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Racial health disparity in cancer: Assessments of need

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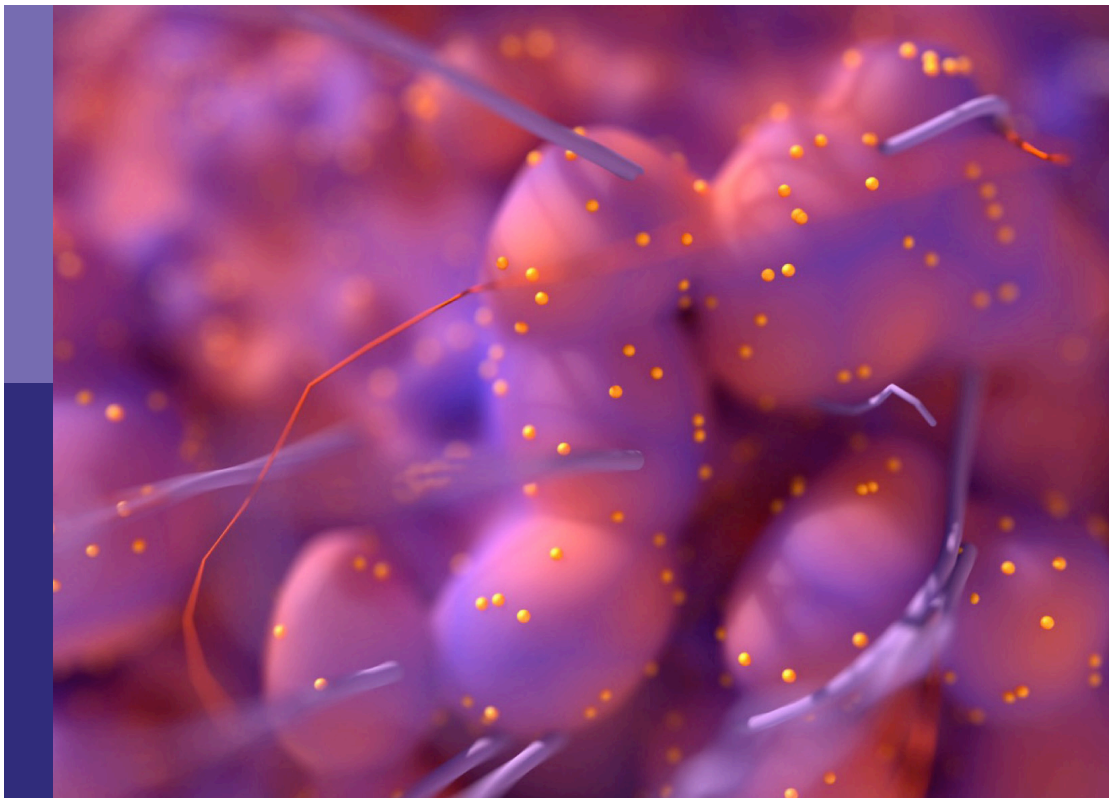

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Racial health disparity in cancer: Assessments of need

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Editorial: Racial health disparity in cancer: assessments of need

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cancer disparities, determinants of cancer burdens, cancer health equity, black indigenous and people of color (BIPOC), structural and systemic racism

Editorial on the Research Topic
Racial health disparity in cancer: assessments of need

Globally, societal inequities and inequalities impact human health and contribute directly to the disparities in cancer incidence, progression, and outcomes between populations. In the United States (US), this includes inequities and inequalities that permeate all aspects of cancer care and control. Disparities are observed across the entirety of the cancer care continuum, including etiology, prevention, early detection, diagnosis, interception, treatment, survivorship, and end-of-life care. This results in higher cancer-related morbidity and mortality in Black, Indigenous, and people of color (BIPOC), people living in poverty and/or rural communities, persons with disability, and individuals who are part of LGBTQA+ communities. This problem persists nearly a century after the initiation of legislation establishing NCI (1937) and despite extensive advances in surveillance mechanisms, prevention, early detection, diagnosis, and treatment of many cancers. With the establishment of SEER in 1973, gender, racial and ethnic disparity have been detected and continue to be monitored. However, it took 27 years after the establishment of SEER before a national concerted effort was put forth to address and mitigate cancer disparity under the purview of NCI Center to Reduce Cancer Health Disparities. And while cancer is declining with advocacy, community partnership, and investment in research and education, African American/Black patients in the US continue to have the highest cancer mortality rates and shortest survival for most cancers (1). In contrast, cancer incidence rates have historically been lower for the US Hispanic/Latino and Asian populations. However, disparities including younger age onset of certain cancers [e.g., colorectal among Hispanics/Latinos (2), breast cancer among Asian women (3)], more infection-related cancers among US Hispanics/Latinos (4) and Asian Americans (5), and disproportionate late-stage diagnoses for some cancers and among subpopulations (4, 5) are emergent concerns; which is further acerbated by the projected growth of these populations.

While racial- and ethnicity-related cancer disparities are often framed in terms of differences in access to care and individual- or group-level adherence to health behaviors, this can be highly counterproductive in efforts to understand, address, and mitigate cancer

disparities. To effectively address this concern, it is important to recognize that individual-level, ancestry-related (e.g., genetics, genomics, and physiology), societal-level (e.g., structural and systemic racism), social-level (e.g., socioeconomic status and educational level), neighborhood-level (e.g., diet and pollution), and institutional-level (e.g., access to care) factors act together and intersect to influence not only an individual's health but also the health of the community, and, therefore, collectively contribute to health disparities that arise therein. With the rapid diversification of the racial and ethnic composition of the US population, including growth among US Hispanics/Latinos, Asian Americans, and individuals of mixed races/ethnicities, wider adoption of methods to disaggregate race and ethnicity to account for individual-level, ancestry-related, societal-, social-, neighborhood-, and institutional-level factors that differ within and between groups will be needed to understand, address, and mitigate the burden of cancer more precisely in communities. These methods will need to include partnering with diverse groups in basic, translational, and clinical cancer research and education. BIPOC, LGBTQA+ populations, rural communities, and low-income people remain underrepresented in cancer research, including genomic projects and clinical trials.

While it is acknowledged that an in-depth 'omics' understanding of the molecular differences in cancers that develop in different populations and communities and how these differences can inform cancer etiology, prevention, detection, diagnosis, interception, treatment, survivorship and end-of-life is essential for advancing and achieving cancer health equity, it is also necessary to understand all of the individual-level, ancestry-related, societal-, social-, neighborhood-, and institutional-level factors that act solely and in concert throughout the natural history of cancer in communities and how these contribute to cancer health disparities. This Research Topic was intended to solicit unpublished research on cancer disparities in racially and ethnically diverse populations. We were looking to generate a publication highlighting the multiple factors that solely and in combination influence cancer and cancer burden at the community-level and contribute to differences between population groups. This included focusing on individual-, ancestry-related-, societal-, social-, neighborhood-, and institutional-level determinants of cancer burdens in different populations and how they individually and jointly contribute to cancer disparities. This Research Topic aimed to promote and advocate for more research efforts toward understanding and addressing the many drivers of cancer health disparities toward ultimately aiding in mitigating cancer health disparities. Nine reports of original cancer research, a perspective, a mini-review, and a methods paper are all included in this Research Topic. Together, these efforts draw attention to the many often interrelated factors (e.g., genetic, genomic, screening, environment, socioeconomic, and racism) contributing to cancer disparities. The works of these authors and their teams also emphasize the greater need to engage racially, ethnically, culturally, and sexual/gender diverse individuals and communities in cancer-relevant research and education as an essential step towards understanding and addressing the cancer burden in communities to advance evidence-based strategies to achieve cancer health equity for all individuals, their families, and their communities.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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Variation in Cancer Incidence Rates Among Non-Hispanic Black Individuals Disaggregated by Nativity and Birthplace, 2005-2017: A Population-Based Cancer Registry Analysis

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Objectives: Compared to other racial and ethnic groups, little to no disaggregated cancer incidence data exist for subgroups of non-Hispanic Blacks (NHBs), despite heterogeneity in sociodemographic characteristics and cancer risk factors within this group. Our objective was to examine age-adjusted cancer incidence by nativity and birthplace among NHB cancer cases diagnosed in New Jersey.

Methods: Race, ethnicity, and birthplace data from the New Jersey State Cancer Registry were used to classify NHB cancer cases diagnosed between 2005-2017. Thirteen waves of population estimates (by county, nativity, gender, age-group) were derived from the American Community Survey using Integrated Public-Use Microdata to approximate yearly demographics. Age-adjusted cancer incidence rates (overall and by site) by birthplace were generated using SEER*Stat 8.3.8. Bivariate associations were assessed using chi-square and Fisher's exact tests. Trend analyses were performed using Joinpoint 4.7.

Results: Birthplace was available for 62.3% of the 71,019 NHB cancer cases. Immigrants represented 12.3%, with African-born, Haitian-born, Jamaican-born, 'other-Caribbean-born', and 'other-non-American-born' accounting for 18.5%, 17.7%, 16.5%, 10.6%, and 36.8%, respectively. Overall, age-adjusted cancer incidence rates were lower for NHB immigrants for all sites combined and for several of the top five cancers, relative to

American-born NHBs. Age-adjusted cancer incidence was lower among immigrant than American-born males (271.6 vs. 406.8 per 100,000) and females (191.9 vs. 299.2 per 100,000). Age-adjusted cancer incidence was lower for Jamaican-born (114.6 per 100,000) and other-Caribbean-born females (128.8 per 100,000) than African-born (139.4 per 100,000) and Haitian-born females (149.9 per 100,000). No significant differences in age-adjusted cancer incidence were observed by birthplace among NHB males. Age-adjusted cancer incidence decreased for all sites combined from 2005-2017 among American-born males, immigrant males, and American-born females, while NHB immigrant female rates remained relatively stable.

Conclusions: There is variation in age-adjusted cancer incidence rates across NHB subgroups, highlighting the need for more complete birthplace information in population-based registries to facilitate generating disaggregated cancer surveillance statistics by birthplace. This study fills a knowledge gap of critical importance for understanding and ultimately addressing cancer inequities.

Keywords: cancer surveillance, cancer incidence, non-Hispanic Black subgroups, within-group differences, cancer inequities, population-based study, cancer registry data

INTRODUCTION

Non-Hispanic Blacks (NHBs) represent the second-largest racial/ethnic minority group in the United States (US)—comprising approximately 13.4% of the population, as of 2019 (1). The NHB population is a diverse group that includes descendants of enslaved Africans brought to the Americas during the transatlantic slave trade beginning in the 16th century and immigrants arriving more recently from across the African diaspora and their descendants. Immigrants account for 10% of the NHB population, with Jamaican-born, Haitian-born, and Nigerian-born individuals accounting for the three largest NHB subgroups by birthplace (2, 3). Inequities in cancer incidence, mortality, and survival exist by race and ethnicity for many cancer sites (4), with evidence showing the highest sex-specific cancer incidence among NHB males and the highest sex-specific mortality among NHB females (5). Furthermore, 5-year relative survival for all cancers combined is lowest among NHBs (5, 6). Despite the knowledge that NHBs disproportionately shoulder the burden of cancer (7) and that NHBs in the US are not a monolithic group (2), little to no cancer surveillance statistics exist for subgroups of NHBs, in contrast to subgroups of Asian American/Pacific Islander (8–15) and Hispanic/Latinx individuals (13, 15–17).

While limited data are currently available on cancer incidence among disaggregated NHB groups (18, 19), a handful of studies show significant heterogeneity in cancer mortality by NHB subgroup in the US (20–23). African-born NHBs have higher incidence of infection-related cancers (18) and Caribbean-born NHBs have lower risk of cancer mortality (20–23) compared to American-born NHBs, suggesting that the aggregation of all NHBs into a singular group in cancer surveillance masks within-group differences and limits the ability to inform targeted intervention needs for higher-risk communities.

Cancer surveillance programs in the US have successfully begun generating cancer profiles for subgroups of Asian American/Pacific Islander (24) and Hispanic/Latinx (25), yet, to our knowledge, no such profiles exist for NHB subgroups. As a starting point, we examined variation in age-adjusted cancer incidence by birthplace among NHB cancer cases diagnosed in New Jersey (NJ)–the fourth most racially/ethnically diverse state in the US, with substantial socioeconomic, geographic, and subgroup diversity within the NHB population. Further, we highlight methodologic limitations related to generation of race and ethnicity subgroup data and next steps for standardization and systematic data collection of NHB subgroups.

METHODS

Age-adjusted cancer incidence rates (overall and by site) were generated using cancer incidence data from the New Jersey State Cancer Registry (NJSCR). The NJSCR is a population-based registry that collects data on all cancer cases diagnosed in NJ. NJSCR consistently receives awards for data quality and completeness from the North American Association of Central Cancer Registries (NAACCR), the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (NPCR), and the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results Program (SEER). The Rutgers University Institutional Review Board approved this study.

All NHB cancer cases diagnosed from 2005-2017 were included. Subgroup categories (American-born, NHB immigrants, and unknown) were created using country of birth and US birth state data from NJSCR. Individuals born in the US and its territories were considered American-born (26); otherwise, they were grouped as NHB immigrants or unknown. NHB immigrant subgroups by birthplace (African-

born, Haitian-born, Jamaican-born, other Caribbean-born, and other NHB immigrants) were created using nativity and country of birth. The group classified as 'other Caribbean-born' included individuals born in Caribbean countries other than Haiti and Jamaica (e.g., Trinidad and Tobago, Grenada, Antigua and Barbuda, Barbados), while other NHB immigrants included individuals not classified in one of the previous subgroups. For NHB population estimates, we used Integrated Public-Use Microdata (IPUMS) from the American Community Survey (ACS, 1-year waves) for 2005–2017. To estimate the NHB population: 1) we considered individuals classified as NHB in some way (e.g., multiracial–NHB and another race) as exclusively NHB in this study (3), and 2) we classified major origin sites of NHB immigrants residing in NJ, including Haitian, Jamaican, other Caribbean countries, and sub-Saharan African.

Cancer incidence data and population estimates were processed in SEER*Prep 2.5.7 to create SEER*Stat databases. We used chi-square and Fisher's exact tests to examine associations between NHB subgroup and age group (0-39, 40-64, or ≥65 years), gender (male or female), vital status (alive or deceased), cancer site (SEER Site Recode based on International Classification of Diseases for Oncology, 3rd edition), cancer stage (SEER summary stage), county of residence (health care regions), and census tract poverty (<5%, 5-<10%, 10-<20%, or ≥20%). Bivariate analyses were completed in SAS 9.4. Statistical significance was set at $p<0.05$.

Incidence rates for all cancers combined and rates by cancer site across NHB subgroups and gender were computed in SEER*Stat 8.3.8. Rates are per 100,000 and age-adjusted to the 2000 US standard population. Trend analysis to examine estimated annual percent change in age-adjusted incidence rates over the study period was performed using Joinpoint 4.7. We used the log-linear model and Monte Carlo Permutation method for significance tests, and the significance level was set at $P<0.05$.

RESULTS

Descriptive Statistics of NHB Cancer Cases Diagnosed in NJ

Between January 1, 2005 and December 31, 2017, there were 71,019 incident cancers diagnosed among NHB individuals in NJ (**Table 1**). Among those with documented birthplace, NHB immigrants represented 12.3%, while American-born represented 87.7%. Among NHB immigrants, 18.5% were born in an African country, 17.7% in Haiti, 16.5% in Jamaica, 10.6% in another Caribbean country (not Haiti or Jamaica), and 36.8% elsewhere (not in the US or an African or Caribbean country). NHB cases with unknown birthplace (37.7%) were younger, diagnosed at earlier stages, and alive at the end of follow-up. The proportion of cases with unknown birthplace varied across the study period, ranging from as low as 28.6% (in 2005) to as high as 50.2% (in 2017) (**Supplementary Table 1**). Compared to American-born NHBs, significantly larger proportions of cases among NHB immigrants were diagnosed at 0-39 years (6.1% vs. 4.1%) and 40-64 years (50.3% vs. 40.9%), and a smaller proportion at age ≥65 years (43.6% vs. 55.0%). Stage distribution was similar between American-born and NHB immigrant cases. There was some variation by birthplace in terms of regions of New Jersey where the largest proportions of NHB cases resided. Larger proportions of NHB immigrant groups regions generally resided in Essex and Passaic counties, Bergen and Hudson counties, and Middlesex and Union counties. NHB immigrant populations increased most in a few contiguous counties, from Essex to Mercer County (**Figure 1**). However, the change in representation of specific ancestries of NHB immigrants varies across the state. For example, southern counties experienced an increase in Haitian and Jamaican populations during the study period.

As of December 31, 2017, 52.3% of NHB cancer cases overall were deceased and there was an indication that the proportion of American-born cases who died was larger than that of NHB immigrants (80.0% vs. 59.2%). Only 10.7% of deceased cases were missing birthplace information. We also found that slightly higher proportions of NHB immigrants were lost to follow-up in earlier years of the study period than American-born cases, but follow-up rates were similar in more recent years (**Supplementary Table 2**).

Age-Adjusted Cancer Incidence Among NHBs in NJ

Relative to American-born individuals, NHB immigrants had lower cancer incidence rates for all cancer sites combined and for several of the top five cancers diagnosed among NHBs. Among NHB males, the age-adjusted cancer incidence rate for all sites combined was 607.9/100,000 (**Table 2**). Age-adjusted cancer incidence was higher in American-born NHB males than immigrant NHB males (271.6 vs. 406.8/100,000). Notably, cancer incidence for all sites combined among other NHB immigrant males was exceptionally high (803.4/100,000). While prostate cancer incidence did not differ among American-born and immigrant NHB males, incidence rates for several cancer sites were lower among NHB immigrants than among American-born males: lung and bronchus (26.2 vs. 77.5/100,000), colon and rectum (30.3 vs. 44.9/100,000), kidney and renal pelvis (7.9 vs. 15.8/100,000), bladder (7.7 vs. 17.1/100,000), and other sites (95.8 vs. 149.7/100,000). Although none of the differences reached statistical significance, cancer incidence rates varied among NHB males across immigrant subgroups.

Among NHB females, age-adjusted cancer incidence for all sites combined was 431.1/100,000. Age-adjusted cancer incidence was lower among immigrant NHB females than American-born females (191.9 vs. 299.2/100,000). Similar to males, cancer incidence for all sites combined among other NHB immigrant females was quite high (614.9/100,000). Cancer incidence rates among NHB females varied across immigrant subgroups: incidence was lower among Jamaican-born (114.6/100,000) and other Caribbean-born females (128.8/100,000) compared to African-born (139.4/100,000) and Haitian-born females (149.9/100,000). All site-specific cancer incidence rates (except corpus and uterine) were lower among

TABLE 1 | Descriptive statistics of non-Hispanic Black (NHB) cancer cases diagnosed in New Jersey by nativity and birthplace, 2005-2017.

Sociodemographic characteristic	All NHB cancer cases[1]	American-born[2]	NHB immigrants[3-7]					Unknown birthplace[8]	P (2,3,4,5,6,7,8)
			African-born[3]	Haitian-born[4]	Jamaican-born[5]	Other Caribbean-born[6]	Other immigrants[7]		
	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Total	71019 (100.0)	38834 (54.7)	1004 (18.5)	960 (17.7)	896 (16.5)	574 (10.6)	1999 (36.8)	26752 (37.7)	
Age Group									<0.0001*
0-39	3772 (5.3)	1600 (4.1)	110 (11.0)	73 (7.6)	46 (5.1)	34 (5.9)	69 (3.5)	1840 (6.9)	
40-64	33540 (47.2)	15886 (40.9)	613 (61.1)	475 (49.5)	459 (51.2)	324 (56.4)	862 (43.1)	14921 (55.8)	
≥65	33707 (47.5)	21348 (55.0)	281 (28.0)	412 (42.9)	391 (43.6)	216 (37.6)	1068 (53.4)	9991 (37.3)	
Gender									<0.0001*
Male	35522 (50.0)	18687 (48.1)	566 (56.4)	457 (47.6)	425 (47.4)	272 (47.4)	989 (49.5)	14126 (52.8)	
Female	35497 (50.0)	20147 (51.9)	438 (43.6)	503 (52.4)	471 (52.6)	302 (52.6)	1010 (50.5)	12626 (47.2)	
Primary Site[¤]									
Male									<0.0001*^
Prostate	14034 (39.5)	4677 (25.0)	239 (42.2)	188 (41.1)	164 (38.6)	125 (46.0)	324 (32.8)	8317 (58.9)	
Lung and Bronchus	4271 (12.0)	3493 (18.7)	30 (5.3)	32 (7.0)	43 (10.1)	14 (5.1)	127 (12.8)	532 (3.8)	
Colon and Rectum	3363 (9.5)	2000 (10.7)	62 (11.0)	45 (9.8)	43 (10.1)	33 (12.1)	112 (11.3)	1068 (7.6)	
Kidney and Renal Pelvis	1510 (4.3)	760 (4.1)	18 (3.2)	6 (1.3)	14 (3.3)	15 (5.5)	25 (2.5)	672 (4.8)	
Urinary Bladder	1161 (3.3)	707 (3.8)	6 (1.1)	4 (0.9)	15 (3.5)	10 (3.7)	27 (2.7)	392 (2.8)	
Other	11183 (31.5)	7050 (37.7)	211 (37.3)	182 (39.8)	146 (34.4)	75 (27.6)	374 (37.8)	3145 (22.3)	
Female									<0.0001*
Breast	10864 (30.6)	5130 (25.5)	145 (33.1)	168 (33.4)	150 (31.8)	120 (39.7)	251 (24.9)	4900 (38.8)	
Lung and Bronchus	4119 (11.6)	3320 (16.5)	21 (4.8)	25 (5.0)	24 (5.1)	9 (3.0)	84 (8.3)	636 (5.0)	
Colon and Rectum	3710 (10.5)	2090 (10.4)	29 (6.6)	36 (7.2)	47 (10.0)	31 (10.3)	117 (11.6)	1360 (10.8)	
Corpus and Uterus NOS	2452 (6.9)	1252 (6.2)	34 (7.8)	45 (8.9)	35 (7.4)	19 (6.3)	104 (10.3)	963 (7.6)	
Pancreas	1200 (3.4)	963 (4.8)	24 (5.5)	24 (4.8)	17 (3.6)	5 (1.7)	41 (4.1)	126 (1.0)	
Other	13152 (37.1)	7392 (36.7)	185 (42.2)	205 (40.8)	198 (42.0)	118 (39.1)	413 (40.9)	4641 (36.8)	
SEER Summary Stage									<0.0001*
In Situ	4904 (6.3)	1771 (4.3)	41 (3.7)	47 (4.4)	62 (6.4)	33 (5.3)	57 (2.7)	2893 (9.3)	
Local	30060 (38.5)	12148 (29.5)	387 (35.3)	346 (32.6)	365 (37.4)	218 (35.2)	576 (27.7)	16020 (51.6)	
Regional	14209 (18.2)	8145 (19.8)	207 (18.9)	223 (21.0)	182 (18.7)	146 (23.6)	348 (16.7)	4958 (16.0)	
Distant	18515 (23.7)	13278 (32.3)	303 (27.7)	294 (27.7)	261 (26.8)	153 (24.7)	766 (36.8)	3460 (11.1)	
Unknown/Unstaged	10319 (13.2)	5792 (14.1)	157 (14.3)	150 (14.2)	105 (10.8)	69 (11.1)	332 (16.0)	3714 (12.0)	
Health Care Region (counties)									<0.0001*^
Region 1 (Sussex, Warren)	334 (0.5)	169 (0.4)	9 (0.9)	5 (0.5)	8 (0.9)	3 (0.5)	11 (0.6)	129 (0.5)	
Region 2 (Essex, Passaic)	21017 (29.6)	11614 (29.9)	318 (31.7)	377 (39.3)	325 (36.3)	188 (32.8)	861 (43.1)	7334 (27.4)	
Region 3 (Bergen, Hudson)	7139 (10.1)	4212 (10.8)	123 (12.3)	102 (10.6)	142 (15.8)	140 (24.4)	240 (12.0)	2180 (8.1)	
Region 4 (Morris, Somerset)	2704 (3.8)	1319 (3.4)	78 (7.8)	28 (2.9)	83 (9.3)	41 (7.1)	89 (4.5)	1066 (4.0)	
Region 5 (Hunterdon, Mercer)	5123 (7.2)	2622 (6.8)	91 (9.1)	70 (7.3)	46 (5.1)	8 (1.4)	108 (5.4)	2178 (8.1)	
Region 6 (Middlesex, Union)	11174 (15.7)	6203 (16.0)	269 (26.8)	295 (30.7)	183 (20.4)	140 (24.4)	315 (15.8)	3769 (14.1)	
Region 7 (Monmouth, Ocean)	4247 (6.0)	2256 (5.8)	33 (3.3)	38 (4.0)	38 (4.2)	27 (4.7)	134 (6.7)	1721 (6.4)	
Region 8 (Burlington, Camden)	11687 (16.5)	6222 (16.0)	58 (5.8)	24 (2.5)	41 (4.6)	19 (3.3)	154 (7.7)	5169 (19.3)	
Regions 9 and 10 (Atlantic, Cape May, Cumberland, Gloucester, and Salem)	7560 (10.6)	4204 (10.8)	25 (2.5)	21 (2.2)	30 (3.3)	8 (1.4)	87 (4.4)	3185 (11.9)	

(Continued)

TABLE 1 | Continued

Sociodemographic characteristic	All NHB cancer cases[1]	American-born[2]	NHB immigrants[3-7]					Unknown birthplace[8]	P (2,3,4,5,6,7,8)
			African-born[3]	Haitian-born[4]	Jamaican-born[5]	Other Caribbean-born[6]	Other immigrants[7]		
Unknown	34 (0.1)	13 (0.03)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (0.1)	
Census Tract Poverty									<0.0001*^
<5%	11567 (16.3)	5616 (14.5)	200 (19.9)	154 (16.0)	173 (19.3)	130 (22.6)	368 (18.4)	4926 (18.4)	
5 - <10%	13781 (19.4)	6982 (18.0)	250 (24.9)	177 (18.4)	187 (20.9)	122 (21.3)	346 (17.3)	5717 (21.4)	
10 - <20%	20580 (29.0)	10989 (28.3)	298 (29.7)	338 (35.2)	296 (33.0)	181 (31.5)	651 (32.6)	7827 (29.3)	
≥20%	24969 (35.2)	15183 (39.1)	256 (25.5)	291 (30.3)	239 (26.7)	141 (24.6)	629 (31.5)	8230 (30.8)	
Unknown	122 (0.2)	64 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	5 (0.3)	52 (0.2)	
Vital Status (as of December 2017)									<0.0001*
Alive	33869 (47.7)	7755 (20.0)	646 (64.3)	484 (50.4)	480 (53.6)	351 (61.1)	254 (12.7)	23899 (89.3)	
Deceased	37150 (52.3)	31079 (80.0)	358 (35.7)	476 (49.6)	416 (46.4)	223 (38.9)	1745 (87.3)	2853 (10.7)	

P-values generated using bivariate analysis comparing sociodemographic characteristics by birthplace and nativity.
[1]Based on NAACCR NHIA, NJSCR Race1, and Birthplace (state and county): NHIA = 0 (Non-Hispanic) and Race1 = 2 (Black).
[2]American-Born: NHB cancer cases born in the United States of America and its territories.
[3]African-born: NHB cancer cases born in any nation of Africa.
[4]Haitian-born: NHB cancer cases born in Haiti.
[5]Jamaican-born: NHB cancer cases born in Jamaica.
[6]Other Caribbean-born: NHB cancer cases born in any Caribbean nation other than Haiti and Jamaica.
[7]Other non-US-born: NHB cancer cases not included in the groups above (non-US-born).
[8]Unknown birthplace: NHB cancer cases missing data on birthplace.
**P-values significant with and without inclusion of cases with unknown birthplace.*
^P-values generated using Chi-square and Fisher's exact tests.
[α]Top 5 cancer sites based on NHB age-adjusted (6 age groups) invasive cancer incidence rates 2005-2017 by gender.

immigrant than American-born NHB females: breast (52.4 vs. 76.2/100,000), lung and bronchus (12.4 vs. 49.0/100,000), colon and rectum (18.5 vs. 31.2/100,000), pancreas (8.6 vs. 14.4/100,000), and other sites (83.5 vs. 110.1/100,000).

Age-Adjusted Cancer Incidence Trends Among NHBs in NJ

We observed significant decreasing trends in age-adjusted cancer incidence for all sites combined from 2005-2017 among American-born males, immigrant males, and American-born females, while NHB immigrant female rates remained relatively stable (**Table 3**). Among American-born NHB males, age-adjusted cancer incidence for all sites combined decreased by 4.57% per year. This group also experienced statistically significant reductions in age-adjusted incidence for several site-specific cancers during this time: prostate (-9.37%), lung and bronchus (-3.70%), colon and rectum (-4.85%). Although not statistically significant, age-adjusted kidney and renal pelvis

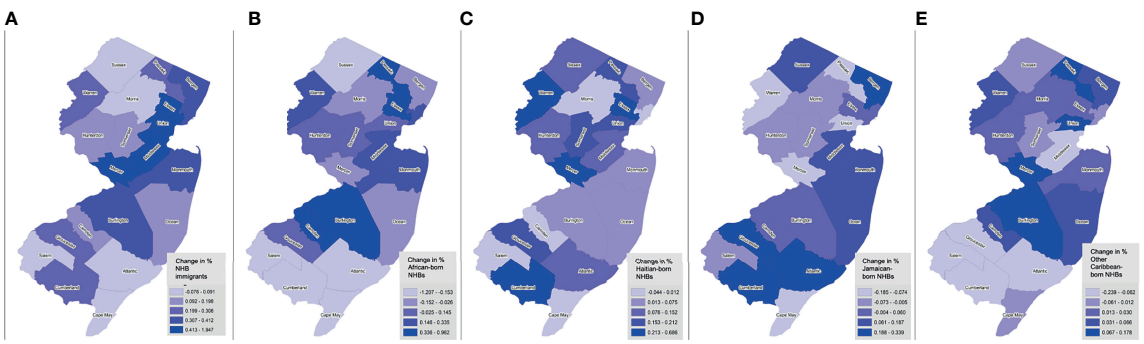

FIGURE 1 | Trends in NHB subgroup populations by birthplace across New Jersey counties, 2005-2017. Shown as change in percent of foreign-born NHBs (overall) **(A)**, African-born **(B)**, Haitian-born **(C)**, Jamaican-born **(D)**, and other Caribbean-born **(E)**, by county.

TABLE 2 | Age-adjusted cancer incidence (per 100,000) among non-Hispanic Black (NHB)[1] individuals in New Jersey by nativity and birthplace, and by gender, 2005-2017.

Gender / Cancer Site[α]	All NHB[1] Rate (95% CI)	American-born[2] Rate (95% CI)	NHB immigrants[3-7] Rate (95% CI)	African-born[3] Rate (95% CI)	Haitian-born[4] Rate (95% CI)	Jamaican-born[5] Rate (95% CI)	Other Caribbean-born[6] Rate (95% CI)	Other NHB immigrants[7] Rate (95% CI)
Male								
All sites combined	607.9 (601.3, 614.5)	406.8 (400.8, 412.9)	271.6 (259.8, 283.9)*	197.2 (176.1, 220.1)	195.2 (174.7, 217.5)	175.8 (156.8, 196.7)	175.1 (151.7, 202.1)	803.4 (750.3, 859.3)††
Prostate	235.9 (231.9, 240.0)	101.9 (98.9, 104.9)	103.8 (96.6, 111.3)	84.2 (70.8, 99.4)	83.6 (70.1, 99.1)	64.0 (53.4, 76.3)	80.4 (65.7, 98.6)	271.2 (240.6, 304.7)
Lung and bronchus	77.5 (75.1, 79.9)	77.5 (74.8, 80.1)	26.2 (22.6, 30.2)*	9.6 (6.0, 15.1)	15.4 (9.9, 23.0)	20.1 (13.9, 28.5)	8.9 (4.5, 18.0)	101.3 (83.2, 122.2)††
Colon and rectum	59.4 (57.3, 61.6)	44.9 (42.9, 46.9)	30.3 (26.3, 34.6)*	22.6 (15.6, 31.6)	19.6 (13.3, 27.8)	17.2 (11.8, 24.5)	20.9 (13.6, 32.4)	92.7 (75.2, 113.2)††
Kidney and renal pelvis	24.4 (23.2, 25.8)	15.8 (14.7, 17.0)	7.9 (6.0, 10.3)*	8.4 (4.1, 15.1)	2.3 (0.8, 5.7)	5.0 (2.7, 9.5)	12.4 (4.2, 27.2)	19.7 (12.2, 30.1)
Urinary bladder	22.5 (21.2, 23.9)	17.1 (15.9, 18.5)	7.7 (5.6, 10.2)*	4.5 (1.2, 10.7)	2.8 (0.6, 7.5)	5.5 (2.8, 10.3)	6.9 (3.0, 15.7)	25.6 (16.4, 38.0)
Other	188.2 (184.5, 191.8)	149.7 (146.1, 153.3)	95.8 (88.9, 103.2)*	68.0 (56.1, 81.7)	71.6 (60.0, 84.9)	64.1 (52.0, 78.3)	45.6 (34.9, 59.8)	292.9 (261.4, 327.1)††
Female								
All sites combined	431.1 (426.6, 435.6)	299.2 (295.1, 303.4)	191.9 (184.3, 199.9)*	139.4 (124.9, 155.1)	149.9 (136.3, 164.7)†	114.6 (103.7, 126.7)†	128.8 (111.2, 148.9)†	614.9 (575.1, 656.8)††
Breast	130.1 (127.6, 132.6)	76.2 (74.1, 78.3)	52.4 (48.8, 56.4)*	40.5 (33.6, 48.6)†	44.7 (38.0, 52.5)	33.8 (28.4, 40.4)†	45.7 (37.5, 56.1)	137.9 (120.3, 157.6)
Lung and bronchus	50.4 (48.8, 51.9)	49.0 (47.4, 50.7)	12.4 (10.5, 14.6)*	8.0 (4.5, 12.9)	8.6 (5.4, 13.2)	5.6 (3.5, 9.3)†	3.7 (1.6, 9.2)†	53.8 (42.4, 67.5)
Colon and rectum	45.6 (44.1, 47.1)	31.2 (29.9, 32.6)	18.5 (16.2, 21.1)*	8.6 (5.4, 13.0)†	10.6 (7.3, 15.1)†	11.4 (8.2, 15.9)†	11.7 (7.8, 18.4)	73.1 (59.8, 88.6)††
Corpus and uterus NOS	29.2 (28.0, 30.4)	18.3 (17.3, 19.3)	16.6 (14.4, 19.0)	13.2 (8.8, 19.0)	13.0 (9.4, 17.8)	8.4 (5.8, 12.4)†	7.8 (4.6, 14.0)†	61.2 (49.2, 75.3)††
Pancreas	15.0 (14.1, 15.9)	14.4 (13.5, 15.3)	8.6 (7.0, 10.5)*	8.4 (4.9, 13.4)	8.6 (5.4, 13.2)	4.3 (2.4, 7.7)	1.6 (0.5, 6.6)†	28.5 (20.1, 39.2)††
Other	160.9 (158.1, 163.7)	110.1 (107.6, 112.6)	83.5 (78.2, 89.0)*	60.7 (51.1, 71.6)†	64.5 (55.3, 74.9)†	51.2 (43.5, 60.1)†	58.3 (44.5, 75.3)†	260.5 (234.3, 288.9)††

[1]*Based on NAACCR NHIA, NJSCR Race1, and Birthplace (state and county): NHIA = 0 (Non-Hispanic) and Race1 = 2 (Black).*
[2]*American-Born: NHB cancer cases born in the United States of America and its territories.*
[3]*African-born: NHB cancer cases born in any nation of Africa.*
[4]*Haitian-born: NHB cancer cases born in Haiti.*
[5]*Jamaican-born: NHB cancer cases born in Jamaica.*
[6]*Other Caribbean-born: NHB cancer cases born in any Caribbean nation other than Haiti and Jamaica.*
[7]*Other non-US-born: NHB cancer cases not included in the groups above (non-US-born).*
[α]*Top 5 cancer sites based on NHB age-adjusted (6 age groups) invasive cancer incidence rates 2005-2017 by gender.*
**Indicates statistically significant difference in incidence rates in comparison to American-born NHBs.*
†*Incidence rates in these immigrant subgroups were significantly lower than rates for NHB immigrants combined.*
††*Incidence rates for these cancers were significantly higher among individuals in the Other NHB immigrant subgroup compared to rates for all NHBs combined.*

cancer incidence decreased by 2.15% per year from 2005-2015 and by 26.22% from 2015-2017. Overall, among NHB immigrant males, age-adjusted cancer incidence for all sites combined decreased by 4.76% per year, and prostate cancer by 9.13% per year. A trend towards decreasing cancer incidence among African-born, Jamaican-born, and other Caribbean-born males was observed, but no estimates reached statistical significance. Conversely, Haitian-born and other NHB immigrant males experienced large reductions in prostate cancer incidence from 2005-2017 (15.16% and 24.27%, respectively).

Among NHB females, cancer incidence trends varied between 2005-2017. Among American-born females, cancer incidence for all sites combined decreased by 3.11% per year from 2005-2012 and 10.44% per year from 2015-2017, while a non-significant increase was recorded from 2012-2015. In this group, incidence of cancers of the breast (-1.98%), lung and bronchus (-1.61% for 2005-2015 only), and colon and rectum (-5.35%) significantly decreased. Although there were no significant trends for all sites combined or most site-specific cancers among NHB immigrant females overall or in subgroups, uterine cancer incidence among Jamaican-born females decreased significantly by 9.06%. Due to zero cases for some cancers among various NHB subgroups by birthplace, we could not calculate annual percent change for some site-specific cancers in some years.

DISCUSSION

This is one of few studies focusing on cancer incidence among NHB, disaggregated by American-born and immigrant subgroups. We observed evidence of within-group differences in age-adjusted cancer incidence rates by NHB subgroup in NJ.

TABLE 3 | Age-adjusted cancer incidence trends for top 5 cancer sites among non-Hispanic Black (NHB)[1] individuals in New Jersey by nativity and birthplace, and by gender, 2005-2017.

Gender / Cancer Site[¤]	American-born[2]		NHB immigrants		African-born		Haitian-born		Jamaican-born		Other Caribbean-born		Other NHB immigrants	
	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC
Male														
All sites combined	2005-2017	-4.57*	2005-2017	-4.76*	2005-2017	-5.23	2005-2017	-8.36	2005-2017	-3.82	2005-2017	-3.38	2005-2017	-13.79*
Prostate	2005-2017	-9.37*	2005-2017	-9.13*	2005-2017	-4.73	2005-2017	-15.16*	2005-2017	-5.48	2005-2017	-2.96	2005-2017	-24.27*
Lung and bronchus	2005-2017	-3.70*	2005-2017	-3.49	–	–	2005-2017	-12.03	2005-2017	-6.02	–	–	2005-2017	-3.38
Colon and rectum	2005-2017	-4.85*	2005-2017	-1.33	2005-2017	-4.50	2005-2017	-12.34	–	–	–	–	2005-2017	-5.42
Kidney and renal pelvis	2005-2015	-2.15*	2005-2017	-1.41	–	–	–	–	–	–	–	–	2005-2017	-11.40
	2015-2017	-26.22	–	–	–	–	–	–	–	–	–	–	–	–
Urinary bladder	2005-2015	-1.78	–	–	–	–	–	–	–	–	–	–	–	–
	2015-2017	-31.13	–	–	–	–	–	–	–	–	–	–	–	–
Female	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC
All sites combined	2005-2012	-3.11*	2005-2017	-0.51	2005-2017	-1.86	2005-2017	-2.47	2005-2017	1.64	2005-2017	-0.36	2005-2017	1.55
	2012-2015	2.39	–	–	–	–	–	–	–	–	–	–	–	–
	2015-2017	-10.44*	–	–	–	–	–	–	–	–	–	–	–	–
Breast	2005-2017	-1.98*	2005-2017	-0.47	2005-2017	-1.18	2005-2017	4.78	2005-2017	3.86	2005-2017	-6.25	2005-2017	0.45
Lung and bronchus	2005-2015	-1.61*	2005-2017	-1.00	–	–	–	–	–	–	–	–	–	–
	2015-2017	-13.20	–	–	–	–	–	–	–	–	–	–	–	–
Colon and rectum	2005-2017	-5.35*	2005-2017	-1.18	2005-2017	-5.77	2005-2017	-4.76	2005-2017	4.38	–	–	2005-2017	1.29
Corpus and uterus NOS	2005-2017	0.77	2005-2017	2.53	–	–	–	–	2005-2017	-9.06*	–	–	2005-2017	4.06
Pancreas	2005-2017	0.99	2005-2017	0.60	–	–	–	–	–	–	–	–	–	–

[¤]*Top 5 cancer sites based on NHB age-adjusted (6 age groups) invasive cancer incidence rates 2005-2017 by gender.*

[1]*Based on NAACCR NHIA, NJSCR Race 1, and Birthplace (state and county): NHIA = 0 (Non-Hispanic) and Race1 = 2 (Black).*

**Annual percent change (APC) is significantly different from zero at alpha = 0.05.*

-Unable to calculate APC due to there being zero case counts in some years.

Notably, NHB immigrant males and females had lower cancer incidence rates than their American-born counterparts for all cancer sites combined and for several of the top five cancers diagnosed among NHBs. Cancer incidence was lower among Jamaican-born and other Caribbean-born females compared to African-born and Haitian-born females. Also, decreasing cancer incidence rates were largely significant for American-born NHBs, but less so for NHB immigrant subgroups. Prior studies examining the relationship between birthplace and cancer outcomes among Hispanic/Latinx populations have shown complex and inconsistent patterns, including a lower probability of being diagnosed with early-stage cancer (27) than their American-born counterparts, while also experiencing lower mortality rates (28). Neighborhood context, including ethnic density and poverty, and length of residence in the US, also influence cancer and other health outcomes differently across subgroups (29–31). More nuanced examination of the structural and neighborhood-level impacts on cancer outcomes is needed within NHB populations moving forward.

Lower cancer incidence rates were observed in the largest NHB immigrant groups compared to American-born NHBs for all cancer sites combined. This observation aligns with previous studies that report lower cancer mortality rates among NHB immigrant compared to American-born cases (20, 21, 32), suggesting higher cancer incidence and mortality rates among NHB compared to other racial groups is not only attributed to Black race. Explanations for lower cancer incidence among NHB immigrants may include the healthy immigrant effect and differences in lifestyle, attitudes, and perceptions among NHB subgroups. For example, tobacco exposure is the primary risk factor attributed to the development of many cancers. A recent

study from the Cancer Prevention and Control Project of Philadelphia (CAP3) showed that Black immigrants have lower smoking prevalence compared to American-born Blacks (3.4% vs. 15%) (33). Findings also showed that as time in the US increased, immigrants had a 4% increase in the odds of ever smoking (33). Further research is, therefore, needed to better understand NHB subgroup differences in smoking behaviors to develop targeted interventions for tobacco exposure among NHB. Additionally, early interventions may be needed for NHB immigrants to prevent the increased likelihood of smoking as their time in the US increases.

The leading cancers among NHB males and females are prostate and breast cancer. We observed no difference in prostate cancer incidence between subgroups of immigrants and American-born NHB, suggesting similar biological risk factors (e.g., such as family history, genetics) and social determinants of health rooted in structural racism (34–37). Studies by the African Caribbean Cancer Consortium (AC3) have compared factors associated with prostate cancer risk between American-born and immigrant NHB men, showing that nativity did not significantly predict the likelihood of prostate cancer screening among NHB men (38). Other studies collectively support the role of genetic polymorphisms in the immune/inflammation genes associated with prostate cancer among both American-born and Caribbean-born NHB men (39–41). This observation is not unusual as there is mounting evidence that the immunologic/inflammatory pathways play an important role in prostate cancer biology among Black men in contrast to White men (42–44). Unlike prostate cancer, we observed lower breast cancer incidence among NHB immigrants compared to American-born females, which might indicate that breast cancer phenotypes differ across NHB subgroups. Among breast cancer cases diagnosed in South Florida from 2006-2017, Caribbean-born NHB immigrants were diagnosed with a larger proportion of estrogen receptor-positive (ER+) and progesterone receptor-positive (PR+) tumors compared to American-born NHB (ER+: 68.7% vs. 61%; P = 0.019 and PR+: 58.3% vs. 50.4%; P = 0.02) (45).

Lung and colorectal cancers are the second and third leading causes of cancer among NHB males and females. NHB immigrants have lower lung cancer incidence than their American-born counterparts. This is expected given the lower smoking prevalence among immigrant groups as described above (33). Kidney and bladder cancers are among the top five cancers for males, and for both cancers, NHB immigrants have lower incidence than American-born NHBs. Again, these differences might be attributed to differences in smoking behaviors between the two groups, as well as to differences in other relevant factors [e.g., diet and hypertension (46, 47)] across NHB groups. NHB immigrants also have lower colorectal cancer incidence than American-born NHBs. Recent findings from the CAP3 study showed that, while NHB immigrants are less likely to have health insurance, they are more likely to adhere to colorectal cancer screening than American-born NHBs (48). Therefore, differences in colorectal cancer incidence may not be related to access issues but to other factors, including diet (46) and neighborhood contextual factors (49, 50).

Uterine and pancreatic cancers are among the top five cancers among NHB females. NHB immigrants females have lower pancreatic cancer incidence than American-born NHBs, which may also be attributed to differences in smoking behavior. However, there was no significant difference in uterine cancer incidence between the two subgroups. This may be due to shared risk factors across birthplace subgroups (e.g., obesity, family history, and other lifestyle factors) (51). It is important to note that Caribbean immigrants are more often diagnosed with uterine cancer at a younger age and have worse survival than their American-born counterparts (51).

NHB immigrants were less likely than American-born NHBs to reside in census tracts with marked poverty, consistent with a national Pew Study showing that NHB immigrants aged >25 years were more likely to have a bachelor's degree and less likely to live in a high-poverty neighborhood than American-born NHBs (52). Moreover, we found that NHB immigrant cases were more likely to be alive at the end of study follow-up. This could be attributed to the "immigrant paradox," where recent immigrants report better overall health than their native-born peers or those who spent more time in the US because of differences in diet, acculturation, and other risk factors associated with cancer development (53). However, this has mostly been studied in Hispanic populations and requires further investigation in NHB populations (53). Differences in neighborhood contextual factors—which are rooted in structural racism (e.g., neighborhood disinvestment, food deserts, environmental chemical exposures)—might also contribute to differences in vital status (54–58).

An important limitation of this study was that missing birthplace data among NHB cancer cases in NJSCR records were relatively high (~38%) and could have led to underestimated cancer incidence rates. Deceased cancer cases are less likely to have unknown birthplace and nativity because death certificate is a major source for this information. This is supported by our findings of lower proportions of unknown birthplace for cancers that tend to be aggressive and/or have lower survival rates (e.g., lung and pancreas) and higher proportions of unknown birthplace for less aggressive cancers and/or those with higher survival rates (e.g., prostate and breast). Another interesting point is that that the proportion of NHB cancer cases with unknown birthplace is higher in recent years compared to earlier years. One reason for this might be that a larger proportion of cases diagnosed at the beginning of the study period (i.e., 2005-2009) are likely to be deceased compared to those diagnosed closer to the end of follow-up (i.e., 2015-2017). While some studies have reported variation in cancer mortality across NHB subgroups (20, 21, 32)—given greater availability of birthplace data among deceased cancer cases (59)—to our knowledge, to date, only one published study has reported variability in cancer incidence between some African-born and US-born individuals (18). Although information on birthplace is routinely collected in Surveillance, Epidemiology, and End Results (SEER) program registries, these data are missing for a large

proportion of cases, likely in a non-random manner (60, 61). The percentage of missing data in our study is similar to cancer incidence studies that focused on Hispanic subgroups (up to 32%) (8, 62). To address missingness, prior studies have applied a series of approaches, including algorithms incorporating surname from cancer registries with (62) and without (8) linkage to death records. Most NHB cases in the current analysis with unknown birthplace were *in situ* or localized stage and <65 years at diagnosis, suggesting that combining incidence and death record data would not improve birthplace data missingness. As an alternative, studies in Hispanic subgroups have imputed missing birthplace using geographic location (62). This, combined with other data sources (e.g., birth records, death records), could further minimize missing birthplace data. Another consideration is that our simplistic definition of "NHB" race might have also led to an underestimation of cancer incidence rates. Relatedly, the use of ACS-based estimates to approximate NHB populations is subject to sampling errors. We also acknowledge that categorizing all African immigrants into one subgroup was not ideal given the geographically, culturally, and ethnically distinct populations that exist in Africa. However, insufficient case counts with birthplaces across multiple African countries (and geographic regions) limited our ability to further disaggregate the African-born subgroup. Nonetheless, we believe this study highlights some important differences in cancer incidence rates among NHB subgroups by birthplace and nativity—albeit in crudely disaggregated categories—that certainly warrant analysis in larger studies in the future. Lastly, the use of cancer registry data limited our ability to assess individual-level cancer risk factors that vary between NHB subgroups as explanations for the observed variation in cancer incidence. Despite the lack of complete data on birthplace and risk factor-related data, our findings add new knowledge about variation in cancer incidence, inclusive of Caribbean-born Black individuals in the US.

Despite these limitations, our novel data—generated from a population-based cancer registry in a state with substantial within-group variation in the NHB population—demonstrate differences in age-adjusted cancer incidence rates among NHBs by nativity and birthplace. Overall, cancer incidence for all sites combined and for the top five cancers, including some screen-detected cancers, was lower among NHB immigrants. Also, variation in cancer incidence trends by birthplace was observed. Improved collection of birthplace and African ancestry information in cancer registries is critically needed to enhance the ability to generate unbiased cancer surveillance statistics in disaggregated NHB groups by birthplace. These data are essential to understanding inequities and informing targeted strategies for cancer prevention and control, especially in subgroups shouldering a disproportionate burden.

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 Rutgers University 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

Conceptualization: AL, JT, JG, AS. Data curation: JL, JG, KP. Formal analysis: JL, JG. Funding acquisition: AL, JT, AS. Methodology: AL, JT, JG, KP, AS. Writing – original draft: AL, FN, JT, SL, CR, AS. Writing – review & editing: All authors. All authors contributed to the article and approved the submitted version.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.857548/full#supplementary-material

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Assessing Real-World Racial Differences Among Patients With Metastatic Triple-Negative Breast Cancer in US Community Practices

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Objective: Real-world data characterizing differences between African American (AA) and White women with metastatic triple-negative breast cancer (mTNBC) are limited. Using 9 years of data collected from community practices throughout the United States, we assessed racial differences in the proportion of patients with mTNBC, and their characteristics, treatment, and overall survival (OS).

Methods: This retrospective study analyzed de-identified data from 2,116 patients with mTNBC in the Flatiron Health database (January 2011 to March 2020). Characteristics and treatment patterns between AA and White patients with mTNBC were compared using descriptive statistics. OS was examined using Kaplan-Meier analysis and a multivariate Cox proportional hazards regression model.

Results: Among patients with metastatic breast cancer, more AA patients (23%) had mTNBC than White patients (12%). This difference was particularly pronounced in patients who lived in the Northeast, were aged 45–65, had commercial insurance, and had initial diagnosis at stage II. AA patients were younger and more likely to have Medicaid. Clinical characteristics and first-line treatments were similar between AA and White patients. Unadjusted median OS (months) was shorter in AA (10.3; 95% confidence interval [CI]: 9.1, 11.7) vs. White patients (11.9; 95% CI: 10.9, 12.8) but not significantly different. After adjusting for potential confounders, the hazard ratio for OS was 1.09 (95% CI: 0.95, 1.25) for AA vs. White patients.

Conclusions: The proportion of patients with mTNBC was higher in AA than White mBC patients treated in community practices. Race did not show an association with OS. Both AA and White patients with mTNBC received similar treatments. OS was similarly poor in both groups, particularly in patients who had not received any documented anti-cancer treatment. Effective treatment remains a substantial unmet need for all patients with mTNBC.

Keywords: triple-negative breast cancer, racial differences, African American, real-world, community practices, Flatiron Health

INTRODUCTION

African American (AA) women with breast cancer have long experienced significant health disparities. Despite having similar breast cancer incidence as White women, AA women are more likely to be diagnosed with late-stage breast cancer and have an approximately 40% higher mortality rate than White women (1).

Breast cancer is heterogeneous in nature, with prognosis and survival varying considerably by subtype. Compared with other breast cancer subtypes, triple-negative breast cancer (TNBC) is a particularly aggressive form of breast cancer. It is more likely to arise in younger women, be of higher histologic grade, present at a more advanced stage, relapse earlier, and show worse prognosis (2–5). Previous epidemiological studies have found the incidence of TNBC to be twice as high among AA women as White women (2, 4, 6). The disproportionally higher incidence of the TNBC subtype in AA women may contribute to the racial disparity in breast cancer mortality.

While there is abundant evidence of racial differences in the prevalence of TNBC, it remains unclear whether there are racial differences in treatment patterns and clinical outcomes between AA and White patients. To date, real-world studies comparing racial differences in treatments and clinical outcomes between AA and White TNBC patients have yielded mixed findings. While some studies reported shorter survival for AA women with TNBC compared with White women (2, 7–11), other studies found no evidence of a survival difference (12–17). Research in this area has often been limited to single-institution data with small sample sizes, regional data from a single state, or databases with limited clinical and treatment variables.

Factors contributing to racial differences in TNBC prevalence and potential differences in outcomes include biological, social, economic, and environmental factors. Emerging preclinical and clinical data suggest that TNBC in AA women may have a uniquely aggressive biology. Some studies comparing the genetic risk factors in TNBC by race found AA patients have a higher rate of pathogenic variants (18) or different gene expression patterns (19). However, the extent to which genetic risk factors contribute to the observed racial difference in incidence and outcomes is unclear. Other biological features that may contribute to the difference in incidence and prognosis between AA and White women with TNBC include differences in the tumor immune microenvironment; expression of breast cancer-associated cancer stem cells; prevalence of obesity, which is known to be linked to an increased risk of metabolic disorder; and tissue inflammation (20).

Beyond biological factors, many sociodemographic factors are associated with health outcomes in breast cancer, including TNBC. Among them, status and type of health insurance coverage are important factors commonly studied and have far-reaching implications for care including time to diagnosis and quality of treatment. Lack of insurance and type of insurance (i.e., Medicaid vs. private insurance) were found to be significantly associated with worse survival in patients with TNBC (21). Other social determinants of health, such as geographic location (rural vs. urban, disadvantaged vs. average neighborhood) and family structure (married vs. unmarried), may also predict the quality of care that patients receive, which ultimately influences outcomes (22, 23).

In this study, we analyzed recent data with wide geographic representation of community oncology practices across the United States. We assessed racial differences across the care continuum of patients, ranging from diagnosis to treatment to survival. Our goal was to better understand how patient and disease characteristics, treatments received, and differential access to care may underlie racial differences in prevalence and outcomes of mTNBC in community oncology practices.

MATERIALS AND METHODS

Data Source: Flatiron Health Database

The Flatiron Health Database is an oncology-focused, real-world database primarily generated from OncoEMR®, a proprietary electronic health record (EHR) system used by community oncologists throughout the USA. This retrospective, observational study evaluated data from Flatiron Health's longitudinal, demographically, and geographically diverse database derived from electronic health record data from more than 280 community-based cancer treatment clinics and academic centers, representing more than 2.2 million active US patients with cancer. The database is composed of patient-level structured and unstructured data, curated via technology-enabled abstraction. Structured data (e.g., patient demographics, drugs ordered) are prespecified by the software and captured during routine patient care. Data were de-identified and provisions were made to prevent re-identification for patient confidentiality. The Flatiron database contains detailed documentation of treatments, biomarkers, and clinical outcomes.

Study Cohort

The study cohort (**Figure 1**) was comprised of all AA and White women (≥18 years of age) with a confirmed diagnosis of metastatic breast cancer (mBC) between January 1, 2011 and January 1, 2020. Patients were required to have data collected during at least one visit within 6 months of their metastatic diagnosis and identifiable information to assess tumor estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. To ensure that only real-world patients treated in a community oncology setting were included in the analysis, patients who received an investigational drug in any line of therapy or were treated in an academic setting were also excluded. In line with previous studies (24), the cohort of patients with mBC was subsequently categorized by breast cancer subtype (HER2+, ER+/PR+, TNBC). The final cohort of patients with mTNBC was identified for outcomes analysis if patients had ≥ 1 negative result for ER and PR and ≥ 1 negative or equivocal result for HER2 status. Among them, those who received HER2-targeted and/or hormonal therapy for mBC were further excluded from the analysis. Patients of races other than AA or White were also excluded from further analysis.

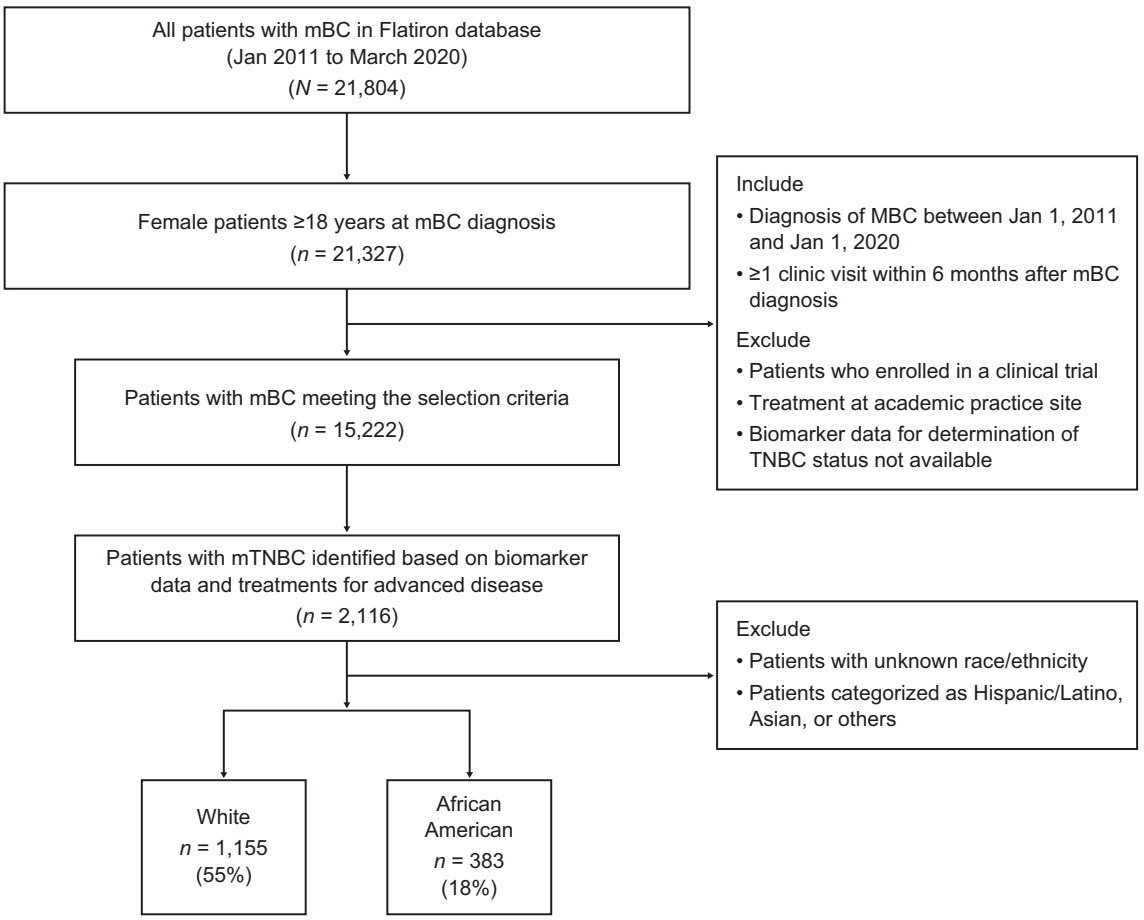


FIGURE 1 | Patient identification in the Flatiron database. mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; TNBC, triple-negative breast cancer.

Study Variables and Outcomes

Race/ethnicity was collected through routine oncology clinical care. Other patient sociodemographic characteristics included age, geographic location (state and region), and insurance status at the time of mBC diagnosis. Disease characteristics included stage at initial diagnosis, metastatic disease type, number and location of metastases, and Eastern Cooperative Oncology Group (ECOG) performance status (the most recent within 1 year of mBC diagnosis).

The primary clinical outcome for this study was overall survival (OS), which was measured from the time of metastatic diagnosis date until time of death. Patients not reported as having died at the time of the analyses were censored at the last activity date or the study end date.

Time to treatment initiation (TTI) was also evaluated as duration between date of metastatic diagnosis and first-line treatment start date. First-line treatments for patients with mTNBC were captured and grouped into broad categories (i.e., single-agent chemotherapy, combination chemotherapy, targeted therapy and/or cancer immunotherapy, and other treatments) and drug class (i.e., taxanes, platinums, anthracyclines, cyclophosphamide, antimetabolites, and microtubule inhibitors).

Statistical Analysis

Descriptive statistics were generated for all study variables, including means, standard deviations, medians, and ranges for continuous variables, and frequencies and counts for categorical variables. Comparisons of patient characteristics and treatment patterns between AA and White patients were conducted using *t*-tests. For categorical variables, Chi-square tests were used when $\leq$ 20% of the groups for comparison had expected frequencies <10; otherwise, the Fisher's exact test was used.

The proportion of each mBC subtype was described as the proportions of TNBC, HER2+, and ER+/PR+ phenotypes out of all mBC patients in the Flatiron Enhanced Data Mart. To further assess racial differences in the proportion of patients with mTNBC in the study cohort, a ratio was constructed by dividing the proportion of mBC that was mTNBC in AA patients by the proportion of mBC that was mTNBC in White patients. These ratios were calculated

for the overall patient cohort as well as for patients in relevant subgroups determined by state of residence, age group, geographic region, insurance status, and disease stage at initial diagnosis.

The Kaplan-Meier method was used to estimate median OS in patients with mTNBC, with log-rank tests performed to compare the unadjusted difference in OS between AA and White patients. A Cox proportional hazards model was used to adjust for the potential effect of key prognostic variables on OS including age (<65 years, ≥65 years), region (Northeast, South, West, Midwest missing), type of occurrence (recurrent, de novo, unknown), ECOG performance status at mTNBC diagnosis (0–1, ≥2, unknown), and treatment (received or not). Differences in OS between AA and White patients were also evaluated within subgroups of patients stratified by age group, insurance type, location, ECOG performance status, disease stage at diagnosis, sites or number of metastases, receipt of treatment, and type of first-line treatment.

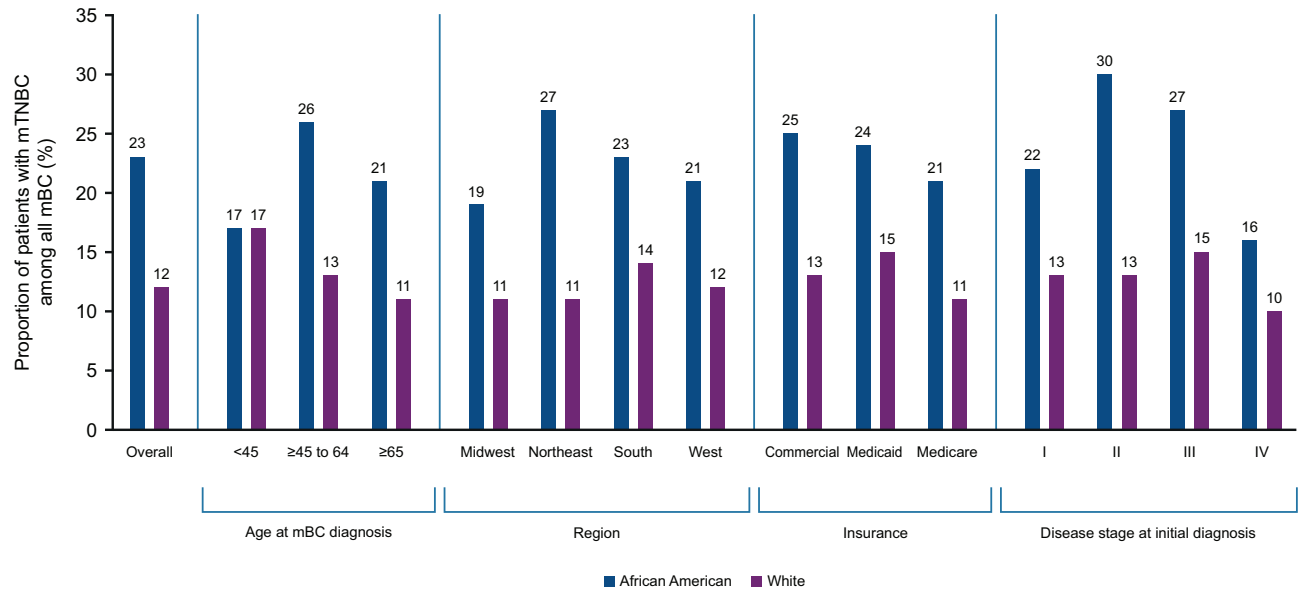
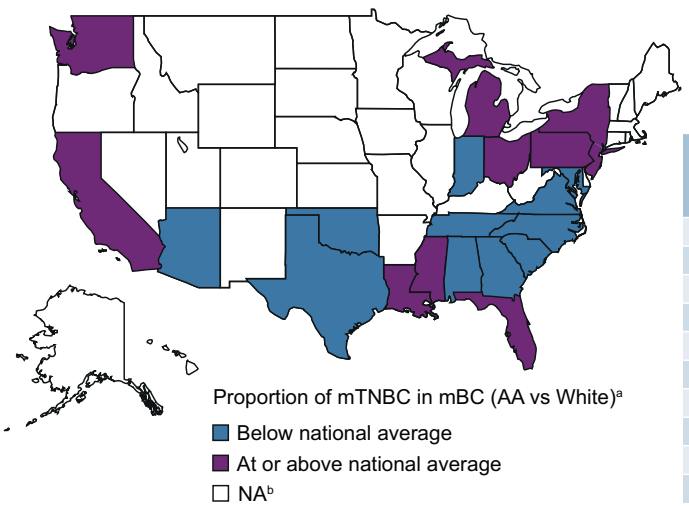


FIGURE 2 | Proportion of mBC that is mTNBC in African American and White patients by key characteristics. mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer.



Top 10 States with Large Racial Differences in mTNBC

States	mTNBC in mBC[c] (%)		Ratio of % mTNBC (AA vs. White)
	AA	White	
NJ	29.13	10.73	2.71
OH	27.27	10.94	2.49
CA	23.68	9.69	2.44
FL	28.41	12.24	2.32
NY	28.13	12.41	2.27
PA	22.92	10.49	2.18
LA	31.82	15.65	2.03
MI	21.98	11.40	1.93
MS	27.11	14.21	1.91
WA	30.00	15.86	1.89

FIGURE 3 | Proportion of mBC that is mTNBC in AA and White patients by US state. [a]Proportion of mTNBC in mBC is 1.86 (22.88%/12.29%) times higher in AA than in White patients (national average using Flatiron data). [b]Data from 18 states were excluded due to small N (<10) of reported mTNBC cases. [c]Source: Flatiron Health Data. AA, African American; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast; NA, not applicable.

RESULTS

Of the 21,804 patients diagnosed with mBC, 1,538 eligible patients with mTNBC were identified (**Figure 1**).

Proportion of mTNBC Subtype

Twenty-one US states reported mTNBC cases by race. Among all mBC patients in the Flatiron data, the proportion of mTNBC subtype in AA patients was approximately 1.9 times that of White patients (AA vs. White: 23 vs. 12%). Racial differences in the proportion of mTNBC (AA vs. White) were particularly pronounced among patients aged 45–65 years (26 vs. 13%; **Supplementary Table 1**), treated in the Northeast (27 vs. 11%), with commercial insurance (25 vs. 13%), and with initial diagnosis at disease stage II (30 vs. 13%). The magnitude of difference in the proportion of TNBC in AA compared with White patients was similar regardless of insurance status (**Figure 2**). Seven states (New Jersey, Ohio, California, Florida, New York, Pennsylvania, and Louisiana) had more than twice as many AA than White mBC patients with the mTNBC subtype. Louisiana had the highest proportion of mTNBC in AA (32%) mBC patients, compared to all states with available data (**Figure 3**).

Patient Characteristics

Patient baseline demographics, clinical characteristics, and first-line treatments are shown in **Table 1**. Compared with White patients at the time of mBC diagnosis, AA patients were younger (mean: 60 years vs. 63 years; $p < 0.001$), more likely to have Medicaid coverage (10 vs. 3%, $p < 0.001$), and less likely to have Medicare coverage (18 vs. 26%, $p = 0.003$). Geographic location differed significantly between AA and White patients, with more AA women residing in the South (68 vs. 44%, $p < 0.001$). Clinical and cancer characteristics were similar between AA and White patients, including the distribution of disease stage at initial diagnosis, disease recurrence, ECOG performance status, and the sites and number of metastases.

Time to Treatment Initiation and First-Line Treatment

TTI and first-line treatment were also similar in AA and White patients. Overall, 25% of patients in each racial group had no documentation in the database of receiving anticancer treatment after mBC diagnosis (**Table 1**).

Among patients who received first-line treatment, more than half initiated treatment <30 days after diagnosis, and median TTI did not differ by race. More than half of the patients received single-agent chemotherapy as their first-line treatment (AA: 53%; White: 55%), with capecitabine being the most frequently administered chemotherapy agent within this class. Combination chemotherapy was used to treat 37% of patients with similar frequencies between AA and White patients; platinum-based therapy was the most frequently administered combination therapy (**Table 1**).

Overall Survival

The median OS was <1 year in both AA and White patients (AA: 10.3 months, 95% confidence interval [CI]: 9.1, 11.7; White: 11.9 months, 95% CI: 10.9, 12.8). Although median OS was numerically shorter in AA patients, this difference was not statistically significant (unadjusted hazard ratio = 1.06 [95% CI: 0.93, 1.21; $p = 0.413$]; **Figure 4**). After adjusting for key prognostic factors, AA patients did not appear to have a significantly greater risk of death compared with White patients (adjusted hazard ratio = 1.09 [95% CI: 0.95–1.25; $p = 0.226$]). We also assessed differences in OS between AA and White patients in subgroups defined by age, insurance type, region, ECOG performance status, disease stage at diagnosis, sites and number of metastases, receipt of treatment, and type of first-line treatment (**Figure 5**). The results consistently showed no association between race and OS, regardless of subgroups, except for patients located in the West.

DISCUSSION

Racial differences in mTNBC prevalence, disease characteristics, and clinical outcomes have been well-documented (19, 20). Most of these data, however, have been derived from single-center studies or from population-based surveillance system data. Single-center data can lack generalizability and often have small sample sizes. While population-based surveillance system databases provide large sample sizes and reliable epidemiologic data, these databases tend to have limited information on patient clinical characteristics and treatment patterns. In this observational study, we sought to gain greater insight into racial differences in the proportion of mBC that is mTNBC and outcomes in real-world settings; we did this by interrogating the Flatiron Health database, a large database which includes data from demographically and geographically diverse community oncology practices in the United States.

We first examined racial differences in the percentage of mBC cases with the triple-negative phenotype in a cohort of mBC patients from January 2011 to March 2020. We found AA women with mBC were more likely to be diagnosed with the mTNBC subtype than White women. The difference between AA and White patients was more pronounced in mBC patients who were younger, had commercial insurance, were initially diagnosed at an earlier stage, and lived in several geographic "hotspot" areas such as Louisiana. These results are not only consistent with data derived from various cancer registries (4, 6, 25), but also expand on these prior findings by comparing the proportion of the mTNBC subtype among all mBC cases by AA and White race in subgroups defined by region, age, insurance type, and disease stage.

We further assessed whether race was associated with clinical outcomes within the cohort of patients with mTNBC, a question that remains inadequately addressed due to the conflicting real-world evidence generated so far. Data generated from this mTNBC patient cohort suggest that OS was poor among the entire cohort and did not differ significantly between AA and White patients overall and within subgroups stratified by

TABLE 1 | Characteristics of patients with mTNBC by race.

	White (n = 1,155)	African American (n = 383)	p-value
Demographic Characteristics			
Mean age at metastatic diagnosis, years (SD)	63 (12)	60 (12)	<0.001
Insurance[a]			
Commercial	469 (41)	146 (38)	0.423
Medicaid	39 (3)	38 (10)	<0.001
Medicare	301 (26)	70 (18)	0.003
Missing	337 (29)	138 (36)	0.014
Region			
Northeast	239 (21)	62 (16)	
Midwest	200 (17)	33 (9)	
South	505 (44)	261 (68)	<0.001
West	176 (15)	18 (5)	
Missing	35 (3)	9 (2)	
Clinical Characteristics			
Disease stage at initial diagnosis			
0–II	474 (41)	141 (37)	
III–IV	585 (51)	215 (56)	0.172
Unknown	96 (8)	27 (7)	
Disease type			
De novo	309 (27)	98 (26)	
Recurrent	751 (65)	258 (67)	0.641
Unknown	95 (8)	27 (7)	
ECOG PS at metastatic diagnosis			
0 or 1	562 (49)	170 (44)	
≥2	118 (10)	38 (10)	0.280
Unknown	475 (41)	175 (46)	
Number of metastases[b]**, median (range)**	2 (1–6)	2 (1–6)	0.960
Sites of metastasis[b]			
CNS/Brain	364 (32)	108 (28)	0.248
Bone	580 (50)	195 (51)	0.859
Liver	410 (35)	127 (33)	0.441
Lung	579 (50)	205 (54)	0.274
Lymph node	544 (47)	179 (47)	0.949
Other	401 (35)	127 (33)	0.621
Treatment Characteristics			
Patients with documented treatment	869 (75)	287 (75)	
First-line regimens—treatment grouping			
Single-agent chemotherapy[c]	477 (55)	151 (53)	
Chemotherapy combination treatment[d]	318 (37)	114 (40)	0.780
Targeted therapy or cancer immunotherapy	69 (8)	20 (7)	
Other therapy	<10	<10	
Time to first-line treatment for mTNBC			
Median time to first-line treatment from metastatic diagnosis, months (range)	1 (<1–40)	1 (<1–36)	
Time to treatment <1 month	469 (54)	154 (54)	
Time to treatment 1 to <2 months	216 (25)	71 (25)	0.939
Time to treatment 2 to <3 months	72 (8)	27 (9)	
Time to treatment ≥3 months	112 (13)	35 (12)	

Data are n (%) unless otherwise stated.

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; mTNBC, metastatic triple-negative breast cancer; SD, standard deviation.

[a]*Insurance type was collected at the time of metastatic diagnosis. Patients may have had multiple insurance types.*

[b]*Sites and number of metastases were measured at the time of metastatic diagnosis. Patients may have had metastases at multiple sites.*

[c]*Antimetabolites were the most frequently used single-agent chemotherapy (African American: 24%; White: 23%), and capecitabine was the most used agent within this class.*

[d]*Platinum-based treatments were the most frequently used chemotherapy combination treatments (African American: 20%; White: 23%).*

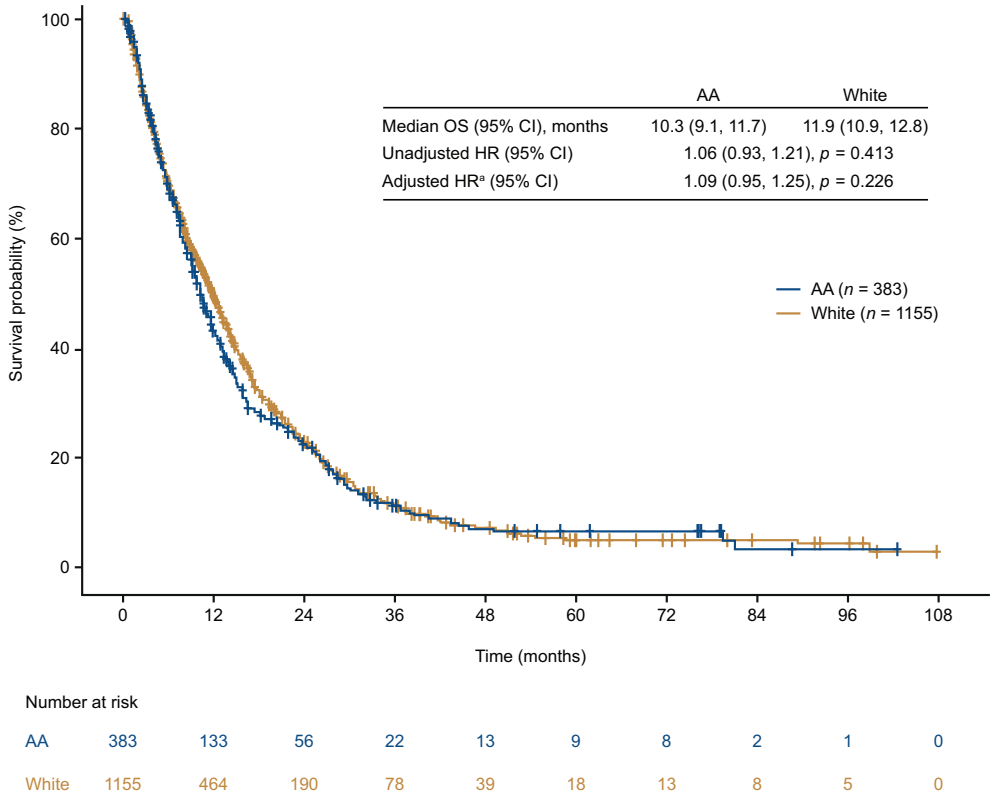


FIGURE 4 | Overall survival from time of mTNBC diagnosis in African American and White patients. [a]Model adjusted for age, geographic region, insurance type, de novo vs. recurrent mBC, ECOG performance status, and receipt of treatment. AA, African American; CI, confidence interval; HR, hazard ratio; OS, overall survival.

demographic, clinical, and treatment characteristics. In contrast to previous reports of population-based surveillance that found significantly increased mortality from TNBC in AA women compared with White women (2, 7), our findings are consistent with more recent data from the National Comprehensive Cancer Network Outcomes database (12), the Carolina Breast Cancer Study database (14), and several single institutions across the United States (13, 15–17). A recent analysis of data from the Surveillance, Epidemiology, and End Results (SEER) program demonstrated greater mortality from non-metastatic TNBC in AA women compared to White women, but the disparity varied by patient, disease, and treatment characteristics (11). The inconsistency among studies is likely a result of the multiple factors that contribute to outcomes including biological factors, as well as various social, economic, and environmental factors that are known to affect access to care. These factors must be carefully considered to accurately discern differences in outcomes. Further it must also be noted that variation is likely to occur in population-based vs. community-based vs. clinical trial-based data.

Our data show that patients who received care in the community oncology setting faced a high unmet need regardless of race. This is not only reflected by the poor OS, but also by the lack of evidence of first-line treatment initiation in a notable proportion of patients in both racial groups. Consistent with a previous study that examined treatment patterns in real-world patients with mTNBC treated in the community setting (10), we found one in four patients with mTNBC in both racial groups had missing documentation of anticancer treatment in the Flatiron database. It is important to note that some patients with mTNBC may have forgone treatment due to poor performance status and concerns about treatment tolerance. However, since reasons for lack of treatment were not documented, this cannot be verified. It is also possible that some patients received cancer treatments outside of the Flatiron network that were not captured in the database.

The present analysis has several limitations that are inherent to electronic health record-based retrospective observational studies. First, there was limited information on the social determinants of health in this dataset, which reduced our ability to further assess how socioeconomic disparities interplay with racial disparity in patients with mTNBC. The adjustment for insurance coverage and geographic location in the regression model can be considered as a proxy for socioeconomic status; however, more granular, multilevel data to characterize access to care, quality of care, and socioeconomic well-being are needed to better understand factors and mechanisms driving racial disparity in mTNBC. Secondly, incomplete/missing information on performance status and comorbidity burden may also lead to misclassification and unmeasured confounding. Thirdly, while

Variable	Category	AA n	AA Median (months)	White n	White Median (months)	Hazard ratio	95% CI
All		383	10.32	1155	11.86	1.06	(0.93, 1.21)
Age at mBC diagnosis	≥65	129	6.57	542	10.02	1.37	(1.10, 1.70)
	≥45 to <65	214	12.25	501	12.91	1.01	(0.84, 1.22)
	<45	40	9.69	112	11.37	0.84	(0.5, 1.25)
Documented treatment	Yes	287	11.70	869	13.47	1.07	(0.92, 1.25)
	No	96	4.47	286	5.19	1.03	(0.79, 1.35)
First-line treatment	Single-agent chemo	151	10.91	477	12.78	1.11	(0.90, 1.36)
	Chemo combination	114	12.39	318	14.42	1.09	(0.85, 1.39)
	Targeted/Immunotherapy	20	13.31	69	14.19	0.81	(0.39, 1.67)
ECOG PS	0 or 1	170	10.15	562	11.6	1.13	(0.93, 1.38)
	≥2	38	2.89	118	5.19	1.37	(0.91, 2.06)
Insurance	Commercial	146	9.76	469	9.86	1.10	(0.89, 1.36)
	Medicaid	38	9.03	39	12.48	1.35	(0.81, 2.26)
	Medicare	70	10.15	301	11.89	1.22	(0.90, 1.65)
Region	Northeast	62	9.69	239	11.99	1.25	(0.91, 1.71)
	Midwest	33	9.03	200	11.70	1.12	(0.74, 1.69)
	South	261	11.56	505	11.14	0.94	(0.79, 1.12)
	West	18	7.39	176	14.69	1.99	(1.14, 3.48)
Stage at initial diagnosis	0–II	141	9.56	474	12.12	1.18	(0.95, 1.45)
	III–IV	215	10.71	585	11.63	0.95	(0.79, 1.14)
Metastasis	CNS/Brain	108	12.85	364	11.76	0.86	(0.68, 1.09)
	Bone	195	8.97	580	11.63	1.16	(0.97, 1.40)
	Liver	127	7.56	410	10.38	1.18	(0.94, 1.47)
	Lung	205	11.24	579	12.06	1.04	(0.87, 1.24)
	Lymph node	179	10.22	544	12.81	1.13	(0.94, 1.37)
Number of metastases	0–3	286	10.58	886	11.86	1.03	(0.88, 1.20)
	≥4	92	9.46	265	11.86	1.13	(0.88, 1.45)

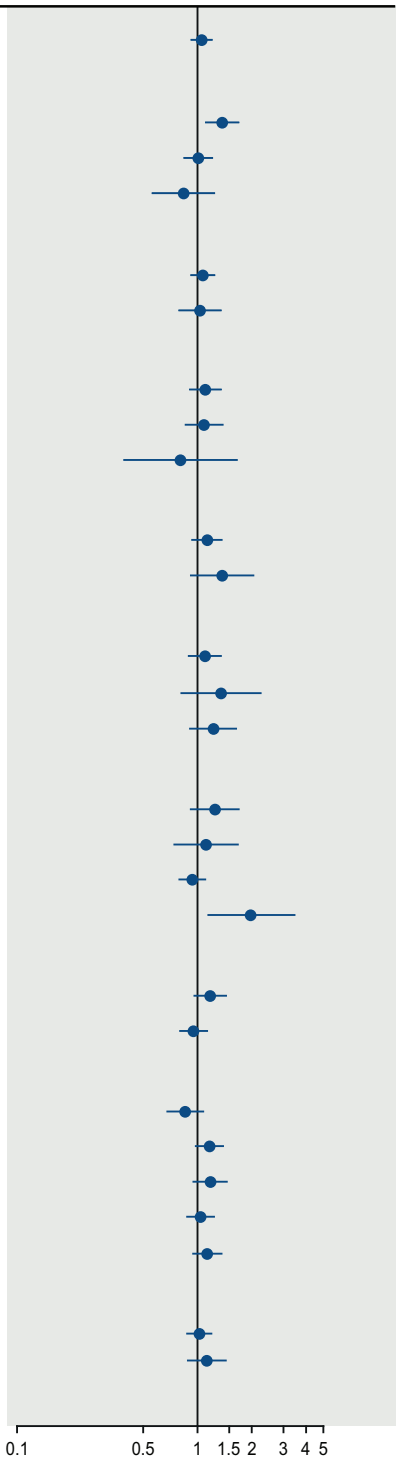


FIGURE 5 | Overall survival from time of mTNBC diagnosis in African American and White patients by patient subgroups. AA, African American; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer.

this study has improved generalizability compared to existing racial disparity research in mTNBC, which is predominantly conducted in regional or single institution settings (2, 7, 13–16), our study cohort was restricted to patients receiving care in the community oncology setting, and findings may not be representative of those treated in other settings (e.g., academic, research institutions) or those who do not engage with the healthcare system. For patients treated in the community oncology setting, there may be disparities in the usage of the Flatiron proprietary data system across urban, suburban, and rural communities. The selection of the Flatiron network for clinical record keeping may also have been preferred by certain types of community practices, leading to potential selection bias that could affect patient outcome. Lastly, our conclusions must be interpreted with respect to how race/ethnic information is captured. In contrast to registries such as SEER or National Program of Cancer Registries, race/ethnicity information in the Flatiron database is self-reported and voluntary. This data acquisition approach may not reliably account for multi-ethnic individuals or other genetic ancestry heterogeneity. In this study cohort, approximately 11% of patients had missing race/ethnicity information, a proportion that is larger than in other registry databases. Overall, we believe these limitations are outweighed by the study's strengths including its large, geographically diverse, well-characterized cohort assessing racial differences in patient outcomes across the care continuum from diagnosis to treatment to OS outcomes.

In summary, we found large differences between AA and White women in the proportion of the mTNBC subtype among women with mBC, especially in younger patients and patients who lived in geographic "hotspots". Time to treatment initiation and type of first-line treatment were similar between AA and white patients. OS was poor among the entire cohort and did not differ significantly between racial groups, suggesting that mTNBC is an aggressive disease, regardless of race. Effective treatment remains a substantial unmet need for patients with mTNBC. Considering the lack of racial differences in this patient cohort, prospective studies are needed to further elucidate the biological differences that may have predictive or prognostic significance for AA patients with mTNBC.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be made available upon request, and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms. Requests to access the datasets should be directed to DataAccess@flatiron.com.

AUTHOR CONTRIBUTIONS

RT, LC, and EM contributed to the conception and design. YY, VS, and B-mD performed data analysis and interpretation. All authors wrote the manuscript and approved the final version. All authors are accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.859113/full#supplementary-material

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Racial Disparities in Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Does Aggressive Surgical Treatment Overcome Cancer Health Inequities?

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Background: Advanced cancer states perpetuate health-related disparities. Peritoneal-based cancers are clinically advanced cancers that present a significant clinical dilemma. Peritoneal cancers are managed aggressively with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). While racial and ethnic disparities are prevalent in cancer, there are no studies investigating if racial disparities exist in patients with peritoneal carcinomatosis managed with CRS and HIPEC. We hypothesized that this advanced disease state further delineates racial disparities.

Methods: A retrospective chart review was conducted on patients with peritoneal carcinomatosis receiving CRS and HIPEC at a single institution from January 1, 2017-October 4, 2021. Descriptive statistics were used to compare racial groups. The Cox Proportional Hazards Model and Log Rank Test were used for multivariate and overall survival analysis.

Results: In total, 67 patients underwent CRS and HIPEC, of which 41 (61.2%) were White, 20 (29.8%) were Black, 3 (4.5%) were Asian, and 3 (4.5%) were Other race. When compared to White patients, Black patients had lower income (p=0.0011), higher incidence of hypertension (p=0.0231), and lower performance status (p=0.0441). Cancer type, including colorectal, appendiceal, ovarian, etc., was similar between groups (p=0.8703). Despite these differences in sociodemographic and morbidity factors, when comparing Black patients to White patients, there were no differences in peritoneal cancer index score (13.2 vs. 12.3, p=0.6932), estimated blood loss (748 vs. 655 mL, p=0.6332), minor/major complication rates (1.1 vs. 1.2, p=0.7281; 0.4 vs. 0.7, p=0.3470, respectively), 30-day readmission rates (25.0% vs. 17.1%, p=0.6210), disease recurrence (40.0% vs. 51.2%, p=0.3667), or 30-day mortality (0.0% vs. 2.4%, p=1.0000). Overall survival was similar for Black and White patients (p=0.2693). The occurrence of a

major complication was the only factor associated with overall survival (HR 2.188 [1.502, 3.188], p< 0.0001).

Conclusions: Despite differences in patient socioeconomic factors and comorbid conditions, outcomes were similar between Black and White patients receiving CRS and HIPEC at our institution. While larger studies with more diverse patient populations are needed to confirm these findings, our data provide evidence that aggressive surgical management across diverse patient populations allows for equitable outcomes.

Keywords: peritoneal carcinomatosis, cytoreductive surgery, HIPEC (heated intraperitoneal chemotherapy), surgical outcomes, racial disparities

INTRODUCTION

Advanced cancer states perpetuate health-related disparities through multiple mechanisms, including tumor biology, genetics, and sociodemographic factors (1). There has been much effort to examine and mitigate these disparities and provide more equitable care for diverse patient populations. Peritoneal carcinomatosis, however, is one such advanced cancer that has largely been overlooked in this realm of research.

Peritoneal carcinomatosis, or peritoneal surface malignancy/metastasis, is the dissemination of cancer along the peritoneum of the abdominal cavity. This peritoneal surface malignancy/metastasis occurs primarily as peritoneal mesothelioma or secondarily to a variety of abdominal and gynecologic cancers including colorectal, appendiceal, gastric, ovarian, and fallopian cancer (2) and represents a Stage IV cancer that is localized to the peritoneal lining. The presence of peritoneal carcinomatosis tends to yield a poor prognosis for patients and previous dogma viewed peritoneal carcinomatosis as an incurable systemic disease process. Fortunately, treatment advances have led to a paradigm shift where peritoneal carcinomatosis is viewed as a localized, potentially curable disease. This shift in clinical management has primarily occurred with the introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), which have been shown to improve survival in select patients (3).

CRS and HIPEC is an advanced, complex, morbid, and aggressive surgical treatment modality for peritoneal surface malignancies. During this treatment modality all macroscopic resectable tumor is removed from the abdomen, which can include a variety of anatomic resections specific to the patient, such as peritonectomy, enterectomy, colectomy, cholecystectomy, omentectomy, hysterectomy, etc. Heated chemotherapy specific to the cancer, is then infused into the abdomen to assist in destruction of any remaining tumor deposits and microscopic disease (4). Morbidity and mortality are high (5), but CRS and HIPEC has been found to have lower 30-day morbidity and mortality than other complex surgical procedures such as an esophagectomy, pancreaticoduodenectomy, and hepatectomy (6). Given the known risks of morbidity and mortality associated with this procedure, it is imperative to identify patient populations that might not only be disproportionately affected by this disease but also those that will clinically benefit from such aggressive surgery.

Few studies have investigated the disparities present in patients with peritoneal carcinomatosis treated with CRS and HIPEC. The limited number of currently published studies have focused primarily on the impact of socioeconomic status and insurance status on patient outcomes, overlooking possible racial disparities within this patient population (7–9). Racial disparities exist in the diagnosis, treatment, management, and survival of cancer (10–15). Black patients have been shown to have higher rates of cancer-related mortality when compared to White patients (11, 16). Additionally, racial disparities are further perpetuated in the surgical treatment of cancer. Black patients undergoing major cancer surgery have been shown to have worse postoperative outcomes, including more complications, higher rates of in-hospital mortality, higher likelihood of needing postoperative blood transfusions, and longer hospital stays (17, 18). Recent encouraging data has shown that cancer surgery-related mortality has improved for both Black and White patients, but Black patients continue to be disproportionately affected compared to White patients (14). Therefore, we feel it is imperative that cancer-related investigations on higher risk and reward surgery in aggressive disease processes for racial/ethnic diverse patient populations should be investigated.

To our knowledge, there have been no studies investigating potential racial disparities in perioperative and postoperative outcomes for patients receiving CRS and HIPEC in the setting of peritoneal carcinomatosis. The aim of this study was to investigate this amongst patients receiving CRS and HIPEC at a single high-volume, tertiary institution. We hypothesized that racial disparities exist amongst patients receiving CRS and HIPEC, and thus, should be identified for improvement of patient outcomes and equity of care.

MATERIALS AND METHODS

Patient Selection and Data

A retrospective chart review was completed for all patients who underwent CRS and HIPEC at our institution from January 1, 2017 to October 4, 2021. Patients eligible for inclusion in this study were 18 years of age and older and received first-time CRS and HIPEC for peritoneal carcinomatosis. Patients were excluded if they were less than 18 years old or received HIPEC exclusively for palliation of ascites. This study was approved by

the institutional review board at Virginia Commonwealth University Health System.

Clinical data including patient demographics, risk factors, oncologic history, and intraoperative and postoperative outcomes were obtained from the electronic medical record for each patient. Demographics included age, sex, race (White, Black, Asian, or Other), ethnicity (Hispanic or Non-Hispanic), insurance status (private payor or government-based payor), distance traveled to the hospital (obtained by calculating the distance from the patient's listed zip code city center to the treating medical center), and median household income (obtained using the patient's listed zip code and US Census Data from the American Community Survey 5-year estimates from 2015 to 2019 (19)).

Risk factors included the patient's preoperative American Association of Anesthesiologist Physical Status Classification System score (ASA score) and Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and presence of comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease, chronic kidney disease, and current smoking status. Oncologic history included the patient's type of cancer and receipt of neoadjuvant chemotherapy prior to CRS and HIPEC.

Intraoperative variables included the length of surgery, calculated peritoneal cancer index (PCI), cytoreduction score (CC score), intraoperative receipt of blood transfusion, estimated blood loss (EBL), number of bowel anastomoses created, and creation of an ostomy. Postoperative variables included minor complications defined by the Clavien-Dindo classification types I-II and major complications defined by the Clavien-Dindo classification types III-IV within 30 days of surgery, length of hospital stay, readmission within 30 days of surgery, 30-day mortality, postoperative recurrence of disease defined by radiographic or biopsy-proven evidence, length of follow-up, and length of survival. Length of survival was calculated from the date of surgery to the patient's known date of death or date of last record in the institution's electronic health system.

Statistical Analysis

The data were stratified by racial groups. Differences between racial groups' demographic factors, preoperative risk factors, intraoperative outcomes, and postoperative outcomes were compared using descriptive and inferential statistics.

Multivariate analysis for clinical factors associated with survival was performed with the Cox Proportional Hazards Model. Explanatory factors included in the model were age, sex, race, insurance, income, neoadjuvant chemotherapy, minor complications, major complications, readmission at 30 days, and recurrence of cancer. The backward selection method was used. The significance level for removing effects from the model was specified at 0.1. Overall survival, the primary outcome, was also calculated and the Log Rank Test was used to compare the distribution of survival time between Black and White patients. Lastly, a power analysis was performed using a two-sided Log Rank Test to ensure adequate sample size for detecting differences in results. An alpha-value of 0.05 was used for determining significance. All statistical analyses were completed using SAS Version 9.4 (Cary, NC).

RESULTS

Patient Characteristics

A total of 67 patients underwent CRS and HIPEC for peritoneal carcinomatosis during the specified time period and met inclusion criteria. The racial breakdown included 41 (61.1%) White patients, 20 (29.9%) Black patients, 3 (4.5%) Asian patients, and 3 (4.5%) patients listed as Other race. Given the small sample sizes for Asian and Other races, these patients were excluded from further analysis.

Patient demographics, preoperative risk factors, and oncologic history are presented in **Table 1**. Age, distribution of sex, and preoperative body mass index (BMI) were similar between Black and White patients. In terms of preexisting comorbidities, Black patients had higher rates of hypertension requiring medication compared to White patients (70.0% vs. 39.0%, p=0.0231), but otherwise comorbidities were present in both populations at comparable rates. Preoperative assessment of risk according to the ASA Score was similar between groups (p=0.9795). However, preoperative patient performance status as measured *via* the ECOG-PS was worse in Black patients compared to White patients (p=0.0441).

Socioeconomic factors were analyzed as well to ascertain any differences in social determinants of health. Both groups were insured with private or government insurance at similar rates; no patient was uninsured. White and Black patients traveled similar distances to the medical center for treatment (63.0 vs. 34.9 miles, p=0.3596). Black patients had significantly lower household income than White patients ($53,719 vs. 69,294, p=0.0011).

With respect to patient oncologic history, the type of cancer as well as receipt of neoadjuvant chemotherapy were similar between racial groups (p=0.8703 and p=0.7608, respectively). In total, the most common cancers were of colorectal (37.8%) and appendiceal (26.2%) origin.

Intraoperative and Postoperative Clinical Outcomes

Intraoperative and postoperative outcomes by race are presented in **Table 2**. A complete breakdown of each complication is reported in **Supplementary Table 1**. At the time of surgery, the mean PCI scores were similar between Black and White patients indicating similar extents of peritoneal disease (13.2 vs. 12.3, respectively). Length of surgery, estimated blood loss, the number of anastomoses created, and creation of an ostomy were similar between Black and White patients as well.

Postoperatively, outcomes were similar between Black and White patients. The mean complication rates for both minor and major complications occurring within 30 days of surgery were similar between Black and White patients. Only one type of postoperative complication was noted to be statistically significant and higher in one group in relation to the other; Black patients experienced higher rates of prolonged intubation (defined as remaining intubated for greater than 48 hours after surgery) compared to White patients (15.0% vs. 0.0%,

TABLE 1 | Patient demographics and preoperative demographics by race.

	Black (n = 20)	White (n = 41)	*p*-value
Age (years)	55.5 (36.0-73.0)	55.3 (23.0-75.0)	0.9540
Sex			0.9416
Female	12 (60.0%)	25 (61.0%)	
Male	8 (40.0%)	16 (39.0%)	
BMI (kg/m^2)	31.9 (21.8-53.9)	30.0 (18.4-57.8)	0.3483
Insurance			0.9354
Private	11 (55.0%)	23 (56.1%)	
Government	9 (45.0%)	18 (43.9%)	
Household Income (USD, mean)	53,719 (27,063-92,069)	69,294 (36,379-107,321)	0.0011
Distance Traveled (miles, mean)	34.9 (3.0-102.0)	63.0 (4.1-822.0)	0.3596
Comorbidities			
Hypertension	14 (70.0%)	16 (39.0%)	0.0231
Coronary artery disease	0 (0.0%)	5 (12.2%)	0.1620
Diabetes mellitus	4 (20.0%)	10 (24.4%)	0.7019
COPD	1 (5.0%)	1 (2.4%)	1.0000
Chronic kidney disease	1 (5.0%)	0 (0.0%)	0.3279
Current Smoker	2 (10.0%)	2 (4.9%)	0.5915
ASA Score			0.9795
1	0 (0.0%)	0 (0.0%)	
2	3 (15.0%)	7 (17.1%)	
3	16 (80.0%)	32 (78.1%)	
4	1 (5.0%)	2 (4.9%)	
5	0 (0.0%)	0 (0.0%)	
ECOG-PS			0.0441
0	11 (55.0%)	34 (82.9%)	
1	8 (40.0%)	7 (17.1%)	
2	1 (5.0%)	0 (0.0%)	
Primary Cancer Type			0.8703
Appendiceal	6 (30.0%)	10 (24.4%)	
Colorectal	7 (35.0%)	16 (39.0%)	
Esophageal	0 (0.0%)	1 (2.4%)	
Gastric	1 (5.0%)	1 (2.4%)	
Ovarian/Fallopian	2 (10.0%)	8 (19.5%)	
Small bowel	1 (5.0%)	2 (4.9%)	
Other	3 (15.0%)	3 (7.3%)	
Neoadjuvant Chemotherapy	13 (65.0%)	25 (61.0%)	0.7608
Preoperative Albumin	4.4 (3.1-4.8)	4.2 (3.6-5.0)	0.1701

p=0.0317). Black and White patients had similar lengths of hospital stay (13.1 vs 11.6 days, respectively; p=0.5012). Readmission to the hospital within 30 days of discharge was also similar between races (p=0.6210). Recurrence of disease after surgery, as evidenced radiographically or biopsy-proven, occurred in 47.5% (29/61) of the patients, but recurrence rates were similar amongst Black and White patients (p=0.3677). Mortality within 30 days of the index operation was not statistically different between Black and White patients (0.0% vs. 2.4%, p=1.000).

TABLE 2 | Patient intraoperative and postoperative outcomes within 30 days of surgery by race.

	Black (n = 20)	White (n = 41)	*p*-value
PCI Score	13.2 (2-35)	12.3 (3-26)	0.6932
Length of Surgery (min)	590 (386-780)	642 (367-1098)	0.2975
EBL (mL)	748 (100-2500)	655 (50-3000)	0.6332
No. of anastomoses (median)	1 (0-3)	1 (0-3)	0.6290
Ostomy Creation	2 (10.0%)	5 (12.2%)	1.0000
Hospital LOS (days)	13.1 (5.0-26.0)	11.6 (3.0-48.0)	0.5012
Minor Complications	1.1 (0-3)	1.2 (0-5)	0.7281
Major Complications	0.4 (0-4)	0.7 (0-8)	0.3470
Total Complications	1.5 (0-7)	2.0 (0-11)	0.4579
Readmission within 30 days	5 (25.0%)	7 (17.1%)	0.6210
30-day mortality	0 (0.0%)	1 (2.4%)	1.0000
Recurrence after surgery	8 (40.0%)	21 (51.2%)	0.3667

Multivariate and Survival Analysis

Multivariate analysis was conducted to identify factors associated with survival. After controlling for explanatory factors, only sex and the occurrence of major complication were included in the final model. The occurrence of a major complication was the only factor, however, associated with survival (HR: 2.188, 95% CI 1.502-3.188, p<0.001), indicating that for each major complication suffered, the risk of death more than doubled. Sex was not found to be significantly associated with survival (HR: 4.195, p=0.0742).

Survival analysis was completed to compare overall survival between Black and White patients with peritoneal carcinomatosis treated with CRS and HIPEC (**Figure 1**). There was no statistically significant difference in the distribution of survival time among Black and White patients (p=0.2693).

Power Analysis

A power analysis for sample size was performed using a two-sided Log Rank Test to ensure the results were not underpowered. Using an overall sample size of 61 subjects (20 Black patients and 41 White patients) a power of 80.5% at a 5% significance level was achieved to detect a hazard ratio of 2.3 (corresponding to a moderate effect size of 0.65, under exponentiality assumptions for the survival functions) between the comparison groups. Two assumptions were made including 4.6 years of follow-up based on the maximum follow-up time of 56 months and no subjects dropping out of the study. This indicates that the study is not underpowered.

DISCUSSION

Health disparity research is at the forefront of cancer research in efforts to establish more equitable care across diverse patient populations. Despite low awareness among surgeons, the surgical management of cancer is fraught with disparities (1, 17, 18, 20–23). There is sparce literature examining health disparities in patients with peritoneal carcinomatosis treated with CRS and HIPEC with no literature evaluating the presence of racial disparities in this population. We present a patient population with comparable preoperative demographics and risk factors, who had similar perioperative outcomes. Despite having lower income and presumably higher financial vulnerability, Black patients in our study had similar outcomes compared to White patients. This finding contrasts the results reported by Rieser et al. who found that for colorectal cancer patients with peritoneal carcinomatosis, patients with lower socioeconomic status had longer lengths of stay, more complications, and higher rates of 90-day readmission and 30-day mortality (7). The authors argued that patients with lower socioeconomic status experience multiple disadvantages and worse overall survival compared to higher socioeconomic status patients that was not explained by individual cancer biology characteristics. Locoregional differences may influence why our results do not corroborate the findings reported by Rieser et al.

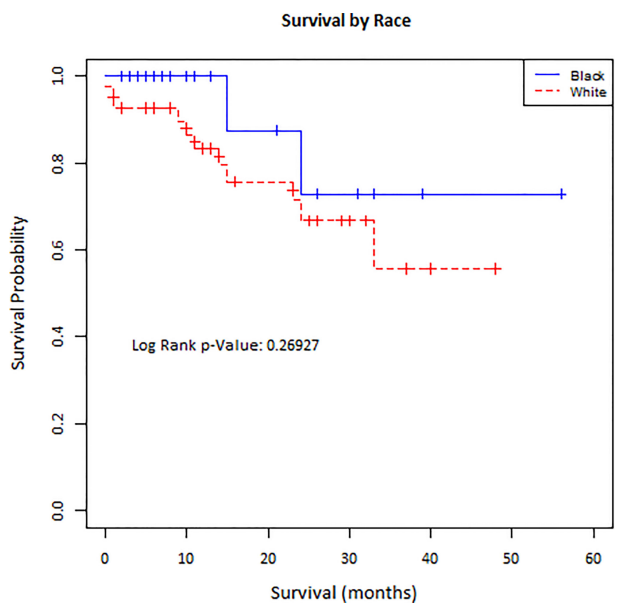

FIGURE 1 | Kaplan-Meier curve of survival for Black and White patients undergoing CRS and HIPEC.

When comparing racial groups, hypertension was the only comorbidity that disproportionately affected Black patients, consistent with prevalence rates of hypertension nationally (24). Interestingly, however, there were no differences in the rates of other comorbidities, although Black patients share a higher burden of diseases such as chronic kidney disease and diabetes (25, 26). This likely reflects the underlying referral and selection patterns for patients that are relatively healthy at baseline and can withstand a complex and morbid surgery.

Previous studies have reported the association of insurance status with overall survival, but insurance was not a predictive factor in our patient population (8, 9). Overall survival was similar between Black and White patients in our study. Stratification by insurance status is the only other sociodemographic factor that has been examined for difference in overall survival with varying results. In a 2021 study of 124 patients with colorectal cancer receiving CRS and HIPEC, patients who were underinsured had worse survival than insured patients (8). However, in a smaller study of 31 patients with varying cancers undergoing CRS and HIPEC, there was no difference in survival by insurance status (9).

We also found that the occurrence of a major complication postoperatively was associated with overall survival. This agrees with results from a similar study investigating colorectal cancer patients undergoing CRS and HIPEC (7).

Notably, our study represents a diverse patient population. Nearly one third of the patients were Black. This is remarkable because other studies have reported proportions of 10% or less, or race was not reported (7, 8). In a 2019 study of the National Cancer Database characterizing the patient population undergoing cytoreductive surgery and perioperative chemotherapy (defined as receipt of HIPEC at the time of surgery or intraperitoneal chemotherapy in the perioperative period) for appendiceal cancer, only 6.60% of patients were reported as Black race, and the majority, 88.2%, were reported as White race, likely disproportionately representing the diversity of the patients with appendiceal cancer

(27). There is otherwise a paucity of literature characterizing the racial distribution of patients that undergo CRS and HIPEC. This raises the larger and more concerning question as to why so few Black patients compared to White patients are receiving CRS and HIPEC, when incidence rates of some cancers treated with CRS and HIPEC are higher among Black patients (28). This also raises the question of what, if any, underlying factors may be preventing this population from potentially receiving treatment.

Our results argue that since postoperative and oncologic outcomes are similar between Black and White patients, Black patients with peritoneal carcinomatosis should be referred for and treated with CRS and HIPEC equitably. However, Byrne et al. reported that in patients with appendiceal cancer, White race and non-Hispanic ethnicity were both positive predictors for receiving CRS and HIPEC (OR: 2.00, 95% CI 1.40-2.86; OR: 1.92, 95% CI 1.21-3.05, respectively) (27). Given that CRS and HIPEC are complex and highly specialized procedures primarily conducted at tertiary care centers, the level of specialization itself may potentially be contributing to lack of access to care. Previous research has shown that hospital factors are influential in racial health disparities for cancer surgery (1, 21). When compared to White patients, Black patients with colorectal cancer were less likely to be referred to high-volume hospitals for the treatment of their cancer (29). However, racial disparities were erased when patients received care for colorectal cancer in the setting of an equal access healthcare system (22).

We do acknowledge the multiple limitations of our study. First, these findings are from a small sample over a four-year timeframe, representative of a single institution's patient population. Therefore, these results may not be applicable to the entire patient population that undergoes this procedure and may reflect the high-quality equitable care delivered at our institution. Although our power analysis indicates that our results are not underpowered, we acknowledge that the sample size is small and further investigation with larger sample sizes is warranted. Second, given limited sample sizes within each cancer type, all patients treated with CRS and HIPEC were grouped together without stratifying for different cancer types. Doing so may potentially neglect the underlying and unique biologic and physiologic differences of each cancer that influence survival. However, this lack of stratification holds validity for viewing CRS and HIPEC as a treatment modality for peritoneal carcinomatosis regardless of the cancer type. Lastly, although racial disparities in referral for or access to CRS and HIPEC are important to assess, such an analysis extends beyond the scope of this current study, which demonstrates that once this treatment modality has been accessed, outcomes are similar regardless of race.

Despite these limitations, these results are encouraging, yet necessitate the need for further investigation. Specifically, further study must be undertaken to investigate any possible racial/ethnic disparities in larger, more nationally diverse and representative patient populations, in hopes of confirming our findings. Additionally, as previously mentioned, there is little data characterizing the patient population that is actually receiving CRS and HIPEC for peritoneal carcinomatosis. This presents an opportunity to better examine which populations are undergoing CRS and HIPEC, and to identify what factors and disparities are present that limit access to a possible cure for cancer.

In conclusion, advanced cancer states perpetuate health disparities, especially with respect to race. We hypothesized that the advanced cancer state of peritoneal carcinomatosis would demonstrate such racial disparities. Our results, however, contradicted this, and demonstrated that regardless of a patients' race, outcomes are similar after CRS and HIPEC, despite differences in socioeconomic status and comorbidities. Therefore, aggressive surgical management of peritoneal carcinomatosis promotes equitable outcomes across diverse patient populations and more efforts should be taken to investigate disparities in this patient population.

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 Virginia Commonwealth University IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DF designed the project, acquired, analyzed and interpreted data, and wrote the manuscript. XD and DB analyzed and interpreted data. VV, AR, and KH interpreted data and revised the manuscript. LF and JT designed the project and revised the manuscript. All authors contributed to the manuscript, approved the submitted version, and are accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.899488/full#supplementary-material

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METHODS
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Addressing Health Disparities Across the Cancer Continuum—a Los Angeles Approach to Achieving Equity

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Introduction: Different models have been developed to address inequities across the cancer care continuum. However, there remains a scarcity of best practices on understanding and responding to the burden of cancer in a defined catchment area.As such, the National Cancer Institute (NCI) recently provided a framework to maximize the impact on cancer burden, including a greater focus on community outreach and engagement. In this paper, we describe how Cedars Sinai Cancer (CSC), a health system that serves one of the most diverse counties in the US, implemented the framework to define its catchment area, characterize its population, identify high risk priority groups, and make decisions to address health disparities.

Methods: We provide a review of the methods used to assess socio-ecological levels of influence. Data were reviewed from numerous national, statewide, and county sources and supplemented by locally administered questionnaires, heat maps, and community profile summaries to gain more localized snapshots of cancer disparities in Los Angeles County. Lastly, feedback was solicited from external peer groups, community stakeholders, and key decision-makers, and the proposed catchment area was aligned with the State's Cancer Plan and the NCI Catchment Area and Community Outreach and Engagement Mandate.

Results: The selected CSC catchment area meets NCI criteria and has potential to demonstrate impact both at the population level and within specialty populations. As a result, strategies are being developed to organize community outreach and engagement, as well as research across basic, clinical, and population sciences to guide cancer control and prevention efforts.

Discussion: To maintain a high level of cultural inclusion and sensitivity, multiple layers of data are needed to understand localized pictures of cancer disparities and underlying causes. Community engagement remains essential to implementing policy, best practice, and translational science for broader impact.

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Impact: The clinical and translation work conducted at any cancer center requires an understanding of the determinants of health that contribute to the differences in cancer incidence and mortality among different groups. The NCI-aligned approach that we highlight is critical to support the design of future cancer control strategies that address and possibly reduce local health inequities.

Keywords: cancer prevention and control, health equity (MeSH), healthcare disparities (MeSH), cultural diversity, social determinants of health (MeSH), community outreach and engagement

INTRODUCTION

Health disparities exist based on social, economic, and environmental factors, including gender, race, ethnicity, gender identity, sexual orientation, age, disability, geographic location, and socioeconomic status (1). Many different models have been developed to suggest how to address these disparities (2–6). What all models have in common is the intersection of multiple health domains (e.g., health behaviors, the built environment, health systems, etc.) and socio-ecological levels of influence (e.g., individual, interpersonal, community, and social levels) (7–10).

The National Cancer Institute (NCI) now requires cancer centers to define their catchment area with geographical boundaries, and address cancer burden and inequities within that region through research and community outreach and engagement (11). To support this goal, the NCI outlined seven areas for research and outreach activities (12): (1) define the catchment area (i.e. select the area and describe the demographics, special populations, and cancer burden); (2) assess the needs of the catchment area (i.e., basic, clinical, and population science research is conducted to address the cancer burden from prevention through survivorship); (3) engage the population in the catchment area (i.e., involvement of the population in setting a research agenda, and reaching out to the population through research, outreach, and education); (4) address disparities (i.e. identify and aim to develop solutions that decrease disparities for the populations experiencing cancer burden in the catchment area); (5) ensure that the demographics of the catchment area are represented in clinical trials (i.e. research studies reflect the demographic distribution of the chosen area); (6) translate research into policy (i.e. research should lead to policy change from local through international levels, including health care systems and government legislation); and (7) extend the reach of research and policy beyond the catchment area (i.e. collaboration with other cancer centers, organizations, and government).

The structure provided by these guidelines is essential when considering the vast diversity of municipal regions of the United States, such as Los Angeles, California, which is home to roughly 10 million people (13). The County has a large Latinx[1] population, is considered the capital of Asia America, has the second-largest sexual and gender minority population in the country, spans a vast socioeconomic gradient, and covers both urban and semirural geographies (14–16). As such, the County is home to a large number of individuals who experience health inequities, with greater vulnerability among those who are foreign-born, lower socio-economic status, and living in areas with high ethnic concentration. Using a mixed methods approach, Cedars-Sinai Cancer embarked on a two-year assessment to meet NCI catchment area criteria while also maintaining a high level of cultural inclusion and sensitivity needed for serving one of the most diverse counties in the US.

Abbreviations: CRHCE, Cancer Research Center for Health Equity; CSMC, Cedars Sinai Medical Center; COE, community outreach and engagement; LAC, Los Angeles County.

[1] Latinx is a term used to represent Latino/a/x populations.

METHODS

Below we highlight the series of steps taken to define, characterize, respond to, and engage the population in our cancer center catchment area.

Step I: Defining the Catchment Area

Decisions were made regarding the catchment area based on geographic considerations, peer review to meet NCI criteria, and having a population size for which we could feasibly demonstrate measurable impact of our community outreach and engagement (COE) activities and COE-facilitated research. Our COE efforts focus on adherence to cancer screening guidelines and major behavioral and lifestyle factors, such as physical activity and tobacco use, and dissemination of the latest, most accurate cancer information. When considering the geographic area, we followed NCI metrics and County data. NCI requires clear geographic boundaries; a population of >4,000,000; greater than 80% of cancer patients residing within catchment area; and that the area is within 60 miles of the medical facility (CSC) to maximize clinical impact (12). These metrics were examined and linked with Los Angeles County (LAC) data on Service Planning Areas (SPAs).SPAs are geographic regions within LAC organized by the Department of Public Health. For each SPA, the county provides public health services, clinical services, and data targeted to the specific health needs of SPA-specific populations (17). Access to these data for smaller regions reveals important disparities that are often overlooked in aggregate data. For example, as noted in **Figure 1**, by breaking down key health indicators by SPA, striking disparities emerge in almost every health category for Antelope Valley (SPA 1), a semirural region in Northern LAC.

We presented the areas that met the NCI metrics to internal committees at CSC, external advisors, community outreach

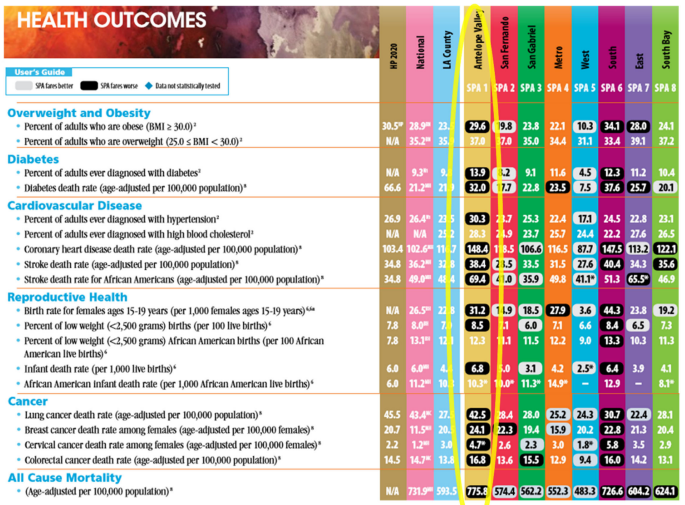


FIGURE 1 | Los Angeles Department of Public Health, Key Indicators of Health by Service Planning Area.

coordinators, and key decision-makers to ensure that we were aligned with the State's Cancer Plan and the NCI Catchment Area and Community Outreach and Engagement Mandate. Ultimately, CSC determined its catchment area to encompass service planning areas: Antelope Valley, San Fernando Valley, Metro, West, South Bay (**Figure 2**).

Characterizing the Population

The selected catchment area has a combined population of 5,768,445 individuals (**Figure 3**).

To gain a better understanding of the catchment area population and its diversity, as well as information on common cancers, secular trends, and mortality, we acquired aggregated and linked data from multiple primary and secondary sources.

Secondary Data Collection

First, we started with data at the national level (NCI, Surveillance, Epidemiology, and End Results Program; The Behavioral Risk Factor Surveillance System; American Community Survey; the American Cancer Society) to characterize national trends in cancer incidence and mortality and assess selected behavioral risk factors for populations of interest in our catchment area. Next, we reviewed statewide data from the California Cancer Registry and the California Health Interview Survey (CHIS). CHIS is the nation's largest state health

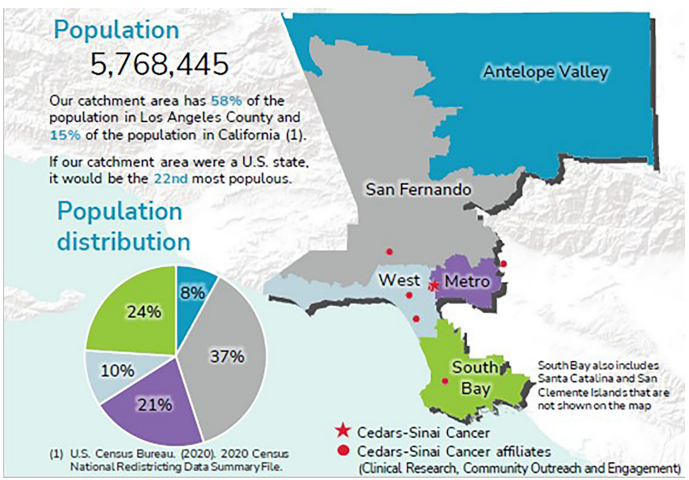
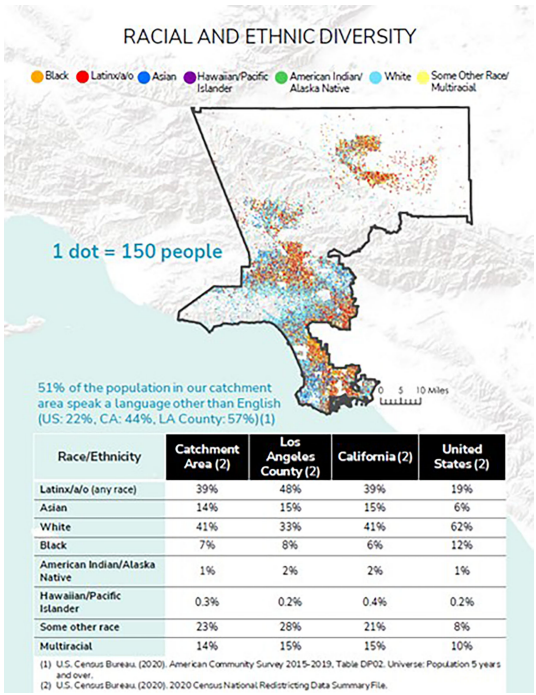


FIGURE 2 | Cedars Sinai Cancer catchment area.



51% of the population in our catchment area speak a language other than English (US: 22%, CA: 44%, LA County: 57%)(1)

Race/Ethnicity	Catchment Area (2)	Los Angeles County (2)	California (2)	United States (2)
Latinx/a/o (any race)	39%	48%	39%	19%
Asian	14%	15%	15%	6%
White	41%	33%	41%	62%
Black	7%	8%	6%	12%
American Indian/Alaska Native	1%	2%	2%	1%
Hawaiian/Pacific Islander	0.3%	0.2%	0.4%	0.2%
Some other race	23%	28%	21%	8%
Multiracial	14%	15%	15%	10%

(1) U.S. Census Bureau. (2020). American Community Survey 2015-2019, Table DP02. Universe: Population 5 years and over.
(2) U.S. Census Bureau. (2020). 2020 Census National Redistricting Data Summary File.

FIGURE 3 | Catchment area population by race and ethnicity.

survey and is conducted by the UCLA Center for Health Policy Research. At the time, the CHIS data cycle did not include comprehensive cancer screening questions; however, we have now partnered with CHIS to include cancer screening questions in the next data cycle (2021-2022) and to oversample CSC's catchment area populations of Latinx and Asians age 50+ to increase the number of participants in these groups. At the county level, we collated information from the Los Angeles County Cancer Surveillance Program and Los Angeles County Department of Public Health. Finally, we applied innovative geospatial mapping of these data to identify local hotspots for screenable cancers diagnosed at late stages with overlays of other relevant data (e.g., density and location of Federally Qualified Health Centers – FQHCs) to better understand local cancer disparities (discussed below).

Primary Data Collection

We supplemented our secondary data collection with additional questionnaires to better understand barriers to adherence that individuals face with cancer preventionand early detection efforts. We focused on social and behavioral risk factors in different racial and ethnic pockets through the administration of culturally adapted questionnaires, as exemplified with the Cancer and Healthcare in Los Angeles Survey (CHILAS). The CHILAS survey was developed with input and feedback from large communities in the catchment area (Korean, Filipinx, and Latinx) to identify major factors that characterize and influence screening behavior, medical history, and health care access. To date, a total of 3,200 surveys have been completed. Of these, 381 surveys have been collected from the Korean community, yielding interesting results. For example, the top barriers for not getting screened were not having health insurance and not feeling sick, suggesting the importance of financial concerns and cultural considerations. Also, we observed that mammography rates among age-eligible women (N=216) were low at 37% (N=80), whereas colonoscopy rates among age-eligible participants (N=284) were higher at 64% (N=182), leading us to question: "What are the unique factors for low mammography screening in Korean women in Los Angeles County (that do not apply to colonoscopy)?"

In the Filipinx community, upon review and feedback from our Filipinx community advisory board, the CHILAS survey was further adapted, and a recruitment strategy was implemented to form a Filipinx Cohort. A total of 1,492 surveys were collected from the Filipinx community in two waves. For screenable cancers, in contrast to Koreans, low adherence to colorectal cancer screening guidelines was identified. In waves 1 and 2, we found that 61% (386 out of 629) of age-eligible men and women had ever had an FOBT and/or colonoscopy, and in wave 2 where the question was updated to ask about most recent screening, only 44% (126 out 287) of age-eligible men and women are up to date with colorectal cancer screening (had FOBT within a year and/or had a colonoscopy within the last 10 years). This finding is consistent with the national trend of Filipinx Americans underutilizing life-saving screening tests for colorectal cancer, resulting in later stage of diagnosis and poorer survival (18). With this information, we began to think about how to best increase screening within this population in our local setting.

Community Profile Snapshots

With both primary and secondary data, we developed community profile summaries for several racial/ethnic/gender/sexual orientation minority groups. These profiles highlight noteworthy cancer trends, as well as other social determinates of health such as income, poverty, access to health care, mental health, and literacy. Further, we examined risk behaviors such as substance abuse, physical inactivity, and poor nutrition (**Supplement A**).

Step 2 & 3: Conduct Community Engaged Research That Addresses the Needs of the Catchment Area

Fifteen different cancer disparities were identified from our initial assessment, which has led to several culturally tailored research initiatives designed to address the needs of the catchment area. Below we provide two examples of studies that span the cancer control continuum, from data collection and interpretation, to designing, implementing, evaluating, and disseminating COE research.

Late-Stage Breast Cancer

In partnership with the Los Angeles County Cancer Surveillance Program, we explored the geographic distribution of late-stage cancer for selected cancers for which there are effective screening protocols. Analysis that examined the geographic distribution of late-stage breast cancer in Los Angeles County found that, using cancer registry data from 2000 through 2017, the densest concentration of late-stage breast cancer for all racial/ethnic

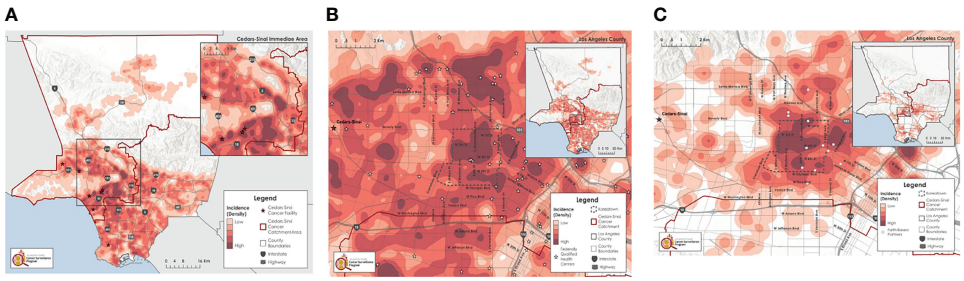


FIGURE 4 | **(A)** All race/ethnicity groups, females, all ages, 2000-2017*. **(B)** Focus on Koreatown, all race/ethnicity groups, females, all ages, 2000-2017*. **(C)** Focus on Koreatown, Korean, females, all ages, 2000-2017*.

groups combined was in our catchment area (**Figure 4A**). In Metro (SPA 4), analysis at finer geographic resolution showed that the Koreatown area has one of the densest concentrations of late-stage breast cancer among all race/ethnic groups (**Figure 4B**). These high-density areas were near many Federally Qualified Health Centers (FQHCs), noted by stars in **Figure 4B**, that offer free or low-cost breast cancer screening services. This includes the Every Woman Counts program funded by the State of California, indicating that these communities remain underserved despite high geographic accessibility to care. Koreatown is one of the few local neighborhoods in Los Angeles County where populations of Korean ancestry predominantly live. To effectively reach these individuals, promote early breast cancer screening, and encourage the use of free or low-cost screening services, our community outreach coordinator conducted in-language workshops in partnership with churches (noted by grey circles in **Figure 4C**). Through these workshops, subsequent focus groups, and existing literature, cultural barriers were identified as an important factor in screening adherence in this population (19). Some of these barriers include: lack of insurance, poor health literacy, not knowing where to go to get screened, lack of follow-up care, fear of being a burden to the family, and inability to afford testing. Another significant challenge was limited English proficiency, which is problematic for navigating an already complicated healthcare system, especially for those who are uninsured or underinsured (20, 21).With this information and building on a network of churches in Los Angeles that have committed to cancer prevention and control activities, grant funding was secured through the California Breast Cancer Research Program to answer the question: Does a culturally adapted "Faith in Action!" curriculum to educate and certify lay health navigators to provide breast cancer screening navigation within faith-based settings increase the adherence to breast cancer screening guidelines among Korean American women? The project is examining an innovative, culturally adapted cancer screening training for lay health navigators to increase adherence to breast cancer screening guidelines among underserved Korean American women. Navigation includes facilitation of follow-up care for those who have an abnormal mammography result, clinical breast exam findings, or are diagnosed with breast cancer. We work closely with members of our Korean Community Advisory Board (CAB), an extensive network of community partners established through our Health and Faith Initiative, to help us articulate the voice of the community to program staff by advising on projects and activities conducted by the research team and providing input to the overall project. Specifically, we have worked together to: (1) refine and finalize the adapted Cancer 101 cancer education training curriculum; (2) participate in decision making for planning of the study development and implementation and help with recruitment based on their knowledge of the population; (3) review the progress of the study; (4) provide guidance on developments in the community that could affect intervention implementation; (5) contribute to interpretation of study findings; and (5) participate in dissemination of study findings. A pastor of one of the larger churches serves as a multi-PI on this intervention study. This is one example of community-engaged research conducted to address the cancer burden in our catchment area that provides the community with a strong voice in all aspects of the study.

Melanoma

In the United States (US), melanoma mortality rates have declined by nearly 18% since 2014 in non-Latinx White (NLW) individuals (2); however, similar trends are not apparent in those of lower socioeconomic status (SES), including the Latinx community, and those living in rural areas (3–10). This may be attributed to less access to the information and services that are critical for preventing, detecting, and treating melanoma.

Data from the California Cancer Registry and other literature show that the melanoma burden is increasing in Latinx adults in California, who represent the largest ethnic group in the state, at 39% (11), and typically presents with more advanced disease (8, 13, 14, 22, 23). While US melanoma incidence rates remain low among Latinx adults compared to NLWs (4.6 vs 24.9 per 100,000 from 2012-2016), melanoma mortality is higher compared with other non-white racial/ethnic groups (13, 15). Differences in primary melanoma location (leg/hip/foot) and clinicopathologic subtypes (acral and nodular) in Latinx adults compared with NLWs tend to hamper early detection (8, 15–17). Likewise, physician- and self-skin examination is reported at lower rates in Latinx adults compared to NLW adults (18). In collaboration with Stanford University, we conducted focus groups among low socio-economic and/or Latinx individuals in

both urban and rural communities across California to better understand awareness of melanoma prevention and screening practices, and to obtain feedback on primary and secondary prevention strategies in local communities. The interview topics included: 1) awareness and views of melanoma risk, prevention, and early detection screening practices; 2) acceptability of primary and secondary prevention strategies in their respective community; and 3) barriers and facilitators of engagement in melanoma prevention and care. Using a hybrid inductive and deductive approach, thematic analysis was used for data analysis. Findings were organized within a socioecological model (individual, interpersonal, community and health system/policy level). These factors include ethnicity, cultural and gender identity, geography, skin color, gender norms, socioeconomic status, lack of trust, and insufficient access to health care. Latinx participants and those living in semi-rural regions reported more barriers (24). As a result, we are now working with the California Cancer Registry to ascertain individuals in these populations who have been recently diagnosed with melanoma, plus their network of family and friends in both high-density (Bay Area, City of Los Angeles) and semi-rural communities (Salinas, Antelope Valley).This pilot intervention, which includes innovative health communications such as storyboard sketches and whiteboard animations using plain language, as well as use of teledermoscopy through mobile devices, was designed with feedback on early concepts to ensure the communications will reach the target audiences. We are testing the efficacy of a culturally and linguistically appropriate health education intervention, delivered by trusted messengers such as community health workers, to promote melanoma prevention and early detection alongside health care navigation. This is another example of the research conducted within our catchment area that directly responds to the needs of the population, this one introducing innovative design, navigation, and teledermoscopy to address reported barriers.

In summary, we used the following process to identify cancers and behaviors of primary, initial focus. 1) We considered publicly available data such as cancer registry data (SEER, California Cancer Registry, LA County Cancer Surveillance Program), with a focus on top five cancers and cancers with increasing incidence rates, such as liver cancer in Latinx and breast cancer in selected Asian populations. 2) We generated our own quantitative data from: a) conducting geospatial analyses of cancer registry data; b) conducting our own survey, CHILAS, described above; c) sexual and gender minority questionnaire; and d) the California Health Interview Survey (CHIS) described above. 3) We also conducted study-specific surveys when useful. 4) In addition, we continue to seek qualitative input from community advisory boards (CABs, described below), townhall meetings, media events, and participation at community events, such as PRIDE events in greater LAC to identify issues of concern to them and to set priorities. 5) We considered strengths at Cedars-Sinai Medical Center (CSMC) that we may leverage to address specific disparities. 6) We aligned our efforts with the NCI Catchment Area and Community Outreach and Engagement Mandate and the State of California's 5-Year Cancer Plan.

RESULTS

Table 1 lists important cancers/behaviors/disparities, as identified by the community and our quantitative analyses, with consideration of our strengths at CSMC using the process we described above.

Step 4: Address Disparities

Through partnerships with churches, community organizations, Federally Qualified Health Centers, non-profit organizations, and trained community navigators, our COE team has reached over

TABLE 1 | Noteworthy Disparities/Risk Behaviors in Current CSC Populations of Scientific Impact.

Population	Cancer Disparity	Social and Behavioral Risk Factors
Latinx	‣ Liver cancer ‣ Late-stage melanoma ‣ Colorectal cancer	‣ Obesity ‣ Physical inactivity
Korean	‣ Breast cancer ‣ Colorectal cancer ‣ Thyroid cancer	‣ Low screening compliance ‣ High rates smoking/alcohol
Filipinx	‣ Thyroid cancer ‣ Breast cancer ‣ Prostate cancer	‣ Obesity ‣ Low screening compliance ‣ Smoking
Black	‣ Prostate cancer ‣ Triple-negative breast cancer ‣ Pancreatic cancer	‣ Smoking ‣ Secondhand smoke
LGBTQ+[2]	‣ Lung cancer ‣ HPV-related cancers	‣ Medical mistrust/discrimination ‣ HPV awareness & vaccine uptake ‣ Smoking, other drug use ‣ Transgenders: adverse health behaviors ‣ Cancer screening disparities
Non-Latinx Whites	‣ Late-stage melanoma	‣ Low SES cancer screening disparities

16,000 community members of Filipinx (18%), Latinx (20%), LGBTQ+ (25%), Korean (27%), and African American and other (10%) descent in our catchment area with science-based tailored cancer information in our newly defined catchment area. Based on pre/post workshop surveys, there was an 84% improvement in knowledge, behavior, and attitudes concerning cancer risk and prevention for all groups if a community member attended community outreach events, while reduction in barriers to cancer screening was most effective through navigator/promotora training. Knowledge of cancer risk and prevention was also shown to have improved more if there were physical events (33.3%), compared to virtual events (16.1%). With this feedback on our COE strategies, we have a more narrowed focus on a smaller set of cancers and behaviors and have built toward step 4 of NCI's guidelines, addressing disparities, by developing culturally sensitive, sustainable, scalable, and exportable interventions. We are investing in areas where we believe we have the potential to make a difference in either incidence (long term), mortality, or survivorship experience.

For the Korean breast cancer example, we started by noting the increasing incidence from cancer registry data, increased density of late-stage breast cancer in Koreatown (from our geospatial mapping), and low adherence to breast cancer screening guidelines from our CHILAS data. The grant-funded intervention we describe was facilitated by the CAB and utilizes capacity building among our community partners, training of navigators, and workshops and media events to increase awareness of this issue in the Korean community.

For the melanoma example, we noted that melanoma mortality rates in the US are highest among older men and individuals of lower socioeconomic status. Our findings from our qualitative exploratory study have enriched existing data regarding inequities in lower SES Latinx and non-Latinx White (NLW) individuals and have been critical in designing current interventions that deliver more effective primary and secondary melanoma prevention for underserved populations across geographic regions. At the healthcare systems and health policy level, this work adds to infrastructure and models for collaboration, and is aligned with the Wipe Out Melanoma - California statewide initiative, which is increasing the number of research studies, clinical trials, educational campaigns, and opportunities for the community to engage in melanoma prevention and early detection.

Key to step 4 in the NCI guidelines is the continued involvement of the population in setting a research agenda, and reaching out to the population through research, outreach, and education. The entire research portfolio developed as a result of the methods employed in this paper span across basic, clinical, and population science to guide cancer control and prevention efforts. Through further development of our community advisory boards, and a bidirectional relationship between community outreach and education and research, the populations in the catchment area are at the center of our endeavors. As part of an ongoing assessment process, community leaders representing populations with cancer disparities serve on four active community advisory boards:1) LGBTQ+ Community Advisory Board, 2) Filipinx Community Advisory Network, 3) Latinx Community Advisory Board, and 4) Korean American Community Advisory Board. Representatives from these advisory boards and networks comprise a larger 22 member Cedars-Sinai Cancer Community Advisory Board, which meets quarterly that helps to maintain engagement, guide research into policy implementation and standards of practice, and facilitate translational research across CSMC.

Policy and Standard of Practice

An example of how we are guiding research into policy is through our collaboration with

The California Dialogue on Cancer and their Health Equity Taskforce. The CRCHE faculty and staff were instrumental in writing for the first time a section on LGBTQ+ and cancer. Given that there are no reliable cancer registry data stratified by sexual and gender minority status, the CRCHE has been engaged in advocacy efforts to help expand the California Cancer Registry's data dictionary to include these important variables. The efforts are currently underway with support from the State's Comprehensive Cancer Control Program which will ultimately impact Surveillance, Epidemiology and End Results (SEER) to become more inclusive of LGBTQ+ populations. This important effort will enable organizations and cancer centers to develop a standardized and coordinated cancer control and research agenda to better serve this population.

Community Outreach and Engagement and Translational Science

For COE to inform and facilitate research in the other research programs, Cancer Biology (CB) and Experimental Therapeutics (ET), senior leadership at CRCHE work closely with the CSMC Executive Committee and Leadership Council, which includes other Associate Directors, program co-leaders, and program members where COE and catchment area topics are addressed on a regular basis. These meetings are exclusively focused on COE and the catchment area. An example that emerged from our meetings with ET is a community-based study of Nonalcoholic fatty liver disease (NAFLD) in the Latinx population that is currently a cross-sectional study of NAFLD prevalence that will facilitate a future, planned intervention trial. An example for CB is the initiative to use organoid models to address selected cancer disparities, such as breast cancer in transgender subjects with a focus on hormones and sex differences in bladder cancer.

DISCUSSION

In this paper, we highlighted how CSC, through guidance from the NCI catchment area framework, has aimed to address health disparities in historically underserved communities. The approach to research and population engagement (steps 2 and 3) has allowed us to work towards solutions that address disparities and aim to alleviate the cancer burden (step 4). Although we have not yet reached the stage of presenting

[2]We use the term lesbian, gay, bisexual, transgender, queer or questioning, plus anyone else that considers themselves part of this community (LGBTQ+) to encompass the diversity of this population.

catchment area-level results, our work has led to funded grants that are implementation science based and are presently in the implementation and evaluation phase. The next step currently underway is step 5, which focuses on the representation of the catchment area population in clinical trials. Inclusion of racial and ethnic minorities in cancer clinical trials is critical to increasing the generalizability and knowledge of the risks and benefits of new interventions; however, evidence points to low participation among racial/ethnic minority populations (25–27). in response, CRCHE continues to consult with our CABs, cancer survivorship groups, and coalitions to identify and address barriers for participating in clinical trials, as well as identify opportunities within our existing initiatives to increase accruals, including partnerships with providers, FQHCs, employer groups, and community organizations.

Each cancer center faces its unique challenges in defining, characterizing, and addressing the needs in their catchment area population. We have found that there is not a 'one size fits all' approach, especially in regions such as Los Angeles County that have diverse populations with pockets of dense, ethnic enclaves. Approaches must aim to be sensitive and inclusive of all races, ethnicities, and sexual and gender identities, a goal achieved through continuous tailoring and community engagement. A consideration of multiple health domains and socio-ecological influence is required, as well as a continued and localized assessments of cancer needs and disparities coupled with understanding of racial/ethnic-specific and localized cancer-relevant social and behavioral risk factors; otherwise, trends can be missed, and disparities can widen. Our mixed-methods approach to implementing that framework set forward by the NCI, in concert with continued community outreach and education partnerships, provides a narrative for other cancer centers aiming to create a sustained population-level reduction of cancer burden for individuals and communities experiencing health 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

LF, CS, RH, ZS contributed to conception and design of the study. LE, MC contributed to data curation and visualization. LF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.912832/full#supplementary-material

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A Cancer Health Needs Assessment Reveals Important Differences Between US-Born and Foreign-Born Latinos in California

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Background: Cancer is the leading cause of death among Latinos, the largest minority population in the United States (US). To address cancer challenges experienced by Latinos, we conducted a catchment area population assessment (CAPA) using validated questions from the National Cancer Institute (NCI) population health assessment supplement at our NCI-designated cancer center in California.

Methods: A mixed-methods CAPA was administered by bilingual-bicultural staff, with a focus on understanding the differences between foreign-born and US-born Latinos.

Results: 255 Latinos responded to the survey conducted between August 2019 and May 2020. Most respondents were foreign-born (63.9%), female (78.2%), and monolingual Spanish speakers (63.2%). Results showed that compared to US-born Latinos, foreign-born individuals were older, had lower educational attainment, were most likely to be monolingual Spanish speakers, were low-income, and were more likely to be uninsured. Foreign-born Latinos had lower levels of alcohol consumption and higher consumption of fruits and vegetables. The rate of preventive cancer screenings for breast, cervical and colorectal cancer did not differ by birthplace, although a low fraction (35.3%) of foreign-born Latinas who were up-to-date compared to US-born Latinas (83.3%) with colorectal cancer screening was observed. Time since the last routine check-up for all preventable cancers (cervical p=0.0002, breast p=0.0039, and colorectal p=0.0196) is significantly associated with being up to date with cancer screening. Individuals who had a check-up of two or more years ago are 84% less likely to be up to date with pap smears than those

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who had a check-up within the year (p=0.0060). Individuals without health insurance are 94% less likely to be up to date with mammograms and colonoscopy/FIT tests (p=0.0016 and p=0.0133, respectively) than those who are insured. There is no significant association between screening and nativity.

Conclusions: Considerable differences in socio-economic and environmental determinants of health and colorectal cancer screening rates were observed between US-born and foreign-born Latinos. The present study represents the foundation for future targeted intervention among immigrant populations at our cancer center's catchment area.

Keywords: health disparities, nativity, needs assessment, Latino health, preventative screenings

INTRODUCTION

Cancer is a leading cause of death among Latinos, the largest racial/ethnic minority group in the United States (1). California has the largest Latino population in the country (39%), with most individuals being of Mexican ancestry (2). Relative to non-Latino whites (NLW), Latinos generally have ~25% lower cancer incidence (3).The incidence of common malignancies such as breast, colorectal, lung, and prostate cancers are lower in individuals from this ethnic category, but members of this minority experience higher incidence rates of infection-related cancers like cervical, gastric, and liver compared to NLWs (3). Given the high prevalence of obesity among Latinos, especially among Mexican-Americans, obesity-related cancer incidence rates have increased in recent years (4, 5). Our group and others have also shown that genetic ancestry (acknowledging that Latinos have varying levels of ancestry derived from Europeans, Africans, and Indigenous Americans (6–9) mediates cancer risk and tumor characteristics in this population (10, 11). In addition to infection, obesity, and genetic ancestry risk factors, socio-environmental factors (e.g., socioeconomic status, access to health care, poor diet, physical activity) can also influence the risk profiles in Latinos (3, 12–15).

The University of California Davis Comprehensive Cancer Center (UCDCCC) has a catchment area with a large Latino population, with counties such as San Joaquin, Merced, Stanislaus, and Colusa, where 50% or more inhabitants have Latino heritage and experience vast socio-economic and environmental disparities (**Figure 1**) (16). A significant fraction of Latinos in these communities are both undocumented and uninsured, representing a major cancer prevention and care challenge. To address health challenges experienced by Latinos in the region, the Latinos United for Cancer Health Advancement (LUCHA) initiative was launched. The goal of LUCHA is to advance health equity in Latino communities through respectful, bi-directional, and community-engaged, translational, clinical, and public health approaches to cancer research. To improve the understanding of local community needs and disentangle cancer health disparities affecting the Latino community, a catchment area health assessment (CAPA) was conducted as an initial LUCHA effort. The CAPA laid the foundation for a strategic plan to better serve the catchment area through health education that emphasizes the importance of public health literacy, early detection, and cancer prevention.

MATERIALS AND METHODS

Measures

A 64-question survey (see details in supplementary material) was developed using validated questions from the National Cancer Institute (NCI) population health assessment supplement (7). Questions in the supplement were reviewed by LUCHA staff, translated to Spanish, edited, and face-validated to ensure that they were culturally appropriate for Latinos residing in California. Data collection took place in the nineteen county UCDCCC catchment area from August 2019 to May 2020. The priority was to capture predictors of cancer screening while also gauging factors influencing the health status of Latinos in the catchment area. The survey included four categories: sociodemographics, lifestyle and behavioral factors, social determinants of health, and cancer screening. Specifically, questions were asked about birthplace, language use, and length of time in the U.S. for foreign-born participants.

Our survey was created in English and was re-written at a 6^{th}-grade reading level to ensure it was easy to understand for most adults in the catchment area. The English version was tested in two groups, one consisting of internal members of the UCDCCC Office of Community Outreach and Education and the other of community members with different educational attainment levels. The internal group consisted of eight staff members who all had at least a bachelor's degree and were of mixed ethnic/racial backgrounds. The external group included all eight members of the UCDCCC's Community Advisory Board who had a diverse educational backgrounds ranging from high school diplomas to medical degrees and had representation from the following ethnic backgrounds: Asian Americans, Blacks, NLWs, and Latinos.

Once the survey was translated into Spanish by LUCHA native Spanish speakers, the translated survey was completed by ten native Spanish-speaking community members to ensure that it was appropriate for the most common Spanish forms

FIGURE 1 | UC Davis Cancer Center 19-County Catchment Area.

(Mexican and Central American) spoken in the region. The external Spanish-speaking group included people from Mexican, Colombian, and Guatemalan backgrounds with varying levels of education, most of which were high school or GED equivalent and a few with college and graduate-level degrees. The internal group included six bilingual staff members with varying levels of Spanish proficiency, all of whom were college-educated and came from different Latin American countries. During group testing, the time it took to complete the survey was measured since the assumption was that most participants would be answering in person and would not want to spend significant amounts of time filling out the survey. Once feedback was received for both the English and Spanish versions, the team implemented the suggestions and resorted to the second round of group testing internally and with a few external stakeholders. After the second round of testing, the survey was finalized and was sent to the UC Davis IRB for final approval.

Participant Identification and Eligibility

The participant eligibility criteria included self-identified Latino adults over 18 years living within the UCDCCC catchment area (**Figure 1**). Candidate participants were asked to complete a brief questionnaire to assess eligibility, and verbal consent was obtained for participation. Pre-survey questions included information on birth year, race/ethnicity, and residence zip code.

Data Collection

The survey was then implemented online and in-person (self-administered and coordinator administered using interviewing techniques such as question and answer dialogue) by the LUCHA bilingual-bicultural team. Data was initially collected in community settings, including outdoor health and wellness events, churches, and partnerships with community clinics, agencies, and family centers. This initial effort resulted in over 200 completed surveys at 17 community events. However, in March 2020, due to the COVID-19 pandemic lockdown, the collection effort was redirected to solely online collection, with the dissemination of survey links occurring through community partners, listservs, online classes, and social media. Surveys were available in both English and Spanish. For surveys collected in person, participants were approached by LUCHA staff to participate. Consent was obtained either verbally and/or in writing. Participants were also given the option to complete the survey at home by taking a flyer with a link to the survey. All study data collected was managed using the Qualtrics Research Suite, a web-based survey tool. Fifty-one surveys were collected online, and 204 were done in person and entered by staff.

Statistical Analysis

We used descriptive statistics to describe socio-demographic variables, health characteristics and behaviors, and cancer screening. As seen in the tables, numbers do not reflect the total number of participants, given that some questions were left unanswered. Denominators reflect those that answered the questions. Analyses focused on comparisons of foreign-born versus US-born Latinos. Chi-square and Fisher's exact tests were used to assess group differences with two-sided tests and a significance level of 0.05. Cancer screening proportions were calculated using recommended age ranges by national guidelines. Multivariable logistic regression models were used to identify variables associated with cancer screening. We used Akaike Information Criterion (AIC) to select optimal variables. Age was kept as a confounding variable, and nativity was kept as a variable of interest. We calculated unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CI) for numerous binary outcomes. Model performance for cancer screenings was assessed using the area under the curve (AUC) analysis under R library pROC() function with bootstrapping technique. Average AUC and 95% confidence intervals are calculated with bootstrap replicates to estimate the second significant digit of the confidence interval.SAS v9.4 and R Studio v4.0.0 were used to conduct statistical analyses.

RESULTS

Socio-Demographics

255 participants completed the surveys and were included in the analysis. A high fraction of participants were foreign-born Latinos (63.9%), female (78.2%), and monolingual Spanish speakers (63.2%). The average age of foreign-born participants was higher than US-born (44.7 versus 36.1, $p<0.0001$, **Table 1**). In general, foreign-born respondents had lower educational attainment, a higher fraction of monolingual Spanish speakers. They reported a lower opinion of their English-speaking ability compared to US-born respondents (21.9% of foreign-born reported speaking English very well vs. 84.6% among US-born participants: $p<0.0001$, see **Table 1**). Moreover, while over 50% of individuals in both groups reported being employed, foreign-born respondents had a larger proportion of homemakers (24.7%

TABLE 1 | Demographics of participants stratified by nativity. *(N=246)*.

Variable	Overall *(N=255)*	U.S. Born *(N=83)*	Foreign-Born *(N=163)*	p-value
Age Group				
18-30y	67 (27.5%)	36 (47.4%)	27 (17.0%)	**<0.0001***
31-40y	60 (24.6%)	17 (22.4%)	42 (26.4%)	
41-50y	53 (21.7%)	12 (15.8%)	40 (25.2%)	
51-65y	52 (21.3%)	7 (9.2%)	42 (26.4%)	
66y+	12 (4.9%)	4 (5.3%)	8 (5.0%)	
Mean Age (sd)	41.9 (14.1)	36.1 (15.2)	44.7 (12.7)	**<0.0001****
Sex				
Male	55 (21.8%)	18 (21.7%)	37 (23.1%)	0.7994
Female	197 (78.2%)	65 (78.3%)	123 (76.9%)	
Language Spoken at Home				
English	41 (16.4%)	29 (35.4%)	10 (6.3%)	**<0.0001**
Spanish	158 (63.2%)	20 (24.4%)	134 (84.3%)	
Both	51 (20.4%)	33 (40.2%)	15 (9.4%)	
English Speaking Ability				
Very Well	72 (38.7%)	44 (84.6%)	28 (21.9%)	**<0.0001***
Well	39 (21%)	7 (13.5%)	30 (23.4%)	
Not Well	64 (34.4%)	1 (1.9%)	61 (47.7%)	
Not At All	11 (5.9%)	0 (0.0%)	9 (7.0%)	
Education				
<High school	61 (25.0%)	3 (3.7%)	52 (34.0%)	**<0.0001***
High school graduate	57 (23.4%)	16 (19.5%)	39 (25.5%)	
Some college/Vocational	65 (26.6%)	30 (36.6%)	34 (22.2%)	
College grad or higher	61 (25.0%)	33 (40.2%)	28 (18.3%)	
Occupational Status				
Employed	140 (57.1%)	51 (62.2%)	87 (55.1%)	**<0.0001***
Student	25 (10.20%)	15 (18.3%)	10 (6.3%)	
Homemaker	40 (16.3%)	1 (1.2%)	39 (24.7%)	
Unemployed/Disabled/Retired	40 (16.3%)	15 (18.3)	22 (13.9%)	
Family Annual Income				
<$35k	107 (47.1%)	28 (35.9%)	74 (52.1%)	**0.0126**
$35k-$74.9k	78 (34.4%)	28 (35.9%)	49 (34.5%)	
$75k+	42 (18.5%)	22 (28.2%)	19 (13.4%)	

*Two-sided p-values form Chi-square test are used, unless a cell had less than 10, Fisher's exact test was used. *denotes Fischer's exact test. **denotes Independent T-Test for continuous variables. Bolded p-value indicates significance level of p<0.05.*

vs. 1.2%, p<0.0001). In contrast, US-born respondents included more students (18.3% vs. 6.3%, p<0.0001, **Table 1**). A larger fraction of foreign-born individuals had an annual income of less than $35,000/year (52.1% vs. 35.9%, p=0.0126).

Health Characteristics and Behaviors

Most participants had health insurance (72.4%). However, the fraction of uninsured was significantly higher among foreign-born than US-born (38.6% vs. 5.2%, p<0.0001, **Table 2**) participants. Only 12.7% of participants reported not having a location to obtain regular healthcare services, and 84.5% of all participants had been seen for a routine check-up in the last two years (**Table 2**). For the location of health care services, foreign-born individuals more commonly went to community clinics/healthcare centers (52.3% vs. 37.2%), emergency rooms (3.4% vs. 2.6%), or some other place (2.6% vs. 0.0%) than their US-born counterparts, who instead reported going to the doctor's office or used HMO most often (52.6% vs. 20.5%, p<0.0001, **Table 2**). Significant differences were not seen between the two groups regarding delayed medical treatment within the last year, opinion of health condition, or confidence in getting medical information.

Analysis of health behaviors showed that nearly 60% of the participants completed the Hepatitis B vaccine series (**Table 2**), with a lower fraction among foreign-born participants (67.9% for US-born vs. 53.1% for foreign-born; p=0.0098, **Table 2**). In general, foreign-born Latinos had healthier lifestyles and diets compared to US-born, with reported lower alcohol consumption (23.1% vs. 42.1%, p=0.0033), and more consumption of fruits (74.3% vs. 53.2%, p=0.0016) and vegetables (63.5% vs. 57.1%, p=0.3594, **Table 2**). No differences were observed in exercise, BMI, and history of cancer (personal and familial).

Cancer Screening Rates

As fewer respondents were old enough to assess their adherence to cancer screenings, our study had limited power to detect differences in screening rates between foreign-born and US-born Latinos. We, however noted that most female participants were up-to-date with pap smears and mammograms (78.5% and 72.9%, respectively, **Figure 2**). The foreign-born group had a lower fraction of women up-to-date with their breast cancer screening (70.1% vs. 86.7%), although this difference was not significant. A low fraction of female participants had colorectal cancer screening (53.5%) or were up to date with screening (41.9%). Furthermore, a lower fraction of foreign-born Latinas was up to date with such screening (35.3% vs. 83.3%, p=0.0666, **Figure 2**).

TABLE 2 | Health characteristics of participants stratified by nativity. (*N = 246*).

Variable	Overall *(N=255)*	U.S. Born *(N=83)*	Foreign-Born *(N=163)*	p-value
Health Insurance				
Private	124 (54.4%)	52 (67.5%)	70 (48.3%)	**<0.0001***
Public	31 (13.6%)	14 (18.2%)	16 (11.0%)	
Some other Source	10 (4.4%)	7 (9.1%)	3 (2.07%)	
None	63 (27.6%)	4 (5.2%)	56 (38.6%)	
Location to get health care services				
Clinic or health center	122 (51.7%)	29 (37.2%)	88 (52.3%)	**<0.0001***
Doctor's office or HMO	72 (30.5%)	41 (52.6%)	31 (20.5%)	
Hospital emergency room	8 (3.4%)	2 (2.6%)	6 (4.0%)	
Some other place	4 (1.7%)	0 (0.0%)	4 (2.6%)	
There is no place	30 (12.7%)	6 (7.7%)	22 (14.6%)	
Time Since Last Routine Check-up				
<1y	169 (70.7%)	62 (78.5%)	103 (66.9%)	0.1298*
1-2y	33 (13.8%)	11 (13.9%)	21 (13.6%)	
2-5y	13 (5.4%)	3 (3.8%)	10 (6.5%)	
5y+	16 (6.7%)	3 (3.8%)	12 (7.8%)	
Never	8 (3.3%)	0 (0.0%)	8 (5.2%)	
Traveling to Another Country for Medical Care				
Yes	34 (13.7%)	9 (11.1%)	25 (15.4%)	0.4352*
No	214 (86.3%)	72 (88.9%)	137 (84.6%)	
Delayed Medical Care in the Last 12 Months				
Yes	70 (30.2%)	21 (26.6%)	47 (31.8%)	0.4175
No	162 (69.8%)	58 (73.4%)	101 (68.2%)	
Opinion of Health Condition				
Excellent	19 (7.9%)	8 (9.8%)	10 (6.6%)	0.7256*
Very Good	43 (17.9%)	17 (20.7%)	26 (17.2%)	
Good	108 (22.1%)	34 (41.5%)	70 (46.4%)	
Fair	53 (22.1%)	19 (23.2%)	33 (21.9%)	
Poor	17 (7.1%)	4 (4.9%)	12 (7.9%)	
Confidence in Getting Medical Information				
Completely Confident	60 (25.0%)	30 (37.0%)	30 (19.7%)	0.0744*
Very Confident	68 (28.3%)	20 (24.7%)	46 (30.3%)	
Somewhat confident	71 (29.6%)	21 (25.9%)	48 (31.6%)	
A little confident	30 (12.5%)	7 (8.6%)	22 (14.5%)	
Not Confident at all	11 (4.6%)	3 (3.7%)	6 (3.9%)	
Hep B Vaccine				
At least 3 doses	80 (57.6%)	36 (67.9%)	43 (53.1%)	**0.0098***
Less than 3 doses	13 (9.4%)	7 (13.2%)	4 (4.9%)	
No doses	46 (33.1%)	10 (18.9%)	34 (42.0%)	
Current Smoker				
Yes	18 (7.6%)	6 (7.3%)	12 (7.8%)	1.0000*
No	218 (92.4%)	76 (92.7%)	141 (92.2%)	
Alcohol Consumption in the Last 30 Days				
Yes	65 (28.8%)	32 (42.1%)	33 (23.1%)	**0.0033**
No	161 (71.2%)	44 (57.9%)	110 (76.9%)	
Atleast One Serving of Fruit/Day				
Yes	148 (66.7%)	41 (53.2%)	104 (74.3%)	**0.0016**
No	74 (33.3%)	36 (46.8%)	36 (25.7%)	
Atleast One Serving of Vegetables/Day				
Yes	133 (60.7%)	44 (57.1%)	87 (63.5%)	0.3594
No	86 (39.3%)	33 (42.9%)	50 (36.5%)	
Exercise per Week (minimum 20min)				
0-3 days	98 (46.0%)	31 (43.1%)	63 (47.0%)	0.5864
4-7 days	115 (54.0%)	41 (56.9%)	71 (53.0%)	
BMI				
Normal	51 (23.9%)	24 (30.8%)	27 (20.8%)	0.1251
Overweight	63 (29.6%)	17 (21.8%)	43 (33.1%)	
Obese	99 (46.5%)	37 (47.4%)	60 (46.2%)	
Malignancy Identified by a Health Professional				
Yes	26 (10.6%)	7 (8.5%)	18 (11.4%)	0.6566*
No	220 (89.4%)	75 (91.5%)	140 (88.6%)	
Family History of Cancer				
Yes	118 (51.1%)	35 (45.5%)	80 (53.7%)	0.2404
No	113 (48.9%)	42 (54.5%)	69 (46.3%)	

*Two-sided p-values from Chi-square test are reported, unless a cell had less than 10, then Fisher's exact test was used. *denotes Fischer's exact test. Bolded p-value indicates significance level of p<0.05.*

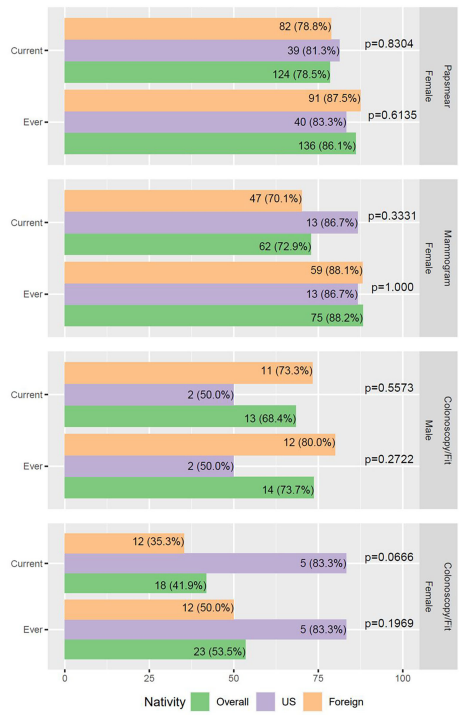

FIGURE 2 | Cancer screening rates in survey participants. Two-sided p-values from Chi-square test or Fisher's exact test are reported. Age inclusion: 21-65yo females for papsmear (N = 158); 40-75yo females for mammogram (N = 85); 50-75yo for colonoscopy/FIT (N = 43).

Multivariable Predictors of Cancer Screening Rates

After adjusting for age, education, health insurance, and place of birth, it was found that the longer it had been since a person had their last routine check-up, the lower their odds of being up-to-date with cervical and breast cancer screenings. For cervical cancer screening, individuals are less likely to be up to date by 58% (p=0.1615) if they had their last check-up after one year and by 84% (p=0.0060) if they had their last check-up after two years compared to individuals who had their check-up within the year (**Table 3**).

When adjusting for education, check-up (not included in colorectal model), health insurance, and place of birth, each one-year increase in age resulted in individuals being 1.09 (1.03-1.15, p=0.0038), 1.10 (0.97-1.25, p=0.1199), and 1.24 (1.05-1.46, p=0.0101) times more likely to be up to datefor cervical, breast, and colon cancer screening (**Table 3**). No statistical association was found between the place of birth and cancer screening rates.

Those who do not have health insurance are less likely to be up to date with cancer screenings than individuals who have health insurance. For breast and colorectal screenings, individuals with no health insurance were 94% less likely to be up to date (p=0.0016 and p=0.0133, **Table 3**).

Our breast screening model has the best performance at area under the curve (AUC) = 0.872 (0.787-0.956) followed by colorectal screening at AUC = 0.813 (0.701-0.925) and cervical screening at AUC = 0.790 (0.679-0.901). Using a person's age, education, nativity, health insurance, and time since the last routine check-up (for cervical and breast, not in the colorectal model) yields acceptable model accuracies (**Figure 3**).

DISCUSSION

To our knowledge, LUCHA is one of the few initiatives at NCI-designated cancer centers that solely focus on advancing Latino cancer health equity. The current study is also the first Latino-population-focused CAPA.

This cancer health needs assessment showed that while individuals who identify as Latino are grouped into one racial/ethnic category, there are substantial differences between foreign-born and US-born Latinos. In California, the state with

TABLE 3 | Unadjusted and adjusted odds ratios (OR) from logistic regression for factors associated with cervical, breast and colorectal cancer screening.

	Cervical Cancer			Breast Cancer			Colorectal Cancer		
Variable	**Unadjusted**	**Adjusted**	**p-value**	**Unadjusted**	**Adjusted**	**p-value**	**Unadjusted**	**Adjusted**	**p-value**
Age (continuous)	1.04 (1.00-1.08)	1.09 (1.03-1.15)	**0.0038**	1.12 (1.02-1.22)	1.10 (0.97-1.25)	0.1199	1.27 (1.1-1.45)	1.24 (1.05-1.46)	**0.0101**
Education									
Some college or more	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	
High school or less	0.37 (0.17-0.83)	0.23 (0.08-0.7)	**0.0092**	0.55 (0.18-1.67)	1.05 (0.22-4.94)	0.9501	0.32 (0.1-0.97)	0.37 (0.08-1.70)	0.1997
Time Since Last Routine Check-up									
≤ 1 year	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	
1-2 years	0.30 (0.11-0.83)	0.42 (0.12-1.41)	0.1615	0.24 (0.06-1.04)	0.64 (0.09-4.64)	0.6590	0.66 (0.04-11.12)	NE	
2 or more years	0.15 (0.05-0.41)	0.16 (0.04-0.59)	**0.0060**	0.14 (0.04-0.51)	0.34 (0.05-2.38)	0.2753	0.09 (0.01-0.82)	NE	
Place of birth									
U.S. born	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	
Foreign born	0.86 (0.36-2.04)	0.84 (0.24-2.92)	0.7843	0.43 (0.09-2.08)	3.73 (0.4-34.86)	0.2487	0.41 (0.09-1.78)	1.30 (0.21-8.07)	0.7794
Health Insurance									
Yes	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	
No	0.59 (0.26-1.38)	0.82 (0.26-2.62)	0.7425	0.11 (0.04-0.37)	0.06 (0.01-0.34)	**0.0016**	0.03 (0.00-0.28)	0.06 (0.01-0.55)	**0.0133**

NE: Not estimated to avoid model overfitting due to small sample size. P-values for the adjusted model are reported, unadjusted p-values not shown. Bolded p-value indicates significance level of p<0.05.

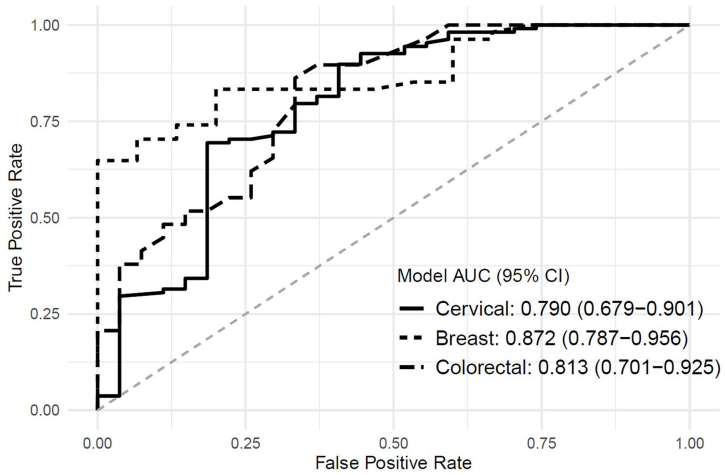

FIGURE 3 | Area Under the curve for multiple logistic regression screening models.

the largest Latino population, about 13.2% are foreign-born, of which 59% are undocumented immigrants from Latin America, making this population particularly harder to reach by the cancer center's community outreach and engagement programs (17). As seen in **Table 1**, the survey showed that foreign-born Latinos were more likely to have lower levels of education, lower levels of English fluency, make less than $35,000/year, and lack healthcare insurance. This reiterates the notion that the relationship between health and the Latino population is very complex (13). For example, a 2017 poll reported that 20% of Latinos experienced discrimination in a healthcare setting, and 17% relayed that they had avoided seeking medical care for themselves or family members due to concerns of being discriminated against or being treated poorly (18, 19). The fear of discrimination, alongside the anxiety of possible deportation among Latino families with mixed statuses, discourages families from seeking health services, leading to later cancer diagnosis, treatment, and outcome (15, 20).

Both social-ecological factors and ethnic heterogeneity play a role in cancer risk and mortality. Despite these differences, there was no association between nativity and cancer screenings among participants of the CAPA survey. Seventy percent or more of our survey respondents were current with their screenings for both breast and cervical cancer (**Figure 2**). However, for colorectal cancer screening, the fraction of up-to-date respondents was significantly smaller, even with a small sample size of screening eligible respondents. **Supplementary Table 1** demonstrates that while nativity was not associated with screening, sociodemographic factors like college education were associated with increased screening adherence. This is not surprising given that college education is linked to an increase in social status and income, which is also linked to better health insurance and, thus, the ability to seek care.

Limitations of this study include the sample size (N=255), the polarized political climate (e.g., national and state election campaigns), a heightened media focus on race issues during the survey period, and the COVID-19 pandemic (15). While the sample size for the current study is relatively small, interesting differences were uncovered that will be explored in future work. Additionally, while the survey did not ask for Protected Health Information (PHI), given the political climate, many individuals might have been hesitant to answer the survey due to fear or anxiety. The COVID-19 pandemic also altered the ability of surveyors to fan out into the community; subsequently, there was a rise in the completion of online surveys when the methodology was changed to a classroom setting (administered to UC Davis undergraduate students), which may explain a younger US-born sample and reflects some sample bias. With a younger group of survey participants, some of them may not have been eligible for cancer screenings which impacts the results. We also did not follow the participants for a period of time and were unable to do a trend analysis.

The rate at which the Latino population is growing and their increasing numbers of new cancer cases make them a critical public health priority. In California, the public health concern lies in the economic burden of cancer care and the unique challenges Latinos face in different geographical areas. The findings reported here suggest a need for more efforts to create health equity and add to current literature that supports the notion that there are differences in healthcare utilization and access among Latinos. At UC Davis, this means bringing health screenings to the community in the form of mobile clinics, vaccine clinics, and hosting health education workshops while patients wait for appointments. We understand that it is unrealistic to expect individuals with limited educational attainment and language fluency to navigate such a complex health system. Moreover, despite the advances in cancer care, Latinos face many different structural and social challenges that influence their cancer prognosis. It is important to understand the gaps in cancer awareness and care access to eliminate cancer health disparities.

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 UC Davis IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JQ, FP, AP, and AV contributed equally. LC-C led the conception and design of the study. FP, AP, JQ, SR, and AM aided in study recruitment. JQ and AV organized the database. JQ, AV, LA, and MN performed the statistical analysis. JQ wrote the first draft of the manuscript. JD, MC, LF, and PL gave input throughout the process. LC-C served as head PI. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Changes in Cancer Mortality by Race and Ethnicity Following the Implementation of the Affordable Care Act in California

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Although Affordable Care Act (ACA) implementation has improved cancer outcomes, less is known about how much the improvement applies to different racial and ethnic populations. We examined changes in health insurance coverage and cancer-specific mortality rates by race/ethnicity pre- and post-ACA. We identified newly diagnosed breast (n = 117,738), colorectal (n = 38,334), and cervical cancer (n = 11,109) patients < 65 years in California 2007-2017. Hazard rate ratios (HRR) and 95% confidence intervals (CI) were calculated using multivariable Cox regression to estimate risk of cancer-specific death pre- (2007-2010) and post-ACA (2014-2017) and by race/ethnicity [American Indian/Alaska Natives (AIAN); Asian American; Hispanic; Native Hawaiian or Pacific Islander (NHPI); non-Hispanic Black (NHB); non-Hispanic white (NHW)]. Cancer-specific mortality from colorectal cancer was lower post-ACA among Hispanic (HRR = 0.82, 95% CI = 0.74 to 0.92), NHB (HRR = 0.69, 95% CI = 0.58 to 0.82), and NHW (HRR = 0.90; 95% CI = 0.84 to 0.97) but not Asian American (HRR = 0.95, 95% CI = 0.82 to 1.10) patients. We observed a lower risk of death from cervical cancer post-ACA among NHB women (HRR = 0.68, 95% CI = 0.47 to 0.99). No statistically significant differences in breast cancer-specific mortality were observed for any racial or ethnic group. Cancer-specific mortality decreased following ACA implementation for colorectal and cervical cancers for some racial and ethnic groups in California, suggesting Medicaid expansion is associated with reductions in health inequity.

Keywords: Affordable Care Act, race and ethnicity, disparities, breast cancer, cervix cancer, colorectal cancer

INTRODUCTION

In the United States (U.S.), cancer care is inextricably linked with health insurance coverage (1). Prior studies have shown that, compared to privately-insured individuals, those who are uninsured or underinsured are less likely to undergo cancer screening and, therefore, more likely to present with later stage disease at time of diagnosis (2–4). Meanwhile, having health insurance is associated with shorter time to treatment initiation, receipt of guideline treatment, and improved survival (5).

The Patient Protection and Affordable Care Act (ACA), which was signed into law on March 23, 2010, and went into full effect January 1, 2014, expanded Medicaid eligibility to nonelderly adults with incomes at or below 138% of the federal poverty level with or without dependent children (6). To date, 39 U.S. states and the District of Columbia have adopted Medicaid expansion. Studies have shown that the ACA Medicaid expansion increased health insurance coverage among adults aged 18 to 64 years (7); moreover, this expansion has contributed to reductions in racial and ethnic disparities in coverage (8). Other provisions of the ACA are also relevant to cancer care. Starting in 2014, private health insurers could no longer deny coverage based on pre-existing conditions such as cancer, raise premiums, or deny coverage for cancer care. The ACA also created health insurance Marketplace plans, allowing the purchase of private health insurance plans, which are required to offer essential health benefits, including but not limited to hospitalizations, ambulatory care, and prescription drugs. The ACA's required coverage for preventive care services, which includes screening for colon, breast, and cervical cancer without cost sharing (9), has begun to show benefits in increased cancer screening (10). These benefits of ACA implementation for cancer patients include reduced proportions of uninsured patients, earlier stage at diagnosis, improved care access, and decreased mortality (10–17). Despite variability in the implementation of Medicaid expansion, due to differences among state policies (18), few studies have reported cancer outcomes in individual states (19–21). Several studies have reported reductions in racial and ethnic disparities in early stage diagnosis (12, 22) but data on survival outcomes for different racial and ethnic groups are scarce (15, 23). Therefore, the true extent to which Medicaid expansion has resulted in specific improvements in cancer outcomes and reduced disparities among racial and ethnic populations remains unknown. Given the well-known racial and ethnic disparities in mortality that exist in the U.S. (24), understanding the extent to which the ACA implementation improves mortality and reduces disparities can help motivate additional initiatives to address mortality among particular racial or ethnic groups.

California was one of five U.S. states—including the District of Columbia—that opted to expand Medicaid coverage to its low-income residents before 2014 (25), and California now hosts the largest Medicaid program in the nation. This early Medicaid expansion in California, in concert with the state's large and diverse population, provides a unique opportunity for assessing cancer outcomes in California following ACA implementation. As National Cancer Institute (NCI)-designated cancer centers in the U. S. charged with assessing and addressing the cancer burden in their catchment areas, results from this study provide important data for these centers in California to work with state and regional stakeholders to improve the health of the nearly 180,000 cancer patients who are diagnosed annually in the state and reduce the estimated 60,000 number of deaths that occur per year (26). Against this backdrop, we examined changes in the distributions of health insurance coverage, in the post- versus pre-ACA periods, among patients under 65 years of age in California with newly diagnosed breast, colorectal, and cervical cancer. In addition, we assessed cancer-specific mortality in the pre- and post-ACA periods for the three cancers, according to race and ethnicity. We limited our analysis to the three screenable cancers as these would benefit from ACA implementation through providing individuals with greater opportunities for early detection and, ultimately, reduced mortality. Breast cancer represents the second leading cause of cancer deaths in women and colorectal cancer is the third leading cause of cancer deaths in the United States (24). Even though cervix cancer is less common, mortality rates are higher in women of color than white women (24).

MATERIALS AND METHODS

Study Participants and Disease Classification

Participants were identified among data retrieved from the California Cancer Registry (CCR), which is the largest population-based state cancer registry in the United States and contains demographic, diagnostic, treatment, and outcome information for cancer patients. The participant population comprised patients diagnosed in California aged less than 65 years with a first primary invasive female breast, colorectal, or cervical cancer between January 1, 2007 and December 31, 2017. We focused on this age group because newly diagnosed patients aged 65 years and older are age-eligible for Medicare coverage and the ACA provisions that affect insurance options affect people younger than age 65 years We used the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) site codes C50.0–50.9 for breast cancer, C18.0–C18.9, C19.9, C20.9, and C26.0 for colorectal cancer, and C53.0–C53.9 for cervical cancer, excluding histology codes 9050–9055, 9140, and 9590–9992. Patients were excluded from analyses hierarchically as follows (See **Supplemental Figure 1**): diagnosis by death certificate or autopsy only (n = 878 breast; n = 1,231 colorectal; n = 77 cervical); not screening-eligible age (n = 98,966 not age 40–64 years for breast; n = 84,965 not age 50–64 years for colorectal; n = 2,604 not age 18–64 years for cervical); stage unknown (n = 4,638 for breast; n = 5,378 for colorectal; n = 863 for cervical); insurance status unknown (n = 2,952 for breast; n = 778 for colorectal; n = 296 for cervical); race and ethnicity other or unknown (n = 656 for breast; n = 255 for colorectal; n = 58 for cervical); no follow-up (n = 50 for breast; n = 38 for colorectal; n = 15 for cervical). The final study population included a total of 167,181 cancer patients:

117,738 breast, 38,334 colorectal, and 11,109 cervical cancer. Our study was approved by the institutional review boards at each of our respective institutions; informed consent was waived because we analyzed de-identified the data retrieved for analysis.

Exposure Variables

Race and ethnicity were classified as American Indian/Alaska Native (AIAN), Asian American, Hispanic, Native Hawaiian/Pacific Islander (NHPI), non-Hispanic Black (NHB), or non-Hispanic White (NHW), according to patient medical records and CCR classification system, supplemented by the North American Association of Central Cancer Registries' identification algorithm for Hispanic population groups using factors such as race and ethnicity, birthplace, and surnames. Primary and secondary sources of payment from the CCR data are based on the last admission for initial diagnosis and/or treatment. Because of the multiple ACA provisions that may affect access to cancer care outcomes, we included patients with all types of health insurance coverage. We classified insurance status according to five categories: private only; Medicare only or Medicare and private; any Medicaid; any military or public insurance other than Medicare or Medicaid; no insurance or self-pay. Given the increased recognition that the context within which we live, work, and play are important upstream determinants of health, we used a multi-component measure of neighborhood socioeconomic (nSES), based on patients' residential census block group at diagnosis and American Community Survey data, categorized into quintiles based on the statewide distribution (27). We considered nSES as a potential confounder in the analysis, as it has been demonstrated in numerous studies to be independently associated with cancer outcomes, independent of individual or patient-level factors (28, 29).

Follow-Up

Diagnosis year was categorized into three time periods: 2007–2010; 2011–2013; 2014–2017. We defined 2007–2010 as the period before the ACA implementation (i.e., pre-ACA) and 2014–2017 as the period after ACA implementation (i.e., post-ACA). Meanwhile, 2011–2013 was defined as the transition period before full Medicaid expansion, when individual counties in California were allowed to expand coverage and did so at different income thresholds (23). Follow-up time was calculated as the number of days from diagnosis until the date that occurred first among the following five: date of cancer-specific death (ICD-10 C50 for breast; C18, C19.9, C20.9, C26.0 for colorectal; C53 for cervical); date of death from another or unknown cause; date of last known contact; date 5 years after diagnosis; study end date of December 31, 2018. Follow-up time for survival extended through 2018 and was truncated at 5 years to allow for more equal opportunity for follow-up across the three time periods, and achieve balance between ensuring maximal inclusion of cases and contribution to follow up time. The median follow-up time for patients diagnosed in 2007–2010 was 5.0 years, and for 2011-2013 and 2014–2017, it was 5.0 years and 2.5 years, respectively.

Statistical Analysis

Changes in insurance type were assessed by calculating the percent point difference between post-ACA (2014–2017) and pre-ACA (2007-2010) periods. For mortality analyses, the hazard rate ratio (HRR) and 95% confidence interval (CI) were calculated using multivariable Cox regression to estimate associations with risk of 5-year cancer-specific death. Patients with an unknown cause of death were excluded from the Cox analysis. The proportional hazards assumption was tested separately for each cancer site by examining the correlation between time and scaled Schoenfeld residuals for all variables. Variables that violated the proportional hazards assumption were included in the model as an underlying stratification factor, which allowed the baseline hazard to vary by the levels of these factors. Models were adjusted for clustering by Census block group using a sandwich estimator of the covariance structure that accounts for intracluster dependence. Breast cancer models included time-period, race and ethnicity, age, insurance status, marital status, tumor size, lymph node involvement, grade, histology, nSES, and diagnosis and/or treatment at an NCI cancer center; with underlying stratification by stage, breast cancer subtype as defined below, surgery, chemotherapy, and radiation; and clustering by block group. Breast cancer subtype was defined according to the following categories: hormone receptor (HR) positive (estrogen and/or progesterone receptor positive)/Her2neu (HER2) positive, HR+/HER2-, HR-/HER2+, and HR-/HER2-. Colorectal cancer models included time-period, race and ethnicity, age, sex, insurance status, marital status, tumor size, lymph node involvement, histology, anatomical subsite, surgery, nSES, and diagnosis and/or treatment at an NCI cancer center; with underlying stratification by stage, grade, chemotherapy, and radiation; and clustering by block group. Colorectal cancer models also were stratified by sex in secondary analysis; results were similar by sex. Cervical cancer models included time-period, race and ethnicity, age, insurance status, marital status, tumor size, lymph node involvement, grade, histology, surgery, nSES, and diagnosis and/or treatment at an NCI cancer center; with underlying stratification by stage, chemotherapy, and radiation; and clustering by block group. Wald global (and individual) tests for interaction were computed using cross-product terms in an overall, fully-adjusted model, which, to make the overall model comparable to the stratified models, featured underlying stratification by the stratification variable (race and ethnicity or time period) and was adjusted for all possible interactions with the stratification variable. Statistical significance was assessed with a threshold of $p < 0.05$. We conducted multivariable models to assess the intersectionality of ACA time period and race and ethnicity for each cancer site; one set of models assessed 5-year cancer-specific mortality by time period (2007–2010; 2011–2013; and 2014–2017) stratified by race and ethnicity and a second set assessed mortality by race and ethnicity stratified by time period. In addition, to assess potential changes resulting from the ACA implementation, we present two sets of multivariable models: one that does not include stage and treatment and one that does. All analyses were performed in SAS 9.4 (SAS Institute, Inc).

To assess the robustness of our Cox regression analysis, given that we do not include data from a non-Medicaid expansion region, we conducted a sensitivity analysis by including cancer patients aged 65 years and older as a comparison group, including 141,026 cancer patients (79,691 breast, 59,084 colorectal, and 2,251 cervical cancer) aged ≥65 years who met the same inclusion/exclusion criteria. A difference-in-difference analysis was used to compare mortality differences in post- vs. pre-ACA implementation between younger and older patients.

RESULTS

We included 117,738 breast, 38,334 colorectal, and 11,109 cervical cancer patients age <65 years who were newly diagnosed between 2007 and 2017 (**Table 1**). Differences in age distributions by cancer site reflect different screening eligibility ages for each cancer type, which resulted in a younger age for cervical cancer patients and an older age for colorectal cancer patients.

We assessed changes in distributions of health insurance coverage in three separate time periods (2007–2010, 2011–2013, and 2014–2017) for breast, colorectal, and cervical cancer (**Table 2**). For breast cancer, after the ACA implementation, the percentage of uninsured women decreased by 0.3 percentage points, while the percentage of women with Medicaid increased by 2.4 percentage points, and those with private insurance decreased by 1.9 percentage points. Meanwhile, among patients with colorectal cancer, post-ACA, the proportion who were uninsured decreased by 2.3 percentage points, while those with Medicaid coverage increased by 9.5 percentage points, and those with privately insured patients decreased by 3.7 percentage points. Of the three cancers assessed, cervical cancer patients represented the highest proportion of uninsured patients pre-ACA (4.6%) and post-ACA (2.0%), exhibiting a 2.6 percentage-point decline. Medicaid coverage among cervical cancer patients increased by 1.4 percentage points, and private insurance increased by 2.3 percentage points. Changes in insurance coverage pre- and post-ACA, by racial and ethnic group, exhibited decreases in the proportion of uninsured patients for all groups, with some variation in the magnitude of the decrease across the groups (**Supplementary Table 1**). The proportion of Medicaid-insured individuals increased among Asian American, Hispanic, NHB, and NHW patients yet not among AIAN or NHPI patients. Private insurance decreased among NHB and NHW patients.

Table 3 shows 5-year cancer-specific mortality, by time period, for breast, colorectal and cervical cancer, stratified by race and ethnicity, for the four largest racial and ethnic groups. No significant differences in mortality were observed over time for breast cancer patients. In the fully-adjusted model, risk of dying from colorectal cancer was significantly lower in the post- vs. pre-ACA periods for Hispanic (HRR = 0.82, 95% CI = 0.74 to 0.92), NHB (HRR = 0.69, 95% CI = 0.58 to 0.82), and NHW (HRR = 0.90, 95% CI = 0.84 to 0.97) patients but not Asian American (HRR = 0.95, 95% CI = 0.82 to 1.10) patients. A statistically significant interaction between race and ethnicity and time period was observed in the fully-adjusted model (global p-interaction = 0.033); specifically, the HRR for NHB cases in 2011-2013 and 2014-2017 (compared to 2007-2010) were statistically significantly lower than the HRR for NHW cases (individual p-interaction = 0.005 for both time-periods). In addition, a statistically significantly lower risk of dying from cervical cancer was observed in the post- vs. pre-ACA period among NHB women in the fully adjusted model (HRR = 0.68, 95% CI = 0.47 to 0.99). When we assessed cancer-specific mortality differences by race and ethnicity stratified by time period, NHB women had a higher risk of dying from breast cancer compared to NHW patients for all three time periods (**Supplemental Table 2**). Whereas for colorectal cancer, NHB cases had a higher risk of dying from colorectal cancer compared to NHW cases only in the pre-ACA time-period.

In a sensitivity analysis, we assessed 5-year cancer-specific mortality by time period for breast, colorectal, and cervical cancer, stratified by race and ethnicity, for cancer patients aged 65 years and older (**Table 4**). Contrary to the mortality differences observed among younger patients in the fully-adjusted models, no statistically significant differences were observed for the post- vs. pre-ACA period for any racial and ethnic group among patients ≥65 years with breast, colorectal, or cervical cancer. **Figure 1** shows results of the difference-in-difference analysis for the associations found to be statistically significant in the younger group. A significantly lower mortality post- vs pre-ACA was observed in younger compared to older NHB colorectal cancer patients (p-interaction < 0.0001).

Given the small number of AIAN and NHPI patients represented in the CCR, we were unable to assess differences over time period stratified by these two racial groups. Nevertheless, in separate analyses to assess 5-year cancer-specific mortality for race and ethnicity stratified by time period (**Supplementary Table 2**), we observed higher (not statistically significant) breast cancer mortality among NHPI patients compared to NHW patients in the three time periods, yet we observed lower mortality for Asian American women. Similar mortality differences between NHPI and Asian American patients compared to NHW patients were observed for colorectal and cervical cancer. A mortality difference across time for AIAN patients compared to NHW patients was observed for cervical cancer: a lower yet non-statistically significant risk of dying was shown in the post-ACA period (HRR = 0.48, 95% CI = 0.20 to 1.17), which was not present before ACA implementation (HRR = 1.17; 95% CI = 0.70 to 1.97).

DISCUSSION

We assessed changes in distributions of health insurance coverage and 5-year cancer-specific mortality following implementation of the ACA among breast, colorectal, and cervical cancer patients younger than age 65 years, in California, an early adopter of Medicaid expansion under the ACA and the most populous U.S. state. Although reports on the

TABLE 1 | Characteristics by Cancer Site in Patients Under 65 Years of Age, California, 2007–2017.

	Cancer Site					
	Female Breast		Colorectal Female & Male		Cervical	
	N	Col %	N	Col %	N	Col %
	117,738	100.0	38,334	100.0	11,109	100.0
Age, Years						
18–39	0	0.0	0	0.0	3,642	32.8
40–49	36,778	31.2	0	0.0	3,517	31.7
50–54	25,802	21.9	11,811	30.8	1,505	13.5
55–59	26,794	22.8	12,671	33.1	1,314	11.8
60–64	28,364	24.1	13,852	36.1	1,131	10.2
Race and Ethnicity						
AIAN	667	0.6	260	0.7	111	1.0
Asian	18,020	15.3	5,603	14.6	1,512	13.6
Hispanic	26,540	22.5	8,972	23.4	4,461	40.2
NHPI	739	0.6	215	0.6	90	0.8
NH Black	7,835	6.7	3,256	8.5	668	6.0
NH White	63,937	54.3	20,028	52.2	4,267	38.4
Health Insurance						
Private only	88,082	74.8	25,134	65.6	5,748	51.7
Medicare only or Medicare + Private	4,727	4.0	2,293	6.0	250	2.3
Any Medicaid	20,767	17.6	7,700	20.1	4,260	38.3
Any military/other public	2,866	2.4	1,966	5.1	477	4.3
No insurance	1,296	1.1	1,241	3.2	374	3.4
Marital Status						
Unmarried	40,812	34.7	14,676	38.3	5,634	50.7
Married	72,540	61.6	22,062	57.6	5,068	45.6
Unknown	4,386	3.7	1,596	4.2	407	3.7
Year of Diagnosis						
2007–2010	40,782	34.6	13,053	34.1	4,160	37.4
2011–2013	32,372	27.5	10,578	27.6	2,980	26.8
2014–2017	44,584	37.9	14,703	38.4	3,969	35.7
AJCC Stage						
I	53,955	45.8	10,070	26.3	5,822	52.4
II	42,669	36.2	8,299	21.6	1,237	11.1
III	15,105	12.8	11,137	29.1	2,464	22.2
IV	6,009	5.1	8,828	23.0	1,586	14.3
Grade						
Grade I	24,814	21.1	4,277	11.2	1,465	13.2
Grade II	48,463	41.2	23,961	62.5	3,381	30.4
Grade III/IV	39,106	33.2	5,809	15.2	3,373	30.4
Unknown	5,355	4.5	4,287	1.2	2,890	26.0
Surgery						
No	7,823	6.6	5,574	14.5	4,077	36.7
Yes	109,890	93.3	32,751	85.4	7,030	63.3
Unknown	25	0.0	9	0.0	<5	0.0
Chemotherapy						
No	57,033	48.4	18,522	48.3	5,775	52.0
Yes	58,794	49.9	18,934	49.4	5,205	46.9
Unknown	1,911	1.6	878	2.3	129	1.2
Radiation						
No	58,547	49.7	31,417	82.0	5,500	49.5
Yes	59,118	50.2	6,906	18.0	5,603	50.4
Unknown	73	0.1	11	0.0	6	0.1
Neighborhood (Census Block Group) Socioeconomic Status Statewide Quintile						
Quintile 1 (low)	14,876	12.6	6,340	16.5	2,812	25.3
Quintile 2	19,415	16.5	7,622	19.9	2,469	22.2
Quintile 3	22,586	19.2	7,878	20.6	2,201	19.8
Quintile 4	26,945	22.9	7,802	20.4	1,890	17.0
Quintile 5 (high)	30,397	25.8	7,355	19.2	1,428	12.9
Not geocodable	3,519	3.0	1,337	3.5	309	2.8
Seen at an NCI-Designated Cancer Center						
No	99,664	84.6	32,995	86.1	8,116	73.1
Yes	18,074	15.4	5,339	13.9	2,993	26.9

AIAN, American Indian or Alaska Native; NHPI, Native Hawaiian or Pacific Islander; NH, non-Hispanic.

TABLE 2 | Insurance Status by Time Period for Breast, Colorectal, and Cervical Cancer Patients Under 65 Years of Age, California, 2007–2017.

	Time Period						Difference[b]
	2007–2010		2011–2013		2014–2017		
	N	%	N	%	N	%	
Breast Cancer							
Insurance status[a]							
Private	31,245	76.6	23,536	72.7	33,301	74.7	-1.9
Medicare	1,622	4.0	1,370	4.2	1,735	3.9	-0.1
Medicaid	6,509	16.0	6,048	18.7	8,210	18.4	2.4
Other public	932	2.3	1,008	3.1	926	2.1	-0.2
Uninsured	474	1.2	410	1.3	412	0.9	-0.3
Colorectal Cancer							
Insurance status							
Private	8,922	68.4	6,698	63.3	9,514	64.7	-3.7
Medicare	795	6.1	686	6.5	812	5.5	-0.6
Medicaid	2,036	15.6	1,978	18.7	3,686	25.1	9.5
Other public	773	5.9	754	7.1	439	3.0	-2.9
Uninsured	527	4.0	462	4.4	252	1.7	-2.3
Cervical Cancer							
Insurance status							
Private	2,139	51.4	1,476	49.5	2,133	53.7	2.3
Medicare	80	1.9	71	2.4	99	2.5	0.6
Medicaid	1,543	37.1	1,188	39.9	1,529	38.5	1.4
Other public	205	4.9	145	4.9	127	3.2	-1.7
Uninsured	193	4.6	100	3.4	81	2.0	-2.6

[a]*Insurance status categories: Private defined as private insurance only; Medicare defined as Medicare insurance only or Medicare and private insurance; Medicaid defined as any Medicaid insurance; Other public defined as any public insurance other than Medicare and Medicaid; Uninsured defined as no health insurance.*
[b]*Difference between 2014–2017 and 2007–2010 time periods.*

effect of this landmark legislation in the U.S. have been published (7–12, 22), data on cancer-specific mortality, particularly by racial and ethnic group, are scarce. In addition to decreases in the proportion of uninsured patients for all three cancers, across all racial and ethnic groups, we observed a decline in cancer-specific mortality following full ACA implementation. These results show the benefits of ACA implementation among NHB and Hispanic colorectal cancer patients and among NHB cervical cancer patients.

One goal of the ACA is to improve patient outcomes, which includes cancer survival. Published data on mortality outcomes for breast and colorectal cancer related to the ACA are mixed and scarce (15, 20, 23). To date, most studies have reported benefits of the ACA on cancer screening and stage at diagnosis (11, 14, 30). According to our research, there are two published reports on cancer mortality changes following ACA implementation, stratified by race and ethnicity (15, 23). One study reported no differences in breast, colorectal, and lung cancer mortality combined, between Black and White patients (15). In the second study (23), a two-year survival benefit associated with Medicaid expansion was greater in NHB patients, which resulted in narrowing disparities in cancer survival, similar to our findings. Our study addresses the limited literature on cancer-specific mortality (15, 20) and extends our understanding of racial and ethnic differences. We observed post-ACA reductions in colorectal cancer mortality of 10% among NHW, 18% among Hispanic, and 31% among NHB patients under age 65 years. Though, no significant changes in mortality were shown following the ACA for patients 65 years and older. These findings are consistent with a report from Kentucky (20) and a large population-based national study (23) yet inconsistent with those reported by Lam et al., (15). Contrary to reported findings (15), we observed no differences in breast cancer mortality when comparing the post- and pre-ACA periods. This could be because (1) the percent of uninsured breast cancer patients in California pre-ACA was very low and (2) the reduction in uninsured women post-ACA was small. For patients with cervical cancer, NHB women exhibited a statistically significant, lower mortality post-ACA compared to pre-ACA, but this was not observed for other racial and ethnic groups. This lack of association could be due to insufficient power to detect differences, given it is a less common malignancy compared to the others. This could be because cervical cancer patients exhibited the smallest gains in Medicaid coverage and had the highest rate of being uninsured following ACA implementation. In addition, for breast and cervical cancer outcomes, the effect of the ACA could be weakened by that of existing screening programs in California for uninsured and low-income women, which has been described in the literature (7, 8). Although our findings suggest a narrowing in some of the racial and ethnic disparities following ACA implementation, we were unable to conduct analyses specific to AIAN and NHPI patients, due to their small representation in the CCR.

Reports on changes in proportions of uninsured cancer patients following ACA implementation show greater reductions in Medicaid expansion states compared to non-expansion states (11, 14, 30–33). Among expansion states, a 2.6–2.9 percentage point drop in the proportion of uninsured cancer patients has been shown for post- vs. pre-ACA periods (11, 14, 26), which is consistent with our results for California. In addition, our results show that

TABLE 3 | Risk of 5-year cancer-specific death for time-period stratified by race/ethnicity among breast, colorectal, and cervix cancer patients less than 65 years of age, California, 2007-2017.

	NH White		Asian American		Hispanic		NH Black		p-int[a,c]	p-int[b,c]
	HRR[a] (95% CI)	HRR[b] (95% CI)	HRR[a] (95% CI)	HRR[b] (95% CI)	HRR[a] (95% CI)	HRR[b] (95% CI)	HRR[a] (95% CI)	HRR[b] (95% CI)		
Breast cancer										
Time-period										
2007-2010	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.061	0.141
2011-2013	0.94 (0.87-1.01)	0.94 (0.87-1.01)	0.96 (0.82-1.14)	0.95 (0.80-1.12)	0.98 (0.88-1.10)	0.95 (0.85-1.05)	1.13[d] (0.99-1.30)	1.07 (0.93-1.23)		
2014-2017	1.02 (0.94-1.11)	0.97 (0.89-1.05)	1.16 (0.98-1.38)	1.10 (0.92-1.31)	1.00 (0.89-1.11)	0.92 (0.82-1.04)	0.97 (0.83-1.13)	0.88 (0.75-1.04)		
Colorectal cancer										
Time-period										
2007-2010	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.455	**0.033**
2011-2013	**1.09 (1.02-1.17)**	1.03 (0.96-1.11)	1.07 (0.93-1.23)	1.03 (0.90-1.19)	1.07 (0.96-1.18)	0.97 (0.87-1.08)	0.97 (0.83-1.13)	**0.81[d] (0.70-0.95)**		
2014-2017	1.03 (0.95-1.10)	**0.90 (0.84-0.97)**	1.09 (0.94-1.26)	0.95 (0.82-1.10)	0.94 (0.84-1.04)	**0.82 (0.74-0.92)**	0.93 (0.79-1.10)	**0.69[d] (0.58-0.82)**		
Cervix cancer										
Time-period										
2007-2010	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.543	0.257
2011-2013	0.98 (0.83-1.17)	0.93 (0.79-1.10)	1.05 (0.76-1.43)	1.14 (0.83-1.58)	1.08 (0.91-1.28)	1.10 (0.93-1.30)	0.93 (0.65-1.32)	1.04 (0.72-1.49)		
2014-2017	1.09 (0.92-1.29)	1.00 (0.85-1.18)	1.09 (0.79-1.49)	1.09 (0.80-1.49)	1.07 (0.90-1.27)	1.03 (0.86-1.22)	0.73 (0.51-1.05)	**0.68 (0.47-0.99)**		

NH, non-Hispanic; HR, hazard rate ratio; CI, confidence interval; nSES, neighborhood socioeconomic status; NCI, National Cancer Institute.

[a]Cox regression. Breast cancer: Model adjusted for age, insurance status, marital status, tumor size, lymph node involvement, grade, histology, nSES, and NCI cancer center; with underlying stratification by HR/HER2 subtype; and clustering by block group. Colorectal cancer: Model adjusted for age, sex, insurance status, marital status, tumor size, lymph node involvement, histology, anatomical subsite, nSES, and NCI cancer center; with underlying stratification by grade; and clustering by block group. Cervical cancer: Model adjusted for age, insurance status, marital status, tumor size, lymph node involvement, grade, histology, nSES, and NCI cancer center; and clustering by block group.

[b]Cox regression. Breast cancer: Same as model in footnote a with additional underlying stratification by stage, surgery, chemotherapy, and radiation. Colorectal cancer: Same as model in footnote a additionally adjusted for surgery; with additional underlying stratification by stage, chemotherapy, and radiation. Cervical cancer: Same as model in footnote a additionally adjusted for surgery; with additional underlying stratification by stage, chemotherapy, and radiation.

[c]Global p-interaction in a fully adjusted overall model with underlying stratification by race/ethnicity and including all possible cross-product interactions with race/ethnicity.

[d]Significantly different from NH White (individual cross-product interaction term P<0.05 in a fully adjusted overall model with underlying stratification by race/ethnicity and including all possible cross-product interactions with race/ethnicity). Bold text indicates statistical significance.

TABLE 4 | Risk of 5-year Cancer-Specific Death for Time Period Stratified by Race and Ethnicity among Breast, Colorectal, and Cervical Cancer Patients 65 Years of Age or Older, California, 2007–2017.

	NH White		Asian American		Hispanic		NH Black		pa
	HRR	(95% CI)	HRR	(95% CI)	HRR	(95% CI)	HRR	(95% CI)	
Breast Cancer[b]									
Time period									
2007–2010	1.00		1.00		1.00		1.00		0.696
2011–2013	1.00	(0.93 to 1.07)	0.99	(0.80 to 1.23)	0.92	(0.79 to 1.08)	0.84	(0.68 to 1.04)	
2014–2017	0.97	(0.90 to 1.05)	1.05	(0.84 to 1.31)	0.89	(0.76 to 1.05)	0.95	(0.77 to 1.18)	
Colorectal Cancer[c]									
Time period									
2007–2010	1.00		1.00		1.00		1.00		0.660
2011–2013	0.99	(0.94 to 1.04)	0.96	(0.86 to 1.07)	0.97	(0.89 to 1.07)	1.01	(0.87 to 1.16)	
2014–2017	0.96	(0.91 to 1.01)	0.94	(0.84 to 1.05)	0.93	(0.85 to 1.03)	1.09	(0.95 to 1.25)	
Cervical Cancer[d]									
Time period									
2007–2010	1.00		1.00		1.00		1.00		0.171
2011–2013	1.35	(1.00 to 1.83)	2.13	(1.11 to 4.09)	1.02	(0.68 to 1.52)	1.01	(0.37 to 2.71)	
2014–2017	1.00	(0.75 to 1.33)	1.79	(0.92 to 3.49)	1.05	(0.70 to 1.56)	0.41	(0.16 to 1.01)	

Bold text indicates statistical significance.

[a]Global p-interaction in a fully adjusted overall model with underlying stratification by race and ethnicity and including all possible cross-product interactions with race and ethnicity.

[b]Breast cancer model adjusted for age, insurance status, marital status, tumor size, lymph node involvement, grade, histology, nSES, and NCI cancer center; with underlying stratification by stage, HR/HER2 subtype, surgery, chemotherapy, and radiation; and clustering by block group.

[c]Colorectal cancer model adjusted for age, sex, insurance status, marital status, tumor size, lymph node involvement, histology, anatomical subsite, surgery, nSES, and NCI cancer center; with underlying stratification by stage, grade, chemotherapy, and radiation; and clustering by block group.

[d]Cervical cancer model adjusted for age, insurance status, marital status, tumor size, lymph node involvement, grade, histology, surgery, nSES, and NCI cancer center; with underlying stratification by stage, chemotherapy, and radiation; and clustering by block group.

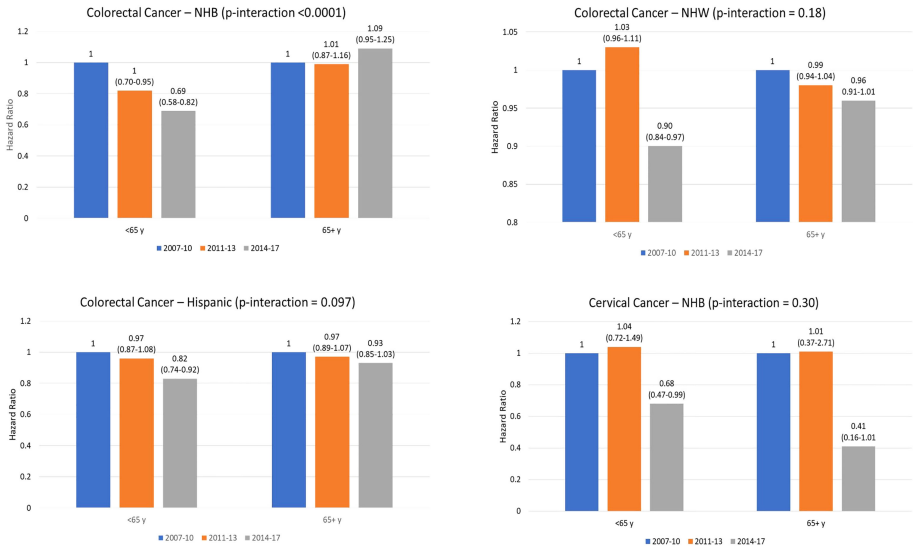

FIGURE 1 | Hazard Ratio (95% coinfedence interval) for cancer-specific death by time period for younger (<65 years) and older (65 years and older) patienets. P-value indicates interaction for difference in mortality between 2014-2017 compared to 2007-2010 between older and younger patients. Note. NHB, non-Hispanic Black; NHW. Non-Hispanic white.

improvements in insurance coverage occurred among all racial and ethnic groups, which range from a 0.6 percentage point decrease in the proportion uninsured for NHW patients to a 1.6 decrease for Hispanic patients. Indeed, Han et al. (26), also have reported these higher decreases among Hispanic patients compared to other racial and ethnic groups. Meanwhile, breast cancer patients exhibited the smallest decrease (0.3%) in being uninsured; however, these patients began with low uninsured rates prior to ACA implementation (1.2%). Larger decreases in the proportion of uninsured individuals were observed for colorectal cancer patients (2.3 percentage points), which could be due to larger reductions in uninsured male compared to female patients, as reported in the literature (12). Although cervical cancer patients exhibited the highest decrease in being uninsured (2.6 percentage points) for all three cancers, these patients also exhibited the highest proportion of uninsured women pre- and post-ACA implementation. These results underscore the challenges faced by cervical cancer patients, who are younger than colorectal and breast cancer patients and, as such, may experience unstable coverage. Our study contributes to and expands the literature through assessing corresponding changes in Medicaid coverage following ACA implementation. Colorectal cancer patients exhibited the largest gains in Medicaid coverage (9.5 percentage points), whereas cervical cancer patients exhibited the lowest increase (1.4 percentage points), changes that are within the range of those reported in the literature (11, 14).

Our study of California exhibits several strengths: the population-based nature of its data; the racial and ethnic diversity of its participants; the relatively long follow-up post-ACA because California was an early-Medicaid expansion state. Nevertheless, with these strengths come some limitations. First, this study is representative of California, which may limit its generalizability to other U.S. states. Indeed, prior studies that have analyzed multiple states comprise a mix of early- and late-Medicaid expansion regions, which feature differences in baseline mortality (15); this mix may obscure results, as has been reported (14). Further, we did not include a non-expansion state for comparison, as others have done. Instead, we compared outcomes to cancer patients 65 years of age and older, who were not affected by the coverage expansion provisions of the ACA we are examining in this study. Second, unmeasured confounders also could have contributed to our observation of decreasing cancer rates, as demonstrated by the down-trending rates in the pre-ACA era. Although we had the advantage of longer follow-up post-ACA, we still were limited by the relatively small number of outcomes for cervical cancer mortality, which resulted in imprecise measures of association, and the relatively small number of AIAN and NHPI cases. Third, because health insurance status, as recorded in CCR data, is based on last admission for initial diagnosis and treatment. We were unable to ascertain health insurance changes following cancer diagnosis or treatment.

In conclusion, following ACA implementation in California, a decrease in the proportion of uninsured patients was observed among non-elderly, newly diagnosed breast, colorectal, and cervical cancer patients, which varied by cancer site and by racial and ethnic group. In addition, lower cancer-specific mortality was observed for NHW, NHB, and Hispanic colorectal cancer patients, and for NHB cervical cancer patients in the post- vs. pre-ACA phase. These results contribute to ongoing discussions regarding healthcare reform in the United States, as additional states consider Medicaid expansion against the backdrop of further efforts to weaken the ACA. Moreover, given the economic impact of the COVID-19 pandemic, which has resulted in unemployment and lost health

coverage, future analyses should assess shifts between health insurance coverage plans on cancer outcomes. Doing so could contribute to expanding Medicaid in particular U.S. states to address health inequity.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: California Cancer Registry: ccrcal.org.

AUTHOR CONTRIBUTIONS

Conceptualization: JM, SLG, DO, KRY, MM. Formal Analysis: AC. Funding acquisition: SLG, MM. Investigation: JM, SLG, MM. Methodology: JM, SLG, DO, AC, MB, MM. Resources: SLG. Software: SLG. Supervision: SLG, MM. Writing – original draft: AC, MB, MM. Writing – review & editing: JM, SLG, DO, AC, WM, RY, MB, MM.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.916167/full#supplementary-material

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Commencing colorectal cancer screening at age 45 years in U.S. racial groups

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Screening for colorectal cancer (CRC) is cost-effective for reducing its mortality among the average-risk population. In the US, CRC incidence and mortality differ among racial/ethnic groups, with non-Hispanic Blacks (NHB) and American Indian/Alaska Natives showing highest incidence and mortality and earlier presentation. Since 2005, some professional societies have recommended CRC screening for NHB to commence at 45 years or earlier; this was not implemented due to lack of recommendation from key groups that influence insurance payment coverage. In 2017 the highly influential U.S. Multi-Society Task Force for Colorectal Cancer recommended screening to commence at 45 years for NHB; this recommendation was supplanted by data showing an increase in early-onset CRCs in non-Hispanic Whites approaching the under-50-year rates observed for NHB. Subsequently the American Cancer Society and the USPSTF recommended that the entire average-risk population move to commence CRC screening at 45 years. Implementing screening in 45–49-year-olds has its challenges as younger groups compared with older groups participate less in preventive care. The US had made extensive progress pre-COVID-19 in closing the disparity gap for CRC screening in NHB above age 50 years; implementing screening at younger ages will take ingenuity, foresight, and creative strategy to reach a broader-aged population while preventing widening the screening disparity gap. Approaches such as navigation for non-invasive and minimally invasive CRC screening tests, removal of financial barriers such as co-pays, and complete follow up to abnormal non-invasive screening tests will need to become the norm for broad implementation and success across all racial/ethnic groups.

KEYWORDS

colon cancer screening, cancer disparity, early onset colon adenocarcinoma, African American (AA), screening age, colonoscopy, fecal immunochemical (FIT) test

Abbreviations: CRC, colorectal cancer; USPSTF, US Preventive Services Task Force; ACG, American College of Gastroenterology; ICSI, Institute for Clinical Systems Improvement; SSA, sessile serrated adenoma; NSAID, non-steroidal anti-inflammatory drug; ACS, American Cancer Society; USMSTF, US Multi-Society Task force of Colorectal Cancer; CT, computed tomography; ACP, American College of Physicians; FIT, fecal immunochemical test; FOBT, fecal occult blood test; NHB, non-Hispanic Black; NHW, non-Hispanic White; AI/AN, American Indian/Alaska Native; CMS, Centers for Medicaid and Medicare Services; MSI, microsatellite instability; mt-sDNA, multitarget-stool DNA test; COVID-19, coronavirus disease-2019.

Introduction

Implementation of colorectal cancer (CRC) screening by non-invasive or minimally invasive means is associated with reduced mortality from CRC. Screening identifies average-risk persons who might harbor neoplasia and identifies patients with CRCs at potentially curable stages (1, 2). CRCs generally develop from precursor adenomas driven by well-described genetic alterations that may take 1 to 2 decades to manifest as cancer (3), affording time to interrupt this process *via* polypectomy (4, 5). Completion of CRC screening after any abnormal test involves the use of colonoscopy. Although colonoscopy is the gold standard and enables polypectomy, there remain challenges for high-quality exams due to the need to have the patient travel to the medical exam with an accompanying person (because sedation is used), and desire for good bowel cleansing preparation. Detection of lesions at colonoscopy and prevention of death from CRC depends on the endoscopist's adenoma detection rate (6). Colonoscopy can still miss right-sided lesions even though it is the best test to detect them, due to discernability of proximal lesions from normal mucosa and differing biology of right-sided lesions (4, 7, 8). Utilization of CRC screening assumes that persons at average-risk are recommended for the test by providers, the person completes the test, and both provider and patient follow-through on results of the test. The intention in the US is universal CRC screening of at-risk men and women; yet pre-COVID-19 screening utilization rates were 65% of the eligible US population, meaning one-third of eligible persons were not getting screened, elevating their risk (1).

The age to commence CRC screening was determined to be 50 years based on the epidemiology of CRC in the 1990s and results of randomized controlled trials of FOBT showing reduction in CRC incidence and identifying earlier-staged lesions (9, 10). In the general population, 95% of CRCs occurred after 50 years, with 5% occurring earlier (10). Guidelines emerged incorporating data from studies into consensus recommendations for those ≥50 years, including tests to use (Table 1), the importance of follow-up of abnormal tests, and differentiating average-risk from high-risk individuals (those with family history of cancer or heritable syndrome, inflammatory bowel disease, or prior identified neoplasia) (11). Race as a risk factor (*see below*) was not considered in any major guidelines until 2017 (11) despite evidence for higher risk for CRC in specific groups. Recent data identifies a shift in age distribution of CRC for the general population, with 88% of CRCs occurring after 50 years and 12% occurring under 50 years, a more than doubling of early-onset cancers over the past 30 years (12–16). This shift is observed in persons born after 1960 with the largest group under 50 years showing increase being 45-49-year-olds (12, 13). This increase in early-onset CRC is environmental and not genetic, with several metabolic factors as possible etiologies (13, 16). Due to increased proportion of persons with CRC under 50 years, professional organizations began to modify recommendations for CRC screening commencement to 45 years (17, 18). The key recommendation for commencing screening at age 45 years came from the USPSTF in 2021, the group that CMS and other insurers generally follow due to their rigorous analytic methods and modeling.

Epidemiology of CRC in racial groups

Initiation of CRC screening in the US was for the entire at-risk population, with age and family history as primary determinants for screening commencement (2, 9, 11). However, the US population is made up of diverse racial and ethnic groups, each showing varying CRC incidence and mortality. Until recently, the non-Hispanic Black (NHB) population has had the highest incidence and mortality from CRC among non-Hispanic Whites (NHW), Asian/Pacific Islanders, American Indian/Alaska Native (AI/AN), and

TABLE 1 Currently available, FDA-approved tests for colorectal cancer screening (11).

Rank Order of Preference	Screening Test	Frequency if no findings
Tier 1	Colonoscopy	Every 10 years
	Fecal Immunochemical Test (FIT)	Annual
Tier 2	Fecal DNA Test combined with FIT	Every 3 years
	CT Colonography	Every 5 years
	Flexible sigmoidoscopy	Every 5 years (10 years with FIT)
Tier 3	Capsule colonoscopy	Every 5 years
Relatively obsolete	Guaiac-based Fecal Occult Blood Test (FOBT)	Replaced by FIT
	Barium Enema	Replaced by CT Colonography
Not recommended	Methylated *SEPTIN9* blood test	–

Fecal DNA Test is also known as multitarget stool DNA test (mt-sDNA) or FIT-DNA test.

Hispanics (2, 10, 19, 20), and has been consistently documented since before the 1990s (21–23). Implementation of CRC screening has lowered incidence and mortality rates for all races and ethnicities; however, disparity still exists for NHB (1, 2, 10, 20, 21). There are several factors that contribute to the disparity. First is underlying socioeconomic inequalities that dictates which zip code one lives, influencing accessibility to fresh produce and high availability of tobacco and alcohol, accessibility to preventive care, and predicts education attainment and level of employment. This, in turn, influences individual metabolic derangements over the lifetime, with alterations in gut microbiome and increased metabolic-induced inflammation. This, in turn, alters colonic cell proliferation and increases genetic mishaps, and likelihood for adenoma formation that can transform into CRC (20). This notion is solidified by observations that NHB have higher incidence of high-risk precursor adenomas (24, 25), and present 0-8 years younger with CRC than NHW (2, 10, 20). Since the 1990s, the proportion of CRCs under 50 years in NHB was 10.6%, about double the rate for NHW for that time period (2, 10, 20). Second, NHB show 7-15% higher prevalence of proximal CRCs (between cecum and splenic flexure) compared to NHW (2, 26), where sensitivity of the highest sensitive screening test, colonoscopy, is less than distal sites at detecting lesions (4). This finding parallels increased prevalence of proximal high-risk adenomas in NHB (24, 25). Earlier age of onset for high-risk adenomas and CRC in NHB coupled with increased prevalence of proximal neoplasia even with colonoscopy as the screening modality could amplify the disparity. Proximal CRCs in NHB are mostly microsatellite stable, with less prevalence of microsatellite unstable (MSI) CRCs compared to NHW (26). Consistent with this, there is no evidence that sessile serrated adenomas (SSAs), which are proximal and demonstrate MSI, are increased in NHB (2, 27, 28). The lower prevalence of MSI CRCs among NHB may itself contribute towards poor outcomes as MSI is associated with longer survival and eligibility for immune checkpoint inhibition therapy (29). Third, colonic microenvironment may be altered in NHB to favor CRC, with increased inflammation to generate inflammation-associated microsatellite alterations (30), which are associated with metastasis and poor survival (31–34). Indeed, use of NSAIDs had no deleterious consequences in older NHB CRC patients as compared to shorter survival for older NHW CRC patients (35). The cytotoxic immune cell response to cancer may be hampered in NHB CRCs compared to NHW (26, 36, 37). The colonic microbiome in NHB often show increase in sulfidogenic bacteria and pro-inflammatory *Fusobacterium* and *Enterobacter* species, all associated with neoplasia (38, 39). Lastly, there has been longstanding screening utilization disparity between racial/ethnic groups in the US, with NHB utilization 15% lower than NHW in the 2000s and 3% lower in 2018 (40). Navigated colonoscopic screening can eliminate incidence and mortality disparity (41). COVID-19 has showcased disparities in outcome, and shares similarities with disparities observed for CRC (42, 43). One consequence of COVID-19 was reduction in population CRC screening that is predicted to cause unnecessary cancer deaths over the next decade (44). Recovery of population-based CRC screening levels is likely to be uneven among racial/ethnic groups, with NHB recovering slower, widening the screening gap (44). Overall, there may be multiple components that contribute to CRC disparities in NHB.

In 2022, AI/AN demonstrate the highest CRC incidence among racial/ethnic groups in the US, overtaking the high rates observed for NHB (1) (Table 2). This observation is buttressed by a now-recognized propensity for AI/AN developing high-risk-adenomas (23). It may be only a few years that CRC mortality for AI/AN surpasses the high rates of NHB (1, 20). This observed incidence increase may be the result of longer life span from improved co-morbidities. CRC screening utilization for AI/AN was 59% in 2018, lower than that of NHB (40). These observations seem to replicate the disparity-driven conditions observed for NHB.

TABLE 2 Age-adjusted colorectal cancer incidence rates, 2014-2018, and age-adjusted colorectal cancer mortality, 2015-2019, among U.S. racial groups. Data are per 100,000 (adjusted to the 2000 US Census) (1).

	All	NH White	NH Black	Asian/PI	Am Indian/Alaska Native	Hispanic
Incidence Overall	36.5	36.1	42.6	29.0	49.2	32.8
Male	42.1	41.5	50.4	34.4	55.8	39.2
Female	31.6	31.3	37.1	24.6	43.9	27.6
*Early-onset (20-44 years)		6.7	7.9	6.3		
Deaths Overall	13.4	13.4	18.1	9.3	17.4	10.8
Male	16.0	15.8	22.7	11.1	21.3	13.7
Female	11.3	11.3	14.8	7.9	14.4	8.5

Data for early-onset colorectal cancer are age-adjusted colorectal cancer incidence rates, 2000-2012 (2000 US Standard Population) (15).

Policy recommendations for commencing CRC screening in racial groups

Risk for CRC derives from factors that are potentially modifiable (diet, weight, physical activity, aspirin use, socioeconomic status, and screening utilization), and factors that are not modifiable (age, family history, race). Major components that determine commencement of CRC screening are age and family history, with subsequent screening intervals determined by findings on the initial screen and family history (9, 20). Race had not been included in CRC screening recommendations (until 2017) despite several decades of demonstrated disparity for incidence and mortality from CRC for NHB in particular (2, 20, 45–47).

Because of the epidemiology observed for NHB for CRC, several organizations have made the recommendation to commence CRC screening in NHB at 45 years or earlier (2, 11, 46, 48) (Figure 1). The rationale for recommendation was shorter time between screening initiation and cancer formation in NHB (2). While the evidence was not deemed the highest-grade, the overall approach to CRC screening recommendations has generally included consideration of natural history and epidemiology for groups of individuals at risk. For instance, as with age, family history is a determinant when CRC screening commences (age 40 years) (11). Specific conditions are addressed in guidelines based on high-risk conditions, including presence of inflammatory bowel disease, Lynch syndrome, familial adenomatous polyposis, or personal history of colonic neoplasia (11). Generally, if a condition has propensity for earlier age of onset for CRC, shows higher morbidity and mortality at younger ages, and possesses higher prevalence of high-risk precursor adenomas (all of which describe the epidemiology of NHB patients with CRC), these observations should provide awareness and bestow rationale for adjusting the CRC screening initiation age (2). Earlier age commencement for CRC screening in NHB was recommended by ACG, ICSI, and ACP over the past 2 decades (11, 46, 48) (Figure 1). These organizations, while influential to large constituencies, do not compel insurers to provide payment coverage for earlier screening. In 2017 the highly influential MSTF made their first-ever recommendation to include race in their guidelines, recommending that NHB commence screening at 45 years (11). This recommendation greatly increased awareness, with some healthcare organizations such as Kaiser Permanente enacting screening for NHB at 45 years (49). Despite awareness, it did not immediately modify private and public insurer payment coverage.

The one modifiable item that providers (and patients) greatly influence is screening utilization. Modifying diet and physical activity are possible but are hard for most individuals to comply over a lifetime. Socioeconomic circumstances for individuals are not readily adjustable to modify CRC risk. Screening, however, is a great equalizer as it can reduce CRC risk *and* erase disparities for incidence and mortality if highly utilized. This was illustrated by the Delaware Cancer Consortium with navigated screening colonoscopies in 10,000 NHB and NHW patients (41). Comparing patients at the start with those at completion of the study, screening for average-risk NHB increased from 47.8% to 73.5% and for average-risk NHW individuals increased from 58.0% to 74.7%, benefiting both groups (41). For NHB, screening implementation reduced advanced CRCs from 78% to 40% and increased local stage CRCs from 15% to 50% (41). Importantly, CRC incidence dropped for both NHB and NHW, completely erasing incidence disparity. CRC mortality disparity was nearly erased, with NHB dropping from 31.27 to 18.35 deaths/100,000, and NHW dropping from 19.45 to 16.94 deaths/100,000 (41). Non-invasive screening can also eliminate disparities. Kaiser Permanente demonstrated increased screening utilization among NHB from 42% to 80% and among NHW from 40% to 83% from 2000 to 2015-2019 (50). CRC incidence dropped for NHW (135 to 78 cases/100,000 from 2009 to 2017-2019) and

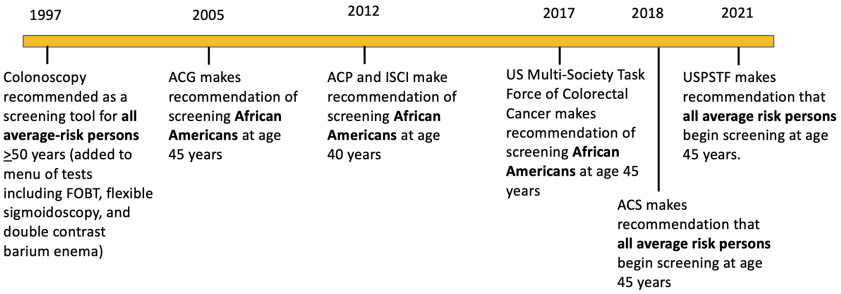

FIGURE 1
Timeline of colorectal screening recommendations for average risk persons and African Americans over the past 3 decades by various organizations (2, 9). ACG: American College of Gastroenterology; ACP, American College of Physicians; ICSI, Institute for Clinical Systems Improvement; ACS, American Cancer Society; USPSTF United States Preventative Services Task Force.

NHB (166 to 82 cases/100,000 from 2010 to 2017-2019), nearly eliminating incidence disparity (50). Likewise, CRC mortality disparity disappeared with reductions for NHW (33 to 20 cases/100,000 from 2007-2009 to 2017-2019) and NHB (54 to 21 cases/100,000 from 2007-2009 to 2017-2019) (50). These data show importance of CRC screening overall for all at-risk populations, as well as impact on health equity. The main factor for success and eliminating disparities in both studies is high utilization of screening across populations.

Initially recommended by ACS in 2018 (17), the age to commence CRC screening was lowered from 50 years to 45 years for the entire at-risk population upon recommendation by USPSTF (18) (Figure 1). USPSTF recommendations generally trigger acceptance by CMS and other insurers to provide payment coverage. The reason for ACS and ultimately USPSTF recommendation was not data specific to NHB, but data showing overall increase in CRC under of 50 years for men and women in the population (12, 17, 18). The NHB CRC trends in CRC incidence under age 50 years has slightly increased from over 11 to over 12/100,000, whereas the NHW CRC incidence has increased from a low of 7 to 12/100,000, indicating that NHW are the larger driver for the recent population increase (17). AI/AN are also known to have among the highest rates for CRC incidence under 50 years (51). The one advantage of a broader recommendation of the 45 year commencement age is that it makes implementation easier *via* a more uniform message and policy for patients and providers.

Lowering CRC screening age to 45 years adds >19M average-risk persons to the screening pool (with 87M average-risk persons 50-74 years already in the screening pool) (52). With ~68% of 50-74 years and ~7% of 45-49 years obtaining screening previously, this policy change increases the unscreened population from ~27M to ~44M at-risk individuals, a 60% increase of pool size (52), and could constrain screening resources. The etiology of more CRCs under 50 years for both NHB and NHW is not known other than it is environmentally-driven; a targeted screening approach for under-age 50-years might be more ideal for resource efficiency if specific biomarkers are identified (13). Biomarker studies have been conducted nearly exclusively in NHW, with diagnostic accuracy of some existing biomarkers (e.g. mt-sDNA markers) not addressed with adequate power in other racial groups (3, 53). Furthermore, diagnostic accuracy has not been extended to those 45-49 years, with extrapolation of diagnostic accuracy from subjects aged ≥50 years. CRC screening utilization *via* colonoscopy is lower in younger age groups compared to older age groups (54), making high utilization among 45-49-year-old individuals challenging. All in all, the approach to screening for this enlarged population will take utilization of non-invasive and minimally-invasive strategies (see Table 1) to optimally screen the at-risk US population beginning at 45 years – rural and urban, all races and ethnicities, all socioeconomic strata, and insured and underinsured/non-insured (55).

Discussion: Removing barriers and effective approaches for optimal CRC screening in racial groups

With modification to 45 years as initial CRC screening age, what test should be used to optimally screen 45-49 year-olds? At present, it is the best test that gets done (see Table 1) (53). Kaiser Permanente commenced screening in 45-49 year-old NHB individuals in 2018 *via* FIT after USMSTF recommended screening this racial group beginning at 45 years (11, 49). NHB aged 45-49 years, compared to NHB 50-54 years and NHW 50-54 years, had the lowest FIT completion rate despite FIT being mailed to 90% of eligible members. However, there were no automated electronic health reminders for this age group, and authors surmised that there was low provider awareness for screening in this age group and in NHB (49). This study reiterates that younger ages tend to have lower screening completion (54), and that there are provider, system, and patient barriers that may reduce CRC screening utilization (47). One study identified among non-screened average risk individuals that greatest barriers to screening with FIT/FOBT, multitarget-stool DNA (mt-sDNA) test, or colonoscopy were lack of knowledge, lack of provider recommendation, and suboptimal access (56). In those who had prior screening, barriers to completing the next FIT/FOBT or mt-sDNA test were lack of provider recommendation and lack of knowledge, and barriers to completing the next colonoscopy were psychosocial barriers and lack of provider recommendation (56, 57). NHB and Hispanic participants were more likely to report lack of knowledge and lack of provider recommendation than NHW individuals (56). Co-morbidities, which are more prevalent in NHB compared to NHW (42), adversely influence screening recommendations and completion (58). To facilitate screening among diverse populations with varying socioeconomic and social challenges, there needs to be contextually-informed, multi-level, multi-component interventions that target patients, providers, health systems, and communities (47, 55, 59). For instance, patients can benefit from navigation, providers can be educated to follow evidence-based guidelines, health systems can use electronic health records for systematic timely reminders to both providers and patients, and communities can address capacity, educational needs, and provide outreach (55). Policies need to be in place to remove barriers and promote uptake of evidence-based interventions, including removal of out-of-pocket costs for screening (55). Culturally-sensitive interactions between provider and patient may improve screening rates, including utilizing providers from the same race/ethnic background as the patient (60).

Navigation has proven to be a powerful tool to increase CRC screening rates in all populations (41, 61, 62). Not only does navigation increase screening utilization, it can erase disparity

for CRC incidence and mortality between NHB and NHW, achieving health equity (41). There is a cost to navigation, which depends on the use of professional or volunteer navigators and the volume of patients for navigation. It is this author's opinion that (a) navigation should be a component of CRC screening for those that need it, (b) should be cost-effective, (c) should be covered by insurance as part of CRC screening, (d) be principally used for colonoscopic screening completion, but components of navigation may be used for non-invasive screening completion, and (e) should be broadly available. Navigation is an ideal tool to increase CRC screening utilization and in particular for NHB and other disparate populations, and may be critical for screening rate improvement in the COVID-19 era (44).

Universal screening for CRC in at-risk individuals beginning at 45 years will require use of non-invasive and minimally-invasive tests. Along the screening continuum, non-invasive tests with abnormal results require follow-up colonoscopy; the two should be coupled together as the screening test (meaning any negative test is listed as completed, whether non-invasive or minimally invasive, but any abnormal non-invasive test is not completed until after the follow-up colonoscopy). Within Kaiser Permanente, 90% of patients with an abnormal FIT test were referred to colonoscopy, but only 52% completed a pre-procedure visit and 43% completed colonoscopy within 1 year (63). Clinic visit transition from primary care to gastroenterology may need to be optimized to prevent leakage of FIT-positive patients (63). Some insurers separate the follow-up colonoscopy after an abnormal non-invasive test and list it as "diagnostic" instead of "screening", triggering co-pays from the patient and creating another (financial) barrier for screening completion. Professional organization advocacy has led to policy changes that at least partially rectified that issue.

Tools exist to remove barriers and increase screening utilization. Use of these tools will need to become the norm for broad implementation and success across all racial/ethnic groups.

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

JC conceived, wrote, and edited this manuscript. The author confirms being the sole contributor of this work and has approved it for publication.

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Molecular and pathological subtypes related to prostate cancer disparities and disease outcomes in African American and European American patients

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Prostate cancer (PCa) disproportionately affects African American (AA) men, yet present biomarkers do not address the observed racial disparity. The objective of this study was to identify biomarkers with potential benefits to AA PCa patients. Differentially expressed genes (DEG) analysis coupled with gene set enrichment analysis (GSEA) and leading-edge genes analysis showed that the keratin family of genes, including *KRT8*, *KRT15*, *KRT19*, *KRT34*, and *KRT80*, constituted the single most prominent family of genes enriched in AA compared to European American (EA) PCa cell lines. In PCa patients (TCGA and MSKCC patient cohorts), *KRT8*, *KRT15*, and *KRT19* expression were relatively higher in AA than in EA patients. The differences in the expression of *KRT15* and *KRT19*, but not *KRT8*, were enhanced by Gleason score and ERG fusion status; in low Gleason (Gleason $\leq$ 6 [TCGA cohort] and Gleason $\leq$ 7 [MSKCC cohort]), the expression of *KRT15* and *KRT19* was significantly ($p \leq 0.05$) higher in AA than in EA patients. Survival analysis revealed that high expression of *KRT15* and *KRT19* was associated with increased risk of biochemical recurrence in low Gleason category patients in the TCGA patient cohort. Interestingly, *KRT15* and *KRT19* expression were also associated with an increased risk of death in the metastatic prostate adenocarcinoma cohort, suggesting the potential to predict the risks of disease recurrence and death in the low Gleason category and advanced disease conditions respectively. Gene set enrichment analysis revealed known oncogenic gene signatures, including *KRAS* and *ERBB2*, to be enriched in patients expressing high *KRT15* and *KRT19*. Furthermore, high *KRT15* and *KRT19* were linked to the basal and LumA PCa subtypes, which are associated with poor postoperative androgen deprivation therapy (ADT) response compared to the LumB subtype. Taken together, the present study identifies genes with high expression in AA than in EA PCa. The identified genes are linked to oncogenic gene signatures, including KRAS and ERBB2, and to basal and LumA PCa subtypes that are associated with poor postoperative ADT response.

This study, therefore, reveals biomarkers with the potential to address biomarker bias in PCa risk stratification and/or prognosis.

KEYWORDS

cancer disparities, molecular subtype classification, prognosis, prostate cancer, oncogenic pathways

Introduction

Prostate cancer (PCa) is the most common cancer and the second leading cause of cancer-related death among men in the United States. African American (AA) men are particularly disproportionately affected; AA men are about twice more likely to be diagnosed with PCa and over two times more like to die from PCa than EA men (1). The underlying cause of PCa health disparity is multifactorial, ranging from molecular differences to the lack of diversity in management strategy. For instance, transmembrane protease, serine 2 (TMPRSS2)-related gene rearrangements are most common in tumors from PCa patients of European ancestry but are significantly less frequent in PCa patients of African and Asian ancestries (2–5). Presently, the management of prostate confined tumors include either active surveillance, radical prostatectomy, or radiation. Active surveillance is recommended for low-risk disease patients: PSA<10 ng/mL, PSA density ≤ 0.15 ng/mL/cm3, clinical-stage ≤ T1c, Gleason sum ≤ 6, positive cores ≤ 2, and cancer involvement per core ≤ 50% (6, 7). However, studies show that active surveillance might not be ideal for some patients, particularly AA men. Studies show AA patients recommended for active surveillance have adverse pathologic features at radical prostatectomy and poorer oncologic outcomes than EA men (6, 8–10). Additionally, the probability of discontinuing active surveillance was higher in black men than in non-black men (11). Furthermore, the disparity in PCa-associated death was observed to be more significant in low-grade (Gleason score ≤ 6) disease patients than in intermediate (Gleason score 7) and high-grade disease (Gleason score ≥8) (10). Different histological, molecular subtypes with racial differences are associated with clinical outcomes have been well accepted in other cancers, like breast, ovarian cancers, etc. This, however, has not been established in PCa. The diverse causes of PCa disparity present a need to diversify management strategies. Thus, proper molecular subtyping would be more relevant to PCa aggressiveness, treatment response, and disparities in PCa. In this report, we aimed to identify biomarkers that may be used in clinical settings for accurate PCa patient risk stratification for a biomarker-guided, personalized treatment approach. Our overall findings demonstrated that cytokeratin 15 (*KRT15*) and *KRT19* are differentially expressed between AA and EA PCa patients; significantly high expression in AA than in EA patients. The findings also linked *KRT15* and *KRT19* expression to the basal and LumA PCa subtypes and further demonstrated that high expression of *KRT15* and *KRT19* was associated with increased risk of biochemical recurrence and reduced overall survival. Our findings may provide new mechanistic insights into PCa disparities and therapeutic approaches.

Materials and methods

Cell culture and RNA-seq

African American PCa cell lines RC77T and RC43T (12) along with RC165 were previously established and characterized in our out lab. The cells were cultured in Keratinocyte basal medium supplemented with 10ng/ml EGF and incubated at 37° C, 5% v/v CO_2. RNA sequencing was isolated from cultured cells using TRIzol® Reagent (Sigma Life Sciences, St. Louis, MO) following the manufacturer's protocol. Library preparation, quality control, and sequencing of extracted RNA were performed by Novogene Corporation Inc. (Sacramento, CA), with the sequencing data compiled as FastQ files for downstream analysis.

RNA-sequence analysis, DEG selection and RT-PCR

RNA-Sequence analyses was completed with Partek® Flow® 8.0 (Copyright®, 2019 Partek Inc., St. Louis, MO, USA) using default settings. Briefly, RNA FastQ files were obtained from Sequence Read Archive (SRA) using accession numbers [SRR8615579] (MDA PCa 2b, LNCaP, and VCaP), and [SRR10575173] (RWPE-2). The FastQ files for the AA cells line RC77T, RC43T, and RC165T were in-house. After the importation of RNA FastQ files into Partek Flow, raw reads were trimmed with a minimum PHRED quality of 20 and then aligned to hg19 using STAR 2.6.1 (13). Using Partek's E/M algorithm (14) and RefSeq Transcripts 90 – 2019-5-03, aligned reads were quantified into raw counts. Differential expression analysis of raw counts was completed using DESeq2 3.5 (15). To identify DEGs of interest, a

pre-ranked gene list was constructed as previously described in Jaynes et al. (16). After importation into *GSEA_4.1.0.app [build: 27]* (17, 18), gene set enrichment analysis (GSEA), of biological processes [c5.go.bp.v7.4.symbols.gmt], was performed using the *GSEA Preranked* tool. Finally, the GSEA Leading-edge analysis tool was used to identify the most frequently occurring genes within the 20 gene sets with the highest normalized enrichment score.

The Cancer Genome Atlas (TCGA) program's PCa (19) and the Memorial Sloan Kettering Cancer Center (MSKCC) PCa cohort (20) data sets, obtained from cbioportal (21, 22), were used to evaluate the differences in gene expression between AA and EA PCa patients. In the TCGA data sets, the gene expression was first compared without patient stratification. After patients were stratified by first, Gleason score (Gleason score ≥ 8 (high-risk), Gleason-score = 7 (intermediate-risk), and Gleason score = 6 (low-risk), and then Gleason score and ERG fusion status before analysis of differences in gene expression. All analyses were performed using RStudio Version 1.4.1103 © 2009-2021 RStudio. Differences in expression were considered significant if $p \leq 0.05$. The MSKCC data set was used to validate gene expression in low Gleason (6 and 7) and ERG fusion negative groups. Both Gleason 6 and 7 were considered low Gleason group in the MSKCC because small sample size.

TRIzol® Reagent (Sigma) was used to isolate RNA, including mRNA from cells. cDNA was obtained from mRNA by reverse transcription using the High-Capacity cDNA Reverse Transcription kit (REF 4374966 or 4368814 by Applied Biosystems) according to the manufacturer's instruction. Quantitative RT–PCR was performed using PowerUpTM SYBR® Green Master Mix (Applied Biosystems) on a 7500 Fast Real-Time PCR System (Applied Biosystems). Each sample was prepared in triplicate and the housekeeping gene beta-actin was used as an internal control for gene expression normalization.

Immunohistochemistry

TMA was constructed from the FFPE blocks of representative ACCs using a manual tissue-arraying instrument. TMA tissue sections (5μM) obtained from core biopsies were used to run Immunohistochemistry (IHC). Tissues were incubated for 1 hour at 60°C, followed by deparaffinization in three Xylene baths. Rehydration was done in graded (100%, 95%, and 75%) ethanol concentrations, later transferred to distilled water. Antigen retrieval was performed with 1X IHC Antigen Retrieval Solution 10X High pH (REF 00-4956-58, eBioscience) for 10 minutes at 20 kPa. Endogenous peroxidase was blocked with 3% hydrogen peroxide in 1X PBS IHC Wash Buffer with Tween 20 (PBST) for 5 minutes. Sections were incubated in 3% goat serum for 45 minutes, followed by one-hour incubation with the primary antibody in 1X PBST. After washing twice with 1X PBST, the sections were incubated with peroxidase-labeled secondary antibody for 45 minutes. The staining was visualized with 3, 3'-diaminobenzidine (DAB) as chromogen. Slides were counterstained with hematoxylin, dehydrated, and then mounted. All slides were interpreted by an experienced pathologist. For all IHC stains, tumors were scored as 0 (negative), 1+ (weakly positive), 2+ (moderate staining), 3+ (strong staining). The H-score was determined by adding the results of multiplication of the percentage of cells with staining intensity ordinal value with highest 300 possible values. *H-Score*=1∗(% *cells* 1+)+2∗(% *cells* 2+)+3∗(% *cells* 3+). The work was carried out in accordance with the guidelines approved by Tuskegee University Institutional Review Board (IRB).

Pathway and function enrichment analysis

The oncogenic and immunogenic gene signature associated with the expression of the DEGs of interest was evaluated in the TCGA PCa cohort. mRNA expression data for the cohort was obtained from cBioportal (21, 22). To identify oncogenic and immunogenic gene signatures associated with gene expression, DEG analysis was performed using iDEP.92 (23). The results of the differentially expressed genes presented as LOG_2FC (fold change) were exported as.csv files for downstream analysis, including gene set enrichment and leading-edge gene analyses to identify enriched oncogenic/immunogenic and leading-edge genes, respectively. For gene set enrichment analysis, a pre-ranked gene list was constructed as previously described (16). After importation, of the pre-ranked gene list into the *GSEA_4.1.0.app [build: 27]* (17, 18), oncogenic and immunogenic gene set enrichment analysis were performed using the *GSEAPreranked* tool (default setting) with either the c6.all.v7.4.symbols.gmt [Oncogenic signature] and the c7.all.v7.4.symbols.gmt [Immunogenic signature] gene sets databases, respectively. Finally, the GSEA Leading-edge analysis tool was used to identify the most frequently occurring genes within the 20 gene sets with the highest normalized enrichment score.

Correlation of DEGs with PAM50 subtypes

To evaluate the association of gene expression with PCa subtypes, including LumA, LumB, and Basal subtypes, we used the PCa Transcriptome Atlas (PCTA) web tool (24) was used to. The analyses were based on the PCTA dataset using the One-way ANOVA test. Differences in expression between the groups were considered significant if $p \leq 0.05$.

Survival outcome analysis

The *Kaplan-Meier Plotter* (25) was used to evaluate the associations of the expression of DEGs of interest with disease

outcomes, including biochemical recurrence (BCR) and overall survival (OS). Patients were split by either the Trichotomization or the Auto select best cutoff tool. The associations of the expression of the DEGs of interest with biochemical recurrence and overall survival were evaluated in the TCGA PCa and SU2C/PCF Dream Team cohorts, respectively. Association with biochemical recurrence was assessed by the Gleason category, including 6, 7, and ≥ 8. The association with overall survival was assessed by follow-up period, including 24, 30, and 60-month follow-up periods. In addition to the association with individual gene expression, the impact of identified DEGs as a panel on overall survival was also evaluated. Association with disease outcome was considered significant if HR (hazard ratio) or p-value was ≥2 or ≤0.05.

Association of DEGs with immune cells infiltration

To quantify the tumor-associated immune cell populations, we used the Tumor Immune Estimation Resource–TIMER2.0 (26) to analyze the association of gene expression with the infiltration of the immune cells: CD8+ T cells, B cells, and macrophages. Associations were considered significant if ≥50% of the algorithms used in TIMER2.0 predicted a statistically significant association.

Results

Genes differentially expressed between African American and European American prostate cancer cells

We performed RNA sequencing analysis, comparing AA PCa cell lines, RC77T, RC165T, RC43T, and MDA PCa 2b with the EA PCa cell lines LNCaP, RWPE2, and VCaP (Figure 1A). Differential gene expression (DEG) analysis revealed 592 significantly downregulated genes ($p \leq 0.05$) and 951 significantly upregulated genes ($p \leq 0.05$) in the AA cell lines compared to the EA cell lines (Figure 1B). Gene set enrichment analysis showed that the AA cell lines were positively enriched in 273 gene sets and negatively in 23 gene sets (Figure 1C), including gene sets associated with keratinocyte differentiation, response to retinoic acid, and keratinization (Figure 1D). Furthermore, Leading-edge analysis, revealed genes, including *KRT8*, *KRT15*, *KRT19*, *KRT34*, and *KRT80*, in the cytokeratin family of genes to be the most common among the leading-edge genes in the top 20 most common genes (Figures 1E, F). The differences in expression of the leading edge cytokeratin family genes observed in the RNA seq data was confirmed by Real-time PCR analysis (Figure 1G). *KRT15, KRT19 and KRT8* were amplified and the expression were significiantly higher in the AA cancer cell lines compared to EA cell lines. *KRT34* and *KRT80* expression levels were too low or were hardly detected in all the prostate cancer cell lines (Data not shown). Additional genes identified, including *HSD17B2*, *CYP27B1*, *ZFP36L1*, *EGR1*, *VDR*, *CAPN1*, *FOXC1*, *EREG*, *GATA6*, *ALOX15B*, *LIPE*, *GJA1*, *ZFP36*, *CDH3*, and *RUNX* (Figure 1E) have been implicated in PCa progression (27–38).

Expression profile of differentially expressed keratins in patient populations

Since the cytokeratin family was the most enriched gene set in the AA cancer cells, we sought to determine if the same trend could be observed in PCa patients. For this analysis, we used the TCGA and MSKCC PCa patient cohorts. The characteristics of the cohorts were described previously in other studies (19, 20). The expression of *KRT8*, *KRT15*, and *KRT19* was relatively higher in AA compared to EA PCa patients in both the TCGA (Supplementary Figures 1A, C) and MSKCC cohorts (Figure 2A); the difference in expression of *KRT15* was statistically significant ($p \leq 0.05$) in the MSKCC (Figure 2A). The difference in expression of identified *KRTs* between AA and EA patients was influenced by the Gleason score and ERG fusion status. For instance, *KRT19* expression was significantly ($p \leq 0.05$) higher in AA in Gleason six patients but was not significant in EA in Gleason seven and Gleason ≥8 patients; a similar trend was observed for *KRT15* (Supplementary Figure 1B). Additionally, the expression of both *KRT15* and *KRT19* was significantly higher in AA than in EA Gleason six, ERG fusion negative patients in the TCGA cohort (Figure 2A). The expression of *KRT80* was lower in AA patients in both the TCGA ($p \leq 0.05$) and MSKCC cohorts and the differences in expression seem not to be influenced by Gleason or ERG fusion status (Supplementary Figure 1B and Figure 2A). The expression of *KRT34 and KRT80* were too low for us to meaningfully evaluate differences in expression between AA and EA patients by the Gleason score and ERG fusion status (Figure 2A). The cytokeratin genes *KRT5*, *KRT14*, *KRT8*, and *KRT18* have been used by multiple groups to distinguish prostatic basal and luminal epithelial cells (39, 40). KRT5 and KRT14 are enriched in basal epithelial cell types, while KRT8 and KRT18 are enriched in the luminal epithelial cell types. In the present study, we also sought to determine if there were differences, between AA and EA PCa patients, in the expression of the epithelial basal and luminal cell cytokeratins. Our analysis showed that the epression of basal cell *KRT5* and *KRT14* were significiantly higher in AA than in EA in the MSCKCC cohort bu only slightly higher in TCGA (Gleason six and ERG fusion negative) cohort, similar to that of *KRT15* and *KRT19* expression (Figure 2B). Luminal markers KRT8 and KRT18 expression had no difference in AA and EA patients in the MSCKCC and TCGA cohorts (Supplementary Figure 1C) and only KRT18 was slightly higher in EA than in AA MSCKCC cohort and in TCGA Gleason six and ERG fusion negativepatients (Figure 2C). To further validate

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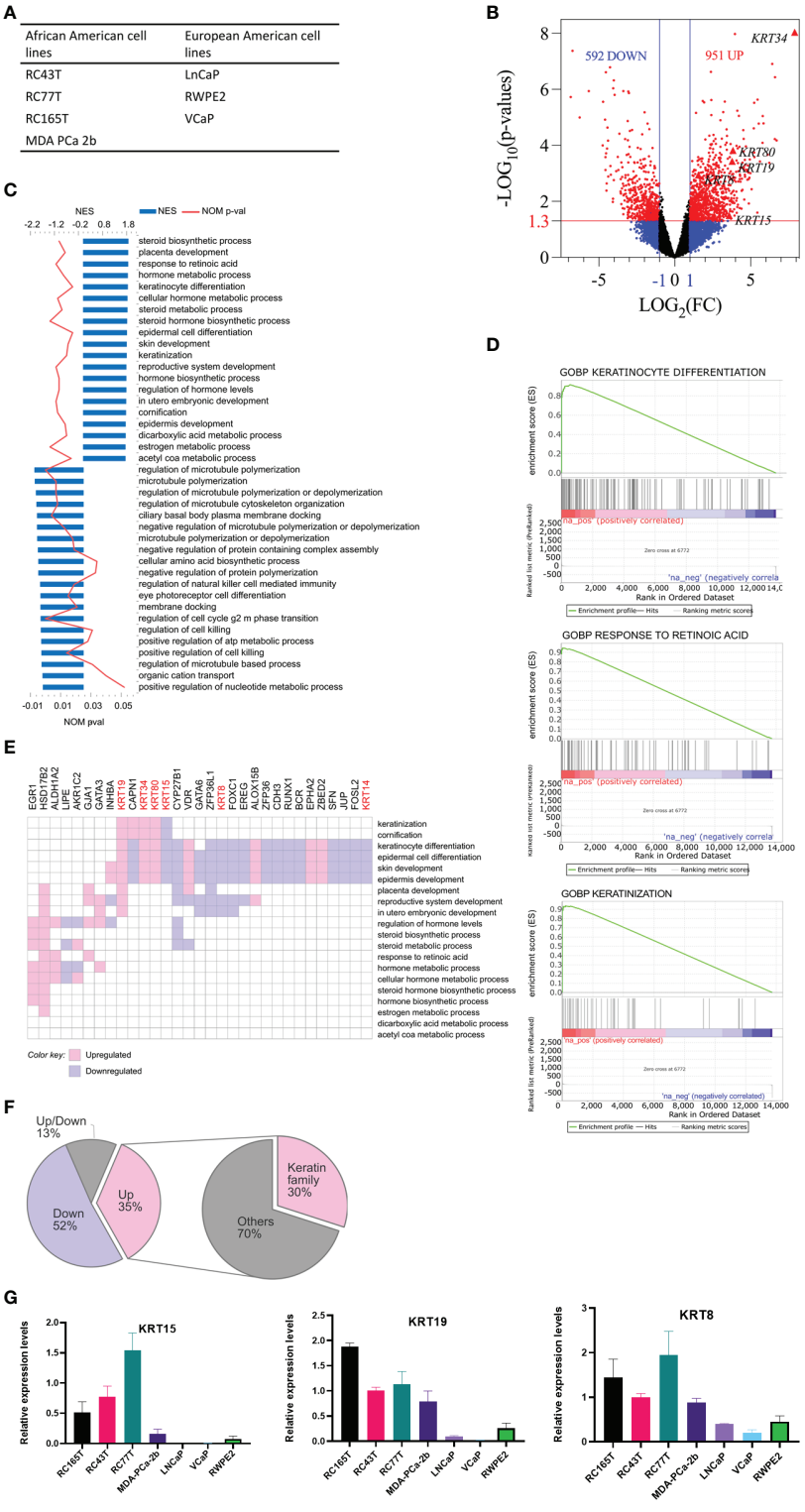

FIGURE 1
Analysis of differentially expressed genes (DEG) between AA and EA PCa cell lines. **(A)** AA and EA PCa cell lines. **(B)** volcano plots of DEGs; genes were differentially expressed if FC ≥ 2 (LOG_2(FC) ≥ 1) and p ≤ 0.05 (-LOG_{10}P = 1.3). **(C)** GOBP (gene ontology biological processes) gene sets enriched in AA PCa cell lines relative to EA PCa cell lines. **(D)** representative gene set enrichment plots. **(E)** leading-edge genes in top 20 positively enriched gene sets. **(F)** proportions of leading-edge genes; the keratin family of genes constituted the single most prominent family of DEGs enriched in AA. **(G)** Validation of RNA-seq data by RT-qPCR. The expression of selected DEGs in cancer cell lines quantified by qRT-PCR were shown.

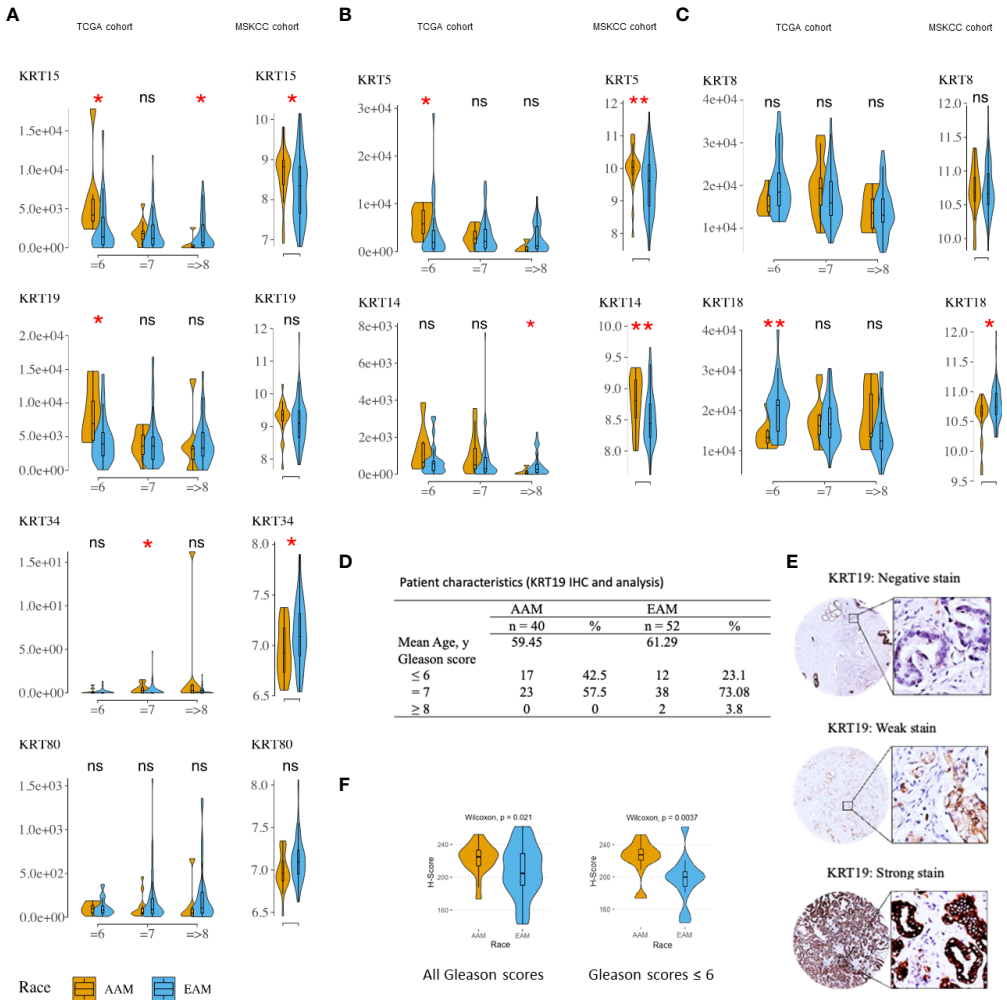

FIGURE 2
Distribution and median expression levels of keratins in AA and EA PCa patients (TCGA [ERG fusion negative] and MSKCC cohorts). **(A)** differentially expressed keratins (excluding *KRT8* – see C) in the TCGA (left column) and MSKCC (right column) cohorts. **(B)** basal cell keratins (*KRT5* and *KRT14*). **(C)** luminal cell keratins (*KRT8* and *KRT18*). Statistically significant differences in gene expression were determined using the nonparametric Wilcoxon-Mann-Whitney test: *p ≤ 0.05; **P ≤ 0.01. TCGA patients were stratified by Gleason (risk) categories; that is Gleason = 6 (low risk), Gleason = 7 (intermediate risk), and Gleason => 8 (high risk) categories. **(D)** Clinicopathological characteristics of prostate cancer patients in the deidentified prostate tumor cohort. **(E)** Immunohistochemical staining of KRT19 in prostate cancer tissues. Representative images of KRT19 negative, weak or strong staining. **(F)** boxplot of KRT19 H-Scores illustrating significant differences in AA Vs. EA prostate cancer patients. * P values < 0.05 were considered statistically significant. All the patients (upper panel) and patients with Gleason ≤6 (lower panel). ns, not significant.

the expression levels of newly identified pivotal and consistant DEGs in AA and EA PCa, KRT15 and KRT19 protein expression levels were validated by Immunohistochemistry (IHC) in prostate tumor samples (Figure 2D). The staining intensities of KRT19 were defined as negative, weak and strong staining (Figure 2E). KRT19 expression H-scores (Figure 2F) were significiantly higher in AA cancer patients compared with EA prostate cancer patients (upper panel, Wilcoxon test: $p<0.05$). The expression H-scores were significiantly higher in AA and lower in EA Gleason score 6 patients, too (Figure 2F, lower panel, Wilcoxon test: $p<0.01$). However, KRT15 expression levels were not statistically significant in AA cancer patients compared with EA prostate cancer patients (data not shown).

KRT15 and *KRT19* expressions correlated with Basal and LumA prostate cancer subtypes

The PAM50 PCa subtypes including Basal, LumA, and LumB subtypes have been implicated in postoperative ADT response; Basal and LumA respond poorly to postoperative ADT compared

to the LumB subtype. Using the PCa Transcriptome Atlas (PCTA) (24), we evaluated the association of *KRT15* and *KRT19* expression with the PAM50 PCa subtype. The expression of both *KRT15* and *KRT19* positively correlated with Basal and LumA PCa subtypes, and negatively with LumB PCa subtype (Figure 3 and Supplementary Figure 2), suggesting a positive correlation between *KRT15* and/or *KRT19* expression and poor response to postoperative ADT treatment.

Association of identified cytokeratin with disease outcomes

Since the expression pattern *KRT15* and *KRT19* was consistent across both the TCGA and MSKCC patient cohorts, we sought to evaluate how *KRT15* and *KRT19* expression levels correlate with disease prognosis in the TCGA patient cohort. Patients were trichotomized into low, intermediate, and high *KRT15* or *KRT19* expression, and the risk of BCR in the high expression group was compared to the low expression group. High expression of *KRT15* (HR = 517524189.71 [0 – Inf]; p = 0.35) or *KRT19* (HR = 477626013.78 [0 – Inf]; p = 0.086) was associated with a reduced probability of BCR free survival in the Gleason 6 patients (Figure 4A). Furthermore, the separation between the BCR risk curve of the high *KRT19* expression group and the low *KRT19* expression group was greater (HR = 1459404193.89 [0 – Inf]; p = 0.059) in Gleason 6 and ERG fusion negative PCa patients (Figure 4D), suggesting the association between *KRT19* expression and risk of BCR is influenced by ERG fusion status. There was no significant association between *KRT15* or *KRT19* expression and risk of BCR Figures 4B, C).

In PCa, metastasis coupled with the development of castration resistance is the leading cause of death. Therefore, we next assessed the correlation of *KRT15* and *KRT19* expression with overall survival in the Metastatic Prostate Adenocarcinoma (SU2C/PCF Dream Team) patient cohort. High expression of both *KRT15* and *KRT19* was associated with a reduced probability of overall survival at both 24 and 30 months (Figures 5A, B). *KRT15* was statistically significant at both 24 (HR = 2.25 [1.17 – 4.33]; p = 0.012) and 30 months (HR = 2.04 [1.04 – 3.98]; p = 0.033), while the association with *KRT19* was statistically significant (HR = 1.98 [1.03 – 3.81]; p = 0.038) at 24-months follow-up and diminished after 30-months (Figure 5C). However when we combined, *KRT15* and *KRT19*, both were better at predicting overall survival (HR = 3.55 [1.48 – 8.53]; p = 0.003; Figure 5D) than either *KRT15* or *KRT19* alone. Taken together, the present result suggests both *KRT15* and *KRT19* could be novel prognosis markers in predicting overall survival in AA PCa patients.

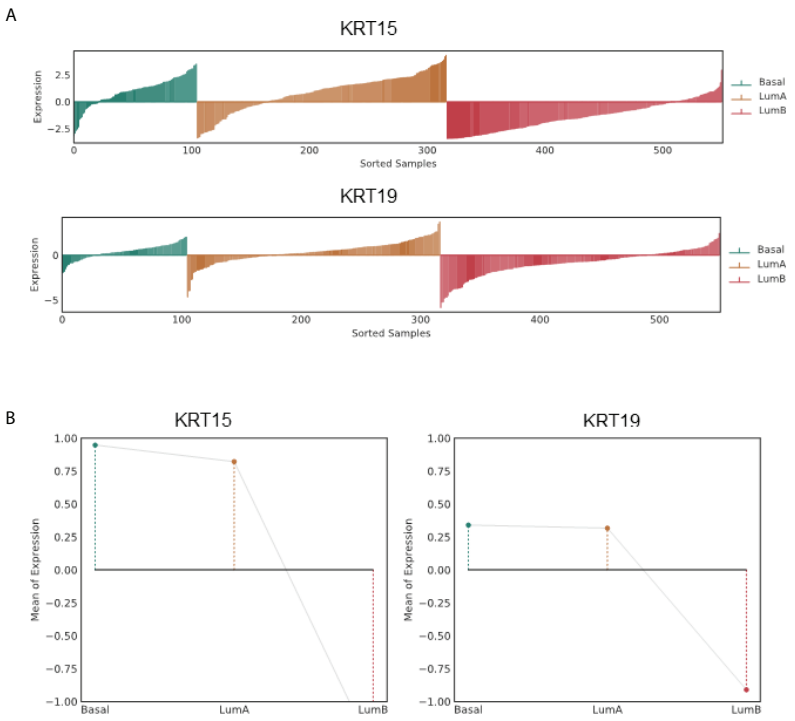

FIGURE 3
Association of *KRT15* and *KRT19* expression with PCa subtypes in the TCGA PCa patient cohort. **(A)** Lollipop plots. **(B)** Lineplots of mean trends. All analyses were performed in PCTA (24) using the default setting.

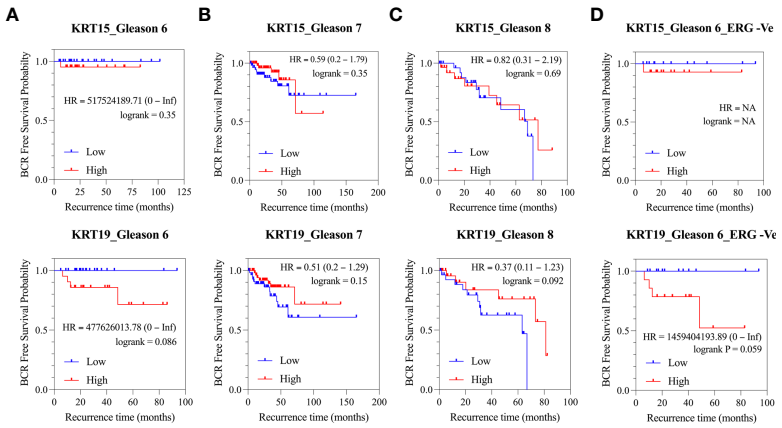

FIGURE 4
Association of *KRT15* and *KRT19* expression with risk of BCR in PCa patients (TCGA cohort). **(A)** Gleason six patients' category. **(B)** Gleason seven patients' category. **(C)** Gleason 8+ patients' category. **(D)** Gleason six and ERG fusion negative patients' category.

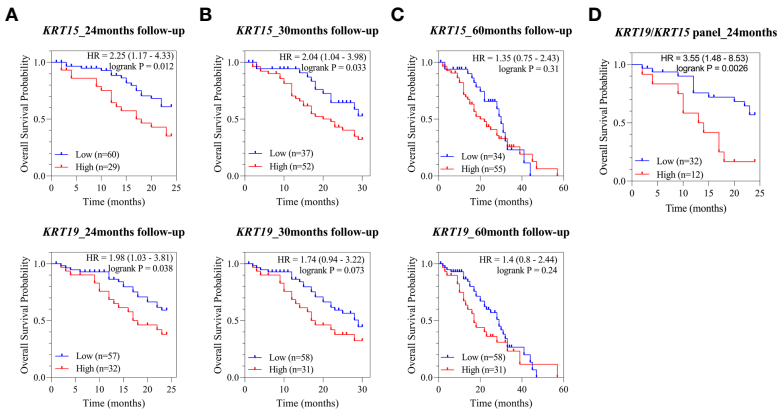

FIGURE 5
Association of *KRT15* and *KRT19* expression with overall survival. **(A)** 24-months follow-up. **(B)** 30-months follow-up. **(C)** 60-months follow-up. **(D)** *KRT15*/*KRT19* panel.

Oncogenic and immunogenic gene signatures associated with *KRT15* and *KRT19* expression

To identify the functional or targetable gene signatures associated with *KRT15* and *KRT19* expression, ERG fusion negative patients (TCGA cohort) who presented with low Gleason were classified by tertile. Patients in the lower tertile were considered KRT19 negative, while those in the higher tertile were considered KRT19 positive. Differential gene expression analysis revealed 347 genes to be upregulated in KRT15 positive patients, while 37 genes were downregulated; in KRT19 positive versus KRT19 negative patients, 667 genes were upregulated, while 95 genes were downregulated (Figure 6A).

Gene set enrichment analysis revealed gene signatures associated with common cancer-related genes including *KRAS*, *PTEN*, *ERBB2*, and *P53* to be significantly (NOM p-val < 0.05 at FDR < 25%) enriched in both KRT15 positive and KRT19 positive patients (Figures 6B, C). Leading-edge analysis revealed *UPK3B*, *CRABP2*, *LGALS7*, *SERPINB13*, *LY6D*, *KRT4*, *KRT16*, *SCGB1A1*, *KRT13*, *TGM1*, *NTF3*, and *DTX2* as the leading genes (present in at least 6 gene sets) in the KRT15 positive patients; *TAGLN*, *NTF3*, *SERPINB13*, *LY6D*, *SLC6A14*, *SPRR3*, *KRT13*, *KRT4*, *KRT16*, *TGM1*, *CEACAM5*, *ANGPTL4*, *BCL3*, and *PTPRU* were the top leading genes (present in at least 5 gene sets) in KRT19 positive patients (Figure 6D). Eight of the leading-edge genes including *SERPINB13*, *LY6D*, *KRT4*, *KRT16*, *SCGB1A1*, *KRT13*, *TGM1*, and *NTF3* were common to

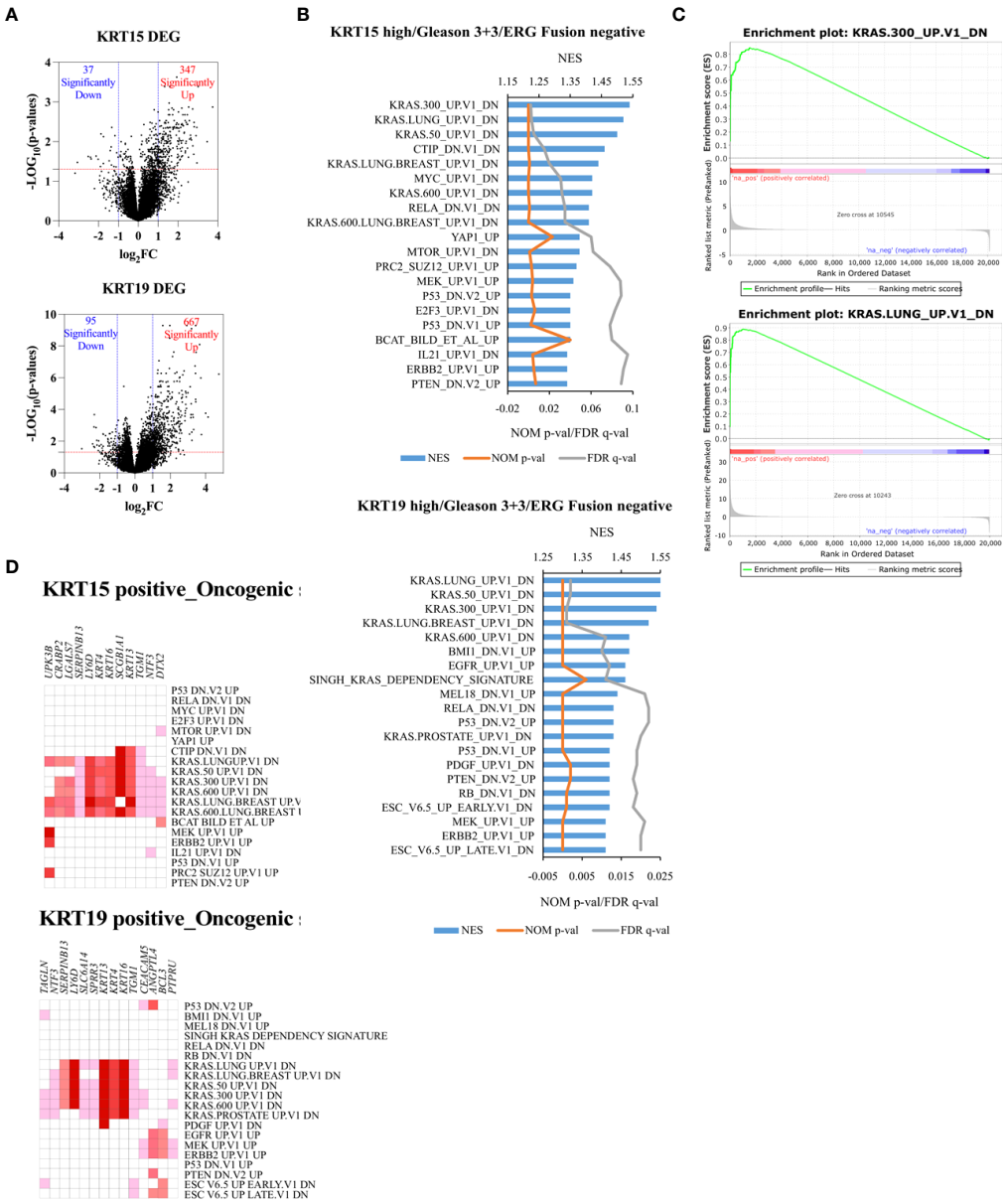

FIGURE 6
Unique oncogenic gene signature associated with *KRT15* and *KRT19* expression in ERG fusion negative and Gleason 3 + 3 patients. Patients were trichotomized by gene expression into T1 (low expression), and T3 (high expression), and differences in gene expression were determined in low versus high expression patients. **(A)** DEG in high versus low *KRT15* and *KRT19* expression. **(B)** oncogenic gene sets positively enriched in high versus low *KRT15* and *KRT19* expression. **(C)** representative enrichment plots. **(D)** Leading-edge genes.

KRT15 positive and KRT19 positive patients. Furthermore, gene sets associated with the activation, inactivation, or functions of CD8+ T cells, B cells, Dendritic cells, CD4+ T cells, and macrophages were enriched in KRT15 positive patients (Figure 7A). In KRT19 positive, enriched gene sets included those associated with the activation, inactivation, or functions of natural killer cells, Treg cells, and monocytes in addition to CD8+ Tc cells, B cells, and macrophages (Figure 7A). Leading-edge analysis revealed genes including *LY6D*, *GPR87*, *DSC3*, *HBEGF*, *MX2*, *AREG*, *DUSP6*, *FOSL1*, *CYP4B1*, *EVC2*, *PADI3*, *NRG1*, *KRT5*, *CXCR2*, *GADD45B*, *CXCL3*, *LCN2*, *MT2A*, *IL1RN*, *CXCL2*, *MX1*, *BCL3*, *ETS2*, and *FGFR2*; only *CXCL2* and *CXCL3* were common to both KRT15 and KRT19 positivity (Figure 7B).

The activation of CXCL2 and its associated receptor CXCR2 by KRAS signaling is thought to suppress immune response and

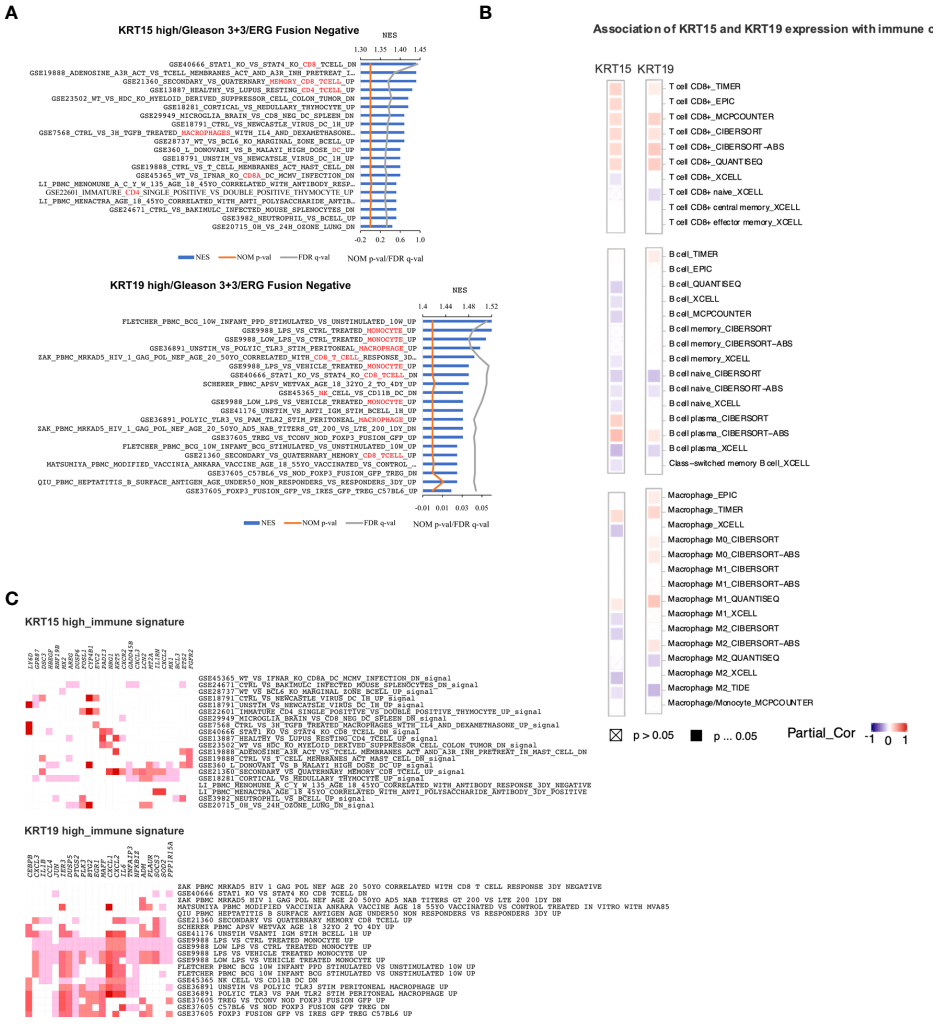

FIGURE 7
Immunogenic gene signatures associated with *KRT15* and *KRT19* expression in ERG fusion negative and Gleason 3 + 3 patients. **(A)** gene sets positively enriched in patients with high expression of *KR15* (top) and *KRT19* (bottom). **(B)** leading-edge genes associated with gene sets positively enriched in patients with high expression of *KRT15* (top) and *KRT19* (bottom). **(C)** immune cells infiltration associated with *KRT15* and *KRT19* expression. Squares with a cross indicate non-significant associations ($p > 0.05$), solid square indicates significant associations ($p \leq 0.05$), and purple-red is association gradient (purple is for negative association and red for positive association).

promote tumor proliferation (41, 42). Immune suppression is critical for tumor cell survival and progression (43). In the present study, using TIMER2.0 (26), we estimated the association of *KRT15* and *KRT19* expression with the infiltration of the immune cells (Figure 7C). The associations were considered significant if ≥50% of the algorithms used in TIMER2.0 predicted a statistically significant association. There was a significant positive association of both *KRT15* and *KRT19* expression with CD8+ T cell infiltration. On the other hand, there was a significantly negative association between B cell infiltration and *KRT15*, but not *KRT19* expression. Macrophage, particularly M0 macrophage infiltration, was positively associated with *KRT19* expression, but not *KRT15* expression.

Discussion

In the United States, PCa disproportionately affects AA men; compared to EA men, AA men are more likely to be diagnosed and to die from PCa (1). While the cause of PCa disparity is multifactorial, mischaracterization of risks of PCa progression, leading to erroneous treatment recommendations, may be a contributing factor. For instance, active surveillance is the treatment option for many men with low-risk PCa. However, more African American men with early-stage cancer may harbor more aggressive disease and are more likely to die from PCa than other patients and may not be good candidates for active surveillance (6, 8–11). In the present

study, we identified gene sets associated with the development and differentiation of epithelial and epidermal cells; and hormone production, function, and metabolism positively enriched in AA PCa cell lines relative to EA PCa cell lines. Leading-edge gene analysis revealed gene sets including cytokeratin (*KRT*) genes: *KRT19*, *KRT8*, *KRT34*, *KRT80*, *KRT15*, and *KRT14* as the most prevalent family of genes in the top 20 most common genes. Other leading-edge genes included *HSD17B2*, *CYP27B1*, *CYP27B1*, *ZFP36L1*, *EGR1*, *VDR*, *CAPN1*, *FOXC1*, *EREG*, *GATA6*, *ALOX15B*, *LIPE*, *GJA1*, *ZFP36*, *CDH3*, and *RUNX*.

Cytokeratins are intermediate filaments involved in normal cell function and also associated with diseased conditions (44). Normal adult prostatic epithelium consists of basal, secretory luminal, and rare neuroendocrine and intermediate cells, which could be classified by cytokeratin and other differentiation markers. Luminal cells are the majority of the prostate epithelia and carry out the secretory function. The low-molecular-weight cytokeratins KRT8 and KRT18 are typical lineage markers for the luminal cells. The basal epithelial subpopulation expressed the classical high-molecular-weight basal cell markers KRT5, KRT14 and p63. In addition to a very small fraction of the epithelial cells called neuroendocrine (NE) cells (express a variety of NE markers (including chromogranins, synaptophysin, and CD56), there is also a population of transit-amplifying or intermediate prostate epithelial cells. These cells co-express markers of both the basal and luminal epithelial cell markers (KRT5, KRT14, KRT8, KRT18, KRT19, p63 and GSTpi). These rare rapid amplifying prostatic intermediate epithelial cells are proposed to be derived from urogenital or basal progenitor/stem cell population and could differentiate into luminal cells expressing KRT8/18. Lineage plasticity is the ability of cells to trasform from one developmental lineage to another, which is essential for embryonic development, tissue repair and maintenance of homeostasis. This highly regulated cell differentiation process is also considered as a source of intratumoural heterogeneity when cancer cells adapt to tumour microenvironment, lineage plasticity can promote tumor progression, metastasis and therapy resistance (39, 40). Instead of undergoing normal differentiation to form the functional prostate, a subset of cells may arrest at an early stage and show aberrant differentiation causing disruption of the precise signaling pathways, which are critical for prostate morphogenesis during early development ultimately resulting in carcinogenesis. The underling mechanisms for increased intermediate epithelial cell population among AA PC patients remain unclear. Answers may lie in varying social conditions, underlying genetic factors, or unidentified biological factors. On the other hand, cytokeratins are implicated in tumorigenesis, drug responsiveness, cancer cell invasion, and metastasis; and are helpful cancer diagnostic and prognostic markers (44–54). In PCa, expression of *KRT8*, *KRT18*, and *KRT19* by tumor cells disseminated to the bone, is associated with a worse prognosis (49); *KRT18* and *KRT5* expression correlates with metastases and hormone-escaped prostate carcinomas, respectively (55). Our findings demonstrate that *KRT15* and *KRT19* are differentially expressed in a Gleason score and ERG fusion status manner, with fusion negative AA patients expressing higher levels of both *KRT15* and *KRT19*. Elevated *KRT15* and *KRT19* expression were also associated with an increased risk of biochemical recurrence in low Gleason score patients, more so in ERG fusion negative patients. Similarly, high expression of *KRT19*, or *KRT15* was associated with worse survival in a metastatic prostate adenocarcinoma patient cohort (SU2C/PCF Dream Team) regardless of ERG fusion status. Similar findings were reported in breast cancer and hepatocellular carcinoma; KRT19 expression correlated with poor prognosis in breast cancer (56) and predicted early postoperative recurrence in hepatocellular carcinoma (57). Interestingly, in clear cell renal cell carcinomas, the detection of KRT19 along with KRT7 was associated with better clinical outome (44). Elucidating how other signaling pathways and developmental regulators are integrated to modulate prostate organogenesis and differentiation will be of particular relevance for understanding their roles in prostate cancer. For example, mechanisms that drive progenitor cell plasticity in the context of epithelial differentiation and repair could also play a role in prostate tumor plasticity in mediating resistance to targeted cancer therapies.

In this study, our investigation identified a two-gene signature that accurately stratified cancer aggressiveness and provide biological measures indicating the likelihood of a more aggressive disease for AA patients newly diagnosed with localized cancers. Over the years, several prognostic tools for PCa have been developed including serum (4K, phi), urine (Progensa, T2-ERG, ExoDx, SelectMDx), and tissue-based bioimarkers (ConfirmMDx, Prolaris, Oncoytype DX, Decipher) (58). However, these markers do not account for differences associated with racial disparities in PCa. In our study, high expression of both *KRT15* and *KRT19* in low-risk ERG fusion negative patients was associated with the enrichment of common cancer-associated gene signatures, especially KRAS. The aberrant activation of KRAS signaling is a common driver of tumor development and progression in different types of cancers, including pancreatic cancer (59), non-small-cell lung cancer (60–63), colorectal cancer and melanoma (64), and pancreatic cancer (65). KRAS signaling is also thought to activate CXCL2 and its associated receptor CXCR2 resulting in suppressed immune response and tumor proliferation (41, 42). Immune suppression is critical for tumor cell survival and progression (43). The present study also shows high expression of *KRT15* and *KRT19* positively correlated with the PAM50 Basal and LumA phenotype, but

negative with the LumB phenotype. The Basal and LumA have been shown to respond poorly to postoperative ADT compared to the LumB subtype (66, 67). Taken together, our study illustrates the potential of *KRT15* and *KRT19* as a PCa prognostic markers for patients who present with low Gleason, particularly African American patients. Although a limitation of our study design is the low number of patients, particularly AA and lack of clinical data, such as biochemical recurrence and overall survival for some patients, further validation with larger sized patient cohorts and mechanistic studies are needed to verify these findings. It's still worthnoting that current findings highlight the value of developing prognostic tools that can distinguish aggressive tumors vs indolent tumors particularly in low risk AA prostate cancer patients.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://www.ncbi.nlm.nih.gov/geo/; GSE203338.

Author contributions

HW and CY conceived the idea for the study and supervised the work. JM, HW, and BK involved in planning the project, carried out the experiments and interpreted the results. JM, JW, IE, and BD performed data and statistical analysis. JM, HW, CY and JW were involved in writing the manuscript with input from all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

CY is a shareholder in Riptide biosciences and is a consultant in QED Therapeutics, Riptide Biosciences, and Amgen.

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.2022.928357/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Expression profile of keratins in all race AAM and EAM patients. **(A, B)** differentially expressed keratins (**A** no patient stratification applied; **B** patients stratified by Gleason score category). **(C)** epithelial basal and luminal cell keratins in all race annotated patients.

SUPPLEMENTARY FIGURE 2
Association of *KRT15* and *KRT19* expression with Basal, LumA, and LumB PCa subtypes (PCTA dataset) (24). **(A)** Lollipop plots. **(B)** Lineplots of mean trends. All analyses were performed in PCTA (24) using the default setting.

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Racial disparities in liver cancer: Evidence for a role of environmental contaminants and the epigenome

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Liver cancer incidence has tripled since the early 1980s, making this disease one of the fastest rising types of cancer and the third leading cause of cancer-related deaths worldwide. In the US, incidence varies by geographic location and race, with the highest incidence in the southwestern and southeastern states and among racial minorities such as Hispanic and Black individuals. Prognosis is also poorer among these populations. The observed ethnic disparities do not fully reflect differences in the prevalence of risk factors, e.g., for cirrhosis that may progress to liver cancer or from genetic predisposition. Likely substantial contributors to risk are environmental factors, including chemical and non-chemical stressors; yet, the paucity of mechanistic insights impedes prevention efforts. Here, we review the current literature and evaluate challenges to reducing liver cancer disparities. We also discuss the hypothesis that epigenetic mediators may provide biomarkers for early detection to support interventions that reduce disparities.

KEYWORDS

liver cancer, race, epigenetic, contaminants, epigenome

Introduction

Primary liver cancer incidence has tripled since the early 1980s, with most cases (~75%) classified as hepatocellular carcinoma (HCC). Liver cancer is among the fastest increasing cancers, and is the third leading cause of cancer-related deaths worldwide and in the US (1). While the incidence increased until 2015, it appears to have plateaued

among Asians/Pacific Islanders. Among non-Hispanic Blacks and American Indians/Alaska Natives, the incidence of HCC continues to increase (2).

In the US, over 40,000 primary liver cancer cases are diagnosed annually, but the incidence not only varies by race/ethnicity, but also by geographic location. The highest liver cancer incidence is in the Western and Southern US and among ethnic minorities. Data from 2005 to 2014 suggest that the US age-adjusted incidence rate was 6–7.7/100,000 overall; yet, in Non-Hispanic Black individuals the rate was 10–13/100,000 and in Hispanics was 13–17/100,000 during the same period (3–6). Moreover, two-year survival is approximately 50%, and prognosis is poorer in minority populations (7–10). While deaths related to other malignancies such as lung, breast, and colorectal cancer declined over 40% from 1990–2016, liver cancer mortality is rising among both men and women (11). Consequently, liver cancer is projected to surpass breast and colorectal cancer by 2030 to become the leading cause of cancer-related death in the US (12). The underlying causes of this rapid increase that disproportionately affects racial minorities are poorly understood.

The majority of HCC (over 90%) occurs in the background of chronic liver disease with cirrhosis of any etiology being the strongest risk factor (13). HCC has traditionally been driven by chronic liver disease from viral infections such as chronic hepatitis B virus (HBV) and hepatitis C virus (HCV). Increased vaccine rates and successful treatments have been associated with major declines in the incidence of HCC from these etiologies. However, the prevalence of these risk factors cannot fully explain the ethnic disparities observed. More recent data support a shifting of the underlying etiologies of HCC primarily due to the high prevalence of metabolic conditions that include obesity and diabetes, which increase the risk of non-alcoholic fatty liver disease (NAFLD) and its progression to NASH and cirrhosis. (14, 15). NAFLD represents a spectrum of chronic liver disease associated with obesity and insulin resistance that includes simple accumulation of fat in the liver (i.e., simple steatosis), to more severe non-alcoholic steatohepatitis (NASH) in which steatosis is complicated by necroinflammation and fibrosis, to cirrhosis, the end stage of fibrosis and scarring of the liver (16, 17). Although the potential for NAFLD to progress to fibrosis, cirrhosis and HCC is well established, progression, and thus HCC risk varies substantially by age and obesity status (Figure 1).

The prevalence of metabolic conditions such as obesity and type II diabetes (but not NAFLD) is also higher in Non-Hispanic Black, Hispanic, and Native American individuals. In the US, 31% of adults are overweight and approximately 10% are severely obese (18). National Health and Nutrition Examination Survey (NHANES) data from 2017–18 suggest that the age-adjusted prevalence of overweight/obesity varies by race among adults, with the highest incidence among Non-Hispanic Black (50%), followed by Hispanic (45%), Non-Hispanic white (42%), and Asian (17%) individuals. Similar race/ethnic prevalence patterns were reported for type II diabetes mellitus: among Non-Hispanic Black and Hispanic individuals, the prevalence is 13.2% and 12.8% respectively, whereas in Asian individuals it is 7.6% and in non-Hispanic white individuals it is 9% (19). Addressing disparities in liver cancer incidence and mortality requires rigorous investigation of upstream factors that give rise to metabolic derangement and progression to NAFLD, fibrosis, and cirrhosis that eventually leads to liver decompensation, liver cancer, and death. Advances in (epi)genomic sequencing technologies may help identify molecular mechanisms and events that promote liver deterioration. Molecular markers of liver cancer, that include genetic variants in genes such as PNPLA3, and epigenetic shifts largely identified from array data, are being developed into early detection tools aimed at reducing HCC risk and inherent ethnic disparities. Here, we review clinical and lifestyle risk factors for liver disease, the potential role of environmental exposures in liver cancer development, and the emerging role of epigenetics as a marker of past exposure to environmental contaminants, and contributor to liver cancer risk.

Epidemiologic and lifestyle risk factors for liver disease

The Centers for Disease Control and the National Academy of Sciences estimates that environmental exposures account for at least 70% of variation in many chronic diseases risk, including liver diseases. Exposure to aflatoxin B_1–lysine, cigarette smoking, mycotoxins, HBV and HCV infection, and poor access to treatment modalities increase liver disease risk including liver

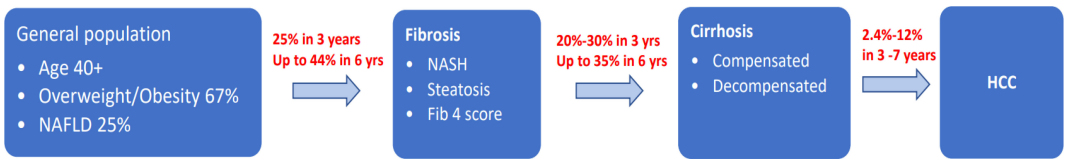

FIGURE 1
Conceptual model for progression from metabolic dysfunction, NAFLD, NASH, Cirrhosis and HCC.

cancer. These findings now inform clinical practice to prevent these exposures and/or reduce the risk of progression. Conversely, habitual coffee intake and long-term statin and metformin use have protective effects on the liver. Indeed, much of this information is included in public health education. Association between comorbidities and drugs used to treat them, lifestyle factors such as diet, physical activity, and non-chemical stressors/social stressors and liver cancer are poorly characterized. Analgesics, such as acetaminophen, may also be linked to liver cancer. Together, data accumulated over the last two decades indicate that the prevalence of these risk factors disproportionately affects ethnic minorities, though data regarding risk factors among these populations remain sparse. Nonetheless, the prevalence of viral hepatitis infections, NAFLD, alcohol use, and exposure to mycotoxins, do not fully explain the continued HCC increase, especially the ethnic or geographic variation in liver disease.

Co-morbidities and the drugs used to treat them may also alter HCC risk. Prenatal acetaminophen exposure in mice results in loss of fetal liver stem cells, altering immune function (20, 21) and in adults, acetaminophen is the leading cause of acute liver injury/failure. Acetaminophen targets the liver and may interact with environmental contaminants such as cadmium that naturally target the liver, to increase risk of liver damage. Acetaminophen is used routinely by ~56% of the US population (22). Conversely, metformin and statins reduce HCC risk (23, 24). Accurate retrospective assessment of pharmaceuticals taken routinely for common ailments e.g., colds, or pain, is challenging. Another challenge is the lag in statistical methods development to investigate the effects of exposure to multiple drugs (i.e., drug mixtures).

Mounting evidence including high-quality randomized trials link anti-inflammatory diets, such a Mediterranean-style diet, to improvement in chronic diseases including cardiovascular diseases (25), reduced breast cancer incidence (26), and reduced metabolic diseases (27, 28). Coffee consumption is associated with lowered HCC risk while processed meat high in nitrates increases liver cancer risk and may also support liver cancer progression and mortality due to carcinogens released from nitrates that accelerate tumor growth. Diets rich in fruits, vegetables, and antioxidants reduce liver cancer risk, severity, and mortality (29–34). Certain dietary patterns (e.g., Mediterranean, glycemic index/load, or dietary inflammation index) decrease other biliary cancer risk (35–37), but little is known about the effects of diet on HCC prognosis. Moreover, non-pregnant minority adults report less adherence to these diets (38, 39). Mechanistically, anti-inflammatory diets reduce systemic free radicals and oxidative stress, leading to decreased circulating pro-inflammatory cytokines and chemokines (40–43).

Physical activity may reduce liver cancer risk and severity and improve outcomes in human studies and animal models. Inconsistent evidence supports the association between light, moderate, or vigorous physical activity and low liver cancer risk (44–47). Lack of consistency in findings is likely because physical activity tends to benefit subsets of populations, likely with other risk factors, such as smokers or obese individuals. However, a recent meta-analysis found that physical activity helped reduce liver cancer risk and mortality in a dose-dependent manner. At a minimum, two hours/week of physical activity was associated with reduced risk of liver cancer mortality (48).

Cigarette smoking is a source of non-occupational exposure to multiple exogenous chemicals, including cadmium, a chemical with oncogenic potential, and alcohol is associated with alcoholic cirrhosis such that these lifestyle factors may either modify or directly interact to increase HCC risk. Conversely, meta-analyses using data accumulated over the last two decades suggest that coffee intake reduces HCC and other liver cancer risk (49–54). However, the mechanisms underlying these connections are unclear.

Social stressors

Social stressors captured at the neighborhood level are persistent risk factors for disparities in a range of cancer outcomes (55). In the US, neighborhood ethnic composition is a strong predictor of hazardous toxicant exposure (56–58). Early data suggests that the racial distribution of the geographic cluster with the highest cadmium exposure is 2% white, 78% Black, and 14% Hispanic (59). Neighborhood disadvantage scores revealed that disadvantage is associated with elevated exposure to environmental contaminants such as cadmium, a probable carcinogen, in adults (59).

Gender differences in HCC

HCC risk is higher in males and mortality varies by sex, as do competing risk factors, e.g., moderate/heavy alcohol intake while overweight status is more common in men and obesity is more common in women. Conversely, women have higher concentrations of contaminants in their bodies, such as cadmium, compared to men who experience similar exposure levels. This may result from higher gastrointestinal absorption of cadmium (60) in women or from competitive binding of cadmium to transporters that are typically bound by nutritive elements such as iron and selenium and may be depleted (60). Moreover, poor cadmium excretion leads to bioaccumulation and increased urinary cadmium with age.

Toxic environmental chemicals and liver diseases

Chronic environmental contaminant exposure is understudied yet may contribute substantially to metabolic dysfunction, fatty liver, fibrosis, and HCC. Increased industrial

applications of toxic metals such as cadmium, arsenic, and lead as well as per- and poly-fluoroalkyl substances (PFAS) (e.g., perfluoro-octanoic acid; PFOA, or perfluoro-octane sulfonic acid; PFOS) coupled with their slow degradation has increased these environmental pollutants in atmospheric, terrestrial, and aquatic systems. Their persistence in the environment provides a stable exogenous source for human exposure. Once in the body, slow excretion leads to bioaccumulation in primary organs of metabolism, including the liver (61), with a half-life in the body of 30–45 years for cadmium (59, 62) and up to 5 years for PFOA (63–65). Toxic metals such as cadmium and arsenic are classified as probable human carcinogens by the International Agency for Research on Cancer (66) and ranked in the top ten environmental chemicals of concern by the Agency for Toxic Substances and Disease Registry (ATSDR) (67), while PFOA is classified as a possible carcinogen. Whereas hepato-toxic effects of contaminants such as cadmium at high levels characteristic of occupational settings are well-documented (reviewed in 66), data are limited regarding exposure at levels experienced by the general population.

PFAS are widely used in food packaging, flame-retardants, scratch-resistant coating, fire-fighting foam, and metal plating. Notably, PFAS were identified as drinking water contaminants throughout the US, with roughly 6 million Americans drinking water that exceeds EPA guidelines for safe levels of PFOA and PFOS (64). When all PFAS are considered or more stringent guidelines are used, the estimate is much higher. Additionally, metal exposure is also widespread; arsenic is naturally present in some water supplies and cadmium is a constituent of tobacco smoke and is present in some commercial fertilizers (68–71) such that ingestion of dietary staples contributes to exposure. In the US, dietary cadmium intake is estimated at ~1 μg/day (72, 73). In pregnant women in Durham, NC, cadmium and PFOA were found to co-contaminate house dust that can be ingested or inhaled (59). Serum PFAS levels are also higher in non-Hispanic white and Hispanic than in non-Hispanic Black pregnant women (74, 75). Further, among all adults, rural African Americans have higher concentrations (76). In contrast, cadmium body burden is highest in African American and Hispanic individuals (62, 77, 78)—populations with a higher HCC incidence. The US National Toxicology Program has called for further research on the effects of these environmental chemicals on organ dysfunction, including liver cancers (79). Multiethnic cohort investigations are needed to determine the impact of toxic metals and PFAS exposure on liver fibrosis and HCC.

Data linking environmental contaminants to NAFLD or HCC are limited. Data from *in vitro* and *in vivo* models accumulated over the last decade support the hypothesis that exposure to PFAS or toxic metals such as cadmium and arsenic induces NAFLD/NASH and liver carcinogenesis (66). However, doses used to induce liver diseases in experimental settings were orders of magnitude higher than those experienced by the general population. The hypothesis that exposure to chemicals such as cadmium increases fatty liver risk and progression to fibrosis, cirrhosis, and HCC is supported by weak evidence in humans. These data include autopsy data that demonstrate that concentrations of both toxic metals such as cadmium, and PFAS such as PFOS and PFOA, are higher in the liver than other organs sites with increasing cancer incidence (e.g., pancreas, ovary) (80–82), indicating that the liver is a main repository for these organic and inorganic chemicals. These autopsy data are supported by murine models data that have demonstrated significantly higher liver fat fractions consistent with fatty liver disease and hepatic neoplastic lesions, found in mice exposed to cadmium at concentrations equivalent to non-occupational exposure (83). In human populations, consistent with geographic information systems (GIS) data (59), findings based on a representative sample of Americans (NHANES) (84) suggest that urinary cadmium—an established dosimeter for long-term exposure, is higher in African American and Hispanic than in white individuals, and is associated with overall liver cancer risk, mortality, and the HCC precursors, NAFLD and NASH. However, there was a limited number of African Americans in the study and the data are cross-sectional.

Although these findings support higher body burdens of at least one toxic metal individually contributing to HCC and precursors such as NAFLD, NASH, and cirrhosis, multiple challenges to defining the link between environmental exposures and liver cancer remain. First, HCC incidence requires a population-based case–control design, relying on cancer registries for case identification. However, cancer registry-based rapid case ascertainment systems for case identification are ill-suited for studying HCC, since most (80%) cases are diagnosed solely based on radiographic imaging. Thus, case-control studies that rely on rapid case ascertainment systems may be biased toward the ~20% of cases whose identification relies on biopsy tissue from transplant patients. Consequently, ethnic minorities at higher risk of liver diseases are likely under-represented. Further, advances in mass spectrometry (MS) (e.g., liquid or gas chromatography (LC/GC) for PFAS and inductively coupled plasma mass spectrometry (ICP-MS) for metals, human data from NHANES, and from our group support environmental co-occurrence of PFAS, such as PFOA and PFOS, and toxic metals, such cadmium, arsenic, and lead (85). These toxins also co-occur in the blood or urine of Americans (86–89). Interaction profiles from *in vitro* models of the ATSDR (67) also support that at least for toxic metals, the effects of toxic metals such as cadmium, lead, and arsenic are synergistic. Yet, statistical methods to identify chemical mixtures contributing to health outcomes are limited and may require large sample sizes. Studies that focus on surmounting these challenges will greatly benefit the field.

Epigenetic marks as biomarkers for early detection

Perhaps one of the biggest challenges in investigating the role of environmental contaminants in liver disease and cancer risk, in general, is the need for retrospective exposure assessment and comparing exposure odds in individuals with and without cancer. Indeed, case–control design is most efficient and is sufficient to investigate exposures such as urinary cadmium, an established dosimeter estimating the cumulative body burden over the life course, to investigate liver cancer etiology. However, the body burden of contaminants such as lead, arsenic, PFOA, and PFOS measured at cancer diagnosis are unlikely to reflect the body before diagnosis. This temporal ambiguity between environmental contaminant assessment and HCC is one of the main complications for causal inference. One way of circumventing this challenge requires molecular profiling that mediates exposure and outcomes.

While twin and familial studies estimate cancer heritability and its precursors such as obesity from 40 to 70%, cancer etiology is complex. Genetic loci contribute to less than 10% of obesity variation. Rather, heritable environmentally induced-epigenetic adaptation, including dysregulation of growth regulating genes, drives heritability, although the regions of the epigenome that contribute to liver diseases are undefined. Epigenetic marks act as exposure archives that approximate past exposure (90, 91). This is in part because epigenetic regulation, a means by which gene expression is altered in response to environmental exposures, can cause long-term changes in expression in mechanistic pathways contributing to liver injury, dysmetabolism, nutrient acquisition, fat deposition, appetite, and satiety. Both covalent DNA methylation at cytosines of CpG dinucleotides and histone modifications regulate chromatin structure and gene expression. The value of DNA methylation as an assay target is its stability. This enables its measurement from nearly any sample type, regardless of handling, by utilizing both targeted and high-throughput bisulfite sequencing methods.

Future research direction using epigenetics

Human epigenetic data linking liver cancer and its precursors to epigenetic dysregulation has three main challenges that hamper identification of epigenomic regions mechanistically involved in cancer development. First, clinically accessible peripheral cells (e.g., blood or buccal cells) may not be appropriate surrogates for tissue types of etiologic significance to liver cancer. Second, epigenetic marks respond to environmental cues throughout the life course such that without serial samples, inference of cause-and-effect between obesity and any epigenetic alterations is difficult. Additionally, epigenetic marks associated with obesity are often identified from known regions or genes, targeted by function. Moreover, agnostic approaches use array technology (e.g., Golden Gate, 14K, 27K, 450K, or EPIC), but there are physical limitations such as the limited number of CpGs per array, and these approaches are selected based on predetermined criteria of likely significance. For example, while target regions have been selected to cover gene promoters and bodies, as well as CpG islands, with >28 million CpG sites in the genome, less than 5% are covered. Thus, the scope of affected regions is unknown. Another genome-wide tool, meDIP, covers ~40% of the genome, but is dependent on antibody precipitation of methylcytosine, and is thus more effective in CG-rich regions. Also, because meDIP captures only methylated sites, accurate quantitation of methylation percentage is not feasible. Reduced representation bisulfite sequencing is genome-wide but covers ~10% of CpG sites due to technological dependence on endonuclease recognition of specific sites. While these methods are all highly informative for measurable regions, many epigenetic regions occur at long (>10-20kb) distances from gene bodies, and in areas of low CG content. Thus, the coverage has selection/sequence bias.

Addressing these challenges in epidemiologic settings requires multiple approaches to identify epigenomic regions of functional relevance that link environmental exposures and liver dysfunction. These include using agnostic genome scale approaches such as whole-genome bisulfite sequencing or agnostic arrays (e.g., EPIC850 methylation array) and case and control specimens to identify genomic regions that differ between cases and controls in a cell type accessible for both cases and controls, e.g., blood. This step is followed by determination of the relevance of the marker, in affected cancer tissues. Among regions with a high likelihood of being functionally important, follow-up investigation determining if the epigenetic marks with case–control differences that are also found in relevant tissues are stable over time, and thus unlikely to be caused by disease, is performed to establish cause-and-effect. Finally, the biological significance in cancer is determined. Because these approaches have limitations to identifying epigenetic markers for liver cancer risk overtime, circumventing these challenges requires inclusion of molecular profiling that mediates exposures and outcomes in large cohorts with long-term follow up, such us the *All of Us* study (https://allofus.nih.gov/news-events-and-media/announcements/all-us-research-program-initial-protocol).

Another limitation of epigenetics studies is that environmental exposures affecting the epigenome may cause temporary changes in methylation that could be reverted after the exposure is no longer present. Thus, it is important to focus on CpG methylation marks that are stochastically established before specifications that control metastable epiallele expression (92) and imprinting control regions (ICR) that regulate imprinted gene monoallelic expression (93, 94). Methylation marker stability with age also makes them long-term 'records' of early exposures that are difficult to obtain through questionnaires or other exposure

assessment assays (93). CpG methylation of metastable epialleles and ICRs is established before gastrulation and are mitotically heritable. Thus, epigenetic marks are similar across tissues and cell types throughout the individual's life. Unlike metastable epialleles, however, ICRs are defined by parent-of-origin specific methylation marks that are important gene dosage regulators based on the allele's parental origin. Consequently, in contrast to epigenetic marks controlling metastable epiallele expression, methylation marks regulating imprinted genes are similar across individuals (95, 96). Importantly, changes in ICR methylation patterns are implicated in adult-onset diseases suspected to have fetal origins, including neurological disorders, cancers, and metabolic diseases stemming from abnormal growth and nutrient acquisition disorders (97, 98). With the recent publication mapping the complete repertoire of human ICRs (99), examining the effects ICR dysregulation on liver diseases, including cancer, should yield new insights.

Chronic exposure to environmental contaminants characteristic of non-occupational settings results in subtle molecular adaptive responses detectable as methylation marks at epigenetically labile CG dinucleotides (100–102). Targeted methylation sequencing approaches demonstrated that cadmium alone or in a mixture with arsenic is associated with hypermethylation of the *DLK1/MEG3* imprinted domain in leukocyte-derived DNA (103). Conversely, untargeted whole genome bisulfite sequencing revealed that cadmium exposure was associated with differential methylation, at ~2,000 loci (104). Recent studies using Illumina Beadchip arrays also support that DNA methylation of two CG dinucleotides, measured in cell-free DNA, can distinguish HCC from cirrhosis with both sensitivity and specificity in excess of 90% (105). Intriguingly, these CG dinucleotides map to two genes that are key components of the extracellular matrix, epithelial to mesenchymal transition, and signaling (106). This is consistent with dying hepatocytes contributing to the pool of circulating DNA in plasma (107) and the observation that up to 70% of cell free DNA in HCC cases is contributed by the liver (107–109). While these data suggest methods for etiologic investigations and early detection using accessible cells of relevance circulating in plasma, the role of environmental contaminants in methylation alterations has not been examined. Further, racial minorities have not been included in case–control design, hampering causal inference.

Similarly, circulating cell-free RNA is comprised of different classes of RNA, including messenger, micro, circular, long-coding, transfer, ribosomal, and mitochondrial RNAs. RNA pools reflect physiological and pathophysiological insight into human health and have the potential for diagnostic and prognostic markers of disease and monitoring (110, 111). The most studied group of cell free RNAs are miRNAs that can target and regulate genomic output through multiple mechanisms (112) and are an emerging class of effector molecules regulated by diet (113). These miRNAs circulate throughout the body and due to their size and stability are found in most bodily fluids including blood, urine, saliva, breast milk, and tears (114, 115). The epigenome regulates miRNAs and in turn, miRNAs reciprocally regulate DNA methylation by inhibiting DNA-modifying enzymes (116). However, inclusion of racial minorities under-represented in epidemiological research studies remains low, which challenges the interpretation of existing data. Better representation of these groups is needed to understand disparities in liver cancer and in the development of early detection methods.

Summary

Racial/ethnic disparities in the incidence of cancers such as HCC is paralleled by increased prevalence of environmental contaminants. The inflammatory effects of environmental exposures may be modulated by disparities in lifestyle factors, comorbidities, and higher body burden of environmental contaminants. Resilience factors such as anti-inflammatory diets may mitigate exposure effects and are linked with a lower liver cancer prevalence among ethnic minorities. However, establishing the effects of risk factors in epidemiologic studies is complicated by retrospective exposure assessment. These shortcomings may be circumvented by a more detailed knowledge of epigenetic responses linking environmental exposures to cancer outcomes.

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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

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Cancer screening and breast cancer family history in Spanish-speaking Hispanic/Latina women in California

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Background: Breast cancer is the most common cancer among women in the U.S. and the leading cause of cancer death among Hispanics/Latinas (H/L). H/L are less likely than Non-H/L White (NHW) women to be diagnosed in the early stages of this disease. Approximately 5-10% of breast cancer can be attributed to inherited genetic mutations in high penetrance genes such as *BRCA1/2*. Women with pathogenic variants in these genes have a 40-80% lifetime risk of breast cancer. Past studies have shown that genetic counseling can help women and their families make informed decisions about genetic testing and early cancer detection or risk-reduction strategies. However, H/L are 3.9-4.8 times less likely to undergo genetic testing than NHW women. We developed a program to outreach and educate the H/L community about hereditary breast cancer, targeting monolingual Spanish-speaking individuals in California. Through this program, we have assessed cancer screening behavior and identified women who might benefit from genetic counseling in a population that is usually excluded from cancer research and care.

Materials and Methods: The "Tu Historia Cuenta" program is a promotores-based virtual outreach and education program including the cities of San Francisco, Sacramento, and Los Angeles. Participants responded to three surveys: a demographic survey, a breast cancer family history survey, and a feedback survey. Survey responses were described for participants and compared by area where the program took place using chi-square, Fisher exact tests, and t tests. Multinomial logistic regression models were used for multivariate analyses.

Results and Conclusion: We enrolled 1042 women, 892 completed the cancer family history survey and 62 (7%) provided responses compatible with referral to genetic counseling. We identified 272 women (42.8% ages 40 to 74 years) who were due for mammograms, 250 women (24.7% ages 25 to 65 years) due for Papanicolaou test, and 189 women (71.6% ages 50+) due for colorectal cancer screening. These results highlight the need of additional support for programs that spread awareness about cancer risk and facilitate access to resources, specifically within the H/L community.

KEYWORDS

breast cancer health disparities, hereditary breast cancer, cancer education, Hispanic/Latina, cancer family history

Introduction

Breast cancer is the most common cancer among women in the United States (1, 2) and the leading cause of cancer death among Hispanics/Latinas (H/L) (3). Furthermore, H/L are less likely than Non-H/L White (NHW) women to be diagnosed in the early stages of disease and are less likely to have access to high-quality care because of factors such as lower socioeconomic status (SES), high uninsured rate (3, 4), and issues communicating with providers (5). Additionally, among women of all ages dying of breast cancer, H/L have a 164% higher risk of dying before the age of 50 years in comparison with NHW women (6).

Approximately 5-10% of breast cancer cases can be attributed to inherited genetic mutations (7). Women with pathogenic variants in high penetrance genes such as *BRCA1* and *BRCA2* have a 40-80% lifetime risk of breast cancer compared to 12% risk in the general population (8). Only about 10% of mutation carriers are aware of their mutation status (9). While awareness (10) and use (11) of genetic testing in different populations has increased over time, disparities in access to hereditary breast cancer risk assessment, genetic counseling, and genetic testing continue to exist in the United States (U.S.) (12), with awareness among H/L being particularly low (33.2%) compared to NHW women (51.9%, $p<0.0001$) based on data from the 2010 National Health Interview Survey (9, 10, 13). Screening for pathogenic mutations can open opportunities for cancer prevention and/or engagement in frequent cancer screening to detect it early (14). Past studies have shown that genetic counseling can help women and their families make informed decisions about genetic testing and early cancer detection or risk-reduction strategies (15, 16). Genetic counseling and testing for breast cancer survivors also is critically important as it can inform targeted treatment, risk management for second primary cancers, and targeted cascade testing for at-risk family members (17). An analysis including 64,717 women who underwent genetic screening between the years 2006-2007 demonstrated that the mutation rate of BRCA1 and BRCA2 was about the same in H/L and NHW women (18, 19); however, H/L were 3.9-4.8 times less likely to undergo genetic testing than NHW women (19). The lower use of genetic testing in H/L and other underrepresented populations compared to NHW women reduces the generalizability of genetic discoveries and leads to challenges in interpreting genetic results (20).

Lack of insurance and economic concerns often are the main barriers for obtaining a genetic risk assessment for hereditary breast and ovarian cancer, and limited English proficiency and cultural factors such as embarrassment, modesty and secrecy also reduce the rate of genetic testing (21). H/L are willing to engage and have a strong desire for counseling and screening despite barriers they experience (21–25), however, within a study of 1622 participants recruited through a state cancer registry and who reported receiving genetic testing, H/L were nearly two times less likely as NHW women to report discussing genetic testing with a health provider (26, 27). A study on H/L found positive attitudes towards genetic testing for cancer prevention, with 87% agreeing it was a good idea and 87.7% agreeing that everyone should get genetic testing for cancer prevention (28). Another study focused on low income women in California, including H/Ls, identified participants at high-risk for hereditary breast and ovarian cancer *via* a phone intervention and reported that 39% accepted and received genetic counseling during the intervention period (29).

Community health educators (*promotores*) are uniquely positioned to bridge the gap between the H/L community and

the health care system (30–34). Promotores are typically from the community in which they work, speak the same language, and understand the culture's idiosincracies (32). They are able to translate medical jargon into practical, realistic steps that can be better understood and followed by members of their communities (34). Promotores-led educational interventions are cost-effective in increasing cancer screenings in the H/L community (35–39). Interventions led by promotores significantly increase breast cancer-related knowledge among participants (37, 40).

There is currently limited work on increasing breast and ovarian cancer genetic screening among H/L (10, 13, 24, 41–43). To address this gap, the research team in partnership with The Latino Cancer Institute developed a program, "Tu Historia Cuenta" (THC), to conduct outreach and educate the H/L community, particularly targeting monolingual Spanish-speaking women (44). Materials were developed to train promotores about hereditary breast cancer as well as to facilitate the interaction between promotores and the community. In this paper, we provide a description of the demographic characteristics of the participants in the program and the results of the breast cancer family history and feedback surveys which highlights the need for further improvement in hereditary breast and ovarian cancer screening in this population.

Methods

Study population

Recruitment of participants started in June 2020 and was led by two promotores organizations in Southern and Northern California (45, 46). As of March 2022, 1062 H/L in California had registered for the THC education session. Of these, 1042 answered the demographic survey, 891 participants answered the breast cancer family history survey, and 525 participants answered the feedback survey. The demographic survey was provided to women after registration, before the educational session. Participants were asked to answer the cancer family history survey after the education session as to maximize their comprehension of the reason for those questions and how to respond to them. As a result, a small number of participants (N=20) registered for the education session but did not complete the demographic survey and 14% (N=151) of participants attended the education session but did not answer the family history survey.

The current report is based on all survey responses available on March 18th, 2022. The inclusion criteria for participants were 1) women 21-75 years of age, 2) Spanish-speaking or bilingual, and 3) self-identifying as H/L. Participants provided verbal informed consent. Data from all surveys were de-identified. The study was approved by the University of California, San Francisco Institutional Review Board.

Program description

THC is a promotores-led outreach and education program with materials developed using a continuous stakeholder engagement approach as previously described (44). The one-hour educational sessions provide participants basic background knowledge on breast cancer with a particular focus on hereditary breast cancer and genetics (44). THC participants completed three surveys: 1) a demographic information and general cancer screening history (i.e., mammography screening, colorectal cancer screening, cervical cancer screening) and exposure to genetic testing (i.e., cancer risk assessment) survey, 2) a breast/ovarian cancer-specific family history survey aimed at identifying women at higher risk of hereditary breast/ovarian cancer (47) that was adapted from the Pedigree Assessment Tool (48, 49), and 3) the post-education session feedback survey which assessed the utility, quality, and compressibility of the educational session components. The family history survey was selected for its ease of administration and its previous validation in low income population including H/L which was done by comparing it to genetic counselors' assessments (50) and to Referral screening tools (RST) (48). When researchers compared the family history survey to RST, the survey had high sensitivity (~92%), specificity (0.94%) and high AUROC (98%); additional details can be found elsewhere (51). Each 'Yes' response on the survey had an associated score of 2, 4, or 6 depending on the age of onset and type of cancer reported for self and family member. Participants with a scores of 6 or higher were considered to have responded in a manner consistent with a strong family history of breast/ovarian cancer.

Women identified as having strong family history based on their score in the breast cancer-family history survey received a recommendation to discuss their family history with a doctor and potentially a genetic counselor. For those without a usual source of care, we provided resources and support to facilitate access.

Survey content

The demographic survey contained questions including city of residence, zip code, age, number of years residing in the U.S., number of people in the household, and employment status. Information regarding English-language proficiency (a. monolingual Spanish speaker, b. limited English use, c. conversational English, d. fully bilingual), medical insurance

(a. no insurance, b. public insurance, c. private insurance), and educational attainment (a. no school, b. elementary school, c. middle school, d. high school, e. associate degree, f. university degree) was obtained. In addition, the demographic survey contained questions regarding genetic testing such as previous knowledge and exposure to genetic testing, and interest in genetic testing. A subset of questions targeted cancer screening behavior (i.e., breast, cervical, and colorectal cancer screening).

The family history of breast cancer survey was adapted from a previously validated survey (51) and collected the following information on the participant and their first- and second-degree relatives: breast cancer diagnoses before age 50 years, after age 50 years, and cancer in both breasts. This survey included additional questions on family history of ovarian cancer, three or more family members on the same side of the family with cancer of the breast, prostate, and/or pancreas, and male family member with breast cancer. At the end of the survey, participants were asked about their willingness to be contacted in the future to learn more about their respective cancer risk if they were identified as having a strong family history of breast cancer.

The feedback survey was given to participants at the end of the education session. This survey was anonymous and had nine questions to help understand how useful participants found the information provided and whether they felt motivated to share the information learned with family and friends and to seek additional information regarding breast cancer.

Data analysis

Average, dispersion (standard deviation-SD) and proportion measures were used to describe the characteristics of the participants and their survey responses. We used chi-square, Fisher's exact test, and two-sided t-tests to compare characteristics and responses between participants in the three areas of outreach: San Francisco, Sacramento, and Los Angeles County, as well as by breast cancer family history score (a. <6, b.6+) and screening status.

We used multivariate multinomial logistic regression analyses to assess the association between different demographic factors and screening behavior among THC participants. The 'never' screened category group was defined as reference in all regression models. All analyses were conducted in RStudio version 4.1.2 (52).

Results

Participants' demographic characteristics

A total of 1042 Spanish-speaking H/L women residing in San Francisco County, Sacramento and Los Angeles provided demographic information after registering for the THC education session. The average age of participants was 43 years and ranged between 21 and 73 years (Table 1). Most individuals were born outside the United States (86.1%) and had lived in the US for an average of 18 years (Min: 1 year, Max: 54 years). Approximately 6.5% of participants reported no formal education, 22.6% graduated from elementary school only, 16.3% middle school, 32.1% high school, 11.9% had an associate degree and 9.1% a university degree. The program's target population was Spanish-speaking H/L, which was reflected by the responses related to English language proficiency: 17.7% were monolingual Spanish-speakers, 30.7% had basic knowledge of English, 36.9% conversational English, and 14.2% were fully bilingual. Half of the participants (50.0%) had public health insurance, 35.8% had no insurance, and 13.4% had private insurance. The average number of individuals leaving in the participants' household was 4.3 (SD= 2.1).

Differences in demographic characteristics between participants in Los Angeles, Sacramento, and San Francisco

Average age of participants varied between the Los Angeles County, Sacramento, and San Francisco recruitment groups, with San Francisco individuals having the lowest mean age (44.7, 42.3, and 40.5 years respectively) (Table 1). Participants from San Francisco had been in the US for an average of 16 years (SD=12), which was lower than the number of years reported by participants in Los Angeles County and Sacramento (20 years, SD=10, and 19 years, SD=8, respectively). Furthermore, San Francisco had the largest proportion of participants with at least conversational English language proficiency and high school education or higher (Table 1). In Los Angeles County and Sacramento, participants were more likely to report being uninsured (44.0%, 44.3%) compared to San Francisco (9.3%). San Francisco participants were more likely to report having public health insurance (77.0% vs. 36.0% for Sacramento and 44.3% for Los Angeles County) (Table 1). On average, participants in Sacramento lived in larger households (4.6 people) compared to participants in Los Angeles County (4.4 people) and San Francisco (3.8 people) (Table 1).

Screening behavior and knowledge about genetic testing

Most participants expressed interest in learning about genetics (98%), and only 1.3% of the individuals stated that they were not interested in learning about genetics or how genetics could be used to prevent or detect cancer early. More than half of the participants reported that they had not heard about genetic tests before (52.2%) (Table 2).

TABLE 1 Demographic characteristics of 1042 'Tu Historia Cuenta' program participants in California overall and by recruitment area.

Variable, N (%) or Mean (SD)	Overall	Los Angeles	Sacramento	San Francisco	p-value
Number of participants	1042 (100)	530 (50.9)	264 (25.3)	248 (23.8)	
Age in years	43.06 (10.24)	44.68 (10.22)	42.26 (9.14)	40.47 (10.79)	<0.001
Place of birth					
Foreign-born	897 (86.1)	420 (79.2)	250 (94.7)	227 (91.5)	<0.001
US-born	101 (9.7)	73 (13.8)	13 (4.9)	15 (6.0)	
Missing	44 (4.2)	37 (7.0)	1 (0.4)	6 (2.4)	
Years in the United States	18.87 (10.15)	20.43 (9.94)	19.27 (8.25)	15.56 (11.63)	<0.001
English Language Proficiency					
Monolingual Spanish Speaker	184 (17.7)	111 (20.9)	35 (13.3)	38 (15.3)	0.015
Limited English Use	320 (30.7)	152 (28.7)	97 (36.7)	71 (28.6)	
Conversational	384 (36.9)	185 (34.9)	91 (34.5)	108 (43.5)	
Fully Bilingual	148 (14.2)	76 (14.3)	41 (15.5)	31 (12.5)	
Missing	6 (0.6)	6 (1.1)	0 (0.0)	0 (0.0)	
Health Insurance Status					
No Insurance	373 (35.8)	233 (44.0)	117 (44.3)	23 (9.3)	<0.001
Public	521 (50.0)	235 (44.3)	95 (36.0)	191 (77.0)	
Private	140 (13.4)	54 (10.2)	52 (19.7)	34 (13.7)	
Missing	8 (0.8)	8 (1.5)	0 (0.0)	0 (0.0)	
Educational Attainment					
No school	68 (6.5)	55 (10.4)	3 (1.1)	10 (4.0)	<0.001
Elementary School	235 (22.6)	134 (25.3)	75 (28.4)	26 (10.5)	
Middle School	170 (16.3)	50 (9.4)	78 (29.5)	42 (16.9)	
High School	335 (32.1)	169 (31.9)	60 (22.7)	106 (42.7)	
Associate Degree	124 (11.9)	55 (10.4)	26 (9.8)	43 (17.3)	
University	95 (9.1)	54 (10.2)	22 (8.3)	19 (7.7)	
Missing	15 (1.4)	13 (2.5)	0 (0.0)	2 (0.8)	
Number of People in Household	4.32 (2.09)	4.41 (2.33)	4.62 (1.53)	3.84 (1.98)	<0.001

Among women within the age range of mammography screening guidelines (40-74 years), 56.1% were current with their mammogram (i.e., mammogram within the last 2 years), and 42.8% of the participants were due for mammograms (i.e., never had obtained a mammogram or their last mammogram was done more than 2 years ago). Of the 163 women who had never had a mammogram, 14% were navigated into the Every Women Counts program (EWC) (53), and of the 109 women who had their mammogram more than 2 years ago, 38% were navigated into this program. It is important to note that the THC education session included information about the EWC program that was shared with all participants. Due to this, women who had not previously received mammograms may not have expressed a need for navigation assistance but still taken advantage of the EWC program.

Cervical cancer screening for women between the ages of 21 to 65 years was observed for 82.1%, with 73.3% of the participants having obtained a Papanicolaou test within the last 3 years. Among participants 50 years of age and older, 23.5% reported ever having colorectal cancer screening (Table 2).

Differences in screening behavior and genetic testing knowledge between participants in Los Angeles County, Sacramento, and San Francisco

Most participants in the program expressed interest in learning about genetics and breast cancer (~98%), however, a larger proportion of participants who resided in the San Francisco area were aware of genetic testing (62.9%) compared to participants in Los Angeles County (42.3%) and Sacramento (41.3%) (Table 2).

A similar proportion of participants in Sacramento and San Francisco were up to date with mammography screening (60.6% and 60.8%, respectively), while a lower proportion was observed among participants in Los Angeles County (52.5%); this difference was not statistically significant (Table 2).

Differences between regions in cervical and colorectal cancer screenings were not statistically significant (Table 2). However, San Francisco had the highest proportion of participants reporting a Papanicolaou test within the last 3 years (84.9%), followed by Sacramento (79.3%) and Los Angeles County (64.8%). Similarly, 30% of participants from San Francisco who were 50 years and

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TABLE 2 Screening behavior and interest in breast cancer genetics among 'Tu Historia Cuenta' study participants (N=1,042) overall and by recruitment area.

Interest and awareness, N (%)	Overall	Los Angeles	Sacramento	San Francisco	P-value
Number of Participants	1,042 (100)	530 (50.9)	264 (25.3)	248 (23.8)	
Interest in learning about genetics and BC					
No Interest	14 (1.3)	11 (2.1)	0 (0.0)	3 (1.2)	<0.001
Some Interest	220 (21.1)	149 (28.1)	23 (8.7)	48 (19.4)	
Very Interested	801 (76.9)	364 (68.7)	240 (90.9)	197(79.4)	
Missing	7 (0.7)	6 (1.1)	1 (0.4)	0 (0.0)	
Genetic Testing Awareness					
Yes	489 (46.9)	224 (42.3)	109 (41.3)	156 (62.9)	<0.001
No	544 (52.2)	297 (56.0)	155 (58.7)	92(37.1)	
Missing	9 (0.9)	9 (1.7)	0 (0.0)	0 (0.0)	
Cancer Screening					
Breast Cancer Screening (Ages 40 to 74)	636	356	160	120	
Up to date with mammogram (<2 years ago)	357 (56.1)	187 (52.5)	97 (60.6)	73 (60.8)	0.200
Due for mammogram (never or 2+ years ago)	272 (42.8)	162 (45.5)	63 (39.4)	47 (39.2)	
Missing	7 (1.1)	7 (2.0)	0 (0.0)	0 (0.0)	
Connected to EWC Program (of those due for mammogram)	64 (23.5)	53 (32.7)	10 (15.9)	1 (2.1)	<0.001
Cervical Cancer Screening (Ages 21 to 65)	1012	512	261	239	
Ever had a pap smear	831 (82.1)	380 (74.2)	233 (89.3)	218(91.2)	<0.001
Up to date with pap smear	742 (73.3)	332 (64.8)	207 (79.3)	203 (84.9)	0.103
Due for Pap. Test (never or 3+ years ago)	250 (24.7)	165 (32.2)	52 (19.9)	33 (13.8)	
Missing	19 (1.9)	14 (2.7)	2 (0.8)	3 (1.3)	
Colorectal Cancer Screening (Age 50+)	264	158	56	50	
Up to date with colonoscopy	62 (23.5)	33 (20.9)	14 (25.0)	15 (30.0)	0.355
Due for colonoscopy	189 (71.6)	116 (73.4)	42 (75.0)	31 (62.0)	
Missing	13 (4.9)	9 (5.7)	0 (0.0)	4 (8.0)	

older obtained colorectal cancer screenings, followed by 25% of participants in Sacramento and 20.9% in Los Angeles County (Table 2).

Demographic characteristics and cancer screening behavior

Participant's age, years residing in the United States, English language proficiency level, health insurance status, educational attainment, and number of residents in the household were all associated with screening behavior (Table 3). In general, screening was more common among bilingual participants with health insurance and formal education. Educational attainment was strongly associated with colorectal cancer screening, with up to 52% of individuals with a university degree reporting colorectal cancer screening compared to 21% of those with only elementary education and 0% of those with no formal education (Table 3). Education was also associated with cervical cancer screening; the largest proportion of women reporting never having had a Papanicolaou test were those with no formal education (29%) (Table 3). English proficiency and insurance status were associated with breast cancer screening; the lowest proportion of current mammograms was reported by monolingual Spanish speakers (42%) and the highest among those with private health insurance (72%) (Table 3).

Multiple factors were associated with mammography screening behavior in multivariate analysis. Age, educational attainment, English fluency and having private insurance were positively associated with being up-to-date with screening (Table 4). Additionally, program participants from Sacramento were approximately 2-fold more likely to be current with mammography screening in adjusted models compared to those from Los Angeles County (P-value 0.008)

Cervical cancer screening behavior was statistically significantly different when comparing participants in Los Angeles County to those in the Northern California cities, with the latter having a higher relative risk of being up to date (P-value <0.001) (Table 5). Participants with private insurance were 3.7 times more likely to be up to date with cervical cancer screening compared to those without health insurance (P-value 0.001).

Colorectal cancer screening behavior was statistically significantly different when comparing education attainment, with those with a high school education or higher having 6.4

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TABLE 3 Cancer Screening behavior among 'Tu Historia Cuenta' study participants by demographic variables.

Variable	Mammography Screening*Mean (SD) or N (%)				Cervical Cancer Screening*Mean (SD) or N (%)				Colorectal Cancer Screening*Mean (SD) or N (%)		
	Up to Date	>2 years	Never	P-value	Up to Date	>3 years	Never	P-value	Yes	No	P-value
	357 (56)	109 (17)	163 (26)		742 (73)	88 (8)	162 (16)		62 (24)	189 (72)	
Age, years	50.5 (7.3)	51.3 (7.7)	45.5 (6.7)	<0.001	42.2 (9.2)	43.7 (8.2)	42.2 (10.8)	0.360	57 (6)	56 (6)	0.312
Year in United States	23.2 (9.6)	21.0 (9.7)	19.0 (8.5)	<0.001	18.2 (8.9)	20.7 (10.0)	18.4 (11.0)	0.113	28 (10)	24 (10)	0.010
Place of birth											
Foreign-born*	316 (57)	95 (17)	139 (25)	0.91	652 (76%)	71 (8)	131 (15)	0.077	54 (24%)	169 (76)	0.43
US-born	28 (56)	8 (16)	14 (28)		65 (66%)	10 (10)	23 (23)		7 (35%)	13 (65)	
missing	13 (45)	6 (21)	10 (34)		25 (62%)	7 (18)	8 (20)		1 (12%)	7 (88)	
English Language Proficiency											
Monolingual Spanish Speaker	45 (42)	22 (21)	39 (37)	0.015	114 (68)	16 (10)	38 (23)	0.003	7 (15)	41 (85)	0.01
Limited English Use	130 (59)	43 (20)	46 (21)		235 (75)	36 (12)	41 (13)		22 (24)	68 (76)	
Conversational	132 (58)	35 (15)	59 (26)		294 (80)	22 (6)	51 (14)		18 (22)	63 (78)	
Fully Bilingual	49 (64)	8 (11)	19 (25)		97 (68)	14 (10)	32 (22)		15 (47)	17 (53)	
Missing data	1 (50)	1 (50)	0 (0)		2 (100)	0 (0)	0 (0)		0 (0.0)	0 (0.0)	
Health Insurance											
No Insurance	104 (47)	45 (20)	73 (33)	<0.001	240 (67)	49 (14)	68 (19)	<0.001	11 (14)	67 (86)	0.013
Public	183 (60)	47 (15)	76 (25)		381 (77)	31 (6)	84 (17)		34 (27)	92 (73)	
Private	69 (72)	14 (15)	13 (14)		117 (87)	8 (6)	10 (7)		17 (37)	29 (63)	
Missing data	1 (20)	3 (60)	1 (20)		4 (100)	0 (0)	0 (0)		0 (0)	1 (100)	
Educational Attainment											
No school	22 (44)	11 (22)	17 (34)	0.410	36 (64)	4 (7)	16 (29)	0.030	0 (0)	36 (100)	<0.001
Elementary School	84 (58)	19 (13)	42 (29)		167 (74)	16 (7)	43 (19)		12 (21)	45 (79)	
Middle School	51 (51)	23 (23)	26 (26)		128 (76)	19 (11)	21 (12)		4 (12)	30 (88)	
High School	117 (60)	31 (16)	47 (24)		255 (79)	27 (8)	40 (12)		19 (30)	44 (70)	
Associate Degree	45 (60)	13 (17)	17 (23)		81 (69)	16 (14)	21 (18)		12 (38)	20 (62)	
University	38 (63)	10 (17)	12 (20)		68 (73)	6 (6)	19 (20)		15 (52)	14 (48)	
Missing data	0 (0)	2 (50)	2 (50)		7 (78)	0 (0)	2 (22)		0 (0)	0 (0)	
Number of People in Household	4.08 (1.8)	3.91 (1.8)	4.6 (1.7)	0.003	4.3 (1.9)	4.4 (1.9)	4.2 (1.9)	0.703	3 (2)	4 (2)	<0.001

*The sample sizes for each screening rate is based on women who answered the survey between targeted age groups: Mammography screening 40-74 years, Cervical cancer screening 21-65 years and Colorectal cancer screening ages 50+

times the odds of being up to date compared to those with no schooling (P-value 0.001) (Table 6). In addition, living in a houseful with more people was negatively associated with being current with screening (P-value 0.042).

Breast cancer family history survey results

We used a previously validated family history survey to identify women with strong breast cancer family histories (51). We obtained a preliminary score and for individuals with scores of 6 or higher, we re-contacted participants to confirm their answers to the survey. THC originally identified 178 participants with a breast cancer family history score of 6 or greater (the 'strong breast cancer family history' category). After confirmation by the promotores, the scores changed as follows: 62 participants maintained a strong breast cancer family history score of 6+, 43 participants moved down to the 'limited family history' category (scores between 2 and 4), and 73 participants moved to the 'no family history' category (score of 0) (Table 7). Reasons for moving categories included:

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TABLE 4 Multivariate multinomial logistic regression model testing the association between breast cancer screening behavior and demographic factors among 'Tu Historia Cuenta' participants ages 40 to 74 (N=587, 42 excluded from 629 due to missing data).

Variable	RRR*	L95%CI	H95%CI	P-value
Never had mammography (reference)				
Mammography up to date				
Age	1.17	1.12	1.22	<0.001
Years residing in the US	0.98	0.95	1.01	0.175
Immigration status (US born vs. foreign born)	0.95	0.34	2.61	0.917
Educational Attainment (ref: no schooling)				
Elementary	2.56	1.00	6.53	0.050
Middle school	1.54	0.52	4.53	0.435
High school	3.00	1.10	8.20	0.032
Associate degree	2.07	0.66	6.48	0.211
University degree	2.28	0.68	7.62	0.182
Region of residence (ref: Los Angeles)				
Sacramento	2.16	1.23	3.81	0.008
San Francisco	1.08	0.58	2.03	0.801
Insurance Status (ref: no insurance)				
Public	1.58	0.98	2.57	0.062
Private	3.19	1.46	6.98	0.004
English Fluency (ref: monolingual)				
Limited English Use	2.38	1.14	4.99	0.021
Conversational	2.16	1.10	4.25	0.026
Fully Bilingual	1.84	0.69	4.91	0.225
Number of people in the household	0.90	0.78	1.02	0.102
Mammography more than 2 years ago				
Age	1.18	1.12	1.25	<0.001
Years in the US	0.97	0.94	1.01	0.118
Immigration status	0.94	0.23	3.79	0.927
Educational Attainment (ref: no schooling)				
Elementary	1.41	0.45	4.48	0.555
Middle school	2.05	0.55	7.63	0.283
High school	2.38	0.69	8.25	0.171
Associate degree	2.43	0.60	9.84	0.214
University degree	2.13	0.48	9.49	0.319
Region of residence (ref: Los Angeles)				
Sacramento	2.33	1.14	4.75	0.020
San Francisco	0.84	0.36	1.94	0.678
Insurance Status (ref: no insurance)				
Public	0.99	0.54	1.84	0.987
Private	1.63	0.61	4.33	0.329
English Fluency (ref: monolingual Spanish)				
Limited English Use	1.60	0.65	3.98	0.307
Conversational	1.18	0.51	2.76	0.694
Fully Bilingual	0.42	0.10	1.71	0.226
Number of people in the household	0.84	0.70	0.99	0.039

*Relative Risk Ratio.

typographical errors when providing answers, answers including distant relatives, confusion between ovarian and cervical cancers, and responses based on other cancer types not linked to breast cancer risk.

Among the participants with a confirmed strong family history score (6+) (N=62), 7 (11.3%) had received genetic counseling before participating in THC, 8 (12.9%) reported having been diagnosed with breast cancer before the age of 50

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TABLE 5 Multivariate multinomial logistic regression model testing the association between cervical cancer screening behavior and demographic factors among 'Tu Historia Cuenta' participants ages 21 to 65 (N=932, 80 excluded from 1012 due to missing data).

Variable	RRR*	L95%	H95%	P-Value
Never had cervical cancer screening	**Reference**			
Cervical cancer screening up to date				
Age	1.00	0.98	1.03	0.929
Years residing in the US	1.01	0.99	1.04	0.314
Immigration status (US born vs. foreign born)	0.56	0.26	1.23	0.150
Educational Attainment (ref: no schooling)				
Elementary	1.37	0.64	2.93	0.424
Middle school	1.37	0.56	3.40	0.492
High school	2.03	0.88	4.70	0.099
Associate degree	1.24	0.48	3.20	0.663
University degree	1.31	0.50	3.41	0.583
Region of residence (ref: Los Angeles)				
Sacramento	2.57	1.56	4.22	<0.001
San Francisco	3.71	2.05	6.71	<0.001
Insurance Status (ref: no insurance)				
Public	1.06	0.70	1.62	0.776
Private	3.73	1.67	8.34	0.001
English Fluency (ref: monolingual)				
Limited English Use	1.21	0.65	2.28	0.548
Conversational	1.46	0.83	2.55	0.184
Fully Bilingual	0.64	0.29	1.40	0.264
Number of people in the household	1.06	0.96	1.17	0.259
Cervical cancer screening 3 years ago				
Age	1.02	0.98	1.06	0.419
Years residing in the US	1.03	0.99	1.07	0.158
Immigration status (US born vs. foreign born)	0.55	0.17	1.80	0.324
Educational Attainment (ref: no schooling)				
Elementary	1.16	0.30	4.49	0.828
Middle school	2.26	0.51	9.96	0.281
High school	2.82	0.69	11.54	0.150
Associate degree	3.65	0.80	16.73	0.095
University degree	1.41	0.27	7.24	0.683
Region of residence (ref: Los Angeles)				
Sacramento	2.58	1.27	5.26	0.009
San Francisco	3.20	1.32	7.74	0.010
Insurance Status (ref: no insurance)				
Public	0.36	0.19	0.69	0.002
Private	0.77	0.25	2.33	0.638
English Fluency (ref: monolingual)				
Limited English Use	1.25	0.48	3.22	0.645
Conversational	0.86	0.35	2.13	0.747
Fully Bilingual	0.78	0.23	2.57	0.678
Number of people in the household	1.13	0.98	1.30	0.088

*Relative Risk Ratio.

years, and one woman (1.6%) after the age of 50 years. Among the 43 participants originally identified as 6+ that moved to the 'limited family history' category, 3 (7%) reported a breast cancer diagnosis after age 50 years (Table 7). No participants had breast cancer diagnosed in both breasts. Among participants whose original breast cancer family history score was less than 6, 7 (0.9%) women reported being diagnosed with breast cancer before the age of 50 years, and 4 (0.5%) women after the age of 50 years. Overall, there were 23 participants (2.5%) who reported a personal history of

TABLE 6 Multivariate logistic regression model testing the association between colorectal screening behavior and demographic factors among 'Tu Historia Cuenta' participants ages 50+ (N=240, 24 excluded from 264 due to missing data).

Never Colonoscopy as reference	OR	L95%	H95%	P-Value
Age	1.04	0.98	1.11	0.165
Years residing in the US	1.00	0.97	1.03	0.882
Immigration status (US born vs. foreign born)	0.98	0.24	3.98	0.980
Educational Attainment (ref: no schooling)				
Less than High School	2.78	1.24	6.47	0.015
High School or more	6.40	2.21	19.37	0.001
Region of residence (ref: Los Angeles)				
Sacramento	1.24	0.52	2.93	0.621
San Francisco	0.99	0.40	2.37	0.974
Insurance Status (ref: no insurance)				
Public	1.24	0.52	2.93	0.621
Private	0.99	0.40	2.37	0.974
English Fluency (ref: monolingual)				
Limited English Use	0.79	0.26	2.54	0.681
Conversational	1.02	0.35	3.14	0.971
Fully Bilingual	1.47	0.39	5.83	0.571
Number of people in the household	0.81	0.66	0.99	0.042

breast cancer, 15 with a diagnosis before the age of 50 years. Follow-up and navigation into genetic counseling and testing for women with a confirmed score of 6+ is currently underway.

Demographic characteristics by family history survey results

Place of birth and educational attainment both were associated with the breast cancer family history score, with a larger proportion of U.S.-born individuals in the 6+ category (strong breast cancer family history) (15%) compared to foreign-born individuals (6%). Furthermore, the proportion of 6+ score individuals was higher among those with a university degree (16%) compared to women with lower level of educational attainment (4-9%) (Table 8).

Feedback survey

Of the participants, 525 (50.3%) responded to the anonymous feedback survey (Table 9). Most of these participants found the educational materials useful when learning about hereditary breast cancer and stated that they would share the information learned from this workshop with

TABLE 7 Breast cancer family history score and personal history of breast cancer by post confirmation score, among individuals originally placed in the 'Strong Family History' category.

	Original Breast Cancer Family History Score 6+*			Original Family History Score <6
New confirmed score	No Family History (0)	Limited Family History (2-4)	Strong Family History (6+)	
	N=73	N=43	N=62	N=756
Received Genetic Counseling prior to THC				
Yes	0 (0.0)	0 (0.0)	7 (11.3)	0 (0.0)
No	73 (100.0)	43 (100.0)	54 (87.1)	756 (100%)
Unsure	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Breast Cancer before 50 (self)				
Yes	0 (0.0)	0 (0.0)	8 (12.9)	7 (0.9)
No	73 (100.0)	43 (100.0)	54 (87.1)	749 (99.1)
Breast Cancer at 50+ (self)				
Yes	0 (0.0)	3 (7.0)	1 (1.6)	4 (0.5)
No	73 (100.0)	40 (93.0)	61 (98.4)	752 (99.5)

TABLE 8 Breast Cancer Family History among 'Tu Historia Cuenta' study participants by demographic variables.

Variable	Family History ScoreMean (SD) or N** (%)		
	Strong (6+)	None & Limited(0-4)	P-value
	60 (7)	800 (92)	
Age, years	45.1 (10.1)	42.7 (10.2)	0.09
Year in United States	20.9 (9.9)	18.6 (9.6)	0.12
Place of birth			
Foreign-born*	46 (6)	687 (94)	0.005
US-born	13 (15)	73 (85)	
missing	1 (2)	40 (98)	
English Language Proficiency			
Monolingual Spanish Speaker	9 (6)	152 (94)	0.17
Limited English Use	26 (10)	245 (90)	
Conversational	16 (5)	293 (95)	
Fully Bilingual	9 (8)	106 (92)	
Missing data	0 (0)	4 (100)	
Health Insurance			
No Insurance	23 (7)	303 (93)	0.17
Public	25 (6)	395 (94)	
Private	12 (11)	96 (89)	
Missing data	0 (0)	6 (100)	
Educational Attainment			
No school	3 (5)	55 (95)	0.019
Elementary School	13 (7)	179 (93)	
Middle School	10 (7)	130 (93)	
High School	12 (4)	263 (96)	
Associate Degree	9 (9)	93 (91)	
University	13 (16)	69 (84)	
Missing data	0 (0)	11 (100)	
Number of People in Household	4.2 (1.5)	4.3 (2.0)	0.226

*This includes individuals who were foreign born or moved to the US before 1 year of age.
**N=860, which is 31 less than all participants with family history information due to only 860 participants having their family history confirmed up to this time.

friends and family (97.7% and 94.9%, respectively). Additionally, individuals expressed interest in obtaining more information from their family about their cancer history (93%), and 64.4% responded that they would look for further information on the internet to learn more about breast cancer. Overall, individuals felt comfortable asking questions during the workshop and felt satisfied in the manner that their questions were answered (98.5%, 99.1%, respectively) (Table 9).

Participants were surveyed regarding which topics they found confusing. Half of the participants did not report confusing topics. Thirteen percent of participants reported that they were confused about the concept of the *BRCA*1/2 genes and 7.8% about the increased risk of breast cancer when carrying a *BRCA* mutation. Other concepts covered by the program (e.g., definition of cancer, benign disease, disease stage) were still unclear by the end of the session for 4-5.5% of participants who responded (Table 9).

Discussion

Tools to screen for breast cancer are important to diagnose cases early and improve outcomes (54). Disparities in breast cancer stage at diagnosis and risk of mortality between H/L and NHW women are partly due to the economic, educational, language, cultural and health care access barriers faced by members of the H/L community (3, 4). With improvement of genetic screening tools, the H/L community is at risk of being left further behind if programs are not in place to help with access and understanding of these opportunities for prevention (18, 19).

The goal of this study was to describe the results of a hereditary breast cancer outreach and education program for Spanish-speaking H/L in California and highlight the need for additional efforts to help the community move from awareness and understanding to screening and prevention.

TABLE 9 'Tu Historia Cuenta' education session feedback survey responses (N=525).

Question	N (%)
Video and discussion were useful to learn about hereditary BC	
Yes	463 (97.7)
Somewhat useful	11 (2.3)
Prior awareness about hereditary genetic risk for BC	
Yes	208 (43.9)
No	266 (56.1)
Will try to obtain more information from family members about cancer history	
Yes	442 (93.2)
No	6 (1.3)
Unsure	26 (5.5)
Will look for information on the internet to learn more about breast cancer	
Yes	302 (64.4)
No	124 (26.4)
Unsure	43 (9.2)
Will share the information learned from this workshop with friends and family	
Yes	445 (94.9)
No	5 (1.1)
Maybe	19 (4.1)
Felt comfortable asking questions during the workshop	
Yes	463 (98.5)
Somewhat comfortable	7 (1.5)
Felt satisfied in the manner questions were answered	
Yes	464 (99.1)
No	3 (0.6)
More or Less	1 (0.2)
The activities conducted during the session were:	
Fundamental	372 (79.5)
Enlightening	90 (19.2)
Unnecessary	6 (1.3)
Concepts that were still confusing after the session	
None	268 (51.0)
Cancer definition	12(4.4)
Difference between benign and malignant tumor	12 (4.4)
Difference between common and hereditary breast cancer	29 (5.5)
Difference between early and advanced stages of breast cancer	21 (4.0)
What a mutation is and how is the mutation hereditary	29 (5.5)
BRCA1/2 Genes	68 (12.9)
Increased risk of breast cancer when there is a BRCA mutation	41 (7.8)
Early detection practices and preventative measures to control BC risk	23 (4.4)

The THC program's target population was Spanish-speaking H/L women in three California cities and surrounding areas (San Francisco, Sacramento, and Los Angeles), who due to their limited English proficiency, socioeconomic and health insurance status, and cultural barriers, might not have access to adequate information and resources for breast cancer prevention, particularly, for prevention of hereditary breast cancer. The demographic characteristics of the program participants were consistent with the target population and supports the crucial role of promotores in connecting with underserved communities (34, 40, 55, 56).

We limited the program to women older than 21 years of age, and the average age for all participants was 43 years, with some variation by geographic area, with San Francisco

participants being younger than those in Los Angeles and Sacramento. The difference in the average age of participants at the different locations might be a reflection of the age of promotores in the different groups, since the average age of an individual's networks is likely to be concordant with their own age. For programs working with promotores, this may be important as it helps demonstrate that promotores may recruit individuals within their social circles that resemble some of their own characteristics. Having promotores of similar age of the target population of a specific program may be important.

California's Medicaid-managed care legislation established a two-plan model in 14 counties with the largest Medicaid population (57). Medicaid recipients in these counties can choose between a local initiative and a commercial plan, with the local initiative being the state's effort to help traditional safety net providers compete to retain Medicaid patients. The Los Angeles Care Healthy Plan and the San Francisco Health Plan resulted from this initiative. San Francisco additionally has a program called Healthy San Francisco which provides access to comprehensive health services for uninsured workers and residents of San Francisco (57, 58). The addition of the comprehensive health care program in San Francisco likely explains why a smaller proportion of individuals were uninsured (9.3%) compared to Los Angeles and Sacramento (44.3% and 44.0%, respectively). The differences in health care access across the cities and the different screening rates observed suggest universal health care may play a role in reducing disparities in cancer screening rates. Additionally, a larger proportion of participants in San Francisco had graduated from high school and had a higher level of English proficiency. Adult immigrants living and working in places where others share their ethnic backgrounds may be less likely to be proficient in English (59). This may explain some of the differences observed between English proficiency levels as H/L make up 48.6% of the population in Los Angeles, 28.9% in Sacramento and 15.2% in San Francisco. The characteristics of the promotores in the three cities might also explain the differences in the demographics of participants, even though the promotores had similar educational and linguistic backgrounds.

A study of breast cancer screening among H/L age 40 years and older in San Diego County found that 76.2% of women had received a mammogram in the past 2 years (60), which is higher than the 56.1% of H/L in our study. This difference may be because 52% of the San Diego County participants had private health insurance and a smaller percent of participants were born outside of the U.S. (76.3%). In addition, our study was conducted during the COVID-19 pandemic which may have affected cancer screening rates (61). However, other studies have also found rates consistent with what we found. A study including Mexican-American respondents of the California Health Interview Survey (CHIS) found that among women who were uninsured or had no usual source of care and were 40 years and older, 37.8-54.6% reported a mammogram in the past 2 years (62), which is consistent with the proportion in our study population. Similarly, 73.3% of women in THC were up to date with cervical cancer screening which is within the range reported for Mexican-American women in the CHIS who were uninsured or had no usual source of care (60.0-80.9%) (62). Among the THC participants who were 50 years and older, 23.5% had obtained a colorectal cancer screening; this percentage is lower compared to past studies that identified 50.2-60% of H/L California residents aged 50 years and older who had ever received colorectal cancer screening (63, 64) but is similar to findings from a Northern California catchment area population assessment (65).

The THC participants who had never obtained a mammogram reported a higher average number of household members, which is a measure that correlates with socioeconomic status, thereby suggesting that participants who never had a mammogram within the THC study may also be those in the lowest income bracket.

Participants expressed interest in learning about hereditary breast cancer and genetics despite limited knowledge at the time of registration. The proportion of participants identified as having strong family history of breast cancer (~7%), is concordant with other estimates in studies assessing breast cancer family history in unaffected women (66–68). The larger proportion of women with a high breast cancer family history score among U.S.-born (15%) compared to foreign-born participants (6%) might be due to differences in the flow of information about cancer family history in these two groups. A similar interpretation can be posed for the higher proportion of women with university degrees with strong breast cancer family history. Comparing the rate of high penetrance mutations by place of birth and reported family history of cancer could provide important information about the carrier status predictive accuracy of the breast cancer family history survey by immigration status/generation among H/L in California.

There were 116 individuals whose breast cancer family history survey scores changed after a second conversation with promotores. Over-reporting of cancer family history has been noted in previous studies (69, 70). The most common reasons for the discordance between the original survey response and that after a second contact were unintentional errors when choosing options and confusion about type of cancer in the family (e.g., ovarian vs. cervical, which has been previously described (71)). Only participants who had initially had a high family history score (greater than or equal to 6) were part of the confirmation group, which could lead to underestimation of the proportion of participants in the strong family history category.

A strength of this study was that we were able to connect to a population that is often excluded from health studies (35.8% of the study participants did not have health insurance and ~48%

were either monolingual Spanish-speakers or had limited English proficiency). Another strength was that researchers worked closely with promotores to ensure the relevance and accessibility of the study materials and process, while engaging community members to obtain their perspective and perceptions of the program (44). Due to the pandemic, all the education sessions were held virtually. Hosting sessions virtually allowed more women to participate, as usual barriers for in person education were removed (e.g., transportation, child and elderly care responsibilities).

The study has some limitations. Participants were enrolled through the work of two organizations and individuals were recruited from promotores' social circles and networks. Consequently, results from this study may not be generalizable to the overall population of Spanish-speaking H/L in San Francisco, Sacramento, and Los Angeles County. Additionally, the education program advertised learning about hereditary breast cancer, which could have influenced people to participate if they had a personal interest based on their family history of cancer. However, the percentage of individuals in the THC study identified as candidates for genetic counseling (7%) was slightly less than what has been reported for the general population of unaffected women in the U.S. (8% to 12%) (66–68), suggesting that the study sample is not enriched for people with strong family history of breast cancer.

Overall, participants found the THC education session to be useful, and most of the participants reported willingness to share the information they acquired in the session with their friends and family. We hope the sharing of information will lead to greater awareness about hereditary breast cancer in California Spanish-speaking H/L communities.

Conclusion

The THC promotores-led outreach, education and breast cancer family history assessment program implemented in San Francisco, Sacramento, and Los Angeles in June 2020 has reached more than 1000 Spanish-speaking H/L. Since then, we have identified 62 women (7%) which based on survey responses could benefit from genetic counseling, 272 (42.8%) women due for mammograms (64 of whom we have navigated to the EWC program), 250 (24.7%) due for Papanicolaou test, and 189 (71.6%) due for colorectal cancer screening. Follow-up of the THC participants who were referred to and/or navigated to genetic counseling and testing will be important to assess the long-term impact of the program on the prevention of advanced breast cancer diagnosis among Spanish-speaking H/L with strong family history of the disease.

The results from the THC study highlight the need for additional programs targeted to this underserved population in order to spread awareness about cancer risk and facilitate access to resources for prevention.

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 University of California, Davis IRB. The patients/participants provided their verbal informed consent to participate in this study. The current study is not subject to HIPAA rules and therefore waived from written informed consent requirements.

Author contributions

LT performed the statistical analysis and wrote the manuscript. LF conceived and designed the study and provided overall supervision of data analyses and manuscript writing. YD contributed to the conception and design of the study and to manuscript revision. FP controlled the quality of the data, organized the database, and contributed to manuscript revision. MH and AM supervised data collection. XH and VZ contributed to data curation and manuscript revision. EZ, SN, and LC-C contributed to manuscript revisions. All authors contributed to the article and approved the submitted version.

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implementing a virtual outreach and education hereditary breast cancer program in the middle of the Covid19 pandemic.

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

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Breast cancer subtype and clinical characteristics in women from Peru

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Introduction: Breast cancer is a heterogeneous disease, and the distribution of the different subtypes varies by race/ethnic category in the United States and by country. Established breast cancer-associated factors impact subtype-specific risk; however, these included limited or no representation of Latin American diversity. To address this gap in knowledge, we report a description of demographic, reproductive, and lifestyle breast cancer-associated factors by age at diagnosis and disease subtype for The Peruvian Genetics and Genomics of Breast Cancer (PEGEN-BC) study.

Methods: The PEGEN-BC study is a hospital-based breast cancer cohort that includes 1943 patients diagnosed at the Instituto Nacional de Enfermedades Neoplásicas in Lima, Peru. Demographic and reproductive information, as well as lifestyle exposures, were collected with a questionnaire. Clinical data, including tumor Hormone Receptor (HR) status and Human Epidermal Growth Factor Receptor 2 (HER2) status, were abstracted from electronic medical records. Differences in proportions and mean values were tested using Chi-squared and one-way ANOVA tests, respectively. Multinomial logistic regression models were used for multivariate association analyses.

Results: The distribution of subtypes was 52% HR+HER2-, 19% HR+HER2+, 16% HR-HER2-, and 13% HR-HER2+. Indigenous American (IA) genetic ancestry was higher, and height was lower among individuals with the HR-HER2+ subtype (80% IA *vs.* 76% overall, p=0.007; 152 cm *vs.* 153 cm overall, p=0.032, respectively). In multivariate models, IA ancestry was associated with HR-HER2+ subtype (OR=1.38,95%CI=1.06-1.79, p=0.017) and parous women showed increased risk for HR-HER2+ (OR=2.7,95%CI=1.5-4.8, p<0.001) and HR-HER2- tumors (OR=2.4,95%CI=1.5-4.0, p<0.001) compared to nulliparous women. Multiple patient and tumor characteristics differed by age at diagnosis (<50 vs. >=50),

including ancestry, region of residence, family history, height, BMI, breastfeeding, parity, and stage at diagnosis (p<0.02 for all variables).

Discussion: The characteristics of the PEGEN-BC study participants do not suggest heterogeneity by tumor subtype except for IA genetic ancestry proportion, which has been previously reported. Differences by age at diagnosis were apparent and concordant with what is known about pre- and post-menopausal-specific disease risk factors. Additional studies in Peru should be developed to further understand the main contributors to the specific age of onset and molecular disease subtypes in this population and develop population-appropriate predictive models for prevention.

KEYWORDS

breast cancer, genetic ancestry, Hispanics/Latinas, Indigenous American, tumor subtype

Introduction

Globally, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women (1, 2). Breast cancer risk and mortality vary based on several risk factors. Age, race/ethnicity category, family history, genetics, lifestyle, anthropometric, reproductive, and hormonal factors have been associated with the risk of developing breast cancer (3–5). In addition, tumor subtype, socioeconomic status, education level, and access to care have been shown to impact mortality after diagnosis (6, 7). Analyses stratified by race/ethnicity category have shown that despite sharing risk factors for developing breast cancer, disease risk, clinical characteristics, and risk of mortality differ between populations (6, 8–10). For example, U.S. Hispanics/Latinas (H/Ls) are less likely to develop breast cancer than non-Hispanic White (NHW) and African American women (11). However, after diagnosis, H/L women are at higher risk of mortality compared with NHW women (12).

The use of gene expression profiles for molecular classification of breast cancer tumors (i.e., PAM50) has identified three main intrinsic subtypes: Luminal (A and B), HER2-enriched, and Basal-like (13, 14). A combination of immunohistochemical markers for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) are routinely used in clinic to classify tumors into these subtypes and to provide relevant information for individualized therapeutic decision making. Hormone receptor (HR) positive tumors, defined by ER and/or PR expression, are classified as HR+HER2− and HR+HER2+, based on the HER2 expression status, and are overrepresented among luminal intrinsic subtypes. HR−HER2+ and HR−HER2− are overrepresented among HER2-enriched and basal-like subtypes, respectively. Besides chemotherapy, patients with an HR+ disease diagnosis can benefit from endocrine therapy, such as tamoxifen or aromatase inhibitors (15), whereas patients with HER2+ tumors can be treated with anti-HER2 therapy (mainly trastuzumab and pertuzumab) (16). For the HR−HER2− subtype, treatment options are limited. Currently, these patients receive systemic therapy, although targeted therapies, such as PARP and immune checkpoint inhibitors, are being evaluated in clinical trials and approved for BRCA1 and BRCA2 mutation carriers (17).

Multiple studies have suggested heterogeneity in the association between established breast cancer risk factors and tumor subtype. Family history of breast cancer in a first-degree relative is associated with increased breast cancer risk (3, 18, 19), and specific patterns of cancer family history increase the risk of particular tumor subtypes (20, 21). For example, having one first-degree relative with a history of breast cancer was shown to be associated with increased risk of HR+ subtypes, whereas having two or more was associated with increased risk of HR− disease (20, 21). However, some studies have failed to confirm these findings (3, 22–24). Among reproductive factors, early menarche, and late menopause increase the risk of developing breast cancer (3, 20, 25–27) with no evidence of heterogeneity by tumor subtype (3, 20, 26, 27). Parity is associated with reduced risk of HR+ disease (3, 19, 20, 27–33) and increased odds for developing HR− subtypes (3, 24, 27, 31, 33–35) in populations of European and African origins. Some studies have reported that older age at first full-term pregnancy was associated with increased risk of HR+ disease (27, 28, 30). Longer breastfeeding history is associated with reduced breast cancer risk with lower odds of developing HR− tumors (19, 20, 25–28, 30–34, 36). Among African Americans, prolonged lactation is associated with reduced risk of HR−, but not HR+ disease, with an increased risk of HR− disease among parous women who have not breastfed (34, 37). This observation has also been described among NHW women (32). Reports on lifestyle factors, such as alcohol intake and smoking history, have shown heterogeneity by tumor subtype, with a stronger association with HR+HER2− subtypes (3, 38).

The effects of some of the abovementioned factors are different among pre- and post-menopausal women. Controversial evidence shows that high BMI (obesity) is protective against breast cancer in premenopausal women, and conversely, it suggests that obesity increases the risk in postmenopausal women (39, 40), especially for HR+ subtypes (41–43). Other factors known to affect breast cancer risk in both groups in the same direction can present different

magnitudes of the effect by menopausal status, such as alcohol intake (44), physical activity (45, 46), and breastfeeding (47).

Previous studies have assessed the association of breast cancer risk with numerous structural, social, environmental, and genetic factors (4, 48–50); however, these studies are primarily composed of individuals of European origin. Few breast cancer studies describe patient characteristics in Latin America (26, 51–54), a region characterized by cultural and genetic heterogeneity (55–57). For example, Indigenous American genetic ancestry estimates vary across different Latin American countries, ranging between ~5% in Puerto Rico and ~80% in Peru and Bolivia (56–58). Previous studies have identified that the degree of Indigenous American genetic ancestry may modify the magnitude and direction of association with currently known breast cancer risk variants among H/L women (59) and is associated with differential lifestyle risk factors (60). Latin American cohorts with high proportions of Indigenous American ancestry are underrepresented in breast cancer research (61).

The Peruvian Genetics and Genomics of Breast Cancer Study (PEGEN-BC) is a hospital-based cohort including patients from the Instituto Nacional de Enfermedades Neoplásicas (INEN) in Lima, Peru. We have previously described the distribution of demographic, anthropometric, reproductive, lifestyle, and clinical factors for 1,312 breast cancer participants, with an emphasis on the distribution by breast tumor subtypes (62). Moreover, we reported that increasing Indigenous American ancestry is associated with higher odds of developing the HR−HER2+ subtype (62). The current report aims to provide a more complete and updated description of these variables by tumor subtype and age at diagnosis, including a total of 1,943 breast cancer patients, highlighting potential heterogeneity in the latter categories.

Methods

Study participants

The Peruvian Genetics and Genomics of Breast Cancer Study (PEGEN-BC) is a hospital-based cohort study. As of April 2022, we have recruited 1,943 participants from the INEN in Lima, Peru. Women were invited to participate if they had a diagnosis of invasive breast cancer in 2010 or later and were between 21 and 79 years of age when diagnosed. A blood sample was drawn by a certified phlebotomist at the INEN central laboratory. The present report includes analyses with a subset of 1,796 patients with available genetic ancestry estimates (63). This study was approved by the INEN and the University of California Davis Institutional Review Boards. All individuals provided written informed consent to participate.

Data collection

Each PEGEN-BC participant completed a standardized survey administered by a trained research coordinator at INEN. The survey includes questions regarding anthropometric (weight and height), demographic (place of birth and residence), lifestyle (alcohol intake and smoking history), and reproductive (menopause status, age at first pregnancy, number of full-term pregnancies, and breastfeeding history) variables, and family history of breast cancer. Weight and height were assessed by trained nurses/professionals at INEN at the time of diagnosis. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared and categorized as underweight (BMI < 18.5 kg/m ^{2}), normal (BMI ≥ 18.5 < 25 kg/m^2), overweight (BMI ≥ 25 < 30 kg/m ^{2}), and obese (BMI ≥ 30 kg/m^2). Alcohol use was assessed as the self-reported frequency of glasses of alcohol consumed per day and categorized as < 1 glass/day, > 1 glass/day, and non-drinker (never). Smoking status was classified into "ever" (current and former) and "never." If there was a history of familial breast cancer, the relative (i.e., mother, sister, and aunt) was indicated to determine cases with breast cancer family history in a first-degree relative. Clinical variables, including ER, PR, HER2, lymph node status, tumor grade, and clinical stage, were extracted from electronic records.

Genetic ancestry estimates for 1,796 PEGEN-BC participants were available from a previous study (63). Briefly, genome-wide genotype data obtained with the Affymetrix Precision Medicine Array were pruned using PLINK v.1.9 (64) [window size = 50, number of variants = 5, variance inflation factor threshold = 2] and merged with data from four reference populations from the 1000 Genomes project (65): Admixed Americans (Peru, Colombia, Mexico, Puerto Rico), Europeans (Americans with Northern and Western European Ancestry, Italy, Spain, Finland, Scotland), East Asians (China, Japan, Vietnam), and African populations (Nigeria, Kenya, Gambia, Sierra Leone). Individual continental, global genetic ancestry was estimated using ADMIXTURE (66) (unsupervised, k = 4), including 122,605 independent variants. The PEGEN-BC study includes a large proportion of patients with > 98% Indigenous American ancestry, as previously reported (62), and therefore provides a source of non-admixed reference samples for this component.

Tumoral tissues were obtained from core biopsy or freshly resected invasive breast cancers pre-treatment that were formalin-fixed and paraffin-embedded following standard protocols at INEN. Tumor subtypes were defined using immunohistochemistry (IHC) markers by a certified pathologist at INEN. HR positivity was defined at 1% or more cells showing ER and/or PR staining. HER2 positivity was defined as 3+ staining by IHC or by gene amplification detected by fluorescence *in situ* hybridization following a 2+ (borderline) IHC result. These markers were used to classify tumors as HR+HER2−, HR+HER2+, HR−HER2+, and HR−HER2−. Two independent pathologists from the University of California San Francisco reviewed the IHC slides at INEN for a subset of 52 patients. The concordance rate was 100% for ER, 87% for PR, and 85% for HER2. Most of the discordant calls for HER2 were scored as "negative" or 1+ at INEN and 2+ by the independent pathologists. Immunohistochemical subtype classification was not available for 141 samples (7%).

Statistical analysis

We performed descriptive analyses of available demographic, anthropometric, reproductive, and clinical characteristics by

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breast cancer subtype. Differences in characteristics between tumor subtypes were tested by means of one-way ANOVA for normally distributed continuous variables and Chi-squared tests for categorical variables. Age at first full-term pregnancy presented a non-normal distribution; therefore, it was $\log_2$ transformed. The correlation between genetic ancestry and continuous and categorical variables was performed using Pearson's correlation coefficient test and Point-Biserial Correlation Coefficient, respectively. Multinomial logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for the association of multiple variables and subtype-specific breast cancer. East Asian and African ancestry proportions were not included in multivariable models due to the low contribution of these components and high correlation with the Indigenous

TABLE 1 Distribution of demographic, lifestyle, and anthropometric characteristics of PEGEN-BC patients overall and by tumor subtype.

Variable	Overall	HR+HER2−	HR+HER2+	HR−HER2+	HR−HER2−	*p*-value
Number of patients, *N* (%)	1943 (100)*	945 (52.4)	337 (18.7)	232 (12.9)	288 (16.0)	
Demographic variables						
Age at diagnosis in years, mean (SD)	49.8 (11.0)	50.3 (11.1)	48.9 (10.2)	50.0 (10.9)	48.8 (12.0)	0.087
Missing, *N* (%)	7 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.34)	
Percent genetic ancestry**, mean (SD)						
Indigenous American	76.5 (16.9)	75.3 (17.4)	76.6 (16.8)	79.5 (14.78)	77.6 (16.5)	0.007
European	18.0 (12.5)	18.7 (12.9)	17.8 (12.0)	16.2 (11.36)	17.4 (12.5)	0.036
African	4.2 (7.7)	4.1 (7.6)	4.6 (8.9)	3.6 (6.26)	4.1 (7.1)	0.494
East Asian	1.4 (6.6)	1.9 (8.6)	1.0 (3.7)	0.8 (2.42)	0.9 (3.1)	0.026
Missing, *N* (%)	147 (7.6)	47 (5.0)	22 (6.5)	10 (4.3)	21 (7.3)	
Region of birth, *N* (%)						
Amazonian	145 (7.5)	69 (7.3)	22 (6.5)	18 (7.8)	23 (8.0)	0.737
Coastal	1078 (55.5)	522 (55.2)	178 (52.8)	124 (53.4)	165 (57.3)	
Mountains	708 (36.4)	346 (36.6)	137 (40.7)	88 (37.9)	98 (34.0)	
Other country***	12 (0.6)	8 (0.8)	0 (0.0)	2 (0.9)	2 (0.7)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Region of residence, *N* (%)						
Amazonian	120 (6.2)	56 (5.9)	18 (5.3)	11 (4.7)	24 (8.3)	0.138
Coastal	1530 (78.7)	757 (80.1)	264 (78.3)	174 (75.0)	216 (75.0)	
Mountains	293 (15.1)	132 (14.0)	55 (16.3)	47 (20.3)	48 (16.7)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Anthropometric and lifestyle variables						
Weight in kg, mean (SD)	64.8 (12.3)	65.2 (12.4)	64.8 (11.9)	63.6 (11.6)	64.6 (12.7)	0.350
Missing, *N* (%)	41 (2.1)	15 (1.6)	4 (1.2)	7 (3.0)	7 (2.4)	
Height in m, mean (SD)	153.3 (6.6)	153.3 (6.5)	153.7 (6.4)	152.1 (6.5)	153.4 (6.5)	0.032
Missing, *N* (%)	47 (2.4)	17 (1.8)	7 (2.1)	10 (4.3)	6 (2.1)	
BMI in kg/m^2, mean (SD)	27.54 (4.8)	27.7 (4.8)	27.4 (4.7)	27.5 (4.9)	27.4 (4.8)	0.705
Missing, *N* (%)	56 (2.9)	22 (2.3)	7 (2.1)	10 (4.3)	8 (2.8)	
BMI categorized, *N* (%)						
Underweight***	22 (1.1)	11 (1.2)	4 (1.2)	4 (1.7)	2 (0.7)	0.852
Normal	564 (29.0)	263 (27.8)	109 (32.3)	65 (28.0)	84 (29.2)	
Overweight	779 (40.1)	383 (40.5)	129 (38.3)	93 (40.1)	117 (40.6)	
Obese	522 (26.9)	266 (28.1)	88 (26.1)	60 (25.9)	77 (26.7)	

(Continued)

TABLE 1 Continued

Variable	Overall	HR+HER2−	HR+HER2+	HR−HER2+	HR−HER2−	*p*-value
Alcohol intake, *N* (%)						
< 1 glass/day	1335 (68.7)	655 (69.3)	223 (66.2)	159 (68.5)	186 (64.6)	0.603
> 1 glass/day	144 (7.4)	66 (7.0)	25 (7.4)	19 (8.2)	26 (9.0)	
Never	446 (23.0)	213 (22.5)	88 (26.1)	51 (22.0)	75 (26.0)	
Missing	18 (0.9)	11 (1.2)	1 (0.3)	3 (1.3)	1 (0.3)	
Smoking history, *N* (%)						
Never	1382 (71.1)	655 (69.3)	242 (71.8)	179 (77.2)	212 (73.6)	0.087
Ever	543 (27.9)	280 (29.6)	94 (27.9)	50 (21.6)	75 (26.0)	
Missing	18 (0.9)	10 (1.1)	1 (0.3)	3 (1.3)	1 (0.3)	

*Immunohistochemical subtype classification was not available for 141 samples (7%). **Estimates of individual continental ancestry were unavailable for 147 patients (7.6%). ***Category not included in the Chi-square test due to small sample size. "Missing" categories were excluded from tests.

American/European axis of ancestry variation. *P*-values (*P*) <= 0.05 were considered statistically significant. All analyses were conducted in R v.3.6.0 (67).

Results

Demographics, anthropometrics, and lifestyle factors in the PEGEN-BC study by tumor subtype

The most common breast cancer subtype among PEGEN-BC study participants was HR+HER2− (52.4%), followed by HR+HER2+ (18.7%), HR−HER2− (16.0%), and HR−HER2+ (12.9%) (Table 1). The average age at diagnosis was 49.8 years (*SD* = 11), and differences by tumor subtype were not statistically significant (p = 0.087). PEGEN-BC study patients included individuals born in the three main biogeographic regions of Peru (Figure 1): The Coastal (55.5%), Mountainous (36.4%), and Amazonian (7.5%) regions. Less than 1% of the patients were born in another country (mainly Venezuela). These groups did not show statistically significant differences in their distribution by tumor subtype (Table 1). Most patients resided in the Coastal region (7%), and differences in the proportion of patients who resided in each biogeographic area by tumor subtype category were not statistically significant (Table 1).

Estimates of individual continental genetic ancestry were available for 1,796 patients. Average Indigenous American ancestry among patients was 76.5%, followed by 18.0% European, 4.2% African, and 1.4% East Asian (Table 1). Furthermore, 92% of PEGEN-BC study participants had > 50% of Indigenous American ancestry, 25% at least 90%, and 12% at least 95% of Indigenous American ancestry (Figure 2A). Seven patients (0.4%) had more than 50% of East Asian ancestry, and eight (0.4%) had more than 50% African ancestry. Principal components analysis showed that the PEGEN-BC patients defined the Indigenous American cluster along principal component (PC) 1 when compared against 1000 Genomes Project reference populations (Figures 2B, C), reflecting the high degree of Indigenous American genetic ancestry that characterizes this cohort.

We found that the average Indigenous American ancestry proportion of participants was different across tumor subtypes. Individuals diagnosed with HR−HER2+ tumors showed the highest average proportion of Indigenous American ancestry (79.5%, *SD* = 15) (Table 1).

FIGURE 1
Biogeographical regions of Peru. Red star shows the location of INEN. This figure was created using the ggmap, maps, and mapdata R packages.

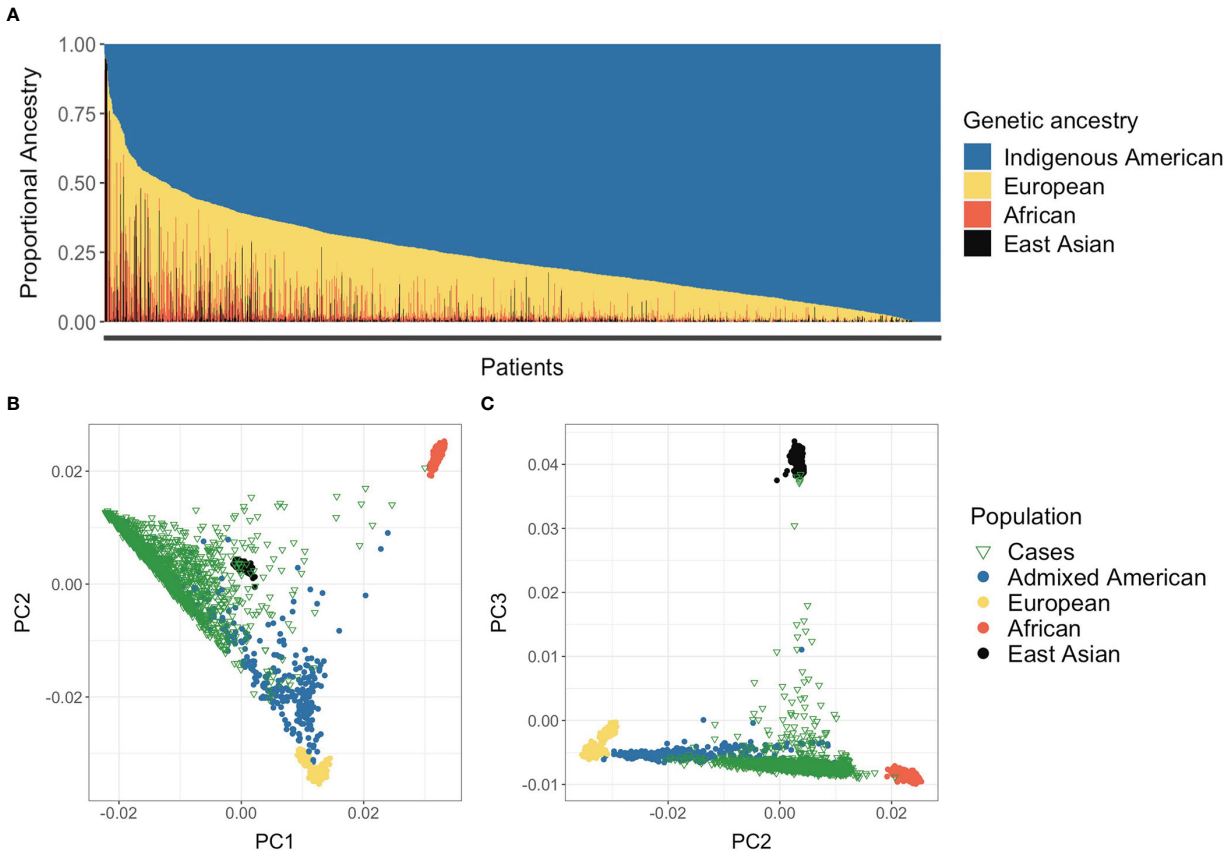

FIGURE 2
Population genetic structure of the PEGEN-BC study participants. **(A)** ADMIXTURE continental ancestry estimates obtained in unsupervised analysis, assuming $K = 4$. **(B, C)** Principal components analysis (PCA) including breast cancer patients and 1000 Genomes Project individuals. The first three principal components are shown.

The average height of patients was 153.3 cm (*SD* = 6.6), with lower average height among patients diagnosed with HR−HER2+ tumors compared with all other subtypes (152.1 *vs.* ~153.6 cm, $p = 0.032$). There were no statistically significant differences in weight or BMI by tumor subtype, with a large overall proportion of patients being overweight (40.1%) (Table 1).

Most PEGEN-BC patients (68.7%) reported low levels of alcohol consumption (< 1 glass/day), whereas 7.4% reported consuming more than one glass per day. Moreover, 27.9% of participants reported being a current or past smoker. There was no statistically significant association between alcohol consumption, smoking history, and tumor subtype (Table 1).

Demographic, anthropometric, and lifestyle variables that did not show statistically significant differences by tumor subtypes did not show significant differences by HR status either (Supplementary Table S1).

Reproductive variables by tumor subtype

The average age at menarche among PEGEN-BC patients was 12.9 years (*SD* = 1.7), the average age at first full-term pregnancy was 23.2 years (*SD* = 5.7), and the average number of full-term pregnancies was 2.42 (*SD* = 1.8). Most study participants reported having had at least one child (83.5%), and 80% of parous women had at least two children (Table 2). The frequency of parous women and number of births differed by tumor subtype, being higher among HR− tumors ($p < 0.001$) (Table 2).

Breastfeeding was a common practice among parous women (96.3%), and we did not observe the differences in the proportion of women who breastfed their children by tumor subtype category (Table 2).

More than 85% of women reported being menopausal at recruitment. Patients with HR+HER2− tumors were more likely to report being menopausal than patients with other tumor subtypes ($p = 0.016$). However, since many of these patients had induced menopause due to treatment, we did not consider this variable in subsequent multivariate analyses and stratified by age at diagnosis instead.

All these variables remained significant in analyses stratified by HR status (Supplementary Table S2). In addition, age at first full-term pregnancy showed a higher average age among patients diagnosed with HR+ disease compared with HR− (23.4 *vs.* 22.7, $p = 0.043$, Supplementary Table S2).

Clinical characteristics by tumor subtype

Overall, approximately 8% of PEGEN-BC study patients reported a family history of breast cancer in a first-degree relative (Table 3).

TABLE 2 Distribution of reproductive variables overall and by tumor subtype.

Variable	Overall	HR+HER2−	HR+HER2+	HR-HER2+	HR−HER2−	*p*-value
Number of patients, *N* (%)	1943 (100)	945 (52.4)	337 (18.7)	232 (12.9)	288 (16.0)	
Age at menarche in years, mean (SD)	12.9 (1.7)	12.9 (1.8)	12.9 (1.7)	13.1 (1.7)	13.0 (1.7)	0.364
Missing, *N* (%)	34 (1.8)	17 (1.8)	3 (0.9)	7 (3.0)	2 (0.7)	
Parous, yes, *N* (%)	1623 (83.5)	765 (81.0)	273 (81.0)	207 (89.2)	263 (91.3)	< 0.001
Missing, *N* (%)	63 (3.2)	32 (3.4)	10 (3.0)	9 (3.9)	4 (1.4)	
Age at first full-term pregnancy in years, mean (SD)	23.2 (5.7)	23.5 (5.8)	23.0 (5.3)	22.9 (6.1)	22.5 (5.4)	0.095
Missing*, *N* (%)	72 (4.4)	40 (5.2)	7 (2.6)	13 (6.3)	6 (2.3)	
Parity, mean (SD)	2.4 (1.8)	2.3 (1.8)	2.3 (1.9)	2.7 (1.8)	2.7 (1.7)	0.002
Missing*, *N* (%)	6 (0.4)	4 (0.5)	1 (0.4)	1 (0.5)	0 (0.0)	
Parity categories, *N* (%)						
No children	275 (14.2)	156 (16.5)	57 (16.9)	19 (8.2)	22 (7.6)	< 0.001
1 child	316 (16.3)	162 (17.1)	47 (13.9)	38 (16.4)	46 (16.0)	
2–3 children	888 (45.7)	410 (43.4)	161 (47.8)	105 (45.3)	148 (51.4)	
>3 children	413 (21.3)	189 (20.0)	64 (19.0)	63 (27.2)	69 (24.0)	
Missing, *N* (%)	51 (2.6)	28 (3.0)	8 (2.4)	7 (3.0)	3 (1.0)	
Breastfed*, yes, *N* (%)	1563 (96.3)	736 (96.2)	264 (96.7)	200 (96.6)	255 (97.0)	0.967
Missing*, *N* (%)	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Postmenopausal, *N* (%)	1681 (86.5)	839 (88.8)	287 (85.2)	198 (85.3)	240 (83.3)	0.016
Missing, *N* (%)	23 (1.2)	12 (1.3)	1 (0.3)	5 (2.2)	1 (0.3)	

*Proportion in relation to the total number of parous women. Missing categories were not included in the analysis.

Differences in breast cancer family history by breast cancer subtype were not statistically significant.

More than 90% of patients were diagnosed with Grades 2 and 3 tumors (Table 3). Patients with HR+HER2− tumors were more likely to be diagnosed with Grades 1 and 2 disease, whereas those with HR−HER2+ and HR−HER2− tumors were more likely to be high grade (Table 3). Most PEGEN-BC participants were diagnosed with stage II or III disease, with a larger number of stage I and II diagnoses among HR+HER2− patients than those with other subtypes (Table 3). Concordant with the distribution of tumor stage, we observed a high proportion of positive lymph node status among patients overall (64.3%), with a statistically significantly higher proportion of lymph node positivity among patients with HR−HER2+ tumors compared with those with other disease subtypes (78.2% *vs.* ~67%) (Table 3). Distribution of these variables by HR status is shown in Supplementary Table S2.

Distribution of patient characteristics by age at diagnosis

We compared the distribution of anthropometric, demographic, reproductive, clinical, and lifestyle risk variables between patients diagnosed before the age of 50 years (N = 981) and at 50 years or older (N = 955). Compared with patients diagnosed at 50 years or older, younger patients had higher average Indigenous American ancestry (78.6 *vs.* 74.3, $p < 0.001$); they were more likely to reside in the Mountainous region (17.3% *vs.* 12.8%, $p = 0.015$), and they were 1.4 cm taller ($p < 0.001$) and had lower prevalence of obesity (25.4% *vs.* 30.0%, $p = 0.036$) (Table 4). Additionally, there was a higher proportion of older patients with more than three children compared with the younger group (31% *vs.* 13%, $p < 0.001$), and a larger proportion of younger patients reported breastfeeding their children (98% *vs.* 95%, $p = 0.001$) (Table 5). Regarding clinical characteristics, younger patients reported lower family history of breast cancer in a first-degree relative (6.5% *vs.* 9.5%, $p = 0.02$) and presented with more advanced disease (44% diagnosed at stage III compared with 42%, $p = 0.017$) (Table 5). We did not observe statistically significant differences in subtype distribution between both age categories.

Additional stratified analyses comparing demographic, anthropometric, reproductive, and clinical factors by tumor subtype in the two different age groups are included as Supplementary Materials (Supplementary Tables S3 and S4). As additional stratification reduced the number of observations per category, we suggest taking these results with caution.

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TABLE 3 Distribution of clinical characteristics of PEGEN-BC study participants overall and by tumor subtype.

Variable	Overall	HR+HER2−	HR+HER2+	HR−HER2+	HR−HER2−	*p*-value
Number of patients, *N* (%)	1943 (100)*	945 (52.4)	337 (18.7)	232 (12.9)	288 (16.0)	
Positive family history of breast cancer**, *N* (%)	149 (7.7)	84 (8.9)	25 (7.4)	9 (3.9)	23 (8.0)	0.091
Missing	61 (3.1)	19 (2.0)	5 (1.5)	7 (3.0)	2 (0.7)	
Grade, *N* (%)						
1	72 (3.7)	58 (6.1)	6 (1.8)	0 (0.0)	4 (1.4)	< 0.001
2	803 (41.3)	550 (58.2)	117 (34.7)	36 (15.5)	37 (12.8)	
3	1005 (51.7)	317 (33.5)	209 (62.0)	192 (82.8)	239 (83.0)	
Missing	63 (3.2)	20 (2.1)	5 (1.5)	4 (1.7)	8 (2.8)	
Stage, *N* (%)						
I	122 (6.3)	67 (7.1)	18 (5.3)	7 (3.0)	23 (8.0)	< 0.001
II	840 (43.2)	480 (50.8)	134 (39.8)	70 (30.2)	109 (37.8)	
III	798 (41.1)	332 (35.1)	158 (46.9)	137 (59.1)	139 (48.3)	
IV	105 (5.4)	49 (5.2)	19 (5.6)	16 (6.9)	12 (4.2)	
Missing	78 (4.0)	17 (1.8)	8 (2.4)	2 (0.9)	5 (1.7)	
Positive lymph node status, *N* (%)	1249 (64.3)	585 (61.9)	227 (67.4)	176 (75.9)	177 (61.5)	0.002
Missing	90 (4.6)	43 (4.6)	9 (2.7)	7 (3.0)	21 (7.3)	

*Immunohistochemical subtype classification was not available for 141 samples (7%). **In a first-degree relative.

TABLE 4 Distribution of demographic and anthropometric variables by age at diagnosis categories.

	Age at diagnosis		
Variable	< 50 years old	>= 50 years old	*p*-value
Number of patients, *N* (%)	981 (50.5)	955 (49.2)	
Demographic variables			
Age at diagnosis in years, mean (SD)	41.0 (5.9)	58.8 (7.0)	–
Missing, *N* (%)	0 (%)	0 (%)	
Percent genetic ancestry*, mean (SD)			
Indigenous American	78.6 (15.1)	74.3 (18.3)	< 0.001
European	16.84 (11.5)	19.1 (13.3)	< 0.001
African	3.6 (6.6)	4.7 (8.6)	0.004
East Asian	1.0 (4.2)	1.9 (8.4)	0.003
Missing, *N* (%)	72 (7.3%)	73 (7.6%)	
Region of birth, *N* (%)			
Amazonian	71 (7.2)	73 (7.6)	0.904
Coastal	548 (55.9)	526 (55.1)	
Mountains	355 (36.2)	351 (36.8)	
Other country**	7 (0.7)	5 (0.5)	
Missing, *N* (%)	0 (%)	0 (%)	
Region of residence, *N* (%)			
Amazonian	63 (6.4)	57 (6.0)	0.015
Coastal	748 (76.2)	776 (81.3)	

(Continued)

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TABLE 4 Continued

	Age at diagnosis		
Variable	< 50 years old	>= 50 years old	*p*-value
Mountains	170 (17.3)	122 (12.8)	
Missing, *N* (%)	0 (%)	0 (%)	
Anthropometric and lifestyle variables			
Weight in kg, mean (SD)	64.8 (12.4)	64.8 (12.3)	0.983
Missing, *N* (%)	17 (1.7)	24 (2.5)	
Height in cm, mean (SD)	154.0 (6.3)	152.6 (6.7)	< 0.001
Missing, *N* (%)	18 (1.8)	29 (3.0)	
BMI in kg/m^2, mean (SD)	27.3 (4.6)	27.8 (4.9)	0.009
Missing, *N* (%)	24 (2.4)	32 (3.3)	
BMI categorized, *N* (%)			
Underweight ***	6 (0.6)	16 (1.7)	0.036
Normal	305 (31.9)	255 (27.6)	
Overweight	403 (42.1)	375 (40.6)	
Obese	243 (25.4)	277 (30.0)	
Alcohol intake, *N* (%)			
< 1 glass/day	664 (67.7)	665 (69.6)	0.161
> 1 glass/day	84 (8.6)	60 (6.3)	
Never	225 (22.9)	220 (23.0)	
Missing, *N* (%)	8 (0.8)	10 (1.0)	
Smoking history, *N* (%)			
Never	704 (71.8)	674 (70.6)	0.705
Ever	270 (27.5)	270 (28.3)	
Missing, *N* (%)	7 (0.7)	11 (1.2)	

*Estimates of individual continental ancestry were available for 92.6% of patients diagnosed before 50 and 92.3% for patients diagnosed at 50 or above. **Category not included in the Chi-square test due to small sample size.

TABLE 5 Distribution of reproductive and clinical variables by age at diagnosis categories.

	Age at diagnosis		
Variable	< 50 years old	>= 50 years old	*p*-value
Number of patients, *N* (%)	981 (50.5)	955 (49.2)	
Reproductive variables			
Age at menarche in years, mean (SD)	12.9 (1.7)	13.0 (1.7)	0.849
Missing, *N* (%)	15 (1.5)	19 (2.0)	
Parous, yes, *N* (%)	815 (85.9)	802 (86.7)	0.652
Missing, *N* (%)	32 (3.2)	30 (3.1)	
Age at first full-term pregnancy in years, mean (SD)	23.19 (5.53)	23.10 (5.83)	0.747
Missing*, *N* (%)	39 (4.8)	33 (4.1)	
Parity, mean (SD)	2.0 (1.34)	2.8 (2.11)	< 0.001
Missing*, *N* (%)	4 (0.4)	2 (0.2)	

(Continued)

TABLE 5 Continued

Variable	Age at diagnosis		
	< 50 years old	>= 50 years old	*p*-value
Parity categories, *N* (%)			
No children	146 (14.9)	128 (13.4)	< 0.001
1 child	190 (19.4)	125 (13.1)	
2–3 children	499 (50.9)	385 (40.3)	
> 3 children	122 (12.4)	290 (30.4)	
Missing, *N* (%)	24 (2.4)	27 (2.8)	
Breastfed*, yes, *N* (%)	798 (98.0)	759 (94.6)	0.001
Missing*, *N* (%)	1 (0.1)	1 (0.1)	
Clinical characteristics			
Positive family history of breast cancer**, *N* (%)	62 (6.3)	87 (9.1)	0.020
Missing, *N* (%)	23 (2.3)	38 (4.0)	
Tumor grade, *N* (%)			
1	37 (3.8)	35 (3.7)	0.421
2	393 (40.1)	410 (42.9)	
3	523 (53.3)	482 (50.5)	
Missing, *N* (%)	28 (2.9)	28 (2.9)	
Positive lymph node status, *N* (%)	636 (64.8)	610 (63.9)	0.460
Missing, *N* (%)	49 (5.0)	38 (4.0)	
Stage, *N* (%)			
I	45 (4.6)	77 (8.1)	0.017
II	428 (43.6)	410 (42.9)	
III	417 (42.5)	381 (39.9)	
IV	53 (5.4)	50 (5.2)	
Missing, *N* (%)	38 (3.9)	37 (3.9)	
Tumor subtype, *N* (%)			
HR+HER2–	476 (48.5)	468 (49.0)	0.328
HR+HER2+	178 (18.1)	159 (16.6)	
HR–HER2+	108 (11.0)	124 (13.0)	
HR–HER2–	155 (15.8)	132 (13.8)	
Missing, *N* (%)	64 (6.5)	72 (7.5)	

*Proportion in relation to the total number of parous women. **In a first-degree relative.

Correlation between Indigenous American genetic ancestry and other patient and tumor characteristics

We assessed the correlation between Indigenous American ancestry and patient and tumor characteristics to better understand the observed patterns in ancestry distribution and those factors by tumor subtype in the PEGEN-BC study. We observed an inverse correlation between Indigenous American ancestry and age at diagnosis ($r = -0.15$, $p < 0.001$), weight ($r = -0.11$, $p < 0.001$), height ($r = -0.25$, $p < 0.001$), age at first full-term pregnancy ($r = -0.08$, $p = 0.002$), family history of breast cancer in a first-degree relative ($r = -0.12$, $p < 0.001$), smoking history ($r = -0.11$, $p < 0.001$), HR+ status ($r = -0.06$, $p = 0.012$) and a positive correlation with age at menarche ($r = 0.06$, $p = 0.017$) and HER2+ status ($r = 0.053$, $p = 0.029$).

Multivariable analyses testing the association between demographic, lifestyle factors, and breast cancer subtype

Variables that showed statistically significant associations at the 10% level with tumor subtype in the univariate analyses (Tables 1–3)

were included in a multivariate model, using HR+HER2− as reference (Table 6). Indigenous American ancestry remained associated with HR−HER2+ subtype (OR per 25% increment in ancestry = 1.38, 95% CI = 1.06–1.79, $p = 0.02$). Smoking history and height were no longer statistically significantly associated with subtype. Parous women were more likely to be diagnosed with HR−HER2+ (OR = 2.72, 95% CI = 1.53–4.83, $p < 0.001$) and HR-HER2- (OR = 2.47, 95% CI = 1.51–4.04, $p < 0.001$) disease compared with the HR+HER2− subtype. Family history of breast cancer in a first-degree relative was not included as a covariate in the multivariate model because the number of patients that reported family history of breast cancer in a first-degree relative was relatively small and rendered unstable estimates when included. We tested models excluding patients with a family history of breast cancer, and results were similar to those using the full dataset (Table 6).

Indigenous American ancestry, region of residence, height, BMI, breastfeeding history, number of full-term pregnancies, and family history of breast cancer in a first-degree relative showed statistically significant associations at the 10% level with age at diagnosis categories. These variables were included in a multivariate model using age at diagnosis < 50 as reference (Table 7). We found that increasing Indigenous American ancestry and increasing height were associated with reduced odds of being diagnosed at 50 years or older (OR = 0.63, 95% CI = 0.53–0.75, $p < 0.001$ and OR = 0.96, 95% CI = 0.95–0.98, $p < 0.001$, respectively). Patients that resided in the Mountainous region had reduced odds of being diagnosed at 50 years of age or older compared with those in the Coastal region (OR = 0.63, 95% CI = 056–0.9, $p = 0.004$). Breastfeeding was associated with lower odds of being diagnosed at 50 years of age or older (OR = 0.35, 95% CI = 0.2–0.7, $p = 0.001$). Compared with nulliparous women, giving birth to at least one child increased the odds of being diagnosed at an older age (OR = 1.55, 95% CI = 0.2–0.7, $p < 0.001$). Increasing BMI was no longer associated with age at diagnosis (Table 7).

TABLE 6 Multivariate multinomial logistic regression models testing the association between demographic and lifestyle variables and breast cancer subtype (HR+HER2− as reference).

		All patients*			Patients without FamHist		
Subtype	Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
HR+HER2+	**Indigenous American ancestry** (Every 25% increment)	1.09	0.89–1.34	0.402	1.14	0.91–1.41	0.255
	Age at diagnosis (Every 5-year increment)	0.99	0.98–1.00	0.062	0.99	0.98–1.00	0.188
	Height (Every 1-cm increment)	1.01	0.99–1.03	0.257	1.01	0.99–1.04	0.196
	Smoking history (Ever *vs.* never [reference])	0.81	0.60–1.10	0.178	0.84	0.61–1.15	0.267
	Parous (Reference: nulliparous)	1.20	0.83–1.74	0.335	1.43	0.96–2.14	0.082
HR−HER2+	**Indigenous American ancestry** (Every 25% increment)	1.38	1.06–1.79	0.017	1.37	1.05–1.80	0.022
	Age at diagnosis (Every 5-year increment)	0.99	0.98–1.01	0.455	1.00	0.98–1.01	0.717
	Height (Every 1-cm increment)	0.98	0.96–1.01	0.166	0.99	0.96–1.01	0.266
	Smoking history (Ever *vs.* never [reference])	0.75	0.52–1.08	0.122	0.74	0.51–1.08	0.118
	Parous (Reference: nulliparous)	2.72	1.53–4.83	< 0.001	2.60	1.46–4.64	0.001
HR−HER2−	**Indigenous American ancestry** (Every 25% increment)	1.17	0.93–1.46	0.177	1.25	0.99–1.59	0.065
	Age at diagnosis (Every 5-year increment)	0.99	0.98–1.00	0.100	0.99	0.98–1.01	0.467
	Height (Every 1-cm increment)	1.01	0.99–1.03	0.446	1.02	0.99–1.04	0.205
	Smoking history (Ever *vs.* never [reference])	0.78	0.56–1.08	0.133	0.72	0.51–1.01	0.061
	Parous (Reference: nulliparous)	2.47	1.51–4.04	< 0.001	2.40	1.44–3.99	0.001

*Only samples for which genetic ancestry was available (n = 1,796) were included in this analysis. FamHist, family history of breast cancer in a first-degree relative (n = 1,628).

TABLE 7 Multivariate logistic regression model testing the association between demographic and lifestyle variables and age at diagnosis (< 50 [reference] *vs.* >= 50).

Variable	OR*	95% CI	*p*-value
Indigenous American ancestry (Every 25% increment)	0.63	0.53–0.75	< 0.001
Height (Every 1-cm increment)	0.96	0.95–0.98	< 0.001
Region of residence (Reference: Coastal region) Amazonian region Mountainous region	 0.68 0.63	 0.43–1.07 0.46–0.86	 0.100 0.004
BMI (Every 1 kg/m2 increment)	1.02	1–1.05	0.080
Parity (Per each additional child)	1.55	1.43–1.69	< 0.001
Breastfed (Yes *vs.* no [reference])	0.35	0.20–0.70	0.001
Family history of breast cancer** (Yes *vs.* no [reference])	1.20	0.78–1.84	0.410

Only samples for which genetic ancestry was available (909 patients < 50 and 881 >= 50 years) were included in this analysis. *Patients diagnosed < 50 years old (reference) vs. >= 50 years. **In a first-degree relative.

Discussion

In the present report, we aimed to provide a more complete description of the distribution of anthropometric, demographic, clinical, and known breast cancer–associated risk factors among Peruvian women that are part of The Peruvian Genetics and Genomics of Breast Cancer Study (PEGEN-BC). This work constitutes an update of a previously reported study, including a larger number of recruited patients and extending analyses to describe the distribution of patient characteristics not only by tumor subtype but also by age at diagnosis (62).

Being a hospital-based cohort, the PEGEN-BC study included a large proportion of women who resided in the Coastal region, where the INEN main hospital is located (Figure 1). Despite this bias in terms of residential representation, when looking at place of birth, the proportion of the cohort's patients from the Coastal region followed closely that of the Peruvian population (58.0% Peru *vs.* 55.5% of cohort patients). The study has an overrepresentation of patients born in the Mountainous region (28.1% Peru *vs.* 36.4% of cohort patients) (68) and an underrepresentation of patients born in the Amazonian region (13.9% Peru *vs.* 7.5% of cohort patients) (68). The proportion of patients within each geographical region is consistent with what has been reported in two studies describing mortality of breast cancer (69) and incidence of triple-negative breast cancer tumors in Peruvian women (70).

A large proportion of patients were overweight/obese (67%), and the prevalence of exposure to alcohol and tobacco was higher than what has been previously reported for Peruvian women (71, 72). The average Indigenous American ancestry among the PEGEN-BC patients is 76.5%, which is higher than the average ancestry proportion of women in other breast cancer studies, including Latin America and U.S. Latinas (12, 51, 60, 73–89). In addition, the average height in our cohort was consistent with what has been reported in the literature for the Peruvian population (90) and with the known inverse correlation with Indigenous American ancestry (91). Overall, some reproductive variables showed a similar trend to what has been reported, including a similar age at menarche (92) and a high breastfeeding rate (93). The number of full-term pregnancies reported here (average of 2.8 children) was more closely related to what has been observed in rural areas of Peru (2.5) compared with urban areas (1.4) (94).

The distribution of tumor subtypes is similar to what has been previously described in other Latin American countries (95), with differences being partially explained by the inclusion of KI-67 expression and tumor grade for subtype classification (95), as indicated by the 2013 St. Gallen consensus (96). This classification criterion was not used in this report since KI-67 was not available for more than 20% of patients, and parameters for subtype determination based on this marker tend to be unstable across populations and studies (97). A study describing patient and tumor characteristics from Peruvian breast cancer patients at INEN diagnosed between 2000 and 2002 (80) (PEGEN-BC patients were recruited if diagnosed in 2010 or later) reported a lower proportion of HR+ tumors compared with PEGEN-BC (62.5% *vs.* 71.1%). This difference is likely to be explained by the higher positivity percentage cutoff value for HR+ status used in the previous report (10%, compared with 1% in PEGEN-BC), increasing the proportion of HR+ tumors in our cohort. Other characteristics, such as age at diagnosis and stage, presented similar distribution to the PEGEN-BC study cohort.

We found statistically significant differences by tumor subtype for Indigenous American genetic ancestry and height. In addition, we observed suggestive associations for age at diagnosis, family history of breast cancer in a first-degree relative and tobacco exposure. Differences were mostly driven by the HR–HER2+ subtype. Among patients with HR–HER2+ disease, we observed that the average height was lower compared with patients diagnosed with other tumor subtypes and was less likely to report smoking or a positive family history of breast cancer in a first-degree relative. Even though

subtype-specific associations have been reported for these variables in other populations (38, 98–101), results in the Peruvian cohort showed that of all the above variables Indigenous American ancestry proportion was the only one that was differentially distributed by tumor subtype in multivariable models.

We did not find statistically significant differences for age at menarche by tumor subtype. Some studies have shown consistent associations between age at menarche and reduced risk of HR+HER2− breast cancer (3, 19, 20). One multicenter study did not find subtype-specific associations (27), consistent with our study. The PRECAMA Study, a Latin American population-based case-control study of premenopausal breast cancer, reported reduced odds for HR− tumors among women who were > 12 years old at menarche, compared with those younger at menarche (26, 51). In the current study, we did not find a statistically significant difference in average age at menarche by tumor subtype despite the observed correlation between the former and Indigenous American ancestry proportion.

We observed a higher frequency of parous women diagnosed with HR− subtypes compared with HR+. Parity (ever *vs.* never) has been associated with a higher risk of HR−HER2− subtypes, especially among women of African origin (33–35). Higher number of full-term pregnancies has been associated with reduced breast cancer risk (19, 31), with lower odds of developing HR+ tumors (3, 19, 20, 24–27, 29–35). We found significant differences in number of births by subtype, being higher among HR− subtypes compared with HR+ (2.7 compared with 2.3, respectively). Results suggested a larger proportion of women with > 3 children among those with HR− disease subtypes. This observation was consistent with studies in African American women reporting a higher number of reported full-term pregnancies among women with HR− disease (33). Studies that have tested the association between age at first full-term pregnancy and subtype-specific risk have shown a decreased risk of developing HR+HER2− tumors with unclear associations for other subtypes (25, 27, 31). In African American cohorts, limited breastfeeding among parous women is associated with an increased risk for HR−HER2− subtypes (34). The current study does not include detailed pregnancy and lactation history for the patients. As a result, we could not assess the association between time to breastfeeding cessation and cumulative time of breastfeeding and HR− subtypes.

There were statistically significant differences in the prevalence of demographic, anthropometric, and reproductive factors by age at diagnosis categories. The multivariate analysis showed that these variables are independently associated with age at diagnosis. Moreover, the differences in BMI by age at diagnosis were concordant with what is known about pre- and post-menopausal–specific disease risk factors (39–43). It must be considered that the observed differences in parity and height by age at diagnosis could be due to the correlation between age and the former (i.e., number of children and height are positively correlated with age) and not to an association between those variables and pre- *versus* post-menopausal disease.

The observed association between tumor subtype and Indigenous American ancestry could be due to a multiplicity of factors that we might not have collected information on in the PEGEN-BC study. For example, the study did not obtain information on the level of education or socioeconomic status of participants; both variables were previously shown to be associated with Indigenous American ancestry) among U.S. Latinas and Mexican women (76, 102, 103). Socioeconomic status can also impact screening, which in turn can affect tumor subtype distribution and mortality rates. Reports showed that less than 20% of Peruvian women 40–59 years of age have had a mammography, with vast differences according to socioeconomic status, educational level, health insurance, and region of residence (104, 105). Plan Esperanza, launched in 2012, has aimed to provide universal cancer screening and decentralize oncological health care across Peru, focusing on underserved commuties (106).

The PEGEN-BC study had some additional limitations. First, since menopause can be induced by treatment, most of the PEGEN-BC participants were postmenopausal at the time of the interview (86%). Therefore, we did not perform stratification by menopausal status and used age at diagnosis (< 50 *vs.* >= 50) instead to differentiate early onset *versus* late onset disease, as it has been widely used in epidemiological studies (107, 108). Even though menopausal status and age at diagnosis are highly correlated, studies have shown that age at diagnosis is a driver for breast cancer heterogeneity, acting as a confounder in analyses stratified by menopausal status (109). For this reason, the use of age as a proxy for menopausal status should be taken with caution. The second limitation concerns the relatively low variability of some of the assessed factors among PEGEN-BC study participants. For example, the assessment of the association between breastfeeding and the number of births and tumor subtype was hampered by the low prevalence of women without children and of women with children who did not breastfeed them. Additionally, we described the distribution of multiple factors across tumor subtypes, which provide evidence of heterogeneity; however, future case-control design studies should further explore subtype-specific breast cancer risk. Finally, average East Asian and African genetic ancestry components showed differences by subtypes in the univariate analyses. However, since ancestry estimates are correlated, and the proportions of East Asian and African genetic ancestries were relatively low as to provide reliable estimates, we focused the current description on the Indigenous American ancestry, which is the dominant component in Peruvians.

In summary, results confirmed the previously reported higher average Indigenous American ancestry among patients with HR−HER2+ breast cancer in this larger sample of PEGEN-BC study participants. Moreover, differences in tumor subtype by age at diagnosis were apparent and concordant with what is known about pre- and post-menopausal–specific disease associated risk factors. Larger studies are needed to understand the consistently observed association between ancestry, age of onset, and disease subtypes, considering the contribution of screening and treatment, to develop population-appropriate predictive models and targeted outreach and prevention campaigns.

Data availability statement

All 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 University of California Davis Institutional Review Boards and the Instituto Nacional de Enfermedades Neoplásicas (INEN). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LF= Conceptualization, Methodology, Investigation, Formal Analysis, Writing- Review and editing, Supervision, Project administration, and Funding acquisition. VZ: Methodology, Investigation, Formal Analysis, Writing- Original Draft, Software, Data curation, and Visualization. TV= Conceptualization, Resources, Project administration at INEN. SC-Z= Resources, Project administration at INEN. JN-V= Investigation, Data curation. CC, GV, MC, JA, HG, HF, RL-P, JC, SN, KR, JV, LM, MG-N= Conducted patient recruitment investigation process. All authors contributed to the article and approved the submitted version.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.938042/full#supplementary-material

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