispanic White and Hispanic/Latino patients in the SPA dataset. In addition, most patients (87.7%) patients had healthcare insurance coverage. Also, more than 50% of them were overweight/obese.

TABLE 3 Diabetes Prevalence by Racial and Ethnic Category, 2021 NHIS[a,b].

Characteristics	Non-Hispanic White N = 461 Unadjusted OR (95% CI)	Non-Hispanic Black N = 67 Unadjusted OR (95% CI)	Non-Hispanic Asian American N = 16 Unadjusted OR (95% CI)	Hispanic/Latino N = 34 Unadjusted OR (95% CI)	Other Single and Multiple Races N = 16 Unadjusted OR (95% CI)	P-value
Diabetes Diagnosis						<.0001
Yes	**Ref**	**1.76 (1.51, 2.03)**	**1.21 (0.99, 1.48)**	**1.34 (1.18, 1.52)**	**1.36 (0.97, 1.90)**	

[a]Race/ethnicity and diabetes diagnosis were included in the univariate model.
[b]ORs were unadjusted.

10.3389/fonc.2022.1099566

TABLE 4 Cancer Patients with Diabetes Characteristics, Patient Data.

Characteristics	Cancer Patients with Diabetes N=3,644 Unweighted %	Cancer Patients with Diabetes Absolute Number
Age		
18-34	1.6	59
35-44	3.2	115
45-54	9.2	336
55-64	22.3	813
≥ 65	63.7	2,321
Gender		
Male	51.3	1,871
Female	48.7	1,773
Race/Ethnicity		
Non-Hispanic White only	37.2	1,355
Non-Hispanic Black only	5.8	211
Non-Hispanic Asian only	18.7	681
Hispanic/Latino	31.9	1,164
Other	6.4	233
Healthcare Insurance Coverage		
Yes	87.7	3,196
BMI		
Overweight/Obese	**65.0**	**2,370**

Conclusion

Compared to non-Hispanic White cancer patients, cancer patients in minority groups have a higher rate of cooccurring diabetes. Based on national-level results, age, race, gender, educational level, healthcare insurance coverage, BMI, and tobacco use were associated with diabetes comorbidity. Particularly, cancer patients who are older, male, in racial/ethnic minority groups, with lower educational levels, and overweight/obese were more likely to develop diabetes as a comorbid condition. In addition, our SPA descriptive analysis results indicated similar status was found: more cancer patients with diabetes were older and overweight/obese.

Discussion

Cancer and diabetes are both serious chronic diseases that lead to huge economic and societal burdens. If patients with cancer developed other comorbid conditions, their medical burden would be increased. Previous studies mainly focused on improving care quality for patients with cancer or diabetes solely, not for patients with both diseases. To have a better understanding of current diabetes prevalence among cancer patients, this study analyzed and described the diabetes prevalence among cancer patients from SPA level and national level.

Results of national-level analyses addressed the importance of various social determinants and provided suggestions for future health policies as well as interventions. This study found educational attainment is significantly associated with the development of diabetes among patients with cancers. One possible reason is patients with lower educational levels face barriers to preventive care. Abnormal BMI is another factor that is significantly associated with the development of diabetes. Healthcare providers and caregivers should address the importance of maintaining normal weight for patients with cancer. In addition, since our study found Hispanic/Latino patients had lower percentages of having healthcare insurance, it is a possible reason for the high prevalence of diabetes among Hispanic/Latino patients. Patient data from the COH cancer center found similar results with national-level analyses, which suggested consistency.

Based on our results, we strongly recommend future public health policies focus more on improving the quality of Whole Person Care. Whole Person Care is patient-centered and aims to improve health outcomes and well-being that cover physical, behavioral, emotional, and social services through the optimal use of different resources (25). Whole Person Care program also aims to improve care coordination services, develop healthcare delivery infrastructure, strengthen the collaboration among providers and communities, and share important data between various healthcare delivery organizations (26). For vulnerable patients, such as patients in minority racial/ethnic groups and patients with low socioeconomic status, Whole

Person Care can take patients' complex needs into account and provide comprehensive, coordinated care responsive to patients' co-occurring illnesses.

Programming focused on MediCal-eligible community members who were homeless, justice-involved, or pregnant, and those with serious mental illnesses, substance use disorders, or complex health conditions.

This study has some limitations. First, patient data only contains limited information. Variables such as educational attainment, marital status, and health behaviors were not collected. Therefore, only descriptive analysis was conducted using patient data. Future research will conduct more statistical analyses when using more comprehensive patient data. Second, the BMI information in the NHIS dataset was self-reported, which may lead to recall bias. We considered using the National Health and Nutrition Examination Survey (NHANES) data since it includes both interviews and physical examinations and physiological measurements are collected by highly trained medical personnel, which will be more accurate (27). However, the most updated NHANES data is 2017-March 2020 Pre-pandemic cycle. Future studies can use new NHANES data when it releases for more accurate BMI information. Third, NHIS has a general question asking if participants had ever been diagnosed with diabetes (any type) and also a question asking if it is Type 1 or Type 2 diabetes. The majority of patients with diabetes were Type 2 diabetes. Considering the impact of analyses caused by sample size and missing responses, this study used the previous NHIS question and analyzed data from patients with diabetes of any type. Future studies will focus on Type 2 diabetes only.

Patients with cancer can have a co-occurring illness as well as develop other comorbid conditions, that increases their medical burden and impact their daily life. Diabetes is one of the most common and serious conditions, especially for patients who are ethnic/racial minority, older, overweight/obese and/or lower educated. In response to our findings and other reports, clinicians and health system including health coverage organizations should develop interventions improving Whole Person, coordinated care that integrates oncology and primary care, especially targeting cancer patients from racial/ethnic minority groups. Additionally, policymakers ought to enact policies improving access to and coverage of integrated primary, oncology, specialty care i.e., endocrine, to equalize quality care for vulnerable patients – who are more likely to suffer greater comorbidity, and inadequate oncology and coordinated care – to reduce disparities. Policies should also focus on facilitating chronic disease prevention programming such as the diabetes prevention programs aimed at engaging racial/ethnic minority (i.e., non-Hispanic Black and Hispanic/Latino), older, overweight/obese and lower educated patients. For cancer patients with diabetes or pre-diabetes symptoms, culturally informed and linguistically appropriate information and care should be provided.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The National Health Interview Survey (NHIS), publicly accessible https://www.cdc.gov/nchs/nhis/2021nhis.htm. Patient data (SPA level data) was collected by City of Hope National Medical Center and provided by disease informatics team.

Ethics statement

The studies involving human participants were reviewed and approved by City of Hope Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RS and VJ provided clinical expertise. GS, KA, and CB contributed to conceptualization and approach. GS conducted analysis. KA and GS worked on manuscript development. All authors overall review and editing. All authors contributed to the article and approved the submitted version.

Funding

CCSG - NIH/P30-CA033572-33

Acknowledgments

The authors would like to acknowledge the City of Hope Center for Informatics and for the utilization of the POSEIDON platforms for data exploration, visualization, analysis, and discovery.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. American Cancer Society. Cancer facts & figures 2022. *American Cancer society* (2022). Available at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html%23:~:text=Estimated%20numbers%20of%20new%20cancer,deaths%20in%20the%20United%20States.

2. American Cancer Society. *Cancer facts & figures 2022*. Atlanta: American Cancer Society (2022).

3. Fowler H, Belot A, Ellis L, Maringe CLuque-Fernandez M, Njagi E, et al. Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers. *BMC Cancer* (2020) 20:2. doi: 10.1186/s12885-019-6472-9

4. Roy S, Vallepu S, Barrios C, Hunter K. Comparison of comorbid conditions between cancer survivors and age-matched patients without cancer. *J Clin Med Res* (2018) 10 (12):911–9. doi: 10.14740/jocmr3617w

5. American Diabetes Association. Know the diabetes-cancer link. *Diabetes Cancer* (2022). Available at: https://diabetes.org/tools-support/diabetes-prevention/diabetes-and-cancer

6. Shahid RK, Ahmed S, Le D, Yadav S. Diabetes and cancer: Risk, challenges, management and outcomes. *Cancers* (2021) 13:5735. doi: 10.3390/cancers1322573

7. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ* (2015) 350:g7607. doi: 10.1136/bmj.g7607

8. Bhandari R, The JB, He T, Nakamura R, Artz AS, Jankowska MM, et al. Social vulnerability and risk of non-relapse mortality after allogeneic hematopoietic cell transplantation. *J Natl Cancer Inst* (2022) 114(11):1484–91. doi: 10.1093/jnci/djac150

9. National Cancer Institute. *Cancer disparities* (2022). Available at: https://www.cancer.gov/about-cancer/understanding/disparities.

10. American Diabetes Association. *Statistics about diabetes* (2022). Available at: https://diabetes.org/about-us/statistics/about-diabetes.

11. Ashing K, Rosales M, Lai L, Hurria A. Occurrence of comorbidities among African-American and latina breast cancer survivors. *J Cancer surviv Res Pract* (2014) 8(2):312–8. doi: 10.1007/s11764-014-0342-x

12. Ashing KT, Lai L, Meyers E, Serrano M, George M. Exploring the association between diabetes and breast cancer morbidity: considerations for quality care improvements among latinas. *Int J Qual Health Care* (2020) 32(2):120–5. doi: 10.1093/intqhc/mzz130

13. *2019 national healthcare quality and disparities report*. Rockville, MD: Agency for Healthcare Research and Quality (2020). Available at: https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/nhqrdr/2019qdr.pdf.

14. Los Angeles Almanac. Racial/Ethnic composition cities & unincorporated communities Los Angeles county. Available at: http://www.laalmanac.com/population/po38.php.

15. Maxwell AE, Sundin P, Crespi CM. Disparities in cancer mortality in Los Angeles county, 1999-2013: an analysis comparing trends in under-resourced and affluent regions. *Cancer causes control CCC* (2020) 31(12):1093–103. doi: 10.1007/s10552-020-01346-5

16. Hales CM, Carroll MD, Kuo T, Simon PA. Diabetes and prediabetes among adults in Los Angeles county and the united states, 1999-2006 and 2007-2014. *Natl Health Stat Rep* (2019) 123:1–8.

17. Los Angeles County Department of Public Health. What is a service planning area? *LA County Dep Public Health* (2022). Available at: http://publichealth.lacounty.gov/chs/spa4/index.htm.

18. National Center for Health Statistics. *About the national health interview survey* (2022). Available at: https://www.cdc.gov/nchs/nhis/about_nhis.htm.

19. National Center for Health Statistics. *National health interview survey, 2021. public-use data file and documentation* (2022). Available at: https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm.

20. National Center for Health Statistics. *National health interview survey, 2021 survey description* (2022). Available at: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2021/srvydesc-508.pdf.

21. City of Hope. *About us* (2022). Available at: https://www.cityofhope.org/.

22. City of Hope. *One city, many locations* (2022). Available at: https://www.cityofhope.org/locations.

23. National Center for Health Statistics. *2021 national health interview survey questionnaire* (2022). Available at: https://www.cdc.gov/nchs/nhis/2021nhis.htm.

24. Heeringa SG, West BT, Berglund PA. *Applied survey data analysis. 2nd ed.* Chapman and Hall/CRC (2017). doi: 10.1201/9781315153278

25. The California Association of Public Hospitals and Health Systems (CAPH). *Whole person care makes progress in care coordination, improving care for vulnerable patients*. California Association of Public Hospitals and Health Systems (2019). Available at: https://caph.org/2019/11/19/whole-person-care-makes-progress-in-care-coordination-improving-care-for-vulnerable-patients/

26. Los Angeles County Department of Health Services. *Whole person care Los Angeles impact report*. (2022). Available at: https://dhs.lacounty.gov/our-services/resources/whole-person-care/

27. National Center for Health Statistics. *National health and nutrition examination survey 2017-march 2020 pre-pandemic* (2022). Available at: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?cycle=2017-2020.

frontiers | Frontiers in Oncology

TYPE Opinion
PUBLISHED 18 January 2023
DOI 10.3389/fonc.2022.1055113

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cancer Epidemiology and Prevention, a section of the journal Frontiers in Oncology

RECEIVED 27 September 2022
ACCEPTED 15 December 2022
PUBLISHED 18 January 2023

CITATION
Kattan C and Kattan J (2023) Accommodation with anticancer drug shortage: A Lebanese harmful solution. *Front. Oncol.* 12:1055113. doi: 10.3389/fonc.2022.1055113

Accommodation with anticancer drug shortage: A Lebanese harmful solution

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KEYWORDS

drug shortage, standard of care, economic crisis, patient safety, rebound effect

The current economic crisis in Lebanon

Since the end of 2019, an accumulation of multiple nested crises has been occurring in Lebanon, starting with the political revolution against the corrupt government, to the COVID-19 pandemic, to the explosion of the port of Beirut in August 2020, and to the economic crisis, resulting in a totally bankrupt country. (1)

The economic crisis is mostly the result of long-lasting political corruption that further resulted in local currency depreciation in 2020. The Lebanese pound devaluation led to the ruin of the central national bank resulting in the destabilization of the healthcare system. The detrimental impact of the economic crisis on the national healthcare system reached three levels: the shortage of imported drugs, collapse of third-party payment systems, and migration of healthcare professionals such as nurses and physicians seeking better job opportunities abroad (2).

Lebanese healthcare system before the crisis

Lebanon has been consistently recognized as one of the most developed healthcare systems in the Middle East and North Africa through its world-renowned physicians and healthcare professionals. It has an excellent private hospital infrastructure and has always been a pioneer in applying innovative treatments and novel equipment. Additionally, almost total coverage of imported anticancer drugs by insurance companies and/or by the Ministry of Public Health offers all Lebanese cancer patients the latest generation of drugs and equity to access state-of-the-art healthcare (3).

Failure of solution implementation by the government

In an attempt to contain the economic crisis, the Central Bank issued, at the end of 2019, an interim measure to subsidize the importation of anticancer medications. To do that, it provided 85% of the foreign currency needed for drug importation at the previously established official exchange rate (LBP 1,500.00 for USD 1.00 instead of the current value of LBP 40,000.00) (4). However, with the continuous currency deterioration, the smuggling of subsidized medications from Lebanon to other countries, and the stockpiling of medications by individuals and local warehouses, the subsidization strategy has led to frequent stock depletion and delays in drug

importation. In parallel, illegal trafficking of counterfeit drugs has benefitted from corrupt dealers in black markets. Patients' desperate need for expensive drugs such as immune checkpoint inhibitors and antiangiogenesis has been exploited by mafia groups. Most patients, being aware of this situation, have had no choice but to succumb to obtaining drugs illegally.

Oncologists' coping solutions

Currently, resilient oncologists who remain in the country are living a nightmare, facing a monthly reduction in their income and the impossibility of doing money transfers for renewing memberships or paying publishing fees secondary to the policy of capital control. However, to help overcome drug shortages and for the sake of their patients, oncologists are tempted by unorthodox approaches such as using on/off prescriptions, switching between different brands of the same drug class, using suboptimal drug dosages, and even deviating from the recommended mode of intake of some drugs.

On/off prescription policy

The on/off prescription policy means that patients are only able to take the drug when it is available. This strategy mainly applies to expensive oral targeted drugs such as cyclin-dependent kinase (CDK) 4/6 inhibitors, new generation antiandrogens, and tyrosine kinase inhibitors (TKIs), and also intravenous drugs such as antiangiogenetic agents and immunotherapy drugs. It is not clear how harmful the on/off policy is. In our current practice, we have encountered a huge number of patients with metastatic breast cancer treated with a combination of CDK 4/6 inhibitors and either aromatase inhibitor or fulvestrant, who were unable to maintain a daily therapy longer than 2 consecutive months because of CDK 4/6 unavailability. As described by Hurvitz et al., when patients stopped taking a CDK 4/6 inhibitor, such as abemaciclib, for more than 4 days, Ki67 rebounded in 69% of the tumors compared with patients who remained on the drug (5). This rebound effect was also described in the literature with different TKIs (6). The use of cabozantinib, for instance, a multi-TKI given for locally advanced rearranged during transfection (RET)-mutated medullary carcinoma (7), achieved a remarkable response when given to one of our patients for 3 consecutive months. However, the disease progressed locally after the drug stopped being taken due to its unavailability and was deemed refractory when drug intake was resumed after 4 months. Similar cases were seen in patients who had been receiving the new generation of antiandrogens, such as enzalutamide given for metastatic castrate-resistant prostate cancer.

Switching of brands in the same drug class

Switching brands based on accessibility is also being practiced, such as moving from one CDK 4/6 inhibitor to another in metastatic hormone-positive HER2 negative breast cancer, or by replacing enzalutamide with abiraterone acetate in metastatic castrate-resistant prostate cancer. These maneuvers, unlike biosimilars, are not recommended in the absence of any evidence of interchangeability between drugs with different mechanisms of action (8).

Use of suboptimal drug doses

Underdosage is also being implemented by oncologists as an attempt to reduce drug expenses. Indeed, multiple expensive cytotoxic drugs such as nab-paclitaxel, cabazitaxel, vinflunine, pemetrexed, and azacitidine have been subject to unrecommended dose reduction. However, coping with the recommended dosage or even intensified dosage has been reported to be more effective with cytotoxic drugs (9).

Deviation from the recommended mode of drug intake

Deviating from intake recommendations is also occasionally imposed. The oral anti-bcl2 venetoclax in relapsed chronic lymphocytic lymphoma (CLL) is recommended, starting with a ramp up schedule to avoid tumor lysis syndrome (10). Dosage is recommended to be increased weekly from 20 mg per day in the first week to reach 400 mg gradually. One of our CLL patients, a 60-year-old woman who was otherwise healthy, was being treated with multiple lines of chemotherapy and immunotherapy. Following this, salvage therapy with a combination of rituximab and venetoclax was prescribed according to the MURANO regimen (11). Venetoclax was not available, and so she received three cycles of rituximab alone, leading to a reduction in the volume of the tumor with the complete disappearance of palpable lymph nodes and normalization of the leucocyte count. However, the patient's condition, her performance status, and her anemia did not improve. It was judged appropriate to introduce venetoclax, regardless of the cost. At our pharmacy, we found an abandoned 100-mg box of venetoclax that was still in date. We prescribed 100 mg of the drug to be taken every other day with a weekly escalation to reach 400 mg, with hydration and anti-uric acid precautions. However, the patient was admitted to the emergency room on the second day, after the first pill, with hyperkalemia, renal insufficiency, hyperuricemia, and pancreatitis. Fortunately, her symptoms were successfully managed during a 1-week stay at the intensive care unit after four hemodialysis sessions.

Future solutions and hopes

It is well known that the high price of anticancer drugs limits treatment options for patients, harming them and society, especially in economically developing nations where such drugs are unaffordable (12). Imported generics, cheaper than branded drugs, could help lower drug bills (13). Importation of generic drugs from cheap manufacturers, such as from India, could be an essential part of the solution once quality control is implemented (14). In addition, manufacturing oncology drugs in local factories could help save money, but this would be difficult to realize in the short term.

Donations from non-governmental organizations (NGOs) or the United Nations (UN) could also be helpful. However, the priorities of developed countries are more oriented toward supporting the Ukraine population rather than other developing countries. (15)

The Ministry of Public Health must urgently face this challenging situation by defining a new policy for drug importation, taking into account the type of drug and the country of origin, and must also fight corruption and prevent smuggling, stockpiling, and illegal drug trafficking.

Conclusions

At present, Lebanese oncologists are extremely limited in their treatment options because expensive and essential oncology drugs are lacking. Standards of care are frequently not observed, putting cancer patients in critical and life-threatening situations. Attempts by oncologists to accommodate and circumvent drug shortages, based on good intentions and common sense but not on evidence, present more harm than solutions. However, until solutions are implemented by the Ministry of Public Health, this risky behavior remains unavoidable.

Author contributions

JK: concept, objectives, and conclusions; CK: references and language improvement. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Mansour HA, Bitar E, Fares Y, Makdessi A, Maalouf A, ElGhoul M, et al. The Beirut port explosion: injury trends from a mass survey of emergency admissions. *Lancet Lond Engl* (2021) 398(10294):21–2. doi: 10.1016/S0140-6736(21)01246-0

2. *Lebanon: Scarce supplies of fuel and medicine push health system to the brink | doctors without borders* . USA. Available at: https://www.doctorswithoutborders.org/latest/lebanon-scarce-supplies-fuel-and-medicine-push-health-system-brink (Accessed August 30, 2022).

3. Elias F, Khuri FR, Adib SM, Karam R, Harb H, Awar M, et al. Financial burden of cancer drug treatment in Lebanon. *Asian Pac J Cancer Prev APJCP* (2016) 17(7):3173–7.

4. *Lebanon: Government recklessness in medication subsidy reform violates right to health and life* . Amnesty International. Available at: https://www.amnesty.org/en/latest/news/2021/12/lebanon-government-recklessness-in-medication-subsidy-reform-violates-right-to-health-and-life/ (Accessed August 30, 2022).

5. Hurvitz SA, Martin M, Press MF, Chan D, Fernandez-Abad M, Petru E, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR+/HER2– breast cancer. *Clin Cancer Res Off J Am Assoc Cancer Res* (2020) 26(3):566–80. doi: 10.1158/1078-0432.CCR-19-1425

6. Pupo E, Ducano N, Lupo B, Vigna E, Avanzato D, Perera T, et al. Rebound effects caused by withdrawal of MET kinase inhibitor are quenched by a MET therapeutic antibody. *Cancer Res* (2016) 76(17):5019–29. doi: 10.1158/0008-5472.CAN-15-3107

7. Colombo JR, Wein RO. Cabozantinib for progressive metastatic medullary thyroid cancer: a review. *Ther Clin Risk Manag* (2014) 10:395–404. doi: 10.2147/TCRM.S46041

8. Nahleh Z, Lyman GH, Schilsky RL, Peterson D, Tagawa S, Chavez- MacGregor , et al. Use of biosimilar medications in oncology. *JCO Oncol Pract* (2022) 18(3):177–86. doi: 10.1200/OP.21.00771

9. Nielson CM, Bylsma LC, Fryzek JP, Saad HA, Crawford J. Relative dose intensity of chemotherapy and survival in patients with advanced stage solid tumor cancer: A systematic review and meta-analysis. *Oncologist* (2021) 26(9):e1609–18. doi: 10.1002/onco.13822

10. Seymour J. Assessment of tumor lysis syndrome in patients with chronic lymphocytic leukemia treated with venetoclax in the clinical trial and post-marketing settings, in: *ASH* (2020). Available at: https://ash.confex.com/ash/2020/webprogram/Paper134938.html (Accessed August 30, 2022).

11. Seymour JF, Kipps TJ, Eichhorst B, Hillman P, D'Rozario J, Assouline S, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med* (2018) 378(12):1107–20. doi: 10.1056/NEJMoa1713976

12. Prasad V, De Jesús K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol* (2017) 14(6):381–90. doi: 10.1038/nrclinonc.2017.31

13. Cheung WY, Kornelsen EA, Mittmann N, Leighi NB, Cheung M, Chan KK, et al. The economic impact of the transition from branded to generic oncology drugs. *Curr Oncol* (2019) 26(2):89–93. doi: 10.3747/co.26.4395

14. Guerin PJ, Singh-Phulgenda S, Strub-Wourgaft N. The consequence of COVID-19 on the global supply of medical products: Why Indian generics matter for the world? *F1000Research* (2020) 9:225. doi: 10.12688/f1000research.23057.1

15. Aljadeeah S, Michielsen J, Ravinetto R, Hargreaves S, Wirtz V, Razum O, et al. Facilitating access to medicines and continuity of care for Ukrainian refugees: exceptional response or the promise of more inclusive healthcare for all migrants? *BMJ Glob Health* (2022) 7(8):e010327. doi: 10.1136/bmjgh-2022-010327

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 27 January 2023
DOI 10.3389/fonc.2023.1072259

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Cancer Epidemiology and Prevention,
a section of the journal
Frontiers in Oncology

RECEIVED 17 October 2022
ACCEPTED 04 January 2023
PUBLISHED 27 January 2023

CITATION
Layne TM, Agarwal P, Rapkin BD,
Jandorf LH and Bickell NA (2023) Cancer
beliefs and screening behaviors: The
impact of neighborhood and other social
determinants of health.
Front. Oncol. 13:1072259.
doi: 10.3389/fonc.2023.1072259

Cancer beliefs and screening behaviors: The impact of neighborhood and other social determinants of health

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Background: Beliefs about cancer influence breast and colorectal cancer (CRC) screening behavior. Screening rates for these cancers differ in the contiguous neighborhoods of East Harlem (EH), Central Harlem (CH), and the Upper East Side (UES), which have distinct socio-demographic compositions. We assessed the belief-screening behavior relationship in these neighborhoods.

Methods: The 2019 Community Cancer Needs Survey included adults eligible for breast and/or colorectal cancer screening. Raking was used to generate neighborhood-specific distribution estimates. Categorical variables were compared using Chi-square tests. Stepwise logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between cancer beliefs and screening.

Results: Our weighted sample included 147,726 respondents. Screening was 75% in CH, 81% in EH, and 90% in the UES for breast cancer, and 71%, 76%, and 92% for CRC, respectively. The fatalistic belief *"There's not much you can do to lower your chances of getting cancer"* differed by neighborhood with screening more likely in CH respondents (breast OR =1.45 and colorectal OR =1.11), but less likely in EH (OR= 0.77 and 0.37, respectively). UES ORs were not generated due to too few unscreened respondents.

Conclusions: Cancer beliefs were inconsistently associated with breast and CRC screening across three NYC neighborhoods. This suggests that a given belief may either motivate or deter screening, depending upon context or interpretation. Once access is addressed, efforts seeking to enhance screening rates should consider implications of communities' varying beliefs.

KEYWORDS

cancer screening, breast cancer, colorectal cancer, community outreach, social determinansts of health

Introduction

Where we live can affect our lives' trajectories (1). Its impact on environmental exposures, social and cultural realities, and the access and availability of services is well described (1–5). Less is known, however, about the impact of neighborhood on cancer beliefs and cancer screening behaviors, though prior research suggests variability across geographic regions distinguished by socioeconomic status (SES) and geographic isolation (6). The influence of neighborhood on cancer beliefs, screening, and health behaviors is relevant as cancer centers seek to better characterize and address the cancer prevention and control needs of their catchment areas (7), and as these areas expand to better capture geographic locales where patients live.

In the current study, we consider neighborhood in the context of cancer screening for breast and colorectal (CRC) cancers for which there are concrete recommendations (8, 9) and evidence that beliefs influence behavior (10–12). Screening rates for these cancers differ within and across the richly diverse neighborhoods of New York City (NYC). Here, we focus on Central Harlem (CH), East Harlem (EH), and the Upper East Side (UES) – contiguous NYC neighborhoods bordering our cancer center that vary in their racial and ethnic, SES, other social determinants of health compositions, and their cancer incidence and mortality rates (13). The latter is evident in the higher odds of developing cancer overall associated with living in CH or EH compared to the UES (14). For CRC, the age-standardized rate of new cases is higher in CH (43.3 per 100,000) and EH (41.4) compared to the UES (28.8) but lower for breast cancer in CH (144.5) and EH (129.7) than the UES (164.4) (15). The age-standardized mortality rate, however, is higher in the Harlem neighborhoods compared to the UES for both CRC (CH 39.7 per 100,000 and EH 35.8 vs. 23.6), and breast cancer (75.3 and 56.7 vs.42.3 (16).

Given the known differences in the distribution of racial/ethnic groups, SES, and breast and colorectal cancer outcomes across these neighborhoods, we examined the relationship between six Health Information Trends Survey (HINTS) cancer beliefs which capture respondents' cancer risk perceptions (17, 18), including beliefs about cancer fatalism and screening, both overall and by neighborhood. We also assessed the relationship between sociodemographic factors, medical mistrust, and healthcare access with cancer screening behavior.

Materials and methods

A random sample of participants were recruited to complete the Icahn School of Medicine at Mount Sinai Community Cancer Needs Survey from two sources: 1) the Mount Sinai Health System electronic medical record (EMR) (N=598), including 18% with a history of cancer based on International Classification of Diseases coding; and 2) community outreach to the Tisch Cancer Institute at the Icahn School of Medicine catchment areas of CH, EH, and the UES (N = 604). Participants were eligible if they were ≥ age 18, spoke either Spanish or English, were able to provide informed consent, and resided in the following neighborhoods based on zip code: CH (zip codes: 10026, 10027, 10030, 10037, 10039), EH (zip codes: 10029, 10035), and the UES (zip codes: 10128, 10021, 10044, 10065, 10075). For recruitment, our target neighborhood distribution was 40% (N=500) each from EH and CH, and 20% from UES (N=200) to ensure strong representation from vulnerable communities. The original unweighted sample included 1,202 participants total, with 480 (40%) from CH, 498 (41%) from EH, and 224 (19%) from the UES.

Participants identified from the EMR were recruited using hard copy and email invitations during the first two months of recruitment. Thereafter, email invite was used given the similar response rate of ~3% across methods. Community outreach participants were recruited from faith-based organizations, health centers, community development and social service organizations, street fairs, parks, storefronts (e.g., supermarkets), public housing, subway and bus stops. All respondents took a 45-minute survey, either assisted or online; and received a $20 gift card for participation. Surveying occurred from April to September 2019.

Survey measures and cancer beliefs

The survey measured domains of: socio-demographics (e.g., age, gender, race/ethnicity, income, education, insurance), cancer screening, cancer beliefs, health information seeking behavior and access, healthcare access, health history, family history of cancer, general health status, and medical mistrust. In addition to HINTS, we used validated items from national surveys (i.e., Behavioral Risk Factor Surveillance System, National Health Interview Survey) (19, 20) as well as newly created or modified questions resulting in a 167-item survey.

We examined six cancer beliefs (17, 18), including four fatalistic questions: 1) *"It seems like everything causes cancer"*, 2) *"There is not much you can do to lower your chances of getting cancer"* 3) *"There are so many different recommendations about preventing cancer, it's hard to know which ones to follow"*, 4) *"When I think of cancer I automatically think of death"*; and two non-fatalistic belief questions: 1) "*Cancer is most often caused by a person's behavior or lifestyle*", and 2) "*I'd rather not know my chances of getting cancer*." All beliefs had the following responses: 1=strongly agree, 2=somewhat agree, 3=somewhat disagree and 4=strongly disagree. In analyses, we compared those who "agree" (combination of responses 1 and 2) to those who "disagree" (combination of 3 and 4). Mistrust was measured using a 6-item Group-based Medical Mistrust scale (21), with response values ranging 1= strongly agree to 5 strongly disagree, and scored (range 6-30) such that lower scores indicated greater mistrust.

Breast and colorectal cancer screening outcomes

Recommended screening was defined as having a mammogram within the past 2 years for women ≥40 years for breast cancer, and having blood stool screening in the past year or colonoscopy in the past 10 years for men and women ≥50 years for CRC.

Statistical analyses

We aimed to recruit individuals representing the census distribution for each neighborhood, however, our final sample distribution was not adequately representative. To obtain better representation of the base population, we combined the EMR and community data sources and then raked the entire dataset, applying population-based weights using data from NYC Health Atlas (22) to obtain estimates based on a cross-classification of age-sex-race-ethnicity-neighborhood factors. Raking, also known as sample-balancing, is an iterative post stratification method that weights the individual survey responses such that the marginal proportions of the survey approximate those of the base population (23, 24). Specifically in this iterative and sequential process, each row of the cross-classified factors are weighted so that the sample row totals are consistent with the totals of the base population. Next, each column of these data are similarly adjusted so that the column totals align with column totals of the base population (24). As a post stratification method, raking is thought to reduce nonresponse bias of the sample data, thereby improving the quality of the sample data (25). However, we acknowledge that raking does not account for or provide an unbiased sample for certain health factors (e.g., access to care) that may differ based on recruitment of participants from the EMR versus the community. We compared categorical variables using Chi-square tests, and estimated odds ratios (OR) and 95% confidence intervals (CI) for stepwise logistic models of the association between beliefs and receipt of screening and used P <0.25 as the threshold for retention in the model. For the forward stepwise analyses, we entered the following factors into the models: age, race/ethnicity, marital status, income, insurance, medical mistrust, general health status, usual source of routine care, difficulty understanding health care provider due to participant's language, personal and family history of cancer, and cancer beliefs. Tables below include final model-specific factors obtained from stepwise regression.

The breast cancer screening model resulted in inconclusive results when all beliefs were entered into the model simultaneously. As such, the following two beliefs were excluded, as they were not statistically significant when evaluated with all other beliefs: "*I'd rather not know my chances of getting cancer* "and "*When I think of cancer I automatically think of death*".

Multivariable models examining the cancer belief-cancer screening relationship by neighborhood were not feasible for all beliefs or for all three neighborhoods due to the lack of convergence for the UES. This is largely due to the relatively low number of UES respondents who did not receive recommended screening. As such, multivariable models of the cancer belief-cancer screening association were only examined for CH and EH. For the EH CRC screening model, we did not enter usual source of routine care as a covariate because 95% of the analytic sample had access to care. We also replaced income with education in the same model as only one individual in the unweighted data had an annual household income ≥$75,000 (the referent category) who did not adhere to recommended screening guidelines. As such, we could not generate sufficient weighted data for comparisons made in this particular analysis.

All analyses were conducted using Statistical Analysis Software (SAS) version 9.4.

This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai.

Results

Descriptive factors, for the overall weighted sample (N=147,726) and each neighborhood, are summarized in Table 1. Looking at the latter breakdown, respondents in CH and EH were younger (56 and 57 years, respectively), compared to those in the UES (64 years), had lower annual household income (52% and 55% <$35K, respectively, compared to 10% in the UES) and education (39.7% and 38.6% with high school education or less, respectively, compared to about 2% in the UES), and a larger proportion were uninsured (10% in CH and 7% in EH vs. about 2% in the UES). In terms of the racial/ethnic majorities in each neighborhood, respondents were largely non-Hispanic Black (59%) in CH, Hispanic in EH (46%), and non-Hispanic White in the UES (90%).

Additionally, a lower proportion of respondents in CH and EH reported their general health status as "excellent" or "very good health" (46% and 43% respectively), relative to those in the UES (56%). While most in all three neighborhoods reported a source of routine care (≥85% for all neighborhoods), difficulty understanding a health provider due to the respondents language was greater in CH (30%) and EH (27%) compared to the UES respondents (4%), and medical mistrust scores indicated greater mistrust in the Harlem neighborhoods (3.8 in CH and 3.9 in EH) relative to the UES (4.6). A lower proportion of respondents in CH and EH reported both a personal and family history of cancer compared to respondents in the UES. In terms of cancer beliefs, respondents in CH and EH reported more agreement with fatalistic cancer beliefs relative to those in the UES. With regard to screening, 75% of CH women reported having breast cancer screening, compared to 81% in EH and 90% in the UES, compared to 74% previously reported for NYC overall (26). For CRC screening, the distribution was 71% in CH, 77% in EH and 92% in the UES, compared to 69% previously reported among NYC the 69% noted here applies to all adults 50 and over, not just women overall (27).

Table 2 summarizes the multivariable modeling results for the relationship between four cancer beliefs and recommended breast cancer screening. Women who agreed "*It seems like everything causes cancer*" were more likely to be screened compared to those that disagreed (OR = 1.09, 95% CI: 1.04-1.15). A similar positive association was observed for those we agreed there are "*too many recommendations, hard to know what to follow*" (OR = 1.12, 95% CI: 1.07-1.18); and "*Cancer is most often caused by behavior or lifestyle*" (OR = 1.35, 95% CI: 1.29-1.42). The latter belief had the strongest point estimate of the belief-screening behavior associations examined. Women who agreed "*There's not much you can do to lower your chances of getting cancer*" were less likely to be screened compared to those who disagreed with this fatalistic cancer belief. Women with less medical mistrust had a greater likelihood of screening (OR for every incremental increase in the score = 1.23, 95% CI: 1.20-1.26). Compared to non-Hispanic White women, Hispanic and non-Hispanic Black women were less likely to be screened in adjusted models, while women of Other race/ethnicity, which includes those

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TABLE 1 Descriptive characteristics of survey respondents to a Community Cancer Needs Survey in Central Harlem, East Harlem, and the Upper East Side.

	Overall N=147,726	Central Harlem N=58,901		East Harlem N=54,055		Upper East Side N=34,770		
Weighted N and %	N	%	N	%	N	%	N	%
Age, Mean (min, max)	58 (40, 92)	56 (40, 91)		57 (40, 91)		64 (41, 92)		
Gender								
Female	76,609	51.9	31,617	54	26,369	49	18,623	54
Male	71,117	48.1	27,284	46	27,686	51	16,147	46
Race/Ethnicity								
Hispanic	38,039	25.7	11,552	20	24,889	46	1,598	5
Non-Hispanic White	49,717	33.7	9,666	16	8,722	16	31,329	90
Non-Hispanic Black	50,126	33.9	34,757	59	15,144	28	225	1
Other	9,844	6.7	2,926	5	5,301	10	1,618	5
Neighborhood								
Central Harlem	58,901	39.9	Not applicable					
East Harlem	54,055	36.6						
Upper East Side	34,770	23.5						
Annual Household Income								
$0-$34,999	63,792	43.2	30,624	52	29,629	55	3,540	10
$35,000 - $74,999	25,719	17.4	11,107	19	10,532	19	4,080	12
$75,000 or more	48,011	32.5	13,358	23	10,566	20	24,086	69
Missing	10,204	6.9	3,812	6	3,328	6	3,064	9
Education								
High School (HS) or less	44,810	30.3	23,407	40	20,846	39	557	2
vocational training or some college	28,288	19.1	12,296	21	12,698	23	3,294	9
college graduate	32,571	22	11,275	19	10,911	20	10,385	30
postgraduate	41,265	27.9	11,335	19	9,601	18	20,329	58
Missing	793	0.5	588	1	0	0	205	1
Insurance								
Employer or Union	49,050	33.2	19,344	33	15,721	29	13,985	40
Medicaid or Other State Program/Exchange	40,161	27.2	18,227	31	17,602	33	4,332	12
Medicare	43,381	29.4	12,548	21	15,539	29	15,294	44
Other	2,959	2	2,000	3	754	1	205	1
No insurance	10,413	7	6,123	10	3,767	7	524	2
Missing	1,762	1.2	658	1	673	1	431	1
General Health Status								
Excellent/Very good	69,617	47.1	27,015	46	23,289	43	19,313	56
Good	41,881	28.4	17,666	30	16,305	30	7,909	23
Fair/Poor/Very poor	35,406	24	13,805	23	14,053	26	7,547	22
Missing	823	0.6	415	1	408	1	0	0
A place usually go for routine or preventive care								

(Continued)

TABLE 1 Continued

	Overall N=147,726		Central Harlem N=58,901		East Harlem N=54,055		Upper East Side N=34,770		
Weighted N and %	N		%	N	%	N	%	N	%
Yes	130,943		88.6	50,046	85	47,786	88	33,110	95
No - there is no place I usually go for routine or preventive care	13,608		9.2	8,143	14	4,841	9	625	2
Missing	3,176		2.1	712	1	1,428	3	1,035	3
How often feel like you do not understand your health provider because of your language									
Always/Often//frequently/sometimes	33,935		23	17,770	30	14,610	27	1,555	4
Never	108,364		73.4	37,788	64	38,117	71	32,460	93
Missing\Don't know\ Don't remember	5,427		3.7	3,343	6	1,329	2	755	2
Medical mistrust (1 = higher mistrust 5 = lower mistrust), Mean (min, max)	4 (1,5)		3.8(1,5)		3.9 (1,5)		4.6 (1,5)		
	Overall N=147,726		Central Harlem N=58,901		East Harlem N=54,055		Upper East Side N=34, 770		
Weighted N and %	N	%	N	%	N	%	N	%	
Personal history of cancer									
Yes	27,455	18.6	6,730	11	10,032	19	10,693	31	
No	119,423	80.8	51,967	88	43,379	80	24,077	69	
Missing	848	0.6	204	0	644	1	0	0	
Family (any) history of cancer									
Yes	99,024	67	35,314	60	35,602	66	28,108	81	
No/Not sure	47,830	32.4	23,435	40	17,733	33	6,662	19	
Missing	873	0.6	152	0	721	1	0	0	
CANCER BELIEFS									
It seems like everything causes cancer									
Strongly agree/Somewhat agree	76,838	52	32,696	56	32,469	60	11,673	34	
Somewhat disagree/Strongly disagree	67,099	45.4	25,050	43	19,642	36	22,407	64	
Missing	3,790	2.6	1,155	2	1,945	4	690	2	
There's not much you can do to lower your chances of getting cancer									
Strongly agree/Somewhat agree	40,283	27.3	20,153	34	14,897	28	5,234	15	
Somewhat disagree/Strongly disagree	103,505	70.1	37,041	63	37,477	69	28,986	83	
Missing	3,939	2.7	1,707	3	1,682	3	550	2	
There are so many different recommendations about preventing cancer, it's hard to know which ones to follow									
Strongly agree/Somewhat agree	96,402	65.3	38,443	65	35,614	66	22,345	64	
Somewhat disagree/Strongly disagree	48,558	32.9	19,152	33	17,326	32	12,080	35	
Missing	2,767	1.9	1,306	2	1,116	2	345	1	
When I think of cancer I automatically think of death									
Strongly agree/Somewhat agree	77,425	52.4	32,630	55	28,148	52	16,647	48	
Somewhat disagree/Strongly disagree	67,417	45.6	24,999	42	24,985	46	17,433	50	
Missing	2,885	2	1,272	2	922	2	690	2	
Cancer is most often caused by a person's behavior or lifestyle									

(Continued)

TABLE 1 Continued

	Overall N=147,726		Central Harlem N=58,901		East Harlem N=54,055		Upper East Side N=34,770		
Weighted N and %	N		%	N	%	N	%	N	%
Strongly agree/Somewhat agree	52,641	35.6	20,034	34	22,584	42	10,023		29
Somewhat disagree/Strongly disagree	90,506	61.3	36,356	62	29,952	55	24,197		70
Missing	4,580	3.1	2,510	4	1,520	3	550		2
I'd rather not know my chances of getting cancer									
Strongly agree/Somewhat agree	46,566	31.5	21,098	36	15,245	28	10,223		29
Somewhat disagree/Strongly disagree	97,540	66	36,418	62	36,920	68	24,202		70
Missing	3,621	2.5	1,385	2	1,891	3	345		1
CANCER SCREENING									
Breast cancer screening among women ≥40 years									
Yes, mammography ≤ 2 years ago	61,980	80.9	23,752	75	21,422	81	16,807		90
Yes, mammography >2 years ago/Never	12,816	16.7	6,892	22	4,108	16	1,816		10
Missing	1,813	2.4	973	3	840	3	0		0
Colorectal cancer screening among men and women ≥50 years									
Yes, blood stool screen in past year or colonoscopy in past 10 years	80,857	78.9	27,649	71	26,570	76	26,638		92
Yes ever/Never	20,917	20.4	11,061	28	7,771	22	2,085		7
Missing	726	0.7	130	0	391	1	205		1

from Asian/Pacific Islander, American Indian/Alaska Native, and multiracial backgrounds, were more likely than their White counterparts to be screened.

Table 3 summarizes the multivariable modeling results for the relationship between all six cancer beliefs and recommended CRC screening. Among women and men age ≥50 years eligible for screening, most fatalistic cancer beliefs were associated with a reduced likelihood of screening. Here again, the strongest association was the belief "*Cancer is most often caused by behavior or lifestyle*", though in the opposite direction than observed for breast cancer (OR = 0.59, 95% CI: 0.56-0.61). Less medical mistrust was similarly associated with a higher likelihood of CRC screening, while Hispanic, NH-Black, and Other race/ethnicity was associated with a reduced likelihood compared to those that are NH-White.

Neighborhood

Results for the evaluation of beliefs in CH and EH are shown in Table 4.The belief that cancer is most often due to a person's behavior or lifestyle was associated with a lower odds of recommended cancer screening for breast and CRC in both neighborhoods, though the association was strongest for CRC among EH respondents (OR = 0.42). A similar pattern and magnitude of association was evident for the belief "*It seems like everything causes cancer*" for both cancer screening outcomes and across neighborhood (OR range = 0.71-0.74), though no estimate could be generated for CRC screening in EH. For both screening outcomes, the belief "*There's not much you can do to lower your chances of getting cancer*" was consistently associated with a higher odds of screening in CH, but a lower odds of screening in EH. For all other beliefs, where estimates could be generated, the associations varied by neighborhood and cancer screening type. Notably, results by neighborhood from multivariable models included adjustment for race/ethnicity.

Discussion

This analysis found that cancer beliefs inform guideline concordant screening behaviors for breast and CRC, and that there are important underlying socio-demographic and neighborhood-level differences in the relationships that require further study. Interestingly, we observed the strongest overall belief-screening behavior association for those that believe cancer is mostly due to behavior or lifestyle; which was associated with an increased likelihood of screening for breast cancer, but decreased likelihood for CRC. These findings highlight important opportunities for cancer centers to create cancer-specific screening interventions that are responsive to the nuanced needs and influences in a given catchment area.

HINTS cancer belief questions similar to those used in the current study have also linked cancer beliefs to cancer screening behavior for breast (10, 11) and CRC screening (28). For mammography among caregivers – defined as those providing care or making decisions for someone with a disability, or health or behavioral condition – those who would rather not know the likelihood of getting cancer were less likely to be screened compared to those that disagreed (11). In a

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TABLE 2 Multivariable logistic regression for association between cancer beliefs, and other factors, with recommended breast cancer screening among women ≥40 years.

	Odds Ratio[†]	95% Confidence Interval		P-value
Cancer Beliefs (Agree vs. Disagree)				
It seems like everything causes cancer	1.09	1.04	1.15	0.0004
There's not much you can do to lower your chances of getting cancer	0.73	0.70	0.77	<.0001
There are so many different recommendations about preventing cancer, it's hard to know which ones to follow	1.12	1.07	1.18	<.0001
Cancer is most often caused by a person's behavior or lifestyle	1.35	1.29	1.42	<.0001
Age	1.01	1.01	1.01	<.0001
Race-Ethnicity (Reference = Non-Hispanic White)				
Hispanic	0.74	0.69	0.79	<.0001
Non-Hispanic Black	0.51	0.48	0.55	<.0001
Other Race/Ethnicity	1.29	1.16	1.44	<.0001
Married vs Other	1.10	1.05	1.16	0.0002
Annual Household Income (Reference = ≥$75,000)				
$0-$34,999	0.95	0.88	1.03	0.2012
$35,000 - $74,999	1.06	0.99	1.14	0.0971
Insurance (Reference = Medicaid)				
Employer or Union	1.23	1.15	1.31	<.0001
Medicare	1.58	1.47	1.69	<.0001
Other Insurance	1.70	1.43	2.02	<.0001
No Insurance	0.54	0.50	0.60	<.0001
Medical Mistrust	1.23	1.20	1.26	<.0001
General Health Status (Reference = Fair/Poor)				
Excellent/Very Good	1.60	1.52	1.69	<.0001
Good	1.25	1.18	1.32	<.0001
A place usually go for routine or preventive care (Reference = Yes)				
No	0.33	0.30	0.36	<.0001
How often feel like you do not understand your health provider because of your language (reference = Never)[‡]				
Ever	[$]			
History of Cancer (Reference = No)				
Personal history of cancer	1.10	1.04	1.16	0.001
Family (any) history of cancer	[$]			

[†]Odds ratio for the outcome of recommended breast cancer screening: Yes, mammography ≤ 2 years ago vs. Yes, mammography >2 years ago/Never. Model covariates include all items listed in the table except where indicated.
[‡]Ever = Always/Often/Frequently/Sometimes.
[$]The stepwise regression model eliminated this variable.

separate study among Asian Americans, cancer fatalism was found to be a predictor of screening adherence for breast and cervical cancers (10), but non-adherence for CRC (12, 28). A prior analysis using four of the HINTS cancer belief questions used in the current study found that CRC fatalism was higher in Asians and Hispanic respondents vs. Whites (28). However, after adjustment for sociodemographic, health status and access information, and fatalistic CRC beliefs, Asians were more likely to adhere to CRC screening compared to White respondents (OR = 2.04) (28). The opposite pattern of association was found among Hispanic respondents, however, such that they were less likely to adhere to CRC compared to White respondents after adjustment for socio-demographic factors and fatalistic cancer beliefs (OR = 0.90) (28). Taken together, findings from prior studies – and our own – suggests SES and culture (29, 30) may have variable influence on cancer beliefs both across and within (10, 12) racial/ethnic groups, and that these beliefs differently influence cancer screening behavior (10).

TABLE 3 Multivariable logistic regression for association between cancer beliefs, and other factors, with recommended colorectal cancer screening among women and men ≥50 years.

	Odds Ratio[†]	95% Confidence Interval		P-value
Cancer Beliefs (Agree vs. Disagree)				
It seems like everything causes cancer	0.72	0.68	0.75	<.0001
There's not much you can do to lower your chances of getting cancer	0.79	0.76	0.83	<.0001
There are so many different recommendations about preventing cancer, it's hard to know which ones to follow	0.80	0.76	0.84	<.0001
Cancer is most often caused by a person's behavior or lifestyle	0.59	0.56	0.61	<.0001
I'd rather not know my chances of getting cancer	0.85	0.81	0.89	<.0001
When I think of cancer I automatically think of death	1.31	1.25	1.37	<.0001
Age	[‡]			
Gender	[‡]			
Race-Ethnicity (Reference = Non-Hispanic White)				
Hispanic	0.47	0.43	0.50	<.0001
Non-Hispanic Black	0.68	0.63	0.72	<.0001
Other Race/Ethnicity	0.28	0.26	0.31	<.0001
Married vs Other	1.79	1.70	1.88	<.0001
Annual Household Income (Reference = ≥$75,000)				
$0-$34,999	0.60	0.56	0.65	<.0001
$35,000 - $74,999	0.49	0.45	0.53	<.0001
Insurance (Reference = Medicaid)				
Employer or Union	2.57	2.40	2.76	<.0001
Medicare	1.86	1.77	1.95	<.0001
Other Insurance	0.84	0.75	0.93	0.0014
No Insurance	0.44	0.41	0.48	<.0001
Medical Mistrust	1.05	1.02	1.07	<.0001
General Health Status (Reference = Fair/Poor)				
Excellent/Very Good	1.70	1.62	1.79	<.0001
Good	1.42	1.35	1.50	<.0001
A place usually go for routine or preventive care (Reference = Yes)				
No	0.67	0.63	0.72	<.0001
How often feel like you do not understand your health provider because of your language (Reference = Never)[§]				
Ever	0.85	0.81	0.89	<.0001
History of cancer (Reference = No)				
Personal history of cancer	1.40	1.32	1.48	<.0001
Family (any) history of cancer	1.29	1.24	1.35	<.0001

[†]Odds ratio for the outcome of recommended breast cancer screening: Yes, mammography ≤ 2 years ago vs.Yes, mammography >2 years ago/Never. Model covariates include all items listed in the table except where indicated.
[‡]The stepwise regression model eliminated this variable.
[§]Ever = Always/Often/Frequently/Sometimes.

Cancer screening campaigns targeting neighborhoods where these groups reside will need to consider such nuances, as a one-size fits all approach will not address the cancer prevention and control needs of these communities.

The relationship between health beliefs and cancer screening behavior has been examined among racial and ethnic minority groups (12, 28, 29), finding racial and ethnic differences in cancer beliefs (10, 28, 31–33), cancer screening behavior (12, 28, 29), and

TABLE 4 Multivariable logistic regression for association between cancer beliefs with recommended colorectal cancer screening in CH and EH.

Cancer Beliefs	Breast Cancer Screening		Colorectal Cancer Screening	
	Odds Ratio[†]			
	CH[‡]	EH[§]	CH[¶]	EH[††]
It seems like everything causes cancer	0.72	0.71	0.74	N/A
There's not much you can do to lower your chances of getting cancer	1.45	0.77	1.11	0.37
There are so many different recommendations about preventing cancer, it's hard to know which ones to follow	1.22	1.62	0.47	2.25
When I think of cancer I automatically think of death	[‡‡]		1.82	1.90
Cancer is most often caused by a person's behavior or lifestyle	0.68	6.58	0.81	0.42
I'd rather not know my chances of getting cancer	[‡‡]		0.53	0.91

[†]Odds ratio for the outcome of recommended breast cancer screening: Yes, mammography ≤ 2 years ago vs. Yes, mammography >2 years ago/Never. Model covariates include the following: age; race/ethnic (Hispanic, Non-Hispanic Black, and Non-Hispanic White (referent); annual household income ($0-$34,999, $35,000-$74,999, and ≥$75K (referent); insurance (private (employer/union), public (Medicare and Medicaid), and Other (referent); medical mistrust; general health status (Excellent/Very Good, Good, and Fair/Poor (referent)); usual source of routine care (no vs. yes); difficulty understanding health care provider (always/often, frequently/sometimes vs. never); every had cancer (yes vs. no) family history of cancer (any) (yes vs. no); marital status (married, others (referent)).
[‡]Stepwise regression eliminated marital status and difficulty understanding health care provider from this model.
[§]Stepwise regression eliminated difficulty understanding provider because of language from this model Same as Model a with no eliminations in the stepwise regression.
[††]Same as Model a except stepwise regression eliminated marital status. Usual source of routine care was not added to this model as 95% of the analytic sample had access to care.
[‡‡]This belief was excluded due to inconclusive results obtained when simultaneously entered into the model with all beliefs.

variations in the association between beliefs and cancer screening behavior across these groups (10, 11, 28, 34–36). The independent and combined influence of socio-demographic factors, such as race and SES, have also been found to be important predictors of cancer beliefs (31). Prior studies have evaluated factors associated with health seeking behavior and health care utilization (37). However, such studies (36, 37) have not consistently captured other relevant factors that impact screening and health seeking behavior such as, access to health care (e.g., insurance), language barriers, demographic, and SES factors (37). This is meaningful given substantial research documenting differences in beliefs across race and SES, with the former having a stronger influence. In a study assessing four of the HINTS questions used in the current study, Black race was directly associated with negative cancer beliefs independent of and beyond SES as measured by income and educational attainment. Notably, SES only partially mediated the relationship between Black race and negative cancer beliefs (31). In the current study, however, associations between cancer beliefs with breast and CRC screening were independent of both race/ethnicity and SES factors.

Geographical differences in cancer beliefs and perceptions have also been observed. Appalachian states differed significantly from a nationally represented sample based on HINTS data on four of five HINTS cancer beliefs examined in the current study (6). Overall, these findings point to variations in cancer beliefs across, and within segments of the population that will be important to understand to meaningfully encourage and sustain cancer control and prevention efforts. This is particularly true in geographic areas defined by considerable differences in race, ethnicity, and SES, as is the case for the three distinct neighborhoods examined in the current study.

Targeted initiatives can successfully engage and improve outcomes. This was true of the NCI's Colorectal Cancer Outreach and Screening Initiative, which increased both awareness, connection to care, and CRC screening in a national sample of racially, ethnically, and culturally diverse groups (38). In addition, identifying factors relevant across the cultural and socio-politically heterogeneous communities that makeup racial/ethnic subgroups (e.g., Hispanic/Latinx communities) will likely have the greatest impact on improving the cancer prevention and control disparities observed among them (39). These findings highlight the importance of truly targeted outreach. Successful engagement with different communities requires cancer centers to develop sensitive and specific approaches to outreach that take into account the influence of culture, beliefs, and sociodemographic factors on behaviors, including cancer screening. Our analysis of New York City neighborhoods with distinct racial, ethnic, and socioeconomic profiles demonstrates the need for more granularity in community needs assessments to help inform cancer prevention and control.

In the current study, we sought to better understand what drove the differential cancer belief-screening behaviors associations across Central and East Harlem. Specifically, we reexamined the dataset – weighted and unweighted data – to identify potential neighborhood-specific differences that might explain the observed findings. We found no evidence of errors, nor did reexamination help explain the observed differences. Our findings may instead reflect a lack of linearity in beliefs, such that a given belief can be both a motivator and barrier to screening in a particular context, or in this case, neighborhood. Additional research, particularly qualitative studies, are needed to directly assess and unpack the predictors of the likely intersection of cancer beliefs and screening behavior.

Limitations of this study include a low response rate among those recruited *via* U.S. mail and e-mail for those recruited through the electronic medical record, and the inability to assess response rates at the community level. Our ability to model neighborhood effects was limited due to the high correlations of sociodemographic factors and neighborhood. However, this feature of our dataset highlights the importance of capturing key differences of populations within a cancer center's purview. In NYC, a city famous for its multi-cultural populace and close proximity of diverse peoples, identifying

such differences and addressing them may hold the key to advancing equitable cancer care. Further, this was a cross-sectional study and we are unable to ascribe cause and effect of beliefs with screening behaviors (40, 41). Cancer screening rates across the two Harlem neighborhoods evaluated were relatively similar and this lack variability in screening rates may have limited our ability to detect meaningful differences in the cancer beliefs-screening behavior relationship across neighborhoods, particularly for those with lower screening rates. Rates of screening behaviors were based on self-report, which have been described as an accurate measure (40, 42, 43). Strengths include use of validated survey items to access cancer beliefs as well as factors relevant to the community's awareness and needs as it relates to cancer services; these survey instruments also allowed for comparison with prior findings. Additionally, we used statistical methods (i.e., raking and weighting) to expand the representativeness of our data to align with the distributions found in the examined neighborhoods. Finally, this study adds to the understanding of the role of cancer beliefs in screening behavior by considering previously studied socio-demographic factors along with neighborhood dynamics. Our findings are consistent with prior research identifying differences in cancer perceptions and beliefs in rural vs. non-rural communities (6); all of which suggests that cancer belief assessments may be valuable tools for better understanding barriers and facilitators of cancer screening in these communities.

Our findings suggest that targeted initiatives to increase cancer screening need to consider structural impediments (e.g., access to care), as well as community-specific beliefs about cancer that influence behavior. Such initiatives might include using data obtained from the regular assessment of community-level cancer beliefs to inform the development of cancer screening awareness materials and advertisements, as well as campaigns designed to connect the community to cancer screening opportunities. In the next phase of this work, larger studies are needed to expand the evaluation across neighborhoods to understand how this environment and its characteristics – the settings in which communities cultivate their beliefs, behaviors, and health – influence cancer beliefs. Investments towards understanding communities, particularly those at high risk for poor cancer outcomes, through such work will better inform development of equitable approaches to improving screening and other cancer detection and control objectives.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Institutional Review Board of the Icahn School of Medicine at Mount Sinai. The participants provided their written informed consent to participate in this study.

Author contributions

TL: Conceptualization, formal analysis, data curation, and writing – original draft and review and editing. PA: Formal analysis, methodology, data curation, and review and editing. BR: Methodology, review and editing. LJ and NB: Conceptualization, supervision, funding acquisition, and review and editing. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the NCI Cancer Center Support Grant P30 CA196521-01.

Acknowledgments

The authors thank the research coordination team, including Radhi Yagnik, Victoria Berges, Rhaisili Rosario, an outstanding group of interns for their valuable contributions, and the Central Harlem, East Harlem, and Upper East Side participants who made this work possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Antonakos CL, Coulton CJ, Kaestner R, Lauria M, Porter DE, Colabianchi N. Built environment exposures of adults in the moving to opportunity experiment. *Hous Stud* (2020) 35(4):703–19. doi: 10.1080/02673037.2019.1630560

2. Nguyen QC, Acevedo-Garcia D, Schmidt NM, Osypuk TL. The effects of a housing mobility experiment on participants' residential environments. *Hous Policy Debate* (2017) 27(3):419–48. doi: 10.1080/10511482.2016.1245210

3. Defeating The ZIP Code Health Paradigm: Data, Technology, And Collaboration Are Key. Health affairs blog, Washington, D.C. (2015).

4. Artiga SaH E. *Beyond health care: The role of social determinants in promoting health and health equity* (2018). Available at: https://www.kff.org/racial-equity-and-health-policy/issue-brief/beyond-health-care-the-role-of-social-determinants-in-promoting-health-and-health-equity/view/footnotes/.

5. Kamath GR, Renteria AS, Jagannath S, Gallagher EJ, Parekh S, Bickell NA. Where you live can impact your cancer risk: a look at multiple myeloma in new York city. *Ann Epidemiol* (2020) 48:43–50.e4. doi: 10.1016/j.annepidem.2020.05.005

6. Vanderpool RC, Huang B, Deng Y, Bear TM, Chen Q, Johnson MF, et al. Cancer-related beliefs and perceptions in Appalachia: Findings from 3 states. *J Rural Health* (2019) 35(2):176–88. doi: 10.1111/jrh.12359

7. Blake KD, Ciolino HP, Croyle RT. Population health assessment in NCI-designated cancer center catchment areas. *Cancer Epidemiol Biomarkers Prev* (2019) 28(3):428–30. doi: 10.1158/1055-9965.EPI-18-0811

8. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American cancer society. *Jama* (2015) 314(15):1599–614. doi: 10.1001/jama.2015.12783

9. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, et al. Colorectal cancer screening: Recommendations for physicians and patients from the U.S. multi-society task force on colorectal cancer. *Gastroenterology* (2017) 153(1):307–23. doi: 10.1053/j.gastro.2017.05.013

10. Guo XM, Tom L, Leung I, O'Brian C, Zumpf K, Simon M. Associations between fatalistic cancer beliefs and cancer-screening behaviors in Chinese American immigrant women. *J Immigr Minor Health* (2021) 23(4):699–706. doi: 10.1007/s10903-021-01144-4

11. Kim SY, Guo Y, Won C, Lee HY. Factors associated with receipt of mammogram among caregivers: a comparison with non-caregivers. *BMC Womens Health* (2020) 20 (1):216. doi: 10.1186/s12905-020-01079-2

12. Jun J, Nan X. Determinants of cancer screening disparities among Asian americans: A systematic review of public health surveys. *J Cancer Educ* (2018) 33 (4):757–68. doi: 10.1007/s13187-017-1211-x

13. Kamath GR, Taioli E, Egorova N, Llovet JM, Perumalswami PV, Weiss JJ, et al. Liver cancer disparities in new York city: A neighborhood view of risk and harm reduction factors. *Front Oncol* (2018) 8:220. doi: 10.3389/fonc.2018.00220

14. Hashim D, Farhat Z, Wallenstein S, Manczuk M, Holcombe RF, Thorpe L, et al. Standardized cancer incidence disparities in upper Manhattan new York city neighborhoods: the role of race/ethnicity, socioeconomic status, and known risk factors. *Eur J Cancer Prev* (2016) 25(4):349–56. doi: 10.1097/CEJ.0000000000000180

15. New York State Cancer Registry. *Cancer Incidence and Mortality in New York State*. (1976-2018). (New York State) Available at: https://www.health.ny.gov/statistics/cancer/registry/.

16. Hashim D, Manczuk M, Holcombe R, Lucchini R, Boffetta P. Cancer mortality disparities among new York city's upper Manhattan neighborhoods. *Eur J Cancer Prev* (2017) 26(6):453–60. doi: 10.1097/CEJ.0000000000000267

17. *Health information national trends survey 5 (HINTS 5) cycle 1. methodological report*. Rockville, MD: Westat (2017).

18. Blake K. *HINTS 5, Cycle 2 dataset* (Rockville, Maryland: Westat). (2019).

19. Pierannunzi C, Hu SS, Balluz L. A systematic review of publications assessing reliability and validity of the behavioral risk factor surveillance system (BRFSS), 2004-2011. *BMC Med Res Methodol* (2013) 13:49. doi: 10.1186/1471-2288-13-49

20. *National center for health statistics. national health interview survey, 2017. public-use data file and documentation* (2018). Available at: https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm.

21. Thompson HS, Valdimarsdottir HB, Winkel G, Jandorf L, Redd W. The group-based medical mistrust scale: psychometric properties and association with breast cancer screening. *Prev Med* (2004) 38(2):209–18. doi: 10.1016/j.ypmed.2003.09.041

22. *New York city neighborhood health atlas* (2020). Available at: https://public.tableau.com/app/profile/nyc.health/viz/NewYorkCityNeighborhoodHealthAtlas/Home.

23. Bishop YMM, Fienberg SE, Holland PW eds. Maximum likelihood estimates for complete tables. In: *Discrete multivariate analysis theory and practice*, vol. p . New York, NY: Springer New York. p. 57–122.

24. Izrael D, Hoaglin DC, Battaglia MP. *A SAS Macro for balancing a weighted sample* [Indianapolis, Indiana: SAS Conference Proceedings: SAS Users Group International 25 (SUGI 25)]. (2000).

25. Battaglia M, Izrael D, Hoaglin D, Frankel M. Practical considerations in raking survey data. *Survey Practice* (2009) 2(5):1–10. doi: 10.29115/sp-2009-0019

26. Myers C, Olson EC, Ramawamy C, Kerker B. *Breast cancer screening among new York city women: NYC vital signs* (2008). Available at: https://www1.nyc.gov/assets/doh/downloads/pdf/survey/survey-2008mammogram.pdf.

27. Weng O. *Timely colonoscopy screening among new yorkers ages 50 and older. NYC vital signs 2020* (2020). Available at: https://www1.nyc.gov/assets/doh/downloads/pdf/survey/colorectal-cancer-screening-2020.pdf.

28. Jun J, Oh KM. Asian And Hispanic americans' cancer fatalism and colon cancer screening. *Am J Health Behav* (2013) 37(2):145–54. doi: 10.5993/ajhb.37.2.1

29. Cudjoe J, Budhathoki C, Roter D, Gallo JJ, Sharps P, Han HR. Exploring health literacy and the correlates of pap testing among African immigrant women: Findings from the AfroPap study. *J Cancer Educ* (2021) 36(3):441–51. doi: 10.1007/s13187-020-01755-9

30. Tang TS, Solomon LJ, McCracken LM. Cultural barriers to mammography, clinical breast exam, and breast self-exam among Chinese-American women 60 and older. *Prev Med* (2000) 31(5):575–83. doi: 10.1006/pmed.2000.0753

31. Assari S, Khoshpouri P, Chalian H. Combined effects of race and socioeconomic status on cancer beliefs, cognitions, and emotions. *Healthcare (Basel)* (2019) 7(1). doi: 10.3390/healthcare7010017

32. Ramírez AS, Rutten LJ, Oh A, Vengoechea BL, Moser RP, Vanderpool RC, et al. Perceptions of cancer controllability and cancer risk knowledge: the moderating role of race, ethnicity, and acculturation. *J Cancer Educ* (2013) 28(2):254–61. doi: 10.1007/s13187-013-0450-8

33. Bea JW, de Heer H, Kinslow B, Valdez L, Yazzie E, Curley P, et al. Perceptions of cancer causes, prevention, and treatment among Navajo cancer survivors. *J Cancer Educ* (2020) 35(3):493–500. doi: 10.1007/s13187-019-01487-5

34. De Jesus M, Miller EB. Examining breast cancer screening barriers among central American and Mexican immigrant women: Fatalistic beliefs or structural factors? *Health Care Women Int* (2015) 36(5):593–607. doi: 10.1080/07399332.2014.973496

35. Luque JS, Tarasenko YN, Chen C. Correlates of cervical cancer screening adherence among women in the U.S.: Findings from HINTS 2013-2014. *J Prim Prev* (2018) 39(4):329–44. doi: 10.1007/s10935-018-0513-z

36. Emami L, Ghahramanian A, Rahmani A, Mirza Aghazadeh A, Onyeka TC, Nabighadim A. Beliefs, fear and awareness of women about breast cancer: Effects on mammography screening practices. *Nurs Open* (2021) 8(2):890–9. doi: 10.1002/nop2.696

37. Johnson CE, Mues KE, Mayne SL, Kiblawi AN. Cervical cancer screening among immigrants and ethnic minorities: a systematic review using the health belief model. *J Low Genit Tract Dis* (2008) 12(3):232–41. doi: 10.1097/LGT.0b013e31815d8d88

38. Whitaker DE, Snyder FR, San Miguel-Majors SL, Bailey LO, Springfield SA. Screen to save: Results from NCI's colorectal cancer outreach and screening initiative to promote awareness and knowledge of colorectal cancer in Racial/Ethnic and rural populations. *Cancer Epidemiol Biomarkers Prev* (2020) 29(5):910–7. doi: 10.1158/1055-9965.EPI-19-0972

39. Erwin DO, Treviño M, Saad-Harfouche FG, Rodriguez EM, Gage E, Jandorf L. Contextualizing diversity and culture within cancer control interventions for latinas: changing interventions, not cultures. *Soc Sci Med* (2010) 71(4):693–701. doi: 10.1016/j.socscimed.2010.05.005

40. Anderson J, Bourne D, Peterson K, Mackey K. *Evidence brief: Accuracy of self-report for cervical and breast cancer screening. VA evidence-based synthesis program reports*. Washington (DC: Department of Veterans Affairs (US (2019).

41. Baier M, Calonge N, Cutter G, McClatchey M, Schoentgen S, Hines S, et al. Validity of self-reported colorectal cancer screening behavior. *Cancer Epidemiol Biomarkers Prev* (2000) 9(2):229–32.

42. White A, Vernon SW, Eberth JM, Tiro JA, Coan SP, Abotchie PN, et al. Correlates of self-reported colorectal cancer screening accuracy in a multi-specialty medical group practice. *Open J Epidemiol* (2013) 3(1):20–4. doi: 10.4236/ojepi.2013.31004

43. Walker MJ, Chiarelli AM, Mirea L, Glendon G, Ritvo P, Andrulis IL, et al. Accuracy of self-reported screening mammography use: Examining recall among female relatives from the Ontario site of the breast cancer family registry. *ISRN Oncol* (2013) 2013:810573. doi: 10.1155/2013/810573

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 03 February 2023
DOI 10.3389/fonc.2023.1056609

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cancer Epidemiology and Prevention, a section of the journal Frontiers in Oncology

RECEIVED 05 October 2022
ACCEPTED 10 January 2023
PUBLISHED 03 February 2023

CITATION
Olorunfemi G, Libhaber E, Ezechi OC and Musenge E (2023) Population-based temporal trends and ethnic disparity in breast cancer mortality in South Africa (1999-2018): Joinpoint and age–period–cohort regression analyses.
Front. Oncol. 13:1056609.
doi: 10.3389/fonc.2023.1056609

Population-based temporal trends and ethnic disparity in breast cancer mortality in South Africa (1999-2018): Joinpoint and age–period–cohort regression analyses

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Globally, breast cancer is the leading cause of cancer deaths, accounting for 15.5% of female cancer deaths in 2020. Breast cancer is also the leading cause of female cancers in South Africa. The rapid epidemiological transition in South Africa may have an impact on the trends in breast cancer mortality in the country. We therefore evaluated the trends in the breast cancer mortality in SA over 20 years (1999–2020).

Methods: Joinpoint regression analyses of the trends in crude and age-standardized mortality rates (ASMR) of breast cancer among South African women were conducted from 1999 to 2018 using mortality data from Statistics South Africa. Age–period–cohort regression analysis was then conducted to evaluate the independent effect of age, period, and cohort on breast cancer mortality, and analysis was stratified by ethnicity.

Results: The mortality rate of breast cancer (from 9.82 to 13.27 per 100,000 women) increased at around 1.4% per annum (Average Annual Percent Change (AAPC): 1.4%, 95% CI:0.8–2.0, P-value< 0.001). Young women aged 30–49 years (1.1%–1.8%, P-value< 0.001) had increased breast cancer mortality. The risk of breast cancer mortality increased among successive birth cohorts from 1924 to 1928 but decreased among recent cohorts born from 1989 to 1993. In 2018, the breast cancer mortality rate among Blacks (9.49/100,000 women) was around half of the rates among the non-Blacks. (Coloreds: 18.11 per 100,000 women; Whites: 17.77/100,000 women; Indian/Asian: 13.24 per 100,000 women).

Conclusions: Contrary to the trends in high- and middle-income countries, breast cancer mortality increased in South Africa especially among young women. Breast cancer prevention programs should be intensified and should also target young women. The marked disparity in ethnic burden of breast cancer should be considered during planning and implementation of interventions.

KEYWORDS

APC analysis, age period cohort analysis, breast cancer mortality rate, ethnic disparity of cancer, female cancer trends, gynecological cancer trends, join point regression, South Africa

Introduction

Globally, breast cancer is the leading cause of cancer deaths, accounting for 15.5% of female cancer deaths in 2020 (1). In high-income countries (HIC), the age-standardized incidence rates of breast cancer are very high as compared with the rates in low- and middle-income countries (LMICs) (1). Nonetheless, the 5-year survival rate of breast cancer exceeds 90% in HICs but is much lower in LMICs (30%–60%) (1). The noted disparity is related to variation in the prevalence of etiological factors, cancer screening facilities, stage at presentation, and access to treatment (1, 2). In South Africa, breast cancer had the second highest national ASMR of 16.0 per 100,000 women after cervical cancer (1).

The etiology of breast cancer is a complex interaction between hormonal, reproductive, and environmental factors (1, 3, 4). Additionally, smoking, prolonged use of oral contraceptive pills, and ethnicity have been associated with breast cancer burden (1, 3–5). Furthermore, genetic predisposition, positive family history, chronic exposure to estrogen such as delayed age at first pregnancy, early menarche, low parity, and short-term breastfeeding practices have been implicated in the evolution of breast cancer (1, 3–6).

South Africa is a middle-income multiethnic country (7, 8). Since the commencement of multiethnic democracy in 1994, the successive South African government promoted policies aimed at reducing socioeconomic inequality and increased access to sexual and reproductive health (SRH) services among the various ethnic groups (9, 10). Hence, current evidence of ethnic disparity in the trends and burden of breast cancer in South Africa can be useful in developing targeted interventions (11). The current epidemiological and health transition in South Africa has led to increased prevalence of obesity, westernization of diet, sedentary lifestyle, and changes in reproductive behavior (such as reduced parity and increased use of COCPs) (12). South Africa has one of the highest prevalences of human immunodeficiency virus (HIV) globally. Although HIV is not implicated in the evolution of breast cancer, studies reported worse survival among HIV-positive women (2).

Cancer surveillance and trend analyses are useful for providing evidence to aid immediate and long-term cancer control efforts (7, 13–16). A useful statistical tool for objectively evaluating cancer trends to inform policy is joinpoint regression modeling. Joinpoint regression modeling can assist to quantify statistically significant segmental and overall trends. Age–period–cohort (A–P–C) modeling is another very useful trend analytic tool for disentangling the impact of age, period, and birth cohorts on cancer trends. It is believed that age ("age effect") can have a biological impact on the risks of many diseases. Thus, evaluating age-specific risks of cancers is important. Furthermore, "period effect" is the impact of public health interventions or population-level policies that can affect the overall risk of diseases among all age groups over a period of time. Some public health initiatives in South Africa such as expansion and easy access to oncological services, commencement of large-scale rollout of free anti-retroviral treatment (ART) in 2004, the implementation of the World Health Organization Framework Convention on Tobacco control from 2005, and the initiation of national breast cancer control policies can cause a "period effect" in the temporal trends in breast cancer mortality in South Africa. A group of people who were born around the same time tend to have a similar exposure to common biological, social, and economic events and may also have a similar reproductive behavior. Such "cohort effect" may lead to unique or cohort-specific risks of a disease. However, majority of national studies on the mortality trends of breast cancer in South Africa and other Sub-Saharan African (SSA) countries did not utilize the joinpoint and A–P–C modeling techniques (11). South Africa is one of the only three countries in Sub-Saharan Africa with a comprehensive civil registration and vital statistics system (CRVS) that can be utilized for research to improve the health needs of the people (17). We therefore aimed to evaluate the trends in breast cancer mortality in South Africa and stratified by ethnicity over a 20-year period (1999–2018) by utilizing both joinpoint and A–P–C regression modeling techniques.

Materials and methods

This study is a temporal trend analysis of breast cancer deaths in South Africa from 1999 to 2018. South Africa is a multiracial middle-income country with an estimated population of 57.79 million in 2018, and around 51% were women (8). In 2018, the proportion of women by population group was as follows: Blacks (Black Africans) (80.4%), Coloreds (mixed ancestry) (8.9%), Whites (European descent) (8.3%), and Indians/Asians (2.4%) (18).

Data source

Data on breast cancer mortality were obtained from the vital statistics records as collected and published by Statistics South Africa (Stats SA). By law, it is mandatory for all deaths in South Africa to be reported to the Department of Home Affairs (DHA) (18). Causes of death were coded by experienced staff of Stats SA using the International Classification of Diseases, Tenth Revision (ICD-10) (19). The code for the underlying cause of death for female breast was ICD10, C50 (11, 20, 21).

The population denominators for calculating the mortality rates were the mid-year population estimates of women (≥15 years) stratified by ethnicity and 5-year age group, as obtained from published data of Stats SA from 2002 to 2018. The annual mid-year population estimates for 1999–2001 were obtained by assuming the constant inter-census rate and increment between two South African population census of 1996 and 2001.

Data quality

The vital registration methodology and records of South Africa have been internationally adjudged to be comprehensive (17). Joubert et al. found that civil registration of South Africa is satisfactory in terms of coverage, completeness of death registration, temporal consistency, age/sex classification, timeliness, and subnational availability (20). The Stats SA data are at present the only source of nationally representative cancer mortality records in South Africa.

Ethical considerations

Ethical approval for the conduct of this study was obtained from the Human Research and Ethics Committee (Medical) of the University of the Witwatersrand (clearance certificate number: M190544). Anonymized data with no risk of re-anonymization were utilized.

Statistical analysis

Data were imported into Stata version 16 (StataCorp, USA) statistical software for statistical analysis. Data validation and data cleaning were done. Descriptive statistics such as frequency and mean (± standard deviation) were analyzed. The annual proportion of breast cancer in relation to all women and gynecological cancer mortality was calculated.

Annual crude and age-standardized rates

The annual crude mortality rate (CMR) was calculated by dividing the annual breast cancer mortality among women aged ≥15 years by the mid-year female population (≥15years). The calculation was stratified by ethnicity (Whites, Coloreds, Blacks, and Asian/Indians) from 1999 to 2018.

Age-specific mortality rate was also calculated by dividing the cumulative age-stratified mortality of each 5-year age group (15–19, 20–24, 25–29…….75+) by cumulative age-stratified mid-year population of each age category. The annual age-standardized mortality rates (ASMR) were calculated using the direct method of standardization, and the Segi world standard population was the weighted population.

$$\text{Thus, the age-standardized rates} = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i} \times 100,000$$

where a_i is the age-specific rate of the i th 5-year age group and w_i is the corresponding number of persons (or the weight) in the same 5-year age group i of the Segi world standard population.

The standardized rates were stratified by ethnicity. All rates were expressed per 100,000 women.

Joinpoint regression modeling

A joinpoint regression analysis of the trends in the overall cancer mortality of breast cancer (stratified by ethnicity and age groups) was performed with the Joinpoint Regression software, version 4.9.0.1 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD). The Joinpoint Regression software fit a Poisson regression in which ln (rate) is the outcome and the year of occurrence is the explanatory variable. Log-linear modeling with four maximum joinpoints and 4,499 Monte Carlo permutation tests were conducted for each of the trends in ASMR.

The equation of the joinpoint trend is: (22–24)

$$\ln(Rate) = \beta \times (Calendar\ \ year) + C \qquad \text{(i)}$$

where β = coefficient of the calendar year, ln = natural logarithm, and C = constant (or intercept)

The annual percent change (APC) of the cancer rates between a previous calendar year "X" and the next calendar year "X+1" is

$$= (\text{Rate}_{(x+1)} - \text{Rate}_{(x)}/\text{Rate}_{(x)}) * 100 \qquad \text{(ii)}$$

From Eq. (i),

$$\text{Rate}_{(x+1)} = e^{\beta(\times+1)+c} \text{and Rate}_{(X)} = e^{\beta(\times)+c}$$

$$\text{Hence, APC} = ((e^{\beta(\times+1)+c} - e^{\beta(\times)+c})/e^{\beta(\times)+c}) \times 100$$

$$= (e^{\beta} - 1) \times 100$$

where e = 2.7

The APC is equivalent to the Average Annual Percent Change (AAPC) if there are no joinpoints. However, when there are joinpoints, the segmental APC (with 95% confidence interval, CI) was calculated and the AAPC was iteratively calculated as a weighted average of all the segmental APCs. Conventionally, a positive or negative AAPC (or APC) with P-value<0.05 was taken as a statistically significant increased or decreased trend. If the P-value of the AAPC was >0.05, the trend is taken as a non-significant increased or decreased trend. If the AAPC is between -0.5 and + 0.5 with P-value >0.05, the trend is reported as stable.

Age period cohort modeling of breast cancers

A–P–C modeling has been used by social scientists, demographers, and epidemiologists to assist in understanding the impacts of age, period, and birth cohort on the trends in prevalence of social, demographic, or disease outcome or rates. This modeling technique assists to disentangle the effect of chronological age (age effect), from "period effect" (impact of improvement in public health interventions, screening, diagnostic tools, and treatment modalities over time) and "cohort effect" (influence of socio-behavioral and reproductive characteristics and environmental impact on the health outcomes of a cohort of people that were born at the same time) (25–29).

Arithmetically, the relationship between age, period, and birth cohort is given as

Age = period (year of event) – cohort (year of birth). (or birth cohort = period – age) …(iii)

However, the A–P–C model assumes a Poisson distribution of the mortality rates (dependent variable) with age, period, and birth cohort as the covariates/independent variables.

The general equation of the A–P–C model is expressed as

$$Y = \alpha_0 + \alpha X_1 + \beta X_2 + \gamma X_3 + \epsilon\,. \quad \text{(iv)}$$

where Y is the breast cancer mortality; X_1, X_2, and X_3 are the age period and birth cohort with their corresponding effect estimates of α, β, and γ, respectively; α_0 is the intercept; and ε is the residual.

Indeed, the natural logarithm of the mortality rates in Eq. (iv) becomes a linear or additive function of age, period, and birth cohort as expressed thus:

$$\ln[E\ (M_{ij})] = \ln(D_{ij}/P_{ij}) = \mu + \alpha_i + \beta_i + \gamma_k \quad \text{(v)}$$

where

$E[Mij]$ represents the expected mortality rate at 5-year age group i (15–19, 20–24, 25–29….75+ years) and period j (1999–2003, 2004–2008, 2009–2013, 2014–2018); D_{ij} and P_{ij} are the number of deaths and corresponding population size in the i age group and the j period, respectively.α_i represents the age effect in the age group I; β_j denotes the period effect during a j period, γ_k corresponds to the cohort effect among the k_{th} ($k = i+j-1$) birth cohort, and μ is the intercept.

Identifiability problem

The above arithmetic equation (iii) of the relationship between age, period, and cohort shows a perfectly linear relationship or linear dependency with inherent problem of collinearity when all of age, period, and birth cohort are added as covariates during the Poisson regression modeling of mortality rates. Therefore, reliable unique estimates for each of age, period, or cohort will ordinarily be difficult to obtain from the regression model because the covariate matrix will not be full-rank. This phenomenon is known as "identification" problem. Multiple methods have been proposed to circumvent the identification problems, but each has its merits and demerits (25). The methods proposed for "overcoming" the "identification" problems broadly entails the application of constraints on one of period, cohort, or both, and utility of estimable function techniques (25). Holford proposed and validated the estimable function algorithm by proving that if age, period, and cohort trends are orthogonally decomposed into linear and non-linear parts, many useful functions and estimates will be produced. To address the identification problems, we utilized the age–period–cohort webtool (Biostatistics Branch, National Cancer Institute, Bethesda, MD, USA). (Age Period Cohort Analysis Tool (cancer.gov) with accompanying R Studio codes (https://github.com/CBIIT/nci-webtools-dceg-age-period-cohort) as developed by Rosenberg et al. to produce estimable parameters of the A–P–C of the trends in breast cancer mortality. The webtool utilized the weighted least squares estimator (26).

Before the A–P–C analysis, data of breast cancer mortality were further prepared. Age was categorized into 5-year age groups from 15 to 75 years (15–19, 20–24, 25–29, 30–34 years, 35–39, 40–45,……75 years and above), and the year of mortality (calendar period) was also categorized into 5-year categories from 1999 to 2018 (1999–2003, 2004–2008, 2009–2013, 2014–2018). A Lexis matrix was then formed with age category of the mortality data as columns and the corresponding period as rows (the diagonal represents the corresponding birth cohort). The corresponding population at risk was also calculated for each age group and period. The above A–P–C data preparation was done for each of breast cancers and then stratified by ethnic groups (Blacks, Whites, Coloreds, and Indian/Asian). These data were then imputed in turn into the A–P–C webtool (26).

Several estimates are obtainable from the A–P–C regression modeling webtool (26). However, we reported the following: (1) net drift, which is equivalent to the overall log-linear trends after adjusting for period and cohort effect—net drift is also equivalent to the AAPC of the mortality trend; (2) local drift, which is equivalent to the APC of mortality trends in each age group; (3) longitudinal age-specific rates (longitudinal age-specific rates in the reference cohort, adjusted for period deviations, i.e., age trend + period trend); (4) cross-sectional age-specific rates (age trend – period trend); (5) cohort effect rate ratio; and (6) period effect rate ratio. The default (middle value) references for the period and cohort estimates were 2004–2008 and 1959–1963, respectively. Wald's test of statistical significance, including the 95% CI of all the estimates, was also reported. Conventionally, the dominant patterns of the trends in the estimable parameters are descriptively reported. Afterward, the pattern is confirmed or further described based on the P-value and 95% CI of the estimates. A two-tailed test of significance was assumed, and P-value< 0.05 was taken as a statistically significant level. Analysis was conducted in both Stata (StataCorp, TX, USA) version 16 and R version 3.6.3 (R Foundation, Vienna, Austria).

Results

During the 20-year period from 1999 to 2018, 4,386,517 deaths were reported among South African women who were 15 years and older. Of these female mortalities, around 8.24% (95% CI: 8.21%–8.26%, n = 361,449) were cancer-related mortalities. Deaths due to breast and gynecological cancers constituted around 37.39% (95% CI: 36.83%–38.13%, n = 134,778) of the cancer mortalities among women in the country. Breast cancer (n = 58,628, 41.27%, 95% CI: 41.01%–

41.54%) was responsible for around 41.27% of breast and gynecological deaths. The proportion of breast and gynecological cancer deaths due to breast cancer appears to be stable during the study period (Table 1).

Trends in breast cancer mortality in South Africa, 1999–2018

Mortality from breast cancer increased from 1,848 in 1999 to 3,790 in 2018 (Figure 1A; Table 1).

The ASMR of breast cancer was second highest behind cervical cancer (Figure 2), and it increased from 9.8 deaths per 100,000 women in 1999 to 13.3 deaths per 100,000 women in 2018 at an average increase of 1.4% per annum (AAPC: 1.4%, 95% CI:0.8–2.0, P-value< 0.001) (Table 1; Figure 1).

Joinpoint regression analysis of breast ASMR showed two trends: the first was a steep rise in ASMR at around 5.9% per annum from 1999 to 2004 (APC: 5.9%, P-value<0.001) and then a slow increase at 0.5% per annum from 2004 to 2018 (APC: 0.5%, P-value< 0.001) (Figure 3; Table 2).

Ethnic trends of breast cancer mortality

Blacks followed by Whites had the highest annual number of breast cancer deaths throughout the study (Figure 1A; Supplementary Table 1). In 2018, the Colored ethnic group (18.11 per 100,000 women) had the highest breast cancer ASMR followed closely by the Whites (17.77/100,000 women) and Indian/Asians (13.24 per 100,000 women). The breast cancer ASMR among Blacks (9.49/100,000 women) was around half the rates among Coloreds or Whites in 2018 (Figure 1B; Supplementary Table 1). All the ethnic groups had varying increases in ASMR with Blacks (AAPC: 3.3%, P-value< 0.001) and Coloreds (AAPC: 2.7%, P-value< 0.001) having the highest increase, whereas Indian/Asians (AAPC: 1.3%, P-value< 0.001) and Whites (AAPC: 0.7%, P-value<0.001) had relatively lower increased rates. The joinpoint regression further showed that Blacks (APC: 5.0% vs. 3.0%) and Indian/Asians (APC: 24.3% vs. 0.6%) tended to have a reduction in the APC of breast ASMR between 2005 and 2018 as compared with the APC of the previous period (1999–2005), whereas Coloreds (APC: -3.5% vs. 3.4%) and Whites (APC: -1.9% vs. 1.1%) had higher annual rates of increase in the later periods of 2005–2018 (Figures 1C, 4A–D; Table 2).

TABLE 1 Trends in the mortality rates and mean age at death of breast cancer in South Africa (1999–2018).

Year	Breast (n = 55,628)			
	Mortality (% of gyne and breast) ≥15 years	Age (mean ± SD)	CMR (per 100,000 women)	ASMR (per 100,000 women)
1999	1,848 (40.03)	59.43 ± 15.55	12.02	9.82
2000	1,897 (39.89)	59.08 ± 16.22	12.02	9.81
2001	2,131 (41.59)	59.61 ± 15.53	13.16	10.89
2002	2,062 (39.63)	59.83 ± 15.25	12.56	10.41
2003	2,113 (39.41)	59.66 ± 15.78	12.43	10.14
2004	2,501 (42.56)	58.99 ± 15.38	15.07	13.64
2005	2,551 (42.26)	59.46 ± 15.41	15.7	12.89
2006	2,474 (40.68)	58.77 ± 15.43	15.02	12.26
2007	2,707 (43.67)	59.93 ± 15.44	16.21	13.14
2008	2,664 (42.61)	59.78 ± 15.44	15.23	12.58
2009	2,729 (40.74)	59.56 ± 15.48	15.37	12.59
2010	2,923 (43.14)	59.55 ± 15.21	16.27	13.46
2011	2,997 (42.24)	60.33 ± 15.24	16.44	13.16
2012	3,026 (42.12)	60.16 ± 15.23	16.4	13.13
2013	3,168 (41.95)	60.22 ± 15.34	16.28	12.58
2014	3,344 (40.83)	60.28 ± 15.55	17.04	12.74
2015	3,424 (40.63)	60.26 ± 15.47	17.27	13.25
2016	3,669 (41.22)	60.41 ± 15.35	18.15	13.98
2017	3,610 (39.73)	60.18 ± 15.69	17.56	13.29
2018	3,790 (40.48)	59.98 ± 15.67	18.02	13.27

CMR, crude mortality rate; ASMR, age-standardized mortality rate.

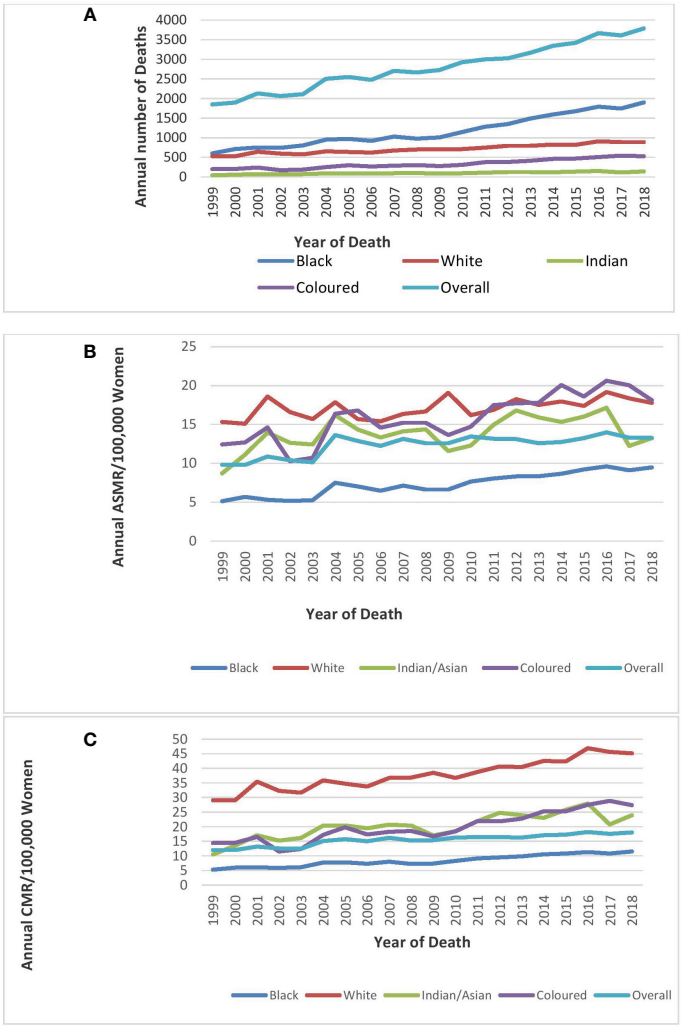

FIGURE 1
Trends in national and ethnic annual deaths **(A)**, age-standardized rates **(B)**, and crude mortality rates **(C)**of breast cancer in South Africa (1999–2018).

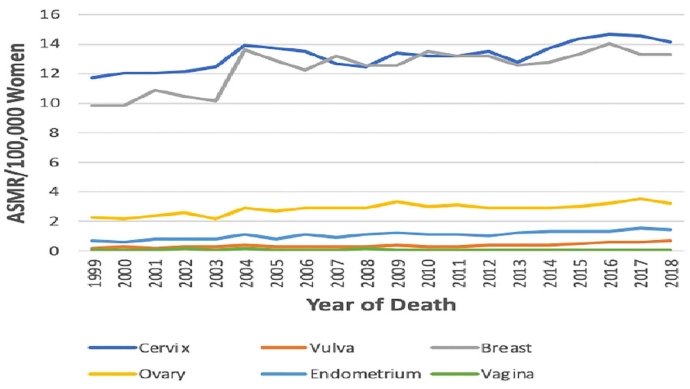

FIGURE 2
Trends in age-standardized mortality rates of breast and Gynaecological cancers in South Africa from 1999 to 2018.

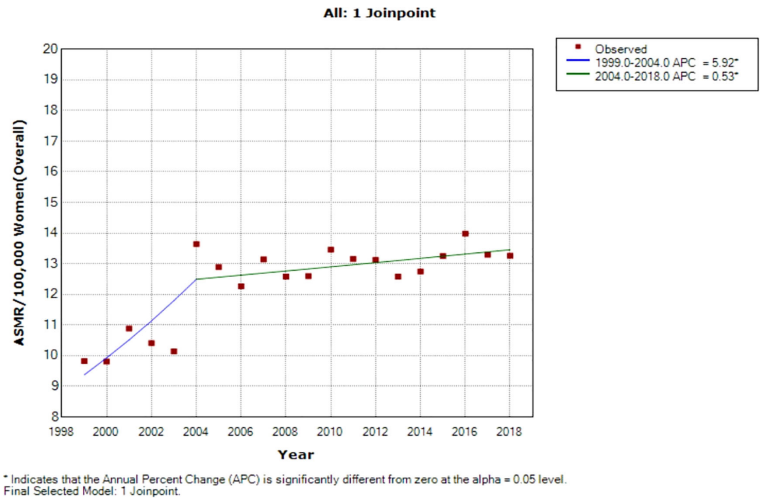

FIGURE 3
Joinpoint regression of national trends in age-standardized mortality rates of breast cancer in South Africa (1999–2018).

TABLE 2 Joinpoint regression estimates of the trends in National and Ethnic age-standardized mortality rates of breast cancers in South Africa (1999–2018).

Cancer type	Trends	Year period		APC	95% CI		P-value	Comment
Breast								
Overall ASMR								
	1	1999–2004		5.9*	3.3	8.6	<0.001	Significant increase
	2	2004–2018		0.5*	0.1	1.0	<0.001	Significant increase
	Full range	1999–2018		1.4*	0.8	2.0	<0.001	Significant increase
Blacks								
	1	1999–2004		5.0*	0.9	9.3	<0.001	Significant increase
	2	2004–2018		3.0*	2.3	3.7	<0.001	Significant increase
	Full range	1999–2018		3.3*	2.7	4.0	<0.001	Significant increase
Indian/Asian								
	1	1999	2001	24.3	-20.0	92.9	0.3	Non-significant increase
	2	2001	2018	0.6	-0.6	1.9	0.3	Non-significant increase
	Full range	1999	2018	1.3*	0.2	2.5	< 0.001	Significant increase
Colored								
	1	1999	2002	-5.0	-18.1	10.0	0.4	Non-significant decrease
	2	2002	2005	12.9	-16.4	52.5	0.4	Non-significant increase
	3	2005	2008	-3.5	-27.1	27.7	0.8	Non-significant decrease
	4	2008	2018	3.4*	1.3	5.6	< 0.001	Significant increase
	Full range	1999	2018	2.7*	1.7	3.6	< 0.001	Significant increase
White								
	1	1999	2001	8.6	-9.3	30.1	0.3	Non-significant increase
	2	2001	2005	-1.9	-9.9	6.8	0.6	Non-significant decrease
	3	2005	2018	1.1*	0.2	2.0	< 0.001	significant increase
	Full range	1999	2018	0.7*	0.2	1.2	< 0.001	Significant increase

*Statistically significant p-value < 0.05.

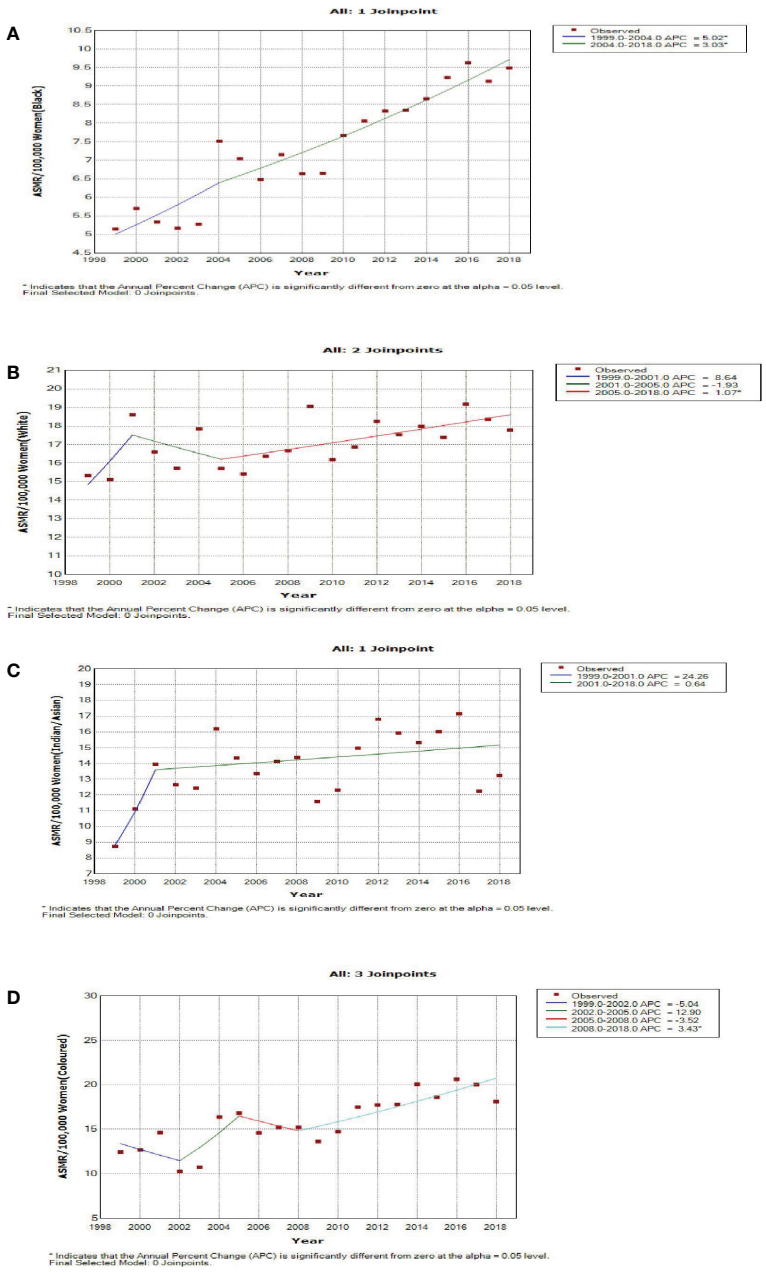

FIGURE 4
Joinpoint regression trends in age-standardized mortality rates of breast cancer in South Africa (1999–2018) for Black **(A)**, White **(B)**, Indian/Asian **(C)**, and Colored **(D)** ethnic groups.

Trends in mean age- and age-specific rates of breast cancer

In 2018, the mean age at death from breast cancer in South Africa was 59.98 ± 15.67 years and had been between 59 and 60 years during the study period (1999–2018) (Table 2). In 2018, the youngest mean age at death from breast cancer occurred among the Blacks (56.00 ± 15.36 years) whereas the average age at death among the Whites occurred around 11 years later (67.40 ± 15.28). Indian/Asians (63.94 ± 14.21 years) and Coloreds (60.63 ± 13.51 years) had a slightly lower mean age at death as compared with the Whites. The mean age at death from breast cancer slightly increased among all the ethnic groups (Whites: from 65 to 67 years; Indian/Asians: from 60 to 63 years; Coloreds: from 57 to 60 years; Blacks: from 55 to 56 years) over the study period (Supplementary Table 1).

Age-specific death rates

In 2018, the age-specific death rates of breast cancer increased with increasing age. Breast cancer mortality rates were lower than cervical cancer rates from 15 years till 60–64 years and then became the highest afterward to reach a peak at 75 years and above (Figure 5A; Supplementary Table 2).

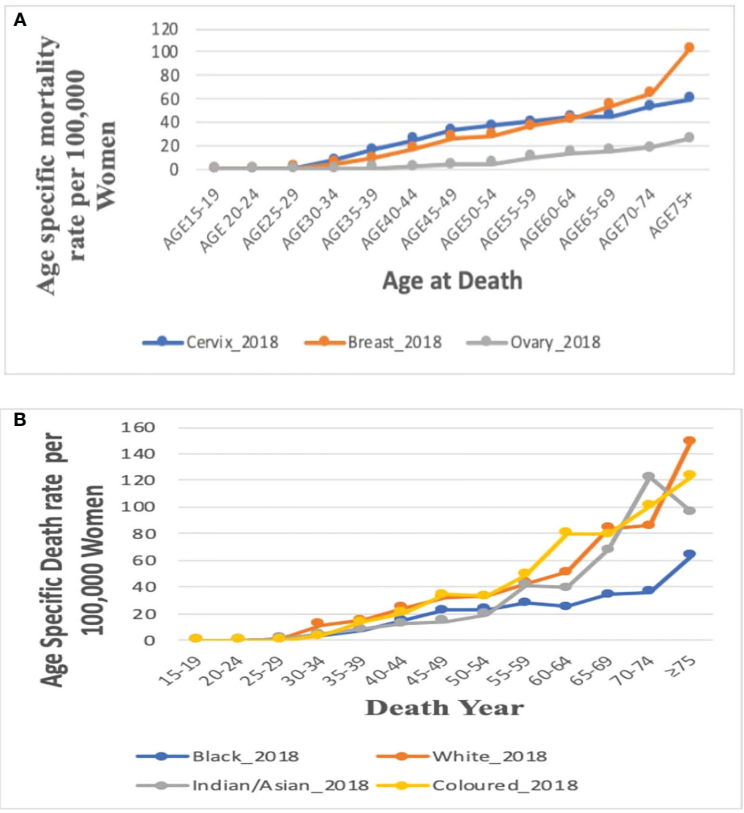

FIGURE 5
(A) Comparison of the overall age-specific death rates in 2018 in South Africa from breast, cervix, and ovaries. Figure 5 **(B)**. Age-specific death rate by ethnicity for breast cancer in 2018.

Age-specific death rate of breast cancer by ethnicity, 2018

In 2018, mortality rates of breast cancer increased with increasing age among all the four ethnic groups. Of the four ethnic groups, mortality was reported only among young Black women aged 15–24 years but the Black women had the lowest mortality rate from age 50 to 54 years. The Whites, Coloreds, and Indian/Asians had breast cancer mortality from 25 to 29 years, whereas Whites and Coloreds had the highest age-specific rates throughout all the age groups. The Indian/Asians had the lowest mortality rates till age 50–54 years, after which the rates increased and was close to the rates among Whites and Coloreds (Figure 5B; Supplementary Table 2).

Joinpoint trends in the overall age-specific mortality rates of breast cancer, 1999–2018

Young women aged 15–24 years had non-statistically significant breast cancer trends. Except for women aged 25–29 and 50–54 years who had stable trends (APC: 0.5%, P-value > 0.05), other women aged 30 years and older generally had an increased annual mortality rate of breast cancer (AAPC range: 0.5% to 2.0%, P-value< 0.05) from 1999 to 2018 (Figures 6, 7; Supplementary Table 3).

Women aged 45–49 years had a rapid increase in mortality rates (APC: 4.9%, P-value< 0.001) between 2004 and 2018, whereas women aged 70 years and older had stable trends during a similar period (Supplementary Table 3; Figures 7–9).

Joinpoint trends in the ethnic age-specific mortality rates of breast cancer, 1999–2018

Joinpoint regression modeling of the age-specific death rates of breast cancer revealed that Black teenagers (aged 15–19 yeas; AAPC: 0.6, P-value = 0.8) and young women aged 20–24 years (AAPC: -2.1, P-value = 0.3) respectively had nearly stable trends and a non-significant decline in breast cancer mortality rates from 1999 to 2018. All Black women aged 25 years and older had increased breast cancer death rates (AAPC range: 1.6% to 4.2%, P-value< 0.001) (Supplementary Figure 1; Supplementary Table 3).

There were few data points among young Whites, Indian/Asians, and Coloreds below 24 years. Thus, the conclusion from the joinpoint regression among these age groups was not reliable. From 1999 to 2018, there was a non-significant decline in breast cancer mortality rates among young Indian/Asians aged 25–34 years (AAPC -1.9 to -1.1, P-value >0.05) whereas there was a non-statistically significant rise in mortality rates among women aged 35–44 years (AAPC: 0.6 to 3.5, P-value > 0.05), 50–54 years (AAPC: 1.5, P-value = 0.3), 60 years and older (AAPC range: 1.0 to 2.0, P-value > 0.05), Indian/Asian aged 45–49 years (AAPC: -0.1, P-value = 1.0) (Supplementary Figure 2; Supplementary Table 3).

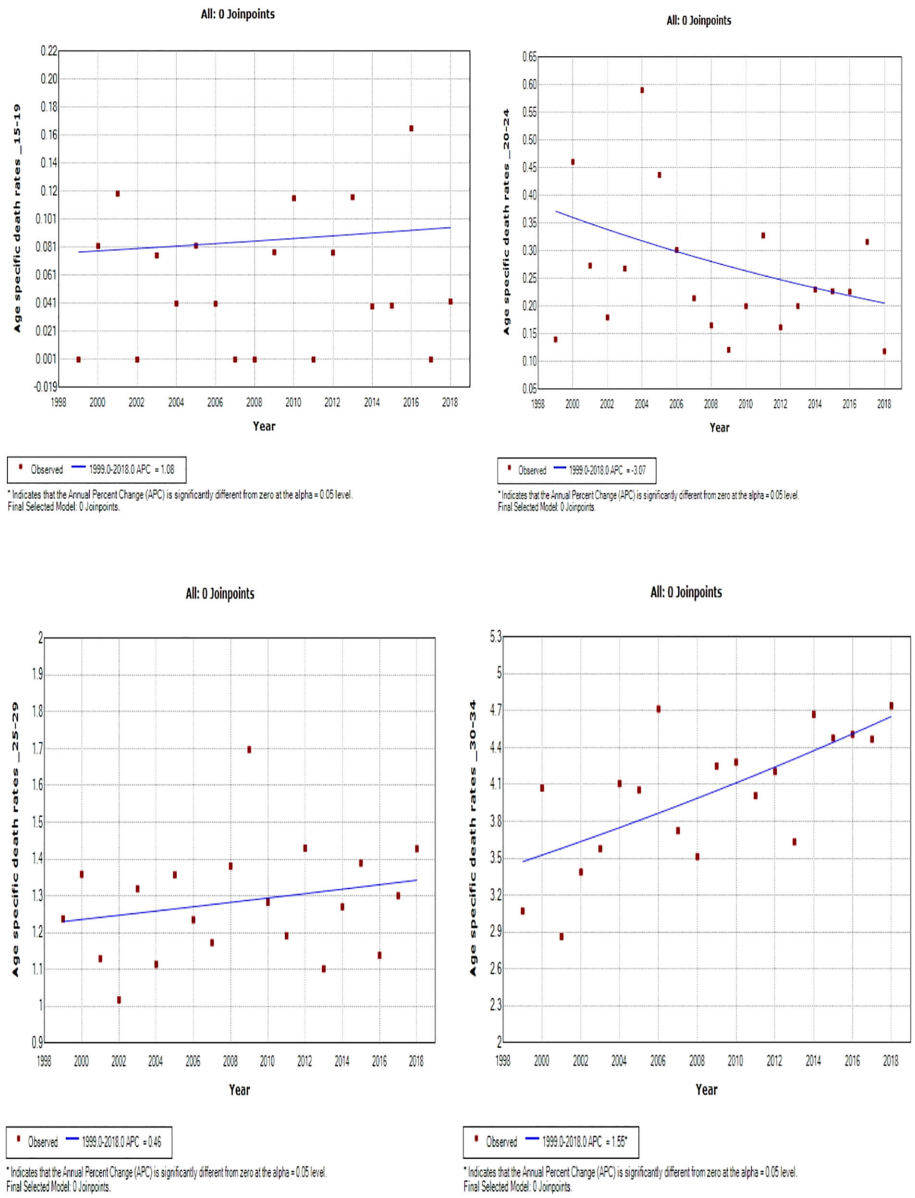

FIGURE 6
Joinpoint trends of age-specific death rates of breast cancer in South Africa. 1999–2018, among 19–34-year-old (5-year group).

From 1999 to 2018, Colored women aged 25–44 years and 50–54 years (AAPC: 1.3 to 1.9, P-value >0.05) had non-statistically significant increased rates whereas women aged 45–49 and 55 years and older (APC range: 2.2 to 6.6, P-value< 0.001) had statistically significant increased mortality rates (Supplementary Figure 3; Supplementary Table 3). From 1999 to 2018, White women aged 30–44 years and those who were 75 years and older (APC range: 0.9%–5.6%, P-value< 0.001) had statistically significant increased mortality rates whereas Whites aged 50–69 years (AAPC: -0.3% to 0.6%, P-value >0.05) had approximately stable rates. However, Whites aged 45–49 (AAPC: 1.0%, P-value = 0.1) and 70–74 years (AAPC: 0.8%, P-value = 0.1) had non-significant increased rates. Young White women aged 25–29 years (AAPC: -2.1%, P-value = 0.3) and older women aged 50–54 (AAPC: -1.7%, P-value<0.001) respectively had a non-statistically significant decline (Supplementary Figure 4; Supplementary Table 3).

Age period cohort analysis of overall and ethnic trends in breast cancer mortality

Local and net drift

After correcting for cohort and period effects, the overall net drift (similar to AAPC) of breast cancer mortality trends over the study period (1999–2018) was around 1.47% per annum (95% CI: 0.91%–2.04%). (Figure 10A; Supplementary Table 4). There was a positive net drift among all the ethnic groups with Blacks (4.55%, 95% CI: 3.94% to 5.16%) having the highest drift followed by the Coloreds (2.46%, 95% CI: 1.30% to 3.62%), Whites (0.83%, 95% CI: -1.13 to 2.82), and Indian/Asian (0.53%, 95% CI: -1.79 to 2.91) (Supplementary Table 5; Figure 10A). The net drifts of the trends in breast cancer mortality for the overall (P-value< 0.001), Blacks (P-value< 0.001), and Coloreds (P-value< 0.001) were statistically significant, whereas the net drifts for Whites (P-value = 0.41) and

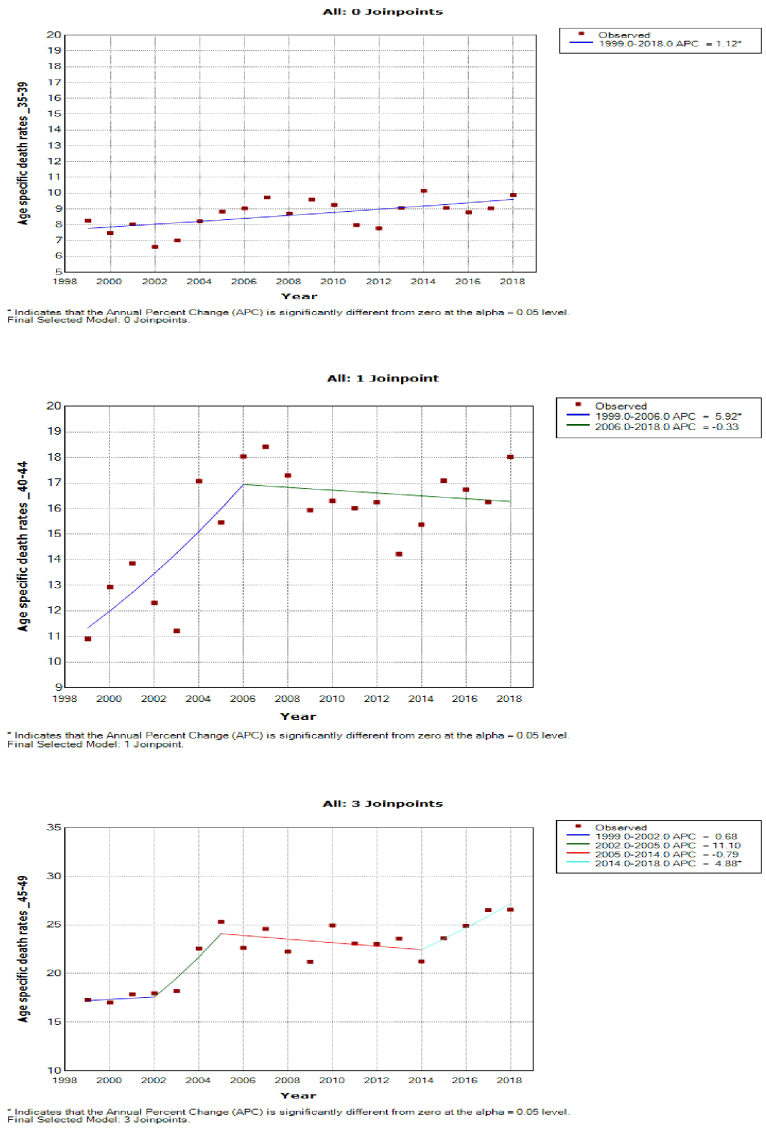

FIGURE 7
Joinpoint trends of age-specific death rates of breast cancer in South Africa, 1999–2018, among 35–49-year-olds (5-year group).

Indian/Asians (P-value = 0.66) were not statistically significant (Table 3).

The overall local drift of breast cancer is<0 (although insignificant) for women younger than 25 years, and women older than 24 years had positive local drifts, with women aged 30–39 years and 75 above having drifts >2% (Supplementary Table 4; Figure 10B; Supplementary Figure 5). Young Blacks (<20 years) and Whites (<30 years) had insignificant local drifts below 0. However, Blacks (from 2.01% to 5.6%) and Coloreds (1.59% to 3.86%) generally had the highest positive local drifts that slightly increased with age from 20 years. Whites and Indian/Asians generally had low positive local drifts, but Whites aged 50–59 years and Indians/Asians aged 40–59 years had negative drifts (Figure 10B; Supplementary Figures 6–9; Supplementary Table 5).

Age effect

Based on the longitudinal/cross-sectional age curve, the relative risk (RR) of overall and ethnic breast cancer mortality increased with age, portraying a J-curve with a steep increase in risk from 70 years (Figure 11A; Supplementary Figure 5; Supplementary Table 4). Blacks (0.018, 95% CI: 0.008–0.042) and Indian/Asians (0.030, 95% CI: 0.001–1.664) had the least and second lowest RR at 15–19 years, but the Blacks' RR (214.30 95% CI: 184.84–248.46 at >74 years) and Indian/Asians' RR (116.83, 95% CI: 86.81–157.25 at >74 years), respectively, became the second highest and the least from 65 years. Coloreds (0.033, 95% CI: 0.003–0.315) and Whites (0.042, 95% CI: 0.002–0.730), respectively, had the third highest and highest RR at 15–19 years, but the Coloreds' RR (283.04 95% CI: 239.51–334.49 at >74 years) and Whites' RR (179.03, 95% CI: 157.22–203.87 at >74 years) became the highest and third highest from 45 years (Supplementary Table 5; Figure 11A; Supplementary Figures 6–9).

Period effect

The period RR for breast cancer mortality increased by around 18% from 1999–2003 to 2004–2008 (RR: 0.82, 95% CI:0.77–0.87) and then increased (although not significant) by 9% from 2004–2008 to

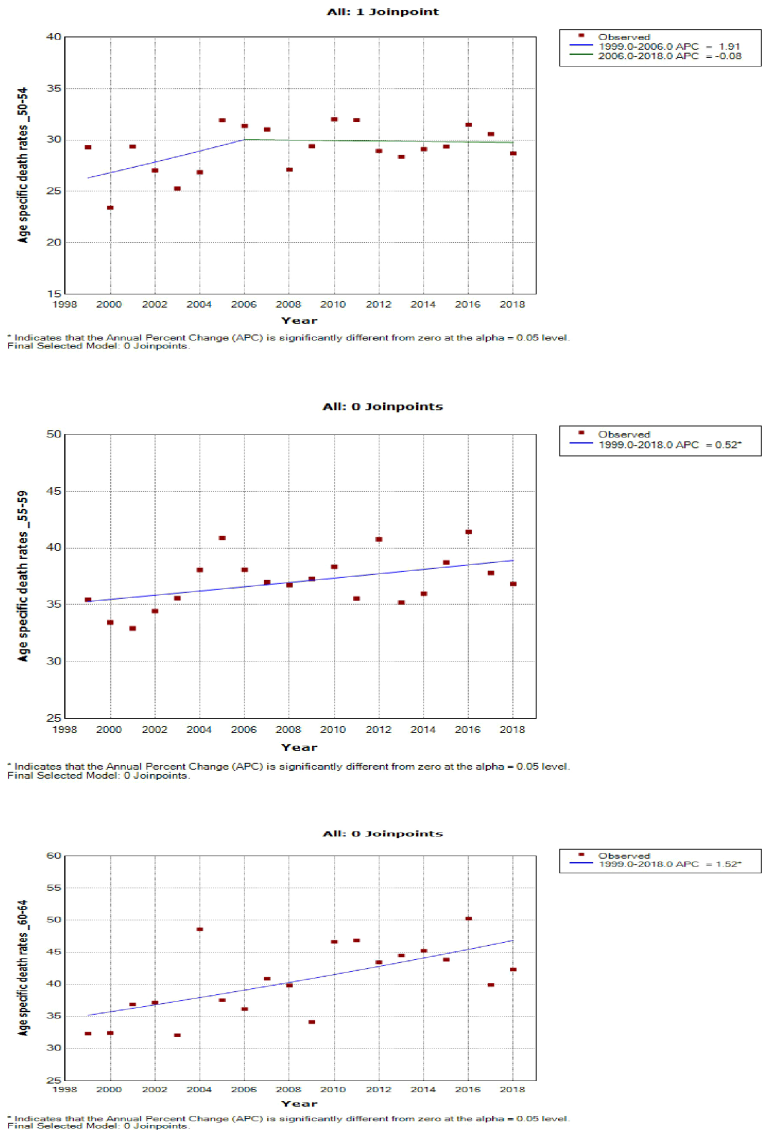

FIGURE 8
Joinpoint trends of age-specific death rates of breast cancer in South Africa, 1999–2018, among 50–64-year-olds (5-year group).

2009–2013 (RR: 1.09, 95% CI: 0.95–1.06). Subsequently, there was a 5% reduction in risk from 2009–2013 to 2014–2018 (RR: 1.04, 95% CI: 0.98–1.11) (Figure 11B; Supplementary Figure 6; Supplementary Table 4). All the ethnic groups had increased period RR from 1999 to 2018 with Blacks (RR: 1.52) having the highest increase between 2014 and 2018, followed by Coloreds (RR:1.21), Whites (RR:1.12), and Indians/Asians (RR:1.10) (Figure 11B; Supplementary Table 5; Supplementary Figures 6–9). The Wald's test of the period effect was statistically significant for overall, Blacks, and Coloreds, but not significant among Whites and Indian/Asians (Table 3).

Cohort effect

The cohort RR of breast cancer mortality among those born during 1924–1928 (RR: 0.5, 95% CI: 0.43–0.57) was the least, and the risk increased among successive cohorts to a peak RR among those born between 1984 and 1988 (RR: 1.64, 95% CI: 1.35–1.99). Afterward, there was a decline in risk among successive birth cohorts to 1.57 among birth cohorts from 1999 to 2003 (Figure 11C; Supplementary Figure 5; Supplementary Table 4). With respect to ethnic cohort variations, the Blacks (RR: 0.16, 95% CI: 0.13–0.19) and the Coloreds (0.31, 95% CI: 0.25–0.40) had a relatively low RR among the cohort that were born between 1924 and 1928 and the risk increased among successive birth cohorts, with the cohort RR of Blacks becoming the highest among the 1964–1993 birth cohorts. The Whites (0.80, 95% CI: 0.69–0.93)) and Indian/Asians (1.00, 95% CI: 0.65–1.54) had a relatively higher cohort RR among the 1924–1928 birth cohorts, and there was minimal change in the mortality risk among their successive cohorts till the 1959–1963 cohort for Whites and 1984–1988 for Indian/Asians. Subsequently, the RR increased among Whites till those born in 1984–1988. While the mortality RR generally increased among successive Indian/Asian cohorts born between 1994 and 2003, the RR of similar birth cohorts of other ethnic groups reduced (Figure 11C; Supplementary Figures 6–9; Supplementary Table 5). The Wald's test showed that the cohort effect was statistically significant for the overall trends and among all the ethnic groups (P-value< 0.001) except for the Indian/Asians (P-value = 0.61) (Table 3).

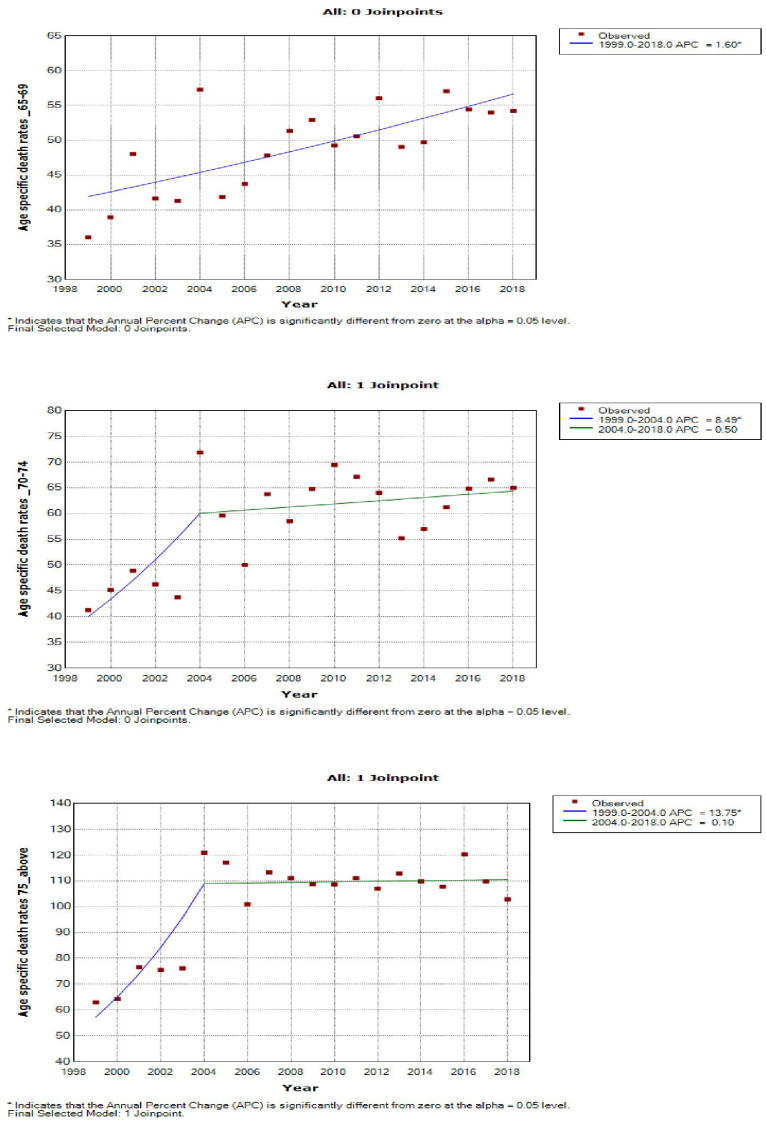

FIGURE 9
Joinpoint trends of age-specific death rates of breast cancer in South Africa, 1999–2018, among 65 years and above (5-year group).

Discussion

To our knowledge, this is the first study in SSA to utilize both joinpoint and A–P–C regression modeling techniques to evaluate the national trends in breast cancer mortality, stratified by ethnicity. This temporal trend analysis over 20 years (1999–2018) in South Africa is necessary to evaluate the impact of previous interventions and guide prioritization of health resources.

Breast cancer mortality trends

The mortality rate of breast cancer in South Africa (13.27 per 100,000 women) was slightly lower than the average rates in Southern Africa (1), but higher than North American rates (1). We found that the mortality to incidence ratio (MIR) of breast cancer in South Africa (13.27 vs. 32.87 per 100,000 women, MIR:0.4) was slightly higher than the average of other Southern African Countries (15.6 vs. 46.2 per 100,000 women, MIR:0.34) and the North American region (12.6 vs. 84.8 per 100,000 women, MIR:0.15) but lower than the average MIR among Western African countries (17.8 vs. 37.3 per 100,000 women, MIR: 0.48) (30, 31).

As reported globally, we observed a significant period effect on the trends of breast cancer mortality in South Africa (27, 28). The net drift and joinpoint regression model indicated a rise in the breast cancer mortality rate by around 1.47% and 1.40% per annum from 1999 to 2018, respectively. Similarly, most countries in SSA and Asia had increasing mortality trends (29, 32, 33). In contrast, there was a decline in breast cancer mortality in most HICs and middle-income countries because of mass screening with mammography and clinical breast examination, hereditary screening of high-risk individuals, molecular and histopathological classification, early patient presentation, and prompt treatment with surgery (mastectomy), adjuvant hormone therapy, chemotherapy, and radiotherapy (32–37). The period RR and segmental APC suggest a reduction in the increasing rate of breast cancer mortality during the later period of

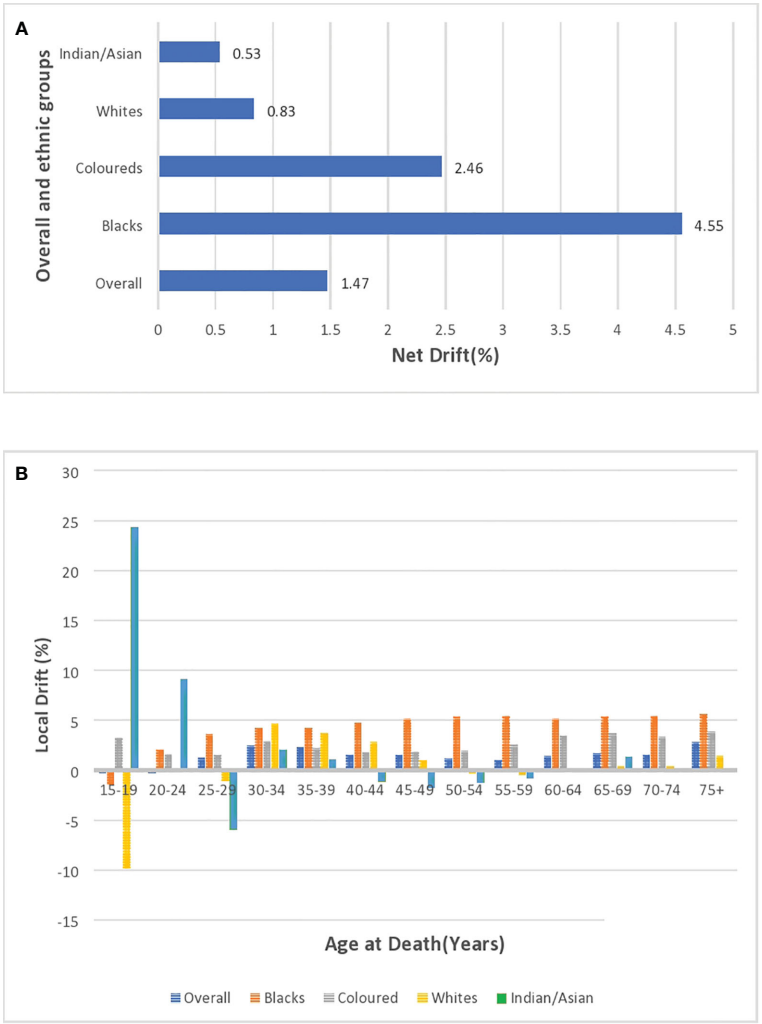

FIGURE 10
(A) Overall and ethnic net drifts of breast cancer mortality in South Africa (1999–2018). **(B)** Overall and ethnic local drifts of breast cancer mortality in South Africa (1999–2018).

2004 to 2018 (5.9% per annum vs. 0.5% per annum). The apparent reduction in APC from 2004 may be partly explained by the reported decline in incidence from 1999 to 2010 (11). After the commencement of the multiracial democratic government in 1994 to replace the apartheid regime, policies were directed at expanding access to free reproductive public health services for majority of the previously marginalized population (especially the Black and Colored population) (9, 11, 38, 39). Furthermore, public enlightenment campaigns, ongoing multiple international and national breast cancer research, some screening programs by non-governmental

TABLE 3 Wald Chi-square test for estimable functions of the age period cohort model in the overall and ethnic trends of breast cancer mortality in South Africa (1999–2018).

Cancer type	NetDrift = 0		All period RR = 1		All cohort RR = 1		All local drifts = net drift	
	Chi-square	P-value	Chi-square	P-value	Chi-square	P-value	Chi-square	P-value
Breast								
Overall	26.59	2.52E-07*	49.45	1.05E-10*	167.26	8.66E-28*	29.53	0.0055*
Black	222.87	2.14E^{-50}*	298.27	2.36E^{-64}*	658.99	1.01E^{-130}*	9.55	0.73
White	0.68	0.41	2.34	0.50	69.68	5.09E^{-09}*	45.54	1.70E^{-05}*
Indian/Asian	0.20	0.66	0.83	0.84	12.93	0.61	12.62	0.48
Colored	17.70	2.58E^{-05}*	25.80	1.05 E^{-05}*	148.38	5.06E^{-24}*	14.05	0.37

*Statistically significant at P-value< 0.05.

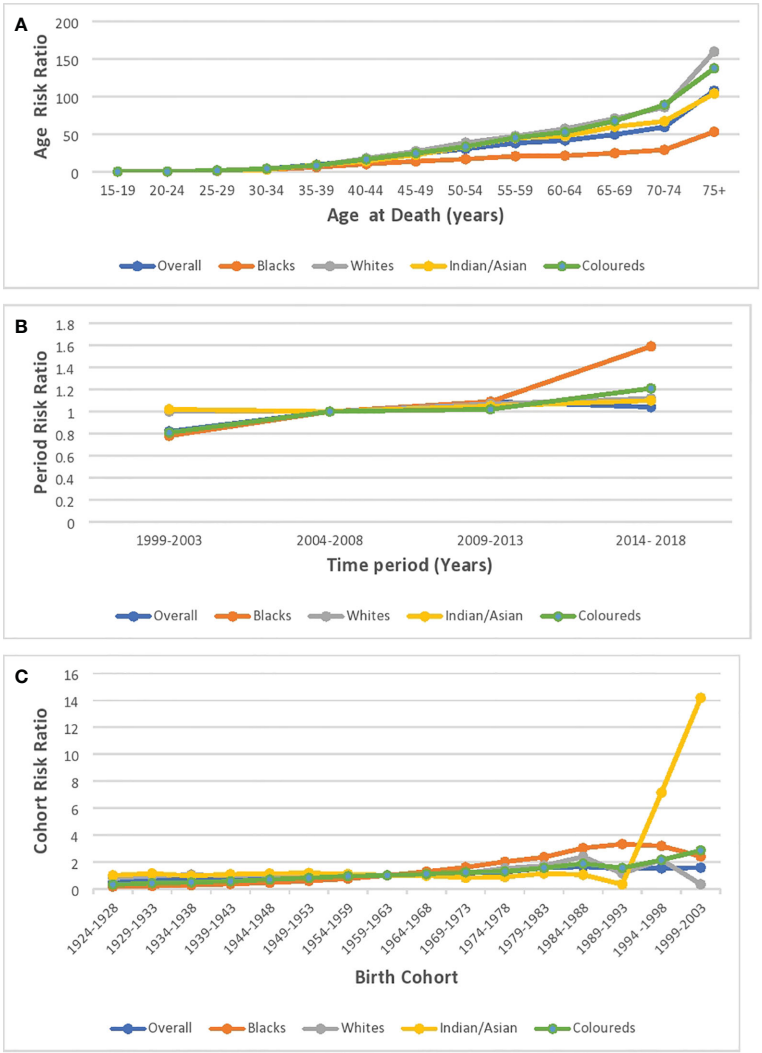

FIGURE 11
Ethnic and national breast cancer mortality risk ratio in South Africa due to **(A)** age, **(B)** period, and **(C)** cohort after the age–period–cohort analysis.

organizations, and reduction of barriers to definitive care are also contributory to the reduced period RR in the later years (11, 40, 41). Since South Africa has one of the highest global HIV prevalences, HIV was hitherto a major competing risk of death in the country (20, 42, 43). Thus, the nationwide rollout of free ART in 2004 can partly explain the reduction in breast cancer mortality rate from 2005 (7, 38, 44).

Age effect of breast cancer mortality trends

In line with previous studies, we found that there was a strong age effect on the breast cancer mortality trends as there was increased risks and rates with increasing age (27, 28, 42). Thus, it can be deduced that biological effect played a role in breast cancer mortality (27, 28, 42). The age effect was also apparent as the annual crude mortality rate of breast cancer was higher than the age-standardized rate among Whites over the study period from 1999 to 2018. South African women aged 30 years and older generally had an increased mortality rate, with that of women aged 30–39 and 75 years and above having a rapid rise (local drift >2%). Furthermore, we found that in the later years (2014–2018), women aged 45–49 years had a rapid rise in breast cancer mortality rate of around 5% per annum. Thus, death from premenopausal breast cancer is fast becoming a major cause of cancer deaths among young South Africans and globally (4, 34, 43, 45, 46). Nonetheless, a decline in mortality rate occurred despite increased incidence among young women in some countries in LMICs and HICs and this was attributed to routine and opportunistic screening during antenatal and contraceptive consultations and a strong cohort effect from the 1950s (45–47).

In comparison with postmenopausal breast cancer, the premenopausal breast cancer type is usually more aggressive, advanced-stage at diagnosis, triple-negative, and with worse prognosis (36, 48). Remarkably, the screening, diagnosis, and treatment of premenopausal breast cancer are a challenge because dense breast tissue of young women may obfuscate pathological tissues (4, 43). Obesity appears to be the major driver of sporadic postmenopausal breast cancer (4, 49).

Notably, South African women aged 50–59 years had nearly stable mortality trends (AAPC = 0.5%). Similarly, women aged 50–69 years

had the lowest AAPC in Sub-Saharan Africa (AAPC:<50 years: 0.53%, 50–69 years: 0.34%, ≥70 years: 0.82%) and in all other global regions from 1990 to 2017 (48). This pattern suggests that women aged 50–59 years generally had routine or opportunistic screening, or there was reduction in perimenopausal HRT use from 2000 (4, 34, 45).

The increased mortality rate of breast cancer among South African women older than 70 years may be associated with increasing life expectancy and comorbid factors (33, 34, 36, 48, 50). Thus, research and public health interventions aimed at reducing the burden of breast cancer should target all age groups from 25 years.

Cohort effect of breast cancer mortality

We reported a rise in RR of breast cancer mortality among South African birth cohorts from 1924 to 1988 (0.5 to 1.64) and a subsequent decline among recent cohorts from 1988 to 2003. A decline in cohort mortality risks around 1920 and 1960 in USA and East Asia, respectively, was previously reported (27, 28, 51, 52). Each successive South African birth cohort experienced increased risk factors (leading to mortality) of breast cancer such as increased prevalence of obesity, smoking, alcohol consumption, low fertility rate, prolonged use of hormonal contraceptive, late age at first pregnancy (usually on account of prolonged years of education), reduced period of breastfeeding (mainly because of pressures of work), and westernization of diet (increased fatty and high-protein diet) (5, 6, 11, 36, 53–56). However, the improved socioeconomic status, educational attainment, health seeking behavior, reduction in smoking prevalence, and increased awareness and access to healthcare among recent South African cohorts especially after the commencement of the multiracial democracy in 1994 might partly explain the reduction in breast cancer cohort mortality risk from 1988 (10, 45, 57, 58).

Ethnic disparity of breast cancer trends

We observed that ethnic disparity in breast cancer mortality in South as Blacks had around half the breast cancer mortality rates of Colored, Whites, and Indian/Asians. In contrast, Blacks had higher breast cancer mortality rates as compared with Whites in USA (35, 59, 60).

Our analysis showed that breast cancer mortality RR increased among successive Black and Colored cohorts from 1924 to 2003 and Blacks had the highest mortality risk among recent cohorts (1974–2003). Historically, Blacks had protective breast cancer risk factors such as increased prevalence of late menarche, early age at first birth (Black South African culture supports early/teenage pregnancy), high parity, prolonged breastfeeding practices, and high-fiber diet (6, 27, 60). However, successive cohorts of Blacks and Coloreds had experienced increased westernized diet, increased use of hormonal contraceptives, decreased fertility rate, and increased prevalence of obesity and sedentary jobs (5, 55, 56, 61). Furthermore, successive cohorts of Coloreds also had increased prevalence of smoking and alcohol rates (62–64). Despite having the lowest breast cancer incidence, Blacks (9.49 vs. 19.32 per 100,000 MIR: 0.49) and Coloreds (18.11 vs. 47.9 per 100,000 women, MIR: 0.38) had the highest MIR as compared with Indian/Asians (13.24 vs. 15.24 per 100,000 women, MIR: 0.26) and Whites (17.77 vs. 84.49 per 100,000 women, MIR:0.21), which suggests a worst survival rate (30, 64, 65). During the apartheid era, successive cohorts of Blacks and Coloreds had worse breast cancer survival because they usually have poor awareness, advanced staged cancer, and poor access to healthcare especially among rural dwellers (6, 38, 66). Furthermore, Blacks usually have an aggressive, premenopausal, and triple-negative form of breast cancer (6). Our study showed that the expected cohort RR decline of breast cancer after the expansion of access to healthcare since the commencement of the multiracial democracy in 1994 has not occurred (9, 38, 57).

The earliest White and Indian/Asian birth cohorts had relatively high mortality RR, which was nearly stable until 1969–1973 when the RR among Whites slightly increased whereas that of Indian/Asian cohorts declined. The increased mortality risk among the recent White cohorts may be driven by modifiable factors such as obesity, smoking, alcohol consumption, and use of hormonal contraceptives, whereas the decline among Indian/Asians is similar to the cohort trends in East Asia and America that was attributable to improved awareness, screening, and improved healthcare (27, 52, 62).

The period effect of breast cancer mortality from 1999 to 2018 was noted among Blacks and Coloreds, with rapid drifts of 4.6% and 2.5% per annum, respectively. The improved socioeconomic status and shift in reproductive behaviors without commensurate access to screening and oncological care among Blacks and Coloreds led to increased breast cancer mortality from 1999 to 2018. Nonetheless, a reduced acceleration among Blacks (APC: 5.0% vs. 3.0%), in the later period (2004–2018), may be attributed to some improvement in public reproductive health and oncological services (9–11, 38, 52, 57). Furthermore, the national rollout of free ART in 2004 partly contributed to death reduction among Black HIV-positive breast cancer patients (38, 44, 67, 68). In contrast, Coloreds (APC: -3.5% vs. 3.4%) had increased breast cancer mortality rates in the later years (2008–2018), suggesting that the public health interventions are yet to impact breast cancer outcome among them. This may also suggest that the cohort and age effects are stronger than the period effect among them.

The period effect of breast cancer mortality was not statistically significant among Whites and Indian/Asians, and they had low net drifts (Whites, 0.83%; Indian/Asian, 0.53%). Indeed, Whites and Indian/Asians had access to private health facility with optimum oncological facilities that are comparable with healthcare services in HICs (11, 57). Thus, sociopolitical and public health interventions by the South African government may not impact on the outcome of breast cancer care among them. However, this study highlighted an increased breast cancer mortality among Whites (APC: -1.9% vs. 1.1%) in the later years (2008–2018), which calls for further research. The apparent decline in mortality rate among Indian/Asians can be attributed to early diagnosis and treatment (27, 52).

Blacks had the youngest average age at death (56 years) followed by Coloreds (60.6 years), Indian/Asian (63.9 years), and White (67.4 years), suggesting that worst survival or more premenopausal deaths occurred among them. The observed rise in breast cancer mortality among the Whites in the later years may be occurring at old age. Indeed, the CMR of breast cancer was around thrice the ASMR among Whites, suggesting that majority of the deaths occurred in the

elderly. Strikingly, women aged 25–39 years generally had the highest rise in breast cancer mortality. Remarkably, deaths from premenopausal breast cancer (<45 years) increased whereas postmenopausal breast cancer deaths declined among Coloreds, possibly suggesting increased modifiable risks and poor access to screening and early care among young Coloreds. The negative drifts among Whites aged 50–69 years and Indian/Asians aged 40–59 years may suggest that women of the two ethnic groups commenced screening at 40–50 years according to international guidelines (27, 33, 47, 69). There is a need for public enlightenment campaigns, modifiable risk reduction, and provision of optimum screening and treatment modalities among women of all ethnic groups over 20 years.

Strength and limitation

We utilized national mortality data that have been adjudged to be of high quality to comprehensively evaluate the trends in breast cancer mortality, based on the A–P–C and joinpoint regression models to unmask cues and information toward control of breast cancer in South Africa (17, 20).

One limitation of this study was the missing information on the stage and histological types of the cancers that can further improve the interpretation of our results (7, 70). Furthermore, there may be some underreporting of deaths that occurred outside health institutions. However, it is mandatory to report all deaths to the Department of Home Affairs before burial. Since our study was population based, we exercised caution while interpreting at the individual level to avoid the risk of ecological fallacy (71).

Conclusion

In conclusion, we found that a significant age period cohort effect was observed for breast cancer mortality trends. There was a breast cancer rise of around 1.5% per annum from 1999 to 2018, largely driven by a rapid rise in deaths among young women (in the last 10 years of the study). The breast cancer mortality risk increased from the early cohorts but started decreasing among the recent cohorts born from 1989 to 2003. The period effect from screening and expansion of healthcare services after multiracial democracy in 1994 only led to minimal reduction in deaths of breast cancer, especially among women aged 50–59 years. The breast cancer mortality rate among Blacks was around half of the rates among the non-Blacks. Each of the four ethnic groups had differential trends and burden on account of peculiar socioeconomic, cultural, screening behavior, access to optimum care, awareness, and sexual and reproductive behavior. The identified disparities and trends are very useful for designing targeted intervention.

Brief policy implications

The South African government launched the national breast program in 2017 to promote prevention and early detection and prompt optimum treatment of breast (72). Such initiative is expected to reverse the current increasing burden of the breast cancer deaths. However, based on the results of our study, we recommend that screening for breast cancer should be intensified in all age groups, as our results suggest strong/highest risks among young cohorts. In contrast to screening policies of HICs, population-based routine screening of breast cancer with mammography was not recommended in the South African guideline, largely on account of cost to the health system (72). However, we recommend that in addition to the current recommendation of promoting awareness, regular clinical breast examination, prompt treatment, and mammography should be considered especially commencing at a young age, possibly 35–40 years, as majority of breast cancer cases are sporadic (4). Opportunistic mammography can also be encouraged as part of routine occupational medical examination (28). Women that can afford mammography should also be offered pending when the health system can provide it for all women.

Since we found that cohort effect is a major driver of breast cancer mortality trends in the country, primary prevention should target all the known risk factors of breast cancer such as reduction of obesity, promoting breastfeeding, and reproductive behaviors. Breast cancer prevention should be part of the social marketing for promoting the cessation of tobacco smoking and alcohol consumption (4, 28). Interventions that target ethnic burden of breast cancer mortality can be considered. Indeed, older White women had higher burden of breast cancer mortality and targeted intervention will be necessary.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The Statistics South Africa website.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research and Ethics Committee (Medical) of the University of the Witwatersrand (Clearance certificate number: M190544). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization and study design: GO, EM, EL, OCE; data acquisition: GO, EM, EL; data management and data analysis: GO; data interpretation: GO, EM, EL, OCE; writing original draft: GO; critical review of manuscript and acceptance on the manuscript submission: GO, EM, EL, OCE; supervision of the project: EM, EL, OCE. All authors contributed to the article and approved the submitted version

Funding

This work was funded by GSK Africa Non-Communicable Disease Open Lab through the DELTAS Africa Sub-Saharan African Consortium

for the Advanced Biostatistics (SSACAB) training program. The views expressed in this publication are those of the author(s) and not necessarily those of GSK (GSK grant number D1702270-01).

Acknowledgments

We thank Statistics South Africa for collecting and making the mortality data publicly available for this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1056609/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. McCormack V, McKenzie F, Foerster M, Zietsman A, Galukande M, Adisa C, et al. Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): A prospective cohort study. *Lancet Glob Heal* (2020) 8(9):e1203–12. doi: 10.1016/S2214-109X(20)30261-8

3. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women: Burden and trends [Internet] . *Cancer Epidemiol Biomarkers Prev* (2017) 26:444–57. doi: 10.1158/1055-9965.EPI-16-0858

4. Heer E, Harper A, Escandor N, Sung H, McCormack V, Fidler-Benaoudia MM. Global burden and trends in premenopausal and postmenopausal breast cancer: A population-based study. *Lancet Glob Heal [Internet].* (2020) 8(8):e1027–37. doi: 10.1016/S2214-109X(20)30215-1

5. Urban M, Banks E, Egger S, Canfell K, Connell D, Beral V, et al. Injectable and oral contraceptive use and cancers of the breast, cervix, ovary, and endometrium in black south african women: Case-control study. *PloS Med* (2012) 9(3):1–12. doi: 10.1371/journal.pmed.1001182

6. Vorobiof DA, Sitas F, Vorobiof G. Breast cancer incidence in south Africa. *J Clin Oncol* (2001) 19(18 SUPPL.):125S–7S.

7. Olorunfemi G, Ndlovu N, Masukume G, Chikandiwa A, Pisa PT, Singh E. Temporal trends in the epidemiology of cervical cancer in south Africa (1994-2012). *Int J Cancer* (1994 - 2012) 143(9):2238–9. doi: 10.1002/ijc.31610.

8. Lehohla P. *South African statistics*. (2015). https://www.statssa.gov.za/publications/P0302/P03022015.pdf

9. Cooper D, Morroni C, Orner P, Moodley J, Harries J, Cullingworth L, et al. Ten years of democracy in south Africa: Documenting transformation in reproductive health policy and status. *Reprod Health Matters.* (2004) 12(24):70–85. doi: 10.1016/S0968-8080(04)24143-X

10. Cooper D, Harries J, Moodley J, Constant D, Hodes R, Mathews C, et al. Coming of age? women's sexual and reproductive health after twenty-one years of democracy in south Africa. *Reprod Health Matters.* (2016) 24(48):79–89. doi: 10.1016/j.rhm.2016.11.010

11. Singh E, Joffe M, Cubasch H, Ruff P, Norris SA, Pisa PT. Breast cancer trends differ by ethnicity: A report from the south African national cancer registry (1994–2009). *Eur J Public Health [Internet].* (2016) 27(1):173–8. doi: 10.1093/eurpub/ckw191

12. Kabudula CW, Houle B, Collinson MA, Kahn K, Gómez-Olivé FX, Clark SJ, et al. Progression of the epidemiological transition in a rural south African setting: Findings from population surveillance in agincourt, 1993-2013. *BMC Public Health* (2017) 17(1):1–15. doi: 10.1186/s12889-017-4312-x

13. Musenge E, Chirwa TF, Kahn K, Vounatsou P. Bayesian Analysis of zero inflated spatiotemporal HIV/TB child mortality data through the INLA and SPDE approaches: Applied to data observed between 1992 and 2010 in rural north East south Africa. *Int J Appl Earth Obs Geoinf* (2013) 22(100):86–98. doi: 10.1016/j.jag.2012.04.001

14. Musenge E, Vounatsou P, Collinson M, Tollman S, Kahn K. The contribution of spatial analysis to understanding HIV/TB mortality in children: A structural equation modelling approach. *Glob Health Action.* (2013) 6(1):19266. doi: 10.3402/gha.v6i0.19266

15. Herrmann C, Ess S, Thürlimann B, Probst-Hensch N, Vounatsou P. 40 years of progress in female cancer death risk: A Bayesian spatio-temporal mapping analysis in Switzerland. *BMC Cancer.* (2015) 15(1):1–10. doi: 10.1186/s12885-015-1660-8

16. Olfatifar M, Karami M, Moghimbeigi A, Motlagh A, Rooshanaee G, Partovipour E, et al. Spatial clustering of breast cancer: An epidemiological analysis of Iranian women. *Iran J Cancer Prev* (2017) In Press(In Press):1–5. doi: 10.17795/ijcp-5402

17. Nkengasong J, Gudo E, Macicame I, Maunze X, Amouzou A, Banke K, et al. Improving birth and death data for African decision making. *Lancet Glob Heal [Internet].* (2020) 8(1):e35–6. doi: 10.1016/S2214-109X(19)30397-3

18. Statistics South Africa. *Mid-year population estimates* Vol. 2015. . South Africa (2015). https://www.statssa.gov.za/publications/P0302/P03022015.pdf

19. Sitas F, Egger S, Bradshaw D, Groenewald P, Laubscher R, Kielkowski D, et al. Differences among the coloured, white, black, and other south African populations in smoking-attributed mortality at ages 35-74 years: A case-control study of 481640 deaths. *Lancet* (9893) 2013:685–93:382. doi: 10.1016/S0140-6736(13)61610-4

20. Joubert J, Rao C, Bradshaw D, Vos T, Lopez AD. Evaluating the quality of national mortality statistics from civil registration in south Africa, 1997-2007. *PloS One [Internet].* (2013) 8(5). doi: 10.1371/journal.pone.0064592.PDF

21. Mak D, Sengayi M, Chen WC, De VCB, Singh E, Kramvis A. Liver cancer mortality trends in south Africa : 1999 – 2015. *BMC Cancer.* (2018) 10:1–9. doi: 10.1186/s12885-018-4695-9

22. Shamseddine A, Saleh A, Charafeddine M, Seoud M, Mukherji D, Temraz S, et al. Cancer trends in Lebanon: A review of incidence rates for the period of 2003-2008 and projections until 2018. *Popul Health Metr* (2014) 12(1):4. doi: 10.1186/1478-7954-12-4

23. Rosenberg D. *Trend analysis and interpretation key concepts and methods for maternal and child health professionals*. Maryland: Maternal and Child health Bureau (1997). p. 1.39. http://www.mchb.hrsa.gov/researchdata/mchirc

24. . *National Cancer Institute. Statistical Research and Applications Branch, Joinpoint Program, Version 4.9.0.0.* (2022). https://surveillance.cancer.gov/joinpoint/

25. Bell A, Bell A. Annals of human biology age period cohort analysis : a review of what we should and shouldn ' t do age period cohort analysis : a review of what we should and shouldn ' t do. *Ann Hum Biol [Internet].* (2020) 47(2):208–17. doi: 10.1080/03014460.2019.1707872

26. Rosenberg PS, Check DP, Anderson WF. A web tool for age – period – cohort analysis of cancer incidence and mortality rates. *Cancer Epidemiol. Biomark. Prev.* (2014) 23:2296–2302.

27. Wang Z, Bao J, Yu C, Wang J, Li C. Secular trends of breast cancer in China, south Korea, Japan and the united states: Application of the age-period-cohort analysis. *Int J Environ Res Public Health* (2015) 12(12):15409–18. doi: 10.3390/ijerph121214993

28. Huang Z, Wen W, Zheng Y, Gao YT, Wu C, Bao P, et al. Breast cancer incidence and mortality: Trends over 40 years among women in shanghai, China. *Ann Oncol* (2016) 27(6):1129–34. doi: 10.1093/annonc/mdw069

29. Lei S, Zheng R, Zhang S, Chen R, Wang S, Sun K, et al. Breast cancer incidence and mortality in women in China: Temporal trends and projections to 2030. *Cancer Biol Med* (2021) 18(3):900–9. doi: 10.20892/j.issn.2095-3941.2020.0523

30. National Cancer Registry. *Cancer in south Africa* (2018). Available at: https://www.nicd.ac.za/centres/national-cancer-registry/https://www.nicd.ac.za/centres/national-cancer-registry/.

31. Vostakolaei FA, Karim-kos HE, Janssen-heijnen MLG, Visser O. The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival. *Eur J Public Health* (2010) 21(5):573–7. doi: 10.1093/eurpub/ckq120

32. Azubuike SO, Muirhead C, Hayes L, McNally R. Rising global burden of breast cancer: The case of sub-Saharan Africa (with emphasis on Nigeria) and implications for

regional development: A review. *World J Surg Oncol* (2018) 16(1):1–13. doi: 10.1186/s12957-018-1345-2

33. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International variation in female breast cancer incidence and mortality rates. *Cancer Epidemiol Biomarkers Prev* (2015) 24(10):1495–506. doi: 10.1158/1055-9965.EPI-15-0535

34. Ilic L, Haidinger G, Simon J, Hackl M, Schernhammer E, Papantoniou K. Trends in female breast cancer incidence, mortality, and survival in Austria, with focus on age, stage, and birth cohorts (1983–2017). *Sci Rep [Internet].* (2022) 12(1):1–10. doi: 10.1038/s41598-022-10560-x

35. Jatoi I, Sung H, Jemal A. The emergence of the racial disparity in U.S. breast-cancer mortality. *N Engl J Med [Internet]* (2022) 86(25):2349–51. doi: 10.1056/NEJMp2200244

36. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. Global cancer in women: Burden and trends. *Cancer Epidemiol Biomarkers Prev* 26(4):444–57. doi: 10.1158/1055-9965.EPI-16-0858

37. Jemal A, Center MM, DeSantis C, Ward EM. The global burden of women's cancers: A grand challenge in global health. *Lancet* (2010) 389(10071):847–60. doi: 10.1016/S0140-6736(16)31392-7

38. Pillay-van Wyk V, Msemburi W, Laubscher R, Dorrington RE, Groenewald P, Glass T, et al. Mortality trends and differentials in south Africa from 1997 to 2012: Second national burden of disease study. *Lancet Glob Heal* (2016) 4(9):e642–53. doi: 10.1016/S2214-109X(16)30113-9

39. Mayosi BM, Benatar SR. Health and health care in South Africa — 20 years after Mandela. *N Engl J Med* (2014) 371(14):1344–53. doi: 10.1056/NEJMsr1405012

40. Joffe M, Ayeni O, Norris SA, McCormack VA, Ruff P, Das I, et al. Barriers to early presentation of breast cancer among women in Soweto, South Africa. *PloS One* (2018) 13 (2):1–16. doi: 10.1371/journal.pone.0192071

41. Dickens C, Joffe M, Jacobson J, Venter F, Schüz J, Cubasch H, et al. Stage at breast cancer diagnosis and distance from diagnostic hospital in a periurban setting: A south African public hospital case series of over 1,000 women. *Int J Cancer.* (2014) 135(9):2173–82. doi: 10.1002/ijc.28861

42. Sathishkumar K, Vinodh N, Badwe RA, Deo SVS, Manoharan N, Malik R, et al. Trends in breast and cervical cancer in India under national cancer registry programme: An age-Period-Cohort analysis. *Cancer Epidemiol* (2021) 74:101982. doi: 10.1016/j.canep.2021.101982

43. Hendrick RE, Helvie MA, Monticciolo DL. Breast cancer mortality rates have stopped declining in U.S. women younger than 40 years. *Radiology* (2021) 299(1):143–9. doi: 10.1148/radiol.2021203476

44. Simelela NP, Venter WDF. A brief history of south africa's response to AIDS. *South Afr Med J [Internet].* (2014) 104(3):249. doi: 10.7196/samj.7700

45. Piechocki M, Koziołek W, Sroka D, Matrejek A, Miziołek P, Saiuk N, et al. Trends in incidence and mortality of gynecological and breast cancers in Poland (1980–2018). *Clin Epidemiol* (2022) 14(January):95–114. doi: 10.2147/CLEP.S330081

46. Silva JDDE, de Oliveira RR, da Silva MT, Carvalho MD de B, Pedroso RB, Pelloso SM. Breast cancer mortality in young women in Brazil. *Front Oncol* (2021) 10(January):1–9. doi: 10.3389/fonc.2020.569933

47. Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K, et al. Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020. *Cancer Commun* (2021) 41(11):1183–94. doi: 10.1002/cac2.12207

48. Lima SM, Kehm RD, Terry MB. Global breast cancer incidence and mortality trends by region, age-groups, and fertility patterns. *EClinicalMedicine [Internet].* (2021) 38:100985. doi: 10.1016/j.eclinm.2021.100985

49. Fowke JH, Shu X-O, Dai Q, Jin F, Cai Q, Gao Y-T, et al. Oral contraceptive use and breast cancer risk: Modification by NAD(P)H:quinone oxoreductase (NQO1) genetic polymorphisms. *Cancer Epidemiol Biomarkers Prev* (2004) 13(8):1308–15. doi: 10.1158/1055-9965.1308.13.8

50. Ayeni OA, Norris SA, Joffe M, Cubasch H, Nietz S, Buccimazza I, et al. The multimorbidity profile of south African women newly diagnosed with breast cancer. *Int J Cancer.* (2020) 147(2):361–74. doi: 10.1002/ijc.32727

51. Tarone RE, Chu KC, Gaudette LA. Birth cohort and calendar period trends in breast cancer mortality in the united states and Canada. *J Natl Cancer Inst* (1997) 89 (3):251–6. doi: 10.1093/jnci/89.3.251

52. Choi Y, Kim Y, Park SK, Shin HR, Yoo KY. Age-period-cohort analysis of female breast cancer mortality in Korea. *Cancer Res Treat* (2016) 48(1):11–9. doi: 10.4143/crt.2015.021

53. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin [Internet].* (2018) 68(6):394–424. doi: 10.3322/caac.21492

54. Dierssen-Sotos T, Palazuelos-Calderón C, Jiménez-Moleón J-J, Aragonés N, Altzibar JM, Castaño-Vinyals G, et al. Reproductive risk factors in breast cancer and genetic hormonal pathways: A gene-environment interaction in the MCC-Spain project. *BMC Cancer* (2018) 18(1):280. doi: 10.1186/s12885-018-4182-3

55. Caldwell JC, Caldwell P. The south African fertility decline. *Popul Dev Rev* (1993) 19(2):225–62. doi: 10.2307/2938436

56. Nglazi MD, Ataguba JEO. Overweight and obesity in non-pregnant women of childbearing age in south Africa: Subgroup regression analyses of survey data from 1998 to 2017. *BMC Public Health [Internet].* (2022) 22(1):1–18. doi: 10.1186/s12889-022-12601-6

57. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of south Africa: Historical roots of current public health challenges. *Lancet [Internet].* (2009) 374(9692):817–34. doi: 10.1016/S0140-6736(09)60951-X

58. Reddy P, James S, Sewpaul R, Yach D, Resnicow K, Sifunda S, et al. A decade of tobacco control: The south African case of politics, health policy, health promotion and behaviour change. *South Afr Med J [Internet].* (2013) 103(12):835–40. doi: 10.7196/samj.6910

59. Singh GK, Williams SD, Siahpush M, Mulhollen A. Socioeconomic, rural-urban, and racial inequalities in US cancer mortality: Part I–all cancers and lung cancer and part II–colorectal, prostate, breast, and cervical cancers. *J Cancer Epidemiol [Internet].* (2011) 2011:1–27. doi: 10.1155/2011/107497

60. Yedjou CG, Tchounwou PB, Payton M, Miele L, Fonseca DD, Lowe L, et al. Assessing the racial and ethnic disparities in breast cancer mortality in the united states. *Int J Environ Res Public Health* (2017) 14(5):486. doi: 10.3390/ijerph14050486

61. Garenne ML, Tollman SM, Collinson MA, Kahn K. Fertility trends and net reproduction in agincourt, rural south Africa, 1992-2004. *Scand J Public Health Suppl [Internet].* (2007) 69(785022301):68–76. doi: 10.1080/14034950701355650

62. Bahk J, Jang SM, Jung-Choi K. Increased breast cancer mortality only in the lower education group: Age-period-cohort effect in breast cancer mortality by educational level in south Korea, 1983-2012. *Int J Equity Health* (2017) 16(1):1–9. doi: 10.1186/s12939-017-0554-6

63. Peltzer K, Davids A, Njuho P. Alcohol use and problem drinking in south Africa. *Afr J Psychiatry* (2011) 1(14):30–7. doi: 10.7196/samj.7700

64. Wagner SE, Hurley DM, Hébert JR, McNamara C, Bayakly AR, Vena JE. Cancer mortality-to-incidence ratios in Georgia: Describing racial cancer disparities and potential geographic determinants. *Cancer [Internet].* (2012) 118(16):4032–45. doi: 10.1002/cncr.26728

65. Asadzadeh Vostakolaei F, Karim-Kos HE, Janssen-Heijnen MLG, Visser O, Verbeek ALM, Kiemeney LALM. The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival. *Eur J Public Health [Internet].* (2011) 21(5):573–7. doi: 10.1093/eurpub/ckq120

66. Herd O, Francies FZ, Cairns A, Muller X, Slabbert JP, Baeyens A. Ethnical differences in breast cancer characteristics in south African population. *Breast J* (2015) 21(4):447–9. doi: 10.1111/tbj.12434

67. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, et al. South African national HIV prevalence, incidence and behaviour survey, 2012. *HSRC Press Cape Town: HSRC Press;* (2014) 194.

68. Johnson LF. Access to antiretroviral treatment in south Africa, 2004 - 2011. *South Afr J HIV Med* (2012) 13(1):1–16. doi: 10.4102/sajhivmed.v13i1.156

69. Li Y, Zheng J, Deng Y, Deng X, Lou W, Wei B, et al. Global burden of female breast cancer: Age-Period-Cohort analysis of incidence trends from 1990 to 2019 and forecasts for 2035. *Front Oncol* (2022) 12:1–13. doi: 10.3389/fonc.2022.891824

70. Statistics South Africa, StatsSA. *Statistical release P0302: Mid-year population estimates* Vol. 2020. Stats SA (2020) p. 1–22. Available at: https://www.statssa.gov.za/publications/P0302/P03022022.pdf.

71. Loney T, Nagelkerke NJ. The individualistic fallacy, ecological studies and instrumental variables: A causal interpretation. *Emerg Themes Epidemiol.* (2014) 11 (1):1–6. doi: 10.1186/1742-7622-11-18

72. South African National Department of Health. *BREAST CANCER CONTROL POLICY* (2016). Available at: https://www2.tri-kobe.org/nccn/guideline/breast/english/breast.pdf.

frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 28 February 2023
DOI 10.3389/fonc.2023.1079037

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cancer Epidemiology and Prevention, a section of the journal Frontiers in Oncology

RECEIVED 24 October 2022
ACCEPTED 10 February 2023
PUBLISHED 28 February 2023

CITATION
Stevens C, Hightower A, Buxbaum SG, Falzarano SM and Rhie SK (2023) Genomic, epigenomic, and transcriptomic signatures of prostate cancer between African American and European American patients. *Front. Oncol.* 13:1079037. doi: 10.3389/fonc.2023.1079037

Genomic, epigenomic, and transcriptomic signatures of prostate cancer between African American and European American patients

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Prostate cancer is the second most common cancer in men in the United States, and racial disparities are greatly observed in the disease. Specifically, African American (AA) patients have 60% higher incidence and mortality rates, in addition to higher grade and stage prostate tumors, than European American (EA) patients. In order to narrow the gap between clinical outcomes for these two populations, genetic and molecular signatures contributing to this disparity have been characterized. Over the past decade, profiles of prostate tumor samples from different ethnic groups have been developed using molecular and functional assays coupled with next generation sequencing or microarrays. Comparative genome-wide analyses of genomic, epigenomic, and transcriptomic profiles from prostate tumor samples have uncovered potential race-specific mutations, copy number alterations, DNA methylation, and gene expression patterns. In this study, we reviewed over 20 published studies that examined the aforementioned molecular contributions to racial disparities in AA and EA prostate cancer patients. The reviewed genomic studies revealed mutations, deletions, amplifications, duplications, or fusion genes differentially enriched in AA patients relative to EA patients. Commonly reported genomic alterations included mutations or copy number alterations of *FOXA1, KMT2D, SPOP, MYC*, *PTEN*, *TP53*, *ZFHX3*, and the *TMPRSS2-ERG* fusion. The reviewed epigenomic studies identified that CpG sites near the promoters of *PMEPA1*, *RARB*, *SNRPN*, and *TIMP3* genes were differentially methylated between AA and EA patients. Lastly, the reviewed transcriptomic studies identified genes (e.g. *CCL4, CHRM3*, *CRYBB2*, *CXCR4, GALR1*, *GSTM3*, *SPINK1*) and signaling pathways dysregulated between AA and EA patients. The most frequently found dysregulated pathways were involved in immune and inflammatory responses and neuroactive ligand signaling. Overall, we observed that the genomic, epigenomic, and transcriptomic alterations evaluated between AA and EA

prostate cancer patients varied between studies, highlighting the impact of using different methods and sample sizes. The reported genomic, epigenomic, and transcriptomic alterations do not only uncover molecular mechanisms of tumorigenesis but also provide researchers and clinicians valuable resources to identify novel biomarkers and treatment modalities to improve the disparity of clinical outcomes between AA and EA patients.

KEYWORDS

prostate cancer, racial disparity, African American (AA), European American (EA), genomics, epigenomics, transcriptomics

1 Introduction

Prostate cancer is the second most common cancer in men with one of the highest incidence rates in the United States (1). It has the second highest mortality rate relative to other malignancies, but the severity of clinical outcomes is reported to vary by race and ethnicity (1). Specifically, African American (AA) men have the highest prostate cancer incidence rate amongst racial or ethnic groups in the United States (2). For example, 1 in 6 AA men are diagnosed with prostate cancer in their lifetime, compared to 1 in 8 European American (EA) men, and the incidence is nearly 60% higher for AA men (2). Moreover, AA prostate cancer patients present with higher grade and stage tumors and have a nearly 2-fold higher mortality rate when compared to EA prostate cancer patients (2). Specifically, AA men have a prostate cancer mortality rate of 37.4 per 100,000 in the period of 2014-2018 versus 19.3 per 100,000 among white non-Hispanic men (3). Furthermore, prostate cancer has a higher growth and metastatic transformation rate for AA men compared to EA men (4). It has been reported that low-grade prostate cancer cells grow and spread more quickly in AA than men of other races (5).

This discrepancy between clinical outcomes appears to be attributable to socioeconomic factors that may cause barriers to medical access, diagnosis, and treatment among AA men (6). For example, AA men experience substandard testing of prostate specific antigen (PSA) relative to their EA counterparts, leading to limited access to early detection of prostate cancer (7–9). In addition to socioeconomic factors, biological factors may further widen the gap between clinical outcomes for AA men relative to EA counterparts. For example, Cheng et al. reported that AA men were more likely to develop prostate cancer relative to their EA counterparts in California after correcting for socioeconomic status (10). Another study emphasizes that the investigation of race-specific biological differences needs to be viewed through a multifactorial lens because factors such as environment, social status, and genetic inheritance can lead to different mechanisms of prostate tumorigenesis in a combinatorial manner (11). Currently, there is lack of comprehensive understanding on the different biological contributions to prostate tumorigenesis between AA and EA patients.

To elucidate possible biological determinants of racial disparities in prostate cancer, prostate tumor cells and tissues from AA and EA patients were obtained through various methods (e.g. transrectal ultrasound (TRUS)-guided biopsy, transperineal biopsy, transurethral resection, prostatectomy, radical prostatectomy), and genetic and molecular assays have been performed with the obtained samples. Over the past two decades after next generation sequencing (NGS) technologies were introduced, prostate tumor samples have been studied using genetic and molecular assays that are coupled with sequencing. Using NGS and microarray techniques that can evaluate genome-wide signals at once, many studies have characterized genetic (e.g. mutations, copy number alterations, fusions) and molecular features (e.g. epigenetic alterations, gene expression changes) of prostate tumors through the lens of AA and EA patient outcome disparities.

Here, we have listed findings from over 20 published studies that profiled the genomes, epigenomes, and transcriptomes of prostate tumor tissues of AA and EA patients. Studies were identified by inputting the following key words into the PubMed search query: “African-American” AND “prostate cancer”. For each category (genome, epigenome, transcriptome), search terms were changed to DNA, methylation, and RNA, respectively. Studies were deemed to be within the scope of this review if they were written in the English language and performed using prostate tumor tissue samples from AA and EA patients, clearly reporting the cohort sizes and methods used. Moreover, we only included studies that directly compared genetic, epigenetic, or transcriptomic profiles of prostate tumor tissues between AA and EA patients (Tables 1–3). These studies uncovered potential race-specific mutations, copy number alterations, fusions, and aberrant DNA methylation and gene expression patterns, using varied methods of DNA, DNA methylation, and RNA analysis, respectively (Figure 1). This review, which details a bigger picture of prostate cancer biological signatures, will provide clinicians and researchers with a better understanding of molecular mechanisms of prostate tumorigenesis and facilitate the development of potential biomarkers and treatment modalities to narrow the gap between AA and EA patient outcomes.

TABLE 1 Studies that compared genomic features between AA and EA patients.

PubMed ID	Name	Sample	Total Cohort Size	Cohort Details	Method	Genes Examined	Key Findings
25056375	Khani F et al, 2014 (12)	Radical prostatectomy tissue	218	105 AA and 113 EA	HRM followed by Sanger sequencing, FISH	FISH: *ERG, PTEN* Sequencing: *SPOP*	Less *ERG* rearrangements in AA Less *PTEN* deleted in AA Less *SPOP* mutated in AA
32651179	Koga et al., 2020 (13)	FFPE tissue	861	WES: 250 AA and 611 EA Targeting sequencing: 436 AA and 3018 EA Microarrays: 171 AA and 626 EA	WES, Hybridization capture-based targeted DNA sequencing, SNP 6.0 microarrays	*CDK12, FOXA1, AR, BRAF, BRCA2, BRIP1, CDKN1B, CDK6, CTNNB1, ERF, ETV3, FGFR1, FLCN, JAK1, KEL, KMT2D, KDM6A, MAP3K1, MCL1, MED12, MYC, NOTCH2, PIK3CA, PTCH1, PTEN, SPOP, TMPRSS2, TP53, CCND1, KMT2D, ZFHX3, NKX3-1*	Less *ERG* rearrangements in AA More *KMT2D, ERF, SPOP* loss of function mutations in AA More *MYC, CCND1, HGF* amplifications in AA More *ZFHX3, ETV3* deleted in AA Less *PTEN* deleted in AA
24948877	Koochekpour et al., 2014 (14)	Radical prostatectomy tissue	300	200 AA and 100 EA	Pyrosequencing	*AR*	More *AR* mutated in AA
26921337	Lindquist et al., 2016 (15)	Radical prostatectomy tissue	24	24 AA and publicly available data sets (TCGA and COSMIC) for EA*	WGS	*TMPRSS2-ERG, PTEN, CDC27-OAT*	More *CDC27-OAT* rearranged in AA More *FOXA1* mutated in AA Less *TP53* mutated in AA Less *PTEN* deleted in AA Less *TMPRSS2-ERG* rearranged in AA Less *MYC* amplifications in AA
33115829	Liu et al., 2020 (16)	FFPE tissue	1031	171 AA and 860 EA	Exome sequencing for 39 selected genes OncoScan CNV microarrays	*AKT1, APC, AR, ATM, BRAF, BRCA2, CASZ1, CBX7, CDK12, CDKN1B, CHD1, CST2, CTNNB1, FOXA1, FRG1, HRAS, IDH1, IL6ST, KDM6A, KIF5A, KMT2C, KMT2D, MED12, NIPA2, NKX3-1, PIK3CA, PIK3CB, PTEN, RB1, REST, SCN11A, SPOP, TBL1XR1, THSD7B, TP53, ZFHX3, ZMYM3, ZNF595, ZNF770*	More *ZMYM3, FOXA1, APC, ATM, BRCA2, KDM6A, KMT2C, KMT2D, MED12, ZFHX3, MAP3K7, BNIP3L* mutated in AA Less *SPOP* and *TP53* mutated in AA More *CNAs in MYC, THADA, NEIL3, LRP1B, BUB1B, MAP3K7, BNIP3L*, and *RBI* in AA Less deleted of *RYBP, TP53*, and *TMPRSS2-ERG* in AA
32168400	Liu et al., 2020 (17)	FFPE tissue	288	147 AA and 141 EA	PCR-RFLPs	*TP53*	No difference in *TP53* mutation frequency between EA and AA

*Generated as part of a previous study.

2 Genomic alterations linked to African American prostate cancer patients

2.1 Methods to profile genomic alterations in cancer

Cancers develop due to the accumulation of genetic alterations such as mutations, amplifications, deletions, and fusions. Deletions and inactivating (loss-of-function) mutations are often found at tumor suppressor genes to dysregulate cell division. Conversely, amplifications and activating mutations are found at oncogenes to increase cancer cell proliferation and survival. Moreover, genetic alterations are observed at non-coding regions such as regulatory regions to activate or inactivate genes involved in carcinogenesis.

To identify genetic alterations in cancer cells, polymerase chain reaction (PCR)-based assays, DNA sequencing and hybridization technology have been applied. Classical techniques that have been utilized to parse out short sequences include Sanger sequencing, pyrosequencing, PCR-restriction fragment length polymorphisms (PCR-RFLP) analysis, and High-Resolution Melting (HRM) analysis (33–37). An example of a classical hybridization technique is Fluorescence *in situ* hybridization (FISH), which utilizes a fluorescently labeled probe targeting a specific sequence to detect copy number variations (CNV). The major drawback of all of the above-mentioned methods is that they are limited to specific regions within the genome. To find high-throughput genetic

TABLE 2 Studies that compared DNA methylation features between AA and EA patients.

PubMed ID	Name	Sample	Total Cohort Size	Cohort Details	Method	Genes Examined	Key Findings
33374332	Barry et al., 2020 (18)	FFPE tissue	89	43 AA and 46 EA	Pyrosequencing	*MYC*	Strong association for *MYC* DNA methylation at one CpG site, but no CpG locations studied were observed to be significantly differentially methylated
25864488	Devaney et al., 2015 (19)	Radical prostatectomy tissue	6	3 AA and 3 EA	Human Methylation450 BeadChip arrays and pyrosequencing	*ABCG5, ACOT7, MST1R, SPTB, SHANK2, SNRPN, WDR70*	Hypermethylation of *SNRPN, MST1R, ABCG5* in AA relative to EA
15800905	Enokida et al., 2005 (20)	Radical prostatectomy tissue	121	44 AA and 77 EA	Methylation specific PCR	*GSTP1*	No significant differences between races
20606036	Kwabi-Addo et al., 2010 (21)	Radical prostatectomy tissue	100*	39 AA and 67 EA*	Methylation specific PCR	*GSTP1, AR, RARB, SPARC, TIMP3, NKX2-5*	Differential methylation of *RARB, SPARC, TIMP3*, and *NKX2-5* between AA and EA patients No significant differences in methylation of *GSTP1* between AA and EA patients
26902887	Rubicz et al., 2019 (22)	FFPE tissue	76	76 AA and 476 EA**	Human Methylation450 BeadChip arrays	450,000 CpG sites throughout the genome	Hypermethylation of *STOX7, SNRPN, TIMP3*, and *PMEPA1* in AA relative to EA with no corresponding changes in mRNA levels
24694733	Sharad et al, 2014 (23)	Radical prostatectomy tissue	77	35 AA and 42 EA	COMPARE-MS (methylated-DNA precipitation and methylation specific restriction enzymes) followed by qPCR	*PMEPA1, GSTP1*	Hypermethylation of *PMEPA1* in AA relative to EA No significant difference in hypermethylation of *GSTP1* between AA and EA
12692786	Woodson et al., 2004 (24)	FFPE tissue	111	47 AA and 67 EA	Methylation specific PCR	*GSTP1, CD44, E-cadherin*	No significant difference in hypermethylation of *GSTP1* between AA and EA Hypermethylation of *CD44*, higher frequency amongst AA patients relative to EA patients No differential methylation of *E-cadherin*

*Based on Table 1 of Kwabi-Addo et al. (21)
**Generated as part of a previous study.
FFPE, Formalin-fixed, paraffin-embedded.

alterations across the genome, DNA microarray-based and NGS techniques were developed (38, 39). DNA microarray technology determines the number of copies of particular genomic regions through sequence-primer hybridization (40, 41). CNV microarrays such as OncoScan can characterize CNVs in 900 cancer genes and 300kb region outside of the cancer genes throughout the genome, based on hybridization (42).

Two main NGS applications have allowed for high-throughput detection of genetic alterations in tumors: targeted DNA sequencing, and whole genome sequencing (WGS) (43, 44). While WGS determines the sequence of the entire genome, targeted DNA sequencing methods such as hybridization capture NGS and amplicon-based NGS sequence specific DNA fragments (44, 45). One major application for targeted DNA-sequencing is the targeting of exons throughout the genome, also known as whole exome sequencing (WES). Overall, DNA microarrays, WES, and WGS have been essential to elucidating cancer-associated mutations and focal copy number alterations, and large-scale chromosomal copy number alterations.

2.2 Genomic alterations frequently observed in prostate tumors

Prostate tumors often harbor inactivating, or loss of function (LOF), mutations or deletions in tumor suppressor genes involved in pathways regulating cell cycle, DNA repair, and transcriptional regulation. Genetic alterations identified at the greatest frequency in prostate cancer related to cell cycle include mutations at *TP53, RB1*, *PTEN*, and deletions at chromosome 10q containing *PTEN* (46–48). Several studies state that *ZFHX3*, which functions to inhibit prostate carcinogenesis by suppressing *MYC* overexpression, is correlated to improved patient survival (49). It is reported that *ZFHX3* is deleted or contains a LOF mutation in prostate tumors (50). Notable tumor

TABLE 3 Studies that compared transcriptomic features between AA and EA patients.

PubMed ID	Name	Sample	Total Cohort Size	Cohort Details	Method	Key Findings
31107158	Echevarria et al., 2019 (25)	Radical prostatectomy tissue	635	127 AA 508 EA	Human Exon 1.0 ST microarrays	*APOD, BCL6, EMP1, MYADM, SRGN* and *TIMP3* upregulated in AA
27359067	Hardiman et al., 2016 (26)	Radical Prostatectomy issue	27	10 AA and 17 EA	TruSeq RNA library preparation kit	Immune and inflammatory genes (ie. *IL2RG, CD1C, CD207, CCL4, CCL8, CXCR4*) upregulated in AA
34680291	Hardiman et al., 2021 (27)	Prostatectomy and biopsy tissue	60	33 AA and 27 EA	TruSeq RNA library preparation kit	*THBS4, CREB3L1, TNN, COL4A4, COL4A3, COL2A1, FGF12, MYC, GNG13, AGTR1, F2RL2, NPY4R*, and *GRIN3A* upregulated in AA *SGK1, ANGPT, FGF11, IL4, IL6, ANGPT4, THBS2, FLT4, NTRK2, PIK3R6, LAMA5 MET, GABRP, ADORA2B, TACR1, TAAR1* and *GABRQ* downregulated in AA
34692584	Nagaya et al., 2021 (28)	Radical prostatectomy tissue	61	31 AA and 30 EA	Ovation universal RNA-seq library preparation kit	*S1PR3* upregulated in AA and *GALR1, CHRM3* and *NPFFR1* downregulated in AA
34316327	Rahmatpanah et al., 2021 (29)	Radical prostatectomy tissue	45	15 AA and 30 EA	TruSeq RNA library preparation kit	*GRIN3A* downregulated in AA
34083737	Rayford et al., 2021 (30)	Radical prostatectomy tissue	1,152	596 AA and 556 EA	Human Exon 1.0 ST microarrays	*CRYBB2* and *GSTM3* upregulated in AA
19724911	Timofeeva et al., 2009 (31)	Radical prostatectomy tissue	27	14 AA and 13 EA	GeneChip HG-U133A 2.0 microarrays, qRT-PCR	*SOS1* upregulated in AA
18245496	Wallace et al., 2008 (32)	Radical prostatectomy tissue	69	33 AA and 36 EA	GeneChip HG-U133A 2.0 microarrays	No difference observed

suppressor genes involved in transcriptional regulation that are frequently deleted or mutated in prostate tumors include *SPOP, MED12, CHD1*, and *ZNF292* (51).

The aforementioned genetic alterations are somatically acquired during tumorigenesis. Germline mutations including *BRCA1*, *BRCA2*, *HOXB13*, *CHEK2*, and *ATM* mutations have been associated with hereditary prostate cancer (52). One of the most common mutations is in *BRCA2* (47, 52). *BRCA1/2*, known as tumor suppressor genes, mediate double-strand break DNA repair (53). *BRCA1/2* mutations are not only associated with an increased risk of prostate cancer, but also with an aggressive prostate cancer phenotype, such as higher grade, advantaged stage, and poor survival (54, 55). *HOXB13* is important in prostate development and this mutation was observed in 0.7-1.4% of prostate cancers, and 6% of early-onset prostate cancer (56). *HOXB13* mutations are also associated with an increased hereditary prostate cancer risk (57, 58). Lu et al. found that the *HOXB13* mutation disrupts the interaction between HOXB13 and histone deacetylase 3 (HDAC3), an epigenetic modifier (59).

Genetic alterations such as fusions, amplifications, translocations, and gain-of function (GOF) mutations are found in oncogenes in prostate cancer. As reported in various studies, androgen receptor (*AR*) has been increasingly implicated in prostate cancer (60). AR is a key transcription factor playing a critical role in prostate cancer initiation and progression. It leads to prostate cancer cell proliferation by mediating transcription of pro-mitotic genes (61, 62). Androgen binding induces a conformational change, resulting in its nuclear translocation (63, 64). Subsequently, AR binds at specific genomic regions and activates transcription of its numerous target genes (64).

Since up to 90% of prostate cancer is dependent on androgens at diagnosis, androgen signaling has been considered a pivotal therapeutic target. Androgen deprivation therapy (ADT), either alone or in combination with chemotherapy, is the mainstay of initial treatment for advanced, high-grade and stage, prostate cancer, albeit many patients eventually will develop progressive disease referred to as castration-resistant prostate cancer (CRPC) (64–66). *AR* genetic alterations including mutations and amplifications are observed in prostate cancer as well as alternative splicing events. There are four domains of AR: amino-terminal transcriptional domain (NTD), DNA-binding domain (DBD), hinge region, and a carboxy-terminal ligand-binding domain (LBD) (66). Splicing variants encode truncated AR forms, such as AR-V7, lacking the LBD and thus making the protein constitutively active regardless of the presence of androgens (67). Interestingly, *AR* mutations and amplification events are nearly

10.3389/fonc.2023.1079037

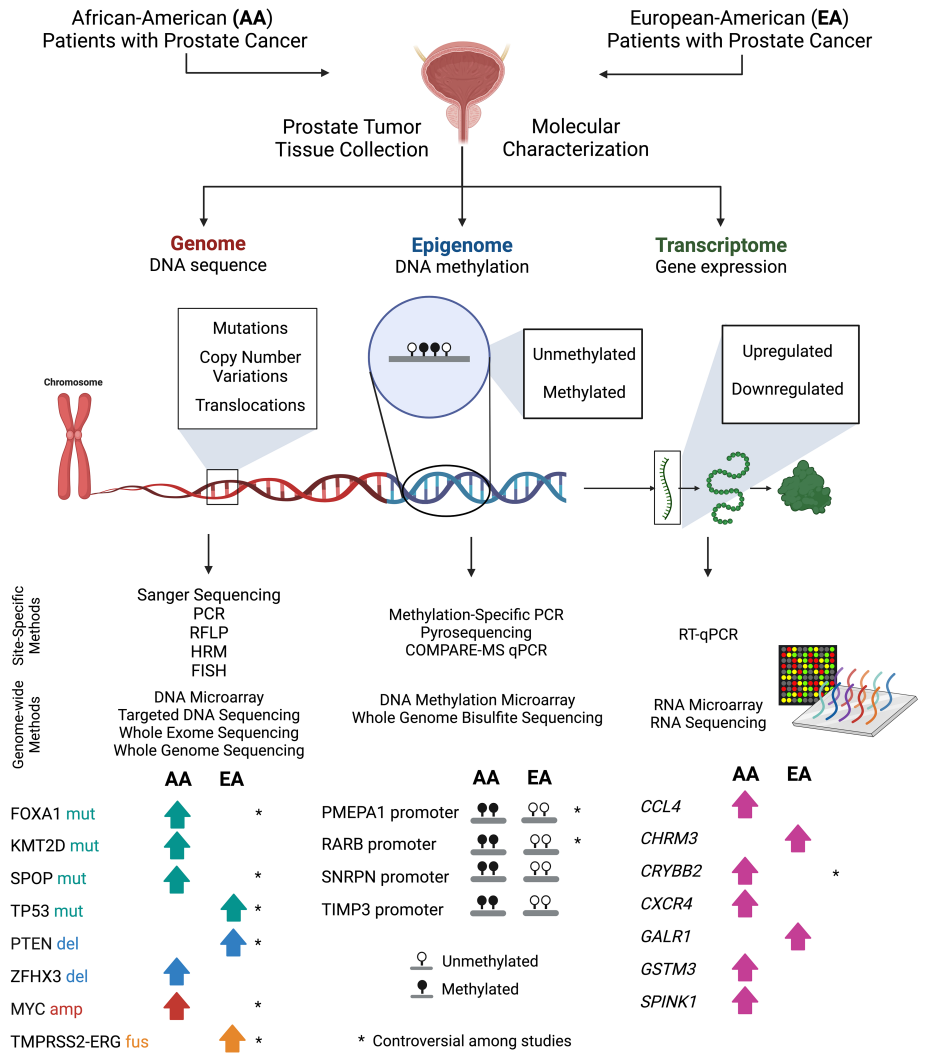

FIGURE 1
Approaches to compare molecular genetic signatures in prostate tumor tissue samples obtained from AA and EA patients. In reviewed studies, prostate tumor tissue samples from both EA and AA patients were collected by either biopsy or prostatectomy. DNA or RNA material was extracted from aforementioned samples and then prepared for molecular characterization at the genome, epigenome, and transcriptome levels. Studies profiled the signatures of prostate tumor tissues using site-specific techniques and genome-wide utilized high-throughput hybridization (microarray) and next-generation sequencing (NGS) technologies. Subsequently, AA and EA patient sample data was compared to uncover potential molecular differences between the two subpopulations. Key molecular differences found by several studies and discussed in this review were included. Comparisons that were not found to have consistent data across studies (or controversial) was denoted with an asterisk (*). PCR, Polymerase chain reaction; RFLP, Restriction fragment length polymorphisms; HRM, High resolution melting analysis; FISH, Fluorescence *in situ* hybridization; and COMPARE-MS, Combination of methylated-DNA precipitation and methylation-sensitive restriction enzymes assay.

exclusively found in metastatic prostate tumor samples, but not in primary tumor samples. *AR* mutation burden usually increases with tumor stage, and alterations oftentimes involve missense mutations in the LBD (68). In this way, there is less specificity of the domain overall, as AR activation can be induced by various ligands beyond its non-pathological activators (68, 69).

Downstream and upstream effectors of AR are also found to be altered in primary tumor samples (47). The most frequent gene rearrangements found in primary prostate tumors are those involving *TMPRSS2* (Transmembrane Serine Protease 2) and members of the *ETS* (erythroblast transformation specific transcription factor) family transcription factors. The *ETS* family includes *ERG*, *ETV1*, *ETV4*, and *FLI1* which can all form fusions with *TMPRSS2*. In the Cancer Genome Atlas (TCGA) prostate adenocarcinoma data, 53% of tumors were found to have *ETS* family gene fusions. The *ETS* family gene members involved in the fusions, the most common being *ERG* (46%), were found to be mutually exclusive. The promoter of *TMPRSS2-ERG* gene is reported to be bound by AR. Interestingly, *AR* genetic aberrations and the fusion proteins under its regulation are seen at variable relative levels. Moreover, most of the *TMPRSS2-ETS* fusion positive tumors also contained *PTEN* deletions (47).

The next most common genetic alterations found in prostate tumors include mutations in *SPOP*, *FOXA1*, and *IDH1*. Interestingly, *SPOP* and *FOXA1* mutant tumors were found to be both mutually exclusive with *TMPRSS2-ETS* fusions and had higher

AR transcriptional activity (47). Lastly, the presence of amplifications, insertions, and deletions, also known as copy number alterations (CNAs), have been shown to be directly correlated to disease severity. For example, *CHD1* deletions and *SPOP* mutations frequently co-occur in prostate tumors (47). Prostate tumors with whole chromosomal arm gains or losses are associated with high grade, Gleason score, and PSA levels (47). Common amplifications span the oncogenes *MYC* (8q24.21), *CCND1* (11q13.2), *FCFR* (12p11.21), and *NSD3* (8p11.23) and common deletions span tumor suppressor genes *PTEN* (10q23), *TP53* (17p13.1), *CDKN1B* (12p13.1), *MAP3K1* (5q11.2 & 6q.12-22), *FANCD2* (3p26), *SPOPL* (2q22.1), and *FOXP1/RYBP/SHQ1* (3p13) (47). Interestingly, aggressive prostate tumors with greater mutational burden or with higher CNA frequencies have more mutations at *KMT2D, TP53*, and *KDM6A* and a higher frequency of *MYC* amplifications (47).

2.3 Genomic alterations differentially identified in AA and EA prostate cancer patients

Due to the reported outcome disparities between AA and EA men with prostate cancer, many studies have sought to evaluate potential genetic alteration differences between tumors obtained from these two subgroups. When we searched for studies that performed their own DNA-sequencing (WGS and WES) or genetic alteration analysis in prostate tumor tissue samples from AA and EA, we found six studies that fulfilled inclusion criteria (12–17) (Table 1). All analyzed data were based on self-identified race, in lieu of comparing samples using ancestry-specific analysis. Sample sizes for participated AA and EA prostate cancer patients varied across studies, as well as methodologies.

Among somatic mutations commonly found in prostate cancer, *TP53, PTEN*, and *ZFHX3* mutations affect cell cycle and growth. As previously mentioned, *TP53* loss of function mutations are relatively common in prostate tumor samples. Two studies, Lindquist et al. and Liu et al., which evaluated DNA with WGS and targeted exome sequencing, respectively, reported that AA patients had relatively less *TP53* inactivating mutations than EA patients (15, 16). Another two studies, Koga et al. and Liu et al., which used WES and PCR, respectively, found that there was no significant difference in *TP53* mutation frequency between AA and EA (13, 17). The correlation between *PTEN* loss and race is largely unclear. The frequency of *PTEN* loss was not found to be significantly different between AA or EA prostate cancer patients by Khani et al. (12) and and Liu et al. (16); the two studies used FISH and the Affymetrix OncoScan FFPE SNP CNV microarray to assess CNV status, respectively (12, 16). However, two other studies reported that *PTEN* loss was less frequent in AA patient tumors using WGS and WES, respectively (13, 15). The *ZFHX3* gene has been found to be more frequently deleted or contain a LOF mutation in AA patients relative to EA across several studies (13, 16). This distinction can prove important to the treatment of AA prostate cancer since functional *ZFHX3* is necessary for effective ESR2 (aka ERß) agonist treatment (49).

Genetic alteration frequency of two genes, *SPOP* and *KMT2D*, which regulate the transcriptional process were investigated between AA and EA across multiple studies. Results describing the frequency of *SPOP* mutations in both AA and EA tumor samples varied. For example, Koga et al. (13) found a higher frequency of *SPOP* mutations in AA compared to EA when considering all tumors, regardless of primary or metastatic, whereas Liu et al. (16) found that the frequency of *SPOP* mutations was lower in AA patients. Additionally, two studies found no differences in mutation frequency between AA and EA (12, 15). *KMT2D* mutations, which are associated with more aggressive disease, were found at a greater frequency in AA patients in multiple studies (13, 16).

Genetic alterations in genes related to androgen signaling (*AR* and *FOXA1*) were also evaluated by multiple studies. The study by Koochekpour et al, which used PCR analysis, found that *AR* mutations were more frequent in AA prostate cancer patient samples than EA (14), but two other studies found no difference in mutation frequency (13, 16). *FOXA1* was found to have a greater mutation frequency in AA patients (15), whereas another study found it not to be statistically significantly different (13). *MYC* amplification was a point of contention between studies. Lindquist et al. reported that AA patients were less likely to have *MYC* amplification (15), whereas other studies reported that AA patients were more likely to have *MYC* amplification (13, 16).

Fusion events were found in many prostate tumors, but these findings were observed in datasets overwhelmingly obtained from EA patient populations, such as the TCGA dataset. Multiple studies found that *TMPRSS2-ERG* fusions were less prevalent in AA patients relative to EA patients (13, 15, 16, 70, 71). Although the absence of these fusions has not been associated with a worse prognosis, the significant difference in prevalence demonstrates the need to evaluate previously established genetic biomarkers of disease in AA patient populations (72). Interestingly, a novel gene fusion, *CDC27-OAT*, was shown to be either specific or more common in AA patients (15).

Other genetic alterations not previously associated with prostate cancer were found to be significantly different between AA that EA patient samples. Lindquist et al. described that those frequent mutations in two genes (*MUC3A* and *PRIM2*) were found more commonly in AA tumor samples, which could be potentially carcinogenic (15). These genes encode proteins involved in cell growth and survival, and DNA replication, respectively. The study by Koga et al. identified a novel deletion spanning *ETV3* (1q23.1), another *ETS* transcription factor, in AA tumor samples (13).

Overall, most of these studies addressing racial differences did not have consistent results for genes related to prostate carcinogenesis although *ZFHX3* and *KMT2D* alterations were found in multiple studies at a greater frequency in AA patients and were associated with increased disease severity. It is possible that a subset of genetic alterations may at least in part contribute to the clinical disparities seen between AA and EA prostate cancer patients. It is therefore important to fully interrogate more samples to understand the contribution of genomic difference to the severity of disease using DNA-sequencing techniques.

3 Epigenomic alterations linked to African American prostate cancer patients

3.1 Methods to profile epigenomic alterations in cancer

Epigenetic alterations change the chromatin state and structure to regulate gene expression without changes in DNA sequence in cancer cells. Chromatin state and structure are important for the maintenance of cell states. Nucleosome positioning, histone modifications as well as DNA methylation define the status and identity of each cell, and they are maintained throughout the cell cycle (73–77). Non-coding RNAs (ncRNAs) are also reported to regulate gene expression and chromatin state to control cell proliferation and differentiation (78). Among those epigenetic alterations, DNA methylation analysis is used most often because DNA samples obtained for the DNA methylation analysis are easily isolated and stored from diverse tissue types. Additionally, DNA methylation analysis can be performed with a small amount of DNA (79).

Classical DNA methylation methodologies include methylation-specific PCR (MSP), pyrosequencing, and Luminometric Methylation Assay (LUMA). MSP involves PCR at a specific CpG site of-interest using site-specific primers, one for methylated CpG and the other for unmethylated CpG detection (80). Although this method interrogates the DNA methylation status at a specific site of interest, the drawback is that only one or two CpG sites can be assessed at a time. Additionally, MSP is difficult to perform in regions that are not CpG islands (81). Pyrosequencing detects DNA methylation levels of CpG sites in a PCR product (82). The advantages of this method are that it is time-efficient, quantitative, and can detect even small differences in methylation (83). However, primer design is difficult, and only a short region can be analyzed (83).

To profile DNA methylation at multiple sites at once, multiple techniques were developed. LUMA technology, which was based on the combined methylation-sensitive restriction enzyme DNA cleavage and pyrosequencing-based polymerase extension, was one of the earliest developed methods (84). A combined method such as Combination of methylated-DNA precipitation and methylation-sensitive restriction enzymes (COMPARE-MS) assay, which uses PCR products of DNA first digested by methylation-sensitive restriction enzymes then precipitated by methyl-binding domain polypeptides, was also developed to detect CpG island DNA methylation (85). However, these assays are only capable of detecting differences in DNA methylation within methylation-sensitive restriction enzyme cut sites, which are not uniformly distributed in the genome. Therefore, these assays cannot exhaust all of the CpG sites in the genome.

To better profile DNA methylation sites, genome-wide, high-throughput techniques coupled with NGS and microarrays have been developed. Methyl-CpG-binding domain sequencing (MBD-seq) and methylated DNA immunoprecipitation sequencing (MeDIP-seq) are based on affinity purification using antibodies (86). Genomic DNA is prepared, sheared, denatured, and then immunoprecipitated. Pull down of methylated DNA is possible by using MBD-seq or MeDIP-seq methodologies (81). MBD proteins bind to double-strand methylated DNA using the methyl-binding domain while MeDIP uses a 5-methylcytosine monoclonal antibody against single-strand DNA (87). Both techniques are cost-effective, are capable of distinguishing between 5mC and 5hmC, induce no mutations, and provide no limitations to enzyme recognition sites. However, both methods are biased toward hypermethylated regions (86). MBD methods tend to be more sensitive to enrichment of CpG islands compared to MeDIP, while MeDIP provides relatively superior profiling of enrichment regions with lower CpG density (86).

Subsequent technologies using bisulfite conversion coupled with hybridization (i.e. DNA methylation microarrays) or sequencing (i.e. whole genome bisulfite sequencing) have been developed to provide insight as to the DNA methylation state of regions of-interest simultaneously and globally. The DNA methylation arrays that are most used were developed by Illumina. The Illumina methylation assay uses BeadChip to generate a genome-wide methylation profile. Similar to pyrosequencing, this method quantifies methylation levels at individual CpG loci within the genome (88). The bisulfite-converted DNA is amplified, fragmented, and hybridized to probes on the microarray, providing targeted-enrichment of methylated regions (89). The main advantages of the DNA methylation microarray method include cost-effectiveness, time-efficiency, and the low DNA input required (51, 89, 90). The initial Infinium Human Methylation27 (HM27) BeadChip contains 27,578 CpG sites. Later, Illumina developed the Infinium Human Methylation450 (HM450) BeadChip assay which interrogates 482,421 CpG sites, including 90% of the sites on the HM27 (89). More recently, the Infinium Methylation EPIC (EPIC) BeadChip has been developed, containing over 850,000 CpG sites including promoters, enhancers, and open chromatin regions (91).

Whole genome methylation sequencing utilizes NGS techniques to obtain DNA methylation data that can include all CpG sites within the genome at single nucleotide resolution (76). Whole genome bisulfite sequencing (WGBS) allows the identification of methylation state at almost every CpG site in the genome, providing highly integrated single base resolution DNA methylation patterning (92). However, this method is high cost, unable to distinguish between 5mC and 5-Hydroxymethylcytosine (5hmC) and causes substantial DNA degradation after bisulfite treatment (86). Reduced representation bisulfite sequencing (RRBS) applies WGBS techniques to specific regions of interest. Because only a fraction of the genome is sequenced, RRBS is highly sensitive and cost-effective compared to WGBS (86).

DNA methylation changes reported by these techniques in cancer results in the silencing of tumor suppressor genes or activation of oncogenes. Compared to normal cells, the promoter regions of tumor suppressors are hypermethylated whereas the promoter regions of oncogenes are hypomethylated (93). Moreover, cancer-specific enhancer regions are hypomethylated (94, 95). Furthermore, long-range hypomethylated regions such as partially methylated domains are detected in cancer cells (96).

The hypomethylation and hypermethylation of specific CpG sites in cancer allows for the understanding of molecular mechanisms of dysregulated of tumor suppressors and oncogenes (97).

3.2 Heterogeneous DNA methylation patterns among prostate tumors

To understand and characterize DNA methylation states of prostate tumor samples relative to normal prostate tissue, several DNA methylation studies have been performed (47, 92, 98–125). For example, in a review written by Lam et al. (99), six genes (*GSTP1*, *APC*, *RARB*, *PITX2*, *CCND2*, and *PTGS2*) along with their corresponding CpG sites were identified as having prognostic importance across several prostate cancer studies (99–125). Of the six genes, *GSTP1, APC, RARB, CCND2*, and *PTGS2* were tumor suppressors identified as having been hypermethylated in prostate tumor tissues. *PITX2*, an oncogene that also bears importance in lung adenocarcinoma, was identified as being hypomethylated in prostate cancer.

Moreover, TCGA, which profiled DNA methylation levels of over 300 prostate tumor tissues using Illumina HM450 arrays, revealed heterogeneous DNA methylation patterns amongst 8 prostate tumor molecular subtypes including: *TMPRSS2-ERG* fusion, *TMPRSS2-ETV1* fusion, *TMPRSS2-ETV4* fusion, *TMPRSS2-FLI1* fusion, *SPOP* mutation, *FOXA1* mutation, *IDH1* mutation, and tumors without genetic alterations (47). For example, *IDH1* mutant tumors exhibited heavy hypermethylation throughout the genome. *SPOP* and *FOXA1* mutant tumors had similar DNA hypermethylation patterns with a moderate number of hypermethylated loci. Compared to *SPOP* and *FOXA1* mutant tumors, two-thirds of *ERG* fusion-positive tumors had relatively low hypermethylated loci. However, one-third of *ERG* fusion-positive tumors had distinct hypermethylation patterns, which include more than twice the number of hypermethylated loci than the remaining two-thirds of the *ERG* fusion-positive tumors. DNA methylation patterns of *ETV1* and *ETV4* fusion-positive tumors were distinct from *ERG* fusion-positive tumors while *FLI1* fusion-positive tumors exhibited similar hypermethylation pattern as the latter two-thirds of the *ERG* fusion-positive tumors, having moderate hypermethylated loci.

Over 150 epigenetically silenced genes in prostate tumors were also identified by TCGA. For example, *SHF, FAXDC2, GSTP1, ZNF154*, and *KLF8* genes had hypermethylated promoters and silenced gene expression across the prostate tumor samples compared to normal prostate samples. In *ETS* fusion-positive tumors, *STAT6* was found to be epigenetically silenced, whereas this silencing was not found in prostate tumors with mutations in *SPOP* and *IDH1*. Unlike other tumor types, *SPOP* mutant tumors had epigenetically silenced *HEXA* (47).

3.3 Differentially methylated regions detected between AA and EA prostate cancer patients

To characterize epigenomic alterations in prostate tumors from AA patients, differential DNA methylation analyses between benign and malignant prostate tissues obtained from AA patients have been performed by multiple research groups. We found seven studies (18–24), of which six investigated DNA methylation signatures at specific genes, and two performed global epigenome analysis (Table 2).

For example, Barry et al. investigated DNA methylation levels at the *MYC* locus (6 CpG sites from exon 3 to the 3′ UTR) in AA and EA prostate cancer patients using pyrosequencing (18). They determined that AA patient samples were relatively hypomethylated at exon 3 of the *MYC* gene, a site that is associated with a higher Gleason score, and therefore severity of disease (18). They showed that DNA methylation level at one of the examined CpG sites is more strongly associated with Gleason score in prostate tumors from AA patients than EA patients. However, subsequent RNA-sequencing data analysis indicated that *MYC* expression was not significantly different regardless of the DNA methylation status at MYC region; the study suggested ncRNA expression to be responsible for the difference (18).

Tang et al. reported that hypermethylation of *RARB* (aka *RARß2*) was significantly associated with a higher risk of prostate cancer in AA men but not in EA men, but this study was not included since it only evaluated cancer risk according to methylation within benign prostate tissue (126). Woodson et al. studied DNA methylation of a set of genes (*GSTP1*, *RASSF1A*, *RARB*, *CD44*, *EDNRB*, *CDH1*, *ANXA2*, and *CAV1*) that were previously implicated in prostate tumorigenesis in AA patient samples and reported that *GSTP1, RASSF1A*, and *RARB* were hypermethylated and *CDH1, EDNRB*, and *CD44* were hypomethylated in tumor samples (24). This group compared the data to EA patients and found no significant differences in overall DNA methylation status for all aforementioned genes, but found *CD44* hypermethylation twice as prevalent in AA men (24). Another study by Kwabi-Addo et al. selected epigenetically altered genes in prostate cancer and found *AR, GSTP1*, *RARB, SPARC, TIMP3*, and *NKX2-5* to be hypermethylated in AA patients (21). Although *TIMP3* was identified by Lam et al. to be hypermethylated in prostate cancer, it was determined to have no prognostic utility. Two of the aforementioned genes, *SPARC* and *NKX2-5*, have been shown to be hypermethylated in prostate cancer (110, 112). When comparing these results with EA samples, Kwabi-Abbo et al. found that there was statistically significant differential methylation solely in the *TIMP3* and *NKX2-5* genes (21).

GSTP1 was also found to be hypermethylated in AA patients by Sharad et al. (23). However, it was not found to be differentially methylated between AA and EA patients. Another study, which investigated the DNA methylation of *GSTP1* across different ethnic groups, also found it universally hypermethylated in prostate cancer, but not significantly different in DNA methylation levels between ethnic groups (20). Sharad et al. also found that the *PMEPA1* gene was found to be significantly more hypermethylated in EA prostate cancer patients compared to AA prostate cancer patients (23). This gene encodes an androgen-sensitive ligase binding protein that is now known to maintain AR protein levels in prostate tissues (23).

Unlike the aforementioned studies that characterized the DNA methylation levels of specific genes of interest, Devaney et al. performed Illumina 450K methylation arrays in AA (7 normal

and 3 cancer) and EA (8 normal and 3 cancer) prostate tumor tissues (19). They identified 25 promoter-associated CpG sites that were differentially methylated by race. The most significantly differentially methylated genes were *MST1R*, *ABCG5*, and *SNRPN* (19). It is important to note that this study had a very small sample size, which may limit statistical power in identifying statistically significantly differentially DNA methylation sites from the array.

Rubicz et al. also performed Illumina HM450 methylation arrays in AA patients, subsequently with RNA-seq (22). They compared DNA methylation levels with EA from Fred Hutch Cancer Research Center (FHCRC) prostate cancer studies (127, 128). They found hypermethylation of *STOX7*, *SNRPN*, *TIMP3*, and *PMEPA1* in AA patients, which were subsequently found to be differentially methylated between AA and EA (22). The hypermethylation of *TIMP3* and *PMEPA1* were found by several other studies (20, 21, 23, 24, 126). However, *SNRPN* hypermethylation did not correspond to lower expression in this study, unlike the findings by Devaney et al. (19). Additionally, they were able to identify differentially methylated regions between AA prostate cancer patients with and without prostate cancer recurrence in the gene bodies and promoter regions of genes involved in specific tumorigenic biological processes such as protein kinase activity and metal ion binding activity. For example, *CDKL2*, *FOXA2*, *NEUROG1*, and *GCK* were found to be hypermethylated at promoter regions with corresponding decreased transcription levels in AA prostate cancer patients with recurrence compared to patients without recurrence (22).

The lack of consistency in the findings between studies could be attributed to insufficient sample sizes, differences of profiling methods, the heterogeneous nature of the subpopulation itself, or non-biological factors. Overall, this shows the necessity for further whole genome methylation sequencing analysis of AA patient prostate cancer tissue samples.

4 Transcriptomic alterations linked to African American prostate cancer patients

4.1 Methods to profile gene expression in cancer

Genomic and epigenomic alterations in tumors lead to the reprogramming of gene expression patterns. Profiling gene expression is crucial to understand carcinogenesis and identify therapeutic targets. For example, amplification of the *MYC* oncogene leads to its overexpression, which in turn activates its target genes, promoting cell proliferation. Moreover, some tumor cells can be targeted directly based on the overexpression of certain transmembrane proteins. For instance, prostate specific membrane antigen (PSMA), which is upregulated in many metastatic prostate tumors, can be targeted with its radiolabeled inhibitor and used for imaging modalities or radiotherapy (129, 130). By comparing gene expression patterns, transcriptional networks and signaling pathways altered in tumors can be also revealed.

In order to better develop the global gene expression profiles of cancer cells, researchers have utilized mRNA quantification techniques such as Reverse Transcriptase Quantitative Polymerase Chain Reaction (RT-qPCR), RNA microarrays, and RNA-sequencing (131, 132). All techniques utilize the conversion of RNA transcripts into cDNA through reverse transcription, but RT-qPCR is limited due to its probing of only known gene regions. Both RNA microarrays and RNA-sequencing are instead capable of profiling entire transcriptomes. However, these two platforms differ in their benefits and limitations. Microarrays allow for the expression profiling of thousands of transcripts through cDNA hybridization using probes simultaneously. This methodology can only interrogate expression of known transcripts and selected exons. It also has a lack of specificity, or high background noise due to cross-hybridization of multiple transcripts to the same probe (132, 133). Examples of microarrays commonly used include the GeneChip Human 525 Exon 1.0 ST, which can interrogate over 1 million exon clusters, with four probes per exon on average. Another commonly used microarray with a smaller breadth of capabilities is the GeneChip HG-U133A 2.0, which interrogates 14,500 well-known genes.

RNA-sequencing instead uses NGS to fully catalog the transcriptome of a sample through sequencing of cDNA transcripts, regardless of whether they are known transcripts or not (134). RNA-sequencing allows for the characterization of transcriptomic features such as alternative splicing events and antisense transcripts (134). The most popular RNA-sequencing technique involves the capture of mRNA based on the presence of polyA tails at the 3' end (polyA RNA-seq); an example of this technique is the Illumina TruSeq RNA library preparation assay (135). Another type of RNA-sequencing (total RNA-seq) is to capture the total RNA after depleting ribosomal RNA, which profiles RNA transcript levels of coding genes, noncoding regions, and small RNAs (136). The major limitation of this method is that it is more expensive than microarray technology. Additionally, RNA-seq libraries are relatively difficult to prepare and analyze compared to RNA microarrays. Overall, when studying global transcriptomic features of tumor cells and tissues, RNA microarrays allow for the consistent generation of tumor expression profiles, and RNA-sequencing technology allows for the discovery of novel transcriptomic events and the quantification of their overall expression.

4.2 Genes and signaling pathways dysregulated in prostate cancer

RNA-sequencing and microarray technologies have been used to analyze the transcriptomes of prostate carcinomas to better understand the gene expression patterns that are specific to the disease and contribute to tumorigenesis. Many of these expression changes are consequences of genomic or epigenomic alterations, which are used to categorize the molecular subtypes mentioned above. Gene expression changes found in prostate cancer can be understood through their effects on AR signaling (137). AR is essential for the normal growth and development of the prostate

gland. Individuals with defective AR signaling do not experience prostate enlargement, and inhibiting AR activity results in reduced prostate size and symptoms (137). During prostate tumor cell transformation and carcinogenesis, AR activity is dysregulated, and androgen dependence and sensitivity is altered. For example, when AR transcriptional activity has been characterized in primary prostate tumors by the expression pattern of the *AR* gene itself as well as the 20 previously described AR target genes, tumors with *SPOP* or *FOXA1* mutations have the highest AR transcriptional activity (47). This pattern is supported by the fact that SPOP mutant has been shown to induce AR signaling (138). FOXA1 mutations in prostate cancer cells are reported to reduce the number of AR binding sites but replaces AR function by increasing the activities of AR target genes (139) AR coactivators and FOXA1 are known to interact with AR by binding to numerous enhancers to increase AR signaling (77). However, AR activity varies among tumors with fusion involving an AR-controlled *ETS* gene (i.e. *TMPRSS2-ERG*, *TMPRSS2-ETV1*, *TMPRSS2-ETV4*, *TMPRSS2-FLI1* fusions) (47). *TMPRSS2-ETS* fusion gene is reported to be regulated by AR, but it is highly expressed in both primary and metastatic prostate tumors, independent of *AR* transcription levels (47). Mechanistic models have been proposed regarding *AR* transcription and signaling, but ultimately the exact mechanisms that result in the formation of molecular subtypes throughout tumorigenesis is unknown (134).

AR signaling alterations are found to be associated with metastatic prostate tumors. For example, the expression of AR-V7 transcript variant that lacks LBD in metastatic prostate tumors is associated with resistance to hormone therapy (140). AR-V7 expression was not associated with the molecular subtypes of primary prostate tumors and AR transcriptional activity, however (47). *AR* expression in metastatic prostate cancer is also reported to altered by epigenetic changes such as enhancer and chromatin interaction changes (141). Additionally, *AR* expression is affected by changes in ncRNA transcripts, and subsequently affects the expression of other ncRNA transcripts (69).

There are additional genes and signaling pathways reported to be altered in prostate cancer. For example, prostate tumor samples with *SPOP* mutations have been associated with the overexpression of *SPINK1* through activating the mitogen-activated protein kinase (MAPK) pathway (142). Other significant pathways found to be upregulated in prostate tumors are the phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), Ras/MAPK, DNA repair, and receptor tyrosine kinase pathways (143, 144).

4.3 Genes differentially expressed between AA and EA prostate cancer patients

Characterizing the genes and pathways linked to AA prostate tumor samples will allow researchers to better understand differences in tumor progression and treatment response between subgroups. When we searched studies that generated RNA-sequencing or microarray data from prostate tissue samples, and directly compared gene expression profiles between AA and EA prostate cancer patients, we found eight different studies (25–32) (Table 3).

The largest study among the 8 studies was performed by Rayford et al., which analyzed the gene expression patterns between 596 AA and 556 EA prostate cancer patients using the Human Exon 1.0 ST microarrays, as well as TCGA RNA-seq data (30). Major findings included the significant association of *SPINK1* overexpression in AA patients relative to EA patients, and lack of *TMPRSS2-ERG* fusions (30). SPINK1 was also found to be overexpressed at the protein level more frequently in AA patient samples in the study by Khani et al. (12). The lack of *TMPRSS2-ERG* fusions in AA patients was also noted in patient samples analyzed by Echevarria et al. (25). Indeed, five (*BCL6*, *EMP1*, *MYADM*, *SRGN*, and *TIMP3*) of the six differentially expressed genes (*APOD*, *BCL6*, *EMP1*, *MYADM*, *SRGN*, and *TIMP3*) that Echevarria et al. suggested to be useful as AA-specific prostate cancer biomarkers were primarily present in the *TMPRSS2-ETS* fusion negative tumor samples (25).

Additionally, Rayford et al. found that the *CRYBB2* and *GSTM3* genes were upregulated in AA prostate cancer patients than EA patients (30). These genes were also reported to be upregulated in TCGA prostate cancer AA patients. *CRYBB2* specifically was found by two studies to be overexpressed in AA men (28, 30) while another study indicated that it was underexpressed in AA men relative to EA men prostate tissue samples (29). Rayford et al. also reported that the biological pathways upregulated in AA patients were related to inflammatory response (e.g. *IL33, IFNG, CCL4, CD3, ICOSLG*), whereas the biological pathways upregulated in EA patients were related to DNA repair (e.g. *MSH2*, *MSH6*), metabolism, cell proliferation, and cell cycle (30). Inflammatory and immune pathway dysregulation was noted by other studies as well. A study by Hardiman et al. in 2016, which performed RNA-sequencing in 10 AA and 17 EA prostate cancer patients, observed that multiple immune and inflammatory pathways (e.g. *IL2RG*, *CD1C*, *CD207*, *CCL4*, *CCL8*, *CXCR4*) were upregulated in AA patients relative to EA patients (26). A study by Rahmatpanah et al., which analyzed RNA-seq data obtained from 15 AA and 30 EA prostate tumors, observed an upregulation of inflammatory and immune pathways (e.g. *CXCL10*, *CXCL2*, *HLA-A*, *CCL2*) (29). Using the Affymetrix GeneChip HU-U133A 2.0 array, Wallace et al. observed upregulation in the inflammatory pathway (e.g. *CXCR4*, *CCL5*, *CCR7*) in tumor samples from 33 AA patients relative to 36 EA patients as well (32).

Nagaya et al. performed RNA-sequencing in prostate tumors from 31 AA and 30 EA men and found 45 differentially expressed genes (28). The identified genes were not involved in the inflammatory and immune pathway. The most notable findings in this study were that four of the 45 differentially expressed genes were found to be in the neuroactive ligand pathway: *GALR1, CHRM3, NPFFR1*, and *S1PR3* (28). *S1PR3* expression level was higher in AA than EA prostate cancer patients whereas *GALR1, CHRM3*, and *NPFFR1* expression level was lower in AA than EA prostate cancer patients (28). Expression changes found for *NPFFR1* and *S1PR3* genes were not reported by other studies (25–32). However, *GALR1* was also found to be downregulated in AA patient samples compared to EA patient samples in one other

study (27) and *CHRM3* was found to be downregulated in two other studies (25, 30). Hardiman et al., which performed RNA-seq in prostate tumors from 33 AA and 27 EA men, reported downregulation of *GALR1* in AA patients relative to EA patients, and reported differential expression of other genes in the neuroactive ligand pathway (27). For example, *GABRP*, *ADORA2B*, *TACR1*, *TAAR1*, and *GABRQ* were modestly downregulated in AA compared to EA, and *AGTR1*, *F2RL2*, *NPY4R* and *GRIN3A* were upregulated in AA compared to EA (27). Rahmatpanah et al. found that *GRIN3A* was also downregulated in AA relative to EA patients (29). The involvement of aberrant neuroactive ligand signaling pathway has been reported in other cancer types (145, 146).

Another pathway found to be differentially expressed between AA and EA prostate cancer patients across studies was the PI3K-Akt pathway, which is involved in cell survival, growth, and proliferation. For example, Rahmatpanah et al. found that genes involved in this pathway such as *PIK3CA* were overexpressed in AA samples relative to EA samples (29). Hardiman et al. also reported that PI3K pathway is altered and that some genes involved in the PIK3-Akt pathway were significantly upregulated (*THBS4*, *CREB3L1*, *TNN*, *COL4A4*, *COL4A3*, *COL2A1*, *FGF12*, *MYC*, and *GNG13*) and downregulated (*SGK1*, *ANGPT2*, *FGF11*, *IL4*, *IL6*, *ANGPT4*, *THBS2*, *FLT4*, *NTRK2*, *PIK3R6*, *LAMA5*, and *MET*) between AA and EA (27). However, these genes were not found to be differentially regulated in the Rahmatpanah study (29).

The Ras/MAPK pathway has also been implicated in prostate cancer. One study by Timofeeva et al. showed the overexpression of *SOS1*, an activator of this pathway, in prostate cancer tissues compared to normal prostate tissues at both mRNA and protein levels (31). The researchers showed that *SOS1* expression was two-fold higher in AA men relative to EA men with prostate cancer (31). Interestingly, its overexpression was correlated to higher Gleason score, indicating that *SOS1* overexpression could be a biomarker for AA disease severity (31).

Although the above eight studies revealed genes that are differentially expressed between AA and EA, these data have not entirely elucidated differences in prostate tumorigenesis in AA versus EA patients. Wallace et al., for example, compared their differentially expressed genes between AA and EA to the top 80 differentially expressed genes in prostate cancer (tumor vs. normal) and found no overlap (32). It is possible, however, that the differentially expressed genes classically found in prostate cancer were not studied with a large amount of AA patient samples, or that there are relatively less significant race-specific biological factors contributing to the progression of disease.

5 Discussion

In this study, we reviewed more than 20 studies that analyzed the genomes, epigenomes, and transcriptomes of prostate tumor tissue samples from AA and EA patients. Although there were several AA-specific alterations reported in more than one study, many of the findings reported by multiple research groups were contradictory to others. Another recent review on prostate tumor genomics also reported that there was no clear association between specific genetic changes and race (147). This could be due to the large variance in sample sizes of both EA and AA groups as the size of samples is crucial for getting statistically significant findings. To further evaluate the biological contributions, if any, to the clinical disparities that disproportionately affect AA men with prostate cancer, there needs to be a greater number of AA-specific studies that take account of genome-wide genomic, epigenomic, and transcriptomic approaches. For example, although there were a significant number of genes that are differentially expressed between normal prostate and prostate cancer, those genes were characterized in patient cohorts that were largely composed of EA men. Additionally, there are very few epigenetic studies relative to the number of genetic and transcriptomic studies. Evaluating prostate cancer in AA men with a whole genome approach with equally large sample sizes could possibly allow researchers to elucidate AA-specific biomarkers. It is recently reported that the RESPOND study (Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress) will characterize molecular genetic signatures from 10,000 AA prostate cancer patients.

Additionally, the methods by which the prostate tissue samples are obtained can bias study results. Prostate tissue for these studies was obtained from patients by different kinds of methods (e.g. biopsy versus prostatectomy, fresh versus frozen versus formalin fixed paraffin embedded tissue (FFPE), etc), which may lead to results that are not comparable. For example, the treatment of tissue samples *ex vivo* (e.g. FFPE) may affect tissue conditions. Moreover, the prostate tumor tissue samples themselves can be heterogeneous within the given subpopulation. For instance, tumor stage, cellularity, and microenvironment can affect genomic, epigenomic, and transcriptomic signals. In addition, there is substantial molecular heterogeneity among prostate tumors. Distinct genetic and molecular signatures have found to define molecular subgroups of prostate cancer. Considering the greater relative incidence and mortality that is suffered by AA men with prostate cancer, it is important that we further characterize prostate cancer molecular subgroups with appropriate AA patient representation.

Lastly, most studies rely on ethnicity information inferred from self-reported ancestry. It has been recently shown by Schumacher et al. that, upon analyzing the GENIE 8.0 registry, genetic mutational frequency differences determined across patients of varying self-reported race were either insignificant or in non-clinically actionable regions as of present, but this study was not included in our analysis due to unclear cohort sizes (148). It is important to confirm and measure ethnicity information from samples using genetic ancestry informative marker data that quantify the high heterogeneity among subpopulations.

In conclusion, to better understand racial disparities in prostate cancer, molecular genetic signatures that are differentially associated between AA and EA patients were characterized using various techniques. By reviewing over 20 published studies, we

revealed that heterogeneous genomic, epigenomic, and transcriptomic alterations are found between AA and EA prostate cancer patients. However, as results are controversial across different studies, additional large-scale investigations that take into account of potential confounding factors are greatly needed. Elucidating molecular mechanisms of tumorigenesis associated with tumor subgroups will provide valuable resources to identify novel biomarkers and treatment modalities to improve the disparity of clinical outcomes between AA and EA patients.

Author contributions

CS and SKR wrote the initial draft and finalized the manuscript. CS, AH, and SKR collected the data and prepared the figure and tables. SKR conceptualized and supervised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Institutes of Health under award numbers R21HG011506, R21CA260082, R21CA264637, U54CA233396, U54CA233444, and U54CA233465, which support the Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center. This work was also supported in part by W81XWH-21-1-0805 grant from the Department of Defense, USC Keck School of Medicine (KSOM) Dean's pilot funding program, and the pilot grant from USC Center for Genetic Epidemiology.

Acknowledgments

We thank other Rhie lab members for providing insightful suggestions.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* (2022) 72(1):7–33. doi: 10.3322/caac.21708

2. Giaquinto AN, Miller KD, Tossas KY, Winn RA, Jemal A, Siegel RL. Cancer statistics for African American/Black people 2022. *CA: A Cancer J Clin* (2022) 72 (3):202–29. doi: 10.3322/caac.21718

3. Johnson JR, Woods-Burnham L, Hooker SE, Batai K, Kittles RA. Genetic contributions to prostate cancer disparities in men of West African descent. *Front Oncol* (2021) 11:770500. doi: 10.3389/fonc.2021.770500

4. Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. *J Urol.* (2010) 183(5):1792–6. doi: 10.1016/j.juro.2010.01.015

5. Mahal BA, Berman RA, Taplin ME, Huang FW. Prostate cancer–specific mortality across Gleason scores in black vs nonblack men. *JAMA*. (2018) 320 (23):2479–81. doi: 10.1001/jama.2018.11716

6. Nyame YA, Cooperberg MR, Cumberbatch MG, Eggener SE, Etzioni R, Gomez SL, et al. Deconstructing, addressing, and eliminating racial and ethnic inequities in prostate cancer care. *Eur Urology*. (2022) 82(4):341–51. doi: 10.1016/j.eururo.2022.03.007

7. Dess RT, Hartman HE, Mahal BA, Soni PD, Jackson WC, Cooperberg MR, et al. Association of black race with prostate cancer–specific and other-cause mortality. *JAMA Oncol* (2019) 5(7):975–83. doi: 10.1001/jamaoncol.2019.0826

8. Kensler KH, Pernar CH, Mahal BA, Nguyen PL, Trinh QD, Kibel AS, et al. Racial and ethnic variation in PSA testing and prostate cancer incidence following the 2012 USPSTF recommendation. *J Natl Cancer Inst* (2020) 113(6):719–26. doi: 10.1093/jnci/djaa171

9. Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL. Racial and ethnic disparities in cancer survival: The contribution of tumor, sociodemographic, institutional, and neighborhood characteristics. *J Clin Oncol* (2018) 36(1):25–33. doi: 10.1200/JCO.2017.74.2049

10. Cheng I, Witte JS, McClure LA, Shema SJ, Cockburn MG, John EM, et al. Socioeconomic status and prostate cancer incidence and mortality rates among the diverse population of California. *Cancer Causes Control.* (2009) 20(8):1431–40. doi: 10.1007/s10552-009-9369-0

11. Nelson WG, Brawley OW, Isaacs WB, Platz EA, Yegnasubramanian S, Sfanos KS, et al. Health inequity drives disease biology to create disparities in prostate cancer outcomes. *J Clin Invest.* (2022) 132(3):e155031. doi: 10.1172/JCI155031

12. Khani F, Mosquera JM, Park K, Blattner M, O'Reilly C, MacDonald TY, et al. Evidence for molecular differences in prostate cancer between African American and Caucasian men. *Clin Cancer Res* (2014) 20(18):4925–34. doi: 10.1158/1078-0432.CCR-13-2265

13. Koga Y, Song H, Chalmers ZR, Newberg J, Kim E, Carrot-Zhang J, et al. Genomic profiling of prostate cancers from men with African and European ancestry. *Clin Cancer Res* (2020) 26(17):4651–60. doi: 10.1158/1078-0432.CCR-19-4112

14. Koochekpour S, Buckles E, Shourideh M, Hu S, Chandra D, Zabaleta J, et al. Androgen receptor mutations and polymorphisms in African American prostate cancer. *Int J Biol Sci* (2014) 10(6):643–51. doi: 10.7150/ijbs.8974

15. Lindquist KJ, Paris PL, Hoffmann TJ, Cardin NJ, Kazma R, Mefford JA, et al. Mutational landscape of aggressive prostate tumors in African American men. *Cancer Res* (2016) 76(7):1860–8. doi: 10.1158/0008-5472.CAN-15-1787

16. Liu W, Zheng SL, Na R, Wei L, Sun J, Gallagher J, et al. Distinct genomic alterations in prostate tumors derived from African American men. *Mol Cancer Res* (2020) 18(12):1815–24. doi: 10.1158/1541-7786.MCR-20-0648

17. Liu W, Zhang Y, Wei S, Bae S, Yang WH, Smith GJ, et al. A CD24-p53 axis contributes to African-American prostate cancer disparities. *Prostate.* (2020) 80 (8):609–18. doi: 10.1002/pros.23973

18. Barry KH, Mohanty K, Erickson PA, Wang D, Shi J, Rose G, et al. MYC DNA methylation in prostate tumor tissue is associated with Gleason score. *Genes (Basel).* (2020) 12(1):12. doi: 10.3390/genes12010012

19. Devaney J, Wang S, Furbert-Harris P, Apprey V, Ittmann M, Wang BD, et al. Genome-wide differentially methylated genes in prostate cancer tissues from African-American and Caucasian men. *Epigenetics.* (2015) 10(4):319–28. doi: 10.1080/15592294.2015.1022019

20. Enokida H, Shiina H, Urakami S, Igawa M, Ogishima T, Pookot D, et al. Ethnic group-related differences in CpG hypermethylation of the GSTP1 gene promoter among African-American, Caucasian and Asian patients with prostate cancer. *Int J Cancer.* (2005) 116(2):174–81. doi: 10.1002/ijc.21017

21. Kwabi-Addo B, Wang S, Chung W, Jelinek J, Patierno SR, Wang BD, et al. Identification of differentially methylated genes in normal prostate tissues from African American and Caucasian men. *Clin Cancer Res* (2010) 16(14):3539–47. doi: 10.1158/1078-0432.CCR-09-3342

22. Rubicz R, Zhao S, Geybels M, Wright JL, Kolb S, Klotzle B, et al. DNA Methylation profiles in African American prostate cancer patients in relation to disease progression. *Genomics.* (2019) 111(1):10–6. doi: 10.1016/j.ygeno.2016.02.004

23. Sharad S, Ravindranath L, Haffner MC, Li H, Yan W, Sesterhenn IA, et al. Methylation of the PMEPA1 gene, a negative regulator of the androgen receptor in prostate cancer. *Epigenetics.* (2014) 9(6):918–27. doi: 10.4161/epi.28710

24. Woodson K, Hanson J, Tangrea J. A survey of gene-specific methylation in human prostate cancer among black and white men. *Cancer Letters.* (2004) 205(2):181–8. doi: 10.1016/j.canlet.2003.11.027

25. Echevarria MI, Awasthi S, Cheng CH, Berglund AE, Rounbehler RJ, Gerke TA, et al. African American Specific gene panel predictive of poor prostate cancer outcome. *J Urology.* (2019) 202(2):247–55. doi: 10.1097/JU.0000000000000193

26. Hardiman G, Savage SJ, Hazard ES, Wilson RC, Courtney SM, Smith MT, et al. Systems analysis of the prostate transcriptome in African–American men compared with European–American men. *Pharmacogenomics.* (2016) 17(10):1129–43. doi: 10.2217/pgs-2016-0025

27. Hardiman G, Savage SJ, Hazard ES, da Silveira WA, Morgan R, Harris A, et al. A systems approach to interrogate gene expression patterns in African American men presenting with clinically localized prostate cancer. *Cancers (Basel).* (2021) 13(20):5143. doi: 10.3390/cancers13205143

28. Nagaya N, Rosenfeld J, Lee GT, Kim IY. RNA-Seq profile of African American men with a clinically localized prostate cancer. *Prostate Int* (2021) 9(3):125–31. doi: 10.1016/j.prnil.2020.11.002

29. Rahmatpanah F, Robles GD, Lilly M, Keane T, Kumar V, Mercola D, et al. RNA Expression differences in prostate tumors and tumor-adjacent stroma between black and white americans. *Oncotarget.* (2021) 12(15):1457–69. doi: 10.18632/oncotarget.28024

30. Rayford W, Beksac AT, Alger J, Alshalalfa M, Ahmed M, Khan I, et al. Comparative analysis of 1152 African-American and European-American men with prostate cancer identifies distinct genomic and immunological differences. *Commun Biol* (2021) 4(1):670. doi: 10.1038/s42003-021-02140-y

31. Timofeeva OA, Zhang X, Ressom HW, Varghese RS, Kallakury BVS, Wang K, et al. Enhanced expression of SOS1 is detected in prostate cancer epithelial cells from African American men. *Int J Oncol* (2009) 35(4):751–60.

32. Wallace TA, Prueitt RL, Yi M, Howe TM, Gillespie JW, Yfantis HG, et al. Tumor immunobiological differences in prostate cancer between African-American and European-American men. *Cancer Res* (2008) 68(3):927–36. doi: 10.1158/0008-5472.CAN-07-2608

33. Sanger F, Coulson AR. A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase. *J Mol Biol* (1975) 94(3):441–8. doi: 10.1016/0022-2836(75)90213-2

34. Sanger F, Nicklen S, Coulson AR. DNA Sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U.S.A.* (1977) 74(12):5463–7. doi: 10.1073/pnas.74.12.5463

35. Saiki RK, Scharf S, Faloona F, Mullis KB, Horn GT, Erlich HA, et al. Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. *Science.* (1985) 230(4732):1350–4. doi: 10.1126/science.2999980

36. Narayanan S. Applications of restriction fragment length polymorphism. *Ann Clin Lab Sci* (1991) 21(4):291–6.

37. Pasay C, Arlian L, Morgan M, Vyszenski-Moher D, Rose A, Holt D, et al. High-resolution melt analysis for the detection of a mutation associated with permethrin resistance in a population of scabies mites. *Med Vet Entomol* (2008) 22(1):82–8. doi: 10.1111/j.1365-2915.2008.00716.x

38. Goodwin S, McPherson JD, McCombie WR. Coming of age: Ten years of next-generation sequencing technologies. *Nat Rev Genet* (2016) 17(6):333–51. doi: 10.1038/nrg.2016.49

39. Slatko BE, Gardner AF, Ausubel FM. Overview of next generation sequencing technologies. *Curr Protoc Mol Biol* (2018) 122(1):e59. doi: 10.1002/cpmb.59

40. Pollack JR, Perou CM, Alizadeh AA, Eisen MB, Pergamenschikov A, Williams CF, et al. Genome-wide analysis of DNA copy-number changes using cDNA microarrays. *Nat Genet* (1999) 23(1):41–6. doi: 10.1038/12640

41. Bentley DR, Balasubramanian S, Swerdlow HP, Smith GP, Milton J, Brown CG, et al. Accurate whole human genome sequencing using reversible terminator chemistry. *Nature.* (2008) 456(7218):53–9. doi: 10.1038/nature07517

42. Jung HS, Lefferts JA, Tsongalis GJ. Utilization of the oncoscan microarray assay in cancer diagnostics. *Appl Cancer Res* (2017) 37(1):1. doi: 10.1186/s41241-016-0007-3

43. Nakagawa H, Fujita M. Whole genome sequencing analysis for cancer genomics and precision medicine. *Cancer Sci* (2018) 109(3):513–22. doi: 10.1111/cas.13505

44. Hodges E, Xuan Z, Balija V, Kramer M, Molla MN, Smith SW, et al. Genome-wide *in situ* exon capture for selective resequencing. *Nat Genet* (2007) 39(12):1522–7. doi: 10.1038/ng.2007.42

45. Samorodnitsky E, Jewell BM, Hagopian R, Miya J, Wing MR, Lyon E, et al. Evaluation of hybridization capture versus amplicon-based methods for whole-exome sequencing. *Hum Mutat* (2015) 36(9):903–14. doi: 10.1002/humu.22825

46. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell* (2010) 18(1):11–22. doi: 10.1016/j.ccr.2010.05.026

47. The Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. *Cell* (2015) 163(4):1011–25. doi: 10.1016/j.cell.2015.10.025

48. Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, et al. Prostate cancer. *Nat Rev Dis Primers.* (2021) 7(1):9. doi: 10.1038/s41572-020-00243-0

49. Hu Q, Zhang B, Chen R, Fu C, A J, Fu X, et al. ZFHX3 is indispensable for ERβ to inhibit cell proliferation *via* MYC downregulation in prostate cancer cells. *Oncogenesis.* (2019) 8(4):28. doi: 10.1038/s41389-019-0138-y

50. Sun X, Frierson HF, Chen C, Li C, Ran Q, Otto KB, et al. Frequent somatic mutations of the transcription factor ATBF1 in human prostate cancer. *Nat Genet* (2005) 37(4):407–12. doi: 10.1038/ng1528

51. Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat JP, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. *Nat Genet* (2012) 44(6):685–9. doi: 10.1038/ng.2279

52. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *New Engl J Med* (2016) 375(5):443–53. doi: 10.1056/NEJMoa1603144

53. Yoshida K, Miki Y. Role of BRCA1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. *Cancer Sci* (2004) 95(11):866–71. doi: 10.1111/j.1349-7006.2004.tb02195.x

54. Sokolova A, Cheng H. Germline testing in prostate cancer: When and who to test. *Oncol (Williston Park).* (2021) 35(10):645–53. doi: 10.46883/ONC.2021.3510.0645

55. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* (2013) 31(14):1748–57. doi: 10.1200/JCO.2012.43.1882

56. Vietri MT, D'Elia G, Caliendo G, Resse M, Casamassimi A, Passariello L, et al. Hereditary prostate cancer: Genes related, target therapy and prevention. *Int J Mol Sci* (2021) 22(7):3753. doi: 10.3390/ijms22073753

57. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline mutations in HOXB13 and prostate-cancer risk. *New Engl J Med* (2012) 366(2):141–9. doi: 10.1056/NEJMoa1110000

58. Karlsson R, Aly M, Clements M, Zheng L, Adolfsson J, Xu J, et al. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. *Eur Urology.* (2014) 65(1):169–76. doi: 10.1016/j.eururo.2012.07.027

59. Lu X, Fong KW, Gritsina G, Wang F, Wang F, Baca SC, Brea LT, et al. HOXB13 suppresses *de novo* lipogenesis through HDAC3-mediated epigenetic reprogramming in prostate cancer. *Nat Genet* (2022) 54(5):670–83. doi: 10.1038/s41588-022-01045-8

60. Aurilio G, Cimadamore A, Mazzucchelli R, Lopez-Beltran A, Verri E, Scarpelli M, et al. Androgen receptor signaling pathway in prostate cancer: From genetics to clinical applications. *Cells.* (2020) 9(12):2653. doi: 10.3390/cells9122653

61. Wang Q, Li W, Zhang Y, Yuan X, Xu K, Yu J, et al. Androgen receptor regulates a distinct transcription program in androgen-independent prostate cancer. *Cell.* (2009) 138(2):245–56. doi: 10.1016/j.cell.2009.04.056

62. Itkonen H, Mills IG. Chromatin binding by the androgen receptor in prostate cancer. *Mol Cell Endocrinology.* (2012) 360(1):44–51. doi: 10.1016/j.mce.2011.09.037

63. Marcelli M, Stenoien DL, Szafran AT, Simeoni S, Agoulnik IU, Weigel NL, et al. Quantifying effects of ligands on androgen receptor nuclear translocation, intranuclear dynamics, and solubility. *J Cell Biochem* (2006) 98(4):770–88. doi: 10.1002/jcb.20593

64. Fitzgerald KA, Evans JC, McCarthy J, Guo J, Prencipe M, Kearney M, et al. The role of transcription factors in prostate cancer and potential for future RNA interference therapy. *Expert Opin Ther Targets.* (2014) 18(6):633–49. doi: 10.1517/14728222.2014.896904

65. Hankey W, Chen Z, Wang Q. Shaping chromatin states in prostate cancer by pioneer transcription factors. *Cancer Res* (2020) 80(12):2427–36. doi: 10.1158/0008-5472.CAN-19-3447

66. Fujita K, Nonomura N. Role of androgen receptor in prostate cancer: A review. *World J Mens Health* (2019) 37(3):288. doi: 10.5534/wjmh.180040

67. Paschalis A, Sharp A, Welti JC, Neeb A, Raj GV, Luo J, et al. Alternative splicing in prostate cancer. *Nat Rev Clin Oncol* (2018) 15(11):663–75. doi: 10.1038/s41571-018-0085-0

68. Heinlein CA, Chang C. Androgen receptor in prostate cancer. *Endocrine Rev* (2004) 25(2):276–308. doi: 10.1210/er.2002-0032

69. Taheri M, Khoshbakht T, Jamali E, Kallenbach J, Ghafouri-Fard S, Baniahmad A. Interaction between non-coding RNAs and androgen receptor with an especial focus on prostate cancer. *Cells.* (2021) 10(11):3198. doi: 10.3390/cells10113198

70. Magi-Galluzzi C, Tsusuki T, Elson P, Simmerman K, LaFargue C, Esgueva R, et al. TMPRSS2-ERG gene fusion prevalence and class are significantly different in prostate cancer of Caucasian, African-American and Japanese patients. *Prostate.* (2011) 71(5):489–97. doi: 10.1002/pros.21265

71. Xiao Q, Sun Y, Dobi A, Srivastava S, Wang W, Srivastava S, et al. Systematic analysis reveals molecular characteristics of ERG-negative prostate cancer. *Sci Rep* (2018) 8(1):12868. doi: 10.1038/s41598-018-30325-9

72. Pettersson A, Graff RE, Bauer SR, Pitt MJ, Lis RT, Stack EC, et al. The TMPRSS2:ERG rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis. *Cancer Epidemiol Biomarkers Prev* (2012) 21(9):1497–509. doi: 10.1158/1055-9965.EPI-12-0042

73. Halsall JA, Andrews S, Krueger F, Rutledge CE, Ficz G, Reik W, et al. Histone modifications form a cell-type-specific chromosomal bar code that persists through the cell cycle. *Sci Rep* (2021) 11(1):3009. doi: 10.1038/s41598-021-82539-z

74. Kiefer JC. Epigenetics in development. *Dev Dyn.* (2007) 236(4):1144–56. doi: 10.1002/dvdy.21094

75. Pal S, Tyler JK. Epigenetics and aging. *Sci Adv* (2016) 2(7):e1600584. doi: 10.1126/sciadv.1600584

76. Lee BH, Rhie SK. Molecular and computational approaches to map regulatory elements in 3D chromatin structure. *Epigenet Chromatin.* (2021) 14:14. doi: 10.1186/s13072-021-00390-y

77. Rhie SK, Perez AA, Lay FD, Schreiner S, Shi J, Polin J, et al. A high-resolution 3D epigenomic map reveals insights into the creation of the prostate cancer transcriptome. *Nat Commun* (2019) 10(1):4154. doi: 10.1038/s41467-019-12079-8

78. Bolton EM, Tuzova AV, Walsh AL, Lynch T, Perry AS. Noncoding RNAs in prostate cancer:the long and the short of it. *Clin Cancer Res* (2014) 20(1):35–43. doi: 10.1158/1078-0432.CCR-13-1989

79. Vaisvila R, Ponnaluri VKC, Sun Z, Langhorst BW, Saleh L, Guan S, et al. Enzymatic methyl sequencing detects DNA methylation at single-base resolution from picograms of DNA. *Genome Res* (2021) 31(7):1280–9. doi: 10.1101/gr.266551.120

80. Ku JL, Jeon YK, Park JG. Methylation-specific PCR. *Methods Mol Biol* (2011) 791:23–32. doi: 10.1007/978-1-61779-316-5_3

81. Kurdyukov S, Bullock M. DNA Methylation analysis: Choosing the right method. *Biology.* (2016) 5(1):3. doi: 10.3390/biology5010003

82. Delaney C, Garg SK, Yung R. Analysis of DNA methylation by pyrosequencing. In: Shaw AC, editor. *Immunosenescence*. New York, NY: Springer New York (2015). p. 249–64. doi: 10.1007/978-1-4939-2963-4_19

83. Zhao F, Bapat B. Chapter 8 - the role of methylation-specific PCR and associated techniques in clinical diagnostics. In: García-Giménez JL, editor. *Epigenetic biomarkers and diagnostics*. Boston: Academic Press (2016). p. 155–73. Available at: https://www.sciencedirect.com/science/article/pii/B9780128018996000085.

84. Karimi M, Johansson S, Stach D, Corcoran M, Grandér D, Schalling M, et al. LUMA (LUminometric methylation assay)–a high throughput method to the analysis of genomic DNA methylation. *Exp Cell Res* (2006) 312(11):1989–95. doi: 10.1016/j.yexcr.2006.03.006

85. Yegnasubramanian S, Lin X, Haffner MC, DeMarzo AM, Nelson WG. Combination of methylated-DNA precipitation and methylation-sensitive restriction enzymes (COMPARE-MS) for the rapid, sensitive and quantitative detection of DNA methylation. *Nucleic Acids Res* (2006) 34(3):e19. doi: 10.1093/nar/gnj022

86. Yong WS, Hsu FM, Chen PY. Profiling genome-wide DNA methylation. *Epigenet Chromatin.* (2016) 9:26. doi: 10.1186/s13072-016-0075-3

87. Neary JL, Perez SM, Peterson K, Lodge DJ, Carless MA. Comparative analysis of MBD-seq and MeDIP-seq and estimation of gene expression changes in a rodent model of schizophrenia. *Genomics.* (2017) 109(3–4):204–13. doi: 10.1016/j.ygeno.2017.03.004

88. Du P, Zhang X, Huang CC, Jafari N, Kibbe WA, Hou L, et al. Comparison of beta-value and m-value methods for quantifying methylation levels by microarray analysis. *BMC Bioinf* (2010) 11(1):587. doi: 10.1186/1471-2105-11-587

89. Pidsley R, Wong CC Y, Volta M, Lunnon K, Mill J, Schalkwyk LC. A data-driven approach to preprocessing illumina 450K methylation array data. *BMC Genomics* (2013) 14(1):293. doi: 10.1186/1471-2164-14-293

90. Huang YW, Huang THM, Wang LS. Profiling DNA methylomes from microarray to genome-scale sequencing. *Technol Cancer Res Treat* (2010) 9(2):139–47. doi: 10.1177/153303461000900203

91. Zhou W, Laird PW, Shen H. Comprehensive characterization, annotation and innovative use of infinium DNA methylation BeadChip probes. *Nucleic Acids Res* (2017) 45(4):e22. doi: 10.1093/nar/gkw967

92. Sun Z, Cunningham J, Slager S, Kocher JP. Base resolution methylome profiling: considerations in platform selection, data preprocessing and analysis. *Epigenomics.* (2015) 7(5):813–28. doi: 10.2217/epi.15.21

93. Robertson KD. DNA Methylation and human disease. *Nat Rev Genet* (2005) 6(8):597–610. doi: 10.1038/nrg1655

94. Mullen DJ, Yan C, Kang DS, Zhou B, Borok Z, Marconett CN, et al. TENET 2.0: Identification of key transcriptional regulators and enhancers in lung adenocarcinoma. *PloS Genet* (2020) 16(9):e1009023. doi: 10.1371/journal.pgen.1009023

95. Rhie SK, Guo Y, Tak YG, Yao L, Shen H, Coetzee GA, et al. Identification of activated enhancers and linked transcription factors in breast, prostate, and kidney tumors by tracing enhancer networks using epigenetic traits. *Epigenet Chromatin.* (2016) 9(1):50. doi: 10.1186/s13072-016-0102-4

96. Berman BP, Weisenberger DJ, Aman JF, Hinoue T, Ramjan Z, Liu Y, et al. Regions of focal DNA hypermethylation and long-range hypomethylation in colorectal cancer coincide with nuclear lamina–associated domains. *Nat Genet* (2011) 44(1):40–6. doi: 10.1038/ng.969

97. Shen H, Laird PW. Interplay between the cancer genome and epigenome. *Cell.* (2013) 153(1):38–55. doi: 10.1016/j.cell.2013.03.008

98. Zhao SG, Chen WS, Li H, Foye A, Zhang M, Sjöström M, et al. DNA Methylation landscapes in advanced prostate cancer. *Nat Genet* (2020) 52(8):778–89. doi: 10.1038/s41588-020-0648-8

99. Lam D, Clark S, Stirzaker C, Pidsley R. Advances in prognostic methylation biomarkers for prostate cancer. *Cancers (Basel).* (2020) 12(10):E2993. doi: 10.3390/cancers12102993

100. Yegnasubramanian S, Kowalski J, Gonzalgo ML, Zahurak M, Piantadosi S, Walsh PC, et al. Hypermethylation of CpG islands in primary and metastatic human prostate cancer. *Cancer Res* (2004) 64(6):1975–86. doi: 10.1158/0008-5472.CAN-03-3972

101. Rosenbaum E, Hoque MO, Cohen Y, Zahurak M, Eisenberger MA, Epstein JI, et al. Promoter hypermethylation as an independent prognostic factor for relapse in patients with prostate cancer following radical prostatectomy. *Clin Cancer Res* (2005) 11(23):8321–5. doi: 10.1158/1078-0432.CCR-05-1183

102. Woodson K, O'Reilly KJ, Ward DE, Walter J, Hanson J, Walk EL, et al. CD44 and PTGS2 methylation are independent prognostic markers for biochemical recurrence among prostate cancer patients with clinically localized disease. *Epigenetics.* (2006) 1(4):183–6. doi: 10.4161/epi.1.4.3530

103. Henrique R, Ribeiro FR, Fonseca D, Hoque MO, Carvalho AL, Costa VL, et al. High promoter methylation levels of APC predict poor prognosis in sextant biopsies from prostate cancer patients. *Clin Cancer Res* (2007) 13(20):6122–9. doi: 10.1158/1078-0432.CCR-07-1042

104. Ellinger J, Bastian PJ, Jurgan T, Biermann K, Kahl P, Heukamp LC, et al. CpG island hypermethylation at multiple gene sites in diagnosis and prognosis of prostate cancer. *Urology.* (2008) 71(1):161–7. doi: 10.1016/j.urology.2007.09.056

105. Alumkal JJ, Zhang Z, Humphreys EB, Bennett C, Mangold LA, Carducci MA, et al. Impact of DNA methylation on the identification of aggressive prostate cancer. *Urology.* (2008) 72(6):1234–9. doi: 10.1016/j.urology.2007.12.060

106. Weiss G, Cottrell S, Distler J, Schatz P, Kristiansen G, Ittmann M, et al. DNA Methylation of the PITX2 gene promoter region is a strong independent prognostic marker of biochemical recurrence in patients with prostate cancer after radical prostatectomy. *J Urol.* (2009) 181(4):1678–85. doi: 10.1016/j.juro.2008.11.120

107. Vanaja DK, Ehrich M, Van den Boom D, Cheville JC, Karnes RJ, Tindall DJ, et al. Hypermethylation of genes for diagnosis and risk stratification of prostate cancer. *Cancer Invest.* (2009) 27(5):549–60. doi: 10.1080/07357900802620794

108. Richiardi L, Fiano V, Vizzini L, De Marco L, Delsedime L, Akre O, et al. Promoter methylation in APC, RUNX3, and GSTP1 and mortality in prostate cancer patients. *J Clin Oncol* (2009) 27(19):3161–8. doi: 10.1200/JCO.2008.18.2485

109. Bañez LL, Sun L, van Leenders GJ, Wheeler TM, Bangma CH, Freedland SJ, et al. Multicenter clinical validation of PITX2 methylation as a prostate specific antigen recurrence predictor in patients with post-radical prostatectomy prostate cancer. *J Urol.* (2010) 184(1):149–56. doi: 10.1016/j.juro.2010.03.012

110. Vasiljeviš N, Wu K, Brentnall AR, Kim DC, Thorat MA, Kudahetti SC, et al. Absolute quantitation of DNA methylation of 28 candidate genes in prostate cancer using pyrosequencing. *Dis Markers.* (2011) 30(4):151–61. doi: 10.1155/2011/157829

111. Rosenbaum E, Begum S, Brait M, Zahurak M, Maldonado L, Eisenberger MA, et al. Aim1 promoter hypermethylation as a predictor of decreased risk of recurrence following radical prostatectomy. *Prostate.* (2012) 72(10):1133–9. doi: 10.1002/pros.22461

112. Vasiljević N, Ahmad AS, Beesley C, Thorat MA, Fisher G, Berney DM, et al. Association between DNA methylation of HSPB1 and death in low Gleason score prostate cancer. *Prostate Cancer Prostatic Dis* (2013) 16(1):35–40. doi: 10.1038/pcan.2012.47

113. Dietrich D, Hasinger O, Bañez LL, Sun L, van Leenders GJ, Wheeler TM, et al. Development and clinical validation of a real-time PCR assay for PITX2 DNA methylation to predict prostate-specific antigen recurrence in prostate cancer patients following radical prostatectomy. *J Mol Diagn.* (2013) 15(2):270–9. doi: 10.1016/j.jmoldx.2012.11.002

114. Richiardi L, Fiano V, Grasso C, Zugna D, Delsedime L, Gillio-Tos A, et al. Methylation of APC and GSTP1 in non-neoplastic tissue adjacent to prostate tumour and mortality from prostate cancer. *PloS One* (2013) 8(7):e68162. doi: 10.1371/journal.pone.0068162

115. Moritz R, Ellinger J, Nuhn P, Haese A, Müller SC, Graefen M, et al. DNA Hypermethylation as a predictor of PSA recurrence in patients with low- and intermediate-grade prostate cancer. *Anticancer Res* (2013) 33(12):5249–54.

116. Vasiljević N, Ahmad AS, Thorat MA, Fisher G, Berney DM, Møller H, et al. DNA Methylation gene-based models indicating independent poor outcome in prostate cancer. *BMC Cancer.* (2014) 14:655. doi: 10.1186/1471-2407-14-655

117. Vasiljević N, Ahmad AS, Carter PD, Fisher G, Berney DM, Foster CS, et al. DNA Methylation of PITX2 predicts poor survival in men with prostate cancer. *biomark Med* (2014) 8(9):1143–50. doi: 10.2217/bmm.14.41

118. Maldonado L, Brait M, Loyo M, Sullenberger L, Wang K, Peskoe SB, et al. GSTP1 promoter methylation is associated with recurrence in early stage prostate cancer. *J Urol.* (2014) 192(5):1542–8. doi: 10.1016/j.juro.2014.04.082

119. Daniunaite K, Jarmalaite S, Kalinauskaite N, Petroska D, Laurinavicius A, Lazutka JR, et al. Prognostic value of RASSF1 promoter methylation in prostate cancer. *J Urology.* (2014) 192(6):1849–55. doi: 10.1016/j.juro.2014.06.075

120. Litovkin K, Van Eynde A, Joniau S, Lerut E, Laenen A, Gevaert T, et al. DNA Methylation-guided prediction of clinical failure in high-risk prostate cancer. *PloS One* (2015) 10(6):e0130651. doi: 10.1371/journal.pone.0130651

121. Carozzi F, Tamburrino L, Bisanzi S, Marchiani S, Paglierani M, Di Lollo S, et al. Are biomarkers evaluated in biopsy specimens predictive of prostate cancer aggressiveness? *J Cancer Res Clin Oncol* (2016) 142(1):201–12. doi: 10.1007/s00432-015-2015-1

122. Rybicki BA, Rundle A, Kryvenko ON, Mitrache N, Do KC, Jankowski M, et al. Methylation in benign prostate and risk of disease progression in men subsequently diagnosed with prostate cancer. *Int J Cancer.* (2016) 138(12):2884–93. doi: 10.1002/ijc.30038

123. Holmes EE, Goltz D, Sailer V, Jung M, Meller S, Uhl B, et al. PITX3 promoter methylation is a prognostic biomarker for biochemical recurrence-free survival in prostate cancer patients after radical prostatectomy. *Clin Epigenetics.* (2016) 8:104. doi: 10.1186/s13148-016-0270-x

124. Ahmad AS, Vasiljević N, Carter P, Berney DM, Møller H, Foster CS, et al. A novel DNA methylation score accurately predicts death from prostate cancer in men with low to intermediate clinical risk factors. *Oncotarget.* (2016) 7(44):71833–40. doi: 10.18632/oncotarget.12377

125. Uhl B, Gevensleben H, Tolkach Y, Sailer V, Majores M, Jung M, et al. PITX2 DNA methylation as biomarker for individualized risk assessment of prostate cancer in core biopsies. *J Mol Diagn.* (2017) 19(1):107–14. doi: 10.1016/j.jmoldx.2016.08.008

126. Tang D, Kryvenko ON, Mitrache N, Do KC, Jankowski M, Chitale DA, et al. Methylation of the RARB gene increases prostate cancer risk in black americans. *J Urol.* (2013) 190(1):317–24. doi: 10.1016/j.juro.2013.01.083

127. Stanford JL, Wicklund KG, McKnight B, Daling JR, Brawer MK. Vasectomy and risk of prostate Cancer1. *Cancer Epidemiology Biomarkers Prev* (1999) 8(10):881–6.

128. Agalliu I, Salinas CA, Hansten PD, Ostrander EA, Stanford JL. Statin use and risk of prostate cancer: Results from a population-based epidemiologic study. *Am J Epidemiol.* (2008) 168(3):250–60. doi: 10.1093/aje/kwn141

129. Weineisen M, Schottelius M, Simecek J, Baum RP, Yildiz A, Beykan S, et al. 68 Ga- and 177 Lu-labeled PSMA I&T: Optimization of a PSMA-targeted theranostic concept and first proof-of-Concept human studies. *J Nucl Med* (2015) 56(8):1169–76. doi: 10.2967/jnumed.115.158550

130. Paschalis A, Sheehan B, Riisnaes R, Rodrigues DN, Gurel B, Bertan C, et al. Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. *Eur Urol.* (2019) 76(4):469–78. doi: 10.1016/j.eururo.2019.06.030

131. Stark R, Grzelak M, Hadfield J. RNA Sequencing: the teenage years. *Nat Rev Genet* (2019) 20(11):631–56. doi: 10.1038/s41576-019-0150-2

132. Wang Z, Gerstein M, Snyder M. RNA-Seq: A revolutionary tool for transcriptomics. *Nat Rev Genet* (2009) 10(1):57–63. doi: 10.1038/nrg2484

133. Okoniewski MJ, Miller CJ. Hybridization interactions between probesets in short oligo microarrays lead to spurious correlations. *BMC Bioinf* (2006) 7(1):276. doi: 10.1186/1471-2105-7-276

134. Ozsolak F, Milos PM. RNA Sequencing: Advances, challenges and opportunities. *Nat Rev Genet* (2011) 12(2):87–98. doi: 10.1038/nrg2934

135. Yang L, Duff MO, Graveley BR, Carmichael GG, Chen LL. Genomewide characterization of non-polyadenylated RNAs. *Genome Biol* (2011) 12(2):R16. doi: 10.1186/gb-2011-12-2-r16

136. O'Neil D, Glowatz H, Schlumpberger M. Ribosomal RNA depletion for efficient use of RNA-seq capacity. *Curr Protoc Mol Biol* (2013) 103(1):4. doi: 10.1002/0471142727.mb0419s103

137. Vickman RE, Franco OE, Moline DC, Vander Griend DJ, Thumbikat P, Hayward SW. The role of the androgen receptor in prostate development and benign prostatic hyperplasia: A review. *Asian J Urol.* (2020) 7(3):191–202. doi: 10.1016/j.ajur.2019.10.003

138. Bernasocchi T, El Tekle G, Bolis M, Mutti A, Vallerga A, Brandt LP, et al. Dual functions of SPOP and ERG dictate androgen therapy responses in prostate cancer. *Nat Commun* (2021) 12(1):734. doi: 10.1038/s41467-020-20820-x

139. Adams EJ, Karthaus WR, Hoover E, Liu D, Gruet A, Zhang Z, et al. FOXA1 mutations alter pioneering activity, differentiation, and prostate cancer phenotypes. *Nature.* (2019) 571(7765):408–12. doi: 10.1038/s41586-019-1318-9

140. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med* (2014) 371(11):1028–38. doi: 10.1056/NEJMoa1315815

141. Takeda DY, Spisák S, Seo JH, Bell C, O'Connor E, Korthauer K, et al. A somatically acquired enhancer of the androgen receptor is a noncoding driver in advanced prostate cancer. *Cell.* (2018) 174(2):422. doi: 10.1016/j.cell.2018.05.037

142. Ateeq B, Tomlins SA, Laxman B, Asangani IA, Cao Q, Cao X, et al. Therapeutic targeting of SPINK1-positive prostate cancer. *Sci Transl Med* (2011) 3(72):72ra17. doi: 10.1126/scitranslmed.3001498

143. Shorning BY, Dass MS, Smalley MJ, Pearson HB. The PI3K-AKT-mTOR pathway and prostate cancer: At the crossroads of AR, MAPK, and WNT signaling. *Int J Mol Sci* (2020) 21(12):4507. doi: 10.3390/ijms21124507

144. Frank S, Nelson P, Vasioukhin V. Recent advances in prostate cancer research: large-scale genomic analyses reveal novel driver mutations and DNA repair defects. *F1000Res* (2018) 7(F1000 Faculty Rev):1173. doi: 10.12688/f1000research.14499.1

145. Fang ZQ, Zang WD, Chen R, Ye BW, Wang XW, Yi SH, et al. Gene expression profile and enrichment pathways in different stages of bladder cancer. *Genet Mol Res* (2013) 12(2):1479–89. doi: 10.4238/2013.May.6.1

146. Liu X, Wang J, Sun G. Identification of key genes and pathways in renal cell carcinoma through expression profiling data. *Kidney Blood Press Res* (2015) 40(3):288–97. doi: 10.1159/000368504

147. Arenas-Gallo C, Owiredu J, Weinstein I, Lewicki P, Basourakos SP, Vince R, et al. Race and prostate cancer: genomic landscape. *Nat Rev Urol.* (2022) 19(9):547–61. doi: 10.1038/s41585-022-00622-0

148. Schumacher FR, Basourakos SP, Lewicki PJ, Vince R, Spratt DE, Barbieri CE, et al. Race and genetic alterations in prostate cancer. *JCO Precis Oncol* (2021) 5):1650–3. doi: 10.1200/PO.21.00324

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 13 March 2023
DOI 10.3389/fonc.2023.1079293

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cancer Epidemiology and Prevention, a section of the journal Frontiers in Oncology

RECEIVED 25 October 2022
ACCEPTED 30 January 2023
PUBLISHED 13 March 2023

CITATION
Pichardo MS, Sanft T, Ferrucci LM, Romero-Ramos YM, Cartmel B, Harrigan M, Velazquez AI, Fayanju OM, Winer EP and Irwin ML (2023) Diet and physical activity interventions in Black and Latina women with breast cancer: A scoping review.
Front. Oncol. 13:1079293.
doi: 10.3389/fonc.2023.1079293

Diet and physical activity interventions in Black and Latina women with breast cancer: A scoping review

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Background: A growing number of lifestyle interventions are being developed to promote weight loss and adoption of a healthful lifestyles among breast cancer survivors; yet Black and Latina women remain underrepresented.

Purpose: We performed a scoping review of the available peer-reviewed literature to describe and compare the content, design, methods, and primary outcomes of current diet and/or physical activity (PA) interventions after a breast cancer diagnosis among Black and Latina women.

Methods: We queried PubMed, EMBASE, CINAHL, MEDLINE, and Clinicaltrials.gov up to October 1, 2022, to identify all randomized controlled trials of diet and/or PA after diagnosis of breast cancer with a majority (>50%) of Black or Latina participants.

Results: Twenty-two randomized controlled trials were included in this review (five efficacy, twelve pilot, five on-going). Nine trials were among Latinas (two diet, four PA, and three diet/PA), six among Blacks (one PA and five diet/PA) and seven included both populations (five PA and two diet/PA), all of which examined different endpoints. Two of the five efficacy studies achieved their *a priori* outcome (one diet trial improved short term dietary intake; one PA trial achieved clinically significant improvements in metabolic syndrome score), both in Latinas. Eight pilot trials intervened on both diet and PA and three of them found favorable behavioral changes. Three (two for Latinas and one for Blacks) out of the nine diet and PA trials and three (all for Latinas) efficacy trials incorporated a culturally focused approach (i.e., traditional foods, music, Spanish content, bicultural health coaches, spirituality). Overall, four trials, including one efficacy trial, had one-year follow-up data, with three finding sustained behavior change. Electronic/mobile components were incorporated in five trials and one involved informal care givers.

Most of the trials were geographically limited to the Northeast USA (n=8, NY, NC, DC, NJ) and Texas (n=4).

Conclusions: Most of the trials we identified were pilot or feasibility studies and of short duration, demonstrating the need for large randomized controlled efficacy lifestyle interventions among Black and Latina breast cancer survivors. Culturally tailored programing was limited but is an important component to incorporate in future trials in these populations.

KEYWORDS

breast cancer, Hispanic/Latina women, Black/African American women, energy balance, diet intervention, physical activity intervention, randomized controlled (clinical) trial, survivorship

Introduction

Breast cancer is the most common type of cancer among women in the United States (US) (1). Historically, Black/African American (herein referred to as Black) and Hispanic/Latina (herein referred to as Latina) women have had lower incidence of breast cancer than Non-Hispanic White (herein referred to as White) women, but this gap is closing (2, 3). Of note, Black women are more likely to be diagnosed with breast cancer at an earlier age (3) and experience a 39% higher disease-specific mortality than White women (4, 5). While Latina women experience lower risk of breast cancer-specific mortality than White women, breast cancer remains the leading cause of cancer death among Latinas (2). Latina women are more likely to be diagnosed with regional or distant breast cancer and tumors with worse prognosis (i.e., Stage IV, larger and hormone receptor negative tumors) compared to White women (6, 7). Further differences exist at the intersection of race and ethnicity, for example among Latinas, Hispanic Black women have higher rates of triple negative breast cancer than Hispanic White women (6). Intervention strategies to improve outcomes in these populations are needed.

Obesity disproportionately burdens Black and Latina women compared to White women (8) and is strongly associated with breast cancer risk (9, 10) and prognosis (11–13). The age-adjusted obesity prevalence from 2013-2014 for Black and Latina women was 53% and 47% compared to 38% for White women (8). Severe obesity is also of concern in Black women; 17% of Black have a body mass index (BMI) over 35 kg/m^2, compared to 9% and 10% of Latina and White women, respectively (8). Central adiposity is an important risk factor for postmenopausal breast cancer (14, 15) and is associated with hormone receptor positive tumors in Black women (16). Gaining weight before menopause is associated with increased breast cancer incidence (15, 17–19) and risk of recurrence (20, 21), as well as disease-specific and all-cause mortality (21–24). Weight gain after a diagnosis of breast cancer and initiation of adjuvant chemotherapy (25–28) increases risk of recurrence and breast cancer mortality (29). Given this evidence, it is crucial to promote physical activity, a healthy diet, and the avoidance of obesity and weight gain after a breast cancer diagnosis through the adoption of healthy lifestyle behaviors. Current guidelines from the American Cancer Society (ACS) recommend that cancer survivors follow a healthy diet (e.g. low in fat, rich in vegetables, fruits, and whole grains) and attain 150-300 minutes of aerobic exercise and do at least two strength training sessions weekly (30). The most recent American Society of Clinical Oncology (ASCO) guidelines recommend engaging in these behaviors as early as possible after diagnosis (31).

Various studies have examined adherence to the lifestyle recommendations among Black women with breast cancer with results showing low adherence to these (32–34). Nonetheless, to our knowledge, there are no studies of adherence to combined diet and physical activity guidelines among survivors of color. Data derived from studies of predominantly White women with breast cancer suggest that engaging in post-diagnosis, healthy lifestyles, consisting of a high-quality diet and any physical activity, is associated with a reduction in risk of both breast-cancer specific and all-cause mortality (35, 36). Lifestyle interventions consisting of both diet and physical activity counseling may help breast cancer survivors adopt and adhere to the recommended guidelines by providing evidence-based tools for survivors to adopt and maintain healthy behaviors (37). For instance, the Lifestyle, Exercise And Nutrition (LEAN) trial, enrolled 100 breast cancer survivors of whom 91% were White and 9% non-White, demonstrated improvements in body weight *via* an intervention on physical activity and consumption of healthy foods in survivors with breast cancer with an in-person or telephone counseling intervention compared to usual care (38).

In addition to promoting weight loss, physical activity may protect against or ameliorate certain complications from breast cancer treatment. Exercise trials during and after breast cancer treatment has improved lymphedema risk, cancer-related fatigue (39–41), quality of life (42, 43), emotional functioning (39), self-esteem (44), depressive symptoms (45), pain symptoms (39, 46), cardiovascular function (43), muscular strength (43, 44), sarcopenia (41) and age-associated muscle loss (i.e., dynapenia) (41), and chemotherapy completion rates (44). Observational studies in cohorts of predominantly White women have documented a link between diet quality and mortality in cancer survivors (35, 47, 48). For example, a study of 2,317 women (5.6% Black and 2% Latina) with invasive breast cancer participating in the Women's Health Initiative found that women with a higher quality diet had a 26% lower risk of

all-cause mortality and 42% lower risk of death from causes other than breast cancer, although no association was found with breast cancer-specific death (47). In a secondary analysis of the Multiethnic Cohort among 17,330 White, 9,014 Black, 17,595 Latina, 4,992 Native Hawaiian, and 21,239 Japanese American women, higher diet quality —measured by various dietary indices—was associated with lower risk of death from all causes, cardiovascular disease and cancer (48). Among 2,437 women enrolled in the Women's Intervention Nutrition Study (WINS), where 5.2% of women identified as Black (n=127), 4% as Latina (n=98), and 6% as Asian/Pacific Islander (n==144), there was a 24% higher 5-year relapse-free survival in women who reduced their dietary fat intake compared to the control group (HR: 0.76; 95% CI, 0.6-0.98) (49, 50). However, the Women's Healthy Eating and Living (WHEL) study conducted among 3,088 women (3.8% Black (n=118), 5.3% Latina (n=165), 3.1% Asian (n=96)), found that a diet high in vegetables, fruits, and fiber and low in fat was not associated with a reduction in additional breast cancer events or mortality (51), demonstrating that uncertainties about the effects of diet on breast cancer outcomes remain.

At present, our knowledge of the benefits of dietary and physical activity interventions for survivors with breast cancer in relation to health outcomes and health-related quality of life is derived from studies targeting mostly White women, with close to 200 lifestyle randomized lifestyle interventions published in this population to date (52). In a systematic review of 17 reviews, Lake and colleagues found that interventions that provided lifestyle counseling and support for both physical activity and diet components, where of longer duration, and were group-based, were the most effective to achieve weight loss and improvements in mental health outcomes among predominantly White breast cancer survivors (52). To better understand the state of lifestyle intervention research in Black and Latina women, we conducted a scoping review to summarize the current state of the evidence (53, 54) of diet and/or physical activity interventions for Black and Latina women after a diagnosis of breast cancer.

Materials and methods

Search strategy

Our scoping review adhered to the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews (PRISMA-SCR) (55). A structured literature search was conducted through October 2, 2022, without date restrictions, in five databases: PubMed, EMBASE, MEDLINE, CINAHL, and clinicaltrials.gov. A PRISMA diagram summarizing our search and screening results is shown in Figure 1. The strategy (Appendix) used for our search was adapted from Spark et al. (56) and modified to include four overarching concepts: 1) breast cancer, 2) diet or physical activity intervention, 3) Black or Latina women, and 4) randomized study design. To identify ongoing studies in the

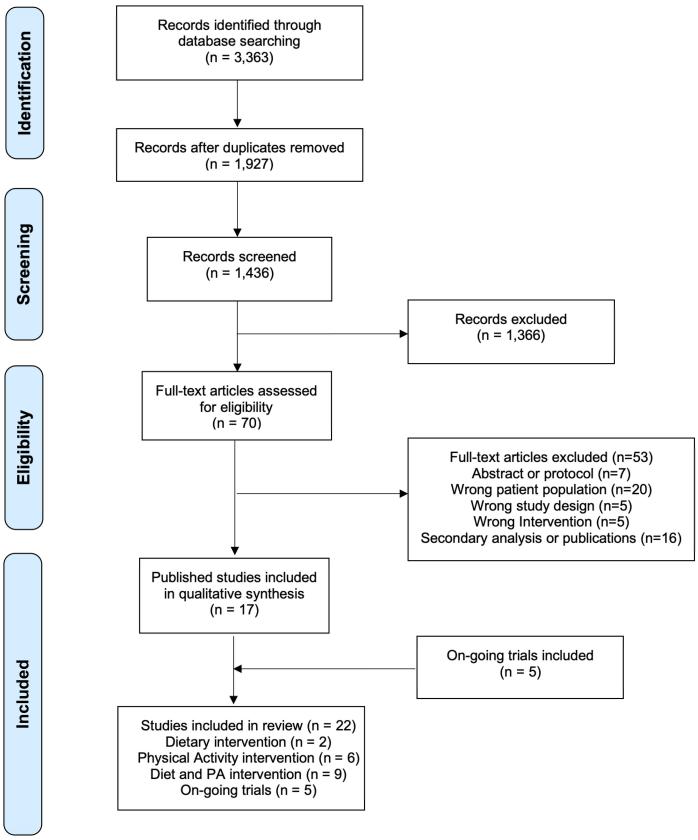

FIGURE 1
Preferred reporting items for systematic reviews and meta-analysis extension for scoping reviews diagram flow of literature search.

clinicaltrials.gov registry, we restricted our search to "breast cancer" disease, studies with a clinical status of "not yet recruiting", "recruiting', or "enrolling by invitation", study types categorized as "interventional (clinical trial)" and used a combination of the following: "diet", "nutrition", "physical activity", "exercise", "African American", "Black", "Hispanic", "Latina".

Trial inclusion criteria

Literature screening was conducted using Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Our search yielded 3,363 publications (Pubmed, n = 821; MEDLINE (OVID), n = 968; EMBASE (OVID), n = 1,415, CINHAL, n = 159). A total of 1,927 duplicates were excluded leaving us with 1,436 publications (Figure 1). For inclusion in this review, the publication had to report on results of a diet and/or physical activity intervention where ≥ 50% of participants identified as a Black or Latina women and had a history of breast cancer. During title and abstract screening, all 1,436 publications were screened by two authors (MSP, YMRR) and 70 studies were identified for full-text review. During full-text review, all studies were reviewed by two authors (MSP, YMRR) and 53 studies were excluded. Any discrepancies between the two reviewers were resolved by discussion among three authors (MSP, YMRR, MI) and by referencing the full text of the manuscript. Exclusion reasons were as follows: publication was a protocol or an abstract (n = 7), study did not include appropriate study population (not breast cancer patient/survivor or participants were not > 50% Black or Latina women; n = 20), study was not a behavioral diet and/or physical activity intervention (n = 5), study was not a randomized controlled trial (n = 5), and study was a secondary analysis or publication from a trial previously included (n = 16). The clinicaltrials.gov registry search resulted in five trials registered as on-going that did not have publications on primary outcomes.

Results

We identified a total of twenty-two diet and/or physical activity intervention articles that met our inclusion criteria. A brief description of key characteristics of published studies is shown in Table 1. A detailed description of completed studies is provided in Table 2. A summary of completed trials with published findings is presented in Table 3. A brief description of trial characteristics and primary outcomes for registered ongoing and withdrawn trials is provided in Table 4.

Among our 22 included trials, five were efficacy trials (57–60, 63), twelve were author-defined feasibility/pilot studies (61, 62, 64, 66–69, 85–89) and five were on-going trials (90, 91) [NCT03120390, NCT02982564, NCT05176756]. Among the 17 completed trials, 2 evaluated a diet intervention, 6 intervened on physical activity, and 9 targeted both diet and physical activity, but these studies differed in outcomes, intervention components, and study duration. Most completed trials (n=14) were conducted in survivors with stage I-III breast cancer, while nine trials also included stage 0 (57–59, 62, 64, 66–69), and three included stage IV breast cancers (60, 67, 87). Three studies did not report disease stage (61, 85, 89). The sample size across the 17 completed studies ranged from 20 to 246, with six trials focusing only on Black women (61, 63–65, 68, 89), five only on Latina women (57, 58, 69, 85, 87) and six including both groups (59, 60, 62, 66, 67, 86). Included trials were geographically limited to the Northeast USA (n=8, NY, NC, DC, NJ), Texas (n=4), California (n=3), Arizona (n=2), Illinois (n=2), Puerto Rico (n=1), Massachusetts (n=1) and one ongoing at three sites (California, New York, and Pennsylvania).

Diet interventions (n = 2)

Efficacy trials (n=2)

The *¡Cocinar Para Su Salud!* trial was a culturally tailored dietary intervention by Greenlee et al. in 70 Latina survivors with breast cancer randomized to either a 12-week intervention arm (n=34) or the usual care arm (n=36) (57). The intervention arm included weekly nutrition education sessions with dietitians and chefs using an adaptation of a commercially available nutrition course, "Cook for Your Life" (www.cookforyourlife.org). The study culturally tailored their intervention by including cultural values (e.g., family and community), a bilingual nurse who self-identified as Hispanic/Latino and Spanish cooking sessions with a chef. The primary goal of the intervention was to test the effectiveness of the program to help women achieve and maintain the dietary behavioral guidelines. At 3-months, the intervention arm compared to controls, had significant improvements in daily servings of all fruits and vegetables (F&V), daily total caloric intake, and total dietary fat percent of daily total energy. At 12 months, maintenance of F&V intake was observed for the intervention group compared to the control arm. However, at 12 months there was no effect of the intervention on maintenance of improvements in intake of dietary fat, weight change, BMI change, and waist circumference.

Zuniga et al. conducted a 1:1 randomized trial of 153 survivors with breast cancer (125 completed the study: 51.2% Latina, 42.4% White, and 6.4% other race/ethnicity) that examined the effect of an education and culinary-based dietary intervention vs. usual care on adherence to the Mediterranean dietary pattern (58). Cultural adaptations were not reported. The primary goal of the intervention was to improve consumption of anti-inflammatory foods, spices, and herbs *via* monthly workshops over a span of 6 months that included hands-on cooking demonstration. Analysis for study completers only demonstrated increased adherence to an anti-inflammatory dietary pattern driven by behavioral changes in 3 out of 14 items in the Mediterranean diet recommendations (reduced intake of red meat and commercial sweets or pastries and increased servings of fish). Long-term follow-up was not conducted.

Physical activity interventions (n = 6)

Efficacy trials (n = 2)

Dieli-Conwright et al. conducted a 1:1 randomized trial of 100 survivors with breast cancer (26% White, 55% Latina, 4% Black, 15% Asian/Pacific Islander) to examine the effect of a 16-week physical activity intervention arm involving three weekly sessions of supervised aerobic and resistance exercise compared to a wait list control arm on metabolic

10.3389/fonc.2023.1079293

TABLE 1 A brief description of key characteristics of published studies (N = 17).

Author	Intervention content	Delivery method	No. of Participant/Race or Ethnicity	Disease stage	Study design	Linguistic and/or culturally tailored?	Long-term follow up (time frame)?	Primary outcome
Greenlee, 2015 (57)	Diet	In-person	70/Latina	0-III	Efficacy	Yes: Content & language	Yes (6 and 12 months)	Intake of fruits and vegetables (F&V) servings; Percent calories from fat
Zuniga, 2018 (58)	Diet	In-person	64 Latina, 53 White, 8 Other	0-III	Efficacy	No	No	Adherence to anti-inflammatory diet
Dieli-Conwright, 2018 (59)	Physical Activity	In-person	55/Latina, 4/Black, 26/White, 15/Asian/Pacific Islander	0-III	Efficacy	No	No	Metabolic syndrome z-score
Moadel, 2007 (60)	Physical Activity	In-person	54/Black, 40/Latina, 29/White, 5/Other	I-IV	Efficacy	No	No	Quality of life score
Mama, 2018 (14)	Physical Activity	In-person; At home	89/Latina	I-IV	Pilot	Yes: Content & language	No	Social cognitive theory measures; Minutes of physical activity
Taylor, 2018 (61)	Physical Activity	In-person	33/Black	Not reported	Pilot	No	No	Psychological and functional outcomes
Lee, 2020 (17)	Physical Activity	In-person	22/Latina, 2/Black, 4/White, 2/Asian/Pacific Islander	I-III	Pilot	No	No	Feasibility
Soltero, 2022 (62)	Physical Activity	In-person	13/Latina, 1/Black, 5/White, 1/Other	0-III	Pilot	No	No	Overall daily steps, BMI, body fat
Stolley, 2017 (63)	Diet and Physical Activity	In-person	246/Black	I-III	Efficacy	Yes: Content only	Yes (12 months)	5% Weight loss
Ferrante, 2018 (64)	Diet and Physical Activity	Electronic (Spark People website)	37/Black	0-III	Pilot	No	Yes (12 months)	5% Weight loss
Valle, 2017 (65)	Diet and Physical Activity	Electronic (Email, Mobile application, Website)	45/Black	I-III	Pilot	No	Yes (6 months)	Weight gain prevention
Greenlee, 2013 (66)	Diet and Physical Activity	In-person	33/Latina, 9/Black,	0-III	Pilot	Yes: Language only	Yes (12 months)	5% Weight loss
Paxton, 2017 (67)	Diet and Physical Activity	Electronic (Email; Individualized website)	59/Black, 8/Latina, 4/Other	0-IV	Pilot	No	No	Meeting exercise/dietary American Cancer Society recommendations
Sheppard, 2016 (68)	Diet and Physical Activity	In-person	31/Black	0-III	Pilot	Yes: Content only	No	5% Weight loss
Buscemi, 2020 (69)	Diet and Physical Activity	Electronic (Mobile application)	80/Latina	0-III	Pilot	Yes: Content & language	No	Dietary intake; Minutes of physical activity
Crane, 2021 (31)	Diet and Physical Activity	Electronic (Telephone)	45/Latina	Not Reported	Pilot	Yes: Content & language	No	Dietary intake; Minutes of physical activity; Feasibility; Acceptability
Allicock, 2021 (32)	Diet and Physical Activity	Electronic (Mobile application)	22/Black	Not Reported	Pilot	No	No	Feasibility

TABLE 2 Description of completed randomized controlled trials focused on dietary and/or physical activity behavioral changes in Black and Latina breast cancer survivors; sample, intervention, and methodology characteristics (N = 17).

Trial name, First Author, Location (Type of Behavior)	Study Design	Sample Characteristics	Intervention \ Characteristics	Study Measures	Primary Outcomes
Diet Interventions (n= 2 efficacy trials)					
¡Cocinar para su Salud!, Greenlee, 2015 (57), New York (Diet) *Other publications* (70–72)	RCT, 2-arm, efficacy	Group (N): 70 I (34); C (36) Sample: Survivors; -77% Dominican -7% Puerto Rican -7% Ecuadorian Stages: 0 - III Mean time since diagnosis: 3.4 y Mean age: 56.6 y Mean BMI: 30.9 kg/m^2 Recruitment: oncology clinics at academic cancer center	Theory: Stages of Change Construct and Social Cognitive Theory Duration: 3mo. Delivery: All: Nutrition educational printed material in Spanish I: Nine in-person Saturday classes lasting 1.5 to 3.5 hours: - 4 nutrition education with a registered dietitian - 3 cooking classes with Latina chef - 2 food shopping field trips to local supermarket and greenmarket C: Usual care Contact: Monthly calls with a dietitian during 3mo. Follow-up: 6mo., 12mo.	Physical Activity measure: Block Physical Activity Screener Dietary measure: Three 24-hour recall assessments (2 weekdays, 1 weekend day, one in person at baseline, two over the phone).	Change in intake of servings of fruits and vegetables % Calories from fat
Zuniga, 2018 (58), Texas (Diet) *Other publications* (73)	RCT, 2-arm, efficacy	Group (N): 153 I (76); C (77) Sample: Survivors; -51.2% Latina -42.4% Non-Hispanic White -6.4% Other Stages: 0 - III Mean time since diagnosis: 2 y Mean age: 57 y Mean BMI: Not Reported Recruitment: Not Reported	Theory: Not Reported Duration: 6mo. Delivery: I: Monthly in-person group nutrition workshops about anti-inflammatory foods and cancer recurrence. - Didactic portion and cooking demonstrations with chef trained in AI food preparation, a tasting, and interactive discussion with participants and research staff. - Encouraged to attend 6 monthly workshops - Received paper copies of presentation material - Received motivational interviewing C: Usual care - Monthly American Institute for Cancer Research informational brochures Contact: Monthly calls with trained patient navigators for 6 mo. Follow-up: none	Physical activity measure: none Dietary measure: 14-item Mediterranean diet assessment tool and a 3-day food record (two weekdays and one weekend day) prior to assessment	Change in adherence to anti-inflammatory dietary pattern
Physical Activity Interventions (n= 2 efficacy trials; n= 4 pilot/feasibility trials)					
Dieli-Conwright 2018 (59), California (Physical Activity) *Other publications* (74)	RCT, 2-arm, efficacy	Group (N): 100 I (50); C (50) Sample: Survivors; -55% White Latina -26% Non-Hispanic White -4% Black -15% Asian/Pacific Islander Stages: 0 – III Mean time since diagnosis: 6.2 mo. Mean age: 53.5 y Mean BMI: 33.5 kg/m^2	Theory: American Cancer Society (ACS) exercise guidelines for cancer survivors. Duration: 4mo. Delivery: All: Asked to maintain dietary behaviors during the study period I: Supervised, one-on-one training provided by a certified cancer exercise	Physical activity measure: Physical activity history measured at baseline with interviewer-administered validated questionnaire. Determined maximal oxygen update with a single stage submaximal treadmill test. Assessed maximal voluntary strength (one-repetition maximum) for chest press, latissimus pulldown, knee	Metabolic syndrome z-score based on the following variables: -Waist circumference -Systolic and diastolic blood pressure -HDL cholesterol -Triglycerides -Glucose

(Continued)

TABLE 2 Continued

Trial name, First Author, Location (Type of Behavior)	Study Design	Sample Characteristics	Intervention \ Characteristics	Study Measures	Primary Outcomes
		Recruitment: academic cancer center and affiliate public hospital	trainer. - 3 weekly sessions of resistance and aerobic exercise lasting ~80 mins for sessions 1 and 3 and of aerobic exercise of ~50 mins long for session 2. - Wore Polar heart monitors during sessions. C: Wait-listed - Wore a daily accelerometer Contact: Weekly for 6mo. Follow-up: 7mo.	extension and knee flexion using the 10-repition maximum method. Dietary measure: 2 week days and 1 weekend day dietary records at baseline, post-intervention and at 3 m follow up for I group only.	
Moadel 2007 (13), New York (Physical Activity)	RCT, 2-arm, efficacy	Group (N):128 I (108); C (44) Sample: Patients and survivors; -42% Black -31% Latina -23% White -4% Other Stages: I - IV Mean time since diagnosis: 1.1 y Mean age: 54.8 y Mean BMI: Not Reported Recruitment: Oncology clinics at academic medical center and private clinics	Theory: Not Reported Duration: 3mo. Delivery: I: immediate intervention 12 in person, 1.5-hour Hatha yoga sessions with certified instructor. Participants able to attend >1 class/wk. C: Wait-listed Contact: Baseline and after 3mo. Follow-up: none	Quality of Life measure: The Functional Assessment of Cancer Therapy (FACT)	Change in Quality of Life
Project *VIVA*! Mama 2018 (14), Texas and Puerto Rico (Physical Activity) *Other publications* (75)	RCT, 3-arm, pilot	Group (N):89 I (59); C (30) Sample: survivors -45 Mexican American -44 Puerto Rican Stages: I-IV Mean time since diagnosis: Not Reported Mean age: 58.5y Mean BMI: 31.0 kg/m^2 Recruitment: Oncology clinics at academic medical center.	Theory: Social cognitive theory Duration: 4mo. Delivery: All: Twice a week home-based exercise program consisting of aerobic exercise, muscular strength, and flexibility training. - Intensity and duration were individually tailored. - Two sets of resistance band, a pedometer. an exercise book and video - Group exercises were held once a month. I-1: Culturally adapted group (n=30) - Culturally relevant images, messages, and examples to Latina breast cancer survivors - Information on self-efficacy, social modeling, and social support I-2: Standard exercise group (n=29) C: Wait-listed Contact: Biweekly phone calls for 4mo. Follow-up: 6mo.	Physical Activity and Sedentary Time: The International Physical Activity Questionnaire (IPAQ) short form to measure Physical Activity and sedentary time over the past seven days. Sedentary behavior: Past-day Adults' Sedentary Time (PAST) Questionnaire. SCT variables: a range of scales to measure exercise self-efficacy, barriers self-efficacy, social modeling of Physical Activity, and social support for exercise.	Compare culturally adapted vs standard intervention on the following: -Social cognitive theory measures -Physical activity -Sedentary time
Taylor 2018 (16), Washington, DC (Physical Activity)	RCT, 2-arm, pilot	Group (N):33 I (18); C (15) Sample: Survivors -100% Black Stages: Not Reported	Theory: Not Reported Duration: 2 mo. Delivery: I: Eight weekly restorative yoga classes of 75 minutes	Fatigue: 9-item self-reported Brief Fatigue Inventory scale, to assess fatigue and impact of fatigue on daily functioning.	Changes on psychological and functional outcomes

(Continued)

TABLE 2 Continued

Trial name, First Author, Location (Type of Behavior)	Study Design	Sample Characteristics	Intervention \ Characteristics	Study Measures	Primary Outcomes
		Mean time since diagnosis: (I) 9.3 y and (C) 6.5 y Mean age: (I) 54.9 y and (C) 52.6 y Mean BMI: (I) 33.8 kg/m^2 and (C) 33.9 kg/m^2 Recruitment: Oncology clinics at academic medical center	per session led by a certified yoga instructor at Howard University. - Yoga breathing techniques Pranayama. C: Wait-listed Contact: Baseline and after 2mo. Follow-up: none	Insomnia: 7-item Insomnia Severity Index (ISI) measure to evaluate the perceived severability of clinically significant insomnia over 2 wks. Depression: Center for Epidemiologic Studies Short Depression Scale (CES-D-R 10). 10-items self-reported, to measure depressive symptomatology. Perceived stress: 4-item Perceived Stress Scale (PSS). Yoga Satisfaction: Assess participants opinion of the yoga program.	
Lee, 2021 (17), California (Physical Activity) *Other publications:* (76–79)	RCT, 2-arm, pilot	Group (N): 30 I (15); C (15) Sample: Patients -13% Non-Hispanic White -73% Latina -7% Black -7% Asian/Pacific Islander Stages: I-III Mean time since diagnosis: 8 wks from completing (neo) adjuvant Mean age: 46.9 y Mean BMI: I (33.1 kg/m^2); C (30.1 kg/m^2) Recruitment: Oncology clinics at academic medical center and affiliate public hospital	Theory: Not Reported Duration: 8 wks Delivery: All: Maximal cycling protocol that included 10 W increase in workload every 60s, starting at 40 W while maintaining 60 rpm to measure their VO2max and PPO (highest power output generated during a maximal cycling test). I: Eight weekly HITT supervised sessions by a certified exercise trainer on a stationary bike. C: Wait-listed Contact: Baseline and after 8 wks. Follow-up: none	Physical Activity measure: Timed up and go (TUG), the 30-s sit-to-stand (30STS) test, the Margaria-Kalamen stair climb test, and the 6-min walk test (6MWT).	Feasibility of utilizing HIT, measured using the average minutes of weekly activity and the number of sessions attended
Soltero 2022 (22), Arizona (Physical Activity)	RCT, 2-arm, pilot	Group (N): 20 Arm 1(10); Arm 2 (10) Sample: Survivors -65% Latina -25% Non-Hispanic White -5% Black -5% Mixed race/ethnicity Stages: 0-III Mean time since diagnosis: 2 wks to 10 y past primary treatment Mean age: Arm 1 (49.6 y), Arm 2 (53.2 y) Mean BMI: Arm 1 (31.0 kg/m^2) Arm 2 (31.1 kg/m^2) Recruitment: Oncology clinic and dissemination through the cancer support community.	Theory: Not Reported Duration: 8 wks Delivery: All: Used a 7-day pedometer and a Tanita TBF-310 body composition analyzer. Twice a week classes. Arm 1: Latin dance classes - Provided by Latin dance instructors, included basic salsa, merengue, chacha and bachata. Arm 2: Qigong/Tai Chi classes - Provided by Tai Chi Easy instructors. There were 7 basic core exercises, 10 additional movements and standardized opening and closing movements. C: none Contact: Baseline and after 8 wks. Follow-up: none	Physical Activity measure: 7-day pedometer protocol	Overall daily steps BMI Percent body fat

(Continued)

TABLE 2 Continued

Trial name, First Author, Location (Type of Behavior)	Study Design	Sample Characteristics	Intervention \ Characteristics	Study Measures	Primary Outcomes
Combined Diet/Physical Activity Interventions (n= 1 efficacy trial; n= 8 pilot/feasibility trials)					
Moving Forward, Stolley 2017 (9), Chicago (Diet and Physical Activity) *Other publications* (80–82)	RCT, 2-arm, efficacy	Group (N): 246 I (125); C (121) Sample: Survivors; -100% Black Stages: I – III Mean time since diagnosis: 6.7 y Mean age: 57.5 y Mean BMI: 36.1kg/m^2 Recruitment: Cancer registry	Theory: Socioecological model Duration: 6mo. Delivery: I: Interventionist-guided program - Class 1: twice-weekly, 90 min. in-person, supervised group exercise sessions followed by 45-60 min learning modules; text messaging counseling - Class 2: standalone, 60 min. exercise session. Provided program binder. C: Self-guided program - Received program binder Contact: Baseline and after 6mo. Follow-up: 12mo.	Physical Activity measure: Modified Activity Questionnaire to determine frequency and duration of moderate and vigorous activity Dietary measure: Block 2005 Food Frequency Questionnaire to determine intake of energy, fruits and vegetables, fat, fiber, meat, and added sugars.	5% weight loss
Ferrante 2018 (23) New Jersey (Diet and Physical Activity, eHealth tools) *Other publications* (83)	RCT, 2-arm, pilot	Group (n): 37 I (20); C (17) Sample: Survivors -100% Black Stages: 0-III Mean time since diagnosis: 6.6 y Mean age: 61.5y Mean BMI: 37.7 kg/m^2 Recruitment: Oncology clinics at academic medical center	Theory: Not Reported Duration: 6 mo. Delivery: I: Instructed to self-monitor diet weekly using SparkPeople website and physical activity levels daily using Fitbit device. - Active phase: Weekly motivational reminders to log into website for 3mo. - Maintenance phase: Additional 3mo. without reminders. C: Wait-listed Contact: Baseline, at 3mo. and after 6mo. Follow-up: 9mo. and 12mo.	Physical Activity measure: Direct data downloads from the Fitabase research platform provided Physical Activity levels. Dietary measure: Caloric intake was quantified by 24-hour diet recall administered by research assistant using the Sparkpeople.com food diary tool.	5% weight loss
Valle 2017 (25), North Carolina (Diet and Physical Activity, eHealth tools)	RCT, 3-arm, pilot	Group (n): 45 I (34); C (11) Sample: Survivors -100% Black Stages: I-III Mean time since diagnosis: 3.1 y Mean age: 53 y Mean BMI: 33.9 kg/m^2 Recruitment: Hospital based-registry/cancer survivorship cohort, oncology clinics at academic medical center, local tumor registry, advertising at community-based events and social media.	Theory: Self-regulation theory of eating and exercise behaviors to prevent weight gain and two additional frameworks used in STOP Regain and SNAP which emphasized daily self-weighing. Duration: 6 mo. Delivery: All (intervention): - In-person individualized sessions - Bluetooth and Wifi-enabled wireless scale (Withings WS-30, Cambridge, MA) - Mobile app with graphs and weight trends - Weekly emails with tailored feedback on weight data. I-1: Self-regulation intervention with objective activity monitoring (n=11) Activity tracker (Withings Pulse, Cambridge, MA)	Physical Activity measure: Paffenbarger Activity Questionnaire (PAQ). Dietary measure: Automated Self-Administered 24-Hour Dietary Recall (ASA-24).	Weight gain prevention

(Continued)

TABLE 2 Continued

Trial name, First Author, Location (Type of Behavior)	Study Design	Sample Characteristics	Intervention \ Characteristics	Study Measures	Primary Outcomes
			I-2: Self-regulation intervention only (n=13) - Encouraged to daily track their activity in addition to weighing themselves C: Wait-listed Follow-up: 6mo.		
La Vida Activa/An Active Life Greenlee 2013, (26), New York (Diet and Physical Activity)	RCT, 2-arm, pilot	Group (n): 42 I (22); C (20) Sample: Survivors; -79% Latina -21% Black Stages: 0 - III Mean time since diagnosis: 1.2 y Mean age: 51 y Mean BMI: 33.2 kg/m^2 Recruitment: oncology clinics at academic medical center	Theory: Not Reported Duration: 6 mo. Delivery: I: Curves Weight Management Program curriculum available to the public. Program includes a 30-minute exercise circuit and a high vegetable/low-fat/ calories-restricted diet. C: Wait-listed Contact: Baseline, 3mo and at 6mo. Follow-up: 9mo and 12mo.	Physical Activity measure: Self-administer adaption of the Kaiser Physical Activity Survey Dietary measure: Spanish version of the Block Questionnaire.	5% weight loss at 6 mo.
ALIVE, Paxton 2017 (27), Texas (Diet and Physical Activity, eHealth tools)	RCT, 2-arm, pilot	Group (n): 71 Arm 1 (34); Arm 2 (37) Sample: Survivors -83% Black -11% Latina -6% Mixed race/ethnicity Stages: 0 - IV Mean time since diagnosis: 8.4 y Mean age: 52.2 y Mean BMI: 30.8 kg/m^2 Recruitment: North Texas metropolitan area	Theory: Social cognitive theory, goal-setting theory, social marketing, and transtheoretical theory Duration: 3 mo. Delivery: All: Weekly emails and links to an individualized website with behavior change strategies tailored to their specific needs and specific to their track. $20 incentive for completing each assessment. Arm 1: Physical activity track: encouraged to meet exercise recommendations (≥150 min of moderate to vigorous Physical Activity per week) Arm 2: Dietary track - Sub-track 1: F&V: encouraged to meet or exceed recommended F&V consumption (≥3.5 cup svgs of F&V) - Sub-track 2: Fats and added sugar: encouraged to decrease consumption of saturated and trans fats and carbohydrates (≤50g/day of added sugars and ≤10% of calories from saturated fats) C: none Contact: Weekly for 3mo. Follow-up: none	Physical Activity measure: Physical Activity Questionnaire (PAQ) adapted from the Cross-Cultural Activity Participation Study (CAPS) Questionnaire. Dietary measure: 35-item NHANES questionnaire	Meet exercise recommendations Meet dietary recommendations
Stepping STONE Sheppard 2016 (28), Washington, DC (Diet and Physical Activity)	RCT, 2-arm, pilot	Group(n): 31 I (15); C (16) Sample: Survivors; -100% Black Stages: 0-III Mean time since diagnosis: Not Reported	Theory: Theory of planned behavior and social cognitive theory Duration: 3 mo. Delivery: I: Biweekly 90-min group sessions (30 min supervised	Physical Activity measure: International Physical Activity Questionnaire Short Form (IPAQ-SF) Dietary measure: Intervention participants	5% weight loss

(Continued)

TABLE 2 Continued

Trial name, First Author, Location (Type of Behavior)	Study Design	Sample Characteristics	Intervention \ Characteristics	Study Measures	Primary Outcomes
		Mean age: 54.7 y Mean BMI: I (35.2 kg/m^2); C (37.4 kg/m^2) Recruitment: Two local hospitals and community outreach in the Washington, DC metropolitan area.	group exercise and 60 min education sessions) co-led by a physiologist and a nutritionist. - 6 individual telephone coaching sessions led by a survivor coach. - Received a pedometer, notebook and individualized step goals that gradually increased to 10,000 steps/day for 12 wks. C: Usual care - NCI booklet "Facing Forward Life after Cancer Treatment" Contact: Baseline and after 3mo. Follow-up: none	were instructed to record daily food/beverage intake.	
MyHealth Smartphone Intervention Buscemi 2020 (29), Chicago (Diet and Physical Activity, eHealth tools) *Other publications* (84)	RCT, 2-arm, pilot	Group(n): 80 Arm 1 (40); Arm 2 (40) Sample: Survivors -100 % Latina Stages: 0-III Mean time since diagnosis: 15.50 m Mean age: 53.54 y Mean BMI: Not Reported Recruitment: Two large academic medical centers in the Chicago metropolitan area and a local community-based organization	Theory: Followed a telecoaching adapted from a model of supportive accountability to promote optimal adherence Duration: 6 wks Delivery: Mobile application on personal phone or borrowed study appointed smartphone All: 15-20 mins telecoaching calls until wk 2 For wks 3-5: - If used app <=90mins, received additional telecoaching calls - If used app >90 mins, received reinforcing text message Arm 1: *My Guide* application (health-related quality of life) Arm 2: *My Health* application for culturally appropriate lifestyle promotion: C: None Contact: Baseline and after 6 wks Follow-up: 8 wks.	Physical Activity measure: 7-item International Physical Activity Questionnaire Dietary measure: 23-item Brief Dietary Assessment Tool for Latinas	Dietary intake Physical activity Breast cancer symptom burden Health-related quality of life domains (breast cancer, physical, emotional, functional well-being)
Nuestra Salud/ Our Health, Crane 2020 (31), Arizona (Diet and Physical Activity, eHealth tools)	RCT, 2-arm, pilot	Group(n): 45 dyads I (28); C (17) Sample: Survivors; -100 % Latina Stages: Not Reported Mean time since diagnosis: Not Reported, completed primary treatment Mean age: 64.35 y Mean BMI: I (31.34 kg/m^2); C (27.08 kg/m^2) Recruitment: Latina cancer survivors from the southern Arizona community, oncology clinics at academic medical center, and a support group in the Arizona, US-	Theory: Social Cognitive Theory Duration: 12 wks Delivery: All: $25 gift card after study completion. I: A 12 weekly Symptom Management and Lifestyle Intervention (SMLI) telephone-based (20 to 30 mins) coaching sessions with trained bicultural health coach in either English or Spanish using the electronic health and intervention platform (eHIP).	Physical Activity measure: A Spanish-translated version of the Women's Health Initiative (WHI) Physical Activity Questionnaire. Dietary measure: A 19-item NCI Dietary Screener Questionnaire 18-item United States Department of Agriculture Food Security Questionnaire	Feasibility & acceptability Efficacy in dietary and Physical Activity adherence Efficacy in symptom improvement

(Continued)

TABLE 2 Continued

Trial name, First Author, Location (Type of Behavior)	Study Design	Sample Characteristics	Intervention \ Characteristics	Study Measures	Primary Outcomes
		Sonora, Mexico border region.	- Printed materials from the Symptom Management and Survivorship Handbook developed by the authors (SMSH). - Fitbit as a strategy for self-monitoring. - Specific, Measurable, Attainable, Relevant, and Timely (SMART) goals composed of increasing the number of steps per day (daily activity); servings of F&V or whole grains per day; reduction of calories from added sugars, fat, and processed and red meat; and reduction in alcohol consumption. C: Usual care Contact: Baseline and after 12 wks. Follow-up: none		
Mobile Health, Allicock 2020 (32), Dallas, Texas (Diet and Physical Activity, eHealth tools)	RCT, 2-arm, pilot	Group (n): 22 I (13); C (9) Sample: Survivors; -100% Black Stages: Not Reported Mean time since diagnosis: Not Reported, ≥6 months since completion of breast cancer treatment Mean age: 52.23 y Mean BMI: I (33.26 kg/m^2); C (38.25 kg/m^2) Recruitment: Word of mouth and flyers in Dallas, Texas metropolitan area.	Theory: Social cognitive theory and control theory Duration: 4 wks Delivery: All: ActiGraph wGT3X-BT accelerometer to use for seven consecutive days at baseline, 4 wks, and 8 wks post-baseline. $30 compensation for each of the three study visits and could earn up to an additional $60 for completing 80% or more of the ecological momentary assessments. I: Completed three types of ecological momentary assessments (daily diary, random sampling, event sampling) through the Creating Healthy Actions through Technology (CHAT) app. - Received tailored messages as feedback to their responses. C: Usual care Contact: Baseline and after 4 wks. Follow-up: 8 wks	Physical Activity measure: Behavioral Risk Factor Surveillance System (BRFSS) physical activity questionnaire Dietary measure: 15-item questionnaire, The National Health Interview Survey 2000	Feasibility (i.e., engagement and acceptability) Efficacy of CHAT in behavioral and health outcomes

syndrome, sarcopenic obesity, and inflammatory biomarkers (59). No cultural adaptations were reported. The primary endpoint was change in metabolic syndrome z-score post intervention (4 months) with a 3-month follow-up in the intervention arm only. A favorable change in metabolic syndrome z-score, sarcopenic obesity and body composition was observed for intervention arm compared to waitlist control arm by the end of the 16-week intervention. At the 3-month follow-up, the percent of participants in the intervention arm with metabolic syndrome was unchanged.

Moadel et al. (60) conducted a study examining the effects of Hatha yoga sessions compared to waitlist control arm on quality of life among Black breast cancer survivors (n=128). The primary goal was to observe changes in quality of life. The study did not report any cultural adaptations for the intervention. Moadel et al. found an unexpected decrease in social well-being for the intervention group, although the decrease was greater in the waitlist control arm (2% vs. 13%, respectively, $p < 0.001$). No long-term results have been reported.

TABLE 3 Findings of completed randomized controlled trials focused on dietary and/or physical activity behavioral changes in a Black and Hispanic/Latina breast cancer survivors (N = 17).

Trial name, First author, location (Type of behavior)	Findings		
	Feasibility	Change from baseline to post-intervention	Change from baseline to follow-up
Diet Interventions			
Efficacy trials (n=2)			
¡Cocinar Para Su Salud!, Greenlee 2015 (1), New York *Other publications* (70–72) (Diet)	End-of-I: -12 wks, I 82/%; C 100% retention Post-I follow-up: 3mo., I 91% and C 100% retention 6mo., I 88/% and C 86% retention 12mo., I 85% and C 80% retention Data analysis: Excluded lost to follow-up	Adjusted means: -All fruit & vegetables, svg: (I) +1.1 vs. (C) -0.3, p=0.05 -Targeted fruit & vegetables, svg: (I) +2.0 vs. (C) +0.2, p=0.004 -Daily total caloric intake (kcal): (I) -672.9 vs. (C) -92.4, p<0.001 -% Fat of daily total energy: (I) -7.1 vs. (C) -1.6, p=0.01	At 6mo. -All fruit & vegetables, svg: (I) +2.0 vs. (C) -0.1, p= 0.005 -Targeted fruit & vegetables, svg: (I) +2.7 vs. (C)+0.5, p=0.002 -Daily total caloric intake (kcal): (I) -562.9 vs. (C) -61.6, p<0.001 -Total fat % of daily total energy: (I) -7.5 vs. (C) -4.4, p= not significant (ns) At 12mo. -All fruit & vegetables, svg: (I) +2.0 vs. (C) -0.4, p= <0.01 -Targeted fruit & vegetables, svg: (I) +2.3 vs. (C) -0.1, p= <0.01 -Daily total caloric intake (kcal): (I) -121.9 vs. (C) 9.3, p= ns -Total fat % of daily total energy: (I) -2.2 vs. (C) -2.1, p= ns
Zuniga, 2018 (5), Texas *Other publications* (73) (Diet)	End-of-I: 6 mo., I 79%; C 84% retention Post-I follow-up: none Data analysis: Excluded lost to follow-up	Marginal means ± standard error (SE) - Mediterranean diet score: (I) +1.6 (0.2) vs. (C) +0.02 (0.2), p<0.001 -Spices and herbs score: (I) +1.9 (0.3) vs. (C) +0.04 (0.2), p<0.001	None
Physical Activity Interventions			
Efficacy trials (n=2)			
Dieli-Conwright 2018 (7)[a], California *Other publications* (74) (Physical Activity)	End-of-I: 4 mo., I 96%; C 90% retention Post-I follow-up: 3 mo., I 92%; C 90% retention Data analysis: Excluded participants lost to follow-up	- Metabolic syndrome, % of participants: - Baseline: (I) 78% vs. (C) 76%, p=0.27 - Post-intervention: (I) 15% vs. (C) 80%, p<0.004	-Metabolic syndrome, participants in exercise group only: 15%
Moadel 2007 (13), New York (Physical Activity)	End-of-I: 12 wks, 69% retention Post-I follow-up: 3mo., I 78%; C 79% retention 6mo., Not Reported Data analysis: Intention To Treat analysis, subgroup analysis for patients not on chemotherapy	- Overall Quality of Life: δ = -0.09; 95%CI = 8.05, 2.63 - Social well-being: δ = -0.22, 95%CI = 3.78, -0.36 - Physical well-being: δ = 0.07; 95%CI = -1.29, 3.05 - Functional well-being δ = -0.06; 95%CI = -3.29, 1.60 - Emotional well-being: δ = -0.07; 95%CI = -2.33, 0.99	Not Reported
Pilot/feasibility trials (n=4)			
Project VIVA! Mama 2018 (14), Texas and Puerto Rico *Other publications* (75) (Physical Activity)	End-of-I: 16 wks, retention not reported Post-I follow-up: 6mo., Not Reported Data analysis: Assessment of completers only	- Exercise self-efficacy: I vs C, *F* (1,77): 9.17, p=0.003 - Moderate physical activity: I vs. C, *F* (1,76): 7.66, p=0.007 - Vigorous physical activity: I vs. C, *F* (1,76): 6.47, p=0.013 - Total Physical Activity: I vs. C, *F* (1,76): 9.32, p=0.003	Not Reported
Taylor 2018 (16)[b], Washington, DC (Physical Activity)	End-of-I: 2mo., 60% retention Data analysis: Assessment of completers only	Baseline and Follow-up Mean (standard deviation (SD)) - Sleep quality: (I)10.18 (8.74) and 7.89 (7.17) vs. (C) 7.56 (6.82) and 6.20 (7.11), p = 0.890 - Fatigue: (I) 3.48 (2.34) and 1.85 (1.61) vs.	None

(Continued)

TABLE 3 Continued

Trial name, First author, location (Type of behavior)	Findings		
	Feasibility	Change from baseline to post-intervention	Change from baseline to follow-up
		(C) 2.50 (2.71) and 2.10 (2.86), p = 0.750 - Depression: (I) 8.79 (4.23) and 4.78 (3.56) vs. (C) 7.08 (5.38) and 6.91 (5.86), p < 0.01 - Perceived stress: (I) 6.00 (2.48) and 5.22 (2.17) vs. (C) 5.08 (3.06) and 4.45 (3.39), p = 0.770 - Adherence was 61% for the yoga group	
Lee, 2021(17) California (Physical Activity) *Other publications* (76, 77, 79)	Adherence to 70% of sessions (17/24) End-of-I: 9 wk, I 100%; C 100% retention, 82.3% mean adherence Post-I follow-up: None - Data analysis: Not Reported	- The amount of overall physical activity was not statistically different between the HIIT group (480.9 ± 85.3 Metabolic equivalent (MET)/week) and the control group (441.9 ± 93.2 METs/week).	None
Soltero 2022 (22), Arizona (Physical Activity)	End-of-I: 8 wks, 100 % retention for both groups. Post-I-follow-up: none Data analysis: included post-intervention data collection assessments	- Physical activity level: Increased from T1 to baseline to T2 to post-intervention when examining both arms together but the change was not significant (Cohen's d= 0.07). - Body composition: No significant changes from T1 to baseline to T2 to post-intervention (Cohen's d= 0.04 and 0.36, respectively).	Not Reported
Combined Diet & Physical Activity Interventions			
Efficacy trials (n=1)			
Moving Forward, Stolley 2017 (9), Chicago *Other publications* (80–82), (Physical Activity)	End-of-I: 6 mo., I 89%; C 84% retention Post-I follow-up: 12 mo., I 86%; C 83% retention Data analysis: Excluded participants lost to follow-up	- Weight loss, %: (I) 3.6 vs. (C) 1.4, p<0.001 - Moderate physical activity, mins/wk: (I) 98.4 vs. (C) 60.6, p= 0.298 - Vigorous physical activity, mins/wk: (I) 17.4 vs. (C) 2.4, p=0.03 - Daily energy intake, kcal: (I) -563.9 vs. (C) -262.4, p=0.004 -Fiber, g/1,000kcal: (I) 3.24 vs. (C) 0.91, p<0.001 - Added sugars, tsps: (I) -6.98 vs. (C) -3.85, p=0.035	-Weight loss, %: (I) 2.6 vs. (C) 1.6, p=0.05 -Moderate physical activity: (I) 97.8 vs. (C) 77.4 p=0.596 -Vigorous physical activity: (I) 14.4 vs (C) -3.00, p=0.014 -Daily energy intake, kcal: (C) -576.0 vs. (2) -353.9, p=0.037 -Fiber, g/1,000kcal: (I) 1.75 vs (C) 0.78, p=0.046 -Added sugars, tsps: (I) -7.25 vs. (C) 11.4, p=0.030
Pilot/feasibility trials (n=8)			
Ferrante 2018 (23) New Jersey *Other publications* (83), (Diet and Physical Activity, eHealth tools)	End-of-I: 6 mo., 97.1% retention Post-I follow-up: 12 mo., 88.6% retention Data analysis: Intention To Treat, excluded 2 participants from intervention group that did not meet eligibility criteria after randomization	Baseline and Follow-up (6 mo.), mean (SD) - Sleep quality: (I)10.18 (8.74) and 7.89 (7.17) vs. (C) 7.56 (6.82) and 6.20 (7.11), p = 0.890 - Fatigue: (I) 3.48 (2.34) and 1.85 (1.61) vs. (C) 2.50 (2.71) and 2.10 (2.86), p = 0.750 - Depression: (I) 8.79 (4.23) and 4.78 (3.56) vs. (C) 7.08 (5.38) and 6.91 (5.86), p < 0.01 - Perceived stress: (I) 6.00 (2.48) and 5.22 (2.17) vs. (C) 5.08 (3.06) and 4.45 (3.39), p = 0.770 - Adherence was 61% for the yoga group	Not Reported
Valle 2017 (25), North Carolina (Diet and Physical Activity, eHealth tools)	End-of-I: 3 m, 94.3% completed both in-person/ online assessments. Post-I follow-up: 6 m, 97.1% retention for in-person and 94.3% for online measurements. Data analysis: Intention To Treat	- % Weight change, median (interquartile range (IQR)): (I-1) -0.94 (-4.42-0.12) vs. (I-2) -0.22 (-4.18-1.28) vs. (C) 0.18 (-0.71-1.73), p (I-1 vs C) = ns, p (I-2 vs C) =0.357 - Weight, kg, median (IQR): (I-1) -1.0 (-4.0-0.1) vs. (I-2) -0.2 (-3.4-1.1) vs. (C) 0.2 (-0.7-1.3), p (I-1 vs C) =0.058, p (I-2 vs. C) = 0.751	Not Reported

(Continued)

TABLE 3 Continued

Trial name, First author, location (Type of behavior)	Findings		
	Feasibility	Change from baseline to post-intervention	Change from baseline to follow-up
La Vida Activa/An Active Life Greenlee 2013, (26), New York (Diet and Physical Activity)	End-of-I: 6 mo., I 95%; C 85% retention Post-I follow-up: 90.5% retention by 12 mo. - Data analysis: Not Reported	- Weight change (kg), mean (SD) - I: 2.87 (3.15); C (waitlist): -1.42 (2.5) p=0.03	- Weight change (kg), mean (SD) - I: 1.76 (3.21); - C (waitlist): -2.14 (3.77)
ALIVE, Paxton 2017 (27)[c], Texas (Diet and Physical Activity, eHealth tools)	End-of-I: 3 mo., 62% retention Post-I follow-up: None Data analysis: Intention To Treat and sub analysis among intervention completers only	Physical Activity change (mean score (SE)): - Minutes of moderate to vigorous physical activity/wk: +97 (42), p<0.01 - Sugar in g/day: +63.9 (2.7), p=ns - Fiber in g/day: +1.1 (1.1), p=ns - fruit & vegetables in cup/day: +0.3 (0.2), p=ns - Saturated fat in g/day: -0.6 (0.8), p=ns - Trans fat in g/day: -0.0 (0.1), p=ns - Carbohydrates in g/day: +8.3 (6.9), p=ns Diet track (mean score (SE)): - Minutes of moderate to vigorous Physical Activity/wk: +49 (40), p<0.01 - Sugar in g/day: -1.5 (2.5), p=ns - Fiber in g/day: +2.9 (1.1), p=ns - Fruit & Vegetables in cup/day: +0.7 (0.2), p<0.05 - Saturated fat in g/day: -1.8 (0.8), p=ns - Trans fat in g/day: -0.2 (0.1), p=ns - Carbohydrates in g/day: +11.4 (6.6), p=ns Effect size between tracks - Minutes of moderate to vigorous Physical Activity/wk: $\delta = 0.20$, p<0.001 - Sugar in g/day: $\delta = 0.35$, p=0.42 - Fiber in g/day: $\delta = 0.27$, p=0.35 - Fruit & vegetables in cup/day: $\delta = 0.34$, p=0.29 - Saturated fat in g/day: $\delta = 0.25$, p=0.40 - Trans fat in g/day: $\delta = 0.30$, p=0.90 - Carbohydrates in g/day: $\delta = 0.08$, p=0.61	Not Reported
Stepping STONE Sheppard 2016 (28)[c], Washington, DC (Diet and Physical Activity)	End-of-I: 3 mo., I 67%; C 75% retention Post-I follow-up: None Data analysis: Excluded non-completers	- Body weight change (mean lbs.): - I: -1.7; C: 0.4, P>0.05	None
MyHealth Smartphone Intervention Buscemi 2020 (29), Chicago (Diet and Physical Activity, eHealth tools) *Other publications* (84)	End-of-I: 6 wks, My Guide (MG) 95%; My Health (MH) 97% retention Post-I follow-up: 8 wks, MG 95%; MH 92% retention Data analysis: Completed cases	Estimated marginal means (SD) at post-intervention Daily fat sources: MG= 2.42(0.22) vs. MH= 2.38 (0.21), p=ns Interaction between MG and MH: Cohen's $d = 0.30$, $p = 0.030$) Daily serving of fruit & vegetables: MG= 3.41(0.28) vs. MH= 3.53 (0.28), p=0.607 Weekly physical activity in MET-mins (mean (95% CI)) -Walking: MG= 301(218, 567) vs MH= 281 (149, 529), p = ns -Moderate physical activity: MG= 12 (7,35), MH= 7 (2,21), p = ns -Vigorous physical activity: MG= 2 (1,7) vs. MH= 4 (1,12), p = ns	Estimated marginal means (SD) at follow up Daily fat sources: MG= 2.36 (0.22) vs. MH= 2.20 (0.22), p= ns Interaction between MG and MH: Cohen's $d = 0.47$, $p = 0.009$) Daily serving of Fruit & Vegetables: MG= 3.26 (0.28), MH= 3.59 (0.28), p= ns Weekly physical activity in MET-mins (mean (95% CI)) -Walking: MG= 262 (190,494) vs. MH= 203 (108, 383), p= ns -Moderate physical activity: MG= 11 (6,32) vs. MH= 76 (1,17), p = ns -Vigorous physical activity: MG= 5 (3,15) vs. MH= 2 (0,6), p = ns
Nuestra Salud (Our Health), Crane 2020 (31), Arizona (Diet and Physical Activity, eHealth tools)	End-of-I: 12 wks, I 86 % retention Post-I follow-up: None Data analysis: comparing cohen's d effect size	Post-intervention (Cohen's *d*, effect size): -fruit & vegetables in cup/day: d = 0.55, p = 0. 22 -Sugar intake (g/day): d= 0.51, p = 0.25 -Vegetables intake in cup/day: d= 0.72, p = 0.11	None

(Continued)

TABLE 3 Continued

Trial name, First author, location (Type of behavior)	Findings		
	Feasibility	Change from baseline to post-intervention	Change from baseline to follow-up
		- Mins of physical activity/week: d= 0.42, p = 0.36 - Fiber intake in g/day: d= 0.40, p = 0.36 - Global symptom distress: d= 0.17, p = 0.73 - Self-efficacy for symptom management d= 0.01, p = 0.99	
Mobile Health, Allicock 2020 (32), Dallas, Texas (Diet and Physical Activity, eHealth tools)	End-of-I: week 4, I 100%; C 100% retention Post-I follow-up: week 8, 100%; C 100% retention Data analysis: Included post-I-follow-up	Post-Intervention, Mean change (SD) Fruit & vegetables servings/day: I = 0.67 (2.35) vs. C= 0.78 (2.48), p = ns Fast-food consumption: I = -1.5 (1.98) vs. C= -1.11 (1.45), p = ns Minutes/day of moderate to vigorous physical activity I = +0.56 (28.10) vs. C= -10.95 (9.93), p = ns Sedentary daily time (hours/day) I = -4.37 (7.14), C= - 2.57 (3.39), p = ns	Post-intervention follow up, Mean change (SD) Fruit & vegetables svg: I = 0.23 (1.88) vs. C= 0.76 (3.11), p = ns Fast-food consumption: I = -1.76 (3.11) vs. C= -0.63 (1.77), ns Minutes/day of moderate to vigorous physical activity I = - 7.28 (15.15) vs. C = - 8.47 (8.09), p = ns Sedentary daily time (hours/day) I = - 3.62 (6.24) vs. C = - 0.88 (2.65), p = ns

I, Intervention; C, Control; mo., month; wk(s), week(s); mins, minutes; yrs, years; hrs, hours, F&V, fruits and vegetables; svg, servings; kcal, kilocalories; tsp, tablespoons; δ, effect size; CI, confidence interval; SD, standard deviation; ns, not significant, MET, metabolic equivalents.
[a]Dieli-Conwright examined change from baseline to 4 months.
[b]Taylor examined change from baseline to 2 months.
[c]Paxton, and Sheppard examined change from baseline to 3 months.

TABLE 4 Withdrawn and ongoing randomized controlled trials targeting physical activity behavioral changes in a Black and Latina breast cancer survivors (N = 5).

Trial name, identifier, location	Sample Characteristics	Target Behavior	Primary Outcomes
Physical activity in reducing metabolic dysregulation (MetD) in Obese Latina Breast Cancer Survivors. NCT03120390 *Trial Withdrawn* Southern California	Sample: 240 Latina women Stage eligibility: newly diagnosed I-III	Physical Activity	Change in MetD
Effect of Low vs Moderate-intensity Endurance Exercise on Physical Functioning Among Breast Cancer Survivors. NCT02982564 Puerto Rico	Sample: 142 Puerto Rican women Stage eligibility: 0-III	Physical Activity	Change in cardiorespiratory fitness Change in quality of life Change in functioning Change in depression Change in body image
RCT of Strategies to Augment Physical Activity in Black and Latina Breast and Prostate Cancer Survivors (ALLSTAR). NCT05176756 California, Pennsylvania and New York	Sample: 150 Black and Latina women Stage eligibility: at least 2 years from cancer diagnosis	Physical Activity	Change in daily step count
Reducing Metabolic Dysregulation in Obese Latina Breast Cancer Survivors Using Physical Activity: The ROSA Trial (33). NCT04717050 Boston	Sample: 160 Latina women Stage eligibility: newly diagnosed I-III	Physical Activity	- Change in MetD: insulin resistance - Change in MetD: visceral adiposity - Change in MetD: metabolic syndrome
Mi Vida Saludable!/My Health Life (34) NCT02780271 Trial completed; results not yet published New York	Sample: 167 Latina Stages: 0 - III	Diet/Physical Activity	Change in daily svgs of F&V Change in energy density

I, Intervention; C, Control; F&V, fruits and vegetables; svg, servings; MetD, Metabolic Dysregulation.

Pilot/feasibility trials (n=4)

Mama et al. conducted Project *VIVA!*, which was a four month, three-arm, randomized pilot intervention among 89 Latina survivors with breast cancer residing in Texas or Puerto Rico (87). The trial compared the effect of a culturally adapted physical activity program and a standard physical activity program to a waitlist control arm on social cognitive theory outcomes and level of physical activity and sedentary time. The culturally tailored approach included culturally relevant images, messages and examples on the topics of self-efficacy, social modeling and social support. At 16 weeks post-intervention, there were no statistical differences between the culturally tailored and the standard physical activity intervention, but there were significant improvements from baseline to follow-up in exercise self-efficacy and physical activity intensity for both intervention arms compared to waitlist control arm. No long-term results have been reported.

Lee et al. conducted an 8-week, two-arm randomized pilot study of a high intensity interval training intervention vs. waitlist control arm on patient reported outcomes (quality of life, cancer-related fatigue, and mindfulness) and physical function among 30 patients with breast cancer (73% Latina) undergoing anthracycline-based chemotherapy (86). No cultural adaptations were reported. No statistically significant differences were found for physical activity level, weight, or BMI between groups, although researchers observed improvements in quality of life and cancer-related fatigue. Adherence was 82.3% for the intervention arm. Long-term results have not been reported.

Soltero et al. conducted an 8-week, 2-arm randomized pilot study of 20 survivors with breast cancer (65% Latina, 25% White, 5% Black, 5% Mixed race/ethnicity) (62) to compare the effect of Latin dancing (intervention arm 1) to that of Qigong/Tai Chi (intervention arm 2) on overall activity (measured daily steps with a 7-day pedometer) and body mass composition. No differences were found by intervention arm for the primary outcomes. Long-term results have not been reported.

Taylor et al. (61) conducted a study examining the effect of a Pranayama yoga intervention compared to a waitlist control arm on changes in psychosocial and functional outcomes among 33 Black breast cancer survivors. Cultural adaptions were not reported. They found significantly lower depression scores on the Center for Epidemiologic Studies Short Depression Scale (CES-D-R 10) at 2 months for the intervention arm compared to the waitlist control arm. Long-term results have not been reported.

Combined diet and physical activity interventions (n = 9)

Efficacy trials (n = 1)

Stolley et al. conducted the Moving Forward trial, a lifestyle intervention for Black survivors with breast cancer that aimed to achieve a 5% weight loss (63) *via* an interventionist-guided (n=125) vs. self-guided (n=121) weight loss program focused on caloric restriction over 6 months. This study did not include a usual care arm. The Moving Forward program was culturally tailored to focus on food, family, music, social roles and relationships, and spirituality and religion for Black survivors. Compared to the self-guided arm, by 6-months the interventionist-guided arm experienced significantly greater weight loss, increase vigorous physical activity, and fiber consumption, and a decrease in daily energy and added sugars. By 12 months, the changes that persisted were improvements in physical activity, daily energy intake, and fiber and sugar consumption.

Pilot/feasibility trials (n=8)

We identified eight pilot/feasibility trials that incorporated both diet and physical activity into the intervention. We further subdivide this section into trials that incorporated an electronic/mobile component and trials that do not.

Pilot trials with an electronic/mobile component (n=5)

Ferrante et al. conducted a two-arm randomized pilot intervention among 37 Black survivors with breast cancer to examine the feasibility and efficacy of a commercially available exercise and diet self-monitoring website (SparkPeople) plus a Fitbit activity tracker (intervention arm) versus a Fitbit only waitlist control arm with a goal of 5% weight loss. No cultural adaptations were used in the study. At six months post-intervention, there was no difference in weight loss in the intervention arm versus the waitlist control arm (64). Long-term results have not been reported.

Valle et al. conducted a three-arm pilot, randomized intervention among 45 Black survivors with breast cancer that allocated participants to self-regulation of diet and exercise behaviors, daily weighing plus activity tracking (intervention arm 1), self-regulation only (intervention arm 2), and waitlist control arm over three months (65). The program focused on self-regulation of diet, exercise behaviors, and daily weighting for weight gain prevention. The study did not report use of cultural adaptations. After the 3-month intervention, no differences in median weight change were observed for the intervention arms compared to the waitlist control arm. Long-term results have not been reported.

Paxton et al. conducted the *A Lifestyle Intervention Via Email* (ALIVE) trial, a two-arm randomized pilot study (dietary arm vs. physical activity arm) delivered *via* an individualized website and interactive emails among 71 survivors with breast cancer (83% Black, 11% Latina ad 6% Mixed-race) (67). Over 3 months, the diet intervention arm focused on achieving intake of ≥ 3.5 fruits and vegetable servings/day, decreasing intake of added sugars to ≤50 g/day and ≤10% of calories from saturated fat, while the physical activity intervention arm aimed on engaging participants in ≥150 min/week of moderate to vigorous physical per week. No cultural adaptations were used in this study. Participants in the physical activity intervention arm increased their moderate to vigorous activity to a greater extent than those in the dietary intervention arm. No differences were observed in change in dietary behaviors between the physical activity and dietary tracks post intervention. Long-term follow-up was not reported.

Buscemi et al. conducted a six-week, two-arm, pilot, randomized mobile application intervention among 80 Latina breast cancer survivors comparing the My Guide app (a health-related quality of life app) to My Health app (a lifestyle focused app), which was designed with culturally appropriate lifestyle promotion information (69). Culturally tailoring of the intervention involved obtaining

feedback from a community partner organization, Latina breast cancer survivors, and physicians. It included English and Spanish materials, all written content available as an audio file and culturally appropriate healthy recipes. At 6 weeks post intervention or at 8 weeks follow-up, no significant differences between the two arms were found for fruit and vegetable intake, physical activity, or sedentary behavior. Long-term follow-up was not reported.

Allicock et al. conducted a 4-week, 2-arm randomized controlled pilot intervention to examine the feasibility and efficacy of the Creating Healthy Actions through Technology (CHAT) mobile application compared to usual care among 22 Black survivors with breast cancer (89). Cultural adaptations of the intervention were not reported. No differences between study arms were observed for fruit and vegetable intake, fast-food intake, moderate to vigorous physical activity or sedentary behavior at post intervention or at the 8-week follow-up. Adherence was high, with 72% of participants completing the program. Long-term follow-up was not reported.

Pilot trials without an electronic/mobile application-based component (n=3)

Greenlee et al. conducted the *La Vida Activa/An Active Life*, a randomized, wait-list controlled pilot study examining the effect of a commercially available Curves exercise and nutrition program on 5% weight loss among 33 Latina and 9 Black survivors (66). Linguistic adaptions, but not cultural, were incorporated with courses were offered in Spanish and English. Greater weight loss in intervention arms compared to the waitlist control arm, was found post intervention and at 12 months, but not at 6 months.

Sheppard et al. conducted The Stepping STONE (Survivors Taking on Nutrition and Exercise) trial, a randomized pilot trial of a 12-week culturally-tailored nutrition and supervised exercise program delivered in person and *via* phone among 31 Black women (68) with the goal of achieving 5% weight loss. To culturally tailor the intervention, researchers incorporated content on faith, spirituality, traditional/cultural foods, body image perceptions and risk-related information relevant to the Black survivor's population. No differences in weight loss were found between the intervention and control arms. However, the intervention arm experienced a 3.6-fold increase in physical activity, improved cardiovascular fitness, and reduced total energy intake, total fat, and percent of energy from fat, as well as increased fiber intake (68). Long-term follow-up was not reported.

Crane et al. reported on the *Nuestra Salud*/Our Health, a two-arm randomized, telephone-based pilot trial involving 45 dyads composed of Latina cancer survivors, 83% of whom had breast cancer, and their caregivers (85) to evaluate the feasibility, acceptability, and efficacy of a 12-week culturally (e.g., bicultural health coach, social support) and linguistically (English and Spanish) appropriate program involving symptom management and a lifestyle intervention focused on meeting diet (2.5 or more cups of fruits and vegetables) and physical activity guidelines (at least 150 minutes of moderate to vigorous activity). None of the participants in the intervention arm met the intervention diet and physical activity guidelines. The trial had high reported acceptability and completion rate (86%). Long-term follow-up was not reported.

Discussion

To our knowledge, this is the first scoping review of randomized dietary and/or physical activity interventions focused on Black and Latina breast cancer survivors. Overall, three efficacy and five pilot studies achieved statistically significant changes at least in one of their measured outcomes, but the diversity in outcomes makes results across studies difficult to compare. In addition, only 2 efficacy and 2 pilot studies captured long-term outcomes up to 12 months, but not beyond, limiting our ability to assess long-term benefits of these interventions. Overall, tailoring of the intervention to meet the unique cultural needs of breast cancer survivors of color across the trials included in this review was limited. Only four efficacy and four pilot studies mentioned the incorporation of a culturally tailored approach. This review highlights the need for lifestyle interventions that incorporate both diet and physical activity behaviors, fully powered efficacy trials and potentially more trials that incorporate electronic/mobile components (92) and informal sources of support/social networks (family, friends, caregivers) (93, 94) as these are important determinants/facilitators of lifestyle behavior change for Black and Latina survivors.

The exercise intervention by Dieli-Conwright and colleagues is the first randomized controlled trial intervention conducted in a majority Latina breast cancer survivor population to demonstrate efficacy in reducing the prevalence of metabolic syndrome by 63% and improving inflammatory biomarker profiles after three supervised, one-on-one exercise sessions per week for 16 weeks (59). The culturally tailored *Moving Forward* diet and physical activity program resulted in weight loss of 3%, although the *a priori* intervention goal was 5% (63). The *¡Cocinar para su Salud!* Trial was highly successful at achieving its *a priori* goal of helping participants meet dietary guidelines; and a secondary analysis of this study concluded that changes in taste and snack preferences for F&V may be the most important mediator for long-term increases in behavioral interventions in Latina women (95). However, this study did not intervene on physical activity which may explain why weight changes were not observed (57). Among the efficacy trials reviewed, only one of them (63) offered a comprehensive lifestyle program of both diet and physical activity—the main components of the ACS recommendations for cancer survivors. We believe lifestyle behavioral interventions that do not incorporate both diet and physical activity may not be maximizing the full potential that favorable changes to both lifestyle behaviors can have on weight loss and ultimately breast cancer outcomes.

Among the pilot/feasibility studies included in this review, eight of them incorporated a comprehensive behavioral change program (diet and physical activity) and cultural adaptations were incorporated into three of the pilot trials (68, 69, 85). None of these pilot trials achieved the behavioral *a priori* goal (64–69, 85, 89). The lack of success in achieving behavioral changes seen in these trials may be attributed, in part, to their small sample sizes and reduced power to detect small differences, having baseline samples with high levels of physical activity, and short intervention durations. In addition, during the design and development of behavioral change interventions for cancer survivors we must take into consideration the

added burden of time, travel distance, and financial considerations of attending in person interventions (96). With the development and penetrance of technology into health care the use of mobile and electronic based tools for the delivery of cancer care, symptom monitoring, and health behavior interventions is increasing (97–99). Since there was broad variability on the different types of technology used, ranging from activity trackers as used by Ferrante and Valle (64, 65) in their pilot studies to the development of mobile apps as used by Buscemi and Allicock (69, 89), it is dificult to fully assess which electronic formats could be most beneficial. Studies evaluating the acceptability and preferences for technology use in behavior interventions among survivors with prostate and breast cancers highlight that while technology interventions seem acceptable, especially given the ubiquitous and even higher rates of use among Latino adults relative to other racial and ethnic groups (92), there is variability in survivor preferences of content and that these interventions may be more intuitive when participant's health literacy and familiarity with technology is optimized (100, 101).

Greenlee et al. (57) and Crane et al. (85) demonstrated successful uptake and maintenance of healthful behaviors in culturally tailored interventions. Some examples of how these interventions were tailored include delivery of intervention by bicultural professionals, having content in Spanish and English, modifying lifestyle recommendations to meet participant's cultural traditions, and incorporating sources of support (i.e., caregivers). Few interventions incorporated social support systems to help survivors with breast cancer adopt healthful behaviors, despite long standing evidence that social networks have important influences on health behaviors and decisions about health and health care, including engaging in cancer preventive behaviors (102). A secondary analysis of the *¡Cocinar para su Salud!* Trial by Greenlee et al. found that that participant's network of family (spouse and children) and friends were perceived as high sources of support to share and engage in food-related and exercise activities, but most participants also perceived family members as a barrier to eating healthy foods (93). Studies that actively engage the participant's network may be more successful in the adoption and long-term maintenance of lifestyle behavior changes after breast cancer.

It is difficult to assess if cultural adaptions to exercise interventions may confer superior benefits over a standard exercise intervention (87), as there is only one pilot trial conducted by Mama et al. which was null (103), but it has a small sample size (culturally adapted intervention, n=30, standard intervention, n=59, control, n=30). Furthermore, this study was conducted with Puerto Rican women residing in Puerto Rico and Mexican women residing in Texas, so these results may not generalize to all Latina women who reside in the continental US as well as those of other ethnic backgrounds. Large-scale efficacy trials with cultural adaptations to exercise with greater Hispanic/Latino ethnic representation from different geographic areas as well as among Black survivors are needed to fully understand the impact adapting content could have on changing physical activity.

While findings from this review suggest that lifestyle interventions may be effective in Black and Latina survivors with breast cancer, there are some important limitations within the published literature in this area of research. Like studies in non-minority populations, there is a lack of long-term data on the existing interventions among racial and ethnic minoritized groups on survival and long-term health benefits of exercise and healthy eating and maintenance of behaviors. In the trials reviewed, only four (57, 63, 64, 66) examined maintenance of healthy eating behaviors at 1-year post-intervention, with only two of them being efficacy trials (57, 63). Future trials should consider incorporating a maintenance assessment component. A better understanding of the long-term adoption of lifestyle behavior changes and the impact on breast cancer outcomes may facilitate the translation of lifestyle interventions into clinical practice. Although nine trials included Latina survivors, it is not clear whether three of the interventions (59, 60, 67) were available in Spanish for non-English speaking survivors or survivors who preferred speaking in Spanish for their treatment-related care. Interventions that are restricted to English-speaking Latina women may not be generalizable to the larger population of Latina survivors with breast cancer and continues to foment underrepresentation of a vulnerable subgroup of Latina women in the US. Trials included in this review included few advanced stage breast cancers which are known to be more prevalent in the Black (36% regional, 9% distant) and Latina (33% regional, 6% distant) breast cancer patient population compared to White (26-30% have regional, 5% distant) women (5, 104) and therefore limit generalizability of findings to wider samples of Black and Latina survivors. Among trials reviewed, only three randomized women with a history of stage IV breast cancer (60, 67, 87). Given the beneficial effects of diet and exercise interventions on treatment adherence (44), quality of life (44, 105, 106), physical functioning (105), and survival (107), researchers should consider expanding inclusion criteria of lifestyle interventions to patients with advanced disease, though the exercise component may need to be modified in some individuals. Additionally, most of the trials in this review did not report intent-to-treat analyses. By assessing the efficacy of an intervention based on who completes the study, rather than who is randomized, we eliminate the benefits provided by a randomized study design and potentially introduce selection bias.

According to the Clinicaltrials.gov registry, five trials in Latina and Black breast cancer survivors, patients, or women at risk of breast cancer are ongoing. Of these, one was withdrawn because the principal investigator changed institutions and one is completed, but findings have yet to be published. The three non-completed ongoing trials only intervene with physical activity and are split between Latina participants (NCT04717050, NCT02982564), and Black/Latina participants (NCT05176756), with the goal to examine change in metabolic dysregulations, various physical and mental health outcomes (cardiovascular fitness, quality of life, physical functioning, depression, and body image), and physical performance scores, respectively. The withdrawn trial (NCT03120390) also intervened on physical activity only and aimed to examine changes in metabolic dysregulation among Latina participants. Lastly, we enthusiastically await the findings for the *Mi Vida Saludable*/My Healthy Life trial by Hershman and colleagues (NCT02780271) that was completed on September 11, 2020 (90) which evaluated the synergistic effects of an in-person hands-on dietary and physical activity change curriculum and e-communication stratifies on behavior change in a 4-arm randomized controlled study (90).

There are a few notable limitations among the four on-going trials, including moderate sized samples ranging from 142-160

participants. Moreover, just one of these trials incorporates both diet and physical activity components to the intervention and none include weight loss as a primary outcome. We believe that incorporating both diet and exercise counseling in lifestyle interventions may be most optimal to achieve clinically meaningful weight loss (5%) and long-term maintenance of improved behaviors. Nonetheless, we look forward to the publication of the findings from all these trials as they may provide additional insights into the development of lifestyle interventions tailored for breast cancer survivors of color.

In alignment with the nature of scoping reviews (53, 54, 108) which is to "provide an overview of the existing evidence regardless of methodological quality or risk of bias" (55), our report provides a synthesis on the evidence on lifestyle interventions for Black and Latina women with breast cancer. We summarized published and ongoing randomized lifestyle interventions, we described the populations that have been included, the type of intervention or programming content used, and the outcomes measured. We summarized each study's findings and concluded by highlighting knowledge gaps and directions for researchers and interventionists in the development of new lifestyle behavior change trials for Black and Latina women with breast cancer. In accordance with expert guidance on reporting of evidence in scoping reviews, our report does not provide a critical appraisal (or a risk of bias assessment) of this body of evidence (53, 55, 108, 109).

In conclusion, this review highlights the immediate need for additional large-scale, multi-site, randomized clinical trials consisting of diet and physical activity behavioral interventions specifically designed for Black and Latina women diagnosed with breast cancer. Trials that remove English-language eligibility criteria and provide interventions in both Spanish and English, according to participant preference, are warranted. Diet and physical activity trialists should also consider interventions that begin at the time of a breast cancer diagnosis and are conducted simultaneously with treatment (110). Intervening immediately upon receipt of a breast cancer diagnosis may be beneficial to limit treatment-related weight gain and reduce side effects, promote timely treatment completion and adherence, and ultimately, improve survival (111, 112). The findings reported in this scoping review should be considered when designing lifestyle interventions in women diagnosed with breast cancer. Randomized trials in Black and Latina women are needed that evaluate efficacy outcomes, that have long-term follow-up, that are culturally tailored, that intervene from moment of diagnosis, and that incorporate electronic/mobile components and social networks/sources of support for survivors of color.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

MSP and MLI contributed to the study conception and design. Material preparation, data collection and analysis were performed by MSP, MLI, and YMR-R. The first draft of the manuscript was written by MSP, and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

MSP, MLI, and TS were supported by National Cancer Institute of the National Institutes of Health under Award Number R01CA207753. Additional funding in part by grants from the Breast Cancer Research Foundation to MLI and EPW. OMF is supported by the NCT of the NIH under Award Number 7K08CA241390. OF is supported by the NCT of the NIH under Award Number 7K08CA241390. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgments

We would like to thank Kate Nyhan, Research and Education Librarian in Public Health at the Cushing Whitney Medical Library at Yale University, for her support and guidance in conducting this scoping literature search.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1079293/full#supplementary-material

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA: A Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/caac.21654

2. Miller KD, Ortiz AP, Pinheiro PS, Bandi P, Minihan A, Fuchs HE, et al. Cancer statistics for the US Hispanic/Latino population, 2021. *CA: A Cancer J Clin* (2021) 71 (6):466–87. doi: 10.3322/caac.21695

3. Giaquinto AN, Miller KD, Tossas KY, Winn RA, Jemal A, Siegel RL. Cancer statistics for African American/Black people 2022. *CA: A Cancer J Clin* (2022) 72:202–29. doi: 10.3322/caac.21718

4. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. *CA: A Cancer J Clin* (2016) 66(1):31–42. doi: 10.3322/caac.21320

5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* (2018) 68 (1):7–30. doi: 10.3322/caac.21442

6. Champion CD, Thomas SM, Plichta JK, Parrilla Castellar E, Rosenberger LH, Greenup RA, et al. Disparities at the intersection of race and ethnicity: Examining trends and outcomes in Hispanic women with breast cancer. *JCO Oncol Pract* (2022) 18(5):e827–e38. doi: 10.1200/OP.20.00381

7. Ooi SL, Martinez ME, Li CI. Disparities in breast cancer characteristics and outcomes by race/ethnicity. *Breast Cancer Res Treat* (2011) 127(3):729–38. doi: 10.1007/s10549-010-1191-6

8. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the united states, 2005 to 2014. *Jama* (2016) 315(21):2284–91. doi: 10.1001/jama.2016.6458

9. Fuentes-Mattei E, Velazquez-Torres G, Phan L, Zhang F, Chou PC, Shin JH, et al. Effects of obesity on transcriptomic changes and cancer hallmarks in estrogen receptor-positive breast cancer. *J Natl Cancer Inst* (2014) 106(7). doi: 10.1093/jnci/dju158

10. Cleary MP, Grossmann ME, Ray A. Effect of obesity on breast cancer development. *Vet Pathol* (2010) 47(2):202–13. doi: 10.1177/0300985809357753

11. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: Evidence, challenges, and opportunities. *J Clin Oncol* (2016) 34(35):4203–16. doi: 10.1200/JCO.2016.68.4480

12. Robinson PJ, Bell RJ, Davis SR. Obesity is associated with a poorer prognosis in women with hormone receptor positive breast cancer. *Maturitas* (2014) 79(3):279–86. doi: 10.1016/j.maturitas.2014.07.004

13. Jain R, Strickler HD, Fine E, Sparano JA. Clinical studies examining the impact of obesity on breast cancer risk and prognosis. *J Mammary Gland Biol Neoplasia* (2013) 18 (3-4):257–66. doi: 10.1007/s10911-013-9307-3

14. Chen GC, Chen SJ, Zhang R, Hidayat K, Qin JB, Zhang YS, et al. Central obesity and risks of pre- and postmenopausal breast cancer: A dose-response meta-analysis of prospective studies. *Obes Rev* (2016) 17(11):1167–77. doi: 10.1111/obr.12443

15. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. *Lancet* (2008) 371(9612):569–78. doi: 10.1016/S0140-6736(08)60269-X

16. Bandera EV, Chandran U, Hong CC, Troester MA, Bethea TN, Adams-Campbell LL, et al. Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER consortium. *Breast Cancer Res Treat* (2015) 150(3):655–66. doi: 10.1007/s10549-015-3353-z

17. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: A secondary analysis of the women's health initiative randomized clinical trials. *JAMA Oncol* (2015) 1 (5):611–21. doi: 10.1001/jamaoncol.2015.1546

18. Alsaker MD, Janszky I, Opdahl S, Vatten LJ, Romundstad PR. Weight change in adulthood and risk of postmenopausal breast cancer: The HUNT study of Norway. *Br J Cancer* (2013) 109(5):1310–7. doi: 10.1038/bjc.2013.403

19. Harvie M, Howell A, Vierkant RA, Kumar N, Cerhan JR, Kelemen LE, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. *Cancer Epidemiol Biomarkers Prev* (2005) 14(3):656–61. doi: 10.1158/1055-9965.EPI-04-0001

20. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA* (2006) 296(2):193–201. doi: 10.1001/jama.296.2.193

21. Azrad M, Demark-Wahnefried W. The association between adiposity and breast cancer recurrence and survival: A review of the recent literature. *Curr Nutr Rep* (2014) 3 (1):9–15. doi: 10.1007/s13668-013-0068-9

22. Chan DS, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* (2014) 25(10):1901–14. doi: 10.1093/annonc/mdu042

23. Kwan ML, Chen WY, Kroenke CH, Weltzien EK, Beasley JM, Nechuta SJ, et al. Pre-diagnosis body mass index and survival after breast cancer in the after breast cancer pooling project. *Breast Cancer Res Treat* (2012) 132(2):729–39. doi: 10.1007/s10549-011-1914-3

24. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: Systematic review and meta-analysis. *Breast Cancer Res Treat* (2010) 123(3):627–35. doi: 10.1007/s10549-010-0990-0

25. Nichols HB, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Holmes MD, Bersch AJ, et al. Body mass index before and after breast cancer diagnosis: Associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev* (2009) 18(5):1403–9. doi: 10.1158/1055-9965.EPI-08-1094

26. Goodwin PJ, Ennis M, Pritchard KI, McCready D, Koo J, Sidlofsky S, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. *J Clin Oncol* (1999) 17(1):120–. doi: 10.1200/JCO.1999.17.1.120

27. Irwin ML, McTiernan A, Baumgartner RN, Baumgartner KB, Bernstein L, Gilliland FD, et al. Changes in body fat and weight after a breast cancer diagnosis: Influence of demographic, prognostic, and lifestyle factors. *J Clin Oncol* (2005) 23(4):774–82. doi: 10.1200/JCO.2005.04.036

28. Rock CL, Flatt SW, Newman V, Caan BJ, Haan MN, Stefanick ML, et al. Factors associated with weight gain in women after diagnosis of breast cancer. Women's healthy eating and living study group. *J Am Diet Assoc* (1999) 99(10):1212–21. doi: 10.1016/S0002-8223(99)00298-9

29. Playdon MC, Bracken MB, Sanft TB, Ligibel JA, Harrigan M, Irwin ML. Weight gain after breast cancer diagnosis and all-cause mortality: Systematic review and meta-analysis. *J Natl Cancer Inst* (2015) 107(12):djv275. doi: 10.1093/jnci/djv275

30. Rock CL, Thomson CA, Sullivan KR, Howe CL, Kushi LH, Caan BJ, et al. American Cancer society nutrition and physical activity guideline for cancer survivors. *CA: A Cancer J Clin* (2022) 72(3):230–62. doi: 10.3322/caac.21719

31. Ligibel JA, Bohlke K, May AM, Clinton SK, Demark-Wahnefried W, Gilchrist SC, et al. Exercise, diet, and weight management during cancer treatment: ASCO guideline. *J Clin Oncol* (2022) 40:2491–507. doi: 10.1200/JCO.22.00687

32. Dennis Parker EA, Sheppard VB, Adams-Campbell L. Compliance with national nutrition recommendations among breast cancer survivors in "Stepping stone". *Integr Cancer therapies* (2013) 13(2):114–20. doi: 10.1177/1534735413503550

33. Springfield S, Odoms-Young A, Tussing-Humphreys L, Freels S, Stolley M. Adherence to American cancer society and American institute of cancer research dietary guidelines in overweight African American breast cancer survivors. *J Cancer Surviv* (2019) 13(2):257–68. doi: 10.1007/s11764-019-00748-y

34. Glenn BA, Hamilton AS, Nonzee NJ, Maxwell AE, Crespi CM, Ryerson AB, et al. Obesity, physical activity, and dietary behaviors in an ethnically-diverse sample of cancer survivors with early onset disease. *J psychosocial Oncol* (2018) 36(4):418–36. doi: 10.1080/07347332.2018.1448031

35. Izano MA, Fung TT, Chiuve SS, Hu FB, Holmes MD. Are diet quality scores after breast cancer diagnosis associated with improved breast cancer survival? *Nutr Cancer* (2013) 65(6):820–6. doi: 10.1080/01635581.2013.804939

36. George SM, Irwin ML, Smith AW, Neuhouser ML, Reedy J, McTiernan A, et al. Postdiagnosis diet quality, the combination of diet quality and recreational physical activity, and prognosis after early-stage breast cancer. *Cancer Causes Control* (2011) 22 (4):589–98. doi: 10.1007/s10552-011-9732-9

37. Shaikh H, Bradhurst P, Ma LX, Tan SYC, Egger SJ, Vardy JL. Body weight management in overweight and obese breast cancer survivors. *Cochrane Database Systematic Rev* (2020) 2020(12). doi: 10.1002/14651858.CD012110.pub2

38. Harrigan M, Cartmel B, Loftfield E, Sanft T, Chagpar AB, Zhou Y, et al. Randomized trial comparing telephone versus in-person weight loss counseling on body composition and circulating biomarkers in women treated for breast cancer: The lifestyle, exercise, and nutrition (LEAN) study. *J Clin Oncol* (2016) 34(7):669–76. doi: 10.1200/JCO.2015.61.6375

39. Mijwel S, Backman M, Bolam KA, Jervaeus A, Sundberg CJ, Margolin S, et al. Adding high-intensity interval training to conventional training modalities: Optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial. *Breast Cancer Res Treat* (2017) 168:79–93. doi: 10.1007/s10549-017-4571-3

40. Lipsett A, Barrett S, Haruna F, Mustian K, O'Donovan A. The impact of exercise during adjuvant radiotherapy for breast cancer on fatigue and quality of life: A systematic review and meta-analysis. *Breast* (2017) 32:144–55. doi: 10.1016/j.breast.2017.02.002

41. Adams SC, Segal RJ, McKenzie DC, Vallerand JR, Morielli AR, Mackey JR, et al. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. *Breast Cancer Res Treat* (2016) 158(3):497–507. doi: 10.1007/s10549-016-3900-2

42. Kirkham AA, Van Patten CL, Gelmon KA, McKenzie DC, Bonsignore A, Bland KA, et al. Effectiveness of oncologist-referred exercise and healthy eating programming as a part of supportive adjuvant care for early breast cancer. *Oncologist* (2017) 23:105–15. doi: 10.1634/theoncologist.2017-0141

43. Fairman C, Focht B, Lucas A, Lustberg M. Effects of exercise interventions during different treatments in breast cancer. *J Community Supportive Oncol* (2016) 14(5):200–9. doi: 10.12788/jcso.0225

44. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. *J Clin Oncol* (2007) 25 (28):4396–404. doi: 10.1200/JCO.2006.08.2024

45. Courneya KS, McKenzie DC, Gelmon K, Mackey JR, Reid RD, Yasui Y, et al. A multicenter randomized trial of the effects of exercise dose and type on psychosocial distress in breast cancer patients undergoing chemotherapy. *Cancer Epidem Biomar* (2014) 23(5):857–64. doi: 10.1158/1055-9965.EPI-13-1163

46. Irwin ML, Cartmel B, Gross CP, Ercolano E, Li F, Yao X, et al. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J Clin Oncol* (2015) 33(10):1104–11. doi: 10.1200/JCO.2014.57.1547

47. George SM, Ballard-Barbash R, Shikany JM, Caan BJ, Freudenheim JL, Kroenke CH, et al. Better postdiagnosis diet quality is associated with reduced risk of death among postmenopausal women with invasive breast cancer in the women's health initiative. *Cancer Epidemiol Biomarkers Prev* (2014) 23(4):575–83. doi: 10.1158/1055-9965.EPI-13-1162

48. Harmon BE, Boushey CJ, Shvetsov YB, Ettienne R, Reedy J, Wilkens LR, et al. Associations of key diet-quality indexes with mortality in the multiethnic cohort: The dietary patterns methods project. *Am J Clin Nutr* (2015) 101(3):587–97. doi: 10.3945/ajcn.114.090688

49. Blackburn GL, Wang KA. Dietary fat reduction and breast cancer outcome: Results from the women's intervention nutrition study (WINS). *Am J Clin Nutr* (2007) 86(3): s878–81. doi: 10.1093/ajcn/86.3.878S

50. Chlebowski RT, Blackburn GL, Hoy MK, Thomson CA, Giuliano AE, McAndrew P, et al. Survival analyses from the women's intervention nutrition study (WINS) evaluating dietary fat reduction and breast cancer outcome. *J Clin Oncol* (2008) 26 (15_suppl):522. doi: 10.1200/jco.2008.26.15_suppl.522

51. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: The women's healthy eating and living (WHEL) randomized trial. *JAMA* (2007) 298(3):289–98. doi: 10.1001/jama.298.3.289

52. Lake B, Damery S, Jolly K. Effectiveness of weight loss interventions in breast cancer survivors: A systematic review of reviews. *BMJ Open* (2022) 12(10):262–7. doi: 10.1136/bmjopen-2022-062288

53. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evidence-Based healthcare* (2015) 13 (3):141–6. doi: 10.1097/XEB.0000000000000050

54. Pollock D, Davies EL, Peters MDJ, Tricco AC, Alexander L, McInerney P, et al. Undertaking a scoping review: A practical guide for nursing and midwifery students, clinicians, researchers, and academics. *J Advanced Nursing* (2021) 77(4):2102–13. doi: 10.1111/jan.14743

55. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann Intern Med* (2018) 169(7):467–73. doi: 10.7326/M18-0850

56. Spark LC, Reeves MM, Fjeldsoe BS, Eakin EG. Physical activity and/or dietary interventions in breast cancer survivors: A systematic review of the maintenance of outcomes. *J Cancer Surviv* (2013) 7(1):74–82. doi: 10.1007/s11764-012-0246-6

57. Greenlee H, Gaffney AO, Aycinena AC, Koch P, Contento I, Karmally W, et al. Inverted exclamation markCocinar para su salud!: Randomized controlled trial of a culturally based dietary intervention among Hispanic breast cancer survivors. *J Acad Nutr Diet* (2015) 115(5):709–23 e3. doi: 10.1016/j.jand.2014.11.002

58. Zuniga KE, Parma DL, Munoz E, Spaniol M, Wargovich M, Ramirez AG. Dietary intervention among breast cancer survivors increased adherence to a Mediterranean-style, anti-inflammatory dietary pattern: The rx for better breast health randomized controlled trial. *Breast Cancer Res Treat* (2018) 173:145–54. doi: 10.1007/s10549-018-4982-9

59. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, Sami N, Lee K, Buchanan TA, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: A randomized controlled trial. *J Clin Oncol* (2018) 36:Jco2017757526. doi: 10.1200/JCO.2017.75.7526

60. Moadel AB, Shah C, Wylie-Rosett J, Harris MS, Patel SR, Hall CB, et al. Randomized controlled trial of yoga among a multiethnic sample of breast cancer patients: Effects on quality of life. *J Clin Oncol* (2007) 25(28):4387–95. doi: 10.1200/JCO.2006.06.6027

61. Taylor TR, Barrow J, Makambi K, Sheppard V, Wallington SF, Martin C, et al. A restorative yoga intervention for African-American breast cancer survivors: A pilot study. *J Racial Ethn Health Disparities* (2018) 5(1):62–72. doi: 10.1007/s40615-017-0342-4

62. Soltero EG, Larkey LK, Kim WS, Rosales Chavez JB, Lee RE. Latin Dance and Qigong/Tai chi effects on physical activity and body composition in breast cancer survivors: A pilot study. *Complementary Therapies Clin Practice* (2022) 47. doi: 10.1016/j.ctcp.2022.101554

63. Stolley M, Sheean P, Gerber B, Arroyo C, Schiffer L, Banerjee A, et al. Efficacy of a weight loss intervention for African American breast cancer survivors. *J Clin Oncol* (2017) 35(24):2820–8. doi: 10.1200/JCO.2016.71.9856

64. Ferrante JM, Devine KA, Bator A, Rodgers A, Ohman-Strickland PA, Bandera EV, et al. Feasibility and potential efficacy of commercial mHealth/eHealth tools for weight loss in African American breast cancer survivors: Pilot randomized controlled trial. *Trans Behav Med* (2018) 10:938–48. doi: 10.1093/tbm/iby124

65. Valle CG, Deal AM, Tate DF. Preventing weight gain in African American breast cancer survivors using smart scales and activity trackers: A randomized controlled pilot study. *J Cancer Surviv* (2017) 11(1):133–48. doi: 10.1007/s11764-016-0571-2

66. Greenlee HA, Crew KD, Mata JM, McKinley PS, Rundle AG, Zhang W, et al. A pilot randomized controlled trial of a commercial diet and exercise weight loss program in minority breast cancer survivors. *Obes (Silver Spring)* (2013) 21(1):65–76. doi: 10.1002/oby.20245

67. Paxton RJ, Hajek R, Newcomb P, Dobhal M, Borra S, Taylor WC, et al. A lifestyle intervention *via* email in minority breast cancer survivors: Randomized parallel-group feasibility study. *JMIR cancer* (2017) 3(2):e13. doi: 10.2196/cancer.7495

68. Sheppard VB, Hicks J, Makambi K, Hurtado-de-Mendoza A, Demark-Wahnefried W, Adams-Campbell L. The feasibility and acceptability of a diet and exercise trial in overweight and obese black breast cancer survivors: The stepping STONE study. *Contemp Clin Trials* (2016) 46:106–13. doi: 10.1016/j.cct.2015.12.005

69. Buscemi J, Oswald LB, Baik SH, Buitrago D, Iacobelli F, Phillips SM, et al. My health smartphone intervention decreases daily fat sources among latina breast cancer survivors. *J Behav Med* (2020) 43(5):732–42. doi: 10.1007/s10865-020-00136-3

70. Greenlee H, Ogden Gaffney A, Aycinena AC, Koch P, Contento I, Karmally W, et al. Long-term diet and biomarker changes after a short-term intervention among hispanic breast cancer survivors: The inverted exclamation markCocinar para su salud! randomized controlled trial. *Cancer Epidemiol Biomarkers Prev* (2016) 25(11):1491–502.

71. Aycinena AC, Jennings KA, Gaffney AO, Koch PA, Contento IR, Gonzalez M, et al. Inverted exclamation markCocinar para su salud! development of a culturally based nutrition education curriculum for hispanic breast cancer survivors using a theory-driven procedural model. *Health Educ Behav* (2017) 44(1):13–22.

72. Hershman DL, Greenlee H, Awad D, Kalinsky K, Maurer M, Kranwinkel G, et al. Randomized controlled trial of a clinic-based survivorship intervention following adjuvant therapy in breast cancer survivors. *Breast Cancer Res Treat* (2013) 138(3):795–806.

73. Ramirez AG, Parma DL, Munoz E, Mendoza KD, Harb C, Holden AEC, et al. An anti-inflammatory dietary intervention to reduce breast cancer recurrence risk: Study design and baseline data. *Contemp Clin Trials.* (2017) 57:1–7.

74. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, Sami N, Lee K, Buchanan TA, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: A randomized controlled trial. *J Clin Oncol* (2018) 36(9):Jco2017757526.

75. Ortiz A, Hughes DC, Mama SK, Tirado-Gomez M, Liao Y, Song J, et al. Effectiveness of a home-based exercise intervention in the fitness profile of hispanic survivors of breast cancer. *Rehabil Oncol* (2021) 39(4):175–83.

76. Lee K, Kang I, Mack WJ, Mortimer J, Sattler F, Salem G, et al. Feasibility of high intensity interval training in patients with breast cancer undergoing anthracycline chemotherapy: a randomized pilot trial. *BMC Cancer* (2019) 19(1).

77. Lee K, Kang I, Mack WJ, Mortimer J, Sattler F, Salem G, et al. Effects of high-intensity interval training on vascular endothelial function and vascular wall thickness in breast cancer patients receiving anthracycline-based chemotherapy: a randomized pilot study. *Breast Cancer Res Treat* (2019) 177(2):477–85.

78. Lee K, Kang I, Mortimer JE, Sattler F, Mack WJ, Fitzsimons LA, et al. Effects of high-intensity interval training on vascular function in breast cancer survivors undergoing anthracycline chemotherapy: design of a pilot study. *BMJ Open* (2018) 8(6):e022622.

79. Lee K, Ortiz K, Goytizolo J, Serrano T, Dieli-Conwright CM. Abstract D033: High-intensity interval training is feasible in hispanic patients with breast cancer undergoing anthracycline chemotherapy. *Poster Presentations - Proffered Abstracts2020*, D033–D.

80. Stolley MR, Sharp LK, Fantuzzi G, Arroyo C, Sheean P, Schiffer L, et al. Study design and protocol for moving forward: A weight loss intervention trial for african-american breast cancer survivors. *BMC Cancer.* (2015) 15:1018.

81. Stolley MR, Sharp LK, Oh A, Schiffer L. A weight loss intervention for african american breast cancer survivors, 2006. *Prev Chronic Dis* (2009) 6(1):A22.

82. Kwarteng JL, Beyer KMM, Banerjee A, Stolley MR. Facilitators of behavior change and weight loss in an intervention for african american breast cancer survivors. *Cancer Causes Control.* (2020) 31(8):737–47.

83. Ferrante JM, Lulla A, Williamson JD, Devine KA, Ohman-Strickland P, Bandera EV. Patterns of fitbit use and activity levels among african american breast cancer survivors during an eHealth weight loss randomized controlled trial. *Am J Health Promot.* (2022) 36(1):94–105.

84. Yanez B, Oswald LB, Baik SH, Buitrago D, Iacobelli F, Perez-Tamayo A, et al. Brief culturally informed smartphone interventions decrease breast cancer symptom burden among latina breast cancer survivors. *Psycho-Oncology* (2019) 29(1):195–203.

85. Crane TE, Badger TA, O'Connor P, Segrin C, Alvarez A, Freylersythe SJ, et al. Lifestyle intervention for latina cancer survivors and caregivers: The nuestra salud randomized pilot trial. *J Cancer Survivorship* (2020) 15(4):607–19. doi: 10.1007/s11764-020-00954-z

86. Lee K, Norris MK, Wang E, Dieli-Conwright CM. Effect of high-intensity interval training on patient-reported outcomes and physical function in women with breast cancer receiving anthracycline-based chemotherapy. *Supportive Care Cancer* (2021) 29 (11):6863–70. doi: 10.1007/s00520-021-06294-7

87. Mama SK, Song J, Ortiz A, Tirado-Gomez M, Palacios C, Hughes DC, et al. Longitudinal social cognitive influences on physical activity and sedentary time in Hispanic breast cancer survivors. *Psycho-oncology* (2017) 26(2):214–21. doi: 10.1002/pon.4026

88. Valle CG, Deal AM, Tate DF. Preventing weight gain in African American breast cancer survivors using smart scales and activity trackers: A randomized controlled pilot study. *J Cancer Survivorship* (2016) 11(1):133–48. doi: 10.1007/s11764-016-0571-2

89. Allicock M, Kendzor D, Sedory A, Gabriel KP, Swartz MD, Thomas P, et al. A pilot and feasibility mobile health intervention to support healthy behaviors in African American breast cancer survivors. *J Racial Ethnic Health Disparities* (2020) 8(1):157–65. doi: 10.1007/s40615-020-00767-x

90. Santiago-Torres M, Contento I, Koch P, Tsai W-Y, Brickman AM, Gaffney AO, et al. ¡Mi Vida saludable! a randomized, controlled, 2 × 2 factorial trial of a diet and physical activity intervention among latina breast cancer survivors: Study design and methods. *Contemp Clin trials* (2021) 110. doi: 10.1016/j.cct.2021.106524

91. Gonzalo-Encabo P, Wilson RL, Kang DW, Norris MK, Uno H, Christopher CN, et al. Reducing metabolic dysregulation in obese latina and/or Hispanic breast cancer survivors using physical activity (ROSA) trial: A study protocol. *Front Oncol* (2022) 12:864844. doi: 10.3389/fonc.2022.864844

92. Lopez M, Gonzalez-Barrera A, Patten E. *Closing the digital divide: Latinos and technology adoption*. Washington, DC. Pew Research Center (2013).

93. Crookes DM, Shelton RC, Tehranifar P, Aycinena C, Gaffney AO, Koch P, et al. Social networks and social support for healthy eating among latina breast cancer survivors: implications for social and behavioral interventions. *J Cancer Surviv* (2016) 10(2):291–301. doi: 10.1007/s11764-015-0475-6

94. Spector D, Battaglini C, Groff D. Perceived exercise barriers and facilitators among ethnically diverse breast cancer survivors. *Oncol Nurs Forum* (2013) 40(5):472–80. doi: 10.1188/13.ONF.472-480

95. Shi Z, Richardson JM, Aycinena AC, Gray HL, Paul R, Koch P, et al. Psychosocial mediators of dietary change among Hispanic/Latina breast cancer survivors in a culturally tailored dietary intervention. *Psycho-oncology* (2018) 27(9):2220–8. doi: 10.1002/pon.4799

96. Gupta A, Eisenhauer EA, Booth CM. The time toxicity of cancer treatment. *J Clin Oncol* (2022) 40(15):1611–5. doi: 10.1200/JCO.21.02810

97. Haggerty AF, Hagemann A, Barnett M, Thornquist M, Neuhouser ML, Horowitz N, et al. A randomized, controlled, multicenter study of technology-based weight loss interventions among endometrial cancer survivors. *Obes (Silver Spring)* (2017) 25 Suppl 2 (Suppl 2):S102–s8. doi: 10.1002/oby.22021

98. Arem H, Moses J, Cisneros C, Blondeau B, Nekhlyudov L, Killackey M, et al. Cancer provider and survivor experiences with telehealth during the COVID-19 pandemic. *JCO Oncol Pract* (2022) 18(4):e452–e61. doi: 10.1200/OP.21.00401

99. Basch E, Schrag D, Henson S, Jansen J, Ginos B, Stover AM, et al. Effect of electronic symptom monitoring on patient-reported outcomes among patients with metastatic cancer: A randomized clinical trial. *Jama* (2022) 327(24):2413–22. doi: 10.1001/jama.2022.9265

100. Phillips SM, Conroy DE, Keadle SK, Pellegrini CA, Lloyd GR, Penedo FJ, et al. Breast cancer survivors' preferences for technology-supported exercise interventions. *Support Care Cancer* (2017) 25(10):3243–52. doi: 10.1007/s00520-017-3735-3

101. Wang EY, Graff RE, Chan JM, Langlais CS, Broering JM, Ramsdill JW, et al. Web-based lifestyle interventions for prostate cancer survivors: Qualitative study. *JMIR Cancer* (2020) 6(2):e19362. doi: 10.2196/19362

102. Cadet T, Burke SL, Naseh M, Grudzien A, Kozak RS, Romeo J, et al. Examining the family support role of older hispanics, African americans, and non-Hispanic whites and their breast cancer screening behaviors. *Soc Work Public Health* (2021) 36(1):38–53. doi: 10.1080/19371918.2020.1852993

103. Mama SK, Schembre SM, O'Connor DP, Kaplan CD, Bode S, Lee RE. Effectiveness of lifestyle interventions to reduce binge eating symptoms in African American and Hispanic women. *Appetite* (2015) 95:269–74. doi: 10.1016/j.appet.2015.07.015

104. Miller KD, Goding Sauer A, Ortiz AP, Fedewa SA, Pinheiro PS, Tortolero-Luna G, et al. Cancer statistics for Hispanics/Latinos. *CA Cancer J Clin* (2018) 2018:425–45. doi: 10.1111/j.1535-6841.2005.00101.x

105. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev* (2017) 52:91–104. doi: 10.1016/j.ctrv.2016.11.010

106. Diggins AD, Hearn LE, Lechner SC, Annane D, Antoni MH, Whitehead NE. Physical activity in black breast cancer survivors: Implications for quality of life and mood at baseline and 6-month follow-up. *Psycho-oncology* (2017) 26(6):822–8. doi: 10.1002/pon.4095

107. Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch AJ, Stampfer MJ, et al. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* (2008) 17(2):379–86. doi: 10.1158/1055-9965.EPI-07-0771

108. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: Scoping review (2020 version). In: Aromataris E, Munn Z, editors. *JBIJBI manual for evidence synthesis*. JBI (2020).

109. Cornell University LIbrary. *A guide to evidence synthesis: 9. Risk of bias assessment* (2022). Available at: https://guides.library.cornell.edu/evidence-synthesis/bias.

110. Sanft T, Harrigan M, Cartmel B, Ferrucci LM, Li FY, McGowan C, et al. Effect of healthy diet and exercise on chemotherapy completion rate in women with breast cancer: The lifestyle, exercise and nutrition early after diagnosis (LEANer) study: Study protocol for a randomized clinical trial. *Contemp Clin trials* (2021) 109:106508. doi: 10.1016/j.cct.2021.106508

111. Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: Meta-analysis of published studies. *Med Oncol* (2011) 28(3):753–65. doi: 10.1007/s12032-010-9536-x

112. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: A review of the evidence. *J Clin Oncol* (2002) 20(15):3302–16. doi: 10.1200/JCO.2002.03.008

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 04 April 2023
DOI 10.3389/fonc.2023.1096882

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Cancer Epidemiology and Prevention,
a section of the journal
Frontiers in Oncology

RECEIVED 12 November 2022
ACCEPTED 06 March 2023
PUBLISHED 04 April 2023

CITATION
Gobin C, Inkabi S, Lattimore CC, Gu T, Menefee JN, Rodriguez M, Kates H, Fields C, Bian T, Silver N, Xing C, Yates C, Renne R, Xie M and Fredenburg KM (2023) Investigating miR-9 as a mediator in laryngeal cancer health disparities.
Front. Oncol. 13:1096882.
doi: 10.3389/fonc.2023.1096882

Investigating miR-9 as a mediator in laryngeal cancer health disparities

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Background: For several decades, Black patients have carried a higher burden of laryngeal cancer among all races. Even when accounting for sociodemographics, a disparity remains. Differentially expressed microRNAs have been linked to racially disparate clinical outcomes in breast and prostate cancers, yet an association in laryngeal cancer has not been addressed. In this study, we present our computational analysis of differentially expressed miRNAs in Black compared with White laryngeal cancer and further validate microRNA-9-5p (miR-9-5p) as a potential mediator of cancer phenotype and chemoresistance.

Methods: Bioinformatic analysis of 111 (92 Whites, 19 Black) laryngeal squamous cell carcinoma (LSCC) specimens from the TCGA revealed miRNAs were significantly differentially expressed in Black compared with White LSCC. We focused on miR-9-5 p which had a significant 4-fold lower expression in Black compared with White LSCC ($p<0.05$). After transient transfection with either miR-9 mimic or inhibitor in cell lines derived from Black (UM-SCC-12) or White LSCC patients (UM-SCC-10A), cellular migration and cell proliferation was assessed. Alterations in cisplatin sensitivity was evaluated in transient transfected cells *via* IC50 analysis. qPCR was performed on transfected cells to evaluate miR-9 targets and chemoresistance predictors, ABCC1 and MAP1B.

Results: Northern blot analysis revealed mature miR-9-5p was inherently lower in cell line UM-SCC-12 compared with UM-SCC-10A. UM -SCC-12 had baseline increase in cellular migration ($p < 0.01$), proliferation ($p < 0.0001$) and chemosensitivity ($p < 0.01$) compared to UM-SCC-10A. Increasing miR-9 in UM-SCC-12 cells resulted in decreased cellular migration ($p < 0.05$), decreased proliferation ($p < 0.0001$) and increased sensitivity to cisplatin ($p < 0.001$).

Reducing miR-9 in UM-SCC-10A cells resulted in increased cellular migration ($p < 0.05$), increased proliferation ($p < 0.05$) and decreased sensitivity to cisplatin ($p < 0.01$). A significant inverse relationship in ABCC1 and MAP1B gene expression was observed when miR-9 levels were transiently elevated or reduced in either UM-SCC-12 or UM-SCC-10A cell lines, respectively, suggesting modulation by miR-9.

Conclusion: Collectively, these studies introduce differential miRNA expression in LSCC cancer health disparities and propose a role for low miR-9-5p as a mediator in LSCC tumorigenesis and chemoresistance.

KEYWORDS

cancer health disparities, laryngeal squamous cell carcinoma, miR-9, head and neck cancer, ABCC1, MAP1B

Introduction

Black Americans carry a higher burden of head and neck squamous cell carcinoma (HNSCC) compared with other races (1–3). The underlying cause is multifactorial. In part, the disparities may be explained by differences in social determinants of health, including socioeconomic status, access to care, education and literacy (4–6). Clinically, Black patients present with HNSCC at younger age, have higher stage cancers, are more likely to present with advanced cancers (T-stage, N-stage) and while mortality rates have for HNC have decreased, a higher mortality rate remains for Black Americans relative to other races (7, 8).

The most commonly involved anatomic sites include the oral cavity, oropharynx, and larynx. Among the three, laryngeal squamous cell carcinoma (LSCC) harbors the lowest 5-year survival rate; moreover, treatment-related comorbidities and loss of quality of life also have resulted in some of the highest rates of suicide (1, 9). Black Americans have maintained a higher incidence of LSCC for over several decades, presenting with a greater likelihood of advanced stage disease and increased mortality (10–12). It is no surprise that socioeconomic and environmental factors play a role in these disparate clinical outcomes, however, after controlling for these factors, a disparity persists (13–15). There are few studies that have considered biology as a contributing factor to LSCC clinical disparate outcomes (16). Moreover, there are none that have explored the role of noncoding RNAs.

microRNAs (miRNAs) are small noncoding RNAs that are prominent players in many physiologic and pathologic processes including cell differentiation, proliferation, and survival (17). Understandably, deregulation of miRNAs can have a profound impact on cellular regulation and gene expression. They have been found to contribute to tumor development and metastasis in many cancers including LSCC (17–19). Differential expression of miRNAs has been found to be a feature of cancers where Blacks carry an unequal burden and have poorer outcomes (20–25). These studies have demonstrated that these biologic mediators and their targets vary by race and ethnicity (26). In addition, these reports suggest that differences in miRNA expression may explain disparate clinical outcomes in Black patients and may be exploited for their prognostic and predictive value (27, 28).

Here, we present our bioinformatic analysis of miRNAs in LSCC using the Cancer Genome Atlas where we use it to explore differential expression of miRNAs in Black compared with White patients. From this analysis, we turned our attention to investigating the role of miR-9-5p. Using two race-specific cell lines, we explore potential role of mir-9 in modulating a malignant phenotype cell and influencing chemoresistance. Finally, we explore the gene expression of two known targets of miR-9. To our knowledge, this is the first study of its kind in head and neck cancer, specifically LSCC. Overall, evaluating differential miRNA expression in the context of LSCC cancer health disparities and subsequently investigating their role as potential mediators of disease may provide opportunities to clinically predict treatment response and survival.

Methods

Bioinformatic analysis

Alignment files (bam files) for 92 White and 19 Black LSCC patients were downloaded from The Cancer Genome Atlas Head-Neck Squamous Cell Carcinoma (TCGA-HNSC). All bam files were converted to fastq files using bedtools (29). The raw reads from fastq files were preprocessed using mapper.pl from miRDeep2 (30). Quality control was performed by removing reads with alphabets other than a, c, g, t, u, n, A, C, G, T, U, N and reads less than 15 nucleotides long from downstream analysis. The remaining reads were aligned to human miRNA precursors downloaded from miRBase release 21 (31) using quantifier.pl from miRDeep2. Alignment between precursor and mature miRNA was performed to generate the final miRNA counts. In doing this, mature miRNA sequences were first downloaded from miRbase and aligned to their miRNA precursors. Then, the alignment between mature miRNAs and the reads were compared and the number of reads falling within

2nt upstream and 5nt downstream of the corresponding miRNA was taken as the read counts for that miRNA.

Differential expression analysis was performed to compare miRNA expression between Black and White tumor samples. Counts were normalized using Relative Log Expression (RLE) implemented from edgeR (32). A negative binomial generalized log-linear model implemented in edgeR was used for differential analysis. EdgeR differential expression analysis was performed using the White tumor group as the reference by default; the direction of the fold-change was reversed *post-hoc* to consider changes in Black tumor samples relative to White tumor samples. Significantly differentially expressed miRNAs identified at a fold change >1.5 and a p value < 0.05.

Sex was not considered as a biological variable due to the limited sample size of females within the TCGA dataset used for analysis. Randomization of the TCGA cohort was irrelevant because the study was specifically designed to explore differential miRNA expression by race. Blinding was also deemed irrelevant to the study design. Power analysis was not conducted for the RNA-Seq TCGA patient data because our exploratory data analysis was constrained by the limited data points available within the database following race stratification (92 White versus 19 Black).

Laryngeal cancer cell lines

Human laryngeal squamous cell carcinoma cell lines, UM-SCC-12 (Black patient derived; RRID: CVCL_7717) and UM-SCC-10A (White patient derived; RRID: CVCL_7713) were authenticated *via* short tandem repeat typing and further genetically characterized (33, 34) prior to purchase from the University of Michigan Head and Neck cell line repository. Both cell lines were age, sex, grade and stage matched (see Supplementary Table 1). Cells were cultured in a T 75cm^2 flask containing Dulbecco Modification of Eagle's Medium 1X (DMEM, 10-013-CV, Corning) supplemented with 10% heat inactivated fetal bovine serum (FBS, 35-011-CV, Corning), and 2% Penicillin/Streptomycin (PENSTREP, 15-140-122, Gibco) within a humidified incubator containing 5% CO_2 at 37°C. Cells were utilized in the following assays upon reaching 80% confluence.

miRNA Northern blot

Preparation of IR labeled probes

IrNorthern probe sequences for U6, miR-191-5p, miR-9-5p, miR-16 and let7a (see Supplementary Table 2). Probes wereconjugated with DBCO-IR dye and then were purified by AMPure XP beads as previously described (35, 36).

Northern blot analyses

Northern blot analyses were performed using near infrared dye-labeled probes as previously described (35, 36). Briefly, 15 µg of total RNA from either UM-SCC-10A or UM-SCC-12 was separated using 15% Urea-PAGE and contents were subsequently transferred to Hybond N+ membrane (GE) using LifeTech transfer module at 0.2 Amp for one hour. The membrane was crosslinked twice using 254nm UV crosslinker at 120 mJ/cm^2. The membrane was then placed in a hybridization oven and incubated with 10ml ExpressHyb hybridization solution (Takara) in a hybridization tube for 30 minutes at 30°C. IR-dye labeled probes and the membrane were then hybridized overnight at 30°C. After overnight hybridization, the membrane was washed twice, with 2x SSC buffer containing 0.1% SDS and 1x SSC buffer containing 0.1% SDS, respectively. For both washes, membrane was shaken at 110 rpm for 10 minutes at room temperature. Following washes, membrane was scanned on Amershan Typhoon scanner (GE health) to detect emission at 600 nm and 800 nm.

Transient transfection

In a 12-well format, UM-SCC-12 or UM-SCC-10A cells were reverse transfected with 50nM of either miR-9 mimic or inhibitor, respectively (see Supplementary Table 3 for oligo sequences and product information). Transfection efficiency was enhanced through the use of Lipofectamine RNAiMAX (13778075, Thermo Fisher) and Opti-MEM I Reduced Serum Medium (31985062, Thermo Fisher) per manufacturer's instructions. Cell growth was optimized to ensure 60-80% confluency by assay endpoint. Length of transfection was dependent upon validation assay performed. All assays were performed in triplicate.

Scratch wound assay

The scratch wound assay was used to assess cell migration. 24 hours post transfection, the confluent cell monolayer was disrupted using a 1000µL pipet tip. Images were captured at 0h, 24h, 48h, and 72h post cell monolayer disruption using the EVOS FL Cell Imaging System (ThermoFisher). The wound healing size tool plugin for ImageJ (RRID: SCR_003070) was used to quantify wound healing at each timepoint.

Cisplatin IC50 assay

Baseline IC50 for cisplatin in UM-SCC-12 and UM-SCC-10A was determined with serial dilutions of Cisplatin (1134357, Millipore Sigma) at concentrations of 200µM, 66.67µM, 22.22µM, 7.41µM, 2.47µM, and 0µM. 48 hours post cisplatin treatment, cisplatin and spent media were aspirated from the wells and a 1:7 dilution of the Cell Titer Blue reagent (G8080, Promega) was applied to the cells in the wells. Baseline fluorescence (560/590 nm) was assessed using the BioTek SYNERGY H1 Multi-Mode Microplate Reader. The gain was adjusted such that all baseline values were similar ~2000nm. The plates were incubated in 5% CO_2 at 37°C with subsequent plate readings taken in 30 min intervals for 4 hours. IC50 to cisplatin was calculated in GraphPad Prism Version 9.40 (RRID: SCR_002798) using percentage of cell viability values. Percentage of cell viability was calculated as follows:

(Average final fluorescence values – average baseline fluorescence values) = x

(x – average fluorescence values of media only wells) = y

(y ÷ average control fluorescence values of 0μM dose) * 100 = % cell viability

Cisplatin IC50 LSCC cell lines after transient transfection

24 hours post transfection with a specific oligo and appropriate control, cells were washed with 1mL of 1x dPBS (1x dPBS, 21-031-CV, Corning) per well. Cells were harvested with 1x TrypLE (12604-013, Gibco), counted and replated as five replicates per condition in a 96-well plate. The next day cells were treated as described above at 48 hours cisplatin treatment.

Cell Proliferation in transient transfected cells

Average fluorescence values generated at no treatment dose (0μM of cisplatin) in transfected cells corresponded with baseline cell proliferation. As such, final average fluorescence values at the 0μM dose were normalized against their baseline average fluorescence values to calculate relative fluorescence which represented cell proliferation in transfected cells.

Reverse transcriptase-PCR

24 hours post transfection, cells were washed with 1mL 1x dPBS per well and collected in cold TRIzol Reagent (15596018, Thermo Fisher). RNA was isolated per manufacturer's instruction. RT-PCR was performed with the Eppendorf Mastercycler gradient to synthesize cDNA from 50ng/μL of RNA and random primers from the high-capacity cDNA reverse transcription kit (4368814, Applied Biosystems).

qPCR

A 1:50 dilution of cDNA was combined with EXPRESS SYBR GreenER qPCR Supermix reagents (11784200, Thermofisher Scientific) and 2μM primer pairs of GAPDH, ABCC1 or MAP1B (see Supplementary Table 4 for primer product information). qPCR experiments were run in triplicate with three biological replicates per condition using Applied Biosystems StepOne Plus Real time PCR system. CT values were normalized against corresponding GAPDH CT values using the $2^{-\Delta CT}$ method and log transformed. A Methods schematic depicts the above described miRNA validation, chemosensitivity, and qPCR assays (Supplementary Figure 1).

Statistical analysis

All data were analyzed using GraphPad Prism (Version 9.40) software, setting the alpha level at 0.05 for all statistical analyses used. All experiments were completed using biological and technical replicates in triplicate. Two-way repeated measures ANOVAs were conducted to assess group differences across time points or drug doses between cell lines or across transfection conditions. A significant phenotypic change x cell line interaction was followed up with Šídák's multiple comparison tests. Paired and unpaired t-tests were performed to assess group differences on single dependent measures when appropriate.

Biological sex was not considered due to the limited sample size of females per racial group in the LSCC TCGA dataset. Randomization and blinding of the TCGA cohort were irrelevant because the study was specifically designed to explore differential miRNA expression by race. Power analysis was not performed as this our study is exploratory and data points are limited.

Results

miRNAs are differentially expressed in Black compared with White laryngeal cancer

Bioinformatic analysis of the 92 White and 19 Black LSCC patients abstracted from the TCGA revealed 132 out of 1902 miRNAs were significantly differentially expressed (FC >1.5, $p < 0.05$) (Supplementary Tables 5, 6) in Black compared with White LSCC. The volcano plot depicts (Figure 1A) a slightly greater number of miRNAs that are significantly lower (68 miRNAs) than higher (64 miRNAs) in Black compared with White LSCC patients. Table 1 shows the top 30 miRNAs that are lower and higher in Black compared with White LSCC patients.

We focused on miR-9-5p as it is one of the more abundant miRNAs that also has been characterized as a potential biomarker in head and neck cancer (37). In addition, a survival curve generated by Kmplotter (38) in Figure 1B shows low miR-9 levels correlate with poor overall survival in HNSCC (HR=0.6, logrank p=0.0057). As one of the top 30 lower expressed miRNAs, miR-9 was found to be 4-fold lower (log FC =-1.41) in Black compared with White LSCC patients at $p = 0.013$.

Characterization of miR-9-5p in Black and White patient-derived LSCC cell lines by Northern blot

To explore the influence of miR-9-5p in the context of race, we sought to identify cell lines derived from patients with similar clinicopathologic characteristics, differing only by self-reported race and miR-9-5p levels (Supplementary Table 1). We discovered two cell lines that fit those parameters, UM-SCC-12 (derived from a Black male patient) and UM-SCC-10A (derived from a White male patient) cell lines that were established at the University of Michigan. To assess the expression of mature miR-9-5p in the cell lines, we performed Northern Blot analysis. miR-9-5p was weakly detectable in the UM-SCC-12 cell line. Strong expression of miR-9-5p was detected in the UM-SCC-10A cell line (Figure 2).

Endogenous U6, miR-191-5p, miR-16, and Let 7A served as internal loading controls.

Characterization of UM-SCC-12 and UM-SCC-10A cellular phenotype and cisplatin chemosensitivity

To properly interpret our miR-9 validation results, we were required to first determine the intrinsic cellular behavior of the cell lines. We characterized baseline differences in cell migration, cell proliferation and chemosensitivity between our two cell lines.

Cell migration was assessed *via* the scratch wound assay and operationalized as percentage of wound closure 24h, 48h, and 72h post monolayer disruption. A two-way repeated measures ANOVA was conducted to assess differences in percentage of wound closure across each time point between the two cell lines. UM-SCC-12 cell line had a significantly greater cellular migration compared with UM-SCC-10A cell line at 24h, 48h, and 72h post monolayer disruption ($p < 0.0001$) by Šídák's multiple comparisons test (Figure 3A).

Cell proliferation was assessed in both cell lines *via* cell titer blue fluorescence assay at 72h. An unpaired t- test was conducted to assess differences in relative fluorescence between the cell lines. Figure 3B shows that UM-SCC-12 cell line had a greater rate of proliferation at 72 hours compared with UM-SCC-10A cell line ($t(4) = 4.96$, $p < 0.001$).

As cisplatin is the primary chemotherapeutic treatment for head and neck cancer, we assessed baseline cisplatin IC50 for both cell lines. Cell line viability was measured at 48h of cisplatin treatment. A two-way repeated measures ANOVA was then conducted to assess differences in cell viability across the cisplatin concentrations between the two cell lines. UM-SCC-12 cell line had decreased sensitivity to cisplatin compared with UM-SCC-10A cell line at the three highest doses of cisplatin treatment: 22.22μM ($p < 0.001$), 66.67μM ($p < 0.0001$), and 200μM ($p < 0.01$) (Figure 3C).

An unpaired t-test was conducted on IC50 values generated from three experimental runs between the cell lines. A nonlinear fit of the normalized percentage of cell viability responses relative to the non-transformed cisplatin concentrations was used to calculate the IC50. The calculated IC50 of cisplatin was significantly greater for the UM-SCC-12 cell line at 15.24 um compared with 10.23 um for UM-SCC-10A ($t(4) = 5.86$, $p < 0.01$, Figure 3D).

Collectively, UM-SCC-12 cells had significantly greater baseline cell migration, cell proliferation, and decreased cell killing by cisplatin, and thus a higher cisplatin IC50 when compared to UM-SCC-10A.

Increasing miR-9 decreases cell migration, cell proliferation and increases chemosensitivity

We next wanted to understand how increasing miR-9 levels in UM-SCC-12 cell line would alter its cellular phenotype. UM-SCC-12 cells were transiently transfected with a miR-9 mimic or mock oligo control. The scratch wound assay was performed. Figure 4A shows representative images of wound closure captured at 0h, 24h, 48h, and 72h post monolayer disruption for miR-9 mimic and mock transiently transfected cells. By multiple comparisons test, the mimic transfected UM-SCC-12 cells had a significantly lower percentage of wound closure compared to mock transfected control cells at 24h ($p < 0.05$), 48h ($p < 0.01$), and 72h post monolayer disruption ($p < 0.01$) (Figure 4B), demonstrating that elevated levels of miR-9 can decrease cellular migration in UM-SCC-12 cell line.

To assess cell proliferation in miR-9 transfected UM-SCC-12 cells, cell titer blue assay was performed on miR-9 transfected UM-

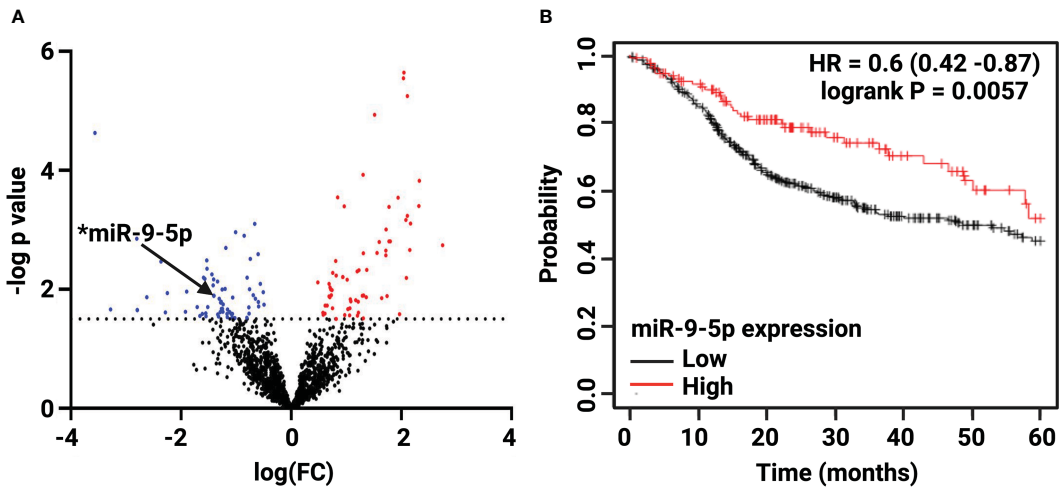

FIGURE 1
Differential expression of miR-9-5p in Black compared with White LSCC by TCGA analysis. **(A)** The Volcano plot depicts 132 differentially expressed miRNAs: 64 higher (red) and 68 lower (blue) in Black LSCC patients. The black arrow highlights low levels of miR-9-5p identified in Black LSCC patients (*p < 0.05). **(B)** Low miR-9-5p predicts poor overall survival in HNSCC as shown by Kaplan Meier survival curve (HR=0.6, logrank p=0.0057).

TABLE 1 Top 30 higher and lower significantly differentially expressed miRNAs in Black compared with White Laryngeal squamous cell carcinoma (LSCC).

miRNA	P-Value	log(FC)	miRNA	P-Value	log(FC)
miR-519a-5p	2.26E-06	2.045041	miR-3180-5p	2.34E-05	-3.56514
miR-518e-5p	2.81E-06	2.038477	miR-21-3p	0.000794	-0.66342
miR-4482-3p	5.61E-06	2.10879	miR-149-5p	0.001089	-1.01261
miR-451a	1.16E-05	1.515035	miR-141-5p	0.001254	-0.85338
miR-144-5p	0.000119	1.303104	miR-876-3p	0.001402	-2.80519
miR-1283-3p	0.000149	2.328334	miR-149-3p	0.002006	-1.18755
miR-363-3p	0.000283	0.841252	miR-30b-3p	0.002554	-0.60359
miR-520a-5p	0.000285	1.941621	miR-200c-5p	0.003081	-0.74309
miR-522-3p	0.000394	2.318118	miR-3155a	0.003242	-1.53699
miR-20b-5p	0.0004	0.963183	miR-934	0.003395	-2.36473
miR-4482-5p	0.000412	1.774413	miR-3691-3p	0.004493	-1.52952
miR-518a-5p	0.000576	2.107811	miR-6087	0.005605	-1.44064
miR-517-5p	0.00078	2.168416	miR-27a-5p	0.006322	-0.80296
miR-526b-5p	0.000984	1.724201	miR-762	0.006354	-1.59308
miR-520a-3p	0.001552	1.773994	miR-6742-3p	0.006649	-1.57277
miR-1323	0.001559	1.799962	miR-4524a-3p	0.006825	-1.41181
miR-518f-5p	0.00159	1.598958	miR-4270	0.007384	-1.34068
miR-514b-5p	0.001809	2.749585	miR-3913-5p	0.00808	-0.56311
miR-521	0.002181	2.152277	miR-190a-3p	0.008571	-1.42109
miR-525-5p	0.002237	1.716953	miR-585-3p	0.009817	-1.20301
miR-518d-5p	0.002445	1.559388	miR-335-3p	0.009953	-0.75986
miR-372-3p	0.002463	1.310864	miR-219b-5p	0.010027	-1.25389
miR-516a-5p	0.002668	1.715929	miR-371b-5p	0.010853	-1.48457
miR-154-3p	0.003342	0.807869	miR-891a-5p	0.0109	-1.89919
miR-4732-3p	0.00472	1.369273	miR-128-1-5p	0.011135	-0.5085
miR-655-5p	0.004743	1.226723	miR-5683	0.011569	-2.25301
miR-1299	0.005	1.19916	miR-210-5p	0.012541	-0.69138
miR-548j-5p	0.005283	0.752899	***miR-9-5p**	0.012751	-1.40489
miR-153-3p	0.005876	0.816662	miR-4289	0.013638	-2.62336
miR-486-5p	0.00618	0.935478	miR-7974	0.013759	-1.0649

SCC-12 cells. A paired samples t-test was conducted on relative fluorescence values across transfection conditions and revealed that the miR-9 transfected UM-SCC-12 cells exhibited lower relative fluorescence compared to mock oligo control, indicating a decrease in cell proliferation ($t(2) = 4.65$, $p < 0.05$) (Figure 4C).

We proceeded to test the effect of increasing miR-9 levels and chemosensitivity. miR-9 transfected UM-SCC-12 cells were treated with cisplatin and the IC50 was recorded. We noted an increase in cell killing/decreased cell viability in miR-9 transfected cells as compared to mock oligo control at three doses of cisplatin treatment: 2.47μM ($p < 0.0001$), 7.41μM ($p < 0.001$), and 22.22μM ($p < 0.001$) (Figure 4D). Furthermore, the calculated IC50 was lower (7.64 μM) compared to than mock oligo control (15.57 μM). Overall, these finding demonstrated that elevated levels of miR-9 can increase UM-SCC-12 sensitivity to cisplatin (Figure 4E).

Reducing miR-9 increases cell migration, cell proliferation and decreases chemosensitivity

Our next step was to determine if reducing miR-9 levels could produce an opposite phenotype as seen in our miR-9 transfected UM-SCC-12 cells. Here, we knockdown miR-9 levels by treating

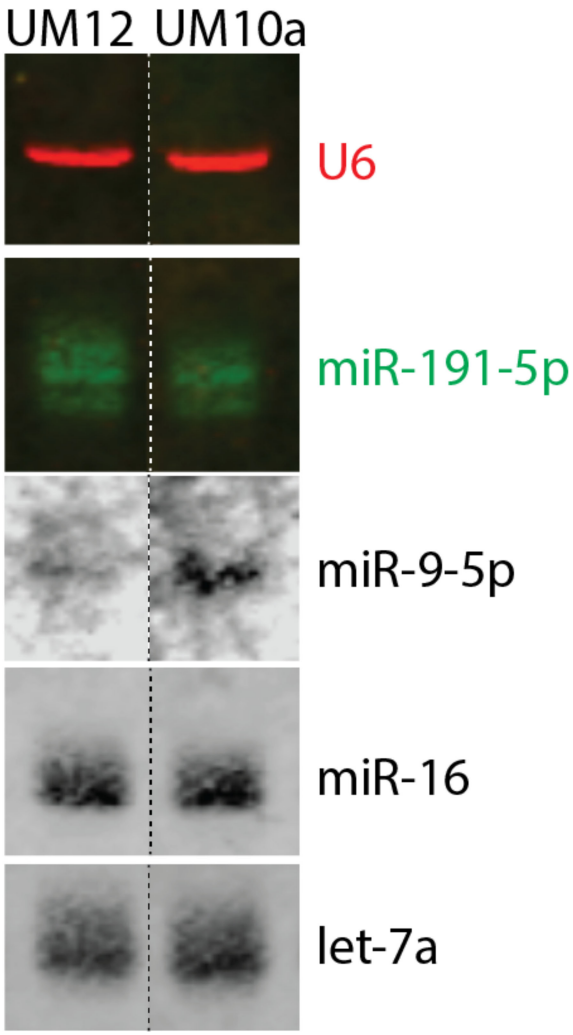

FIGURE 2
Characterization of miR-9-5p in race-specific LSCC cell lines. Northern blot analysis revealed that Black patient derived UM-SCC-12 cell line has barely detectable levels of mature miR-9-5p whereas the White-patient derived UM-SCC-10A cell line has a greater level of mature miR-9-5p. U6, miR-191-5p, miR-16, and Let 7A were used as internal loading controls.

UM-SCC-10A cells with a miR-9 inhibitor. The scratch assay was performed. Figure 5A shows a panel of representative images of miR-9 inhibited UM-SCC-10A cells at 0h, 24h, 48h, and 72h compared with mock oligo control, showing lower miR-9 levels can significantly increase cell migration at each time point, 24h ($p < 0.01$), 48h ($p < 0.001$), and 72h post monolayer disruption ($p < 0.001$) (Figure 5B).

Cell proliferation was evaluated in miR-9 inhibited UM-SCC-10A transfected cells at 72 hours. Relative fluorescence values across transfection conditions was compared *via* paired t test. Figure 5C shows that cell proliferation was higher in miR-9 inhibited cells relative to the mock oligo control ($t(2) = 4.94$, $p < 0.05$).

We next compared chemosensitivity in miR-9 inhibited UM-SCC-10A transfected cells compared to mock oligo control. We found that lowering miR-9 levels decrease cell killing/decreased chemosensitivity at three doses of cisplatin treatment: 2.47μM ($p < 0.0001$), 7.41μM ($p < 0.0001$), and 22.22μM ($p < 0.05$) (Figure 5D). The IC50 values was higher (14.57 μM) compared to than mock oligo control (10.71 μM). These findings signify that lower miR-9 levels can decrease cellular sensitivity to cisplatin ($t(2) = 28.79$, $p < 0.01$) (Figure 5E).

miR-9 modulates ABCC1 and MAP1B gene expression in LSCC cell lines

ABCC1 and MAP1B are reported gene targets of miR-9-5p that have been found to predict chemoresistance in cancer (39–42). Thus, as mediators of chemoresistance, we were interested in investigating whether these genes were regulated by miR-9 in LSCC. Initial studies involved determining baseline expression of ABCC1 and MAP1B in UM-SCC-12 and UM-SCC-10A by qPCR. Unpaired t-tests were conducted to assess differences in the log transformed $2^{-\Delta CT}$ values between the two cell lines. UM-SCC-12 had significantly higher baseline gene expression of ABCC1 ($t(4) =$

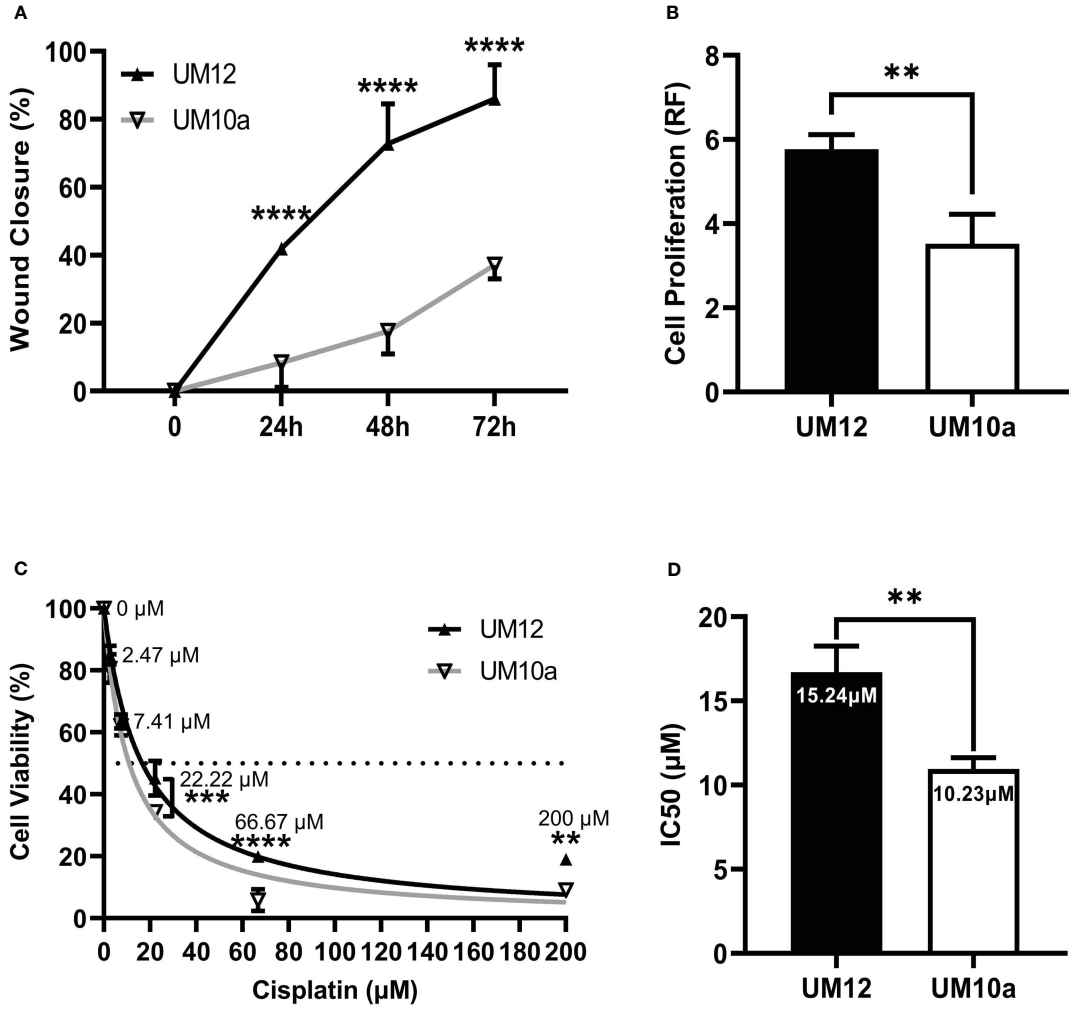

FIGURE 3
Characterization of UM-SCC-12 and UM-SCC-10A cellular phenotype and cisplatin chemosensitivity. UM-SCC-12 cells had significantly greater baseline **(A)** cell migration across 24h, 48h, and 72h time points **(B)** and cell proliferation, **(C)** decreased cell killing by cisplatin at 22.22 μM, 66.67μM and 200μM, and thus a **(D)** higher cisplatin IC50 when compared to UM-SCC-10A. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

7.69, $p < 0.01$) and MAP1B (t(4) = 18.69, $p < 0.0001$) compared with the UM-SCC-10A cell line (t(4) = 7.69, $p < 0.01$) (Figures 6A, B).

Using miR-9 transfected UM-SCC-12 and miR-9 inhibited transfected UM-SCC-10A cells, we sought to determine if miR-9 regulated ABCC1 and MAP1B expression. 24 hours after transfection, gene expression for both ABCC1 and MAP1B was determined by qPCR. Figure 7A shows increased levels of miR-9 in UM-SCC-12 cells significantly decreased ABCC1 gene expression relative to the mock oligo control (t(2) = 4.63, $p < 0.05$). Conversely, reducing miR-9 levels in UM-SCC-10A significantly increased ABCC1 expression compared with mock oligo control ((t(2) = 7.42, $p < 0.05$) (Figure 7B).

Similar qPCR results were seen with MAP1B whereby increasing miR-9 in UM-SCC-12 cells reduced MAP1B gene expression relative to mock oligo control (t(2) = 6.19, $p < 0.05$, Figure 8A). Figure 8B shows that reducing miR-9 in UM-SCC-10A cells resulted in increased levels MAP1B relative to mock oligo control (t(2) = 5.22, $p < 0.05$). Taken together, these studies suggest that miR-9 regulates ABCC1 and MAP1B levels in LSCC cell lines.

Discussion

Genomic studies investigating heritable somatic alterations associated with racially disparate clinical outcomes have been dedicated to breast, colon, and prostate cancers (43–45); however, genomic alterations in LSCC been largely unexplored where Black Americans are disproportionately affected, harboring the lowest 5-year survival rates among all races. Investigators have identified ancestral-related nucleotide signatures in key driver genes, in particular PIK3CA in Black and White LSCCs from the TCGA but characterization of noncoding RNAs, namely miRNAs, has not been explored (16). We employed computation analysis of LSCCs in the TCGA and uncovered a panel of miRNAs that were significantly different in Black LSCC compared with White. Through a series of validation studies, we investigated miR-9 in LSCC tumorigenesis and uncovered its ability to influence sensitivity to cisplatin and predict chemoresistance–employing race-specific cell lines.

Our study is the first to report differential miRNA expression in Black and White head and neck cancer, specifically laryngeal

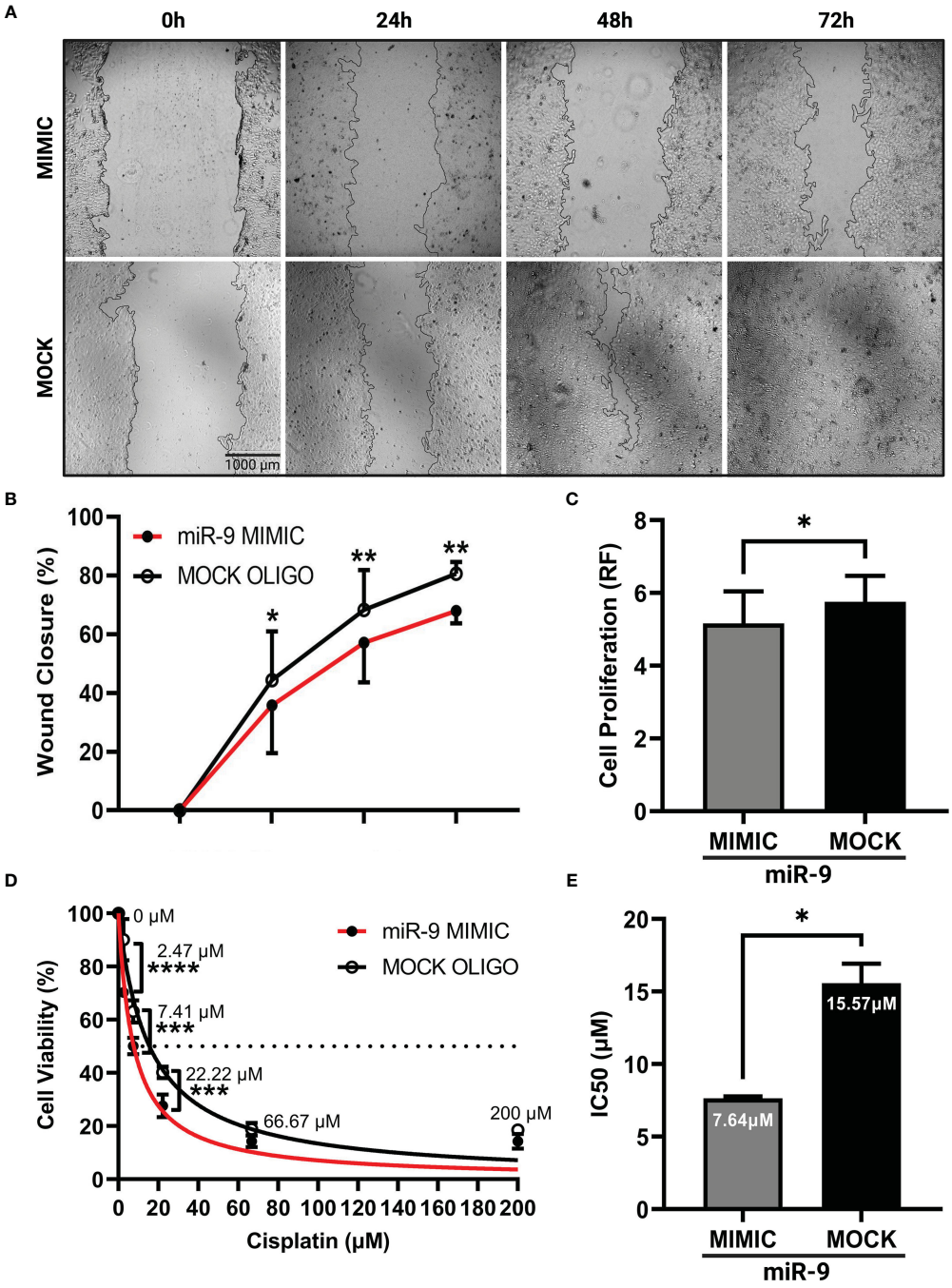

FIGURE 4
Increasing miR-9 decreases, cell migration, decreases cell proliferation, and increases chemosensitivity in UM-SCC-12 cells. **(A)** Representative images of cell migration of miR-9 mimic and mock oligo control transfected UM-SCC-12 cells across time points. Transient transfection of miR-9 mimic in UM-SCC-12 cells resulted in significantly decreased **(B)** cell migration at 24h, 48h, and 72h, **(C)** and cell proliferation, **(D)** increased sensitivity to cisplatin at 2.47 µM, 7.41µM and 22.22µM and **(E)** a lowering of its IC50 to cisplatin compared to mock oligo control. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

cancer. Our findings may facilitate the development of miRNA signatures for LSCC that are associated with race. miRNA signatures have been reported for multiple cancers and linked to differential signaling pathway activation in known oncogenic drivers that impact clinical outcomes. In multiple myeloma, for example, a signature of six upregulated miRs was associated with the WNT signaling pathway, whereas a signature of four downregulated miRs was associated with the MAPK pathway (46). Inamoto and colleagues determined from 84 urothelial cancer of the bladder (UCB) patients that there was specific signature of nine miRs associated with an aggressive phenotype compared with a nonaggressive phenotype. Furthermore, six of those miRs were associated with a high-risk UCB phenotype and poor outcomes, whereas a signature of 3 miRs was found to be

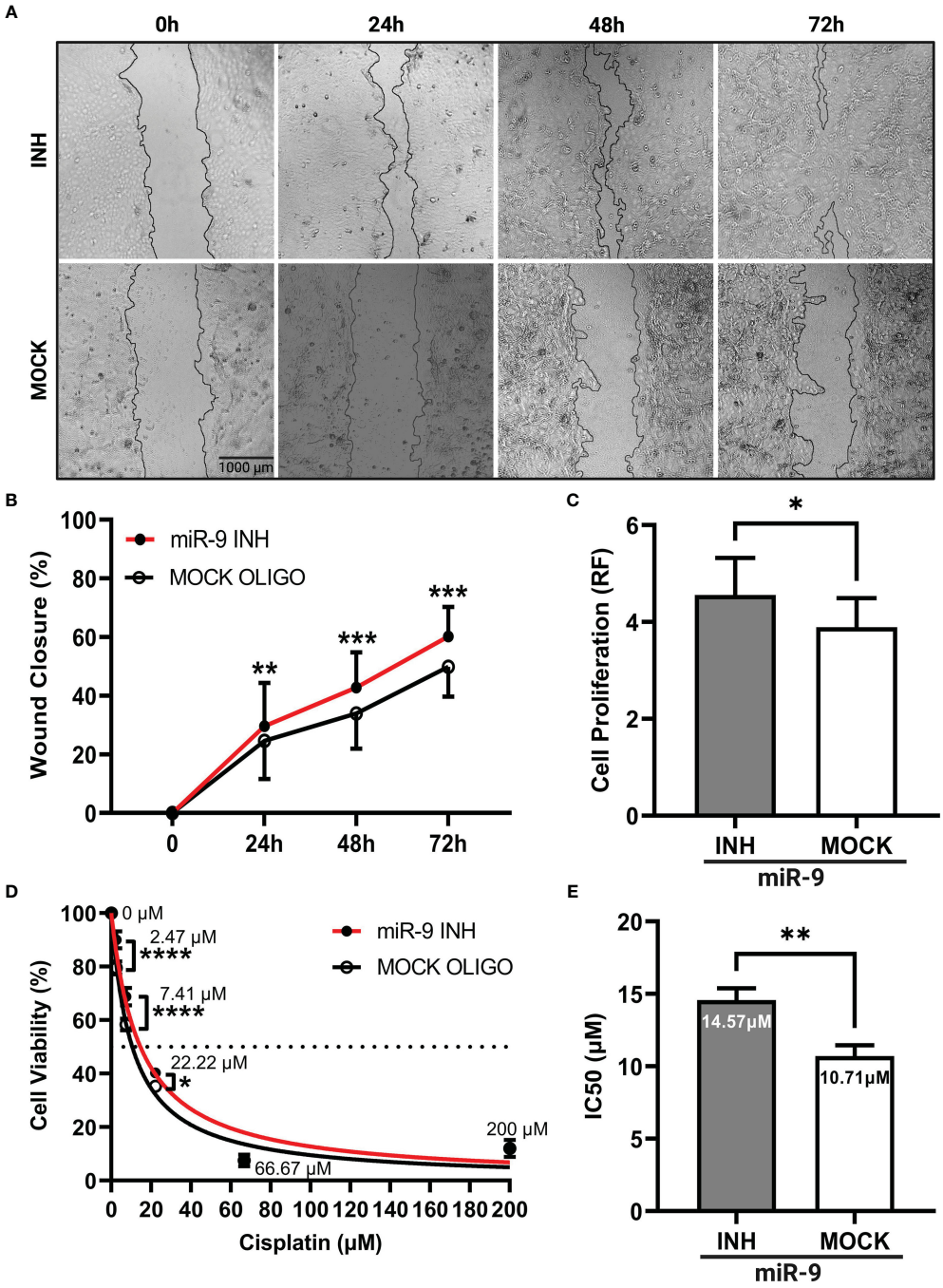

FIGURE 5
Reducing levels of miR-9 increases cell migration, increases cell proliferation, and decreases chemosensitivity in UM-SCC-10A cells. **(A)** Representative images of cell migration of miR-9 inhibitor or mock oligo control transfected UM-SCC-10A cells across time points. Transient transfection of miR-9 inhibitor in UM-SCC-10A cells resulted in significantly increased **(B)** cell migration at 24h, 48h, and 72h, **(C)** and cell proliferation, **(D)** decreased sensitivity to cisplatin at 2.47 µM, 7.41µM and 22.22µM and **(E)** an increase its IC50 to cisplatin compared to mock oligo control. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

protective (47). Multiple miRNA signatures have been identified and demonstrated as robust predictors for the diagnosis of LSCC (48); however, they have not been identified in the context of LSCC racial health disparities. Our laboratory is currently utilizing computational analysis to expand on our expression data by exploring differentially expressed miRNA mediated pathway differences in the context of race.

Of the differentially expressed miRNAs, we turned our attention to miR-9 for several reasons; we observed greater abundance of miR-9 in the TCGA samples in both Black and White compared with several of the other differentially miRNAs, making it ideal as a potential biomarker; its low expression has been found to predict poor overall survival (37); and its role appears critical to development and disease (49). Overall, our hope was to evaluate

miR-9 as a potential mediator LSCC tumorigenesis while also considering it as a potential biomarker for cancer health disparities.

miR-9 is a key regulator of neuronal development; playing critical role in spatial and temporal regulation of neurogenesis (50). As a regulator of cancer development, miR-9 has been shown to promote a cancerous phenotype depending on its expression levels and tumor origin. As an example, elevated levels of miR-9 have been associated with development of cervical and brain cancers and downstream activation of CAM and JAK/STAT pathways, respectively (51, 52). Decreased levels of miR-9 have been linked to tumorigenesis of triple negative breast cancer and ovarian cancer were signaling pathways of NOTCH1 and NF-kB have been proposed to play a role in their tumorigenesis (53, 54). Overall, the versatile expression of this miRNA across cancers indicates that unique pathways are activated depending on its expression levels. Using the TCGA, we found that miR-9 was significantly lower in Black patient LSCC samples compared with White. We sought to validate the relevance of low miR-9 levels in laryngeal cancer in two patient-derived LSCC cells lines. Distinctly, we took into consideration reported racial background of the patient-derived cell line, matched the provided clinicopathologic data, and ensured by Northern analysis that expression differences corresponded to the TCGA findings. Our validation studies suggest that low miR-9 levels influence LSCC tumorigenesis *via* increases in cell proliferation and migration. Our findings are similar to studies in oral squamous cell carcinoma where miR-9 levels were found to be lower in tumor than normal paired tissues from Southeast Asian patients (55). The authors demonstrated that overexpression of miR-9 could decrease migration, proliferation, and arrest the cell cycle. Furthermore, low miR-9 has been proposed to mediate OSCC tumorigenesis through WNT and CDK4/6 signaling in OSCC (55, 56). The means of low miR-9 expression in HNSCC was addressed by Minor and colleagues who demonstrated, in both *in vivo* and vitro model systems, that hypermethylation could reduce miR-9 levels in oral and oropharyngeal cancers (57).

It is important to note others have found high levels of miR-9 in HNSCC *via* computational analysis of the TCGA (58). Our contrary findings may be attributed to our race-centered analysis. It has been reported that there is greater representation of White patients compared other races in the TCGA (59). As such, this allows the genomic profiles of White patients to overshadow the biologic differences extant in individuals from underrepresented groups. Our findings may highlight a described limitation of using one database to define tumor biology for an entire population (60).

On that note, we also understand that a limitation to our findings is the small sample size of Black LSCC patients within the TCGA. However, we believe, by investigating miR-9, we can begin to address the significance of differential miRNA expression in LSCC tumorigenesis with cancer health disparities in the forefront. Our findings are supported by studies in other racial disparate cancers where certain miRNAs have been characterized as potential mediators of cancer health disparities. Yates and colleagues were the first to identify differential expression of mir-26a in Black compared with White prostate cancer cell lines. miR-26a was found to be overexpressed 13-fold in Black tumors compared with White tumors (25). The authors suggested that higher expression was associated with more aggressive phenotype whereas low miR-26a expression was associated with better survival. Similar studies have been performed in colorectal cancer (CRC) and breast cancers. In CRC, miR-182 was found to be upregulated in Black American CRC and further associated with reduction of the miR-182 targets–FOXO1 and FOXO3A (61). As tumor suppressors, FOXO1 and FOXO3 were suggested to be downstream mediators of CRC cancer health disparities. Taken together, these studies introduce the concept that versatile expression of a miRNA is not only associated with tumor origin but may also be associated with race.

Cisplatin is the primary drug used to treat all head and neck cancers. Primary or acquired resistance to cisplatin is a major clinical challenge (62). Based on studies in oral cavity and

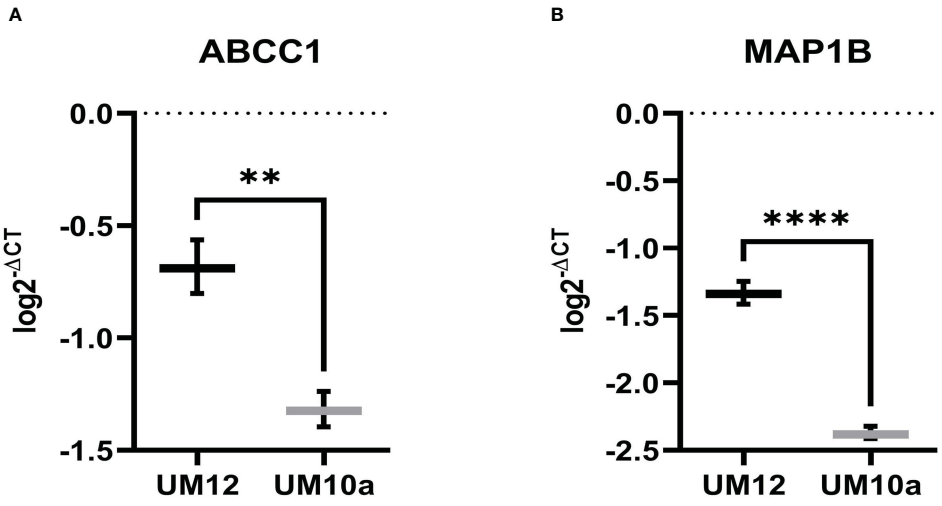

FIGURE 6
ABCC1 and MAP1B baseline gene expression in LSCC cell lines. **(A)** ABCC1 and **(B)** MAP1B gene expression is significantly higher in UM-SCC-12 cell line compare with UM-SCC-10A. $^{**}p < 0.01$, $^{****}p < 0.0001$.

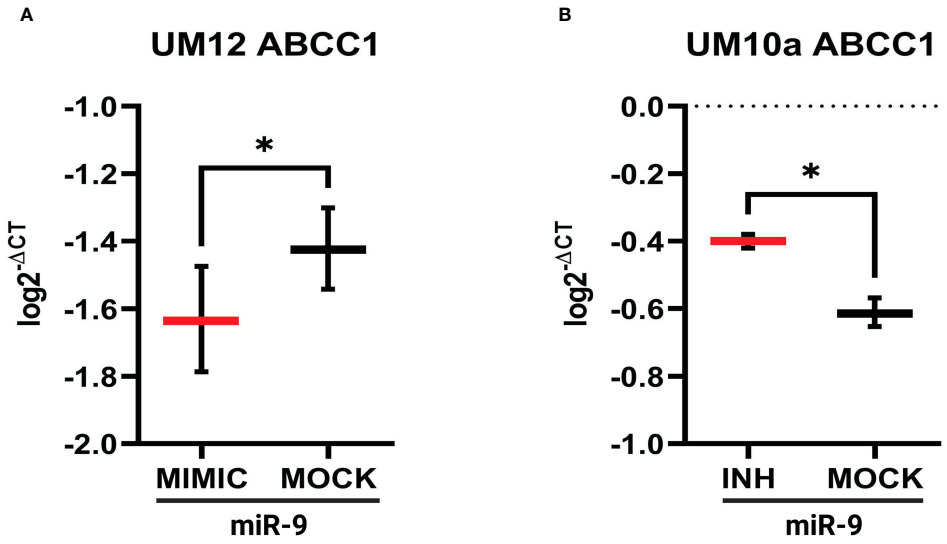

FIGURE 7
miR-9 modulates ABCC1 gene expression in LSCC cell lines. **(A)** Increasing miR-9 levels in UM-SCC-12 resulted in a significant decrease in ABCC1 gene expression compared with mock oligo control. **(B)** Decreasing miR-9 levels in UM-SCC-10A resulted in a significant increase in ABCC1 gene expression compared with mock oligo control. *$p < 0.05$.

hepatocellular cancers that showed low levels of miR-9 confer chemoresistance, we sought to further explore a potential role for miR-9 in LSCC disparate clinical outcomes by investigating its role in cisplatin chemosensitivity (63, 64). Indeed, we demonstrated in LSCC cell lines that lowering miR-9 levels can decrease cell killing in response to cisplatin and that increasing miR-9 can increase cell killing in response to cisplatin. These findings would suggest that low miR-9 may influence survival through its modulating cisplatin chemosensitivity, conferring a chemoresistant phenotype.

ABCC1 and MAP1B are recognized miR-9 gene targets that have a potential role of chemoresistance. ABCC1 is one of the most studied multidrug resistant proteins. Its overexpression has been associated with chemotherapeutic drug resistance, distant metastasis, and poor clinical outcomes (40). As such, it has a been touted as a putative marker or a multi-marker panel member to predict chemoresistance (65). MAP1B is a member of the family of proteins essential to stabilizing microtubules. Disrupting microtubule assembly is a common target for

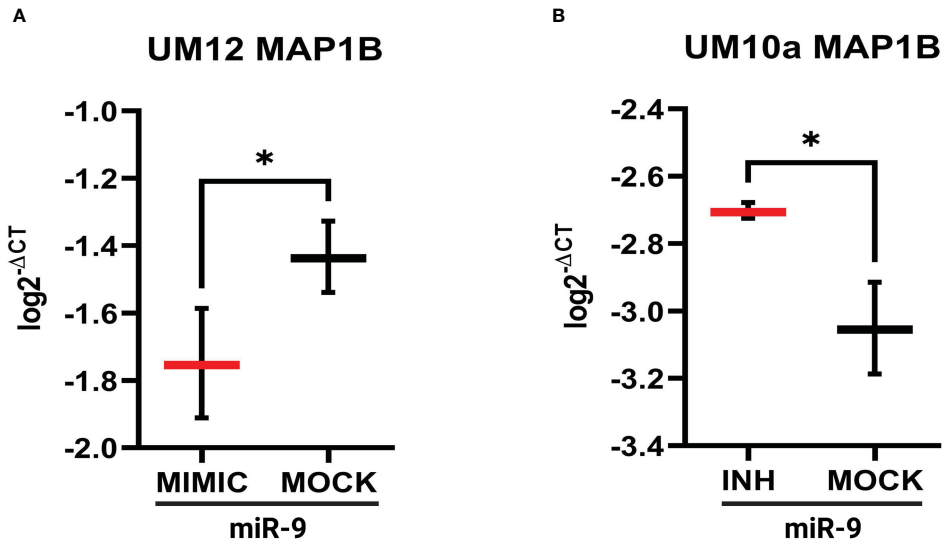

FIGURE 8
miR-9 modulates MAP1B gene expression in LSCC cell line. **(A)**. Increasing miR-9 levels in UM-SCC-12 resulted in a significant decrease in MAP1B gene expression compared with mock oligo control. **(B)** Decreasing miR-9 levels in UM-SCC-10A resulted in a significant increase in ABCC1 gene expression compared with mock oligo control. *$p < 0.05$.

chemotherapeutic drugs. Overexpression of MAP1B has been found to correlate with adverse clinical outcomes and predict unfavorable prognostic factors in urothelial carcinoma and glioblastoma (66). Using our patient-derived cells, we showed that our Black patient derived cell line with low miR-9 levels had significantly higher levels of both ABCC1 and MAP1B compared with the White patient derived cell line with higher miR-9 levels. By modulating miR-9 levels we were able to significantly alter gene expression levels of ABCC1 and MAP1B, suggesting that these genes are targets of miR-9 in LSCC. Consequently, we may have identified potential miR-9 downstream mediators of LSCC cancer health disparities that may be exploited for future therapeutic intervention.

In summary, our study investigates miR-9 influence on the cancer cell phenotype and modulating chemoresistance in LSCC cell lines. We understand a primary limitation to our investigation is the small number of LSCC samples in the TCGA and we are currently validating these findings in an additional cohort of samples taking ancestry into account. Nevertheless, our work may open the door for new therapies for LSCC based on targets of differentially expressed miRNAs and the expression of specific downstream pathways. Elucidating the biologic mechanisms underlying LSCC clinical disparate outcomes may provide better avenues for treatment and reduce mortality for all patient suffering with this cancer.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://portal.gdc.cancer.gov.

Author contributions

CG: Technical work, writing of manuscript, review, editing, conceptualization, statistics. SI: Foundational technical work and methodology CL: Technical and computational work, writing, editing, TG: Computational work. JM and MR: Technical work. HK: Computational methodology. CF and TB: Technical instruction. NS: Conceptualization. CX: Methodology and technical support. CY: Foundational conceptualization. RR: Foundational work. MX: Technical work, methodology, and foundational work, writing and editing. KF: Primary conceptualization, technical work, writing of manuscript, editing, and review. All authors contributed to the article and approved the submitted version.

Funding

This research reported in this publication was supported by the National Cancer Institute, Center for Reducing Cancer Health Disparities of the National Institutes of Health under award numbers U54CA233396, U54CA233444, & U54CA233465, which support the Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center; the University of Florida (UF) CTSI KL2 and pilot funding from the UF Health Cancer Center; Us Army Med Res Acquisition grant CA210915. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The final peer-reviewed manuscript is subject to the National Institutes of Health Public Access Policy.

Conflict of interest

During the writing of this report, CY received personal fees from Riptide Biosciences, QED Therapeutics, and Amgen, and other income from Riptide Biosciences outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1096882/full#supplementary-material

References

1. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the united states: A site-specific analysis of the SEER database. *Int J Cancer* (2005) 114(5):806–16. doi: 10.1002/ijc.20740

2. DeSantis CE, Siegel RL, Sauer AG, Miller KD, Fedewa SA, Alcaraz KI, et al. Cancer statistics for African americans, 2016: Progress and opportunities in reducing racial disparities. *CA Cancer J Clin* (2016) 66(4):290–308. doi: 10.3322/caac.21340

3. Goodwin WJ, Thomas GR, Parker DF, Joseph D, Levis S, Franzmann E, et al. Unequal burden of head and neck cancer in the united states. *Head Neck* (2008) 30 (3):358–71. doi: 10.1002/hed.20710

4. Lenze NR, Farquhar D, Sheth S, Zevallos JP, Blumberg J, Lumley C, et al. Socioeconomic status drives racial disparities in HPV-negative head and neck cancer outcomes. *Laryngoscope* (2021) 131(6):1301–9. doi: 10.1002/lary.29252

5. Nallani R, Subramanian TL, Ferguson-Square KM, Smith JB, White J, Chiu AG, et al. A systematic review of head and neck cancer health disparities: A call for innovative research. *Otolaryngol Head Neck Surg* (2022) 166(6):1238–48. doi: 10.1177/01945998221077197

6. Thomas GR. Racial disparity in head and neck cancer. *Cancer* (2021) 127 (15):2612–3. doi: 10.1002/cncr.33555

7. Jassal JS, Cramer JD. Explaining racial disparities in surgically treated head and neck cancer. *Laryngoscope* (2021) 131(5):1053–9. doi: 10.1002/lary.29197

8. Voora RS, Kotha NV, Kumar A, Qiao EM, Qian AS, Panuganti BA, et al. Association of race and health care system with disease stage and survival in veterans with larynx cancer. *Cancer* (2021) 127(15):2705–13. doi: 10.1002/cncr.33557

9. Kam D, Salib A, Gorgy G, Patel TD, Carniol ET, Eloy JA, et al. Incidence of suicide in patients with head and neck cancer. *JAMA Otolaryngol Head Neck Surg* (2015) 141(12):1075–81. doi: 10.1001/jamaoto.2015.2480

10. Genden EM, Ferlito A, Silver CE, Jacobson AS, Werner JA, Suárez C, et al. Evolution of the management of laryngeal cancer. *Oral Oncol* (2007) 43(5):431–9. doi: 10.1016/j.oraloncology.2006.08.007

11. Gourin CG, Conger BT, Sheils WC, Bilodeau PA, Coleman TA, Porubsky ES. The effect of treatment on survival in patients with advanced laryngeal carcinoma. *Laryngoscope* (2009) 119(7):1312–7. doi: 10.1002/lary.20477

12. Li MM, Zhao S, Eskander A, Rygalski C, Brock G, Parikh AS, et al. Stage migration and survival trends in laryngeal cancer. *Ann Surg Oncol* (2021) 28(12):7300–7309. doi: 10.1245/s10434-021-10318-1

13. Molina MA, Cheung MC, Perez EA, Byrne MM, Franceschi D, Moffat FL, et al. African American And poor patients have a dramatically worse prognosis for head and neck cancer: an examination of 20,915 patients. *Cancer* (2008) 113(10):2797–806. doi: 10.1002/cncr.23889

14. Naghavi AO, Echevarria MI, Strom TJ, Abuodeh YA, Ahmed KA, Venkat PS, et al. Treatment delays, race, and outcomes in head and neck cancer. *Cancer Epidemiol* (2016) 45:18–25. doi: 10.1016/j.canep.2016.09.005

15. Ragin CC, Langevin SM, Marzouk M, Grandis J, Taioli E. Determinants of head and neck cancer survival by race. *Head Neck* (2011) 33(8):1092–8. doi: 10.1002/hed.21584

16. Ramakodi MP, Kulathinal RJ, Chung Y, Serebriiskii I, Liu JC, Ragin CC. Ancestral-derived effects on the mutational landscape of laryngeal cancer. *Genomics* (2016) 107(2-3):76–82. doi: 10.1016/j.ygeno.2015.12.004

17. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci U S A* (2004) 101(9):2999–3004. doi: 10.1073/pnas.0307323101

18. Huang Y, Gu M, Tang Y, Sun Z, Luo J, Li Z. Systematic review and meta-analysis of prognostic microRNA biomarkers for survival outcome in laryngeal squamous cell cancer. *Cancer Cell Int* (2021) 21(1):316. doi: 10.1186/s12935-021-02021-8

19. Lamichhane SR, Thachil T, Gee H, Milic N. Circulating MicroRNAs as prognostic molecular biomarkers in human head and neck cancer: A systematic review and meta-analysis. *Dis Markers* (2019) 2019:8632018. doi: 10.1155/2019/8632018

20. Jones J, Grizzle W, Wang H, Yates C. MicroRNAs that affect prostate cancer: Emphasis on prostate cancer in African americans. *Biotech Histochem* (2013) 88 (7):410–24. doi: 10.3109/10520295.2013.807069

21. Martin DN, Starks AM, Ambs S. Biological determinants of health disparities in prostate cancer. *Curr Opin Oncol* (2013) 25(3):235–41. doi: 10.1097/CCO.0b013e32835eb5d1

22. Singh SK, Lillard JW, Singh R. Molecular basis for prostate cancer racial disparities. *Front Biosci (Landmark Ed)* (2017) 22:428–50. doi: 10.2741/4493

23. Theodore SC, Davis M, Zhao F, Wang H, Chen D, Rhim J, et al. MicroRNA profiling of novel African American and Caucasian prostate cancer cell lines reveals a reciprocal regulatory relationship of miR-152 and DNA methyltranferase 1. *Oncotarget* (2014) 5(11):3512–25. doi: 10.18632/oncotarget.1953

24. Yao S, Graham K, Shen J, Campbell LE, Singh P, Zirpoli G, et al. Genetic variants in microRNAs and breast cancer risk in African American and European American women. *Breast Cancer Res Treat* (2013) 141(3):447–59. doi: 10.1007/s10549-013-2698-4

25. Yates C, Long MD, Campbell MJ, Sucheston-Campbell L. miRNAs as drivers of TMPRSS2-ERG negative prostate tumors in African American men. *Front Biosci (Landmark Ed)* (2017) 22:212–29. doi: 10.2741/4482

26. Farran B, Dyson G, Craig D, Dombkowski A, Beebe-Dimmer JL, Powell IJ, et al. A study of circulating microRNAs identifies a new potential biomarker panel to distinguish aggressive prostate cancer. *Carcinogenesis* (2018) 39(4):556–61. doi: 10.1093/carcin/bgy025

27. Bovell LC, Shanmugam C, Putcha BD, Katkoori VR, Zhang B, Bae S, et al. The prognostic value of microRNAs varies with patient race/ethnicity and stage of colorectal cancer. *Clin Cancer Res* (2013) 19(14):3955–65. doi: 10.1158/1078-0432.CCR-12-3302

28. Turkistani S, Sugita BM, Fadda P, Marchi R, Afsari A, Naab T, et al. A panel of miRNAs as prognostic markers for African-American patients with triple negative breast cancer. *BMC Cancer* (2021) 21(1):861. doi: 10.1186/s12885-021-08573-2

29. Quinlan AR, Hall IM. BEDTools: A flexible suite of utilities for comparing genomic features. *Bioinformatics* (2010) 26(6):841–2. doi: 10.1093/bioinformatics/btq033

30. Friedlander MR, Mackowiak SD, Li N, Chen W, Rajewsky N. miRDeep2 accurately identifies known and hundreds of novel microRNA genes in seven animal clades. *Nucleic Acids Res* (2012) 40(1):37–52. doi: 10.1093/nar/gkr688

31. Kozomara A, Birgaoanu M, Griffiths-Jones S. miRBase: From microRNA sequences to function. *Nucleic Acids Res* (2019) 47(D1):D155–D62. doi: 10.1093/nar/gky1141

32. Robinson MD, McCarthy DJ, Smyth GK. edgeR: a bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics* (2010) 26 (1):139–40. doi: 10.1093/bioinformatics/btp616

33. Brenner JC, Graham MP, Kumar B, Saunders LM, Kupfer R, Lyons RH, et al. Genotyping of 73 UM-SCC head and neck squamous cell carcinoma cell lines. *Head Neck* (2010) 32(4):417–26. doi: 10.1002/hed.21198

34. Mann JE, Kulkarni A, Birkeland AC, Kafelghazal J, Eisenberg J, Jewell BM, et al. The molecular landscape of the university of Michigan laryngeal squamous cell carcinoma cell line panel. *Head Neck* (2019) 41(9):3114–24. doi: 10.1002/hed.25803

35. Fields C, Sheng P, Miller B, Wei T, Xie M. Northern blot with IR fluorescent probes: Strategies for probe preparation. *Bio Protoc* (2019) 9(8):e3219. doi: 10.21769/BioProtoc.3219

36. Miller BR, Wei T, Fields CJ, Sheng P, Xie M. Near-infrared fluorescent northern blot. *RNA* (2018) 24(12):1871–7. doi: 10.1261/rna.068213.118

37. Sun L, Liu L, Fu H, Wang Q, Shi Y. Association of decreased expression of serum miR-9 with poor prognosis of oral squamous cell carcinoma patients. *Med Sci Monit* (2016) 22:289–94. doi: 10.12659/MSM.895683

38. Gyorffy B, Surowiak P, Budczies J, Lanczky A. Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small-cell lung cancer. *PLoS One* (2013) 8(12):e82241. doi: 10.1371/journal.pone.0082241

39. Dajas-Bailador F, Bonev B, Garcez P, Stanley P, Guillemot F, Papalopulu N. microRNA-9 regulates axon extension and branching by targeting Map1b in mouse cortical neurons. *Nat Neurosci* (2012) 15(5):697–9. doi: 10.1038/nn.3082

40. Kunická T, Souček P. Importance of ABCC1 for cancer therapy and prognosis. *Drug Metab Rev* (2014) 46(3):325–42. doi: 10.3109/03602532.2014.901348

41. Laks DR, Ases-Prieto JA, Alvarado AG, Nakashima J, Chand S, Azzam DB, et al. A molecular cascade modulates MAP1B and confers resistance to mTOR inhibition in human glioblastoma. *Neuro Oncol* (2018) 20(6):764–75. doi: 10.1093/neuonc/nox215

42. Sun J, Zhang H, Li L, Yu L, Fu L. MicroRNA-9 limits hepatic fibrosis by suppressing the activation and proliferation of hepatic stellate cells by directly targeting MRP1/ABCC1. *Oncol Rep* (2017) 37(3):1698–706. doi: 10.3892/or.2017.5382

43. Carethers JM, Murali B, Yang B, Doctolero RT, Tajima A, Basa R, et al. Influence of race on microsatellite instability and CD8+ T cell infiltration in colon cancer. *PLoS One* (2014) 9(6):e100461. doi: 10.1371/journal.pone.0100461

44. Keenan T, Moy B, Mroz EA, Ross K, Niemierko A, Rocco JW, et al. Comparison of the genomic landscape between primary breast cancer in African American versus white women and the association of racial differences with tumor recurrence. *J Clin Oncol* (2015) 33(31):3621–7. doi: 10.1200/JCO.2015.62.2126

45. Petrovics G, Li H, Stümpel T, Tan SH, Young D, Katta S, et al. A novel genomic alteration of LSAMP associates with aggressive prostate cancer in African American men. *EBioMedicine* (2015) 2(12):1957–64. doi: 10.1016/j.ebiom.2015.10.028

46. Dong X, Lu G, Su X, Liu J, Chen X, Tian Y, et al. Identification of key miRNA signature and pathways involved in multiple myeloma by integrated bioinformatics analysis. *Hematology* (2021) 26(1):976–84. doi: 10.1080/16078454.2021.2003980

47. Inamoto T, Uehara H, Akao Y, Ibuki N, Komura K, Takahara K, et al. A panel of MicroRNA signature as a tool for predicting survival of patients with urothelial carcinoma of the bladder. *Dis Markers* (2018) 2018:5468672. doi: 10.1155/2018/5468672

48. Takeuchi T, Kawasaki H, Luce A, Cossu AM, Misso G, Scrima M, et al. Insight toward the MicroRNA profiling of laryngeal cancers: Biological role and clinical impact. *Int J Mol Sci* (2020) 21(10):3693. doi: 10.3390/ijms21103693

49. Nowek K, Wiemer EAC, Jongen-Lavrencic M. The versatile nature of miR-9/9(*) in human cancer. *Oncotarget* (2018) 9(29):20838–54. doi: 10.18632/oncotarget.24889

50. Yuva-Aydemir Y, Simkin A, Gascon E, Gao FB. MicroRNA-9: Functional evolution of a conserved small regulatory RNA. *RNA Biol* (2011) 8(4):557–64. doi: 10.4161/rna.8.4.16019

51. Kim TM, Huang W, Park R, Park PJ, Johnson MD. A developmental taxonomy of glioblastoma defined and maintained by MicroRNAs. *Cancer Res* (2011) 71(9):3387–99. doi: 10.1158/0008-5472.CAN-10-4117

52. Liu W, Gao G, Hu X, Wang Y, Schwarz JK, Chen JJ, et al. Activation of miR-9 by human papillomavirus in cervical cancer. *Oncotarget* (2014) 5(22):11620–30. doi: 10.18632/oncotarget.2599

53. Guo LM, Pu Y, Han Z, Liu T, Li YX, Liu M, et al. MicroRNA-9 inhibits ovarian cancer cell growth through regulation of NF-kappaB1. *FEBS J* (2009) 276(19):5537–46. doi: 10.1111/j.1742-4658.2009.07237.x

54. Mohammadi-Yeganeh S, Mansouri A, Paryan M. Targeting of miR9/NOTCH1 interaction reduces metastatic behavior in triple-negative breast cancer. *Chem Biol Drug Des* (2015) 86(5):1185–91. doi: 10.1111/cbdd.12584

55. Shang A, Lu WY, Yang M, Zhou C, Zhang H, Cai ZX, et al. miR-9 induces cell arrest and apoptosis of oral squamous cell carcinoma *via* CDK 4/6 pathway. *Artif Cells Nanomed Biotechnol* (2018) 46(8):1754–62. doi: 10.1080/21691401.2017.1391825

56. Yu T, Liu K, Wu Y, Fan J, Chen J, Li C, et al. MicroRNA-9 inhibits the proliferation of oral squamous cell carcinoma cells by suppressing expression of

CXCR4 *via* the wnt/beta-catenin signaling pathway. *Oncogene* (2014) 33(42):5017–27. doi: 10.1038/onc.2013.448

57. Minor J, Wang X, Zhang F, Song J, Jimeno A, Wang XJ, et al. Methylation of microRNA-9 is a specific and sensitive biomarker for oral and oropharyngeal squamous cell carcinomas. *Oral Oncol* (2012) 48(1):73–8. doi: 10.1016/j.oraloncology.2011.11.006

58. Fang XN, Yin M, Li H, Liang C, Xu C, Yang GW, et al. Comprehensive analysis of competitive endogenous RNAs network associated with head and neck squamous cell carcinoma. *Sci Rep* (2018) 8(1):10544. doi: 10.1038/s41598-018-28957-y

59. Spratt DE, Chan T, Waldron L, Speers C, Feng FY, Ogunwobi OO, et al. Racial/Ethnic disparities in genomic sequencing. *JAMA Oncol* (2016) 2(8):1070–4. doi: 10.1001/jamaoncol.2016.1854

60. Spratt DE. Are we inadvertently widening the disparity gap in pursuit of precision oncology? *Br J Cancer* (2018) 119(7):783–4. doi: 10.1038/s41416-018-0223-6

61. Li E, Ji P, Ouyang N, Zhang Y, Wang XY, Rubin DC, et al. Differential expression of miRNAs in colon cancer between African and Caucasian americans: Implications for cancer racial health disparities. *Int J Oncol* (2014) 45(2):587–94. doi: 10.3892/ijo.2014.2469

62. Amable L. Cisplatin resistance and opportunities for precision medicine. *Pharmacol Res* (2016) 106:27–36. doi: 10.1016/j.phrs.2016.01.001

63. Bao Y, Zhang Y, Lu Y, Guo H, Dong Z, Chen Q, et al. Overexpression of microRNA-9 enhances cisplatin sensitivity in hepatocellular carcinoma by regulating EIF5A2-mediated epithelial-mesenchymal transition. *Int J Biol Sci* (2020) 16(5):827–37. doi: 10.7150/ijbs.32460

64. Blower PE, Chung JH, Verducci JS, Lin S, Park JK, Dai Z, et al. MicroRNAs modulate the chemosensitivity of tumor cells. *Mol Cancer Ther* (2008) 7(1):1–9. doi: 10.1158/1535-7163.MCT-07-0573

65. Hipfner DR, Deeley RG, Cole SP. Structural, mechanistic and clinical aspects of MRP1. *Biochim Biophys Acta* (1999) 1461(2):359–76. doi: 10.1016/S0005-2736(99)00168-6

66. Chien TM, Chan TC, Huang SK, Yeh BW, Li WM, Huang CN, et al. Role of microtubule-associated protein 1b in urothelial carcinoma: Overexpression predicts poor prognosis. *Cancers (Basel)* (2020) 12(3):630. doi: 10.3390/cancers12030630

frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 09 June 2023
DOI 10.3389/fonc.2023.1124447

OPEN ACCESS

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RECEIVED 15 December 2022
ACCEPTED 03 May 2023
PUBLISHED 09 June 2023

CITATION
Patel SR, Suero-Abreu GA, Ai A, Ramachandran MK, Meza K and Florez N (2023) Inequity in care delivery in cardio-oncology: dissecting disparities in underrepresented populations. *Front. Oncol.* 13:1124447. doi: 10.3389/fonc.2023.1124447

Inequity in care delivery in cardio-oncology: dissecting disparities in underrepresented populations

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It is well known that patients with cancer have a significantly higher cardiovascular mortality risk than the general population. Cardio-oncology has emerged to focus on these issues including risk reduction, detection, monitoring, and treatment of cardiovascular disease or complications in patients with cancer. The rapid advances in early detection and drug development in oncology, along with socioeconomic differences, racial inequities, lack of support, and barriers to accessing quality medical care, have created disparities in various marginalized populations. In this review, we will discuss the factors contributing to disparities in cardio-oncologic care in distinct populations, including Hispanic/Latinx, Black, Asian and Pacific Islander, indigenous populations, sex and gender minorities, and immigrants. Some factors that contribute to differences in outcomes in cardio-oncology include the prevalence of cancer screening rates, genetic cardiac/oncologic risk factors, cultural stressors, tobacco exposure rates, and physical inactivity. We will also discuss the barriers to cardio-oncologic care in these communities from the racial and socioeconomic context. Appropriate and timely cardiovascular and cancer care in minority groups is a critical component in addressing these disparities, and there need to be urgent efforts to address this widening gap.

KEYWORDS

equity, cancer, cardiology, cardiooncology, cardiotoxicity, oncology

1 Introduction

A diagnosis of cancer, irrespective of the primary cancer site, is associated with an increased risk for cardiovascular death and nonfatal morbidity (1–3). Among cancer patients and survivors, cardiovascular disease (CVD) is the primary cause of death, and patients with cancer have 2-6 times higher cardiovascular (CV) mortality risk than the general population (4). A recent study among more than 7.5 million cancer patients

showed that CVD contributed to 5.24% of deaths among all cancer patients with a heart disease-specific mortality rate of 10.61/10,000-person-years. In addition, the mortality ratio of fatal heart disease among all cancer patient studied was 2.24 times that of the general population, with variability due to age, race, primary cancer type, and follow-up time (2).

Similarly, prior large retrospective studies based on the Surveillance, Epidemiology, and End Results (SEER) database have characterized CVD mortality risk in cancer patients. A study with more than 3 million patients, including 28 cancers over 40 years, found that 11.3% died from CVD. The risk of CV mortality was highest in patients diagnosed <35 years and within the first year after a cancer diagnosis. Furthermore, the mortality risk remained elevated through follow-up compared to the general population (5). Similarly, a subsequent SEER-based study with more than one million patients diagnosed with breast cancer over 17 years found a 4.6% incidence of fatal heart disease, which increased at longer follow-up comprising up to 28% of deaths from non-primary cancer at 10 years (6). Another interesting study used SEER data in nearly 5 million patients over 14 years and showed that the higher rate of cardiac death for cancer patients is not uniform in all patients and is higher for non-white ethnic groups. Specifically, the risk of cardiac death in cancer patients was 1.16% higher than in the general population, but when stratified by ethnicity, the risk was 1.76, 2.28, 3.68, 2.65, and 1.84 for Whites, Blacks, American Indians/Alaska Natives, Asians/Pacific Islanders, and Hispanic/Latinx, respectively (7). These observations highlight the elevated risk of CV mortality from the point of a cancer diagnosis into survivorship and the need for earlier and more aggressive CV care in cancer patients. As such, the field of cardio-oncology has rapidly expanded in the United States (US) and globally to address the increased heart-specific mortality risk in cancer patients.

Cardiac complications of cancer therapy include myocardial dysfunction, coronary artery disease or peripheral vascular disease, valvular disease, arrhythmias, arterial hypertension, and thromboembolism (8). These cardiotoxicities have been associated with many categories of cancer therapy and relevant data on disparities in treatment-associated cardiotoxicities are described when affecting specific populations in subsequent sections of this review. Cancer and CV disease are linked, not only through the deleterious effects of oncologic treatments on CV health but also due to common risk factors, including age, obesity, diet, alcohol, and physical activity (9, 10). Over the past decade, the range of CV toxicities has expanded due to the introduction and rapid uptake of numerous targeted therapies, immune checkpoint inhibitors, and antibody-drug conjugates (11). As the overlap between heart disease and cancer patients continues to increase, the emerging field of cardio-oncology aims to identify patients at risk of CV complications related to cancer treatments, provide early detection and intervention for CVD, and develop strategies to prevent or minimize these complications. By addressing CV risk factors and managing CVD, cancer patients may have better outcomes and quality of life. Several professional organizations, including the American College of Cardiology, the American Society of Clinical Oncology, and the European Society of Cardiology, have recognized the importance of cardio-oncology and have developed guidelines and recommendations for managing CVD in cancer patients (12, 13). Despite the field's rapid growth, there is a need to improve access to care at the local, state, and national levels and to underrepresented populations. Furthermore, there is a lack of resources about cardio-oncology within community-based oncology practices, thus, expanding into these areas is critical to provide care to significant segments of the cancer population (14).

The most common CV diagnoses in patients with cancer are hypertension (HTN), coronary artery disease (CAD), heart failure (HF), and arrhythmias. The incidence of these specific diseases in cancer patients varies depending on several factors, including the type of cancer, cancer treatment received, and preexisting CV risk factors. HTN is a common occurrence in cancer patients, with estimates of around 38% in cancer populations compared with approximately 26% of the general population (15–17). The incidence of developing CAD in cancer patients is increased compared to the general population and highest in the first six months after the initial cancer diagnosis (18–20). A study compared patients treated for breast cancer or lymphoma to age-matched controls and found that within 5 years of their cancer diagnosis, the risk of HF was 3x higher than in people without cancer. Furthermore, 10% of the survivors developed HF within 20 years compared with 6% of control subjects (21). A large-scale study assessing the bleeding risk of anticoagulation in patients with cancer found an incidence of ~20% compared to the prevalence known in the US between 1-2% (22, 23).

It is known that certain patient groups face unique challenges related to these cardiotoxicities and access to specialized cardio-oncology services. Special clinical and research efforts have been made in studying long-term CV risks of survivors of childhood cancers and monitoring the effect of this heightened risk on their CV health outcomes in adulthood. Care of elderly patients with cancer is also a unique challenge given their higher rate of co-morbidities which increase their risk of developing cancer treatment-related cardiotoxicities (24). Notably, little is known about how racial and ethnic disparities alongside structural, economic, and socioenvironmental factors impact cardio-oncology care. Particularly, access to appropriate and timely CV and cancer care by minority groups is a key element driving persistent disparities in cardio-oncology care. Existing evidence suggests that socioeconomic inequality affects the incidence, treatments, and outcomes of patients with cancer and CVD. Furthermore, a recent study highlighted the impact of social vulnerability on mortality rates in cardio-oncology patients showing worse outcomes in counties with greater social vulnerability (25, 26).

In this review, we will discuss cardio-oncological disparities in a variety of marginalized populations, including Black, Hispanic/Latinx, Asian and Pacific Islander (AAPI), indigenous populations, sex and gender minorities (SGM), rural populations, and immigrants. These populations at risk and distinct factors contributing to disparities in cardio-oncology care are outlined in Figure 1. We will expand on disparities that affect these minority groups, including the prevalence of cancer screening rates,

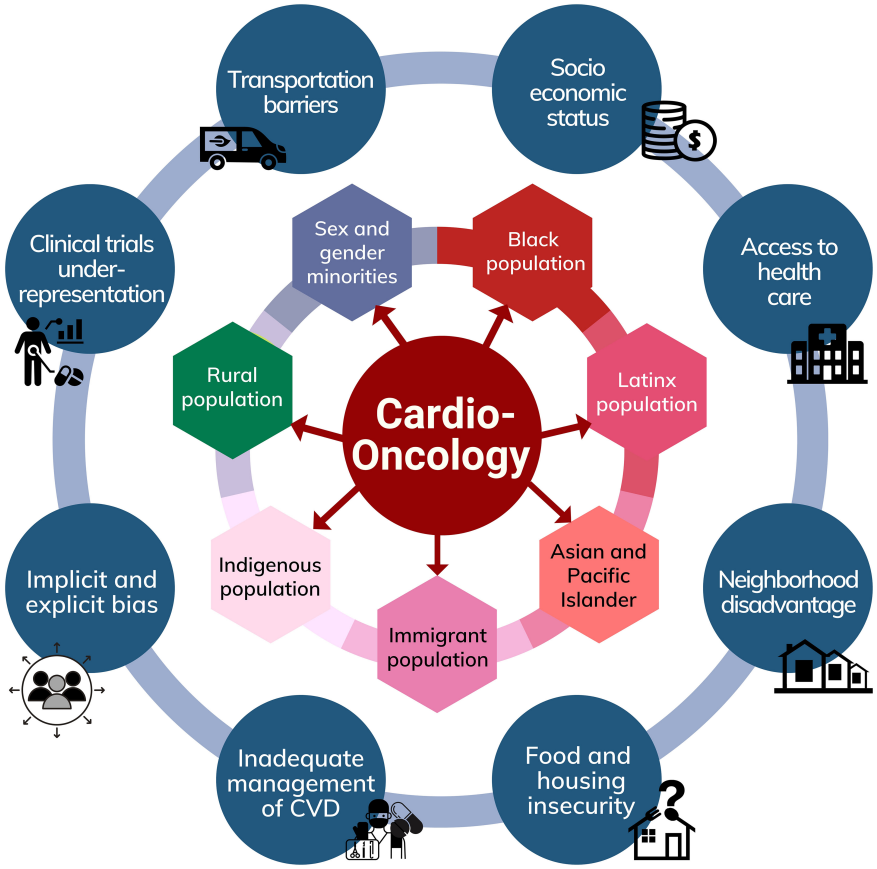

FIGURE 1
Factors contributing to disparities in Cardio-Oncology and populations at risk.

cardiometabolic and genetic risk factors, and cultural factors. We will also discuss the barriers to cardio-oncologic care in these communities arising from the racial and socioeconomic context.

There is a known association between pre-treatment CV risk factors and post-treatment cardiac dysfunction, and it is imperative to discuss these disparities to understand how it affects cardio-oncology care (27). While the prevalence of CV disease has been declining in non-Hispanic white (NHW) populations, these rates remain stable in Hispanic/Latinx, Asian, and Black population (28). The COVID-19 pandemic in the US has led to a significant increase in deaths caused by heart disease and cerebrovascular disease especially among Black, Hispanic/Latinx, and Asian populations. This suggests that these groups have been disproportionately affected by the pandemic's indirect effects (29). In Hispanic/Latinx populations, cancer is one of the leading causes of death, and these patients are diagnosed with more advanced stages of breast, lung, and colorectal cancers compared with NHW individuals (30).

Irrespective of a biological difference, these disparities in cancer outcomes are also largely influenced by structural factors such as lack of insurance, transportation issues, decreased educational attainment, financial security, and less access to high-quality preventative care or specialized services (31–33). Furthermore, these patients do not have equal access to novel, high-quality therapies and are consistently underrepresented in clinical trials (34–36). In addition, the COVID-19 pandemic delayed the diagnosis and treatment of cardiac conditions and cancer, with implications that are still unclear to date. Importantly, it also highlighted the association of race and ethnicity–based disparities in CV and cancer care delays, medical care disruptions, and concerns about crucial socioeconomic factors alongside systemic and structural racism (37).

Despite significant advances in early diagnosis, risk factor mitigation, and drug development in the cutting-edge fields of cardiology and oncology, inequities in the structural, economic, and environmental systems continue to contribute to the long-standing higher prevalence and worse outcomes due to CVD and cancer care that consequently underlie disparities in cardio-oncology care (38). We present an overview of these disparities in cardio-oncology care from the viewpoint of special populations to raise awareness of the urgent efforts needed to improve the outcomes of these patients.

2 Cardio-oncology disparities in the Hispanic/Latinx population

The Hispanic/Latinx population constitutes nearly 20% of the US population and is the second largest racial/ethnic group. Despite a considerable underestimation in the 2020 census data, the Hispanic/Latinx population reached 62 million (39). Cancer and CVD are the two leading causes of death for Hispanic/Latinx

individuals in the US (40). According to the American Cancer Society, there were 43,079 deaths due to cancer and 41,794 deaths due to heart disease among the Hispanic/Latinx population in 2019, representing 20% of total deaths (30). The mortality rates due to cancer and CVD among the Hispanic/Latinx population are impacted by social determinants of health (SDOH) and by challenges in immigration status, lack of health insurance, and healthcare bias (25, 41–44). Approximately 18 million foreign-born Hispanic/Latinx adults reside in the US, with about two-thirds being noncitizens and/or undocumented (45). Non-citizens and undocumented immigrants may not be eligible for health insurance and may lack employment opportunities that could offer it. Consequently, Hispanic/Latinx people represent a large amount of the US uninsured population at 30.1%, compared with the NHW population at 11.1% (39). Therefore, disparities in cardio-oncology care in Hispanic/Latinx patients partly stem from the impact of increased social vulnerability, low socioeconomic status, and lack of insurance, which causes barriers to accessing care and receiving timely preventive cancer and CV interventions.

For instance, there are known reduced screening rates in the Hispanic/Latinx population and, consequently, delayed diagnosis of preventable cancer such as lung, breast, and colorectal compared to NHW people (30, 44). This sometimes translates into advanced cancer stages at diagnosis and ineligibility for novel, less cardiotoxic regimens with a higher risk of cardiac dysfunction and worse patient outcomes (30, 38, 46, 47). Based on the American Heart Association report on heart disease and stroke statistics for the Hispanic/Latinx population in 2021, 52.3% of males and 42.7% of females had CVD alongside an increased burden of risk factors such as obesity (>78%), hyperlipidemia, (37%), hypertension (>40%), physician-diagnosed diabetes (15%), lifetime tobacco use (52%) and sedentarism (35%) (48, 49). For example, Puerto Ricans and Mexican individuals have more than twice the prevalence of diabetes mellitus compared with NHWs (50). Despite having higher rates of CV risk factors, the Hispanic/Latinx population in the US has lower rates of CV mortality compared to NHW Americans. The reasons for this paradox are not entirely clear, but some potential explanations include protective cultural and social factors, such as strong family ties and support, and healthy dietary habits (27). However, recent studies focused on the effect of neighborhood segregation and CVD among Hispanic/Latinx showed that county-level Hispanic/Latinx ethnic density is associated with increased CVD mortality. It also linked these areas to higher rates of uninsured individuals, fewer primary care physicians, and other adverse environmental factors (42). Similarly, in a large US population-based study, Hispanic/Latinx adults <45 years of age had higher mortality due to comorbid cancer and CVD than for either disease alone in counties with greater social vulnerability (25).

Unfortunately, there is a lack of data specific to the Hispanic/Latinx population regarding cardiotoxicity from cancer-directed therapies, and this is particularly disturbing as cancer and CV disease often co-exist in the same individual alongside other complex comorbidities (51, 52). An important element that limits our knowledge of cardiotoxicity risk specific to Hispanic/Latinx patients is that most studies report the Hispanic/Latinx population using aggregated data, which masks risk profiles and affects the accuracy of the results given their diverse demographics. More than 33 million Hispanics/Latinx in the US report two or more races in origin (53). However, this heterogeneity is not reflected in clinical studies, tailored therapies, or research on specific disease outcomes. Hispanic/Latinx patients are typically classified as a single group without distinction to their heritage, socioeconomic status, immigration pattern, and cultural characteristics. Thus, standardizing clinical care and research with disaggregation of Hispanic/Latinx subgroups will be critical to further understanding the cardiotoxicity risk profile within these groups. Another area to be further studied is the implication of specific cultural characteristics shared across the Hispanic/Latinx subgroups, such as *familismo*, *personalismo*, and strong religious values that tend to influence health behaviors and outcomes (46). For example, studies suggest that residence in close communities and *familismo*, where family members are a vital source of support with health issues, may explain why the Hispanic/Latinx population has lower mortality despite the described poor baseline cardiometabolic risk profiles (54–56). However, data shows that these cultural factors may be offset by both acculturation and duration of residence in the US, which have been associated with a negative impact on CV outcomes as more people assimilate US behaviors and diets, which may further increase the risk profile for these patients (42, 56).

There is also a chronic underrepresentation of Hispanic/Latinx people in clinical trials in cardiology and oncology (57, 58). This limits our understanding of potential biological differences related to cardiotoxicity in these populations and delays efforts for individualized care in the era of precision medicine. The lack of representation within clinical trial also delays patients ability to receive newer therapies increasing the differences in overall survival between the populations. Limited enrollment in clinical trials is attributed to several factors such as linguistic barriers, limited understanding of treatment options, inability to navigate the complex medical system, difficulties with the informed consent process, distrust of the health system, physician bias, structural racism, poor communication with their physicians, and financial concerns related to the logistical burden of trial participation (59, 60). There is a need for an intentional effort to improve Hispanic/Latinx representation in cardio-oncology trials and to promote diversification of the clinical trial workforce and leadership to increase diversity and equity in the field.

3 Cardio-oncology disparities in the Black population

The Black population is the third largest racial group in the US and represents 13.6% of the population. Black patients face significant obstacles in cancer risk reduction, early detection, and treatment and typically are diagnosed with a higher tumor burden and advanced stage. Additionally, for most cancers, Black patients have the shortest survival and highest rate of death compared to any other racial/ethnic group (61). Currently, the largest disparity in Black patients exists in uterine, stomach, prostate, and plasma cell cancers, for which death rates are twice as high in Black people (61).

Black individuals are known to have earlier onset of traditional CV risk factors due to a variety of systemic and biological factors that increases the incidence of HF, stroke and peripheral vascular disease (62). The higher prevalence of CVD linked to poorer access to primary care (63), which is ultimately linked to the fact that Black populations face a disproportionate amount of adverse social and environmental characteristics in the US. This disparity in pre-treatment cardiac function further increases the risk of cardiac dysfunction with anti-cancer therapies and patient been started in cardiotoxic therapies without prior CVD evaluation or risk assessment (64). Based on the national US cancer database, Black women with breast cancer were at a 25% greater risk of CV death compared to NHW women (65). Differences in underlying CV disease risk contribute to the difference in mortality risk, in addition to other known contributors such as social determinants of health, as Black women with breast cancer are 40% more likely to die than NHW women (66, 67). Black women also have a higher risk of triple negative breast cancer which leads to higher rates of chemotherapy and radiation, which further increases CV risk. Furthermore, Black patients with breast cancer experience more significant psychosocial stress from unmet informational, financial, and practical needs. The perceived discrimination and racism experienced by Black women have also been shown to contribute to low-grade chronic inflammation and CV disease (68).

A majority of the data on cardiotoxicity historically has been with anthracyclines and trastuzumab, although there is a growing interest in the cardio-oncology community to understand the cardiotoxicity of the newer targeted agents. A historical retrospective dataset demonstrated that Black patients treated with doxorubicin had a 3-fold higher risk of cardiotoxicity compared with non-Black patients (69). Furthermore, another study of patients with breast cancer demonstrated that Black women were greater than 2 times more likely to develop trastuzumab-related cardiotoxicity compared to NHW women, even after controlling for baseline CV risk factors (70). Furthermore, a meta-analysis across North America and European patient populations demonstrated that Black race was an independent predictor, similar to CV risk factors, of clinical and subclinical cardiotoxicity in breast cancer (71). Most of the prior cardio-oncology research in Black patients has focused on breast cancer in which clear disparities have been demonstrated, further research in other tumor types is necessary, as well as long-term follow-up data in this high-risk population. In addition to expanding research, strategies to assess and intervene in patient's needs with the addition of interdisciplinary resources are critical

4 Cardio-oncology disparities in the Asian American and Pacific Islander population

The Asian American and Pacific Islander population (AAPI) is one of the fastest-growing racial groups in the US, with a 35.5% increase in population since the 2010 census (72). While often grouped, the term Asian American encompasses a wide range of ethnicities and racial groups and is remarkably heterogeneous. In recent years, there has been a push to disaggregate data related to the Asian Pacific Islander community, as it results in misleading inflation of survival statistics for this population (65, 73–76). Currently, major registries aggregate cancer data from Asian, Native Hawaiian, and Other Pacific Islander (NHOPI) and other Asian American populations, so we will cite data as initially collected in this section. Compared to individuals from another racial or ethnic group, Asian Americans have the lowest rate of developing cancer; however, cancer is the leading cause of death for Asians in the US (73). It was found that even when census tract poverty rates are accounted for AAPI men have a lower 5-year survival rate than NHW (58). Asian Americans are disproportionately affected by cancers because of infectious origins (ex. Hepatitis-B related liver cancer) and have the highest lung cancer rates among never-smoking women (77). Regarding CV comorbidities among the AAPI community, few studies have examined the subgroups separately (78). Generally, when looking at traditional CVD risk factors, it was found that there are associations similar to those reported in NHW Americans (79), however, there is known discordance between CV risk estimates depending on racial/ethnic groups (78).

Regarding cardio-oncology specifically, Asian American and NHOPI individuals are a small percentage of clinical trial participants, which limits the information regarding side effects and toxicities in this population. In a meta-analysis of randomized control trials for CV disease, of the 45 trials identified, only 11 reported race; of that 11, only 4 of those trials reported Asian American inclusion, ranging from 1.4% to 5% (80). A recent study showed that AAPI, and Hispanic/Latinx people, had the highest relative increase in cardio-oncology mortality between the 4th and 1st social vulnerability index (SVI) quartiles compared to the other population studies (25). It is clear that further research regarding the intersection must be done.

5 Cardio-oncology disparities in the Indigenous population

The Indigenous population in the US comprises approximately 9.7 million people and is incredibly diverse, with 574 federally recognized tribes and more than 200 unrecognized tribes (39). This population has the highest racial misclassification in health data compared to other groups in the US, so any disparities are likely an underestimation (81). It is essential to put the health of the Indigenous population in the US, as with all minority groups, into a historical context. European colonization and policies on the national and state level have all contributed to the existing health disparities in the Indigenous population, which have led to large health disparities (82, 83). Cancer disproportionately affects the Indigenous population in the US (65, 84, 85). Interestingly, there are differences in cancer risk and disparities seen when comparing Indigenous people living in different regions of the US. For example, compared to the White population, the incidence rate for all cancers combined is 23% lower in the American Indian/Alaska Native (AI/AN) population living in the

Southwest but 49 percent higher in those living in the Southern Plains (86).

CVD is the second leading cause of death for the Indigenous population in the US (supplanted by COVID-19 in recent years), with over a third of CVD-related deaths occurring before the age of 65 (87). One study found that among a study population of almost 100,000 Native Americans, the prevalence of peripheral arterial disease in indigenous Americans was nearly twice the rate compared to NHW, even when controlling for atherosclerotic risk factors (88). This inequity is further exacerbated by the fact that hospitals in areas that serve indigenous populations often lack specialized services such as cardio-oncology. A recent scientific statement from the American Heart Association emphasized the need and importance of future studies and interventions to reduce and eliminate inequities faced by the Indigenous population of the US (89).

6 Cardio-oncology disparities in sex and gender minorities

The number of individuals identifying as part of a sexual and gender identity minority (SGM) is growing. The most recent projections estimate roughly 7.1% of the US adult and pediatric population identifying as lesbian, gay, bisexual, or trans* (LGBT), up from 3.5% in 2012 (90). Given the stigma associated with identifying as SGM and structural inequalities, it is often thought that these numbers are an underestimation of the actual population of SGM in the US (91). Unfortunately, data regarding cancer incidence, outcomes, and treatment responses for SGM people is sparse. Similarly, there is a large gap in understanding CV disease relating to the SGM community (92). Despite the paucity of research, it is clear that SGM populations face disparities relating to care due to experiencing multiple barriers to receiving health care (93). For example, lesbian and bisexual females are more likely to have difficulty accessing care with a regular provider than heterosexual females (94). Other potential barriers to adequate health care for LGB individuals are implicit bias and overt discrimination during health care encounters, which may lower trust in health care providers and the health care system (94, 95).

There are known cancer disparities in SGM communities, which include increased rates of melanoma in cisgender gay men and increased rates of Kaposi sarcoma, lymphomas, and anal cancer in those populations at increased risk for HIV infection, including cisgender gay men and transgender women (96). Additionally, as cross-sex hormones administered for gender affirmation may be delivered at high doses over decades, the carcinogenicity and cardiotoxicity of hormonal therapy in transgender people is an area of continued research. Outside of these specific disparities, however, there is still much to learn.

Similarly, there is evidence that within the CV disease space, there are disparities related to the LGBTQ population, which was recently called to attention by the American Heart Association. When examining risk factors for CV health, sexual minority women exhibited greater CVD risk related to tobacco use, alcohol consumption, illicit drug use, poor mental health, and body mass index. In contrast, sexual minority men experienced excess risk related to tobacco use, illicit drug use, and poor mental health (97, 98). While the SGM group has often been examined as a monolith, there have been increased efforts to parse out variations in CVD risk by the sex assigned at birth, gender identity, sexual orientation, and race (92). One area of interest is the relationship between gender-affirming therapy and CVD (99). When examining from a lens of cardio-oncology space, minimal data exists, and further research is needed to expand appropriate care to this expanding population.

7 The impact of immigration status on disparities in immigrant populations

The term immigrant is defined as a person who comes to a country to establish permanent residence. In the U.S. immigration law, "immigrant" means explicitly those inspected and admitted as lawful permanent residents (100). Notably, this technical definition may underestimate population-data analysis of the total foreign-born population present in the US based on limited information on the legal status. Typically, it does not include the institutionalized population, which is primarily people in nursing homes and prisons. Immigrants will be denoted in this paper based on the Census Bureau definition, including three principal legal-status groups (naturalized citizens, legal permanent residents, and undocumented immigrants). Based on the Census Bureau's monthly Current Population Survey (CPS) by the Center for Immigration Studies, the total foreign-born or immigrant population in the US reached 47.9 million in September 2022. This represents 14.6 percent of the US population or one in seven US residents and an increase of 2.9 million since January 2021. This is also one of the largest numbers in the US government census compared to the high records reached in 1890 and 1910 (101). Immigrants are considered a vulnerable population, but there is heterogeneity among the different ethnic and socioeconomic groups and language barriers, which relates to the degree to which they are vulnerable to inadequate health care (100). Most of the studies on immigrants and health care have focused on Hispanic/Latinx people as one of the largest immigrant groups, followed by Asians (a term that masks great ethnic diversity) and, more recently, on Black and Black/Caribbean immigrants. Across these groups, many similar factors influence inadequate health care in immigrant populations affecting their CV and cancer care and consequently increases disparities in cardio-oncology (102, 103). These factors include socioeconomic background; immigration status; food and housing insecurity, language barriers; lack of access to federal, state, and local policies on health care services; residential segregation; neighborhood disadvantage, marginalization, and stigma (104, 105). Of the 47.9 million immigrants in the country in September, 18.5 million were unemployed. This certainly correlates with immigrants having lower rates of health insurance, less access to health care, and ultimately receiving a lower quality of care than US-born populations. Furthermore, it is estimated that immigrants from Latin American countries other than Mexico

represent about 60 percent and undocumented immigrants account for 61 percent (approximately 1.8 million) of the growth in the foreign-born population since January 2021 (101). Unfortunately, the number of undocumented immigrants is likely to continue to grow, given the current restrictions and delays in immigration policy which were aggravated in recent years and during the pandemic. In addition, deportation policies in the US may influence undocumented immigrants and their families hesitant to seek medical care. Many immigrants are relatively young and healthy when arriving to the US to work, and there is evidence of better health outcomes than their U.S.-born counterparts. However, immigrants' health worsens over time, likely due to acculturation and poor access to care (56). Health policies at a local and federal level can help address the factors that increase these inequities in CV, oncological, and cardio-oncological care. These can be related at the intersection of health, immigration, and employment laws that ensure access to housing, living wages, education, and healthcare for these vulnerable patients.

8 Cardio-oncology disparities in the rural population

As a new subspecialty, cardio-oncology care is localized in urban areas at large academic institutions. This leads to significant disparities in cardio-oncology care for rural populations due to decreased access to tertiary care sites and the benefits of subspecialty care, testing, and clinical trial enrollment. The International Cardio-Oncology Society registry shows 21 countries with national cardio-oncology programs, and 81% of centers are in upper-middle to high-income countries (106). A study of oncologists in the central US showed 67.5% practiced in exclusively urban locations, 11.3% in exclusively rural locations, and 21.1% in both rural and urban locations (107). Per 2010 US Census Bureau data, 19.3% of the population is rural (108) and therefore may not have local access to specialized cardio-oncology care. One study showed that mean travel time for medical care for rural patients is 3 times longer *vs.* urban patients (128.9 min *vs.* 41.5 min, $p<0.001$) (109). Reduced access to care may then result in worse outcomes. Multiple studies in Europe and the US have demonstrated that both increased geographic distance and travel time were independently associated with worse outcomes (110, 111).

A qualitative study in rural Scotland that explored patients' perspectives on disparities in oncologic care demonstrated that transportation is a major issue (112). American Community Survey data from 2020 showed that 1.6 million rural households do not have access to cars (113). Given the higher poverty levels and hospital closures in these pockets located in the South, Appalachia, the Southwest, and Alaska, many rural patients do not have access to tertiary care hospitals or specialized cardio-oncology care. It is well-established that close and early collaboration between cardiologists, oncologists, and primary care providers achieves higher rates of cardiac optimization and support of optimal cancer treatment and survival (114). Since rural residents have limited access to specialists, and the burden of managing patients undergoing active cancer treatment falls on the primary care provider or the rural oncologist without specialized training in cardio-oncology, which may result in worse outcomes (115). Furthermore, rural patients are underrepresented in clinical trials, which offer novel treatments essential to high-quality cancer care. Most trials are run at urban academic centers with large catchment areas, and rural patients have decreased interest in clinical trials due to financial and transportation barriers (116). Thus, it is crucial to engage in interinstitutional efforts such as connecting community-based cancer centers in rural areas to larger specialists from large academic centers as a gateway to cardio-oncology care and access to novel treatments and trials. This in turn, could also help with more inclusive recruitment of populations that are typically underrepresented in clinical trials

9 Social and financial disparities in cardio-oncology care

Social and financial disparities are multifaceted in the highly complex cardio-oncology patient population. CVD and cancer share many risk factors influenced by the social determinants of health (SDOH). And when these two chronic conditions co-exist, there is a cumulative effect in the disparities in medical care and the economic hardship faced by patients and their families (117). Low socioeconomic status, racial inequities, lack of support, and barriers to accessing quality medical care have been associated with increased death and CV co-morbidities. Due to limited access to insurance and follow-up care, patients from immigrant and underserved groups historically have increased CVD at baseline and have advanced cancer stages at the time of diagnosis, requiring more cardiotoxic regimens and close surveillance with specialized cardio-oncology care (118, 119). However, the geographic availability of cardio-oncology centers is mainly limited to academic institutions in major cities, which tend to be more challenging to access by these patients of lower socioeconomic status and those without health insurance. Even in large academic centers, appointment availability is sparse and patients often wait months prior to being seen by a specialist in cardio-oncology. Additional barriers to access to care and focused surveillance include the availability of transportation and the ability to attend medical appointments relative to employment status and job flexibility, which are often more difficult for patients of lower socioeconomic backgrounds and minority populations. In addition, there is a higher psychological burden related to financial distress linked with cardio-oncology care in these populations due to the inability to pay medical bills, cost-related delayed care, medication non-adherence, and food and job insecurity.

Economic hardship due to chronic illness has long-term consequences, with cancer being one of the most cited reasons for medical cost-associated bankruptcy in the US (120, 121). There are also population-level disparities in equitable access to specialized care and affordable diagnostic procedures and treatments (37, 122).

Understanding the intersection of race, ethnicity, and these socioeconomic disparities is crucial. Furthermore, there are institution-level disparities as patients with challenges due to low income or lack of health insurance tend to receive care in public or safety net hospitals with limited specialized services. There is a need to determine quality metrics in the systems of care for cardio-oncology patients within and between institutions and how this relates to SDOH to improve patient outcomes for all communities, particularly those from underrepresented racial, ethnic, and lower socioeconomic backgrounds.

10 Strategies and future directions

A multi-pronged approach is critical to address disparities in the abovementioned populations. Additionally, each group has unique challenges that need to be overcome to achieve equity in the delivery of cardio-oncology care. It is critical that community and healthcare-based efforts are started promptly while research-based efforts are continued to find ways to ensure sustained and long-term equity. Some solutions for improvement on a community and healthcare level include expanding government-sponsored insurance and support programs nationwide to help facilitate access to high-quality and specialized cardio-oncology centers. This can potentially assist at-risk and underserved populations in addressing financial barriers such as coverage for diagnostic studies, medications, and services, as well as reduce issues surrounding care access such as transportation, missed workdays, and childcare. It is vital to design studies and interventions that define, screen for, and mitigate the financial consequences of cardio-oncology care through financial navigation plans. However, further investigation is needed to develop effective policies and methods at a system level focused on value-based care and lower financial burden on cardio-oncology patients, as well as to better understand the unique challenges faced by underrepresented and underserved populations in accessing cardio-oncology care.

While some studies have assessed the socioeconomic factors influencing financial hardship in patients (123–125), there is a need to move toward integrating specific methods and policies at a system level. Furthermore, patients from underrepresented and underserved populations, such as immigrants that could be non-English speakers or undocumented, face heightened challenges that require adequate assistance to fully understand the complex medical and financial issues in accessing cardio-oncology care. Promoting a diversified physician workforce and engaging community health workers with language and cultural experience can help bridge the existing gap and provide guidance to culturally specific resources available to these communities.

It is also key to increase awareness of the multiple social and financial inequities in cardio-oncology care. Advocacy efforts from stakeholders are crucial to developing pathways that provide optimal care while supporting patients in these areas of inequity. Addressing SDOH and the financial toxicity due to chronic CV and cancer care can help improve patient outcomes and enable the participation of underserved minorities in clinical trials in cardio-oncology.

Author contributions

Study conception and design: SP, GS-A, and NF; data collection, analysis, and interpretation of results: SP, GS-A, AA, and MR; draft manuscript preparation: SP, GS-A, AA, MR, and NF. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. *JAMA Oncol* (2019) 5(12):1749–68. doi: 10.1001/JAMAONCOL.2019.2996

2. Stoltzfus KC, Zhang Y, Sturgeon K, Sinoway LI, Trifiletti DM, Chinchilli VM, et al. Fatal heart disease among cancer patients. *Nat Commun* (2020) 11(1). doi: 10.1038/S41467-020-15639-5

3. Paterson DI, Wiebe N, Cheung WY, Mackey JR, Pituskin E, Reiman A, et al. Incident cardiovascular disease among adults with cancer: a population-based cohort study. *JACC CardioOncol* (2022) 4(1):85–94. doi: 10.1016/J.JACCAO.2022.01.100

4. Herrmann J. From trends to transformation: where cardio-oncology is to make a difference. *Eur Heart J* (2019) 40(48):3898–900. doi: 10.1093/EURHEARTJ/EHZ781

5. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J* (2019) 40(48):3889–97. doi: 10.1093/EURHEARTJ/EHZ766

6. Agha A, Wang X, Wang M, Lehrer EJ, Horn SR, Rosenberg JC, et al. Long-term risk of death from heart disease among breast cancer patients. *Front Cardiovasc Med* (2022) 9:784409/BIBTEX. doi: 10.3389/FCVM.2022.784409/BIBTEX

7. Gad MM, Saad AM, Al-Husseini MJ, Abushouk AI, Salahia S, Rehman KA, et al. Temporal trends, ethnic determinants, and short-term and long-term risk of cardiac death in cancer patients: a cohort study. *Cardiovasc Pathol* (2019) 43. doi: 10.1016/J.CARPATH.2019.08.001

8. Chang HM, Okwuosa TM, Scarabelli T, Moudgil R, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 2. *J Am Coll Cardiol* (2017) 70(20):2552–65. doi: 10.1016/J.JACC.2017.09.1095

9. Johnson CB, Davis MK, Law A, Sulpher J. Shared risk factors for cardiovascular disease and cancer: implications for preventive health and clinical care in oncology patients. *Can J Cardiol* (2016) 32(7):900–7. doi: 10.1016/J.CJCA.2016.04.008

10. Barac A, Murtagh G, Carver JR, Chen MH, Freeman AM, Herrmann J, et al. Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. *J Am Coll Cardiol* (2015) 65(25):2739–46. doi: 10.1016/J.JACC.2015.04.059

11. Hahn VS, Zhang KW, Sun L, Narayan V, Lenihan DJ, Ky B. Heart failure with targeted cancer therapies. *Circ Res* (2021) 128(10):1576–93. doi: 10.1161/CIRCRESAHA.121.318223

12. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol* (2020) 31(2):171–90. doi: 10.1016/J.ANNONC.2019.10.023

13. Lyon AR, López-Fernánde T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. ESC Guidelines on cardio-oncology developed in collaboration with the European hematology association (EHA), the European society for therapeutic radiology and oncology (ESTRO) and the international cardio-oncology society (IC-OS)Developed by the task force on cardio-oncology of the European society of cardiology (ESC). *Eur Heart J* (2022) 43(41):4229–361. doi: 10.1093/EURHEARTJ/EHAC244

14. Sadler D, Arnold A, Herrmann J, Daniele A, Silva CMPDC, Ghosh AK, et al. Reaching across the aisle: cardio-oncology advocacy and program building. *Curr Oncol Rep* (2021) 23(6). doi: 10.1007/S11912-021-01059-1

15. Fraeman KH, Nordstrom BL, Luo W, Landis SH, Shantakumar S. Incidence of new-onset hypertension in cancer patients: a retrospective cohort study. *Int J Hypertens* (2013) 2013. doi: 10.1155/2013/379252

16. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* (2004) 291 (20):2441–7. doi: 10.1001/JAMA.291.20.2441

17. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* (2005) 365(9455):217–23. doi: 10.1016/S0140-6736(05)17741-1

18. Strongman H, Gadd S, Matthews A, Mansfield KE, Stanway S, Lyon AR, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. *Lancet* (2019) 394(10203):1041. doi: 10.1016/S0140-6736(19)31674-5

19. Velders MA, Hagström E, James SK. Temporal trends in the prevalence of cancer and its impact on outcome in patients with first myocardial infarction: a nationwide study. *J Am Heart Assoc* (2020) 9(4). doi: 10.1161/JAHA.119.014383

20. Lange SA, Reinecke H. Coronary artery disease and cancer: treatment and prognosis regarding gender differences. *Cancers (Basel)* (2022) 14(2). doi: 10.3390/CANCERS14020434

21. Larsen CM, Garcia Arango M, Dasari H, Arciniegas Calle M, Adjei E, Rico Mesa J, et al. Association of anthracycline with heart failure in patients treated for breast cancer or lymphoma, 1985-2010. *JAMA Netw Open* (2023) 6(2):e2254669. doi: 10.1001/JAMANETWORKOPEN.2022.54669

22. Vedovati MC, Giustozzi M, Verdecchia P, Pierpaoli L, Conti S, Verso M, et al. Patients with cancer and atrial fibrillation treated with doacs: a prospective cohort study. *Int J Cardiol* (2018) 269:152–7. doi: 10.1016/J.IJCARD.2018.07.138

23. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* (2001) 285(18):2370–5. doi: 10.1001/JAMA.285.18.2370

24. Ruddy KJ, Patel SR, Higgins AS, Armenian SH, Herrmann J. Cardiovascular health during and after cancer therapy. *Cancers* (2020) 12(12):3737. doi: 10.3390/CANCERS12123737

25. Ganatra S, Dani SS, Kumar A, Khan SU, Wadhera R, Neilan TG, et al. Impact of social vulnerability on comorbid cancer and cardiovascular disease mortality in the united states. *JACC CardioOncol* (2022) 4(3):326–37. doi: 10.1016/J.JACCAO.2022.06.005

26. Alcaraz KI, Wiedt TL, Daniels EC, Yabroff KR, Guerra CE, Wender RC. Understanding and addressing social determinants to advance cancer health equity in the united states: a blueprint for practice, research, and policy. *CA Cancer J Clin* (2020) 70(1):31–46. doi: 10.3322/CAAC.21586

27. Fazal M, Malisa J, Rhee JW, Witteles RM, Rodriguez F. Racial and ethnic disparities in cardio-oncology: a call to action. *Cardio Oncol* (2021) 3(2):201–4. doi: 10.1016/J.JACCAO.2021.05.001

28. *Center for health statistics n. racial and ethnic disparities in heart disease* . Available at: https://www.cdc.gov/nchs/hus/spotlight/HeartDiseaseSpotlight_2019_0404.pdf (Accessed April 25, 2023).

29. Wadhera RK, Figueroa JF, Rodriguez F, Liu M, Tian W, Kazi DS, et al. Racial and ethnic disparities in heart and cerebrovascular disease deaths during the COVID-19 pandemic in the united states. *Circulation* (2021) 143:2346–54. doi: 10.1161/CIRCULATIONAHA.121.054378

30. Miller KD, Ortiz AP, Pinheiro PS, Bandi P, Minihan A, Fuchs HE, et al. Cancer statistics for the US Hispanic/Latino population, 2021. *CA Cancer J Clin* (2021) 71 (6):466–87. doi: 10.3322/CAAC.21695

31. Zavala VA, Bracci PM, Carethers JM, Carvajal-Carmona L, Coggins NB, Cruz-Correa MR, et al. Cancer health disparities in racial/ethnic minorities in the united states. *Br J Cancer* (2020) 124:2. doi: 10.1038/s41416-020-01038-6

32. Jiang C, Deng L, Wang Q, Perimbeti S, Han X. Transportation barriers to health care and mortality risk among the U.S. adults with history of cancer. *J Clin Oncol* (2021) 39(28_suppl):121–1. doi: 10.1200/JCO.2020.39.28_SUPPL.121

33. Albano JD, Ward E, Jemal A, Anderson R, Cokkinides VE, Murray T, et al. Cancer mortality in the united states by education level and race. *J Natl Cancer Inst* (2007) 99(18):1384–94. doi: 10.1093/JNCI/DJM127

34. Armenian SH, Sun CL, Shannon T, Mills G, Francisco L, Venkataraman K, et al. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. *Blood* (2011) 118(23):6023. doi: 10.1182/BLOOD-2011-06-358226

35. Morris AM, Rhoads KF, Stain SC, Birkmeyer JD. Understanding racial disparities in cancer treatment and outcomes. *J Am Coll Surg* (2010) 211(1):105–13. doi: 10.1016/J.JAMCOLLSURG.2010.02.051

36. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol* (2017) 35(8):893–911. doi: 10.1200/JCO.2016.70.5400

37. Patel MI, Ferguson JM, Castro E, Pereira-Estremera CD, Armaiz-Peña GN, Duron Y, et al. Racial and ethnic disparities in cancer care during the COVID-19 pandemic. *JAMA Netw Open* (2022) 5(7):e2222009–e2222009. doi: 10.1001/JAMANETWORKOPEN.2022.22009

38. Ohman RE, Yang EH, Abel ML. Inequity in cardio-oncology: identifying disparities in cardiotoxicity and links to cardiac and cancer outcomes. *J Am Heart Assoc* (2021) 10(24). doi: 10.1161/JAHA.121.023852

39. *U.S. census bureau QuickFacts: united states* . Available at: https://www.census.gov/quickfacts/fact/table/US/PST045221 (Accessed December 13, 2022).

40. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* (2022) 72(1):7–33. doi: 10.3322/CAAC.21708

41. Khan SU, Lone AN, Yedlapati SH, Dani SS, Khan MZ, Watson KE, et al. Cardiovascular disease mortality among Hispanic versus non-Hispanic white adults in the united states, 1999 to 2018. *J Am Heart Assoc* (2022) 11(7):22857. doi: 10.1161/JAHA.121.022857

42. Rodriguez F, Hu J, Kershaw K, Hastings KG, López L, Cullen MR, et al. County-level Hispanic ethnic density and cardiovascular disease mortality. *J Am Heart Association: Cardiovasc Cerebrovascular Disease* (2018) 7(19). doi: 10.1161/JAHA.118.009107

43. Pichardo MS, Pichardo CM, Talavera GA, Gallo LC, Castañeda SF, Sotres-Alvarez D, et al. Neighborhood segregation and cancer prevention guideline adherence in US Hispanic/Latino adults: results from the HCHS/SOL. *Front Oncol* (2022) 12:1024572/BIBTEX. doi: 10.3389/FONC.2022.1024572/BIBTEX

44. Olazagasti C, Ehrlich M, Seetharamu N. One size does not fit all: evaluating disparities in lung cancer screening eligibility amongst the Hispanic population. *Front Oncol* (2022) 12:995408/BIBTEX. doi: 10.3389/FONC.2022.995408/BIBTEX

45. *U.S. unauthorized immigration total lowest in a decade | pew research center* . Available at: https://www.pewresearch.org/hispanic/2018/11/27/u-s-unauthorized-immigrant-total-dips-to-lowest-level-in-a-decade/ (Accessed December 13, 2022).

46. Suero-Abreu GA, Patel S, Duma N. Disparities in cardio-oncology care in the Hispanic/Latinx population. *JCO Oncol Pract* (2022) 18(5):404–9. doi: 10.1200/op.22.00045

47. Prasad P, Branch M, Asemota D, Elsayed R, Addison D, Brown SA. Cardio-oncology preventive care: racial and ethnic disparities. *Curr Cardiovasc Risk Rep* (2020) 14(10). doi: 10.1007/s12170-020-00650-8

48. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics - 2021 update: a report from the American heart association. *Circulation* (2021) 143(8). doi: 10.1161/CIR.0000000000000950

49. *National diabetes statistics report | diabetes | CDC* . Available at: https://www.cdc.gov/diabetes/data/statistics-report/index.html (Accessed April 14, 2023).

50. Swenson CJ, Trepka MJ, Rewers MJ, Scarbro S, Hiatt WR, Hamman RF. Cardiovascular disease mortality in hispanics and non-Hispanic whites. *Am J Epidemiol* (2002) 156(10). doi: 10.1093/aje/kwf140

51. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/CAAC.21654

52. Lau ES, Paniagua SM, Liu E, Jovani M, Li SX, Takvorian K, et al. Cardiovascular risk factors are associated with future cancer. *JACC CardioOncol* (2021) 3(1). doi: 10.1016/j.jaccao.2020.12.003

53. Khubba S, Heim K, Hong J. *National census coverage estimates for people in the united states by demographic characteristics 2020 post-enumeration survey estimation report*. (2020). Available at: https://www2.census.gov/programs-surveys/decennial/coverage-measurement/pes/national-census-coverage-estimates-by-demographic-characteristics.pdf. (Last accessed May 2023).

54. Daviglus ML, Talavera GA, Avilés-Santa ML, Allison M, Cai J, Criqui MH, et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the united states. *JAMA* (2012) 308(17):1775–84. doi: 10.1001/JAMA.2012.14517

55. Diaz CL, Shah NS, Lloyd-Jones DM, Khan SS. State of the nation's cardiovascular health and targeting health equity in the united states: a narrative review. *JAMA Cardiol* (2021) 6(8):963–70. doi: 10.1001/JAMACARDIO.2021.1137

56. Rodriguez CJ, Allison M, Daviglus ML, Isasi CR, Keller C, Leira EC, et al. Status of cardiovascular disease and stroke in hispanics/latinos in the united states: a science advisory from the american heart association. *Circulation* (2014) 130(7):593–625. doi: 10.1161/CIR.0000000000000071/FORMAT/EPUB

57. Duma N, Aguilera JV, Paludo J, Haddox CL, Gonzalez Velez M, Wang Y, et al. Representation of minorities and women in oncology clinical trials: review of the past 14 years. *J Oncol Pract* (2018) 14(1). doi: 10.1200/JOP.2017.025288

58. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer disparities by Race/Ethnicity and socioeconomic status. *CA Cancer J Clin* (2004) 54(2). doi: 10.3322/canjclin.54.2.78

59. Allison K, Patel D, Kaur R. Assessing multiple factors affecting minority participation in clinical trials: development of the clinical trials participation barriers survey. *Cureus* (2022). doi: 10.7759/cureus.24424

60. Fisher JA, Kalbaugh CA. Challenging assumptions about minority participation in US clinical research. *Am J Public Health* (2011) 101(12). doi: 10.2105/AJPH.2011.300279

61. Giaquinto AN, Miller KD, Tossas KY, Winn RA, Jemal A, Siegel RL. Cancer statistics for African American/Black people 2022. *CA Cancer J Clin* (2022) 72(3):202–29. doi: 10.3322/CAAC.21718

62. Carnethon MR, Pu J, Howard G, Albert MA, Anderson CAM, Bertoni AG, et al. Cardiovascular health in African americans: a scientific statement from the American heart association. *Circulation* (2017) 136(21):e393–423. doi: 10.1161/CIR.0000000000000534

63. Khatib R, Glowacki N, Lauffenburger J, Siddiqi A. Race/Ethnic differences in atherosclerotic cardiovascular disease risk factors among patients with hypertension: analysis from 143 primary care clinics. *Am J Hypertens* (2021) 34(9):948. doi: 10.1093/AJH/HPAB053

64. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the north central cancer treatment group N9831 adjuvant breast cancer trial. *J Clin Oncol* (2008) 26(8):1231–8. doi: 10.1200/JCO.2007.13.5467

65. Sengupta R, Honey K. AACR cancer disparities progress report 2020: achieving the bold vision of health equity for racial and ethnic minorities and other underserved populations. *Cancer Epidemiol Biomarkers Prev* (2020) 29(10):1843. doi: 10.1158/1055-9965.EPI-20-0269/351510/P/AACR-CANCER-DISPARITIES-PROGRESS-REPORT-2020

66. Howlader N, Noone A, Krapcho M, et al. *Cancer statistics review, 1975-2018 - SEER statistics* (2020). Available at: https://seer.cancer.gov/archive/csr/1975_2018/ (Accessed December 14, 2022).

67. Agurs-Collins T, Dunn BK, Browne D, Johnson KA, Lubet R. Epidemiology of health disparities in relation to the biology of estrogen receptor-negative breast cancer. *Semin Oncol* (2010) 37(4):384–401. doi: 10.1053/J.SEMINONCOL.2010.05.002

68. Conway-Phillips R, Dagadu H, Motley D, Shawahin L, Janusek LW, Klonowski S, et al. Qualitative evidence for resilience, stress, and ethnicity (RiSE): a program to address race-based stress among black women at risk for cardiovascular disease. *Complement Ther Med* (2020) 48:102277. doi: 10.1016/J.CTIM.2019.102277

69. Hasan SP, Dinh K, Lombardo F, Kark J. Doxorubicin cardiotoxicity in African americans. *J Natl Med Assoc* (2004) 96(2):196.

70. Litvak A, Batukbhai B, Russell SD, Tsai HL, Rosner GL, Jeter SC, et al. Racial disparities in the rate of cardiotoxicity of HER2-targeted therapies among women with early breast cancer. *Cancer* (2018) 124(9):1904–11. doi: 10.1002/CNCR.31260

71. Lotrionte M, Biondi-Zoccai G, Abbate A, Lanzetta G, D'Ascenzo F, Malavasi V, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Cardiol* (2013) 112(12):1980–4. doi: 10.1016/j.amjcard.2013.08.026

72. Bureau UC. *Asian American And pacific islander heritage month*. (2022). Available at: https://www.census.gov/newsroom/facts-for-features/2022/asian-american-pacific-islander.html#:~:text=Asian%20American%20and%20Pacific%20Islander%20Heritage%20Month%3A%20May%202022. (Last accessed May 2023).

73. Chen MS, Lee RJ, Madan RA, Ta Park V, Shinagawa SM, Sun T, et al. Charting a path towards Asian American cancer health equity: a way forward. *JNCI J Natl Cancer Institute* (2022) 114(6):792. doi: 10.1093/JNCI/DJAC055

74. Pinheiro PS, Morris CR, Liu L, Bungum TJ, Altekruse SF. The impact of follow-up type and missed deaths on population-based cancer survival studies for hispanics and asians. *J Natl Cancer Inst Monogr* (2014) 2014(49):210. doi: 10.1093/JNCIMONOGRAPHS/LGU016

75. Taparra K, Harding M, Deville C. Healing and health equity for Asian American, native Hawaiian, and pacific islander populations. *JAMA* (2021) 326 (23):2432–3. doi: 10.1001/jama.2021.19243

76. Quint JJ, Van Dyke ME, Maeda H, Worthington JK, Dela Cruz MR, Kaholokula JK, et al. Disaggregating data to measure racial disparities in COVID-19 outcomes and guide community response {[/amp]]mdash; Hawaii, march 1, 2020–February 28, 2021. *MMWR Morb Mortal Wkly Rep* (2021) 70(37). doi: 10.15585/mmwr.mm7037a1

77. Torre LA, Sauer AMG, Chen MS, Kagawa-Singer M, Jemal A, Siegel RL. Cancer statistics for Asian americans, native hawaiians, and pacific islanders, 2016: converging incidence in males and females. *CA Cancer J Clin* (2016) 66(3). doi: 10.3322/caac.21335

78. Palaniappan LP, Araneta MRG, Assimes TL, Barrett-Connor EL, Carnethon MR, Criqui MH, et al. Call to action: cardiovascular disease in Asian americans: a science advisory from the American heart association. *Circulation* (2010) 122(12). doi: 10.1161/CIR.0b013e3181f22af4

79. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* (2008) 118(25). doi: 10.1161/CIRCULATIONAHA.108.790048

80. Minocher Homji RS, Lakhoo S, Ray JG. Recruitment of immigrant and ethnic minorities in primary prevention trials of cardiovascular disease. *QJM* (2011) 104(6). doi: 10.1093/qjmed/hcr027

81. Jim MA, Arias E, Seneca DS, Hoopes MJ, Jim CC, Johnson NJ, et al. Racial misclassification of American indians and Alaska natives by Indian health service contract health service delivery area. *Am J Public Health* (2014) 104(SUPPL. 3). doi: 10.2105/AJPH.2014.301933

82. Gone JP, Hartmann WE, Pomerville A, Wendt DC, Klem SH, Burrage RL. The impact of historical trauma on health outcomes for indigenous populations in the USA and Canada: a systematic review. *Am Psychol* (2019) 74(1). doi: 10.1037/amp0000338

83. Jones DS. The persistence of American Indian health disparities. *Am J Public Health* (2006) 96(12). doi: 10.2105/AJPH.2004.054262

84. Guadagnolo BA, Cina K, Helbig P, Molloy K, Reiner M, Cook EF, et al. Assessing cancer stage and screening disparities among native American cancer patients. *Public Health Rep* (2009) 124(1). doi: 10.1177/003335490912400111

85. Guadagnolo BA, Petereit DG, Coleman N. Cancer care access and outcomes for American Indian populations in the US: challenges and models for progressdoi: 10.1016/j.semradonc.2016.11.006

86. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019 (US statistics). *CA Cancer J Clin* (2019) 69(1):7–34. doi: 10.3322/caac.21551

87. *FastStats - health of American Indian or Alaska native population* . Available at: https://www.cdc.gov/nchs/fastats/american-indian-health.htm (Accessed December 14, 2022).

88. Baxter AR, Jacobowitz GR, Guo Y, Maldonado T, Adelman MA, Berger JS, et al. Increased prevalence of moderate and severe peripheral arterial disease in the American Indian (AI)/Alaskan native (AN) population; a study of 96,000 AI/AN. In: *Annals of vascular surgery*. (2017) 38:e948–59. doi: 10.1016/j.avsg.2016.08.002

89. Breathett K, Sims M, Gross M, Jackson EA, Jones EJ, Navas-Acien A, et al. Cardiovascular health in American indians and Alaska natives: a scientific statement from the American heart association. *Circulation* (2020) 46(5):1–11. doi: 10.1161/CIR.0000000000000773

90. *LGBT identification in U.S. ticks up to 7.1%* . Available at: https://news.gallup.com/poll/389792/lgbt-identification-ticks-up.aspx (Accessed December 14, 2022).

91. Caba AE, Mallory AB, Simon KA, Rathus T, Watson RJ. Complex outness patterns among sexual minority youth: a latent class analysis. *J Youth Adolesc* (2022) 51 (4). doi: 10.1007/s10964-022-01580-x

92. Caceres BA, Streed CG, Corliss HL, Lloyd-Jones DM, Matthews PA, Mukherjee M, et al. Assessing and addressing cardiovascular health in LGBTQ adults: a scientific statement from the American heart association. *Circulation* (2020) 142(19). doi: 10.1161/CIR.0000000000000914

93. Domogauer J, Cantor T, Quinn G, Stasenko M. Disparities in cancer screenings for sexual and gender minorities. *Curr Probl Cancer* (2022). doi: 10.1016/j.currproblcancer.2022.100858

94. Sabin JA, Riskind RG, Nosek BA. Health care providers' implicit and explicit attitudes toward lesbian women and gay men. *Am J Public Health* (2015) 105(9). doi: 10.2105/AJPH.2015.302631

95. Tracy JK, Lydecker AD, Ireland L. Barriers to cervical cancer screening among lesbians. *J Womens Health (Larchmt)* (2010) 19(2). doi: 10.1089/jwh.2009.1393

96. Braun H, Nash R, Tangpricha V, Brockman J, Ward K, Goodman M. Cancer in transgender people: evidence and methodological considerations. *Epidemiol Rev* (2017) 39(1). doi: 10.1093/epirev/mxw003

97. Caceres BA, Brody A, Luscombe RE, Primiano JE, Marusca P, Sitts EM, et al. A systematic review of cardiovascular disease in sexual minorities. *Am J Public Health* (2017) 107(4):e13. doi: 10.2105/AJPH.2016.303630

98. Streed C, Caceres B, Mukherjee M. Preventing cardiovascular disease among sexual and gender minority persons. *Heart* (2021) 107(13). doi: 10.1136/heartjnl-2021-319069

99. Streed CG, Harfouch O, Marvel F, Blumenthal RS, Martin SS, Mukherjee M. Cardiovascular disease among transgender adults receiving hormone therapy: a narrative review. *Ann Intern Med* (2017) 167(4). doi: 10.7326/M17-0577

100. Gimeno-Feliu LA, Calderón-Larrañaga A, DÍaz E, Laguna-Berna C, Poblador-Plou B, Coscollar-Santaliestra C, et al. The definition of immigrant status matters: impact of nationality, country of origin, and length of stay in host country on mortality estimates. *BMC Public Health* (2019) 19(1). doi: 10.1186/s12889-019-6555-1

101. Camarota SA, Zeigler K. Foreign-born population hits nearly 48 million in September 2022. *J Migr Hum Secur* (2022) 9(1):31–43. doi: 10.1177/2331502421993746

102. Fang CY, Ragin CC. Addressing disparities in cancer screening among U.S. immigrants: progress and opportunities. *Cancer Prev Res* (2020) 13(3). doi: 10.1158/1940-6207.CAPR-19-0249

103. Guadamuz JS, Durazo-Arvizu RA, Daviglus ML, Calip GS, Nutescu EA, Qato DM. Citizenship status and the prevalence, treatment, and control of cardiovascular disease risk factors among adults in the united states, 2011-2016. *Circ Cardiovasc Qual Outcomes* (2020) 13(3):1–4. doi: 10.1161/CIRCOUTCOMES.119.006215

104. Derose KP, Escarce JJ, Lurie N. Immigrants and health care: sources of vulnerability. *Health Aff* (2007) 26(5). doi: 10.1377/hlthaff.26.5.1258

105. Friedman AS, Venkataramani AS. Chilling effects: US immigration enforcement and health care seeking among Hispanic adults. *Health Aff (Millwood)* (2021) 40(7). doi: 10.1377/hlthaff.2020.02356

106. Kappel C, Rushton-Marovac M, Leong D, Dent S. Pursuing connectivity in cardio-oncology care–the future of telemedicine and artificial intelligence in providing

equity and access to rural communities. *Front Cardiovasc Med* (2022) 9:927769. doi: 10.3389/FCVM.2022.927769

107. Ellis SD, Thompson JA, Boyd SS, Roberts AW, Charlton M, Brooks JV, et al. Geographic differences in community oncology provider and practice location characteristics in the central united states. *J Rural Health* (2022) 38(4):865–75. doi: 10.1111/JRH.12663

108. Bureau UC. Urban areas facts. Available at: https://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural/ua-facts.html. (Accessed May 2023)

109. Segel JE, Lengerich EJ. Rural-urban differences in the association between individual, facility, and clinical characteristics and travel time for cancer treatment. *BMC Public Health* (2020) 20(1). doi: 10.1186/s12889-020-8282-z

110. Panagopoulou P, Gogas H, Dessypris N, Maniadakis N, Fountzilas G, Petridou ET. Survival from breast cancer in relation to access to tertiary healthcare, body mass index, tumor characteristics and treatment: a hellenic cooperative oncology group (HeCOG) study. *Eur J Epidemiol* (2012) 27(11). doi: 10.1007/s10654-012-9737-z

111. Celaya MO, Rees JR, Gibson JJ, Riddle BL, Greenberg ER. Travel distance and season of diagnosis affect treatment choices for women with early-stage breast cancer in a predominantly rural population (United states). *Cancer Causes Control* (2006) 17(6). doi: 10.1007/s10552-006-0025-7

112. Bain NSC, Campbell NC. Treating patients with colorectal cancer in rural and urban areas: a qualitative study of the patients' perspective. *Fam Pract* (2000) 17(6). doi: 10.1093/fampra/17.6.475

113. Bureau UC. American Community survey data. Available at: https://www.census.gov/programs-surveys/acs/data.html. (Accessed at: May 2023)

114. Pareek N, Cevallos J, Moliner P, Shah M, Tan LL, Chambers V, et al. Activity and outcomes of a cardio-oncology service in the united kingdom–a five-year experience. *Eur J Heart Fail* (2018) 20(12). doi: 10.1002/ejhf.1292

115. Charlton M, Schlichting J, Chioreso C, Ward M, Vikas P. Challenges of rural cancer care in the united states. *Oncol (Williston Park)* (2015) 29(9).

116. Caston NE, Williams CP, Wan C, Ye S, Pywell C, Ingram SA, et al. Associations between geography, decision-making style, and interest in cancer clinical trial participation. *Cancer* (2022) 128(22):3977–84. doi: 10.1002/CNCR.34455

117. Valero-Elizondo J, Chouairi F, Khera R, Grandhi GR, Saxena A, Warraich HJ, et al. Atherosclerotic cardiovascular disease, cancer, and financial toxicity among adults in the united states. *JACC CardioOncol* (2021) 3(2). doi: 10.1016/j.jaccao.2021.02.006

118. Kramer H, Han C, Post W, Goff D, Diez-Roux A, Cooper R, et al. Racial/ethnic differences in hypertension and hypertension treatment and control in the multi-ethnic study of atherosclerosis (MESA). *Am J Hypertens* (2004) 17(10). doi: 10.1016/j.amjhyper.2004.06.001

119. Jatoi I, Sung H, Jemal A. The emergence of the racial disparity in U.S. breast-cancer mortality. *New Engl J Med* (2022) 386(25):2349–52. doi: 10.1056/NEJMP2200244/SUPPL_FILE/NEJMP2200244_DISCLOSURES.PDF

120. O'Connor JM, Sedghi T, Dhodapkar M, Kane MJ, Gross CP. Factors associated with cancer disparities among low-, medium-, and high-income US counties. *JAMA Netw Open* (2018) 1(6). doi: 10.1001/jamanetworkopen.2018.3146

121. Arsanjani R, Khera N. Financial toxicity in cancer and cardiovascular disease: a threat to access and quality of care. *JACC CardioOncol* (2021) 3(2). doi: 10.1016/j.jaccao.2021.04.002

122. Patel MI, Lopez AM, Blackstock W, Reeder-Hayes K, Moushey EA, Phillips J, et al. Cancer disparities and health equity: a policy statement from the american society of clinical oncology. *J Clin Oncol* (2020) 38(29). doi: 10.1200/JCO.20.00642

123. Khera N, Holland JC, Griffin JM. Setting the stage for universal financial distress screening in routine cancer care. *Cancer* (2017) 123(21). doi: 10.1002/cncr.30940

124. Khera N, Kumbamu A, Langer SL, Jatoi A, Kamath CC, Mathew E, et al. Developing an educational intervention to address financial hardship in cancer patients. *Mayo Clin Proc Innov Qual Outcomes* (2020) 4(4). doi: 10.1016/j.mayocpiqo.2020.04.004

125. Shankaran V, Leahy T, Steelquist J, Watabayashi K, Linden H, Ramsey S, et al. Pilot feasibility study of an oncology financial navigation program. *J Oncol Pract* (2018) 14(2). doi: 10.1200/JOP.2017.024927

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 04 July 2023
DOI 10.3389/fonc.2023.1156237

OPEN ACCESS

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RECEIVED 01 February 2023
ACCEPTED 19 June 2023
PUBLISHED 04 July 2023

CITATION
Zhuo L, Kong Y, Chen S, Ma Y, Cai T, Pan J, Wang X, Gao Y, Lu H, Li X, Zhao H, Mackay L, Dong W, Zhuo L and Dong D (2023) Effect of sedated colonoscopy with different cost coverage on improving compliance with colorectal cancer screening in China.
Front. Oncol. 13:1156237.
doi: 10.3389/fonc.2023.1156237

Effect of sedated colonoscopy with different cost coverage on improving compliance with colorectal cancer screening in China

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Background: Colorectal cancer is the third most common cancer worldwide. Colonoscopy is the gold standard for colorectal cancer screening. However, the colonoscopy participation rate in China is much lower than that in Europe and the United States. As only non-sedated colonoscopies are offered in colorectal cancer screening programs in China, the absence of sedation may contribute to this gap.

Methods: To explore the effect of free and partially participant-paid sedated colonoscopy on improving colorectal screening participation, we conducted a cross-sectional study under the framework of the Cancer Screening Program in Urban China in Xuzhou from May 2017 to December 2020. The Quanshan district was set as the control group and provided free non-sedated colonoscopy, the Yunlong district was set as a partial cost coverage group and offered partially participant-paid sedated colonoscopy, and the Gulou district was set as the full cost coverage group and offered free sedation colonoscopies. Multivariate logistic regression was used for multivariate analysis of colonoscopy participation and colorectal lesion detection rates between the groups.

Results: From May 2017 to May 2020, 81,358 participants were recruited and completed questionnaire, 7,868 subjects who met high-risk conditions for CRC were invited to undergo colonoscopy. The colonoscopy participation rates in the control group, partially cost coverage, and full cost coverage groups were 17.33% (594/3,428), 25.66% (542/2,112), and 34.41% (801/2,328), respectively. Subjects in the partial and full cost coverage groups had 1.66-fold (95% CI: 1.48–1.86) and 2.49-fold (95% CI: 2.23–2.76) increased rates compared with those in the control group. The adjusted PARs for the partially and the full cost coverage group was 9.08 (95% CI: 6.88–11.28) and 18.97 (95% CI: 16.51–21.42), respectively. The

detection rates of CAN in the control, partial-cost coverage, and full-cost coverage groups were 3.54% (21/594), 2.95% (16/542), and 5.12% (41/801), respectively. There were no significant differences in the detection rates between the group. However, sedated colonoscopy increases costs.

Conclusion: Sedated colonoscopy increased colonoscopy participation rates in both the partial and full cost-covered groups. A partial cost coverage strategy may be a good way to increase colorectal cancer participation rates and quickly establish a colorectal cancer screening strategy in underfunded areas.

KEYWORDS

colorectal cancer, screening, sedated colonoscopy, compliance, cost coverage

Introduction

Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer-related deaths worldwide, with an estimated 1.9 million more new cases and 935,000 deaths in 2020 (1). In China, CRC is the fifth most common cancer in both men and women and is a major public health issue (2). Most CRC occur through the "adenoma-carcinoma" pathway, which usually lasts 5–10 years (3, 4). Screening and early intervention have been shown to be effective in improving survival and preventing CRC development (5, 6).

To reduce cancer incidence and mortality, many countries and regions, including the United States and Europe, have established national colorectal cancer screening programs. The Chinese government also initiated the population-based Cancer Screening Program in Urban China (CanSPUC) in October 2012, which targeted common cancers that are most prevalent in urban areas, including CRC. Eligible participants were recruited from communities in the study regions and invited to undergo cancer screening free of charge. Participants were first invited to take a cancer risk assessment by an established Clinical Cancer Risk Score System, and those who were evaluated to be at high risk for CRC were recommended to undergo subsequent colonoscopy at tertiary-level hospitals designated by the program. The CanSPUC recruited 1,381,561 eligible participants aged 40–69 years from 16 provinces in China from 2012 to 2015, and 182,927 participants were evaluated to be at high risk for CRC; however, only 25,593 participants underwent colonoscopy as recommended, with a participation rate of 14.0% (7). This colonoscopy participation rate is much lower than the 22.9% (Netherlands) to 60.7% (Norway) reported in the Nordic-European Initiative on Colorectal Cancer (NordICC) study conducted in four European countries (Norway, the Netherlands, Poland, and Sweden) (8) and 60.8% among adults aged 50–75 years in the United States (9), seriously affecting the effectiveness of colorectal cancer screening in China.

As only non-sedated colonoscopies are offered in the CanSPUC, whereas sedated colonoscopies are commonly offered in Europe and the United States (8, 10–12), the absence of sedation may contribute to the gap in colonoscopy participation rates between China, Europe, and the United States. Sedated colonoscopy has many advantages, such as analgesia and anxiolysis (10–12), which may be important for improving colonoscopy participation, as pain and anxiety are partly responsible for poor colonoscopy participation. However, sedated colonoscopy also increases the risk of hypotension and hypoxemia and requires a specially qualified medical team comprising nurses, anesthetists, and incurs additional costs compared with non-sedation colonoscopy (10–12). Colorectal cancer screening in CanSPUC is currently paid for by a special government fund but will be covered by the Basic Medical Insurance Pooling Fund in the future. China's Basic Medical Insurance system is divided into pooling and individual accounts. The pooling fund account is funded by employers and national financial subsidies and is shared by all insured persons, while individual accounts are funded by individuals and owned by themselves. In recent years, the participation rate in China's Basic Medical Insurance has remained stable at approximately 95%. For mass screening programs, it is not possible to increase the cost of providing free-sedated colonoscopy when its effectiveness is uncertain. This problem may have been solved by the participants paying for additional sedation at their own discretion. However, the results of a study in Guangzhou, China, showed that the participation rate in free colonoscopy was higher than that in paid colonoscopy (20.27% *vs*. 10.70%), and most participants could not accept paying more than 300 yuan for CRC screening (13, 14).

To explore the effect of free and partially participant-paid sedated colonoscopy on improving colorectal screening participation and advise on health policy improvements, we conducted a cross-sectional study under the framework of the CanSPUC in Xuzhou. Xuzhou is the central city of the Huaihai Economic Zone (which has a population of 119 million, covers an area of 178,000 km^2, and consists of 20 cities), located at the junction of four provinces (Jiangsu, Anhui, Shandong, and Henan), southeast of the North China Plain, and a gateway to East China. The participation rate of Basic Medical Insurance in

Xuzhou was approximately 98.5%. From May 2017 to December 2020, Colorectal cancer screening was conducted in the Quanshan, Yunlong, and Gulou districts, and different cost coverage strategies were provided in each district.

Methods

Study design and population

We conducted this study using the CanSPUC framework. CanSPUC is an ongoing national cancer screening program in the urban areas of China, and Xuzhou joined this program in August 2014. Briefly, a cluster sampling method was adopted to conduct simple random sampling of the community as a group in the main urban area of Xuzhou. Residents living in selected communities aged 40–74 years were approached by trained staff *via* phone calls and personal encounters. After obtaining signed written informed consent, all eligible participants (aged 40–74 years, local permanent resident population, no major diseases) were interviewed by trained staff to collect information about their exposure to risk factors and to evaluate their cancer risk using conditions set by the National Cancer Center. To optimize the use of limited colonoscopy resources and to enhance the detection rate of colorectal neoplasia, only participants who met the high-risk conditions for CRC were recommended to undergo colonoscopy at Xuzhou Cancer Hospital, designated by the programmer free of charge. All data collection processes were conducted using an information system built specifically for CanSPUC by the National Cancer Center.

From May 2017 to May 2020, colorectal cancer screening was conducted in the Quanshan, Yunlong, and Gulou districts. Different colonoscopy and cost coverage strategies were provided for each district. The Quanshan District was set as the control group and provided free non-sedated colonoscopy according to the CanSPUC technical protocol. The Yunlong district was set as a partial cost coverage group and offered partially participant-paid sedated colonoscopy, CanSPUC funding paid for colonoscopy, and participants paid for their own sedation (about 376 yuan, can pay with Basic Medical Insurance Personal Account). Participants who refused to pay for sedation also had the option of undergoing an unsedated colonoscopy free of charge. The Gulou District was set as full cost coverage group and offered free sedation colonoscopies; all costs were covered by CanSPUC funds. Participants who refuse to undergo sedation can undergo free non-sedation colonoscopies.

A total of 81,358 participants were recruited and completed the questionnaire; 7,868 subjects (9.67%) who met the high-risk conditions for CRC were invited to undergo colonoscopy, and 1,937 subjects (24.62%) completed colonoscopy. A recruitment flowchart is shown in Figure 1. This study was approved by the Ethics Committee of Xuzhou Cancer Hospital (approval number: 2018-02-23-H01).

Sample size

The colonoscopy participation rate and number of subjects invited for colonoscopy in each group were used to calculate the power. When the colonoscopy participation rate of the control group, the partially cost coverage group and the full cost coverage group were 17.33%, 25.66%, and 34.41%, respectively, and the number of subjects invited for colonoscopy were 3,428, 2,112, and 2328, respectively, the power of comparison of colonoscopy participation rate between groups was 0.999. This means that the sample size of this study was sufficient to compare the differences in colonoscopy participation rates between the groups.

Colonoscopy screening

The nature, benefits, and risks of colonoscopy were explained to all subjects prior to the examination, and a colonoscopy risk

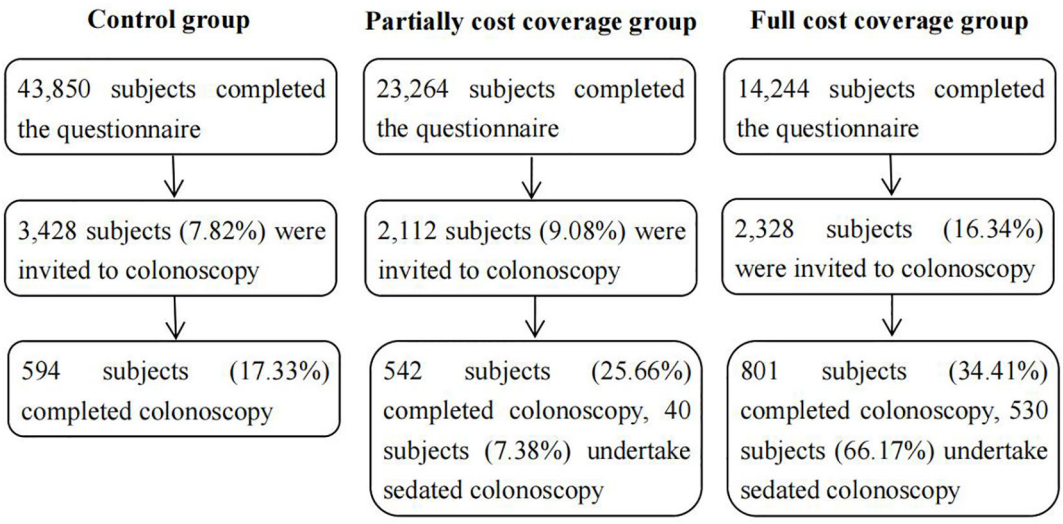

FIGURE 1
Recruitment flow chart of this study.

notification form was signed. We used polyethylene glycol (HYGECONR, Jiangxi Hygecon Pharmaceutical Co., Ltd., China) as a standard bowel preparation regimen for all participants, and an electrocardiogram was also performed before colonoscopy to prevent unexpected events. Propofol (Yangzijiang; Yangzijiang Pharmaceutical Group Co., Ltd., China) was used as a sedative for subjects selected for sedated colonoscopy. A team of experienced physicians, colorectal surgeons, nurses, and anesthetists performed all colonoscopy procedures at the endoscopy Center of Xuzhou Cancer Hospital. All abnormal findings were pathologically examined in accordance with the clinical procedures, and the results and images were uploaded to the project information system. Colorectal advanced neoplasia (CAN) was the most important abnormal finding and was defined as CRC or any colorectal adenoma measuring 1 cm or more in diameter, high-grade dysplasia, or tubular-villous histologic features. To ensure the quality of the examination, the quality control team, composed of the chief physician and deputy chief physician, reviewed all results.

Statistical analysis

Statistical analyses were performed using Stata version 16.0. Statistical significance was defines as a two-tailed *P*-value <0.05. The basic characteristics of the study population were first described and compared between the study groups using the Pearson χ^2 test. The Pearson χ^2 test was also used for the univariate analysis of colonoscopy participation rates. Multivariate logistic regression was used for multivariate analysis of colonoscopy participation rates and colorectal lesion detection rates between the groups, and adjusted ORs and P-values were reported. Based on the adjusted ORs, the adjusted RRs and PARs were calculated. The cost of colonoscopy in the different groups paid by funds was also calculated.

Results

Characteristics of the study population

From May 2017 to May 2020, 81,358 participants were recruited to complete the questionnaire. A total of 7,868 subjects who met the high-risk conditions for CRC were included in the analysis and invited to undergo colonoscopy, including 3,428 in the control group, 2,112 in the partial cost coverage group, and 2,328 in the full cost coverage group. The characteristics of the study population in the different groups are shown in Table 1, and all factors were different between the three groups (P <0.05).

Colonoscopy participation rate

The colonoscopy participation rates in the control, partial cost coverage, and full cost coverage groups were 17.33% (594/3,428), 25.66% (542/2,112), and 34.41% (801/2,328), respectively (Figure 2). The sedated colonoscopy uses rates of the partial cost coverage and full cost coverage groups were 7.38% (40/542) and 66.17% (530/801), respectively. In the partial-cost coverage group, all subjects who chose to undergo sedated colonoscopy were paid for their own sedation using the Basic Medical Insurance Individual Account.

Univariate analysis

In the univariate analysis, group, age, sex, educational background, family history of CRC among first-degree relatives, previously detected colonic polyps, and fecal occult blood test results were all risk factors for colonoscopy participation rate (P <0.05), and the results are shown in Table 2.

Multivariate analysis

In the multivariate analysis, after adjusting for age, sex, educational background, family history of CRC among first-degree relatives, previously detected colonic polyps, and fecal occult blood test results, subjects in the partial cost coverage group and the full cost coverage group had 1.66-fold (95% CI: 1.48–1.86) and 2.49-fold (95% CI: 2.23–2.76) increased rates of colonoscopy participation, respectively, compared with those in the control group (Table 3). The adjusted PARs for the partial cost coverage group and full cost coverage group were 9.08 (95% CI: 6.88–11.28) and 18.97 (95% CI: 16.51–21.42), respectively.

Detection rate

The detection rates of CAN in the control, partial-cost coverage, and full-cost coverage groups were 3.54% (21/594), 2.95% (16/542), and 5.12% (41/801), respectively. There was no significant difference in the detection rate of CAN between the partial cost coverage group and the control group [OR = 0.74 (0.37–1.46), P = 0.387], or between the full cost coverage group and the control group [OR = 1.21 (0.68–2.12), P = 0.515] (Table 4).

Cost

The average cost of colonoscopy in the control, partial cost coverage, and full cost coverage groups paid by funds were 266, 266, and 515 yuan, respectively. The cost of colonoscopy needed to detect one case of CAN in each group paid by the fund was 7,524, 9,010, and 10,057 yuan (Table 5).

Discussion

This is the first study in China to investigate the effect of sedated colonoscopy with different cost coverages on improving compliance with CRC screening in asymptomatic community populations. This study found that sedated colonoscopy increased colonoscopy

10.3389/fonc.2023.1156237

TABLE 1 Characteristics of the study population in different groups [n (%)].

Factors	Control group (n = 3,428)	Partial cost coverage group (n = 2,112)	Full cost coverage group (n = 2,328)	*P*
Age				<0.001
40–44	287 (8.37)	136 (6.44)	81 (3.48)	
45–49	536 (15.64)	298 (14.11)	198 (8.51)	
50–54	669 (19.52)	363 (17.19)	272 (11.68)	
55–59	696 (20.30)	363 (17.19)	390 (16.75)	
60–64	758 (22.11)	399 (18.89)	333 (14.30)	
65–69	440 (12.84)	358 (16.95)	648 (27.84)	
70–74	42 (1.23)	195 (9.23)	406 (17.44)	
Sex				<0.001
Male	1,567 (45.71)	906 (42.90)	1,533 (65.85)	
Female	1,861 (54.29)	1,206 (57.10)	795 (34.15)	
Education background				0.003
<High school	2,086 (60.85)	1,239 (58.66)	1,442 (61.94)	
High school and equivalent	905 (26.40)	627 (29.69)	572 (24.57)	
≥Postsecondary graduate	437 (12.75)	246 (11.65)	314 (13.49)	
Family history of CRC among the first-degree relatives				<0.001
No	3,005 (87.66)	1,886 (89.30)	2,174 (93.38)	
Yes	423 (12.34)	226 (10.70)	154 (6.62)	
Previously detected colonic polyp				<0.001
No	2,987 (87.14)	1,714 (81.16)	1,783 (76.59)	
Yes	441 (12.86)	398 (18.84)	545 (23.41)	
Fecal occult blood test				<0.001
Negative result or no	3,189 (93.03)	1,983 (93.89)	1,982 (85.14)	
Positive result	239 (6.97)	129 (6.11)	346 (14.86)	

participation rates in both partial and full cost-covered groups, and there was no statistical difference in the detection rate of CAN compared with the control group. However, sedated colonoscopy also increases costs.

Participation rate is critical for determining the effectiveness of CRC screening. An Australian modeling study (15) showed that increasing colonoscopy participation from 40% to 60% could reduce 37,300 CRC cases and 24,800 CRC deaths over the next 25 years. In a 2012–2015 Chinese study (7), the diagnostic yield was not optimal using colonoscopy screening in high-risk populations, given the relatively low participation rate. But in this study, partial and full cost covered sedated colonoscopy increased participation rates by 9.08% [RR = 1.66 (1.48–1.86)] and 18.97% [RR = 2.49 (2.23–2.76)], respectively, demonstrating the effectiveness of the sedated colonoscopy screening policy in increasing participation rates. However, it is important to note that this study was a real-world field trial conducted in the real world. Due to the limitations of the research conditions, no randomization was conducted, and no balanced comparable control group was available. Community-based randomized controlled trials are recommended to further explore the association between sedated colonoscopy use and colorectal cancer screening participation when conditions permit it.

However, even in the full cost coverage group, the colonoscopy participation rate of the subjects in this study was only 34.41%, which was lower than the 40.0% in Europe (8) and 60.8% in the United States (9). The difference may be related to the basic characteristics of the population, such as the age of the subjects (CanSPUC, 40–74 years, NordICC, 55–64 years, United States, 50–75 years) (7–9). Age

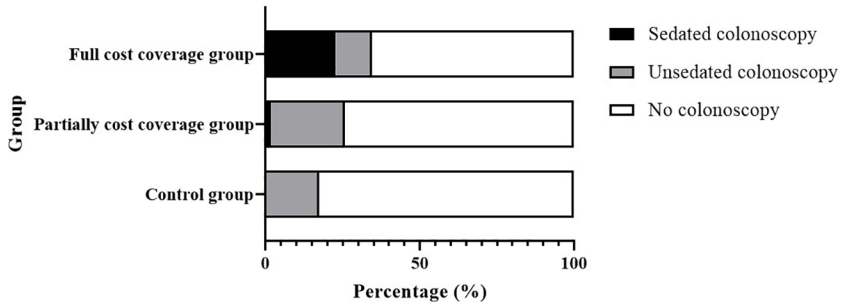

FIGURE 2
Colonoscopy participation rate and sedated colonoscopy use rate in different groups.

is an important factor for colonoscopy participation in countries around the world (7, 8, 16, 17). According to a French analysis (16), uptake was significantly lower in the youngest (50–59 years) and oldest (70–74 years) persons, compared with intermediate ages (60–69 years), with OR = 0.70 (95% CI: 0.63 to 0.77) and OR = 0.82 (95% CI: 0.72 to 0.93), respectively. In a study conducted in Henan, China (17), participants aged 50–64 years were more likely to undergo colonoscopy.

The high rate of colonoscopy participation in the United States is closely related to earlier scientific research and active health policies (18–20). From the mid-1970s to the 1990s, colonoscopy was established as a superior CRC screening modality in the United States (18). In 1997 and 2001, The Balanced Budget Act and Consolidated Appropriations Act were passed to provide access to screening colonoscopies. In 2014, the National Colorectal Cancer Roundtable of the American Cancer Society launched 80% by 2018 (19, 21). Although the target was not met that year, CRC screening rates in the United States have been gradually increasing and achieved good results (9, 20–22). In contrast, China's nationwide CRC screening program was later launched. Although the National Cancer Center has made many explorations (such as CanSPUC and TARGET-C) (7, 23–25) and wrote the Chinese guidelines for the screening, early detection, and early treatment of colorectal cancer (2020, Beijing) (26), China does not have a national CRC screening policy at present, and the exploration of CRC screening strategies needs to continue to obtain sufficient evidence for CRC screening to be covered by the Basic Medical Insurance Pooling Fund in the future.

In addition, sedated colonoscopy has other advantages, such as easy scope advancement, less examination time, and better cecal intubation rates, which may help further improve the effectiveness of CRC screening (10). However, a study conducted by Liang et al. (27) showed that although sedated colonoscopy improved patient satisfaction, it did not affect the adenoma and polyp detection rates. Sedated colonoscopy did not improve the detection rate of advanced neoplasms and polyps in this study. However, from another perspective, the increase in colorectal cancer screening participation caused by sedated colonoscopy did not dilute the detection rate of colorectal lesions. Studies have also shown that the use of sedated colonoscopies increases the risk of aspiration pneumonia (28, 29), but not bowel perforation or splenic injury (29). Safety is a prerequisite for colorectal cancer screening; endoscopists and anesthesiologists should carefully explain to participants before performing sedated colonoscopy and perform pre-examination assessments to avoid adverse events.

In addition to effectiveness and safety, cost-effectiveness is an important factor to consider when developing a screening strategy. In this study, the full cost coverage group had the best effectiveness, but the highest average colonoscopy cost and highest cost of colonoscopy needed to detect one case of CAN. Additional screening costs may still be economical and preferred in areas where colorectal screening is adequately funded, and a formal

TABLE 2 Univariate analysis of colonoscopy participation rate.

Factors	Participants undertaking colonoscopy (%)	χ^2	*P*
Group		219.62	<0.001
Control group	594 (17.33)		
Partially cost coverage group	542 (25.66)		
Full cost coverage group	801 (34.41)		
Age		67.98	<0.001
40–44	99 (19.64)		
45–49	283 (27.42)		
50–54	376 (28.83)		
55–59	379 (26.16)		
60–64	390 (26.17)		
65–69	316 (21.85)		
70–74	94 (14.62)		
Sex		6.37	0.012
Male	938 (23.41)		
Female	999 (25.87)		
Education background		53.44	<0.001

(Continued)

TABLE 2 Continued

Factors	Participants undertaking colonoscopy (%)	χ^2	*P*
<High school	1,049 (22.01)		
High school and equivalent	569 (27.04)		
≥Postsecondary graduate	319 (32.00)		
Family history of CRC among the first-degree relatives		49.41	<0.001
No	1,658 (23.47)		
Yes	279 (34.74)		
Previously detected colonic polyp		156.97	<0.001
No	1,414 (21.81)		
Yes	523 (37.79)		
Fecal occult blood test		184.82	<0.001
Negative result or no	1,612 (22.53)		
Positive result	325 (45.52)		

cost–benefit analysis is required. However, unsedated colonoscopy is used in many parts of the world (30). The partial cost coverage strategy could be a possible way to increase the participation rate in underfunded areas of CRC screening, with no increase in colonoscopies paid for by the fund since participants pay for sedation themselves. This approach may also be used to help regions that do not already have colorectal cancer screening and quickly establish effective screening strategies at a low financial cost.

This study has several strengths. First, to our knowledge, this is the first study in China to investigate the effect of sedated colonoscopy with different cost coverage on improving compliance with CRC screening in asymptomatic community populations. Second, this study was conducted under the framework of CanSPUC, which used rigorous standards to guarantee the integrity and accuracy of the collected data, including a review mechanism to ensure the quality of data and the development of a data system to monitor all the processes of the study. Third, we evaluated the participation rate, detection rate, and cost of sedation colonoscopy with different cost coverages, and the results were comprehensive.

This study has several limitations. First, for practical reasons, only CRC screening data of the population in Xuzhou were used in this study. Second, due to the limitations of the conditions, the subjects were not randomly grouped in this study, which may have led to selection bias. In addition, only participants who met the

TABLE 3 Adjusted ORs, RRs, and PARs of factors associated with participation rate in colonoscopy.

Factors	*OR (95% CI)*	*P*	*RR (95% CI)*	*PAR (%, 95% CI)*
Group				
Control group	*Reference*		*Reference*	*Reference*
Partially cost coverage group	1.78 (1.55–2.04)	<0.001	1.66 (1.48–1.86)	9.08 (6.88–11.28)
Full cost coverage group	2.92 (2.55–3.35)	<0.001	2.49 (2.23–2.76)	18.97 (16.51–21.42)
Age				
40–44	1.95 (1.40–2.70)	<0.001	1.86 (1.38–2.50)	8.51 (4.20–12.78)
45–49	2.89 (2.20–3.80)	<0.001	2.65 (2.08–3.34)	15.17 (11.54–18.76)
50–54	3.05 (2.34–3.98)	<0.001	2.78 (2.20–3.48)	16.21 (12.79–19.59)
55–59	2.75 (2.12–3.57)	<0.001	2.54 (2.01–3.17)	14.31 (11.06–17.52)
60–64	2.97 (2.29–3.85)	<0.001	2.71 (2.16–3.38)	15.70 (12.43–18.93)
65–69	1.98 (1.53–2.56)	<0.001	1.89 (1.49–2.38)	8.76 (5.72–11.84)
70–74	*Reference*		*Reference*	*Reference*
Sex				
Male	*Reference*		*Reference*	*Reference*
Female	1.14 (1.02–1.28)	0.018	1.13 (1.02–1.25)	2.30 (0.39–4.20)
Education background				
<High school	*Reference*		*Reference*	*Reference*

(Continued)

TABLE 3 Continued

Factors	*OR (95% CI)*	*P*	*RR (95% CI)*	*PAR (%, 95% CI)*
High school and equivalent	1.22 (1.08–1.39)	0.002	1.20 (1.07–1.34)	3.43 (1.26–5.60)
≥Postsecondary graduate	1.53 (1.30–1.80)	<0.001	1.46 (1.27–1.68)	7.58 (4.53–10.62)
Family history of CRC among the first-degree relatives				
No	*Reference*		*Reference*	*Reference*
Yes	1.75 (1.48–2.06)	<0.001	1.64 (1.42–1.88)	10.40 (7.08–13.70)
Previously detected colonic polyp				
No	*Reference*		*Reference*	*Reference*
Yes	1.67 (1.46–1.90)	<0.001	1.57 (1.40–1.76)	9.40 (6.81–11.98)
Fecal occult blood test				
Negative result or no	*Reference*		*Reference*	*Reference*
Positive result	2.22 (1.88–2.62)	<0.001	2.00 (1.74–2.29)	15.54 (11.92–19.12)

OR, Odds ratio; RR, Risk ratio; PAR, Population attributable risk; CI, Confidence interval.

TABLE 4 Colorectal lesion detection rate in different groups.

Colorectal lesion	Control group	Partial cost coverage group	Full cost coverage group	Partial cost coverage group vs Control group		Full cost coverage group vs Control group	
				*OR (95% CI)**	*P*	*OR (95% CI)**	*P*
CAN	21 (3.54%)	16 (2.95%)	41 (5.12%)	0.74 (0.37–1.46)	0.387	1.21 (0.68–2.12)	0.515
CNA	117 (19.70%)	68 (12.55%)	139 (17.35%)	0.58 (0.42–0.80)	0.001	0.80 (0.60–1.06)	0.120
Polyp	76 (12.79%)	88 (16.24%)	130 (16.23%)	1.35 (0.97–1.90)	0.077	1.30 (0.95–1.78)	0.095
Any neoplasm	214 (36.03%)	172 (31.73%)	310 (38.70%)	0.82 (0.63–1.05)	0.113	1.04 (0.83–1.30)	0.738

CAN, Colorectal advanced neoplasm; CNA, Colorectal non-advanced neoplasm; OR, Odds ratio; CI, Confidence interval.
*Adjusted age, sex.

TABLE 5 Cost of colonoscopy in different groups paid by fund (Yuan).

Cost	Control group	Partial cost coverage group	Full cost coverage group
Total cost	158,004	144,172	412,346
Average cost	266	266	515
Cost needed to detect one case of CAN	7,524	9,010	10,057
Cost needed to detect one case of any neoplasm	738	838	1,330

CAN, Colorectal advanced neoplasm.

high-risk conditions for CRC were recommended to undergo colonoscopy because of examination due to limited resources when CanSPUC was conducted. There may have been a decrease in colonoscopy participation in the average-risk population, but this did not affect the conclusions of this study.

In summary, sedated colonoscopy increased colonoscopy participation rates in both the partial and full cost-covered groups, and the diagnosis rate remained unchanged. The full cost-covered strategy works better but comes with additional costs. A partial cost coverage strategy may be a good way to

increase colorectal cancer participation rates and quickly establish a colorectal cancer screening strategy in underfunded areas.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xuzhou Cancer Hospital (approved number: 2018-02-23-H01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LiZ, YK, and LaZ conceived and designed the study. YK, YM, HZ, WD, and DD contributed to the acquisition of the data. LiZ, YK, SC, YM, TC, JP, XW, YG, HL, XL, LM, and LaZ were involved in the analysis and interpretation of the data. All authors were involved in the writing, reviewing, and editing of the manuscript. YK, YM, and DD confirm the authenticity of all the raw data. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the CAMS Innovation Fund for Medical Sciences (2017-I2M-1-006) and the National Key Public Health Program: Cancer Screening Program in Urban China.

Acknowledgments

We sincerely thank all the research staff from Xuzhou Cancer Hospital, Xuzhou Center for Disease Control and Prevention and Community Health Service Centers for their involvement in data collection for this study. We are grateful to the participants for their participation in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* (2016) 66:115–32. doi: 10.3322/caac.21338

3. Gupta N, Kupfer SS, Davis AM. Colorectal cancer screening. *JAMA* (2019) 321:2022–3. doi: 10.1001/jama.2019.4842

4. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. *Gut* (2007) 56:1585–9. doi: 10.1136/gut.2007.122739

5. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* (2019) 394:1467–80. doi: 10.1016/s0140-6736(19)32319-0

6. Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif KInternational Agency for Research on Cancer Handbook Working Group. The IARC perspective on colorectal cancer screening. *N Engl J Med* (2018) 378:1734–40. doi: 10.1056/nejmsr1714643

7. Chen H, Li N, Ren J, Feng X, Lyu Z, Wei L, et al. Participation and yield of a population-based colorectal cancer screening programme in China. *Gut* (2019) 68:1450–7. doi: 10.1136/gutjnl-2018-317124

8. Bretthauer M, Kaminski MF, Løberg M, Zauber AG, Regula J, Kuipers EJ, et al. Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. *JAMA Intern Med* (2016) 176:894–902. doi: 10.1001/jamainternmed.2016.0960

9. National Center for Health Statistics. *Health, United States, 2019*. Hyattsville, MD (2021). Available at: http://dx.doi.org/10.15620/cdc:100685

10. Zhang K, Yuan Q, Zhu S, Xu D, An Z. Is unsedated colonoscopy gaining ground over sedated colonoscopy? *J Natl Med Assoc* (2018) 110:143–8. doi: 10.1016/j.jnma.2016.12.003

11. Khan F, Hur C, Lebwohl B, Krigel A. Unsedated colonoscopy: impact on quality indicators. *Dig Dis Sci* (2020) 65:3116–22. doi: 10.1007/s10620-020-06491-0

12. Aljebreen AM, Almadi MA, Leung FW. Sedated vs unsedated colonoscopy: a prospective study. *World J Gastroenterol* (2014) 20:5113–8. doi: 10.3748/wjg.v20.i17.5113

13. Yan L, Liu HZ, Lin GZ, Liang YR, Wang SX, Li K, et al. Results of colorectal cancer screening in Guangzhou, 2015. *China Caner* (2016) 25:422–5. doi: 10.11735/j.issn.1004-0242.2016.06.A004

14. Zhou Q, Li Y, Liu HZ, Liang YR, Lin GZ. Willingness to pay for colorectal cancer screening in Guangzhou. *World J Gastroenterol* (2018) 24:4708–15. doi: 10.3748/wjg.v24.i41.4708

15. Lew JB, St John DJB, Xu XM, Greuter MJE, Caruana M, Cenin DR, et al. Long-term evaluation of benefits, harms, and cost-effectiveness of the national bowel cancer screening program in Australia: a modelling study. *Lancet Public Health* (2017) 2:e331–40. doi: 10.1016/s2468-2667(17)30105-6

16. Pornet C, Dejardin O, Morlais F, Bouvier V, Launoy G. Socioeconomic determinants for compliance to colorectal cancer screening. a multilevel analysis. *J Epidemiol Community Health* (2010) 64:318–24. doi: 10.1136/jech.2008.081117

17. Zhang J, Xu H, Zheng L, Yu J, Chen Q, Cao X, et al. Determinants of participation and detection rate of colorectal cancer from a population-based screening program in China. *Front Oncol* (2020) 10:1173. doi: 10.3389/fonc.2020.01173

18. Montminy EM, Karlitz JJ, Landreneau SW. Progress of colorectal cancer screening in united states: past achievements and future challenges. *Prev Med* (2019) 120:78–84. doi: 10.1016/j.ypmed.2018.12.004

19. Henley SJ, Thomas CC, Lewis DR, Ward EM, Islami F, Wu M, et al. Annual report to the nation on the status of cancer, part II: progress toward healthy people 2020 objectives for 4 common cancers. *Cancer* (2020) 126:2250–66. doi: 10.1002/cncr.32801

20. Kanth P, Inadomi JM. Screening and prevention of colorectal cancer. *BMJ* (2021) 374:n1855. doi: 10.1136/bmj.n1855

21. Wender R, Brooks D, Sharpe K, Doroshenk M. The national colorectal cancer roundtable: past performance, current and future goals. *Gastrointest Endosc Clin N Am* (2020) 30:499–509. doi: 10.1016/j.giec.2020.02.013

22. Centers for Disease Control and Prevention. *United States cancer statistics colorectal cancer stat bite* (2022). Available at: https://www.cdc.gov/cancer/uscs/about/stat-bites/index.htm (Accessed December 19, 2022).

23. Chen H, Li N, Shi J, Ren J, Liu C, Zhang Y, et al. Comparative evaluation of novel screening strategies for colorectal cancer screening in China (TARGET-c): a study protocol for a multicentre randomised controlled trial. *BMJ Open* (2019) 9:e025935. doi: 10.1136/bmjopen-2018-025935

24. Chen H, Lu M, Liu C, Zou S, Du L, Liao X, et al. Comparative evaluation of participation and diagnostic yield of colonoscopy vs fecal immunochemical test vs risk-adapted screening in colorectal cancer screening: interim analysis of a multicenter randomized controlled trial (TARGET-c). *Am J Gastroenterol* (2020) 115:1264–74. doi: 10.14309/ajg.0000000000000624

25. Chen H, Shi J, Lu M, Li Y, Du L, Liao X, et al. Comparison of colonoscopy, fecal immunochemical test, and risk-adapted approach in a colorectal cancer screening trial (TARGET-c). *Clin Gastroenterol Hepatol* (2022) S1542-3565(22):00767–4. doi: 10.1016/j.cgh.2022.08.003

26. National Cancer Center, China, Expert Group of the Development of China Guideline for the Screening, Early Detection and Early Treatment of Colorectal Cancer. China Guideline for the screening, early detection and early treatment of colorectal cancer (2020, Beijing). *Chin J Oncol* (2021) 43:16–38. doi: 10.3760/cma.j.cn112152-20210105-00010

27. Liang M, Zhang X, Xu C, Cao J, Zhang Z. Anesthesia assistance in colonoscopy: impact on quality indicators. *Front Med (Lausanne)* (2022) 9:872231. doi: 10.3389/fmed.2022.872231

28. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med* (2013) . 173:551–6. doi: 10.1001/jamainternmed.2013.2908

29. Bielawska B, Hookey LC, Sutradhar R, Whitehead M, Xu J, Paszat LF, et al. Anesthesia assistance in outpatient colonoscopy and risk of aspiration pneumonia, bowel perforation, and splenic injury. *Gastroenterology* (2018) 154:77–85.e3. doi: 10.1053/j.gastro.2017.08.043

30. Leung FW, Aljebreen AM, Brocchi E, Chang EB, Liao WC, Mizukami T, et al. Sedation-risk-free colonoscopy for minimizing the burden of colorectal cancer screening. *World J Gastrointest Endosc* (2010) 2:81–9. doi: 10.4253/wjge.v2.i3.81

frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 01 November 2023
DOI 10.3389/fonc.2023.1187585

OPEN ACCESS

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RECEIVED 16 March 2023
ACCEPTED 10 October 2023
PUBLISHED 01 November 2023

CITATION
Leon C, Manley E Jr., Neely AM, Castillo J, Ramos Correa M, Velarde DA, Yang M, Puente PE, Romero DI, Ren B, Chai W, Gladstone M, Lamango NS, Huang Y and Offringa IA (2023) Lack of racial and ethnic diversity in lung cancer cell lines contributes to lung cancer health disparities.
Front. Oncol. 13:1187585.
doi: 10.3389/fonc.2023.1187585

Lack of racial and ethnic diversity in lung cancer cell lines contributes to lung cancer health disparities

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Lung cancer is the leading cause of cancer death in the United States and worldwide, and a major source of cancer health disparities. Lung cancer cell lines provide key *in vitro* models for molecular studies of lung cancer development and progression, and for pre-clinical drug testing. To ensure health equity, it is imperative that cell lines representing different lung cancer histological types, carrying different cancer driver genes, and representing different genders, races, and ethnicities should be available. This is particularly relevant for cell lines from Black men, who experience the highest lung cancer mortality in the United States. Here, we undertook a review of the available lung cancer cell lines and their racial and ethnic origin. We noted a marked imbalance in the availability of cell lines from different races and ethnicities. Cell lines from Black patients were strongly underrepresented, and we identified no cell lines from Hispanic/Latin(x) (H/L), American Indian/American Native (AI/AN), or Native Hawaiian or other Pacific Islander (NHOPI) patients. The majority of cell lines were derived from White and Asian patients. Also missing are cell lines representing the cells-of-origin of the major lung cancer histological types, which can be used to model lung cancer development and to study the effects of environmental exposures on lung tissues. To our knowledge, the few available immortalized alveolar epithelial cell lines are all derived from White subjects, and the race and ethnicity of a handful of cell lines derived from bronchial epithelial cells are unknown. The lack of an appropriately diverse collection of lung cancer cell lines and lung cancer cell-of-origin lines severely limits racially and ethnically inclusive lung cancer research. It impedes the ability to develop inclusive models, screen

comprehensively for effective compounds, pre-clinically test new drugs, and optimize precision medicine. It thereby hinders the development of therapies that can increase the survival of minority and underserved patients. The noted lack of cell lines from underrepresented groups should constitute a call to action to establish additional cell lines and ensure adequate representation of all population groups in this critical pre-clinical research resource.

KEYWORDS

lung cancer, cell lines, underrepresented, diversity, cancer health disparities, lung adenocarcinoma, squamous cell lung cancer, *in vitro* models

Introduction

Lung cancer remains the leading cause of cancer death in the United States (1, 2) and in the world (3) and is a prominent source of cancer health disparities (4). In the United States, Black men have the highest rate of lung cancer mortality among all groups (5). Lung cancer deaths in the United States have steadily declined due in large part to a decrease in smoking rates, particularly within Black men and women (4, 6). As a result, the gap in lung cancer deaths between Black and White men is slowly closing (1). Yet Black men in the United States still show a 12% higher lung cancer incidence rate and a 15% higher lung cancer death rate compared to White men (4, 6). Many factors are thought to contribute to this disparity, including socioeconomic factors, such as a lower frequency of screening, lack of awareness of and access to molecular testing, lack of awareness and participation in clinical trials, mistrust of the medical profession, and lack of diversity in the biomedical workforce (7–9). Importantly, genetic differences between Black and White subjects likely also play a role (10–14), with further studies required to uncover additional associations (15). It has been determined that genetics can affect lung cancer risk (16, 17), for example through differences in nicotine and carcinogen uptake (18–24) or the strength of detoxification responses (10, 25–27). Genetic background/ancestry can also affect the nature of driver mutations acquired by tumors (28–32), tumor mutational burden (33), and patient response to therapy (34). Given the numerous possible effects of genetic background on lung cancer development, pathology, and treatment, it is vital that race/ethnicity be considered in lung cancer research (35).

There are many established model systems to study lung cancer *in vitro* or *in vivo* (36). Among these, lung cancer cell lines represent a versatile and relatively affordable resource that can be widely disseminated to the scientific community (36, 37). Cell lines can be used to gain molecular insights into the development and progression of lung cancer and to pre-clinically test prospective lead candidate drugs (36, 37). Given the disproportionate impact of lung cancer on Black individuals as documented in the United States (4–6), we investigated the availability of lung cancer cell lines from Black and other underrepresented population groups, in order to determine whether available cell lines adequately represent the diversity in histological type, gender, race, and ethnicity required for optimal lung cancer research. The current review summarizes our findings.

Lung cancer types

An important consideration for the use of cancer cell lines is that they must represent the diversity of cancer types for a given organ. In the case of lung cancer, the major histological types of lung cancer should be represented. Historically, four major histological types were designated: lung adenocarcinoma (LUAD), squamous cell carcinoma (LUSQ), small cell lung cancer (SCLC), and large cell carcinoma (LULCC) (Figure 1). Based on the 2015 World Health Organization reclassification of the 2004-designated lung cancer histological types, these four groups were reclassified into three major types: Lung adenocarcinoma, squamous cell carcinoma, and neuroendocrine tumors (40–42), the latter including small cell lung cancer and large cell carcinoma. Lung adenocarcinoma (LUAD), arising in the air sacs (alveoli) of the distal lung, is the most frequently occurring histological type and commonly presents in the following subtypes: lepidic, acinar, papillary, micropapillary, and solid (42). In addition, LUAD can present as invasive mucinous, colloid, fetal, enteric, and minimally invasive (42). Squamous cell lung cancer (LUSQ) is thought to arise in the airways, is the second most common major lung cancer type, and shows clearly present squamous morphologic patterns. LUSQ can be subclassified as keratinizing, nonkeratinizing, and basaloid. Within neuroendocrine tumors, the most common type is small cell lung cancer (SCLC), a very aggressive cancer that is thought to arise mainly from rare pulmonary neuroendocrine cells [though therapy-resistant lung adenocarcinoma can recur as SCLC, through genetic alterations and a possible stem cell intermediate (43, 44)]. Large cell lung carcinomas (LULCC) are poorly differentiated and when neuroendocrine morphology or staining patterns are seen, large cell lung cancers are referred to as large cell neuroendocrine carcinomas. Large cell carcinomas lacking neuroendocrine markers have been largely reclassified and assigned to other

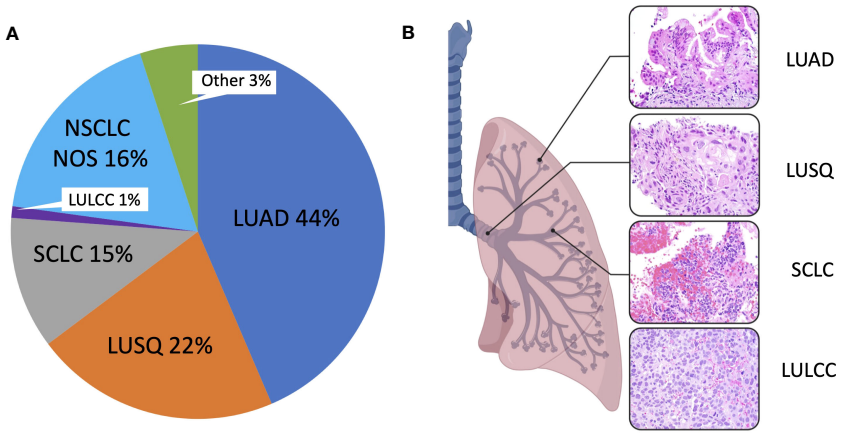

FIGURE 1
Major lung cancer histological subtypes. **(A)** Pie chart showing mortality data indicating the proportion of different histological subtypes. Mortality data was obtained from the Surveillance, Epidemiology, and End Results (SEER) Program based on 17 registries in different regions of the United States (www.seer.cancer.gov). SEER*Stat Database: Incidence-Based Mortality - SEER Research Data, 17 Registries, Nov 2021 Sub (2000-2019) - Linked To County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2022, based on the November 2021 submission. Mortality was calculated via incidence-based mortality (IBM), a method to capture population-level mortality which can be attributable to particular tumor types or other variable reported to SEER registries. IBM calculations were done as described (38). ICD-O-3 morphology codes were grouped together to form the main histologic subtypes, as described (39). LUAD, Lung adenocarcinoma; LULCC, Lung large cell carcinoma; LUSQ, Lung squamous cell cancer; NOS, Lung cancer, not otherwise specified; Other, Other specified carcinoma, including but not limited to carcinoid carcinoma, adenosquamous carcinoma, salivary gland-type carcinomas; SCLC, Small cell lung cancer. **(B)** Hematoxylin and eosin-stained sections of different lung cancer types at 400x magnification.

groups depending on immunohistochemical analyses, leaving only a small group of highly undifferentiated cancers designated as large cell carcinomas (~ 1%) (42).

We used data from the Surveillance, Epidemiology and End Results (SEER, https://seer.cancer.gov/) program, a large United States-based cancer registry that at present includes over 331 million subjects from 17 regions, to assess lung cancer mortality for different races/ethnicities for the main histological types (Figure 2). The data shows LUAD as the most common histological type across all gender and racial/ethnic categories. Black men and White women show the highest age-adjusted mortality rates for LUAD. Squamous cell lung cancer is the second most common histological type, with Black men and women showing the highest age-adjusted mortality rates for LUSQ. Age-adjusted mortality rates for SCLC are highest for White men and women, while for LULCC they are highest for Black men. Cell lines have been established from the most common lung cancer types (36), with lung adenocarcinoma cell lines predominating because cultures were relatively easy to establish. It should be noted that the histological classifications of cell lines are based on the WHO classification in use at the time the lines were established and may thus not fully match current designations.

Cell lines as model systems

Lung cancer cell lines allow the *in vitro* study of human lung cancer, and are especially important for facilitating research when tumor samples are difficult to obtain. SCLC is one such case; it is rarely surgically resected because patients usually present with metastases. In principle, cell lines can be propagated indefinitely and relatively cheaply and are easily disseminated, which allows different labs to study the same cells and compare their results, for example in drug screens. Another advantage of cancer cell lines is that they are pure populations of cells, lacking contaminating stroma and other cell types, thereby allowing detailed genetic and epigenetic studies. This lack of context also has its drawbacks, but these can be addressed using certain culture conditions and model systems as described in a later section.

The first cancer cell line to be cultured was the HeLa cell line, derived from Henrietta Lacks, a black woman with cervical cancer (46). Important ethical questions have been raised about the fact that the cells were obtained at the time without informed consent from the patient (47). The establishment of the HeLa cell line was a scientific breakthrough, and HeLa cells have been widely used in academic and biotech laboratories (47). The demonstrated ability to culture tumor cells from a human patient set the stage for subsequent work establishing cell lines from many kinds of cancer, including lung cancer cell lines.

Due in large part to intensive efforts by Drs. Gazdar, Minna, and Carney to optimize methods to derive cell cultures from patient lung tumors, a large number of cell lines were established (37, 48). With their collaborators, these investigators ultimately cultured more than 200 lung cancer cell lines of different histological types, initially at the National Cancer Institute (NCI-designated lung cancer cell lines), and later at UT Southwestern Medical Center at the Hamon Cancer Center (HCC-designated cell lines).

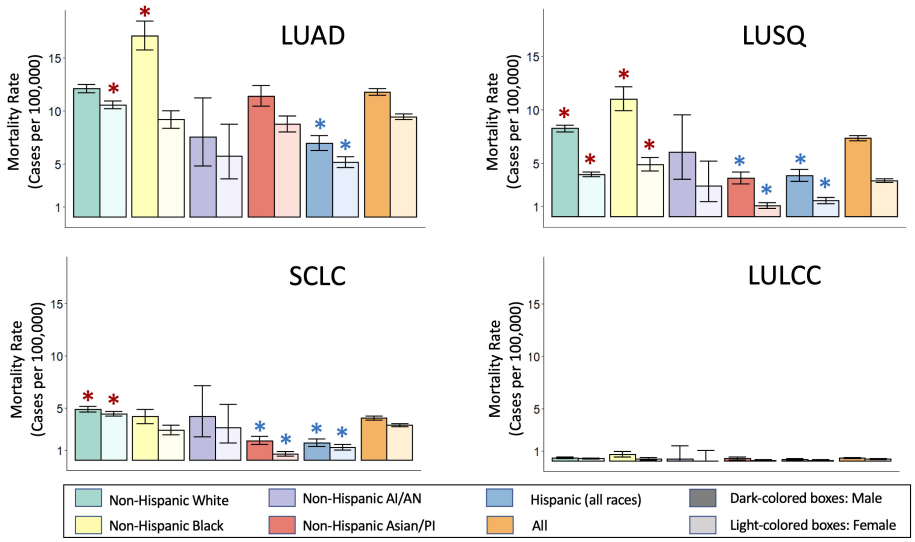

FIGURE 2
Race and ethnicity-specific mortality data for lung cancer histological subtypes. Mortality data was obtained from the Surveillance, Epidemiology, and End Results (SEER) Program based on 17 registries in different regions of the United States (www.seer.cancer.gov). SEER*Stat Database: Incidence-Based Mortality - SEER Research Data, 17 Registries, Nov 2021 Sub (2000-2019) - Linked To County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2022, based on the November 2021 submission. Mortality rates are given for each group per 100,000 individuals in that group. Mortality rates were calculated via incidence-based mortality (IBM), a method to capture population-level mortality which can be attributable to particular tumor types or other variable reported to SEER registries. IBM calculations were done as described (38). ICD-O-3 morphology codes were grouped together to form the main histologic subtypes, as described (39). Rate ratio comparison for mortality between individual race/ethnic groups compared to the overall rate of the respective gender were requested as outputs from SEER*Stats, which utilizes the Tiwari method (45). Taking into account a Bonferroni correction for the 40 comparisons, made, we considered the rate ratio significantly different compared to the "All" rate of their respective gender (orange bars) for p-value<0.00125. *,Significantly higher than the All rates for that gender; *,Significantly lower that the All rates for that gender. LUAD, Lung adenocarcinoma; LULCC, Lung large cell carcinoma; LUSQ, Lung squamous cell cancer; SCLC, Small cell lung cancer.

Combined with the efforts of other investigators across the world, over 400 lung cancer cell lines have been reported (36). Many of these cell lines have been cultured for decades, raising concerns among some investigators that the lines might experience genetic drift. Fortunately, the genetic and epigenetic alterations seen in lung cancer cell lines have remained relatively stable over time (37). It has also been asked how well the obtained cell lines represent the tumors from which they are derived. A comparison between a large number of lung cancer cell lines and primary lung cancers has demonstrated that many key genetic and epigenetic changes seen in lung cancer tumors have also been observed in cell lines (37).

Cell line quality and authentication

Two important considerations when using cell lines for research are cell line quality and authenticity. The presence of contaminating microorganisms, particularly mycoplasma, and the cross-contamination with other cell lines can invalidate performed research (49, 50). Mycoplasma is a type of infectious prokaryote lacking a rigid cell wall. While primary cells can be contaminated, laboratory personnel can also be a source of infection (49). Infection can affect cell growth and physiology, thereby nullifying experimental results and making it imperative that cultures be routinely tested so that contaminated cultures be discarded (49, 51–54). If discarding is not an option because a cell line is rare or even irreplaceable, treatment with antibiotics may be considered (55). Authentication of cell lines is also of critical importance. A previous lack of cell line authentication has resulted in large numbers of publications based on incorrect cell types, including many cell lines found to be, in truth, HeLa cells (56). Thus, cell lines should be obtained from reliable sources and should be routinely authenticated through DNA fingerprinting, i.e., the use of short tandem repeats (STRs) (47, 51, 53, 54, 57) (see Table 1 for useful web sites). Journals and granting agencies can help minimize misidentification by requiring authors to authenticate cell lines used in publications (58, 59), such as required by the National Institutes of Health (https://grants.nih.gov/grants/guide/notice-files/not-od-15-103.html). Current recommendations are to test cell lines for mycoplasma and authenticity when they first reach a new laboratory, before publication, and every two months while in culture.

Representation of different races/ethnicities in current lung cancer cell line collections

We investigated the availability of lung cancer cell lines representing different races/ethnicities using the resources listed in Table 2. We identified over 800 lung cancer cell lines (Supplementary Table 1). A substantial fraction of these are

TABLE 1 Cell line verification web sites.

Goal	Web site
Identify cell lines	https://www.atcc.org/search-str-database
Identify cell lines	https://www.cellosaurus.org/
Identify cell lines	https://www.dsmz.de/services/human-and-animal-cell-lines/online-str-analysis
Find mislabeled cell lines	https://www.atcc.org/the-science/authentication/reclassified-cell-lines

isogenic (derived from the same parental line) or derived from different sites of the same patient. We identified almost 200 lung cancer cell lines from White subjects (Supplementary Table 1A), 6.5-fold more than the 31 cell lines available from Black patients (Table 3, Supplementary Table 1B). One of the 31 cell lines appears to be a duplicate (NCI-H2108 lists identical patient age, gender, cancer histology, and cell line STR analysis to NCI-H2107). Of the 30 unique Black lung cancer cell lines, 6 were derived from lung adenocarcinomas, 4 from squamous cell cancers, 11 from SCLCs, and the remainder were from unspecified non-small cell lung cancers (3), adenosquamous carcinomas (2), large cell carcinomas (2), a carcinoid tumor, a giant cell carcinoma, and a mucinoepidermoid carcinoma. Ancestry information was available for 24 of these lines, and showed African ancestry, ranging from 56% to 91%.

We identified 390 cell lines from Asian lung cancer patients (Supplementary Table 1C), of which 20% appear to be non-unique (e.g. from different metastatic sites in the body of a given patient), or sister cell lines derived through manipulation of the original cell line.

We did not identify any cell lines representing H/L, AI/AN, or NHOPI individuals. It is possible that H/L ethnicity has not been properly documented for existing cell lines and thus, that such cell lines might be present in the current collection. However, while cell line race can be retrospectively examined using ancestry informative markers (single nucleotide polymorphisms that help infer ancestry admixtures (70–73)), H/L individuals in the Unites States represent an admixture population that may include White, Black, and AI/AN components and would be difficult to genetically identify. Going forward, ethnicity information would need to be documented at the time of sample collection.

TABLE 2 Resources from which lung cancer cell line information was obtained.

Resource Name	Web site
ATCC: The Global Bioresource Center	https://www.atcc.org/
cBioPortal for Cancer Genomics	https://www.cbioportal.org/
Expasy - Cellosaurus.	https://www.cellosaurus.org/
Wellcome Sanger Institute. Cell model Passports. A Hub for Preclinical Cancer Models.	https://cellmodelpassports.sanger.ac.uk/passports?tissue=lung

Additional data was obtained from the literature (36, 37, 50, 60–69).

We found almost 300 cell lines for which race/ethnicity is unknown (Supplementary Table 1D). Thus, there may be Black, AI/AN, and NHOPI cell lines among these unclassified lines and it may be worth determining their genetic ancestry (70–73).

We noted that the number of cell lines developed from men was over 2-fold higher than cell lines developed from women, and this excess was most prominent for the cell lines developed from Asian individuals (almost 7-fold) (Supplementary Table 1). This difference exceeds what might be expected based on the higher frequency of lung cancer detected in males, and indicates a disparity in the representation of female individuals in lung cancer cell lines. Overall, we conclude that there is a marked lack of cell lines from underrepresented populations and an underrepresentation of cell lines from women.

Cell lines representing the cells-of-origin of different types of lung cancer

In addition to cell lines derived from tumors, it is also important to establish cell lines derived from the cells-of-origin for the different lung cancer histological types. These cells can be useful for modeling the sequential development of the different lung cancer histological types and the effects of environmental exposures on lung cells from the airway or alveolar compartments. Genetic background can affect lung cancer predisposition as well as the metabolism and detoxification of tobacco smoke components (10, 18–27, 74). Thus, just as we need lung cancer cell lines from different races and ethnicities, we need cell-of-origin cell lines from different races and ethnicities to appropriately model lung cancer development. Normal lung cells derived from humans are not immortal and will undergo senescence when propagated *in vitro* (75). Immortalized cell lines must therefore be created using either viral genes such as Simian Virus 40 large T antigen (SV40LgT) (76, 77) or human papillomavirus E6+E7 genes (78), or overexpression/modification of human genes that allow cell cycle progression and prevent telomere shortening and the resulting senescence (79).

LUAD arises from alveolar epithelium, and to model human lung adenocarcinoma development *in vitro*, human immortalized alveolar epithelial cells are required. Four immortalized alveolar epithelial cell lines (hAECs) were established using SV40LgT antigen (80, 81). Race is only known for 3 of these cell lines, which were derived from White subjects (81). In addition, a polyclonal alveolar epithelial cell line of unknown race/ethnicity was established using a proprietary cocktail of 33 immortalization genes (82) and from it, a monoclonal cell line (Arlo) was recently derived (83). It will be important to develop additional immortalized alveolar epithelial cell lines for other racial/ethnic groups, given that LUAD is the most common lung cancer histological type in the United States for both genders and all races and ethnicities (Figure 2).

Human bronchial epithelial cells, the putative cells of origin of LUSQ, have been immortalized with SV40LgT, resulting in the BEAS-2B cell line (84), and by using overexpression of the telomerase gene in combination with either overexpression of G1

10.3389/fonc.2023.1187585

TABLE 3 Lung cancer cell lines from Black patients.

Name	Sex	Age	Histol. Type	Smoking	% African	Mutations
201T	M	68Y	LUAD	U	89	*TP53*
HCC1195	M	47Y	LUAD	U	70	*TP53, NRAS*
HCC122	M	48Y	LUAD	U	U	U
NCI-H23	M	51Y	LUAD	U	68	*TP53, KRAS, STK11, ATM*
NCI-H1373	M	56Y	LUAD	SM (30 py)	72	*TP53, KRAS*
NCI-H1648	M	39Y	LUAD	SM	69	*TP53*
NCI-H125*	M	61Y	LUADSQ	U	U	*TP53*
NCI-H513	M	61Y	LUADSQ	U	84	U
HLF-a**	F	54Y	LUSQ	U	91	U
NCI-H1385	F	49Y	LUSQ	SM (33 py)	69	*KRAS*
HCC15	M	47Y	LUSQ	U	77	*TP53, RB1, NRAS, EP300, CTNNB1*
HCC1897	M	47Y	LUSQ	U	77	U
NCI-H64	F	48Y	SCLC	SM (30 py)	68	*TP53*
NCI-H128	M	60Y	SCLC	U	70	*TP53*
NCI-H220	M	51Y	SCLC	NS	U	U
NCI-H250	M	34Y	SCLC	NS	91	*TP53, RB1*
NCI-N390	M	49Y	SCLC	U	U	U
NCI-H748	M	62Y	SCLC	SM (30 py)	86	*TP53, BRCA2*
NCI-H1048	F	53Y	SCLC	NS	70	*TP53, RB1, PIK3CA*
NCI-H1339	F	49Y	SCLC	U	71	*TP53*
NCI-H1963	M	56Y	SCLC	U	56	*TP53, RB1*
NCI-H2107	M	36Y	SCLC	U	U	*TP53*
NCI-H2108***	M	36Y	SCLC	SM (26 py)	U	U
NCI-H835	F	48Y	LUCART	NS	80	U
HCC1359	F	55Y	LUGCC	U	86	*TP53*
HCC3051	M	63Y	LULCC	U	U	U
NCI-H810	M	51Y	LuLCC	U	82	*TP53, DDR2*
NCI-H292	F	32Y	LUMEC	U	81	*NF2*
EMC-BAC-1	M	U	NSCLC	U	74	*TP53, STK11*
NCI-H2110	U	U	NSCLC	NS	83	U
NCI-H2172	F	U	NSCLC	NS	82	U

*Cell line discontinued; **Cell line reported to be contaminated; ***Duplicate cell line (H2107); Sex: M, Male; F, Female; Age: Y,Years; Subtype: LUAD, Lung adenocarcinoma; LUADSQ, Lung adenosquamous carcinoma; LUCART, Lung carcinoid tumor; LUGCC, Lung giant cell carcinoma; LULCC, Lung large cell carcinoma; LUMEC, Lung mucoepidermoid carcinoma; LUSQ, Lung squamous cell cancer; NSCLC, non-small cell lung cancer; SCLC, Small cell lung cancer; Smoking: NS, non-smoker; SM, Smoker; py, pack years; U, Unknown; % African: Percentage African ancestry; U, Unknown; Mutations: known mutations are indicated; U, Unknown. Additional information can be found in Supplementary Table 1B.

cell cycle kinase CDK4 or short hairpin RNA-based knockdown of cell cycle regulatory proteins $p16^{INK4A}$ and $p14^{ARF}$. The latter yielded human bronchial epithelial cells (HBECs) and small airway epithelial cells (SAECs) (85, 86). BEAS-2B, HBEC, and SAEC cell lines can be useful to model the development of squamous cell lung cancer or determine the effects of environmental exposures on airway cells. To our knowledge, the race/ethnicity of the individuals from whom the cell lines were derived is unknown. Thus, ancestry tests of these lines would be useful, as would establishing more of these types of cell lines representing diverse races.

The availability of methods to establish immortalized alveolar and airway cells allows progress to be made in deriving additional cell lines from racially and ethnically diverse subjects. However,

there is one important cell type for which no immortalized human cell lines have yet been established: pulmonary neuroendocrine (PNE) cells, the main cell-of-origin of SCLC (87). Immortalized PNE cells would be an important added tool to study the development of SCLC and may be especially relevant for studies of Black SCLC, as this type of cancer may arise at an earlier age in Black subjects than in other races (88, 89). However, PNE cells are rare (less than 1% of lung epithelial cells) making their isolation and immortalization challenging. One possible strategy is to derive these cells from induced pluripotent stem cells (iPSCs), a feat that was recently achieved (90).

Derivation of cell line types from induced pluripotent cells has also been used to obtain bronchial epithelial cells (91) and alveolar epithelial cells (92–94). The availability of racially/ethnically diverse iPSCs (95) provides an opportunity to derive diverse cell lines representing lung cancer cells-of-origin. However, iPSC-derived cell populations can consist of mixed cell types, and considerable time and expertise are required to differentiate them correctly (96, 97). Whether the epigenomes of such iPSC-derived cells fully match those of the corresponding adult differentiated cell types would also need to be determined. Using cell lines with the correct initial epigenome is particularly relevant in studies of the effect of environmental exposures (98). Epigenetic changes play a role in the development of all cancer types (99) and can be driven by environmental exposures such as tobacco smoke (100, 101). Using cell lines with epigenomes matching the natural cells-of-origin is also highly relevant for the study of disease-risk single nucleotide polymorphisms (SNPs) (98). Most risk SNPs, including those for lung cancer, lie in intergenic regions or introns, and likely affect risk by introducing changes in epigenetic regulatory elements (102). If cells differentiated from iPSCs do not epigenetically match their normal mature counterparts, regulatory elements may be missing or altered, thus affecting the correct interpretation of risk SNP epigenetic environments.

Applications of lung cancer cell lines and immortalized lung cell lines

Lung cancer cell lines and cell-of-origin cell lines can be used in a wide variety of ways to study lung cancer (36). In the simplest form, they can be grown on Petri dishes in two-dimensional culture or, in the case of classic SCLC cell lines, in suspension (48). Such *in vitro* cultures can be useful for the study of cancer driver and tumor suppressor genes, epigenetic changes in cancer cells, the effects of environmental exposures, and the investigation of lung cancer risk SNPs, among other topics. Cell lines provide a relatively pure population of cells compared to heterogeneous tumor or tissue samples that can contain variable amounts of contaminating blood cells and stroma. This simplification can greatly facilitate analyses and provides one powerful strategy to leverage cell-based models. However, it lacks the complexity arising from growth in three-dimensional space or from the interactions with other cell types, such as fibroblasts and blood vessels. Growth of pure cell lines with a defined medium in three dimensions can provide the next level of complexity, while the addition of fibroblasts, endothelial, and blood cells can further simulate *in vivo* characteristics. Even further advanced are three-dimensional models, so-called "organs-on-a-chip", which may incorporate an air-liquid interface and/or the movement associated with breathing (103, 104). Organ-on-a-chip devices allow epithelial cells to be coated on a main channel and supportive cells or endothelial cells on a parallel secondary channel separated by a thin porous membrane (105). They can be used to study cancerous cells or cancer cells-of-origin, and should be considered for drug testing as the cellular microenvironment can affect cancer cells' susceptibility to drugs (106, 107).

No matter how advanced an *in vitro* model is, it will not provide a natural tumor microenvironment identical to that found *in vivo*. To achieve the latter, implantation of cell lines into model organisms such as mice is required. To avoid rejection, immunocompromised ("nude") mice or humanized mice need to be used. Such models, known as xenografts, can be made using human cancer cell lines, primary patient tumors, or even circulating tumor cells (108). Subcutaneous implantation is often used; while not fully mimicking the natural microenvironment, it allows easy monitoring of tumor size and thereby any therapeutic responses. However, if the cells used do not capture the racial and ethnic diversity of lung cancer patients, all models will fall short in moving lung cancer research forward for all population groups.

Discussion

Lung cancer cell lines and cell lines from lung cancer cells-of-origin are a key part of the research toolkit needed to advance knowledge on the development, progression, diagnosis, and treatment of lung cancer. However, in order to ensure that the knowledge gained, tools developed, and treatments devised are applicable to the population regardless of race or ethnicity, we need to ensure that cell lines representing all groups are available. In particular, cell lines representative of Black males should be at hand as Black males show the highest rates of lung cancer death. Here, we investigated the availability of lung cancer cell lines from underrepresented minority populations. We identified over 800 lung cancer cell lines, including ~200 unique lung cancer cell lines from White subjects and over 300 from Asian subjects. This contrasted with just 30 unique lung cancer cell lines available from Black patients. No lung cancer cell lines from H/L, AI/AN, or NHOPI individuals were identified, though some maybe present among the almost 300 lung cancer cell lines of unknown race/ethnicity. It is important to carry out ancestry analyses of existing cell lines to verify which race these lines best represent. In addition, a concerted effort should be made to generate more cell lines from women and underrepresented groups, and to document ethnicity at the time of tissue collection. Expanding the cell line repertoire is even more relevant for cell-of-origin lines, of which there are very few, and to our knowledge none from underrepresented groups.

It should be considered that certain racial/ethnic groups may have cultural objections to donating cells or tissues. Those desires should be respected, even if it means that population groups may

not be represented in research. It is also important to keep in mind that broadly defined race/ethnicity groups do not capture the heterogenicity of admixed populations. For example, an analysis of Hispanic men in Florida showed that while lung cancer mortality rates were lower than those of White men, they were 50% higher in Puerto Rican than non-Puerto Rican men (109). Once cell lines from all groups willing to participate have been collected and represent all three major lung cancer types and cells-of-origin (from both men and women), thought should be given to key subpopulations that may merit disaggregation.

One short-term way to partially alleviate the current paucity of lung cancer cell lines representing different racial/ethnic groups is to use genome engineering to derive isogenic cell lines from the handful of underrepresented cell lines available. Cancer driver genes present in the cell lines can be replaced by other driver genes to generate cell lines in which the effects of different driver genes within a similar genomic context can be examined. This would expand the cell line repertoire available for molecular and drug development studies. However, to do this in a biologically meaningful way, the key cancer driver genes present in the different racial/ethnic populations of lung cancer patients must be identified. Unfortunately, cancer driver genes in underrepresented populations are under-studied. For example, in the public database The Cancer Genome Atlas (https://www.cancer.gov/ccg/research/genome-sequencing/tcga), the number of sequenced lung cancer samples from White patients outnumbers that of Black patients by almost 9:1. Thus, data on driver mutations in underrepresented patients must also be expanded. Clearly, much work remains to be done. The first step is to highlight current shortcomings in knowledge and resources, and to disseminate information to lung cancer patients of all races and ethnicities about the need for cell lines representing lung cancer in their communities. Explaining how lung cancer cell lines and cell-of-origin lines can be used to improve research and develop new therapies for people of the patients' own racial/ethnic backgrounds can help patients make an informed decision about whether to participate. In addition, it would be beneficial if the donations of tissues/cells were discussed with patients by researchers and/or clinicians from their own racial/ethnic group, supporting mutual trust and a better understanding of research goals (7–9). To this end, all races and ethnicities should be well-represented in the medical and biomedical research professions. Thus, we need to build not only the tools, but also foster the success of clinicians and biomedical researchers who can advocate for the establishment and implementation of those tools.

Author contributions

CL, EM, DIR, NSL, PEP, YH and IAO conceived of the study. CL identified and tabulated lung cancer cell lines. CL, AMN, MRC, DAV, MY, BR, WC, DIR, and MG drafted sections of the manuscript. JC extracted data from SEER and generated figures, all authors assisted with editing, and IAO oversaw and finalized the manuscript. All authors contributed to the article and approved the submitted version.

Positionality statement

The authors represent the following racial/ethnic groups: White Hispanic/LaIn(x) (CL, JC, MRC, DAV, PEP, DIR, MG), Black non-Hispanic(EM,Jr, AMN, NSL), White non-Hispanic (IAO), and Asian (MY, BR, WC, YH).

Funding

This study was supported by grants U54CA233396, U54CA233444, and U54CA233465 from the National Institutes of Health (NIH)/National Cancer Institute (NCI), R21HL162405 from the NIH/National Heart, Lung, and Blood Institute (NHLBI), the Norris Comprehensive Cancer Center core grant, award number P30CA014089 from the NIH/NCI. IAO is supported in part by NIH/NHLBI grant R35HL135747, the California Tobacco-Related Disease Research Program (T31IP913 and T32IP5392), the Wright Foundation, and generous donations from Mrs. Judy Glick and Mrs. Conya Pembroke. MG is supported by the Keck School of Medicine Dean's Fellowship. AMN is supported by a fellowship from the Hastings Center for Pulmonary Research.

Acknowledgments

The authors gratefully acknowledge all the members of the Florida-California Cancer Research Education and Engagement ($CaRE^2$) Health Equity Center for their support as well as members of the Offringa and Dr. Crystal Marconett labs for helpful discussions.

Conflict of interest

EM sits on an advisory board for Takeda.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1187585/full#supplementary-material

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/caac.21654

2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* (2023) 73(1):17–48. doi: 10.3322/caac.21763

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

4. DeSantis CE, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for African Americans, 2019. *CA Cancer J Clin* (2019) 69(3):211–33. doi: 10.3322/caac.21555

5. Cronin KA, Scott S, Firth AU, Sung H, Henley SJ, Sherman RL, et al. Annual report to the nation on the status of cancer, part 1: National cancer statistics. *Cancer* (2022) 128(24):4251–84. doi: 10.1002/cncr.34479

6. Giaquinto AN, Miller KD, Tossas KY, Winn RA, Jemal A, Siegel RL. Cancer statistics for African American/black people 2022. *CA Cancer J Clin* (2022) 72(3):202–29. doi: 10.3322/caac.21718

7. Byrd GS, Edwards CL, Kelkar VA, Phillips RG, Byrd JR, Pim-Pong DS, et al. Recruiting intergenerational African American males for biomedical research Studies: a major research challenge. *J Natl Med Assoc* (2011) 103(6):480–7. doi: 10.1016/S0027-9684(15)30361-8

8. Lin JJ, Mhango G, Wall MM, Lurslurchachai L, Bond KT, Nelson JE, et al. Cultural factors associated with racial disparities in lung cancer care. *Ann Am Thorac Soc* (2014) 11(4):489–95. doi: 10.1513/AnnalsATS.201402-055OC

9. Mitchell E, Alese OB, Yates C, Rivers BM, Blackstock W, Newman L, et al. Cancer healthcare disparities among African Americans in the United States. *J Natl Med Assoc* (2022) 114(3):236–50. doi: 10.1016/j.jnma.2022.01.004

10. Byun J, Han Y, Li Y, Xia J, Long E, Choi J, et al. Cross-ancestry genome-wide meta-analysis of 61,047 cases and 947,237 controls identifies new susceptibility loci contributing to lung cancer. *Nat Genet* (2022) 54(8):1167–77. doi: 10.1038/s41588-022-01115-x

11. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* (2006) 354(4):333–42. doi: 10.1056/NEJMoa033250

12. Jones CC, Bush WS, Crawford DC, Wenzlaff AS, Schwartz AG, Wiencke JK, et al. Germline genetic variants and lung cancer survival in African Americans. *Cancer Epidemiol Biomarkers Prev* (2017) 26(8):1288–95. doi: 10.1158/1055-9965.EPI-16-0998

13. Mitchell KA, Shah E, Bowman ED, Zingone A, Nichols N, Pine SR, et al. Relationship between West African ancestry with lung cancer risk and survival in African Americans. *Cancer Causes Control* (2019) 30(11):1259–68. doi: 10.1007/s10552-019-01212-z

14. Stram DO, Park SL, Haiman CA, Murphy SE, Patel Y, Hecht SS, et al. Racial/ethnic differences in lung cancer incidence in the multiethnic cohort study: an update. *J Natl Cancer Inst* (2019) 111(8):811–9. doi: 10.1093/jnci/djy206

15. Ryan BM. Lung cancer health disparities. *Carcinogenesis* (2018) 39(6):741–51. doi: 10.1093/carcin/bgy047

16. Basu A, Kopulos L, Geissen N, Sukhal S, Smith SB. Analysis of the 30-pack-year smoking threshold in African Americans from an underserved lung cancer screening program. *J Am Coll Radiol* (2021) 18(1 Pt A):27–33. doi: 10.1016/j.jacr.2020.08.017

17. Etzel CJ, Kachroo S, Liu M, D'Amelio A, Dong Q, Cote ML, et al. Development and validation of a lung cancer risk prediction model for African-Americans. *Cancer Prev Res (Phila)* (2008) 1(4):255–65. doi: 10.1158/1940-6207.CAPR-08-0082

18. Amos CI, Gorlov IP, Dong Q, Wu X, Zhang H, Lu EY, et al. Nicotinic acetylcholine receptor region on chromosome 15q25 and lung cancer risk among African Americans: a case-control study. *J Natl Cancer Inst* (2010) 102(15):1199–205. doi: 10.1093/jnci/djq232

19. Blackman E, Ashing K, Gibbs D, Kuo YM, Andrews A, Ramakodi M, et al. The Cancer Prevention Project of Philadelphia: preliminary findings examining diversity among the African diaspora. *Ethn Health* (2021) 26(5):659–75. doi: 10.1080/13557858.2018.1548695

20. Hancock DB, Guo Y, Reginsson GW, Gaddis NC, Lutz SM, Sherva R, et al. Genome-wide association study across European and African American ancestries identifies a SNP in DNMT3B contributing to nicotine dependence. *Mol Psychiatry* (2018) 23(9):1911–9. doi: 10.1038/mp.2017.193

21. Hansen HM, Xiao Y, Rice T, Bracci PM, Wrensch MR, Sison JD, et al. Fine mapping of chromosome 15q25.1 lung cancer susceptibility in African-Americans. *Hum Mol Genet* (2010) 19(18):3652–61. doi: 10.1093/hmg/ddq268

22. Murphy SE, Park SL, Balbo S, Haiman CA, Hatsukami DK, Patel Y, et al. Tobacco biomarkers and genetic/epigenetic analysis to investigate ethnic/racial differences in lung cancer risk among smokers. *NPJ Precis Oncol* (2018) 2:17. doi: 10.1038/s41698-018-0057-y

23. Perez-Stable EJ, Herrera B, Jacob P 3rd, Benowitz NL. Nicotine metabolism and intake in black and white smokers. *JAMA* (1998) 280(2):152–6. doi: 10.1001/jama.280.2.152

24. Quach BC, Bray MJ, Gaddis NC, Liu M, Palviainen T, Minica CC, et al. Expanding the genetic architecture of nicotine dependence and its shared genetics with multiple traits. *Nat Commun* (2020) 11(1):5562. doi: 10.1038/s41467-020-19265-z

25. Arauz RF, Byun JS, Tandon M, Sinha S, Kuhn S, Taylor S, et al. Whole-exome profiling of NSCLC among African Americans. *J Thorac Oncol* (2020) 15(12):1880–92. doi: 10.1016/j.jtho.2020.08.029

26. Boldry EJ, Patel YM, Kotapati S, Esades A, Park SL, Tiirikainen M, et al. Genetic determinants of 1,3-butadiene metabolism and detoxification in three populations of smokers with different risks of lung cancer. *Cancer Epidemiol Biomarkers Prev* (2017) 26(7):1034–42. doi: 10.1158/1055-9965.EPI-16-0838

27. Taioli E, Ford J, Trachman J, Li Y, Demopoulos R, Garte S. Lung cancer risk and CYP1A1 genotype in African Americans. *Carcinogenesis* (1998) 19(5):813–7. doi: 10.1093/carcin/19.5.813

28. Carrot-Zhang J, Soca-Chafre G, Patterson N, Thorner AR, Nag A, Watson J, et al. Genetic ancestry contributes to somatic mutations in lung cancers from admixed Latin American populations. *Cancer Discovery* (2021) 11(3):591–8. doi: 10.1158/2159-8290.CD-20-1165

29. Heath EI, Lynce F, Xiu J, Ellerbrock A, Reddy SK, Obeid E, et al. Racial disparities in the molecular landscape of cancer. *Anticancer Res* (2018) 38(4):2235–40. doi: 10.21873/anticanres.12466

30. Kytola V, Topaloglu U, Miller LD, Bitting RL, Goodman MM, D. Agostino RBJ, et al. Mutational landscapes of smoking-related cancers in Caucasians and African Americans: precision oncology perspectives at wake forest baptist comprehensive cancer center. *Theranostics* (2017) 7(11):2914–23. doi: 10.7150/thno.20355

31. Lusk CM, Watza D, Dyson G, Craig D, Ratliff V, Wenzlaff AS, et al. Profiling the mutational landscape in known driver genes and novel genes in African American non-small cell lung cancer patients. *Clin Cancer Res* (2019) 25(14):4300–8. doi: 10.1158/1078-0432.CCR-18-2439

32. Soh J, Toyooka S, Matsuo K, Yamamoto H, Wistuba II, Lam S, et al. Ethnicity affects EGFR and KRAS gene alterations of lung adenocarcinoma. *Oncol Lett* (2015) 10(3):1775–82. doi: 10.3892/ol.2015.3414

33. Schenk A, Lopez S, Kschischo M, McGranahan N. Germline ancestry influences the evolutionary disease course in lung adenocarcinomas. *Evol Appl* (2020) 13(7):1550–7. doi: 10.1111/eva.12964

34. Sausville LN, Jones CC, Aldrich MC, Blot WJ, Pozzi A, Williams SM. Genetic variation in the eicosanoid pathway is associated with non-small-cell lung cancer (NSCLC) survival. *PloS One* (2017) 12(7):e0180471. doi: 10.1371/journal.pone.0180471

35. Harrison S, Judd J, Chin S, Ragin C. Disparities in lung cancer treatment. *Curr Oncol Rep* (2022) 24(2):241–8. doi: 10.1007/s11912-022-01193-4

36. Gazdar AF, Hirsch FR, Minna JD. From mice to men and back: an assessment of preclinical model systems for the study of lung cancers. *J Thorac Oncol* (2016) 11(3):287–99. doi: 10.1016/j.jtho.2015.10.009

37. Gazdar AF, Gao B, Minna JD. Lung cancer cell lines: Useless artifacts or invaluable tools for medical science? *Lung Cancer* (2010) 68(3):309–18. doi: 10.1016/j.lungcan.2009.12.005

38. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med* (2020) 383(7):640–9. doi: 10.1056/NEJMoa1916623

39. Lewis DR, Check DP, Caporaso NE, Travis WD, Devesa SS. US lung cancer trends by histologic type. *Cancer* (2014) 120(18):2883–92. doi: 10.1002/cncr.28749

40. Rodak O, Peris-Diaz MD, Olbromski M, Podhorska-Okolow M, Dziegiel P. Current landscape of non-small cell lung cancer: epidemiology, histological classification, targeted therapies, and immunotherapy. *Cancers (Basel)* (2021) 13(18). doi: 10.3390/cancers13184705

41. Travis WD. The 2015 WHO classification of lung tumors. *Pathologe* (2014) 35 (Suppl 2):188. doi: 10.1007/s00292-014-1974-3

42. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 world health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* (2015) 10(9):1243–60. doi: 10.1097/JTO.0000000000000630

43. Offin M, Chan JM, Tenet M, Rizvi HA, Shen R, Riely GJ, et al. Concurrent RB1 and TP53 Alterations Define a Subset of EGFR-Mutant Lung Cancers at risk for Histologic Transformation and Inferior Clinical Outcomes. *J Thorac Oncol* (2019) 14(10):1784–93. doi: 10.1016/j.jtho.2019.06.002

44. Quintanal-Villalonga A, Taniguchi H, Zhan YA, Hasan MM, Chavan SS, Meng F, et al. Multiomic analysis of lung tumors defines pathways activated in neuroendocrine transformation. *Cancer Discovery* (2021) 11(12):3028–47. doi: 10.1158/2159-8290.CD-20-1863

45. Tiwari RC, Clegg LX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. *Stat Methods Med Res* (2006) 15(6):547–69. doi: 10.1177/0962280206070621

46. Scherer WF, Syverton JT, Gey GO. Studies on the propagation in *vitro* of poliomyelitis viruses. IV. Viral multiplication in a stable strain of human Malignant epithelial cells (strain HeLa) derived from an epidermoid carcinoma of the cervix. *J Exp Med* (1953) 97(5):695–710. doi: 10.1084/jem.97.5.695

47. Masters JR. HeLa cells 50 years on: the good, the bad and the ugly. *Nat Rev Cancer* (2002) 2(4):315–9. doi: 10.1038/nrc775

48. Carney DN, Gazdar AF, Bepler G, Guccion JG, Marangos PJ, Moody TW, et al. Establishment and identification of small cell lung cancer cell lines having classic and variant features. *Cancer Res* (1985) 45(6):2913–23.

49. Drexler HG, Uphoff CC. Mycoplasma contamination of cell cultures: Incidence, sources, effects, detection, elimination, prevention. *Cytotechnology* (2002) 39(2):75–90. doi: 10.1023/A:1022913015916

50. Gazdar AF, Girard L, Lockwood WW, Lam WL, Minna JD. Lung cancer cell lines as tools for biomedical discovery and research. *J Natl Cancer Inst* (2010) 102 (17):1310–21. doi: 10.1093/jnci/djq279

51. Dennert K, Kumar R. Traceability methods for cell line authentication and mycoplasma detection. *SLAS Technol* (2021) 26(6):630–6. doi: 10.1177/24726303211030290

52. Olarerin-George AO, Hogenesch JB. Assessing the prevalence of mycoplasma contamination in cell culture *via* a survey of NCBI's RNA-seq archive. *Nucleic Acids Res* (2015) 43(5):2535–42. doi: 10.1093/nar/gkv136

53. Uphoff CC, Drexler HG. Eradication of Mycoplasma contaminations from cell cultures. *Curr Protoc Mol Biol* (2014) 106:28 5 1– 5 12. doi: 10.1002/0471142727.mb2805s106

54. Young L, Sung J, Stacey G, Masters JR. Detection of Mycoplasma in cell cultures. *Nat Protoc* (2010) 5(5):929–34. doi: 10.1038/nprot.2010.43

55. Molla Kazemiha V, Shokrgozar MA, Arabestani MR, Shojaei Moghadam M, Azari S, Maleki S, et al. PCR-based detection and eradication of mycoplasmal infections from various mammalian cell lines: a local experience. *Cytotechnology* (2009) 61 (3):117–24. doi: 10.1007/s10616-010-9252-6

56. Horbach S, Halffman W. The ghosts of HeLa: How cell line misidentification contaminates the scientific literature. *PloS One* (2017) 12(10):e0186281. doi: 10.1371/journal.pone.0186281

57. Eltonsy N, Gabisi V, Li X, Russe KB, Mills GB, Stemke-Hale K. Detection algorithm for the validation of human cell lines. *Int J Cancer* (2012) 131(6):E1024–30. doi: 10.1002/ijc.27533

58. Babic Z, Capes-Davis A, Martone ME, Bairoch A, Ozyurt IB, Gillespie TH, et al. Incidences of problematic cell lines are lower in papers that use RRIDs to identify cell lines. *Elife* (2019) 8. doi: 10.7554/eLife.41676

59. Souren NY, Fusenig NE, Heck S, Dirks WG, Capes-Davis A, Bianchini F, et al. Cell line authentication: a necessity for reproducible biomedical research. *EMBO J* (2022) 41(14):e111307. doi: 10.15252/embj.2022111307

60. Bepler G, Jaques G, Neumann K, Aumuller G, Gropp C, Havemann K. Establishment, growth properties, and morphological characteristics of permanent human small cell lung cancer cell lines. *J Cancer Res Clin Oncol* (1987) 113(1):31–40. doi: 10.1007/BF00389964

61. Bepler G, Koehler A, Kiefer P, Havemann K, Beisenherz K, Jaques G, et al. Characterization of the state of differentiation of six newly established human non-small-cell lung cancer cell lines. *Differentiation* (1988) 37(2):158–71. doi: 10.1111/j.1432-0436.1988.tb00806.x

62. Blanco R, Iwakawa R, Tang M, Kohno T, Angulo B, Pio R, et al. A gene-alteration profile of human lung cancer cell lines. *Hum Mutat* (2009) 30(8):1199–206. doi: 10.1002/humu.21028

63. Ghandi M, Huang FW, Jane-Valbuena J, Kryukov GV, Lo CC, McDonald ER 3rd, et al. Next-generation characterization of the cancer cell line encyclopedia. *Nature* (2019) 569(7757):503–8. doi: 10.1038/s41586-019-1186-3

64. Gottschling S, Jauch A, Kuner R, Herpel E, Mueller-Decker K, Schnabel PA, et al. Establishment and comparative characterization of novel squamous cell non-small cell lung cancer cell lines and their corresponding tumor tissue. *Lung Cancer* (2012) 75 (1):45–57. doi: 10.1016/j.lungcan.2011.05.020

65. Klijn C, Durinck S, Stawiski EW, Haverty PM, Jiang Z, Liu H, et al. A comprehensive transcriptional portrait of human cancer cell lines. *Nat Biotechnol* (2015) 33(3):306–12. doi: 10.1038/nbt.3080

66. Nusinow DP, Szpyt J, Ghandi M, Rose CM, McDonald ER 3rd, Kalocsay M, et al. Quantitative proteomics of the cancer cell line encyclopedia. *Cell* (2020) 180(2):387–402 e16. doi: 10.1016/j.cell.2019.12.023

67. Phelps RM, Johnson BE, Ihde DC, Gazdar AF, Carbone DP, McClintock PR, et al. NCI-Navy Medical Oncology Branch cell line data base. *J Cell Biochem Suppl* (1996) 24:32–91. doi: 10.1002/jcb.240630505

68. Sekido Y, Sato M, Usami N, Shigemitsu K, Mori S, Maeda O, et al. Establishment of a large cell lung cancer cell line (Y-ML-1B) producing granulocyte colony-stimulating factor. *Cancer Genet Cytogenet* (2002) 137(1):33–42. doi: 10.1016/S0165-4608(02)00536-8

69. Zheng C, Sun YH, Ye XL, Chen HQ, Ji HB. Establishment and characterization of primary lung cancer cell lines from Chinese population. *Acta Pharmacol Sin* (2011) 32(3):385–92. doi: 10.1038/aps.2010.214

70. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. *Genome Res* (2009) 19(9):1655–64. doi: 10.1101/gr.094052.109

71. Galanter JM, Fernandez-Lopez JC, Gignoux CR, Barnholtz-Sloan J, Fernandez-Rozadilla C, Via M, et al. Development of a panel of genome-wide ancestry informative markers to study admixture throughout the Americas. *PloS Genet* (2012) 8(3): e1002554. doi: 10.1371/journal.pgen.1002554

72. Kosoy R, Nassir R, Tian C, White PA, Butler LM, Silva G, et al. Ancestry informative marker sets for determining continental origin and admixture proportions in common populations in America. *Hum Mutat* (2009) 30(1):69–78. doi: 10.1002/humu.20822

73. Phillips C, Salas A, Sanchez JJ, Fondevila M, Gomez-Tato A, Alvarez-Dios J, et al. Inferring ancestral origin using a single multiplex assay of ancestry-informative marker SNPs. *Forensic Sci Int Genet* (2007) 1(3-4):273–80. doi: 10.1016/j.fsigen.2007.06.008

74. Zanetti KA, Wang Z, Aldrich M, Amos CI, Blot WJ, Bowman ED, et al. Genome-wide association study confirms lung cancer susceptibility loci on chromosomes 5p15 and 15q25 in an African-American population. *Lung Cancer* (2016) 98:33–42. doi: 10.1016/j.lungcan.2016.05.008

75. Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res* (1965) 37:614–36. doi: 10.1016/0014-4827(65)90211-9

76. Bryan TM, Reddel RR. SV40-induced immortalization of human cells. *Crit Rev Oncog* (1994) 5(4):331–57. doi: 10.1615/CritRevOncog.v5.i4.10

77. Jha KK, Banga S, Palejwala V, Ozer HL. SV40-mediated immortalization. *Exp Cell Res* (1998) 245(1):1–7. doi: 10.1006/excr.1998.4272

78. Halbert CL, Demers GW, Galloway DA. The E6 and E7 genes of human papillomavirus type 6 have weak immortalizing activity in human epithelial cells. *J Virol* (1992) 66(4):2125–34. doi: 10.1128/jvi.66.4.2125-2134.1992

79. Lundberg AS, Hahn WC, Gupta P, Weinberg RA. Genes involved in senescence and immortalization. *Curr Opin Cell Biol* (2000) 12(6):705–9. doi: 10.1016/S0955-0674(00)00155-1

80. Kemp SJ, Thorley AJ, Gorelik J, Seckl MJ, O'Hare MJ, Arcaro A, et al. Immortalization of human alveolar epithelial cells to investigate nanoparticle uptake. *Am J Respir Cell Mol Biol* (2008) 39(5):591–7. doi: 10.1165/rcmb.2007-0334OC

81. Tran E, Shi T, Li X, Chowdhury AY, Jiang D, Liu Y, et al. Development of human alveolar epithelial cell models to study distal lung biology and disease. *iScience* (2022) 25(2):103780. doi: 10.1016/j.isci.2022.103780

82. Kuehn A, Kletting S, de Souza Carvalho-Wodarz C, Repnik U, Griffiths G, Fischer U, et al. Human alveolar epithelial cells expressing tight junctions to model the air-blood barrier. *ALTEX* (2016) 33(3):251–60. doi: 10.14573/altex.1511131

83. Carius P, Jungmann A, Bechtel M, Grissmer A, Boese A, Gasparoni G, et al. A monoclonal human alveolar epithelial cell line ("Arlo") with pronounced barrier function for studying drug permeability and viral infections. *Adv Sci (Weinh)* (2023) 10(8):e2207301. doi: 10.1002/advs.202207301

84. Reddel RR, Ke Y, Gerwin BI, McMenamin MG, Lechner JF, Su RT, et al. Transformation of human bronchial epithelial cells by infection with SV40 or adenovirus-12 SV40 hybrid virus, or transfection *via* strontium phosphate coprecipitation with a plasmid containing SV40 early region genes. *Cancer Res* (1988) 48(7):1904–9.

85. Ramirez RD, Sheridan S, Girard L, Sato M, Kim Y, Pollack J, et al. Immortalization of human bronchial epithelial cells in the absence of viral oncoproteins. *Cancer Res* (2004) 64(24):9027–34. doi: 10.1158/0008-5472.CAN-04-3703

86. Smith JL, Lee LC, Read A, Li Q, Yu B, Lee CS, et al. One-step immortalization of primary human airway epithelial cells capable of oncogenic transformation. *Cell Biosci* (2016) 6:57. doi: 10.1186/s13578-016-0122-6

87. Sutherland KD, Proost N, Brouns I, Adriaensen D, Song JY, Berns A. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung. *Cancer Cell* (2011) 19(6):754–64. doi: 10.1016/j.ccr.2011.04.019

88. Tapan U, Furtado VF, Qureshi MM, Everett P, Suzuki K, Mak KS. Racial and other healthcare disparities in patients with extensive-stage SCLC. *JTO Clin Res Rep* (2021) 2(1):100109. doi: 10.1016/j.jtocrr.2020.100109

89. Thomas PL, Madubata CJ, Aldrich MC, Lee MM, Owonikoko TK, Minna JD, et al. A call to action: dismantling racial injustices in preclinical research and clinical care of black patients living with small cell lung cancer. *Cancer Discovery* (2021) 11 (2):240–4. doi: 10.1158/2159-8290.CD-20-1592

90. Hor P, Punj V, Calvert BA, Castaldi A, Miller AJ, Carraro G, et al. Efficient generation and transcriptomic profiling of human iPSC-derived pulmonary neuroendocrine cells. *iScience* (2020) 23(5):101083. doi: 10.1016/j.isci.2020.101083

91. McIntyre BA, Alev C, Mechael R, Salci KR, Lee JB, Fiebig-Comyn A, et al. Expansive generation of functional airway epithelium from human embryonic stem cells. *Stem Cells Transl Med* (2014) 3(1):7–17. doi: 10.5966/sctm.2013-0119

92. Kanagaki S, Ikeo S, Suezawa T, Yamamoto Y, Seki M, Hirai T, et al. Directed induction of alveolar type I cells derived from pluripotent stem cells *via* Wnt signaling inhibition. *Stem Cells* (2021) 39(2):156–69. doi: 10.1002/stem.3302

93. Korogi Y, Gotoh S, Ikeo S, Yamamoto Y, Sone N, Tamai K, et al. *In vitro* disease modeling of Hermansky-Pudlak syndrome type 2 using human induced pluripotent stem cell-derived alveolar organoids. *Stem Cell Rep* (2019) 12(3):431–40. doi: 10.1016/j.stemcr.2019.01.014

94. Yamamoto Y, Gotoh S, Korogi Y, Seki M, Konishi S, Ikeo S, et al. Long-term expansion of alveolar stem cells derived from human iPS cells in organoids. *Nat Methods* (2017) 14(11):1097–106. doi: 10.1038/nmeth.4448

95. Chang EA, Tomov ML, Suhr ST, Luo J, Olmsted ZT, Paluh JL, et al. Derivation of ethnically diverse human induced pluripotent stem cell lines. *Sci Rep* (2015) 5:15234. doi: 10.1038/srep15234

96. Meng G, Liu S, Rancourt DE. Synergistic effect of medium, matrix, and exogenous factors on the adhesion and growth of human pluripotent stem cells

under defined, xeno-free conditions. *Stem Cells Dev* (2012) 21(11):2036–48. doi: 10.1089/scd.2011.0489

97. Volpato V, Webber C. Addressing variability in iPSC-derived models of human disease: guidelines to promote reproducibility. *Dis Model Mech* (2020) 13(1). doi: 10.1242/dmm.042317

98. Stueve TR, Marconett CN, Zhou B, Borok Z, Laird-Offringa IA. The importance of detailed epigenomic profiling of different cell types within organs. *Epigenomics* (2016) 8(6):817–29. doi: 10.2217/epi-2016-0005

99. Jones PA, Baylin SB. The epigenomics of cancer. *Cell* (2007) 128(4):683–92. doi: 10.1016/j.cell.2007.01.029

100. Stueve TR, Li WQ, Shi J, Marconett CN, Zhang T, Yang C, et al. Epigenome-wide analysis of DNA methylation in lung tissue shows concordance with blood studies and identifies tobacco smoke-inducible enhancers. *Hum Mol Genet* (2017) 26 (15):3014–27. doi: 10.1093/hmg/ddx188

101. Vaz M, Hwang SY, Kagiampakis I, Phallen J, Patil A, O'Hagan HM, et al. Chronic cigarette smoke-induced epigenomic changes precede sensitization of bronchial epithelial cells to single-step transformation by KRAS mutations. *Cancer Cell* (2017) 32(3):360–76 e6. doi: 10.1016/j.ccell.2017.08.006

102. Yang C, Stueve TR, Yan C, Rhie SK, Mullen DJ, Luo J, et al. Positional integration of lung adenocarcinoma susceptibility loci with primary human alveolar epithelial cell epigenomes. *Epigenomics* (2018) 10(9):1167–87. doi: 10.2217/epi-2018-0003

103. Agraval H, Sharma JR, Dholia N, Yadav UCS. Air-liquid interface culture model to study lung cancer-associated cellular and molecular changes. *Methods Mol Biol* (2022) 2413:133–44. doi: 10.1007/978-1-0716-1896-7_14

104. Si L, Bai H, Rodas M, Cao W, Oh CY, Jiang A, et al. A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics. *Nat BioMed Eng* (2021) 5(8):815–29. doi: 10.1038/s41551-021-00718-9

105. Bai H, Ingber DE. What can an organ-on-a-chip teach us about human lung pathophysiology? *Physiol (Bethesda)* (2022) 37(5):0. doi: 10.1152/physiol.00012.2022

106. Breslin S, O'Driscoll L. The relevance of using 3D cell cultures, in addition to 2D monolayer cultures, when evaluating breast cancer drug sensitivity and resistance. *Oncotarget* (2016) 7(29):45745–56. doi: 10.18632/oncotarget.9935

107. Edmondson R, Broglie JJ, Adcock AF, Yang L. Three-dimensional cell culture systems and their applications in drug discovery and cell-based biosensors. *Assay Drug Dev Technol* (2014) 12(4):207–18. doi: 10.1089/adt.2014.573

108. Lallo A, Schenk MW, Frese KK, Blackhall F, Dive C. Circulating tumor cells and CDX models as a tool for preclinical drug development. *Transl Lung Cancer Res* (2017) 6(4):397–408. doi: 10.21037/tlcr.2017.08.01

109. Pinheiro PS, Callahan KE, Siegel RL, Jin H, Morris CR, Trapido EJ, et al. Cancer mortality in hispanic ethnic groups. *Cancer Epidemiol Biomarkers Prev* (2017) 26 (3):376–82. doi: 10.1158/1055-9965.EPI-16-0684

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