frontiers | Research Topics

The impact of specific environmental exposures on breast, lung, and colon cancer: advancing public health strategies for enhanced outcomes

Edited by
Chitra Thakur, Fei Chen and Uttara Saran

Published in
Frontiers in Public Health

ISSN 1664-8714
ISBN 978-2-8325-6050-1
DOI 10.3389/978-2-8325-6050-1

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

The impact of specific environmental exposures on breast, lung, and colon cancer: advancing public health strategies for enhanced outcomes

Topic editors

Chitra Thakur — Stony Brook University, United States

Fei Chen — Stony Brook University, United States

Uttara Saran — University of Texas MD Anderson Cancer Center, United States

Citation

Thakur, C., Chen, F., Saran, U., eds. (2025). *The impact of specific environmental exposures on breast, lung, and colon cancer: advancing public health strategies for enhanced outcomes*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-6050-1

Table of contents

frontiers | Frontiers in Public Health

TYPE Editorial
PUBLISHED 14 February 2025
DOI 10.3389/fpubh.2025.1483915

OPEN ACCESS

EDITED AND REVIEWED BY
Curt DellaValle,
National Cancer Institute (NIH), United States

*CORRESPONDENCE
Uttara Saran
usaran@mdanderson.org

RECEIVED 20 August 2024
ACCEPTED 15 January 2025
PUBLISHED 14 February 2025

CITATION
Thakur C, Saran U and Chen F (2025) Editorial: The impact of specific environmental exposures on breast, lung, and colon cancer: advancing public health strategies for enhanced outcomes.
Front. Public Health 13:1483915.
doi: 10.3389/fpubh.2025.1483915

Editorial: The impact of specific environmental exposures on breast, lung, and colon cancer: advancing public health strategies for enhanced outcomes

Chitra Thakur[1], Uttara Saran[2]* and Fei Chen[1]

[1]Stony Brook Cancer Center and Department of Pathology, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, United States, [2]Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

KEYWORDS

environmental carcinogens, breast cancer, lung cancer, colon cancer, public health strategies, cancer risk

Editorial on the Research Topic
The impact of specific environmental exposures on breast, lung, and colon cancer: advancing public health strategies for enhanced outcomes

Cancer remains one of the most formidable public health challenges, with breast, lung, and colon cancer being the most prevalent and deadly cancer types worldwide (1, 2). It has become increasingly clear, that aside from genetic disposition, lifestyle choices and environmental factors have a profound impact on increasing an individual's risk of developing cancer (3–6). Exposure to harmful environmental agents—ranging from air pollutants to toxic chemicals—significantly influences cancer incidence, particularly in vulnerable populations (7). To effectively combat these cancers and reduce disparities among patients/survivors, public health strategies must be refined to address environmental risks, improve early detection, and ensure equitable access to care. This Research Topic focuses on advancing our understanding of the specific environmental exposures implicated in breast, lung, and colon cancer, primarily focusing on informing and advancing public health strategies. By exploring breakthrough information related to these cancers, we seek to uncover novel insights into the associations between these environmental exposures and their impact on carcinogenesis.

The relationship between environmental risk factors and cancer incidence is well-documented, yet it often lacks visibility in public discourse. Carcinogenic substances like tobacco, industrial pollutants, etc. are known to increase cancer incidence, particularly for lung, breast, and colon cancers. For example, prolonged exposure to air pollutants, such as particulate matter, has been directly linked to an increased incidence of lung cancer (8). Similarly, chemicals found in pesticides and plastics have been associated with breast cancer, while environmental influences on diet, such as the availability of processed foods, contribute to the incidence of colon cancer (9–11). In this Research Topic, several

studies from various parts of the world as well as the United States present evidence of a growing risk of breast, colon, and lung cancer incidence due to prolonged exposure to environmental pollutants. Dos Santos et al. (12) in their study, showed that occupational exposure to pesticides in rural working women induced significant changes in the levels of cytokines necessary for tumor control and were positively correlated with worse prognostic outcomes. A meta-analysis study by Liu et al. (13) demonstrated significant associations between exposure to endocrine-disrupting chemicals (EDCs), which have the potential to interfere with the function of normal hormones, and an increased risk of breast cancer. They found that breast cancer risk was increased by exposure to certain EDC congeners and their metabolites, such as benzene, chlordane, hexachlorocyclohexane, and polychlorinated biphenyls. Similarly, Yuan et al. conducted a prospective cohort study to determine the relationship between Bisphenol A (BPA) exposure and cancer mortality. BPA, an environmental phenol, is utilized in various products, including baby bottles, and food containers (14), and has been shown to be detectable in more than 90% of urine samples in the general population in the United States (15), promoting some states to enforce regulations to restrict the use of BPA. The authors of this study determined that a lower level of BPA of <1.99 ng/mL was associated with a higher risk of cancer mortality. In their scoping review on military environmental exposures (MEE) including volatile organic compounds (VOCs), endocrine-disrupting chemicals (EDCs), tactile herbicides, airborne hazards and open burn pits (AHOBP), and depleted uranium on the risk of breast cancer among service members and Veterans, Jester et al. determined that MEE poses a unique risk to women veterans who were affected by MEE during their service. However, the authors concede that further studies are needed to validate these findings owing to the mixed and limited availability of literature on MEE and breast cancer among veterans.

Socio-economic demographics, resulting in higher carcinogen exposures and higher behavioral risk factors such as diet, physical activity, and obesity, or substance use such as smoking and alcohol consumption, also play integral roles in increasing cancer risk (16–19). For example, one-third of cancer deaths in the United States are attributed to diet, lack of physical activity, and obesity, while another third is correlated to exposure to tobacco products (20). In their perspective article, Atchade et al. highlight changes in Westernized dietary patterns in the United States as a significant contributor impacting the colonic microbiome and contributing to the recent surge of early-onset CRC (EOCRC). To determine the correlation between caffeine consumption and the prevalence of colon cancer, Qu et al. applied weighted logistic regression to the National Health and Nutrition Examination Survey (NHANES) dataset to evaluate correlations. They determined a potential dose–response relationship between an increased risk of colon cancer and higher caffeine intake levels. In continuation of their previous work demonstrating alcohol exposure selectively activates mammalian p38 mitogen-activated protein kinase (MAPK) in breast cancer cells, in their current study, Li et al. aimed to determine if Pirfenidone (PFD), an antifibrotic compound and pharmacological inhibitor of p38γ MAPK, could inhibit alcohol-induced promotion of breast cancer. Their results demonstrate that PFD successfully inhibited mammary tumor growth and alcohol-promoted metastasis, suggesting that this agent, which is currently approved for the treatment of idiopathic pulmonary fibrosis, could be re-purposed and used to treat aggressive breast cancer and alcohol-promoted mammary tumor progression.

It is also important to note that exposure to environmental carcinogens is not evenly distributed across populations, creating environmental inequity. Studies have shown that higher exposures to hazardous air pollutants as well as non-air-pollutant-related hazards, including water contaminants such as lead (21), lack of greenspace (22, 23), and poor walkability scores (24, 25) among socially and/or economically disadvantaged populations (26–32). An assessment of differences in colorectal cancer (CRC) survival between urban and rural areas by Fu et al., revealed a notable difference in CRC survival, highlighting the importance of considering urban–rural disparities in CRC prognosis and the influence of socioeconomic factors on survival outcomes. Higher total and CRC-specific mortality rates were found in rural areas as compared to urban areas. Interestingly, household incomes below $75,000 and $55,000 were found to be independent prognostic factors for the overall survival of CRC in urban and rural areas, respectively. The study also identified several independent prognostic factors influencing the overall survival of CRC patients, such as age over 40 years, male gender, black ethnicity, tumor location in the right colon, advanced stages (stage III and stage IV), and tumor size over 5 cm. To understand the impact of industrial installations such as steel plants, oil refineries urban discharges, etc.) two articles in the current Research Topic present their findings regarding correlations between residence in areas with high environmental pressures and death rates with a focus on female breast cancer characteristics (Giannico et al.) and bronchus/lung cancer characteristics (Mincuzzi et al.) respectively. Both studies found several independent prognostic factors for breast and lung cancer characteristics, respectively. While neither study was able to determine a clear association between these prognostic factors and living in the contaminated site of national interest (SIN) of Taranto, Italy, they did find a correlation between residential sites and an increased all-cause death rate. Interestingly, Mincuzzi et al. also found an association between male gender and a higher prevalence of poorly differentiated cancer and squamous-cell carcinoma. Finally, Zhao et al. sort to determine associations among incidence and mortality of Tracheal, Bronchus, and Lung (TBL) cancer, air pollutants, and greenspaces (which are known to improve air quality). The authors found positive associations between green spaces and air pollutants with TBL cancer, particularly among individuals aged 20 to 54. In summary, this study suggests that more green spaces/forests serve as protective factors, along with higher health care coverage, better health status, and participation in physical activities.

Despite the clear connection between environmental exposures and cancer incidence, public health efforts to mitigate these risks are often insufficient. This is especially concerning given that cancer survivors in underserved communities frequently face disparities in outcomes due to continued exposure to environmental hazards. Addressing these disparities requires a comprehensive approach that targets environmental risk factors and prioritizes the needs of vulnerable populations. Nolazco et al., in their cross-sectional study

utilizing self-reported cancer histories from 39,578 participants in the Behavioral Risk Factor Surveillance System (BRFSS) database, found current and former smokers exhibited significantly poorer health-related quality of life (HRQoL) when compared to never smokers. These findings highlight the need to prioritize smoking cessation among cancer survivors. In conjunction, Tesfaw et al., in their systematic review to assess the comprehensive and common mortality-related risk factors of lung cancer, identified positive correlations between age, gender, stage, and comorbidities such as cardiovascular disease, hypertension, and diabetes on lung cancer mortality. In their nested case-control study, Xu et al. determined that prior history of chronic bronchitis, long-term wheezing symptoms, as well as exposure to environmental pollutants such as smoking, and biofuel combustion increased the risk of chronic obstructive pulmonary disease (COPD). Finally, Xiao et al.'s study investigating the epidemiological characteristics of lung cancer among healthcare workers in the Hunan Province, as well as the occupational risk factors, revealed that the prevalence of lung cancer among this cohort was much higher than that of the general population. Moreover, the prevalence of lung cancer was found to increase exponentially with age. In summary, this article highlights the occupational risks faced by general practitioners and medical imaging technicians, and the need to implement better personal safety measures.

Thus, addressing the impact of environmental exposure on breast, lung, and colon cancer requires a concerted effort from governments, public health officials, healthcare providers, and communities. By strengthening regulations, promoting environmental justice, enhancing public education, investing in research, and integrating environmental health into healthcare, we can advance public health strategies that lead to better outcomes for all. The fight against cancer is ongoing, but with a focus on environmental factors, we can make significant strides toward reducing its burden and improving the health and wellbeing of future generations.

In conclusion, the time is now for a proactive and comprehensive approach to addressing the environmental causes of cancer. By prioritizing this Research Topic within the broader public health agenda, we can move closer to a future where the incidence of breast, lung, and colon cancer is significantly reduced, and where all individuals have the opportunity to live in healthier environments.

Author contributions

CT: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. US: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. FC: Supervision, Writing – review & editing.

Conflict of interest

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

Publisher's note

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* (2024) 74:12–49. doi: 10.3322/caac.21820

2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2024) 74:229–63. doi: 10.3322/caac.21834

3. Wu S, Powers S, Zhu W, Hannun YA. Substantial contribution of extrinsic risk factors to cancer development. *Nature.* (2016) 529:43–7. doi: 10.1038/nature16166

4. Yuan H, Kehm RD, Daaboul JM, Lloyd SE, McDonald JA, Mu L, et al. Cancer incidence trends in New York State and associations with common population-level exposures 2010-2018: an ecological study. *Sci Rep.* (2024) 14:7141. doi: 10.1038/s41598-024-56634-w

5. Larsen K, Rydz E, Peters CE. Inequalities in environmental cancer risk and carcinogen exposures: a scoping review. *Int J Environ Res Public Health.* (2023) 20:5718. doi: 10.3390/ijerph20095718

6. Tybjerg AJ, Friis S, Brown K, Nilbert MC, Morch L, Køster B. Updated fraction of cancer attributable to lifestyle and environmental factors in Denmark in 2018. *Sci Rep.* (2022) 12:549. doi: 10.1038/s41598-021-04564-2

7. Carpenter DO, Bushkin-Bedient S. Exposure to chemicals and radiation during childhood and risk for cancer later in life. *J Adolesc Health.* (2013) 52:S21–9. doi: 10.1016/j.jadohealth.2013.01.027

8. Hill W, Lim EL, Weeden CE, Lee C, Augustine M, Chen K, et al. Lung adenocarcinoma promotion by air pollutants. *Nature.* (2023) 616:159–67.

9. Koval LE, Dionisio KL, Friedman KP, Isaacs KK, Rager JE. Environmental mixtures and breast cancer: identifying co-exposure patterns between understudied vs breast cancer-associated chemicals using chemical inventory informatics. *J Expo Sci Environ Epidemiol.* (2022) 32:794–807. doi: 10.1038/s41370-022-00451-8

10. Rodgers KM, Udesky JO, Rudel RA, Brody JG. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. *Environ Res.* (2018) 160:152–82. doi: 10.1016/j.envres.2017.08.045

11. Papier K, Bradbury KE, Balkwill A, Barnes I, Smith-Byrne K, Gunter MJ, et al. Diet-wide analyses for risk of colorectal cancer: prospective study of 12,251 incident cases among 542,778 women in the UK. *Nat Commun.* (2025) 16:375. doi: 10.1038/s41467-024-55219-5

12. Dos Santos SBG, da Silva JC, Jaques HD, Vecchia MFD, Ferreira MO, Rech D, et al. Occupational exposure to pesticides dysregulates systemic Th1/Th2/Th17 cytokines and correlates with poor clinical outcomes in breast cancer patients. *Front Immunol.* (2023) 14:1281056. doi: 10.3389/fimmu.2023.1281056

13. Liu H. et al. *Endocrine-disrupting chemicals and breast cancer: a meta-analysis Front Oncol.* (2023) 13:1282651. doi: 10.3389/fonc.2023.1282651

14. Jamal A, Rastkari N, Dehghaniathar R, Nodehi RN, Nasseri S, Kashani H, et al. Prenatal urinary concentrations of environmental phenols and birth outcomes in the mother-infant pairs of Tehran Environment and Neurodevelopmental Disorders (TEND) cohort study. *Environ Res.* (2020) 184:109331. doi: 10.1016/j.envres.2020.109331

15. Lehmler HJ, Liu B, Gadogbe M, Bao W. Exposure to Bisphenol A, Bisphenol F, and Bisphenol S in U.S. adults and children: the national health and nutrition examination survey 2013-2014. *ACS Omega.* (2018) 3:6523–6532. doi: 10.1021/acsomega.8b00824

16. Kairouz S, Greenfield TK, A. comparative multi-level analysis of contextual drinking in American and Canadian adults. *Addiction.* (2007) 102:71–80. doi: 10.1111/j.1360-0443.2006.01655.x

17. Kong AY, Myers AE, Isgett LF, Ribisl KM. Neighborhood racial, ethnic, and income disparities in accessibility to multiple tobacco retailers: Mecklenburg County, North Carolina, 2015. *Prev Med Rep.* (2020) 17:101031. doi: 10.1016/j.pmedr.2019.101031

18. Schoufour JD, de Jonge EAL, Kiefte-de Jong JC, van Lenthe FJ, Hofman A, Nunn SPT, et al. Socio-economic indicators and diet quality in an older population. *Maturitas.* (2018) 107:71–7. doi: 10.1016/j.maturitas.2017.10.010

19. Eagle TF, Sheetz A, Gurm R, Woodward AC, Kline-Rogers E, Leibowitz R, et al. Understanding childhood obesity in America: linkages between household income, community resources, and children's behaviors. *Am Heart J.* (2012) 163:836–43. doi: 10.1016/j.ahj.2012.02.025

20. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin.* (2006) 56:254–81. doi: 10.3322/canjclin.56.5.254

21. Delpla I, Benmarhnia T, Lebel A, Levallois P, Rodriguez MJ. Investigating social inequalities in exposure to drinking water contaminants in rural areas. *Environ Pollut.* (2015) 207:88–96. doi: 10.1016/j.envpol.2015.08.046

22. Pinault L, Christidis T, Toyib O, Crouse DL. Ethnocultural and socioeconomic disparities in exposure to residential greenness within urban Canada. *Health Rep.* (2021) 32:3–14.

23. Wen M, Zhang X, Harris CD, Holt JB, Croft JB. Spatial disparities in the distribution of parks and green spaces in the USA. *Ann Behav Med.* (2013) 45:S18–27. doi: 10.1007/s12160-012-9426-x

24. Doiron D, Setton EM, Shairsingh K, Brauer M, Hystad P, Ross NA, et al. Healthy built environment: Spatial patterns and relationships of multiple exposures and deprivation in Toronto, Montreal and Vancouver. *Environ Int.* (2020) 143:106003. doi: 10.1016/j.envint.2020.106003

25. Rajaee M, Echeverri B, Zuchowicz Z, Wiltfang K, Lucarelli JF. Socioeconomic and racial disparities of sidewalk quality in a traditional rust belt city. *SSM Popul Health.* (2021) 16:100975. doi: 10.1016/j.ssmph.2021.100975

26. Kruize H, Droomers M, van Kamp I, Ruijsbroek A. What causes environmental inequalities and related health effects? An analysis of evolving concepts. *Int J Environ Res Public Health.* (2014) 11:5807–27. doi: 10.3390/ijerph110605807

27. Kershaw S, Gower S, Rinner C, Campbell M. Identifying inequitable exposure to toxic air pollution in racialized and low-income neighbourhoods to support pollution prevention. *Geospat Health.* (2013) 7:265–78. doi: 10.4081/gh.2013.85

28. Collins TW, Grineski SE, Morales DX. Sexual orientation, gender, and environmental injustice: unequal carcinogenic air pollution risks in greater houston. *Ann Am Assoc Geogr.* (2017) 107:72–92. doi: 10.1080/24694452.2016.1218270

29. Lievanos RS. Race, deprivation, and immigrant isolation: the spatial demography of air-toxic clusters in the continental United States. *Soc Sci Res.* (2015) 54:50–67. doi: 10.1016/j.ssresearch.2015.06.014

30. Mikati I, Benson AF, Luben TJ, Sacks JD, Richmond-Bryant J. Disparities in distribution of particulate matter emission sources by race and poverty status. *Am J Public Health.* (2018) 108:480–5. doi: 10.2105/AJPH.2017.304297

31. Young GS, Fox MA, Trush M, Kanarek N, Glass TA, Curriero FC. Differential exposure to hazardous air pollution in the United States: a multilevel analysis of urbanization and neighborhood socioeconomic deprivation. *Int J Environ Res Public Health.* (2012) 9:2204–25. doi: 10.3390/ijerph9062204

32. Grineski SE, Collins TW, Morales DX. Asian Americans and disproportionate exposure to carcinogenic hazardous air pollutants: a national study. *Soc Sci Med.* (2017) 185:71–80. doi: 10.1016/j.socscimed.2017.05.042

frontiers | Frontiers in Immunology

TYPE Brief Research Report
PUBLISHED 24 October 2023
DOI 10.3389/fimmu.2023.1281056

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Kranthi Kiran Kishore Tanagala,
Columbia University, United States
Paramita Pal,
Takeda, United States
Shashikala Sasidharan,
The State University of New Jersey,
United States

*CORRESPONDENCE
Carolina Panis
carolpanis@hotmail.com
Dalila Moter Benvegnú
dalila.benvegnu@uffs.edu.br

†These authors have contributed equally to this work

RECEIVED 21 August 2023
ACCEPTED 06 October 2023
PUBLISHED 24 October 2023

CITATION
Santos SBGd, da Silva JC, Jaques HdS, Dalla Vecchia MF, Ferreira MO, Rech D, Sierota da Silva MRN, Santos RBGd, Panis C and Benvegnú DM (2023) Occupational exposure to pesticides dysregulates systemic Th1/Th2/Th17 cytokines and correlates with poor clinical outcomes
in breast cancer patients.
Front. Immunol. 14:1281056.
doi: 10.3389/fimmu.2023.1281056

Occupational exposure to pesticides dysregulates systemic Th1/Th2/Th17 cytokines and correlates with poor clinical outcomes in breast cancer patients

Stephany Bonin Godinho dos Santos[1†], Janaína Carla da Silva[2], Hellen dos Santos Jaques[3], Marina Ferronato Dalla Vecchia[3], Mariane Okamoto Ferreira[1,3], Daniel Rech[1,3,4], Matheus Ryan Noah Sierota da Silva[5], Roberta Bonin Godinho dos Santos[6], Carolina Panis[1,3*†] and Dalila Moter Benvegnú[1,7*†]

[1]Programa de Pós-Graduação em Ciências Aplicadas à Saúde, Universidade Estadual do Oeste do Paraná, Francisco Beltrão, Paraná, Brazil, [2]Department of Biochemistry and Molecular Medicine, Université de Montréal, Montreal, Quebec, Canada, [3]Laboratório de Biologia de Tumores, Universidade Estadual do Oeste do Paraná, Francisco Beltrão, Paraná, Brazil, [4]Department of Surgery, Hospital de Câncer de Francisco Beltrão, Francisco Beltrão, Paraná, Brazil, [5]Curso de Graduação em Engenharia Ambiental e Sanitária, Universidade Tecnológica Federal do Paraná, Francisco Beltrão, Paraná, Brazil, [6]Curso de Graduação em Farmácia, União de Ensino do Sudoeste do Paraná, Francisco Beltrão, Paraná, Brazil, [7]Programa de Pós-graduação em Saúde, Bem-estar e Produção Animal Sustentável na Fronteira Sul, Universidade Federal da Fronteira Sul, Paraná, Brazil

Pesticides are compounds known to cause immunetoxicity in exposed individuals, which have a potential to substantially modify the prognosis of pathologies dependent on an efficient immune response, such as breast cancer. In this context, we examined the circulating cytokine profile of Th1/Th2/Th17 patterns in women occupationally exposed to pesticides and their correlation with worse prognostic outcomes. Peripheral blood samples were collected from 187 rural working women with breast cancer, occupationally exposed or not to pesticides, to quantify the levels of cytokines IL-1β, IL-12, IL-4, IL-17-A, and TNF -α. Data on the disease profile and clinical outcomes were collected through medical follow-up. IL-12 was reduced in exposed women with tumors larger than 2 cm and in those with lymph node metastases. Significantly reduced levels of IL-17A were observed in exposed patients with Luminal B subtype tumors, with high ki67 proliferation rates, high histological grade, and positive for the progesterone receptor. Reduced IL-4 was also seen in exposed women with lymph node invasion. Our data show that occupational exposure to pesticides induces significant changes in the levels of cytokines necessary for tumor control and correlates with poor prognosis clinical outcomes in breast cancer.

KEYWORDS

breast cancer, prognosis, immune response, cytokines, dysregulation

Introduction

Breast cancer is a multifactorial disease whose origin is influenced by genetic and environmental risk factors. In recent years, growing evidence has been accumulated regarding pesticide exposure's impact on cancer risk (1–6), and mechanisms include oxidative stress generation, hormonal disbalance, epigenetic changes, and immunological deregulation, among others (7–10).

The immune response is a critical factor in avoiding breast cancer development. Due to the sustained carcinogenic challenges faced by the human body, cancerous or precancerous cells arise lifelong, and most of them are eliminated by a healthy immune system. However, some cells can escape immunosurveillance and origin cancer mainly due to immune failure during its elimination (11).

After tumor establishment, immune responses can also act by favoring its progression (12). In this context, cytokines play a pivotal role by affecting tumor-promoting processes such as growth, invasion, and metastatic capacity (13, 14), determining disease prognosis. Because of this dual role, it is unclear when or why the immune response will work in favor of or against breast cancer. Thus, the exposure of patients carrying breast tumors to pro-carcinogenic factors such as pesticides must negatively affect their immune response and disease evolution.

In vitro data have evidenced that pesticide exposure favors malign breast cancer cells' capabilities as migration, angiogenesis (15) and proliferation (16), which are biological features linked to highly aggressive breast tumors in humans. Also, *in vitro* data has pointed out the immunogenotoxicity of pesticides (16–19). However, little is known regarding the relationship between pesticide exposure, breast cancer behavior and immune response. In the same way, evidence concerning pesticide-induced immune deregulation in breast cancer patients has been recently pointed out, but they are preliminary and allow limited conclusions. It has been reported that rural women occupationally exposed to pesticides have reduced circulating levels of the antitumor cytokines TNF-α and IL-1β (20). In addition, a recent study demonstrated that a specific set of immune response components are affected by occupational exposure to pesticides in breast cancer patients, including tumor CTLA-4 overexpression and systemic IL-12 decrease, specifically in those under intermediate disease risk and recurrence (21).

Considering that breast cancer is a disease with systemic immunological implications (22), such findings suggest that expanding this investigation to more cytokines and other clinicopathological parameters could help establish a systemic cytokine signature linked to disease aggressiveness in women chronically exposed to pesticide mixtures and correlate it to specific prognosis features. To reach this goal, this study characterized the Th1/Th2/Th17 circulating profiles and investigated their relationship to clinicopathological features that are determinants of poor disease prognosis.

Materials and methods

Study design

The Institutional Ethics Committee approved this study under CAAE 35524814.4.0000.0107, opinion number 810.501. Only patients who signed the informed consent were included. After screening 422 women, a total of 187 were included. Women attended at the Francisco Beltrão Cancer Hospital – Paraná, Brazil, between 2015 and 2021, from 27 municipalities included in the 8th Health Regional of Paraná, were evaluated. A data collection instrument validated for this population was used to obtain the occupational exposure profile to pesticides (23). The exposure criteria were based on women's continuous, unprotected, and direct handling of pesticides. Rural women with a history of direct handling of pesticides without wearing protective gloves during the preparation and dilution of the concentrated pesticide solution, or that spray pesticide, and/or were responsible for decontaminating personal protective equipment (PPE), and/or washing of clothes used during spraying, and that reported living at least 50% of their lives under direct pesticide handling at least twice a week during all weeks of the year were classified as occupationally exposed. The unexposed group consisted of urban female workers with no previous or current history of occupational exposure to pesticides (24).

The clinicopathological profile was categorized by collecting data from medical records. The following prognostic information was evaluated, based on the National Comprehensive Cancer Network (NCCN) guidelines (25) and the Saint Gallen Consensus (26): estrogen receptor (ER) and progesterone (PR) expression, human epidermal growth factor receptor 2 (HER2) overexpression, ki67 proliferation index, breast cancer molecular subtype, histological grade, presence of intratumoral emboli, presence of metastases in axillary lymph nodes, presence of distant metastasis, age at diagnosis, menopausal status at diagnosis, body mass index (BMI), the occurrence of recurrence and survival profile in the period studied.

Sample collection and Th1/Th2/Th17 cytokine profiling

Samples of heparinized peripheral blood were collected and centrifuged for 5 minutes at 4.000 rpm to obtain plasma, which was frozen until the analysis.

To quantify the plasma levels of cytokines, interleukin 1 β (IL-1β), interleukin 12 (IL-12), and tumor necrosis factor-alpha (TNF-α) were measured for the Th1 profile of the patients; interleukin 4 (IL-4) for the Th2 profile and interleukin 17 A (IL-17-A) for the Th17 profile. Enzyme-linked immunoassay commercial kits were used (e-Biosciences®, USA). Plasma aliquots were incubated on a plate containing a capture antibody specific for each cytokine, followed by successive washes and incubation with streptavidin-labeled secondary antibody. A specific substrate was added for

reaction detection, and the plate read at 642 nm. Results were calculated in pg/ml from standard curve data for each cytokine. The detection limit of the kits was 2 pg/mL.

Statistical analysis

The statistical study was conducted to assess whether there are differences between the immunological profile of cytokines in cancer patients occupationally exposed and not occupationally exposed to pesticides under different clinicopathological parameters. The sample was also characterized concerning the clinicopathological aspects of the patients, comparing the women exposed and those not occupationally exposed to pesticides.

The frequencies of the categories of each clinicopathological variable were compared for patients belonging to both groups using the chi-square test for adherence. In addition, this same test was used to compare groups according to the categories of each variable. Tests were performed with 5% statistical significance.

The Chi-square test for independence was also performed for each variable to analyze the association between categories and groups. In injury situations with the assumption of a minimum expected frequency of 5, the Monte Carlo method was used as an association test, also with a 5% significance level. The purpose of this test is the same as the Chi-square test for independence. However, it is statistically more robust when the assumptions are not verified. Data analyzes were performed using the R software (27).

For cytokine level analyses, GraphPad Prism version 9.0 was used. Data distribution was tested by using the Shapiro-Wilk test. Variables normally distributed were analyzed with parametric tests, and nonparametric tests were used to analyze the nonparametric ones (Student's t-test or the Mann-Whitney test, respectively). Data are presented as box-plot and described in results as means (parametric data) or medians (nonparametric data). For all analyses, a $p \leq 0.05$ was considered significant. P values are shown in Table 1 as follows: p-value1 of the chi-square test for adherence comparing the categories of each variable for patients not exposed to pesticides; p-value2 of the chi-square test for adherence comparing the categories of each variable for patients exposed to pesticides; p-value3 of the Chi-square test for adherence comparing the groups according to the categories of each variable. A multivariate analysis, based on the principal component analysis (PCA) was conducted concerning cytokines and pesticide exposure. Only data with a p-value < 0.05 were showed as Figures.

Results

We included 187 women in the study (111 occupationally exposed to pesticides and 71 non-exposed). As shown in Table 1, estrogen receptor was positive in about 65% of cases in the unexposed group, while HER2 expression was negative in 78.87% of women in this group. The ki67 was over or equal to 14% for most cases (52.11%). The most frequent molecular subtypes were Luminal A (29.58%) and Luminal B (30.99%). Tumor size was greater than 20 mm (47.89%), with the prevalence of intratumoral emboli (66.20%). No lymph node was affected in 60.56% of the women; distant metastasis was found in 8.45%. In most cases, women were in menopause (66.20%) and overweight/obese (56.34%). Most of the patients were responsible for the first-line treatment (cytotoxic chemotherapy, 63.38%) without disease recurrence (83.10%) or death (90.14%). There was no statistical difference between the categories of variables PR, tumor aggressiveness according to its molecular subtype (more aggressive = triple-negative *vs.* less aggressive = Luminal), and histological grade.

Concerning women exposed to pesticides, it was found that the ER was positive in about 62% of the cases, and the amplification of HER2 was negative in 78.38% of the women in this group. The most common molecular subtypes were Luminal A (34.23%) and triple-negative (29.58%). Tumor size was greater than 20 mm (53.15%), with histological grade 2 (45.05%) and absence of intratumoral emboli (54.05%). No lymph node invasion was found in 53.15% of the women, and distant metastasis was found in 10.81%. In most patients in this group, women were in menopause (65.77%) and overweight/obese (61.26%). Most were responsible for the first-line treatment (63.06%) without recurrence (86.49%) or death (94.59%) in most patients. There was no statistical difference between the categories of variables PR, ki67>14%, and tumor aggressiveness.

In exposed patients, higher lymph nodal invasion was identified (34.23%) compared to non-exposed women (23.94%) (p-value 3 <0.0001; Table 1). We also found higher BMI in this group, indicating overweight or obesity (p-value 3 = 0.0001; Table 1).

Figure 1 shows the significant changes observed concerning cytokines from the Th1 axis. Reduced IL-12 was observed in exposed patients carrying tumors lower than 2 cm (Figure 1A, range: 12.70-147.1 pg/mL to unexposed and 9.29-182.8 pg/mL to the exposed ones, p = 0.051). Patients with lymph nodal invasion presented a reduced IL-1β (Figure 1B, range: 48.80-141.2 pg/mL to unexposed and 12.70-111.2 pg/mL to the exposed ones, p = 0.0105). Regarding IL-4 levels, a significant reduction was observed in the group of exposed women with lymph nodal invasion (Figure 1C, range:13.07-117.1 pg/mL to unexposed and 12.00-63.01 pg/mL to the exposed ones, p = 0.0414).

Main variations were observed in the Th17 axis, represented here by IL-17-A (Figure 2). A significant decrease in circulating levels of this cytokine was observed in patients occupationally exposed to pesticides, when compared to those not exposed, in the following conditions: carriers of luminal molecular subtype B tumors (Figure 2A, range: 36.36-222.7 pg/dL to the unexposed and 13.52-133.7 pg/dL to the exposed ones, p = 0.0176), with high proliferation tumors (ki67 >14%, Figure 2B, range: 12.12-291.1 pg/mL to the unexposed and 13.52-173.00 pg/mL to the exposed ones, p = 0.0493), with high histological grade tumors (Figure 2C, range: 60.80-222.70 pg/mL to the unexposed and 15.02-52.88 pg/mL to the exposed ones, p = 0.0159) and in those with progesterone receptor-positive tumors (Figure 2D, range: 12.12-221.70 pg/mL to the unexposed and 13.52-133.7 pg/mL to the exposed ones, p = 0.0263). A significant increase in IL-17-A was observed in eutrophic patients exposed to pesticides compared to those not exposed (Figure 2E, range: 12.12-106.7 pg/mL to the unexposed and 42.52-204.1 pg/mL to the exposed ones, p = 0.0119).

10.3389/fimmu.2023.1281056

TABLE 1 Frequency (n) and percentage (%) of clinicopathological data (discrete variables) considering exposure to pesticides.

		Not exposed		Exposed		
Variable	Category	%	p-value$_1$	%	p-value$_2$	p-value$_3$
Estrogen receptors	Negative	19.72	**<0.0001**	22.52	**<0.0001**	**0,0127**
	Positive	64.79		62.16		**0,0024**
	NA	15.49		15.32		
Progesterone receptors	Negative	42.25	0.8563	41.44	0.8834	**0,0094**
	Positive	43.66		42.34		**0,0104**
	NA	14.08		16.22		
HER2 expression	Negative	78.87	**<0.0001**	78.38	**<0.0001**	**0,0002**
	Positive	7.04		5.41		0,6698
	NA	14.08		16.22		
Ki67%	14	33.80	**0.0186**	37.84	0.1447	**0,0017**
	14	52.11		46.85		**0,0245**
	NA	14.08		15.32		
Tumor aggressiveness	Less aggressive	36.62	0.1032	40.54	0.6600	**0,0014**
	More aggressive	49.30		43.24		**0,0436**
	NA	14.08		16.22		
Molecular subtypes	Luminal A	29.58	**0.0009**	34.23	**<0.0001**	**0,0017**
	Luminal B	30.99		6.31		0,1617
	HER2	18.31		16.22		0,4142
	Triple-negative	14.08		29.58		0,1336
	NA	34.23		30.99		
Tumor size (mm)	20	32.39	**0.0394**	32.43	**0.0008**	**0,0167**
	20	47.89		53.15		**0,0002**
	NA	19.72		14.41		
Histological grade	1	26.76	0.1433	23.42	**<0.0001**	0,1400
	2	36.62		45.05		**<0,0001**
	3	22.54		15.32		0,8055
	NA	14.08		16.22		
Intratumoral emboli	No	66.20	**<0.0001**	54.05	**<0.0001**	**0,0755**
	Yes	19.72		29.73		**<0,0001**
	NA	14.08		16.22		
Lymph nodal metastasis	None acometed	60.56	**<0.0001**	53.15	**0.0026**	**0,0251**
	At least one acometed	23.94		34.23		**<0,0001**
	NA	15.49		12.61		
Distant metastasis	No	76.06	**<0.0001**	76.58	**<0.0001**	**0,0002**
	Yes	8.45		10.81		**0,0455**
	NA	15.49		12.61		
Diagnosis	Early	40.85	**0.0291**	35.14	**<0.0001**	0,2195
	Late	59.15		64.86		**<0,0001**

(Continued)

10.3389/fimmu.2023.1281056

TABLE 1 Continued

		Not exposed		Exposed		
Variable	Category	%	p-value$_1$	%	p-value$_2$	p-value$_3$
Menopause at diagnosis	No	32.39	**<0.0001**	30.63	**<0.0001**	**0,0008**
	Yes	66.20		65.77		**0,0394**
	NA	1.41		3.60		
Trophic-adipose status	Eutrophic	38.03	**0.0247**	32.43	**<0.0001**	0,1088
	Overweight/Obese	56.34		61.26		**0,0001**
	NA	5.63		6.31		
Chemoresistance	No	63.38	**<0.0001**	63.06	**<0.0001**	**0,0010**
	Yes	19.72		19.82		0,0593
	NA	16.90		17.12		
Recurrence	No	83.10	**<0.0001**	86.49	**<0.0001**	**<0,0001**
	Yes	12.68		11.71		0,2278
	NA	4.23		1.80		
Death	No	90.14	**<0.0001**	94.59	**<0.0001**	**<0,0001**
	Yes	9.86		5.41		0,6949

NA, data not available. The frequency of the NA category was not considered in the statistical analyses. Values in bold indicate that there was a statistical difference between the categories of the variable.

Spearman's correlation analysis (Figure 3A) performed in the exposed patients' group showed that PR positively correlated to IL-1β levels (R = 0.4481 for percent expression and 0.3373 for the presence of PR, p<0.05). For IL-4, positive correlations were found between its levels and disease aggressiveness (R = 0.2613, p<0.05), as well as the presence of intratumoral emboli (R =0.2678, p<0.05). TNF-α levels positively correlated to tumor size (R = 0.2624, p<0.05) and negatively to lymph nodal invasion (R = -0.2633, p<0.05). For IL-17-A, a negative correlation was found concerning BMI categorization (R = - 0.3276, p< 0.05). No significant correlations were observed regarding IL-12.

Figure 3B shows the results from PCA analysis among cytokine levels and pesticide exposure. The principal component 1 (PC1) strongly correlated positively to IL-1β and TNF-α (loadings 0.836 and 0.779, respectively), while the principal component 2 (PC2) strongly correlated positively to pesticide exposure and IL-17-A (loadings 0.654 and 0.786, respectively).

Discussion

Immune response polarization is crucial to determine the outcome of diseases whose prognosis depends on this, such as breast cancer. In this study, we demonstrated that chronic and continued exposure to pesticides significantly and simultaneously affects the levels of circulating Th1/Th2/Th17 cytokines in association with clinicopathological characteristics of worse prognosis.

Pesticides are immunotoxic by multiple mechanisms, interfering with innate and adaptative responses that are crucial against cancer (8), and it is suggested that the chronic antigenic

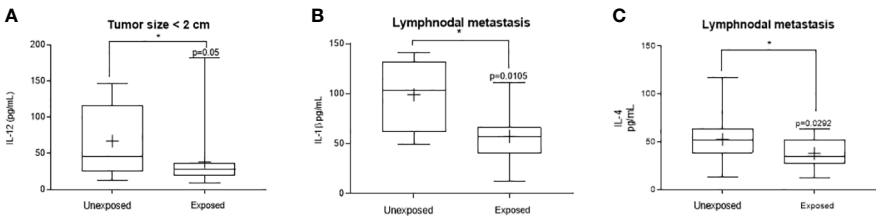


FIGURE 1
Significant variants in the systemic Thl profile of women with breast cancer occupationally exposed or not to pesticides. The Thl profile was determined through plasma levels of interleukin 12 (IL-12), interleukin 1β (IL-1β,) and tumor necrosis factor alpha (TNF-α). Levels detected in the exposed and non-exposed groups according to the following clinicopathological variables: **(A)** – Tumorsize under 2 cm for IL-12, **(B)** – presence of lymph node metastasis for IL-1β and **(C)** – Lymphnodal metastasis for IL-4. Data are shown as a box-plot of minimum, maximum and median variations. + represents the mean of each group. The p values are shown in the graphs, p<0.05 was considered significant.

10.3389/fimmu.2023.1281056

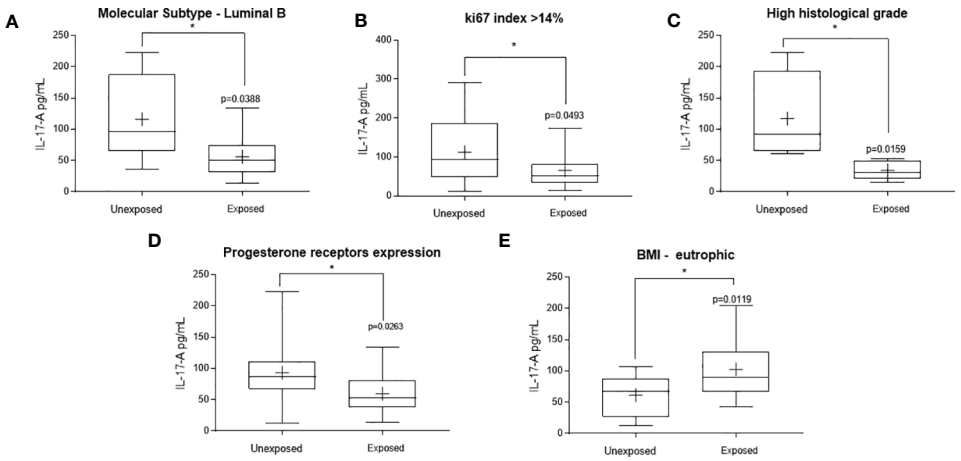


FIGURE 2
Significant variations in the systemic Thl7 profile of women with breast cancer occupationally exposed or not pesticides. The Thl7 profile was determined by measuring plasma interleukin 17 A (IL-17A). Levels detected in the exposed and non-exposed groups according to the following clinicopathological variables: **(A)** – Luminal molecular subtype B, **(B)** – ki67 proliferation index, **(C)** – tumor histological grade, **(D)** – Presence of progesterone receptors and **(E)** – Eutrophic patients. Data are shown as a box-plot of minimum, maximum and median variations. + represents the mean of each group. The p values are shown in the graphs, $p<0.05$ was considered significant.

stimulus due to continuous pesticide exposure can induce immune exhaustion (10). In this context, the imbalance in the production of cytokines enrolled in carcinogenesis is described (28).

The immune response against cancer has as its central mechanism a network of cytokines, whose production and signalling work in a homeostatic way within the T helper polarization patterns to effectively combat tumours (29, 30). The Th1 response, represented in our work by the circulating levels of IL-1β, IL-12, and TNF-α, was negatively affected by pesticide exposure, resulting in more aggressive clinicopathological conditions. For example, we observed depletion of IL-12, a main tumor-fighting cytokine. Specifically, women with tumors smaller than 2 cm exposed to pesticides had lower circulating levels of IL-12 compared to non-exposed women. This cytokine has potent antineoplastic activity by inducing a Th1-type response and tumor rejection (31), correlated with increased survival (32). Failure to produce it, even at a stage where the tumor represents a small mass, can influence the development of large tumor masses in the long term, potentially resulting in aggressive tumor behaviours such as the occurrence of metastases observed in such exposed patients (33).

In the present study, we observed that IL-1β levels were reduced in patients with lymph node metastasis, reinforcing the immune dysfunction reported in breast cancer patients exposed to pesticides reported by others (34–36). Th1-mediated immunity is known for its antitumor activity and is associated with longer life expectancy, unlike patients with tumors associated with Th2 subpopulation markers,

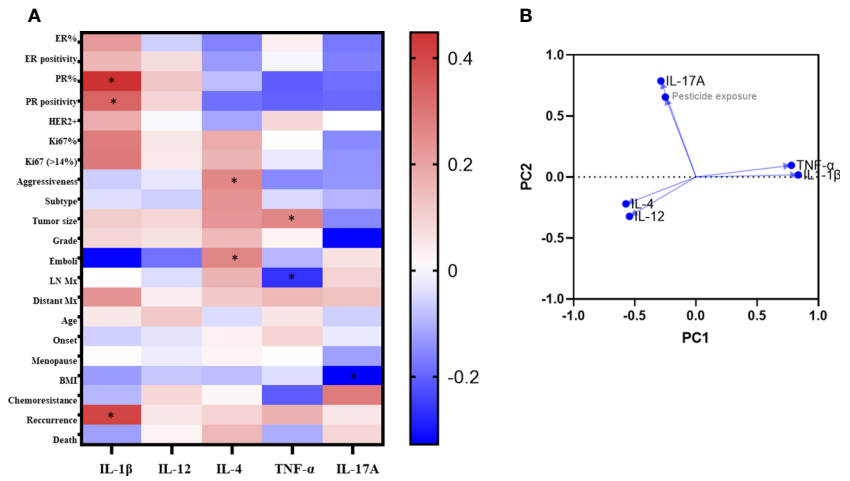


FIGURE 3
Correlaion analysis of clinicopathological data according to systemic levels of cytokines of exposed breast cancer patients. In **A**, the heatmap of Spearman's R values. Red squares indicate positive correlations. Blue squares indicate the negative ones. As intense the color as stronger the correlation (range from 0 = no correlation to 1 = total correlation). *p<0.05. In **B**, the principal component analysis. ER, estrogen receptors; PR, Progesterone receptors; HER2, amplification to the receptor of the human epidermal growth factor 2; LN, lymphnodal; Mx, metastasis.

with a more unfavorable prognosis (37). Thus, the pesticide-driven reduction of Th1 cytokines observed here may represent a substantial impairment for the immune responses against breast cancer.

Some mechanisms are pointed out concerning how pesticide exposure can affect Th1 cytokines. Our study population is under chronic handling of a mix of glyphosate, atrazine, and 2,4D pesticides. Atrazine, for example, changes the secretome pattern of immunoregulatory compartments as the mesenchymal stromal stem cells, attenuating Th1-related molecule production (38). A study (39) investigating the *in vitro* impact of this mixture at low concentrations demonstrated significant disturbances in macrophage polarization in association with a decrease in pro-inflammatory cytokine secretion. Healthy greenhouse workers occupationally exposed to pesticides exhibit significant reduction of circulating pro-inflammatory cytokines such as IL-2, IL-8, IL-12p70 and IFN-γ (35), and the same depletion pattern has been reported for exposed macrophages (40). These data support the idea that pesticides may have a direct deleterious effect on immune cells, which could explain our findings concerning Th1 cytokines depletion in poor prognosis patients. Human data in this context is scarce, which highlights the relevance of the present investigation.

We further demonstrated that pesticide exposure substantially modified the circulating levels of IL-17-A, a Th17 cytokine. The responses modulated by this axis involve innate and adaptive immunity inflammatory processes, affecting the production of other cytokines that modulate breast cancer progression (41). We observed a significant reduction in IL-17-A levels in patients occupationally exposed to pesticides compared to the non-exposed group under several conditions that determine a worse prognosis, such as in patients with proliferative and high-grade tumors. No data was found in literature about IL-17A deregulation in the context of pesticide exposure and breast cancer. In non-cancer conditions, IL-17A levels do not vary in workers exposed to pesticides (42), but *in vitro* and *in vivo* studies show that IL-17-A is related to cancer mechanisms (41, 43, 44). Distinct pesticides seem to act by different mechanisms on Th17 axis. For example, paraquat enriches the gene expression for IL17 signalling in human cells (45). Murine exposure to glyphosate leads to IL-17A reduction in peripheral blood at low doses and has been linked to immune deregulation across generations (46).

Pesticide exposure also augmented IL-17A in eutrophic breast cancer patients. Despite obesity dysregulates IL17-A production (47), and no data was found concerning its meaning in eutrophic patients, these findings support that pesticide exposure induce significant immunological changes in breast cancer patients, which vary according to the clinicopathological status of patients.

Our findings suggest that the combination of both pesticide exposure and breast cancer depletes this cytokine systemically in exposed women. PCA analysis reinforced the strong correlation between this cytokine and pesticide exposure. No data was found regarding atrazine or 2,4D exposures, and there is no information concerning IL-17A changes in the context of breast cancer and pesticide exposure.

Our study has limitations, including the need for measuring other cytokines, the single-point analysis instead of multiple collection points, and the modest sample size. Despite this, we believe that the main novelty and contribution relies on the fact that this is the first study to point out systemic changes in cytokine profiles induced by human exposure to pesticides in the context of breast cancer. Although the specific mechanisms by which pesticides induce such changes in breast cancer patients are unclear, our data reinforce pesticide exposures as potential immunological disruptors of cytokines produced in the immune response against breast cancer, especially in clinical conditions linked to worse prognoses.

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 humans were approved by State University of West Paraná Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SG: Data curation, Investigation, Writing – original draft. JS: Formal Analysis, Investigation, Writing – original draft. HJ: Data curation, Formal Analysis, Writing – original draft. MD: Data curation, Writing – original draft. MF: Data curation, Methodology, Writing – original draft. DR: Data curation, Investigation, Supervision, Writing – original draft. MS: Investigation, Resources, Writing – original draft. RS: Methodology, Writing – original draft. CP: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DB: Supervision, Writing – original draft.

Funding

This work was supported in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES), Fundação Araucária, Programa de Pesquisa Para o SUS – PPSUS, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Edital Universal). The authors are grateful for all Lab and Hospital personnel, funding agencies and patients. Carolina Panis was supported by CNPq Grants 402364/2021-0 and 305335/2021-9.

Conflict of interest

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

Publisher's note

References

1. Hofmann JN, Beane Freeman LE, Murata K, et al. Lifetime pesticide use and monoclonal gammopathy of undetermined significance in a prospective cohort of male farmers. *Environ Health Perspect* (2021) 129(1):17003. doi: 10.1289/EHP6960

2. Lerro CC, Beane LEF, DellaValle CT. Pesticide exposure and incident thyroid cancer among male pesticide applicators in agricultural health study. *Environ Int* (2021) 146:106187. doi: 10.1016/j.envint.2020.106187

3. Werder EJ, Engel LS, Satagopan J, et al. Herbicide, fumigant, and fungicide use and breast cancer risk among farmers' wives. *Environ Epidemiol* (2020) 4(3):e097.

4. Engel LS, Werder E, Satagopan J, et al. Insecticide use and breast cancer risk among farmers' Wives in the agricultural health study. *Environ Health Perspect* (2017) 125(9):097002. doi: 10.1289/EHP1295

5. Bonner MR, Freeman LEB, Hoppin JA, et al. Occupational exposure to pesticides and the incidence of lung cancer in the agricultural health study. (2017) 125(4):544–51. doi: 10.1289/EHP456

6. Panis C, Candiotto LZP, Gaboardi SC, et al. Widespread pesticide contamination of drinking water and impact on cancer risk in Brazil. (2022) 165:107321. doi: 10.1016/j.envint.2022.107321

7. Ataei M, Abdollahi M. A systematic review of mechanistic studies on the relationship between pesticide exposure and cancer induction. *Toxicol Appl Pharmacol* (2022) 456:116280. doi: 10.1016/j.taap.2022.116280

8. Cestonaro LV, Macedo SMD, Piton YV, Garcia SC, Arbo MD. Toxic effects of pesticides on cellular and humoral immunity: an overview. *Immunopharmacol Immunotoxicol* (2022) 44(6):816–31. doi: 10.1080/08923973.2022.2096466

9. Nicolella HD, de Assis S. Epigenetic inheritance: intergenerational effects of pesticides and other endocrine disruptors on cancer development. *Int J Mol Sci* (2022) 23(9):4671. doi: 10.3390/ijms23094671

10. Jacobsen-Pereira CH, Cardoso CC, Gehlen TC, Regina Dos Santos C, Santos-Silva MC. Immune response of Brazilian farmers exposed to multiple pesticides. *Ecotoxicol Environ Saf* (2020) 202:110912. doi: 10.1016/j.ecoenv.2020.110912

11. Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* (2007) 117 (5):1137–46. doi: 10.1172/JCI31405

12. Tommasi C, Pellegrino B, Diana A, et al. The innate immune microenvironment in metastatic breast cancer. *J Clin Med* (2022) 11(20):5986. doi: 10.3390/jcm11205986

13. Yang Y, Hou J, Liu J, Bhushan S, Wu G. The origins of resident macrophages in mammary gland influence the tumorigenesis of breast cancer. *Int Immunopharmacol* (2022) 110:109047. doi: 10.1016/j.intimp.2022.109047

14. Arici M, Abudayyak M, Boran T, et al. Does pendimethalin develop in pancreatic cancer induced inflammation? (2020) 252:126644. doi: 10.1016/j.chemosphere.2020.126644

15. Go RE, Lee HK, Kim CW, et al. A fungicide, fenhexamid, is involved in the migration and angiogenesis in breast cancer cells expressing estrogen receptors. *Life Sci* (2022) 305:120754. doi: 10.1016/j.lfs.2022.120754

16. Lu YS, Yang SL, Gou CL, et al. Integrated metabolomics and transcriptomics analysis reveals new biomarkers and mechanistic insights on atrazine exposures in MCF −7 cells. *Ecotoxicol Environ Saf* (2022) 232:113244. doi: 10.1016/j.ecoenv.2022.113244

17. Maddalon A, Masi M, Iulini M, Linciano P, Galbiati V, Marinovich M, et al. Effects of endocrine active contaminating pesticides on RACK1 expression and immunological consequences in THP 1 cells. *Environ Toxicol Pharmacol* (2022) 95:103971. doi: 10.1016/j.etap.2022.103971

18. Ma Y, Li S, Ye S, Hu D, Luo S, Wei L, et al. Effect of propiconazole on neutrophil extracellular traps formation: Assessing the role of autophagy. *Food Chem Toxicol* (2022) 168:113354. doi: 10.1016/j.fct.2022.113354

19. Maddalon A, Iulini M, Galbiati V, Colosio C, Mandić-Rajčević S, Corsini E. Direct effects of glyphosate on *in vitro* T helper cell differentiation and cytokine production. *Front Immunol* (2022) 13:854837. doi: 10.3389/fimmu.2022.854837

20. Pizzatti L, Kawassaki ACB, Fadel B, et al. Toxicoproteomics disclose pesticides as downregulators of TNF-α, IL-1β and estrogen receptor pathways in breast cancer women chronically exposed. (2020) 10:. doi: 10.3389/fonc.2020.01698

21. Silva JC, Scandolara TB, Kern R, et al. Occupational exposure to pesticides affects pivotal immunologic anti-tumor responses in breast cancer women from the intermediate risk of recurrence and death. *Cancers (Basel)* (2022) 14(21):5199. doi: 10.3390/cancers14215199

22. Kawaguchi K, Maeshima Y, Toi M. Tumor immune microenvironment and systemic response in breast cancer. *Med Oncol* (2022) 39(12):208. doi: 10.1007/s12032-022-01782-0

23. Panis C, Gaboardi SC, Kawassaki ACB, Dias ECM, Teixeira GT, Silva DRP, et al. Characterization of occupational exposure to pesticides and its impact on the health of rural women. *Rev Ciênc Farm Básica Apl* (2022) 43:e748. doi: 10.4322/2179-443X.0748

24. Da Silva RG, Ferreira MO, Komori IM, Oliveira HR, MaChado MG, Orrutea JF, et al. Brief research report: pesticide occupational exposure leads to significant inflammatory changes in normal mammary breast tissue. *Front Public Health* (2023) 11:1229422. doi: 10.3389/fpubh.2023.1229422

25. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* (2022) 20(6):691–722. doi: 10.6004/jnccn.2022.0030

26. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Panelists of the St Gallen Consensus Conference. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol* (2021) 32(10):1216–35. doi: 10.1016/j.annonc.2021.06.023

27. Core Team R. *R: A language and environment for statistical computing* . Vienna: R Foundation for Statistical Computing. Available at: https://www.R-project.org (Accessed February 10, 2022). The wrap-up release of the R-4.1.x series was 4.1.3.

28. Standish LJ, Sweet ES, Novack J, et al. Breast cancer and the immune system. *J Soc Integr Oncol* (2008) 6(4):158–68.

29. Dhouib I, Jallouli M, Annabi A, et al. From immunotoxicity to carcinogenicity: the effects of carbamate pesticides on the immune system. *Environ Sci pollut Res Int* (2016) 23(10):9448–58.

30. Girard L, Reix N, Mathelin C. Impact des pesticides perturbateurs endocriniens sur le cancer du sein [Impact of endocrine disrupting pesticides on breast cancer]. *Gynecol Obstet Fertil Senol* (2020) 48(2):187–95.

31. Colombo MP, Trinchieri G. Interleukin-12 in anti-tumor immunity and immunotherapy. *Cytokine Growth Factor Rev* (2002) 13(2):155–68.

32. Guida M, Casamassima A, Monticelli G, et al. Basal cytokines profile in metastatic renal cell carcinoma patients treated with subcutaneous IL-2-based therapy compared with that of healthy donors. *J Transl Med* (2007) 22:5–51. doi: 10.1186/1479-5876-5-51

33. Mirlekar B, Pylayeva-Gupta Y. IL-12 family cytokines in cancer and immunotherapy. *Cancers (Basel)* (2021) 13(2):167. doi: 10.3390/cancers13020167

34. Calaf GM. Role of organophosphorous pesticides and acetylcholine in breast carcinogenesis. (2021) 76:206–17. doi: 10.1016/j.semcancer.2021.03.016

35. Costa C, Rapisarda V, Catania S, et al. Cytokine patterns in greenhouse workers occupationally exposed to α-cypermethrin: An observational study. *Environ Toxicol Pharmacol* (2013) 36(3):796–800. doi: 10.1016/j.etap.2013.07.004

36. Volker D, Wolfgang H, Klausdieter B, et al. Associations of dichlorodiphenyltrichloroethane (DDT) 4.4 and dichlorodiphenyldichloroethylene (DDE) 4.4 blood levels with plasma IL-4. (2010) 57(6):541–7.

37. Ruffell B, DeNardo DG, Affara NI, et al. Lymphocytes in cancer development: polarization towards pro-tumor immunity. *Cytokine Growth Factor Rev* (2010) 21 (1):3–10. doi: 10.1016/j.cytogfr.2009.11.002

38. Uwazie CC, Pirlot BM, Faircloth TU, Patel M, Parr RN, Zastre HM, et al. Effects of Atrazine exposure on human bone marrow-derived mesenchymal stromal cells assessed by combinatorial assay matrix. *Front Immunol* (2023) 14:1214098. doi: 10.3389/fimmu.2023.1214098

39. Almeida Roque A, Filipak Neto F, Cosio C, Barjhoux I, Oliveira Ribeiro CA, Rioult D. Immunotoxicity of relevant mixtures of pesticides and metabolites on THP-1 cells. *Toxicology* (2023) 493:153557. doi: 10.1016/j.tox.2023.153557

40. Skolarczyk J, Pekar J, Nieradko-Iwanicka B. Immune disorders induced by exposure to pyrethroid insecticides. *Postepy Hig Med Dosw (Online)* (2017) 71(0):446–53. doi: 10.5604/01.3001.0010.3827

41. Karpisheh V, Ahmadi M, Abbaszadeh-Goudarzk K, et al. The role of Th17 cells in the pathogenesis and treatment of breast cancer. (2022) 22:108. doi: 10.1186/s12935-022-02528-8

42. Fenga C, Gangemi S, Catania S, et al. IL-17 and IL-22 serum levels in greenhouse workers exposed to pesticides. *Inflamm* (2014) 63:895–7. doi: 10.1007/s00011-014-0769-6

43. He TT, Zuo AJ, Wang JG, et al. Organochlorine pesticides accumulation and breast cancer: A hospital-based case-control study. *Tumour Biol* (2017) 39 (5):1010428317699114. doi: 10.1177/1010428317699114

44. Ye J, Livergood RS, Peng G. The role and regulation of human Th17 cells in tumor immunity. *Am J Pathol* (2013) 182(1):10–20. doi: 10.1016/j.ajpath.2012.08.041

45. Miao C, Fan D. Identification of differentially expressed genes and pathways in diquat and paraquat poisoning using bioinformatics analysis. *Toxicol Mech Methods* (2022) 32(9):678–85. doi: 10.1080/15376516.2022.2063095

46. Buchenauer L, Junge KM, Haange SB, Simon JC, von Bergen M, Hoh AL, et al. Glyphosate differentially affects the allergic immune response across generations in mice. *Sci Total Environ* (2022) 850:157973. doi: 10.1016/j.scitotenv.2022

47. Zhang X, Gao L, Meng H, Zhang A, Liang Y, Lu J. Obesity alters immunopathology in cancers and inflammatory diseases. *Obes Rev* (2023). doi: 10.1111/obr.13638

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 09 November 2023
DOI 10.3389/fonc.2023.1282651

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Shashikala Sasidharan,
Rutgers, The State University of New Jersey, United States
Kathrin Schilling,
Columbia University, United States
Nisha Gautam,
Rutgers University, Newark, United States

*CORRESPONDENCE
Changfu Hao
haochangfu@126.com

RECEIVED 25 August 2023
ACCEPTED 16 October 2023
PUBLISHED 09 November 2023

CITATION
Liu H, Sun Y, Ran L, Li J, Shi Y, Mu C and Hao C (2023) Endocrine-disrupting chemicals and breast cancer: a meta-analysis.
Front. Oncol. 13:1282651.
doi: 10.3389/fonc.2023.1282651

Endocrine-disrupting chemicals and breast cancer: a meta-analysis

Haiyan Liu[1], Yukun Sun[1], Longkai Ran[2], Jiuling Li[1], Yafei Shi[3], Chunguang Mu[1] and Changfu Hao[1]*

[1]Department of Child and Adolescent Health, School of Public Health, Zhengzhou University, Zhengzhou, Henan, China, [2]Department of Traditional Chinese Medicine, The First People's Hospital of Guiyang, Guiyang, Guizhou, China, [3]Department of Clinical Nutrition, Jiaozuo Coal Industry (Group) Co. Ltd. Central Hospital, Jiaozuo, Henan, China

Background: Globally, the burden of breast cancer has increased significantly in recent decades. Emerging evidence suggested that endocrine-disrupting chemicals (EDCs), which have the potential to interfere with the function of normal hormones, may play a crucial role in this trend. However, the potential relationships were inconsistent in various studies.

Objective and search methods: In our study, we sought to fully evaluate the currently available epidemiological evidence to ascertain whether certain EDC congeners and their metabolites are related to breast cancer risk. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we conducted a comprehensive literature search of original peer-reviewed publications in three electronic databases: PubMed, Web of Science, and Embase. Publications that covered xenobiotic EDC exposures and breast cancer–confirmed histological results or antecedent medical records or reporting to health registers were taken into consideration.

Outcomes: The final result of the literature search was 6,498 references, out which we found 67 publications that matched the requirements for meta-analysis and eight publications for qualitative trend synthesis. In this meta-analysis, statistically significant associations revealed that (i) 1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene (p,p'-DDT) and its major metabolite 2,2-bis(4-chlorophenyl)-1,1-dichloroethylene (p,p'-DDE) were somewhat related to a greater risk of breast cancer. However, this relationship only existed in blood serum but not in adipose tissue. (ii) Breast cancer risk was increased by exposure to chlordane and hexachlorocyclohexane. (iii) Five polychlorinated biphenyls (PCB 99, PCB 105, PCB 118, PCB 138, and PCB 183) can increase the risk of breast cancer. (iv) One phthalate congener (BBP) and one per- and polyfluoroalkyl substance congener (PFDoDA) were negatively associated with breast cancer risk. Unfortunately, heterogeneity was not well explained in our review, and a limited number of available prospective studies investigating the associations between EDC exposure and breast cancer were

included in our meta-analysis. To elucidate the overall associations, future large, longitudinal epidemiological investigations are needed.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD 42023420927.

KEYWORDS

endocrine-disrupting chemicals, breast cancer, epidemiological studies, pesticides, polychlorinated biphenyl, meta-analysis

Introduction

The global burden of breast cancer is increasing significantly. According to GLOBOCAN 2020 (2021), an estimated of 2.3 million new breast cancer cases were diagnosed in 2020, which contributed to the most female cancer deaths globally (1). These numbers are expected to double by 2040, particularly in low- and middle-income countries (2). Epidemiological evidence has correlated different factors for the high incidence and death rates in breast cancer, such as obesity, late age for marriage, first childbirth, menopause, and early age at menarche. However, these factors only partially contributed to breast cancer risk (3). Recently, there has been an ongoing topic of debate regarding whether endocrine-disrupting chemicals (EDCs), which have evidence of being hormonally active, are partly attributed to breast cancer risk.

EDCs, which have the potential to interfere with the function of normal hormones and thus have a negative impact on an intact organism's or its offspring's health (4), are ubiquitous in the environment, and they can be widely absorbed by the human body through the skin, inhaled, and ingested. Although some EDC compounds have been banned in many countries, pollution still exists in the environment and in the food chain (5, 6). For example, dichloroethylene (DDT) and hexachlorocyclohexane (HCH), which were banned in 1983, are still detectable at considerable levels in some soils in China (7). EDC exposure is one stressor that might adversely affect normal human development. Adverse health outcomes, such as cardiovascular risk, autoimmune defects, male reproductive disorders, earlier timing of pubertal onset, and behavioral disorders are linked to EDC exposure (4, 8, 9). In addition, accumulating evidence has shown that the estrogenic properties of EDCs are potentially linked to the increasing rates of breast cancer. However, there is presently no consensus. In 2022, a systematic review, including 131 publications, identified that EDC exposure played a potential role in elevating the risk of breast cancer (10). However, no meta-analyses were conducted in this review. In light of recent epidemiological data, a meta-analysis study of the effects of environmental endocrine-disrupting xenobiotics on breast cancer has become necessary. In this meta-analysis, we conducted a comprehensive peer-reviewed of original literature search to obtain epidemiological evidence and analyzed whether 10 certain compound groups of common EDCs [bisphenol A (BPA), dioxins, parabens, phthalates diesters and their metabolites, flame retardants, polyaromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), organochloride pesticides, per- and polyfluoroalkyl substance (PFAS), and triclosan] and their metabolites (using biomarker measures) are related to breast cancer risk.

Methods

Protocol

This meta-analysis was carried out entirely in accordance with the protocol registered at PROSPERO.org (registration number CRD 42023420927) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11).

Search strategy

The available research on EDC exposure and breast cancer was identified through a comprehensive peer-reviewed of original literature search in three electronic databases, namely, PubMed, Web of Science, and Embase, from 1961 to May 2023. The identified search terms were divided into three search blocks: the first dealt with the EDC exposure, the second covered the outcome (breast cancer), and the last covered study design (case–control and cohort study). A manual search of the included article's reference lists was subsequently performed. The search protocol provided the search specifications and respective hits in each search block (Supplementary Table 1).

Inclusion criteria

Original research papers published in English were included in our analysis. The full text of the corresponding article was reviewed after the title and abstract had been evaluated. Publications were considered eligible for inclusion if they met all the below criteria.

1. Exposures: Exposures to certain EDCs documented by measurements in biological specimens (blood, urine, and

adipose tissue) were included in the meta-analysis. The following 10 compound groups of EDCs were investigated in the included publications: (i) BPA, (ii) dioxins, (iii) parabens, (iv) phthalates diesters and their metabolites, (v) flame retardants, (vi) PAHs, (vii) PCBs, (viii) organochloride pesticides, (ix) PFAS, and (x) triclosan.
2. Breast cancer: Breast cancer–confirmed histological results or antecedent medical, records, or reporting to health registers were taken into consideration.
3. Risk estimates [relative risk (RR), odds ratio (OR), and hazard ratio (HR)] and their 95% confidence intervals (95% CI) as an outcome according to higher versus lower levels of EDC exposure contacts within the given study.
4. Only cohort studies and case–control studies were included in our analysis.

Exclusion criteria

Criteria for exclusion of studies were as follows:

1. Research studies conducted on animals, case reports, cross-sectional researches, reviews, conference proceedings/abstracts, letters, editorials, and comments were not included in our analysis.
2. Publications that discussed prescription hormones, did not report risk estimates, or reported repeated estimates from other publications were excluded.
3. Publications that reported DDT, PCBs, PFAS, and phthalate congener summary estimates but no specific risk estimates were excluded.
4. Self-reported breast cancer was excluded.

Data extraction

The process of data extraction was performed independently by KR and YS, and any inconsistency was resolved by JL. The following information was extracted from each publication including author, location, study design, number of cases and referents, biospecimens, exposure contrast, and substance. Risk estimates with 95% CIs were recorded for each measured compound. When risks according to several levels of exposure were reported, The risk estimate of the highest versus lowest levels was chosen. If a study reported that the OR value was in both unadjusted and adjusted models, then we gave preference to the adjusted OR value.

Statistical analysis

Studies were eligible in the meta-analysis when the effect sizes were reported as an relative risk (OR, RR, and HR) and sample types were human specimens. Separate forest plots for each EDC exposure were conducted to illustrate summary ORs with 95% CIs. The random-effects model was used to summarize the risk estimates. A meta-analysis was performed independently when ≥3 studies reported the compound. Heterogeneity was assessed using the degree of I^2-test statistic and p-value. Significant heterogeneity was defined as $I^2 > 50\%$ or value of $p < 0.10$. Low, moderate, and high degrees of heterogeneity were defined with I^2-values of 25%, 50%, and 75% (12). Subgroup analysis was used to determine the source of heterogeneity when it was assessed as moderate or high degree. We stratified our analysis into categories on the basis of the study design (case–control and nested case–control) and sample type (blood, adipose tissue, or urine). The leave-one-out method was used to perform sensitivity analysis. All statistical analyses of the data were performed using STATA software (version 15.0; State Corporation, College Station, Texas, USA) with a significance level of 0.05.

Risk of bias and quality assessment

The process of risk of bias and quality assessment was performed independently by two authors (KR and YS), and any inconsistency was resolved by a third author (JL). Each study was assessed for the completeness of reporting using a standardized form adapted from (9). There are a total of 11 items that need to be evaluated, and the 11 areas were equally weighted with the value one given for adequate reporting. We deemed a total of 8 to be adequate for reporting completion. A standardized questionnaire that was derived from (13) was used to assess the potential sources of bias in each study. There are a total of seven items, including reporting of tested hypotheses, sample size justification, selection bias, information bias, confounding, measuring of confounding factors, and exposure contrast, that need to be evaluated and each area was either rated as high risk, uncertain risk, or low risk (the evaluation form is available in Supplementary Table 11). If two or more of the specified areas were found to carry a high risk of bias, then publications were deemed to be biased in that direction. The potential sources of bias are showed in Supplementary Table 12.

Results

Study selection and characteristics

Figure 1 depicts the screening and selection procedure for the study. A total of 6,498 records were retrieved from PubMed, Web of Science, and Embase, of which 1,186 were duplications. Another 5,147 were disqualified when the titles and abstracts were examined because these studies were review articles, conference abstracts, or case reports or without measures of EDC exposure. No full-text studies were also disqualified. The full texts of 165 articles were reviewed after reading the titles and abstracts. Finally, 67 publications met the qualifying requirements for meta-analysis and eight publications for qualitative trend synthesis. All included studies concerned breast cancer only in women. Supplementary

Tables 2–10 provide an overview of the characteristics of the included publications.

Pesticides

The relationship between pesticides and breast cancer has received the most attention because of their persistence in the environment (14). However, the results were inconsistent in various studies. In this meta-analysis, we included 38 publications addressing pesticides. The characteristics of the studies in our review are shown in Supplementary Tables 2–5.

DDT and breast cancer

There were twenty-eight case–control articles and eight nested case–control studies (Supplementary Table 2). Of these, six publications reported DDT levels from adipose tissues, whereas others presented concentrations of DDT from blood samples. Thirty-six case-referent studies provided thirty-four risk estimates for p,p′-DDE, twenty-five risk estimates for p,p′-DDT, four risk estimates for o,p′-DDT, and four risk estimates for p,p′-DDD. The summary OR based on twenty-four studies showed that there was a positive association between p,p′-DDT and breast cancer (OR, 1.22; 95% CI, 1.03–1.45) with high heterogeneity (I^2 = 77.7%, P < 0.001) (Figure 2). In subgroups stratified by study design and sample type, the OR for case–control studies was close to unity but not statistically significant (OR, 1.22; 95% CI, 1.00–1.49; I^2 = 81.7%; P < 0.001), whereas the blood serum p,p′-DDT was associated with an increase in breast cancer (OR, 1.32; 95%CI, 1.03-1.70; I^2 = 80.5%; P < 0.001) (Supplementary Figures 1, 2). The pooled OR found that p, p′-DDE was associated with a significant increase in breast cancer (OR, 1.15; 95% CI, 1.01–1.30) with high heterogeneity between them (I^2 = 59.9%, P < 0.001) (Figure 3). In subgroups stratified by study design and sample type, the OR for case–control studies was 1.17 (95% CI, 1.02–1.34; I^2 = 63.4; P < 0.001), and the OR for blood serum was close to unity but not significant (OR, 1.15; 95% CI, 1.00–1.32; I^2 = 59.7%; P < 0.001) (Supplementary Figures 3, 4). There were only four studies that addressed o,p'-DDT in blood and an inverse association was observed in the meta-analysis (OR, 0.62; 95% CI, 0.42–0.92; I^2 = 5.6%; P = 0.365) (Supplementary Figure 5). The summary OR for p,p′-DDD in blood was slightly elevated but not statistically significant (OR, 2.78; 95% CI, 0.62–12.41; I^2 = 97.6%; P < 0.001) (Supplementary Figure 6).

Hexachlorobenzene and breast cancer

There were twelve case–control articles and two nested case–control studies (Supplementary Table 3). Of these, three publications reported hexachlorobenzene (HCB) levels from adipose tissues, whereas others presented concentrations of HCB from blood samples. As shown in Figure 4, the overall OR for the highest vs. lowest HCB levels was 1.06 (95% CI, 0.68–1.65), with high heterogeneity among these studies (I^2 = 77.4%). The heterogeneity was not affected by subgroups of sample type (Supplementary Figure 7).

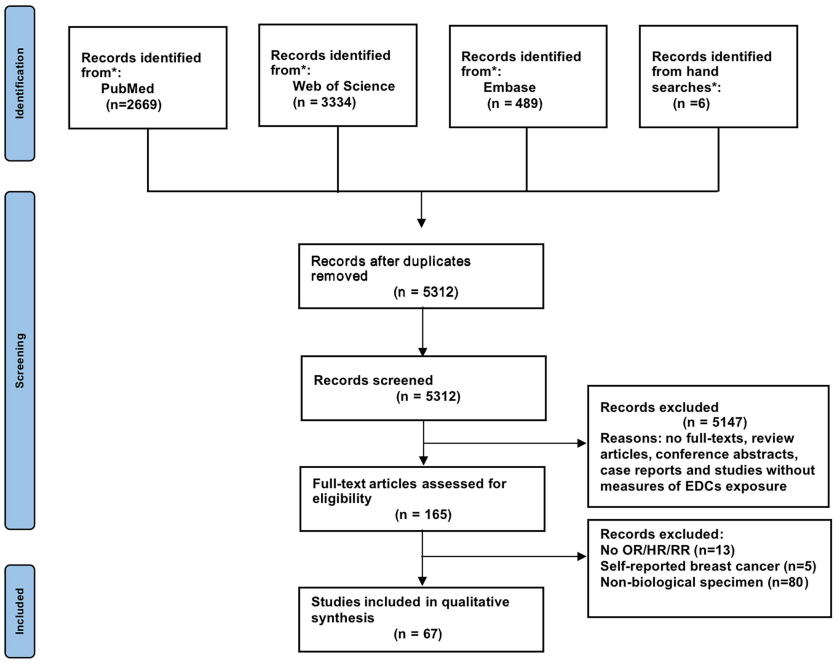


FIGURE 1
Flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol recommendations.

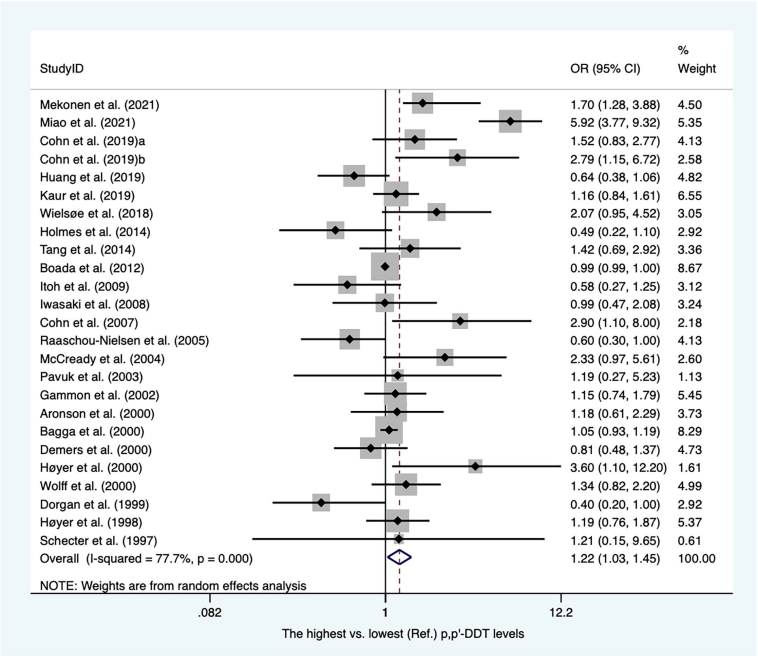


FIGURE 2
Summary estimates of the meta-analysis: association between p,p′-DDT exposure and breast cancer.

Hexachlorocyclohexane and breast cancer

Sixteen case-referent studies provided twenty-two risk estimates for hexachlorocyclohexane (HCH). There were 12 case–control articles and four nested case–control studies (Supplementary Table 4). Of these, three publications reported HCH levels from adipose tissues, whereas others presented concentrations of HCH from blood samples. As shown in Figure 5. The pooled OR showed that higher blood/fat levels of HCH was associated with a substantial increase in the risk of breast cancer in individuals (OR, 1.33; 95% CI, 1.05–1.67; I^2 = 70.3%; P < 0.001). The heterogeneity was affected by subgroups of sample type and study design. In blood serum, the concentrations of HCH were associated with a significant increase in breast cancer (OR, 1.48; 95% CI, 1.19–1.86; I^2 = 64.2%; P < 0.001). The summary OR for HCH in adipose tissue was significantly reduced (OR, 0.61; 95% CI, 0.42–0.90) with no heterogeneity (Supplementary Figure 8). The summary estimate risk of twelve case–control publications was a statistically significant increase (OR, 1.47; 95% CI, 1.15–1.87; I^2 = 67%; P < 0.001) (Supplementary Figure 9).

Other pesticides

There were 17 publications that reported the associations between other pesticide exposure and breast cancer. Supplementary Table 5 details the features of the studies included in our meta-analysis. The pooled OR for chlordane showed a significant increase in the risk of breast cancer (OR, 2.36; 95% CI, 1.20–4.63; I^2 = 88.5%; P < 0.001). No significant increase were observed in other pooled ORs. The results are summarized in Figure 6.

PCBs and breast cancer

Twenty-two studies were enrolled, including four nested case–control studies and eighteen case–control studies (Supplementary Table 6). Of these, eight publications reported PCB concentrations from adipose tissues, whereas others presented concentrations of PCBs from blood samples. Twenty-two publications provided 13 summary risk estimates for breast cancer. The pooled ORs showed that individuals with higher blood/fat levels of PCB 99, PCB 105 and PCB 183 increased the risk of breast cancer (OR 1.43; 95% CI, 1.17-1.76; OR 2.05; 95% CI, 1.42-2.97; OR 1.57; 95% CI, 1.27-1.94) with no heterogeneity (Figures 7A–C). The summary ORs for PCB 118 and PCB 138 were statistically significantly elevated with high heterogeneity between them (OR, 1.28; 95% CI, 1.01–1.62; I^2 = 74.0%; OR, 1.33; 95% CI, 1.10–1.60; I^2 = 52.9%) (Figures 7D, E). These heterogeneities were affected by subgroups of sample type and study design. In subsequent subgroup analysis, we found that PCB 118 in case–control studies and PCB 138 in blood samples were positively associated with breast cancer risk (OR, 1.38; 95% CI, 1.04–1.83; I^2 = 77.7%; and OR, 1.29; 95% CI, 1.05–1.60; I^2 = 30.8%) (Supplementary Figures 10, 11). The summary estimate for PCB 187 was near to unity (OR, 1.23; 95% CI, 1.00–1.53) with low heterogeneity (I^2 = 24.6%) (Supplementary Figure 12). In addition, the pooled ORs of PCB 52, PCB 74, PCB 101, PCB 153, PCB 156, PCB 170, and PCB 180 showed no significant increase in breast cancer (Supplementary Figures 13–19).

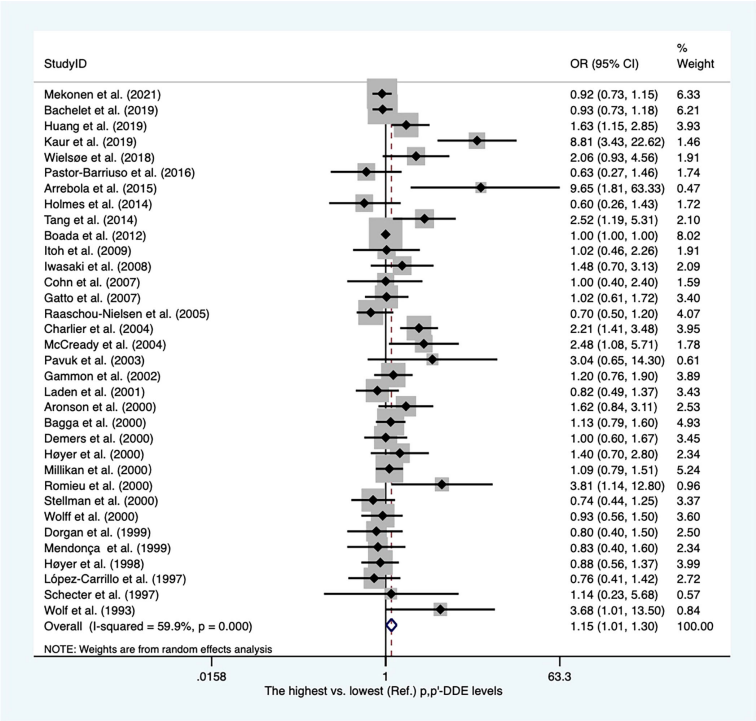


FIGURE 3
Summary estimates of the meta-analysis: association between p,p′-DDE exposure and breast cancer.

Phthalates and breast cancer

The characteristics of the studies included in our review are shown in Supplementary Table 7. Six publications provided five summary risk estimates for breast cancer. The urinary benzyl butyl phthalate (BBP) was negatively associated with breast cancer (OR, 0.76; 95% CI, 0.61–0.95; I^2 = 33.0%; P = 0.1888). However, the overall ORs for DBP, DEHP, DEP, and DIBP were not statistically significant (Supplementary Figures 20–24). The results are summarized in Figure 8.

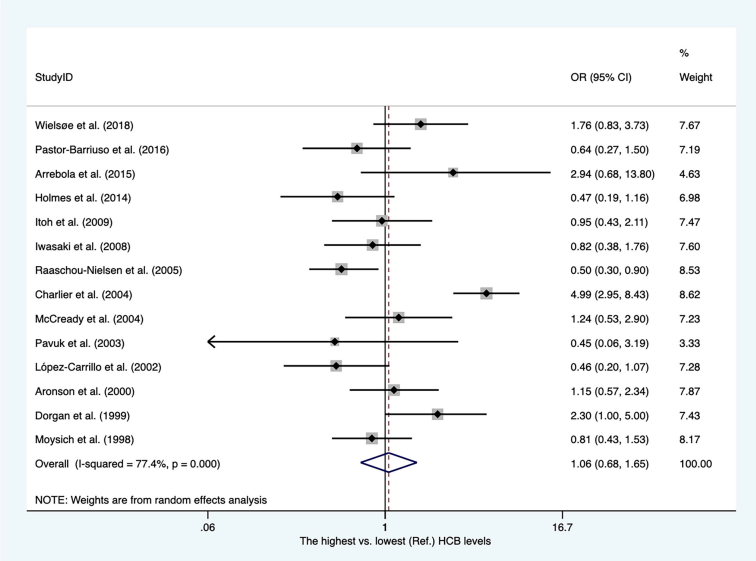


FIGURE 4
Summary estimates of the meta-analysis: association between HCB exposure and breast cancer.

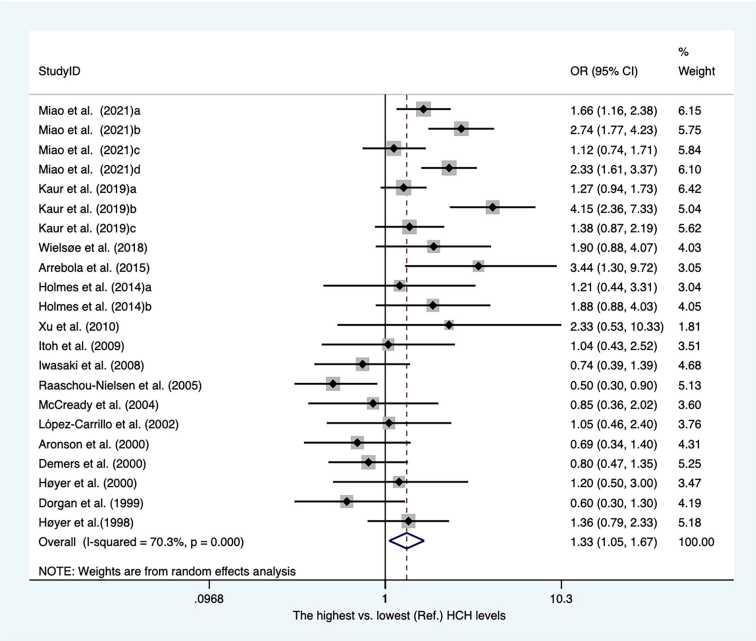


FIGURE 5
Summary estimates of the meta-analysis: association between HCH exposure and breast cancer.

Per- and polyfluoroalkyl substances and breast cancer

The characteristics of the studies included in our review are shown in Supplementary Table 8. Eleven publications provided nine summary risk estimates for breast cancer following exposure to PFASs. The summary estimates were above unity for perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorodecanoic acid (PFDA), perfluorohexanesulfonic acid (PFHxS), and perfluoro heptanoic acid (PFHpA) but were not statistically significantly elevated. Conversely, the pooled ORs were below unity for perfluorononanoic acid (PFNA), perfluoro undecanoic acid (PFUnDA), perfluoro-n-tridecanoic acid (PFTrDA), and perfluorododecanoic acid (PFDoDA) but only statistically significantly decreased for PFDoDA (OR, 0.69; 95% CI, 0.50–0.95; I^2 = 21.7%). The results are summarized in Figure 9.

Polybrominated diphenyl ethers and breast cancer

There were only four publications for polybrominated diphenyl ethers (PBDEs) included in our meta-analysis. The characteristics of the studies are shown in Supplementary Table 9. As shown in Figure 10, the overall OR for the highest versus lowest PBDE levels was 1.04 (95% CI, 0.82–1.30; I^2 = 45.1%).

Bisphenol A and breast cancer

The characteristics of the studies included in our meta-analysis are shown in Supplementary Table 10. There were four case–control studies and one nested case–control study. Four articles reported PBA levels from blood serum. As shown in

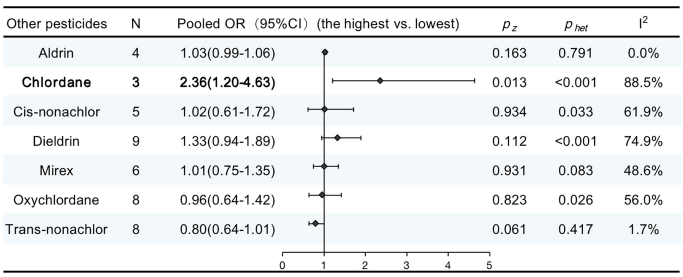


FIGURE 6
ORs (95% CI) of the summary estimate of analyses for associations between other pesticides and breast cancer.

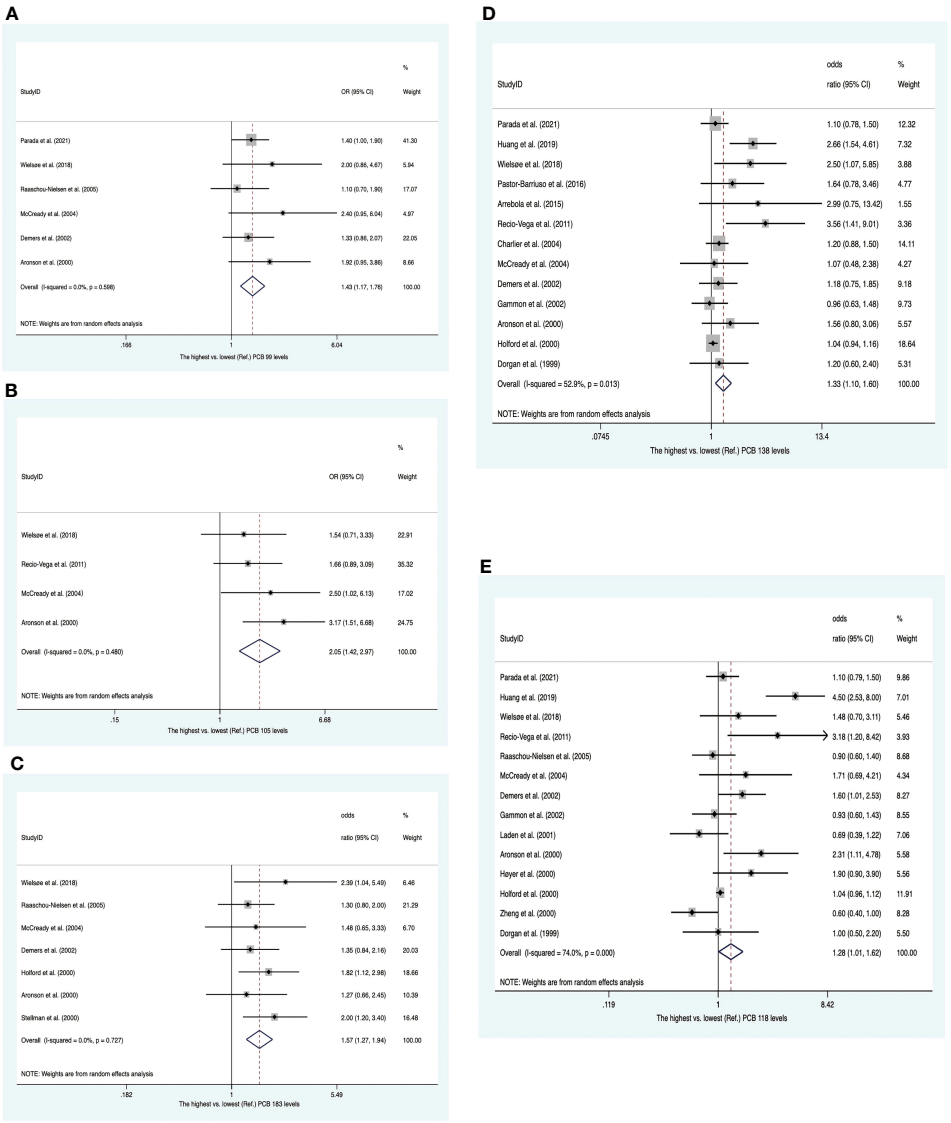


FIGURE 7
Summary estimates of the meta-analysis. **(A)** Associations between PCB 99 and breast cancer. **(B)** Associations between PCB 105 and breast cancer. **(C)** Associations between PCB 183 and breast cancer. **(D)** Associations between PCB 138 and breast cancer. **(E)** Associations between PCB 118 and breast cancer.

Figure 11, the overall OR for the highest versus lowest PBA levels was 0.91 (95% CI, 0.77–1.07).

Risk of bias assessment

Figure 12 summarizes the risk of bias assessment for randomized controlled trials and crossover trials that are included. Overall, most of the included publications reported tested hypotheses, and there was a low risk of bias for information bias. More than 90% of studies considered relevant confounders and measured confounding factors. Five of all papers were considered to have a high risk of selection bias, and the bias in the other 31 studies were not clearly described. Approximately 30% of all studies did not report whether they addressed sample size in the discussion. Fourteen articles had a high risk of exposure contrast because exposure categories were split by the median or by *ad-hoc* grouping comparison of median values in cases and controls rather than divided by tertiles and quantiles (or more detailed) or by grouping of levels. For example, this case–control study that only contrasted the median values in cases and control has assessed as high risk of exposure contrast (15).

Discussion

This meta-analysis aimed to pool available epidemiological evidence on 10 compound groups of EDCs and breast cancer. We finally pooled six compound groups because of limited publications. We included publications with real measurements of the chemical

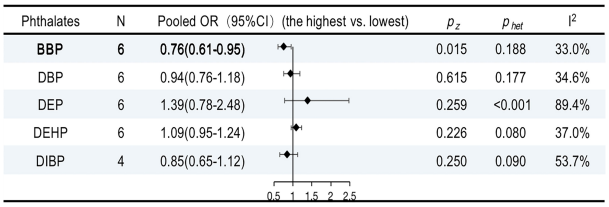


FIGURE 8
ORs (95% CI) of the summary estimate of analyses for associations between phthalates and breast cancer.

in biospecimens because reliable exposure assessment is necessary for the compounds of interest. This is a meta-analysis that, to our knowledge, has rigorously assessed the epidemiological data on the association between common endocrine-disrupting compounds and breast cancer. A total of 67 articles provided over 300 risk estimates regarding EDC exposure and breast cancer.

Meta-analysis

DDT and breast cancer

Paul Müller discovered that DDT can kill insects in 1939, and it has been widely used in agriculture since then (16). The results of this meta-analysis showed that the most recent body of literature supported a moderately positive relationship between DDT/DDE and breast cancer. DDT was a common organochlorine pesticide (OCP) during the 1940s and 1950s (17). Although many countries banned DDT from agricultural usage in the 1970s, especially in developed countries, the pollution still exists in the environment and in the food chain (5). There is growing interest in DDT/DDE exposure to breast cancer that has been evaluated and recognized by many systematic reviews and meta-analyses (11, 18, 19). Differing from meta-analyses conducted in 2013, we analyzed the risk of four isoforms of DDT: p,p′-DDT, p,p′-DDE, o,p′-DDT, and p,p′-DDD, respectively. These statistical results revealed that p,p′-DDT and p,p′-DDE were marginally associated with a higher risk of breast cancer with moderate to high levels of heterogeneity although the associations were weak. However, we did not observe consistent results after stratifying by study design and sample type. Overall, DDT/DDE in blood serum, not in adipose tissue, was positively associated with breast cancer. One possible explanation was that most of the control's adipose tissues came from those people with benign breast disease, which may confuse our final results. Unfortunately, we did not observe a positive relationship from nested case–control publications. There were only eight publications designed as prospective cohort, and these nested case–control publications most published before 2009 excluded one published in 2019. Cohn et al. found that blood serum p,p′-DDT was positively associated with breast cancer risk in 2019 (20), which was consistent with our analysis. A growing body of studies have analyzed the underlying mechanisms. Among of them, the estrogen-like properties of DDT are considered the most likely mechanism because overexpression of the estrogen hormone is associated with an increased risk for breast cancer (21, 22). Unfortunately, there were only four publications regarding o,p′-DDT and p,p′-DDD, respectively. Thus, the impact of o,p′-DDT and p,p′-DDD exposure on breast cancer cannot be determined in our review. More prospective studies are needed to clarify the relationship between DDT/DDE and breast cancer.

Other pesticides and breast cancer

In addition, we pooled another nine OCPs. Thereinto, HCH and chlordane were also related to breast cancer risk. However, in subgroups stratified by sample type, the summary OR for HCH in adipose tissue was significantly reduced. There were only three publications addressing HCH in adipose tissues, and these articles were published before 2005. Meanwhile, no association was observed for HCH from nested case–control studies and breast cancer. There were only four nested case–control publications, and these studies were conducted before 2008. To our knowledge, this is the first meta-analysis to analyze the relationship between HCH and breast cancer.

PCBs and breast cancer

The International Agency for Research on Cancer (IARC) upgraded PCBs to group 1 "Carcinogenic to humans" in 2015, on the basis of sufficient evidence of an excess risk for melanoma (23). In recent decades, an increasing number of epidemiological studies have investigated the connection between PCBs and the risk of breast cancer. However, the results were inconsistent. Two meta-analyses were conducted to investigate the relationship between individual PCB congeners and breast cancer in 2015 and 2016 (24,

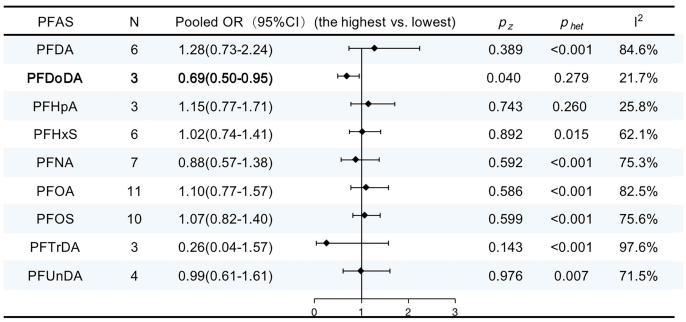


FIGURE 9
ORs (95% CI) of the summary estimate of analyses for associations between PFAS and breast cancer.

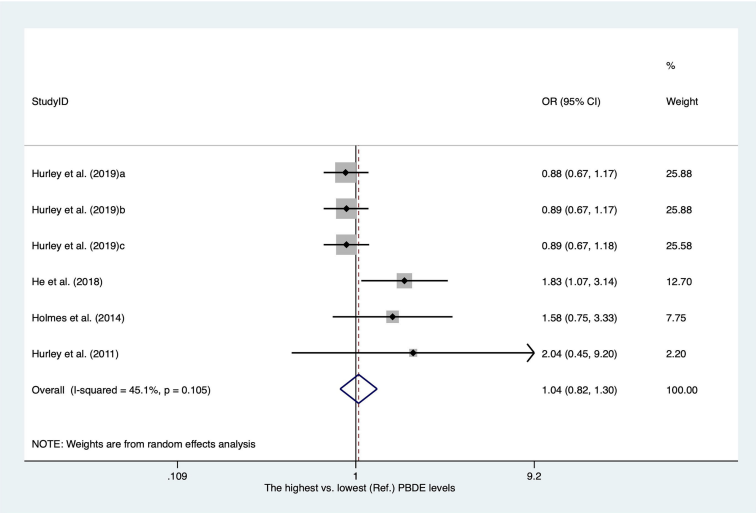


FIGURE 10
Summary estimates of the meta-analysis: association between PBDE exposure and breast cancer.

25). As epidemiological evidence has been updated in recent years (26–31), we further evaluated the association between PCBs and breast cancer. In 1995, Wolff and Toniolo classified PCB congeners into three groups: (i) group 1, containing PCBs that act as estrogen agonists, such as PCB 187; (ii) group 2, containing PCBs that act as dioxin, such as PCB 105, PCB 118, PCB 138, PCB 156, and PCB 170; and (iii) group 3, containing PCBs that work by stimulating cytochrome P450 enzymes, such as PCB 99, PCB 153, PCB 180, and PCB 183 (32). Zhang et al. found that group 2 and group 3 PCB exposure, but not group 1 PCB exposure, increased the risk of breast cancer in 2015 (25). However, it proved challenging to identify which specific PCB congeners are associated with breast cancer. In our review, 13 PCB congeners were reported by more than two studies. Similarly, we found that the highest (vs. lowest) tertiles of PCB 99 and PCB 183 (group 3) were positively associated with the risk of breast cancer in our analysis, which was consistent with the meta-analysis conducted in 2016. In addition, we also found that the risk of breast cancer can be increased by PCB 105, PCB 118, and PCB 138 (group 2).

Other EDCs and breast cancer

There are numerous unavoidable and accidental causes of exposure to BPA, phthalates, PBDEs, and PFASs in daily life. We found that one PFAS congener (PGDoDA) and one phthalate congener (BBP) were passively linked with the risk of breast cancer. However, only three publications addressing PGDoDA matched the requirements for meta-analysis. More studies are needed to identify the association. The impact of other phthalates, PFAS, BPA, and PBDE on breast cancer was not sufficiently supported by the results.

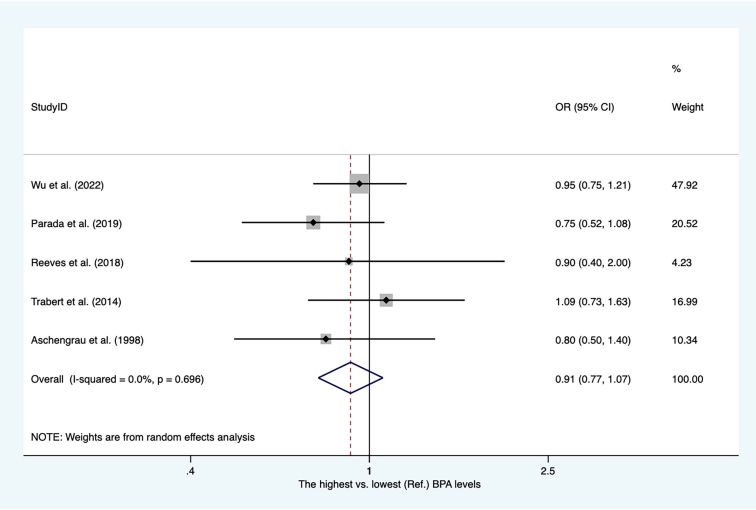


FIGURE 11
Summary estimates of the meta-analysis: association between PBA exposure and breast cancer.

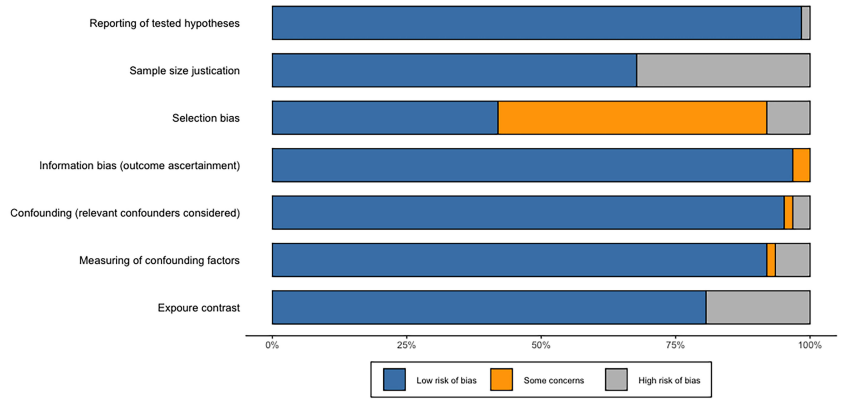


FIGURE 12
Risk of bias. The proportion of included publications with each of the identified risk categories (low risk, some concerns, and high risk).

Studies not eligible for meta-analysis

In addition, there were four compound groups of EDCs that were not eligible for meta-analysis because of limited studies. Further larger population-based studies are needed to clarify the real relationship between environmental EDCs and breast cancer.

There were only two studies addressing the relationship between parabens and breast cancer. Wu et al. found that breast cancer was inversely associated with total parabens (OR, 0.77; 95% CI, 0.62–0.97) in a nested case–control study in 2021 (33). Parada et al. found that there was no association between the risk of breast cancer and the highest (vs. lowest) quintiles of urine propylparaben (OR, 1.31; 95% CI, 0.90–1.90) and total parabens (OR, 1.35; 95% CI, 0.93–1.97), but the positive association was found between methylparaben and breast cancer (OR, 1.50; 95% CI, 1.03–1.18) (34). 2,3,7,8-Tetrachlorodibenzo-p-dioxins (TCDD), the most toxic congener of dioxin, is a widespread environmental contaminant that has been classified as carcinogenic to humans by the IARC (35). Two studies, conducted in 2002 and 2011, found that the TCDD levels in serum were not associated with the risk of breast cancer (36, 37). However, Rhee et al. found that residential exposure to dioxin emissions may confer an increased risk of breast cancer (38). Larger longitudinal studies are necessary to clarify the relationship between TCDD and breast cancer. Triclosan is a nonpersistent EDC that has caused serious public health concerns because it is widely absorbed through the skin, inhaled, and ingested. To date, only two studies have addressed the effect of individual exposure to triclosan on breast cancer. These two publications suggested that exposure to triclosan was not associated with breast cancer (33, 34). Two nested case–control studies found inconsistent results for PHA and breast cancer. In 2017, Shen et al. found that plasma PHA was positively associated with breast cancer risk (39). However, Wu et al. found no significant association between PHA and breast cancer in 2021 (40).

Strengths and limitations of the review

We have rigorously assessed the epidemiological data on 10 compound groups of EDCs (BPA, dioxins, parabens, phthalates diesters and their metabolites, flame retardants, PAHs, PCBs, organochloride pesticides, PFAS, and triclosan) and breast cancer and, finally, summarized risk estimates for six compounds (organochloride pesticides, PCBs, phthalates diesters and their metabolites, PFAS, flame retardants, and BPA). To our knowledge, we have for the first time summarized the relationship between HCH and breast cancer, and found that HCH was positively related to breast cancer risk. Meanwhile, the relationships between several common EDC congeners and breast cancer have been updated. such as DDT, PCBs, and phthalates. This facilitated a better understanding of the association between each type of EDCs and breast cancer. Unfortunately, heterogeneity was not well explained in our review, and a limited number of available prospective studies investigating the associations between EDC exposure and breast cancer were included in our meta-analysis. More attention was given to women, not men, perhaps because breast cancer is more common in women. To elucidate the overall associations, future large, longitudinal epidemiological investigations are needed.

Conclusions

In this meta-analysis, statistically significant associations revealed that (i) p,p′-DDT and its major metabolite p,p′-DDE were somewhat related to a greater risk of breast cancer. However, this relationship only existed in blood serum but not in adipose tissue. (ii) Breast cancer risk was increased by exposure to chlordane and HCH. (iii) Five polychlorinated biphenyls (PCB 99, PCB 105, PCB 118, PCB 138, and PCB 183) can increase the risk of breast cancer. (iv) One phthalate congener (BBP) and one PFAS congener (PFDoDA) were negatively associated with breast cancer risk. Our meta-analysis suggested that exposure to a few specific EDCs was identified as a risk factor for breast cancer. More effective preventive measures should be taken to control the environmental pollution of EDCs.

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

HL: Software, Data curation, Formal analysis, Writing – original draft. YKS: Data curation, Formal analysis, Writing – review & editing. LR: Data curation, Formal analysis, Writing – review & editing. JL: Data curation, Formal analysis, Writing – review & editing. YFS: Data curation, Formal analysis, Writing – review & editing. CM: Data curation, Formal analysis, Writing – original draft. CH: Conceptualization, Data curation, Project administration, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

Author YFS was employed by the company Jiaozuo Coal Industry Group Co. Ltd. Central Hospital.

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1282651/full#supplementary-material

References

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

2. Sher G, Salman NA, Khan AQ, Prabhu KS, Raza A, Kulinski M, et al. Epigenetic and breast cancer therapy: Promising diagnostic and therapeutic applications. *Semin Cancer Biol* (2022) 83:152–65. doi: 10.1016/j.semcancer.2020.08.009

3. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, et al. Global increase in breast cancer incidence: risk factors and preventive measures. *BioMed Res Int* (2022) 2022:9605439. doi: 10.1155/2022/9605439

4. Uldbjerg CS, Koch T, Lim YH, Gregersen LS, Olesen CS, Andersson AM, et al. Prenatal and postnatal exposures to endocrine disrupting chemicals and timing of pubertal onset in girls and boys: a systematic review and meta-analysis. *Hum Reprod Update* (2022) 28:687–716. doi: 10.1093/humupd/dmac013

5. Ma Y, Yun X, Ruan Z, Lu C, Shi Y, Qin Q, et al. Review of hexachlorocyclohexane (HCH) and dichlorodiphenyltrichloroethane (DDT) contamination in Chinese soils. *Sci Total Environ* (2020) 749:141212. doi: 10.1016/j.scitotenv.2020.141212

6. Melymuk L, Blumenthal J, Sáňka O, Shu-Yin A, Singla V, Šebková K, et al. Persistent problem: global challenges to managing PCBs. *Environ Sci Technol* (2022) 56:9029–40. doi: 10.1021/acs.est.2c01204

7. Hu W, Huang B, Zhao Y, Sun W, Gu Z. Distribution, sources and potential risk of HCH and DDT in soils from a typical alluvial plain of the Yangtze River Delta region, China. *Environ Geochem Health* (2014) 36:345–58. doi: 10.1007/s10653-013-9554-7

8. Ismanto A, Hadibarata T, Kristanti RA, Maslukah L, Safinatunnajah N, Kusumastuti W. Endocrine disrupting chemicals (EDCs) in environmental matrices: Occurrence, fate, health impact, physio-chemical and bioremediation technology. *Environ Pollut* (2022) 302:119061. doi: 10.1016/j.envpol.2022.119061

9. Bonde JP, Flachs EM, Rimborg S, Glazer CH, Giwercman A, Ramlau-Hansen CH, et al. The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: a systematic review and meta-analysis. *Hum Reprod Update* (2016) 23:104–25. doi: 10.1093/humupd/dmw036

10. Wan MLY, Co VA, El-Nezami H. Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies. *Crit Rev Food Sci Nutr* (2022) 62:6549–76. doi: 10.1080/10408398.2021.1903382

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj* (2021) 372:n71. doi: 10.1136/bmj.n71

12. Zhang X, Zhou Q, Qi Y, Chen X, Deng J, Zhang Y, et al. The effect of tomato and lycopene on clinical characteristics and molecular markers of UV-induced skin deterioration: A systematic review and meta-analysis of intervention trials. *Crit Rev Food Sci Nutr* (2023), 1–20. doi: 10.1080/10408398.2022.2164557

13. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. *J Clin Epidemiol* (2010) 63:1061–70. doi: 10.1016/j.jclinepi.2010.04.014

14. Calaf GM. Role of organophosphorous pesticides and acetylcholine in breast carcinogenesis. *Semin Cancer Biol* (2021) 76:206–17. doi: 10.1016/j.semcancer.2021.03.016

15. Mekonen S, Ibrahim M, Astatkie H, Abreha A. Exposure to organochlorine pesticides as a predictor to breast cancer: A case-control study among Ethiopian women. *PLoS One* (2021) 16:e0257704. doi: 10.1371/journal.pone.025770

16. Yang J, Ward MD, Kahr B. Abuse of rachel carson and misuse of DDT science in the service of environmental deregulation. *Angew Chem Int Ed Engl* (2017) 56:10026–32. doi: 10.1002/anie.201704077

17. Yipei Y, Zhilin L, Yuhong L, Meng W, Huijun W, Chang S, et al. Assessing the risk of diabetes in participants with DDT DDE exposure- A systematic review and meta-analysis. *Environ Res* (2022) 210:113018. doi: 10.1016/j.envres.2022.113018

18. Ingber SZ, Buser MC, Pohl HR, Abadin HG, Murray HE, Scinicariello F. DDT/DDE and breast cancer: a meta-analysis. *Regul Toxicol Pharmacol* (2013) 67:421–33. doi: 10.1016/j.yrtph.2013.08.021

19. Eve L, Fervers B, Le Romancer M, Etienne-Selloum N. Exposure to endocrine disrupting chemicals and risk of breast cancer. *Int J Mol Sci* (2020) 21. doi: 10.3390/ijms21239139

20. Cohn BA, Cirillo PM, Terry MB. DDT and Breast Cancer: Prospective Study of Induction Time and Susceptibility Windows. *J Natl Cancer Inst* (2019) 111:803–810. doi: 10.1093/jnci/djy198

21. Bornman M, Delport R, Farías P, Aneck-Hahn N, Patrick S, Millar RP, et al. Alterations in male reproductive hormones in relation to environmental DDT exposure. *Environ Int* (2018) 113:281–9. doi: 10.1016/j.envint.2017.12.039

22. Belachew EB, Sewasew DT. Molecular mechanisms of endocrine resistance in estrogen-positive breast cancer. *Front Endocrinol (Lausanne)* (2021) 12:599586. doi: 10.3389/fendo.2021.599586

23. Zani C, Ceretti E, Covolo L, Donato F. Do polychlorinated biphenyls cause cancer? A systematic review and meta-analysis of epidemiological studies on risk of

cutaneous melanoma and non-Hodgkin lymphoma. *Chemosphere* (2017) 183:97–106. doi: 10.1016/j.chemosphere.2017.05.053

24. Leng L, Li J, Luo XM, Kim JY, Li YM, Guo XM, et al. Polychlorinated biphenyls and breast cancer: A congener-specific meta-analysis. *Environ Int* (2016) 88:133–41. doi: 10.1016/j.envint.2015.12.022

25. Zhang J, Huang Y, Wang X, Lin K, Wu K. Environmental polychlorinated biphenyl exposure and breast cancer risk: A meta-analysis of observational studies. *PloS One* (2015) 10:e0142513. doi: 10.1371/journal.pone.0142513

26. Arrebola JP, Belhassen H, Artacho-Cordón F, Ghali R, Ghorbel H, Boussen H, et al. Risk of female breast cancer and serum concentrations of organochlorine pesticides and polychlorinated biphenyls: a case-control study in Tunisia. *Sci Total Environ* (2015) 520:106–13. doi: 10.1016/j.scitotenv.2015.03.045

27. Parada H Jr., Benmarhnia T, Engel LS, Sun X, Tse CK, Hoh E, et al. A congener-specific and mixture analysis of plasma polychlorinated biphenyl levels and incident breast cancer. *Epidemiology* (2021) 32:499–507. doi: 10.1097/ede.0000000000001356

28. Bachelet D, Verner MA, Neri M, Cordina Duverger É, Charlier C, Arveux P, et al. Breast Cancer and Exposure to Organochlorines in the CECILE Study: Associations with Plasma Levels Measured at the Time of Diagnosis and Estimated during Adolescence. *Int J Environ Res Public Health* (2019) 16. doi: 10.3390/ijerph16020271

29. Huang W, He Y, Xiao J, Huang Y, Li A, He M, et al. Risk of breast cancer and adipose tissue concentrations of polychlorinated biphenyls and organochlorine pesticides: a hospital-based case-control study in Chinese women. *Environ Sci Pollut Res Int* (2019) 26:32128–36. doi: 10.1007/s11356-019-06404-3

30. Wielsøe M, Kern P, Bonefeld-Jørgensen EC. Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. *Environ Health* (2017) 16:56. doi: 10.1186/s12940-017-0269-6

31. Pastor-Barriuso R, Fernández MF, Castaño-Vinyals G, Whelan D, Pérez-Gómez B, Llorca J, et al. Total effective xenoestrogen burden in serum samples and risk for breast cancer in a population-based multicase-control study in Spain. *Environ Health Perspect* (2016) 124:1575–82. doi: 10.1289/ehp157

32. Wolff MS, Toniolo PG. Environmental organochlorine exposure as a potential etiologic factor in breast cancer. *Environ Health Perspect* (1995) 103 Suppl 7:141–5. doi: 10.1289/ehp.95103s7141

33. Wu AH, Franke AA, Wilkens LR, Tseng C, Conroy SM, Li Y, et al. Risk of breast cancer and prediagnostic urinary excretion of bisphenol A, triclosan and parabens: The Multiethnic Cohort Study. *Int J Cancer* (2021) 149:1426–34. doi: 10.1002/ijc.33692

34. Parada H Jr., Gammon MD, Ettore HL, Chen J, Calafat AM, Neugut AI, et al. Urinary concentrations of environmental phenols and their associations with breast cancer incidence and mortality following breast cancer. *Environ Int* (2019) 130:104890. doi: 10.1016/j.envint.2019.05.084

35. Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al. A review of human carcinogens–Part F: chemical agents and related occupations. *Lancet Oncol* (2009) 10:1143–4. doi: 10.1016/s1470-2045(09)70358-4

36. Warner M, Mocarelli P, Samuels S, Needham L, Brambilla P, Eskenazi B. Dioxin exposure and cancer risk in the Seveso Women's Health Study. *Environ Health Perspect* (2011) 119:1700–5. doi: 10.1289/ehp.1103720

37. Warner M, Eskenazi B, Mocarelli P, Gerthoux PM, Samuels S, Needham L, et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect* (2002) 110:625–8. doi: 10.1289/ehp.02110625

38. Rhee J, Medgyesi DN, Fisher JA, White AJ, Sampson JN, Sandler DP, et al. Residential proximity to dioxin emissions and risk of breast cancer in the sister study cohort. *Environ Res* (2023) 222:115297. doi: 10.1016/j.envres.2023.115297

39. Shen J, Liao Y, Hopper JL, Goldberg M, Santella RM, Terry MB. Dependence of cancer risk from environmental exposures on underlying genetic susceptibility: an illustration with polycyclic aromatic hydrocarbons and breast cancer. *Br J Cancer* (2017) 116:1229–33. doi: 10.1038/bjc.2017.81

40. Wu HC, Yang HI, Lin PH, Chen CJ, Santella RM, Terry MB. Reproductive and environmental exposures and the breast cancer risk in Taiwanese women. *Sci Rep* (2021) 11:15656. doi: 10.1038/s41598-021-95290-2

Glossary

BBP	Benzyl butyl phthalate
BPA	Bisphenol A
EDCs	Endocrine-disrupting chemicals
DBP	Dibutyl phthalate
DDT	1,1-(2,2,2-trichloroethane-1,1-diyl)bis (4-chlorobenzene)
DEP	Diethyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DIBP	Diisobutyl phthalate
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
HR	Hazard ratio
IARC	International Agency for Research on Cancer
OCPs	Organochlorine pesticide
o,p'-DDT	1-methoxy-2-[2,2,2-trichloro-1-(4 methoxyphenyl)ethyl]benzene)
OR	Odds ratio
PAHs	Polyaromatic hydrocarbons
PBDE	Polybrominated diphenyl ethers
PCB	Polychlorinated biphenyls
PFAS	Per- and polyfluoroalkyl substances
PFDA	Perfluorodecanoic acid
PFDoDA	Perfluorododecanoic acid
PFHpA	Perfluoro heptanoic acid
PFHxS	Perfluorohexanesulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid
PFTrDA	Perfluoro-n-tridecanoic acid
PFUnDA	Perfluoro undecanoic acid
p,p′-DDE	2,2-bis(4-chlorophenyl)-1,1-dichloroethylene
p,p′-DDT	1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene
p,p′-DDD	2,2-bis(4-chlorophenyl)-1,1-dichloroethane
RR	Relative risk
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxins
95% CI	95% confidence interval

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 08 December 2023
DOI 10.3389/fpubh.2023.1303097

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Priyanka Sharma,
Rutgers, The State University of New Jersey, United States
Ronak Loonawat,
Wuxi Advanced Therapeutics, Inc., United States

*CORRESPONDENCE
Chengshui Chen
✉ chenchengshui@wmu.edu.cn
Haizhou Mao
✉ mhz@zjitc.edu.cn

†These authors have contributed equally to this work

RECEIVED 27 September 2023
ACCEPTED 22 November 2023
PUBLISHED 08 December 2023

CITATION
Xu Y, Zhao H, Yu C, Wang Y, Xu H, Weng Z, Chen C and Mao H (2023) An investigation of the risk factors of chronic obstructive pulmonary disease in natural population-based cohorts in China – a nested case-control study.
Front. Public Health 11:1303097.
doi: 10.3389/fpubh.2023.1303097

An investigation of the risk factors of chronic obstructive pulmonary disease in natural population-based cohorts in China – a nested case-control study

Yixin Xu[1†], Hongjun Zhao[1,2†], Chunchun Yu[1], Yuqian Wang[1], Hao Xu[1,2], Zhe Weng[1], Chengshui Chen[1,2*] and Haizhou Mao[3*]

[1]Key Laboratory of Interventional Pulmonology of Zhejiang Province, Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, [2]Department of Pulmonary and Critical Care Medicine, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Quzhou, China, [3]Department of Mathematics, Zhejiang Industry and Trade Vocational College, Wenzhou, Zhejiang, China

Background: Chronic obstructive pulmonary disease (COPD) has become one of the most significant chronic diseases in China. According to conventional wisdom, smoking is the pathogenic factor. However, current research indicates that the pathophysiology of COPD may be associated with prior respiratory system events (e.g., childhood hospitalization for pneumonia, chronic bronchitis) and environmental exposure (e.g., dust from workplace, indoor combustion particles). Dyspnea, persistent wheezing, and other respiratory symptoms further point to the need for pulmonary function tests in this population. Reducing the burden of chronic diseases in China requires a thorough understanding of the various factors that influence the occurrence of COPD.

Methods: Using a cohort from the natural population, this study used nested case-control analysis. We carried out a number of researches, including questionnaire surveys and pulmonary function testing, in the Northwest and Southeast cohorts of China between 2014 and 2021. After removing any variations in the baseline data between patients and control subjects using propensity score matching analysis, the risk factors were examined using univariate or multivariate regression.

Result: It was discovered that prior history of chronic bronchitis, long-term wheezing symptoms, and environmental exposure—including smoking and biofuel combustion—were risk factors for COPD. Dyspnea, symptoms of mobility limitation, organic matter, and a history of hospitalization for pneumonia at an early age were not significant in the clinical model but their incidence in COPD group is higher than that in healthy population.

Discussion: COPD screening effectiveness can be increased by looking for individuals with chronic respiratory symptoms. Smokers should give up as soon as they can, and families that have been exposed to biofuels for a long time should convert to clean energy or upgrade their ventilation. Individuals who have previously been diagnosed with emphysema and chronic bronchitis ought to be extra mindful of the prevention or advancement of COPD.

KEYWORDS

chronic obstructive pulmonary disease, exposures, symptoms, previous history, analyze

Introduction

The significant death rate linked with chronic obstructive pulmonary disease (COPD) has made it a global public health concern. By 2030, it is predicted to rank as the third most common cause of death globally (1, 2). A survey on the prevalence of COPD in China was carried out by Zhong et al. between 2002 and 2004 In China, the overall COPD prevalence was 8.2% (males: 12.4%; females: 5.1%) (3). Ten years later, the Chinese Lung Health (CPH) survey by Wang et al. revealed that 8.6% (95% CI7.5–9.9) of Chinese people had COPD overall in 2012–2015 (4). It is anticipated that China's COPD burden would continue to increase significantly (5).

Small airway disease and lung parenchymal damage work together to develop COPD. Chronic inflammation brought on by a variety of conditions results in lung parenchymal damage, small airway stenosis, structural abnormalities, and impaired mucociliary function (6). Smoking cessation should be the first priority in the treatment due to it is one of the main risk factors for COPD (7, 8). Hazardous gases, dust at work and indoor air pollution are all regarded as environmental exposures that require attention. Fuel exposure and occupational exposure are probably the second most important risk factors for COPD after smoking in developing and developed countries, respectively (9, 10). COPD risk can be decreased by adding exhaust fans or upgrading biomass burners (11). Workers who have been exposed to a range of dangerous compounds have demonstrated a greater incidence of COPD and a corresponding rise in death (10, 12). A few prior conditions, particularly those pertaining to the respiratory symptoms, may potentially serve as early indicators of COPD (4). Additional risk variables for COPD included age, gender, and a low body mass index (3). The aforementioned impacting elements will be covered in this paper.

We discovered that the majority of COPD researches had been regionally oriented since Zhong et al.'s (3) survey on the total prevalence of COPD in China and Wang et al.'s (4) study. Nonetheless, China has an unequal demographic and economic distribution, which could have an effect on how the risk factors for COPD are determined. In order to conduct a retrospective inquiry and analysis, this study chose the population cohorts from 2014 to 2021 in the Northwest and Southeast of China, respectively, and then qualifying people were chosen to be included in the study. Moreover, we did not restrict our investigation to exposure to dust or gasoline. The study refined categories of exposure and included traceability of previous clinical conditions, which were not available in the two previous population-based national cohort studies.

Methods

Study design and subjects

A natural population cohort study served as the foundation for our cross-sectional survey investigation. Due to the significant economic and social difference between the Southeast and Northwest regions of China, the study was first separated into two lines. Zhejiang Province was picked to represent Southeastern China, and the province of Gansu was chosen to represent Northwestern China. In the second round, software was utilized to generate random numbers, which were used to select three districts or counties in each province. Third, depending on differences in urban and rural development, equal share of urban streets or rural towns were randomly selected from the designated urban or county. Lastly, based on population size, cluster units made up of villages or urban settlements were chosen with using a random cluster sampling technique. Tests of pulmonary function and questionnaire surveys were conducted among individuals who were 40 years of age or older. After the two provinces' natural population cohorts were established, specific groups were screened for the case–control research.

The institutional review boards of the participating centers in each province approved the study's protocol and procedures.

Data collection

The goal of the study was explained to the subjects, and their informed consent was acquired. Every tester employed identical instruments, protocols, and questionnaires. Prior to conducting the survey, operators and interviewers underwent rigorous training. We obtained data from the research participants through a combination of in-person interviews, comprehensive physical examinations, and laboratory testing. A standardized and structured questionnaire was used by interviewers with training. The worldwide BOLD study was followed in developing the questionnaire's content (13). Certain things were added or removed based on the social and economic conditions in two different provinces. Demographic, socioeconomic, lifestyle, diet, employment history, occupational exposure, self-reported medical history, and other details were included in the information. The definition of exposure to relevant substances was indicated in the questionnaire. For example, A smoker was classified as someone who had smoked for more than 6 months straight. Occupational exposure was defined as more than a year of exposure to chemicals or dust at work (14). The discussion section goes over other pertinent definitions. Exclusions included recent surgery, history of stroke, pregnancy, and other conditions that would influence the pulmonary function test (15). Following the determination of spirometry eligibility, the individuals were scheduled for spirometry evaluation.

Diagnostic criteria

Although some studies have suggested that the LLN (lower limit of normal) is more valuable for the diagnosis of COPD, we adhere to the GOLD criteria: COPD was defined as FEV1/ FVC < 70% (FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; The ratio serves as an indicator of the extent of airway obstruction) after the bronchodilator test (inhalation of salbutamol 400 μg for at least 15 min) (16, 17). All populations using uniform spirometeres. All subjects underwent pulmonary function tests twice. If the post-bronchodilator FEV1/FVC was less than 0.70 during the two tests, we confirmed it on a separate occasion by repeating lung function test. This is because of the inaccuracy of making a diagnosis of COPD based on a single lung function measurement (18). Bronchodilators were prohibited for 48 h prior to testing.

Data processing

Chi-square tests were used to ascertain differences across variables, and exposure rates were computed as crude rates and 95%

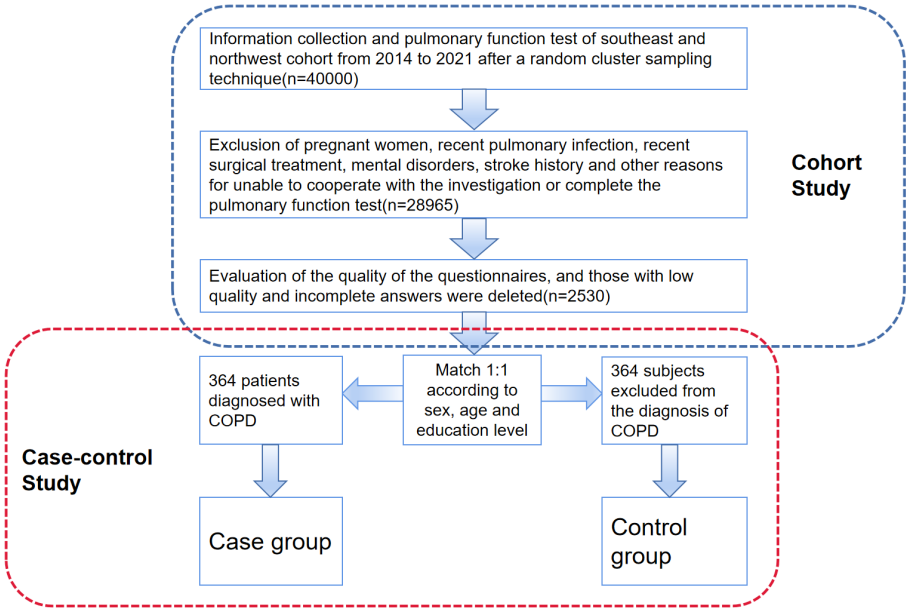


FIGURE 1
Procedures for data acquisition, screening and inclusion of subjects. The nested case-control study's technical path is depicted in this figure. The original cohort's formation is displayed in the upper portion of the image, along with the inclusion and exclusion criteria. The PSM method and the portion of the case-control research are displayed in the lower part of the figure.

TABLE 1 The basic demography characteristics of inclusion objects.

Characteristics	Total (n = 728)	Cases (n = 364)	Controls (n = 364)	p-value[b]
Sex				0.39
Male	548	279	269	
Female	180	85	95	
Age (years)[a]	60.74 ± 9.22	60.68 ± 9.10	60.80 ± 9.35	0.85
Education				0.73
Less than primary	348	175	173	
Middle or high school	363	179	184	
College or above	17	10	7	

[a]Mean (standard deviation, SD).
[b]Case group vs. control group.

confidence intervals. Using univariate/multivariate regression, the odd ratio (OR) and 95% confidence interval (CI) of COPD and possible risk variables were determined. SPSS version 27 and SAS version 9.4 were used for data analysis. Based on two-sided tests with a significant level of 0.05, all stated p values have been calculated.

Results

Participants characteristics

Included in the initial natural population cohort were more than 40,000 people. 2,530 people meet every requirement included in the analysis, as seen in Figure 1. Following 1:1 propensity score matching (PSM) based on age, gender, and educational attainment between the case group and the control group, 728 patients were ultimately chosen for the nested case-control investigation.

Between the two groups, the average age was 60.74 (SD = 9.22). Men made up 75.3% of the population, far more than women. The majority of them only completed middle school or less, so the population under study has a low average level of education. The data presented in Table 1 indicates that there is no statistically significant variation in gender, age, or cultural level among the various groups.

Clinical signs and symptoms

The rate at which symptoms emerge varies significantly between the COPD group and the healthy population. According to Table 2, the case group experienced greater respiratory symptoms than the control group. Long-term cough and phlegm did not differ between the two

TABLE 2 Different clinical symptoms of 2 groups.

Symptoms	Cases *n* (%)	Controls *n* (%)	*p*-value[a]	OR (95%CI)
Cough				
Yes	94 (25.8)	90 (24.7)	0.73	1.06 (0.76,1.48)
No	270 (71.2)	274 (75.3)		1.00 (reference)
Expectoration				
Yes	93 (25.5)	76 (20.9)	0.14	1.30 (0.92–1.84)
No	271 (74.5)	288 (79.1)		1.00 (reference)
Pant				
Yes	103 (28.3)	58 (15.9)	< 0.05	2.08 (1.45–2.99)
No	261 (71.7)	306 (84.1)		1.00 (reference)
Dyspnea				
Yes	161 (44.2)	102 (28.0)	< 0.05	2.04 (1.50–2.77)
No	203 (55.8)	262 (72.0)		1.00 (reference)
Activity limitation				
Yes	45 (12.4)	24 (6.6)	< 0.05	2.00 (1.19–3.36)
No	319 (87.6)	340 (93.4)		1.00 (reference)

CI, confidence interval.
[a]Case group vs. control group.

TABLE 3 Exposure factors comparison between 2 groups.

Exposures	Cases *n* (%)	Controls *n* (%)	*p*-value[b]	OR (95%CI)
Smoking				
Yes	233 (64.0)	199 (54.7)	<0.05	1.48 (1.10–1.99)
No	131 (36.0)	165 (45.3)		1.00 (reference)
SHS[a]				
Yes	176 (48.4)	189 (51.9)	0.34	0.87 (0.65–1.16)
No	188 (51.6)	175 (48.1)		1.00 (reference)
Fuel exposure				
Biofuels	203 (55.8)	177 (48.6)	<0.05	1.33 (1.00–1.78)
Coal fuel	98 (26.9)	92 (25.3)	0.61	1.09 (0.78–1.52)
None	131 (36.0)	176 (48.4)		1.00 (reference)
Winter heating				
Yes	237 (64.3)	246 (67.6)	0.48	0.90 (0.66–1.22)
No	127 (34.9)	118 (32.4)		1.00 (reference)
Dust exposure				
Chemical	42 (11.5)	51 (14.0)	0.32	0.80 (0.52–1.24)
Metal	12 (3.3)	8 (2.2)	0.37	1.52 (0.61–3.76)
Inorganic minerals	30 (8.2)	29 (8.0)	0.89	1.04 (0.61–1.77)
Organic matter	24 (6.6)	11 (3.0)	<0.05	2.27 (1.09–4.70)
Crops	94 (25.8)	90 (24.7)	0.73	1.06 (0.76–1.48)
None	221 (60.7)	230 (63.2)		1.00 (reference)

CI, confidence interval.
[a]Secondhand smoke.
[b]Case group vs. control group.

groups, but the case group experienced significantly greater rates of panting (28.3 vs. 15.9%), dyspnea during activities (44.2 vs. 28.0%), and limited mobility due to breathing difficulties (12.4 vs. 6.6%; $p < 0.05$).

Exposure factors

The respondents' prior exposure history was charted in Table 3. According to the majority of published research, smoking was discovered to be a risk factor for COPD. Both the case and control groups had more than half of their participants smoking (both past and present); the case group even reached 64.0%, which was statistically different from the control group. The case group had less secondhand smoke (SHS) exposure than the control group, but the difference was not statistically significant.

We separated the fuels into biofuels (straw and animal dung) and coal (kerosene and coal) based on the economic and environmental conditions of the two sites. We also divided the occupational exposure

TABLE 4 Comparison of past disease between 2 groups.

Past history	Cases *n* (%)	Controls *n* (%)	*p*-value[a]	OR (95%CI)
Hospitalization for pneumonia in childhood				
Yes	24 (6.6)	11 (3.0)	<0.05	1.27 (1.09–4.70)
No	340 (93.4)	353 (97.0)		1.00 (reference)
Asthma				
Yes	25 (6.9)	17 (4.7)	0.21	1.51 (0.80–2.84)
No	339 (93.1)	347 (95.3)		1.00 (reference)
Chronic bronchitis				
Yes	67 (18.4)	32 (8.8)	<0.05	2.34 (1.49–3.67)
No	297 (81.6)	332 (91.2)		1.00 (reference)
Emphysema				
Yes	29 (8.0)	1 (0.3)	<0.05	31.42 (4.26–231.96)
No	335 (92.0)	363 (99.7)		1.00 (reference)
Allergic rhinitis				
Yes	6 (1.6)	10 (2.7)	0.32	0.59 (0.21–1.65)
No	358 (98.4)	354 (97.3)		1.00 (reference)
Pulmonary tuberculosis				
Yes	5 (1.4)	3 (0.8)	0.48	1.68 (0.40–7.07)
No	359 (98.6)	361 (99.2)		1.00 (reference)
Hypertension				
Yes	76 (20.9)	88 (24.2)	0.29	0.83 (0.58–1.17)
No	288 (79.1)	276 (75.8)		1.00 (reference)
Coronary heart disease				
Yes	6 (1.6)	8 (2.2)	0.59	0.75 (0.26–2.17)
No	358 (98.4)	356 (97.8)		1.00 (reference)
Diabetes				
Yes	19 (5.2)	17 (4.7)	0.73	1.12 (0.58–2.20)
No	345 (94.8)	347 (95.3)		1.00 (reference)

CI, confidence interval.
[a]Case group vs. control group.

into five categories: metal dust, inorganic dust (silica, coal mining, cement manufacturing, etc.), chemical dust (detergent, hair dye, smoke, etc.), organic dust (poultry feathers or other animal hair), and crop dust (planting soil, grain dust, cotton dust, etc.). The case group's rate of long-term biofuel use was greater than that of the other group's (55.8 vs. 48.6%) in terms of solid particle matter exposure. Although there were comparable numbers of coal users in the two groups, the case group's rate was generally higher. In terms of occupational dust exposure, the case group was slightly more than the control group, and the two groups' exposure amounts to various chemicals were comparable. Only the exposure to organic compounds (6.6 vs. 3.0%) showed differences.

Previous history

The participant's past medical history, including a few common chronic conditions, was included in our questionnaire (Table 4). In the case group, the percentage of subjects who had been hospitalized for pneumonia in childhood (6.6 vs. 3.0%), or who had been diagnosed with chronic bronchitis (18.4 vs. 8.8%) or emphysema (8.0 vs. 0.3%), was significantly higher than that of the control group, according to the comparison of prior diseases. The prior history of bronchial asthma, which has diagnostic criteria comparable to COPD but is significantly reversible with bronchodilators, did not, however, show a statistically significant difference. Additionally, there was no change in the factor—a history of tuberculosis. Furthermore, chronic diseases like diabetes and cardiovascular disease were excluded from the clinical model since there was no evidence linking them to the illness.

Establish clinical model

While multi-factor analysis can adjust for the influence of multiple confounding factors and change the study's findings, univariate analysis frequently yields results that are not very dependable. Figure 2's risk factors that showed statistical significance in univariate regression were examined using logistic regression, and our clinical

Exposures	P	OR	95% CI
Pulmonary tuberculosis	0.72	1.31	0.29-5.86
Chronic bronchitis	<0.05	2.13	1.31-3.44
Asthma	0.5	0.79	0.39-1.59
Hospitalization for pneumonia	0.27	1.55	0.72-3.33
Organic matter	0.16	1.73	0.80-3.73
Biofuels	<0.05	1.36	1.00-1.85
Smoking	<0.05	1.5	1.10-2.05
Dyspnea	0.07	1.42	0.97-2.06
Activity limitation	0.25	1.41	0.78-2.53
Pant	<0.05	1.65	1.09-2.49

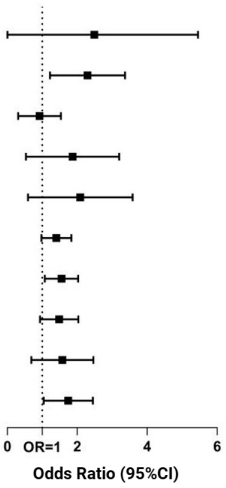


FIGURE 2
Odds ratios of different risk factors in clinical model. The screened exposure factors are displayed on the left side of the figure, while the corresponding OR values and 95%CI are displayed on the right side. The clinical model was adjusted for gender, age and education. Indicators that were positive in the comparison of respiratory symptoms, exposure factors and history of past illness were included. According to the findings, the clinical model of COPD includes smoking, using biofuel, having a history of bronchitis, and having pant symptoms as risk factors ($p < 0.05$).

model contained variables that showed statistical significance in multivariate regression. Using references to pertinent literature, the clinical model also incorporated the respiratory system's past history. Despite the fact that the univariate regression showed a substantial correlation (OR = 31.42) between the onset of the disease and a prior history of emphysema, we did not incorporate this into the clinical model due to the small number of patients with emphysema in the control group. There were worries that adding it would cause the result to be inaccurate. In the clinical model following multivariate regression, the symptoms of wheezing (OR = 1.65), smoking history (OR = 1.50), exposure to biofuels (OR = 1.36), and prior history of bronchitis (OR = 2.13) were identified as risk factors for COPD.

Discussion

COPD is a type of chronic lung disease. In order to increase screening efficiency, a well-designed COPD screening questionnaire revealed that respiratory symptoms like cough, expectoration, dyspnea, and wheezing could be useful in identifying individuals who would benefit most from pulmonary function testing (19). The percentage of individuals in both groups who had expectoration and cough was comparable. On the other hand, the case group experienced almost twice as many symptoms of wheezing or activity limitation as the control group. Dyspnea affected a notably higher number of individuals in the case group. Using a symptom-based questionnaire in the community can increase the effectiveness of COPD screening (20). It is recommended that individuals exhibiting respiratory symptoms, particularly those with persistent wheezing, should promptly undergo a pulmonary function test to ascertain the presence of COPD. Those with respiratory problems should receive extra consideration when being screened. The COPD disease burden can be decreased with early diagnosis (21).

Smoking was found to be a significant risk factor for COPD by both Ma et al. (OR value = 1.51) and Zhong et al. (OR value between 1.27 and 1.72) (2, 3). They were all rather close to the 1.50 OR value found in our investigation. Without a question, the most important factor in COPD is smoking. It has the potential to hasten FEV1 decrease. Accelerated airway oxidative stress, airway collapse, and inadequate lung tissue repair are some of the pathophysiological processes (22). The aetiology of COPD has been steadily revealed in recent years to involve occupational exposure to substances other than tobacco smoke and air pollution (2, 23). Our research, however, does not support the conception that exposure to secondhand smoke (SHS) increases the risk of developing COPD. Our questionnaire did not specify the precision of exposure time and degree, but we hypothesize that only a certain amount of secondhand smoking exposure can cause COPD (24). Patients may experience greater success quitting smoking if their respiratory symptoms are more acute. It may be more successful to implement interventions to improve COPD patients' adherence to smoking cessation therapy (8). It makes sense to counsel smokers to give up their habit (2, 25), not only to slow down the deterioration of their lungs but also to lessen the amount of secondhand smoke that they are exposed to in the community.

In addition to tobacco use, solid fuel use is a significant risk factor for COPD, particularly in developing nations (26, 27). The combustion of these solid fuels in domestic inefficient household stoves is the main source of indoor air pollution and have a negative impact on the respiratory system (11, 28). In Xuanwei, Yunnan Province, lung cancer and COPD have been discovered to be directly linked to the burning of these fuels (10, 29). According to the aforementioned extensive epidemiological study of COPD in China conducted by Zhong et al., exposure to indoor biomass for heating or cooking was linked to COPD (OR = 1.35 95%CI:1.20–1.52). In comparison to clean fuels, coal had an HR of 1.16 (95%CI, 1.04–1.29) and wood had an HR of 1.21 (95%CI, 1.09–1.35) for heating, according to a large prospective

domestic study (30). The use of coal fuel did not significantly differ between individuals with and without COPD, according to our research. However, compared to the control group, COPD patients were more likely to use biomass fuel. After the multivariate analysis, the OR value of biomass fuel exposure was 1.36 (95%CI, 1.00–1.85), which was comparable to the findings of Zhong et al. We consider the following factors could be at play: In rural China, coal and biofuels are the primary sources of heat and cooking for almost half the population (31). About 10% of the energy used by rural homes comes from coal, while about 80% comes from biomass (32). The majority of the responders are from rural areas in northwest China. Southeast China, on the other hand, has strict control of coal due to the increased popularity of clean fuels like natural gas. The amount of coal used nationwide is lower than the amount of biofuels. Delaying the onset of COPD can be achieved by weaning off of solid fuel exposure. As a result, some members of the exposed population who burned coal fuel did not go on to get COPD. Thus, we recommend that the government tighten regulations on the use of coal and biofuels while also promoting the use of clean fuels. In order to lower PIC (products of incomplete combustion) emissions, homeowners should be encouraged to install ventilation equipment and upgrade their stoves. This is especially important for residents living in rural regions (9, 29, 32).

Apart from smoking, occupational dust exposure may have a major role in pathophysiology of COPD in developed countries (10). Proteases can be released, oxidative stress reactions can be triggered, and epithelial cells can be harmed by the accumulation of occupationally hazardous particles in the respiratory tract. These particles include inorganic dust, soot, metals, and irritants (33). During agricultural activities, the inflammatory response in the airways may be caused by microbial components in organic dust (34). According to the Jinchang cohort research in Northwest China, the adjusted OR values for the metal exposure groups with moderate and high exposure were 1.22 (95%CI, 0.85–1.76) and 1.50 (95%CI, 1.03–2.18), respectively. Like the Jinchang cohort, a sizable number of our cohort's members were from northwest China, but the Jinchang cohort's members were regularly exposed to heavy metals (2). Like the Jinchang cohort, a sizable number of our cohort's members were from northwest China, but the Jinchang cohort's members were regularly exposed to heavy metals. The goal of our research is to determine which occupational exposure affects the pathophysiology of COPD. However, in univariate and multivariate analysis, exposure to organic dust was the only factor that was significant. It has been determined that allergens, microbes, and disinfectants exposed to animal feed are risk factors for COPD (35). We did not detect any appreciable changes in the exposure rates of inorganic compounds and metal dust between the two groups, despite the fact that we thoroughly described the meaning of exposure and the common types of various substances during the questionnaire-filling procedure. The confirmation of occupational exposure in many studies, including ours, was based on self-reports. The subjects' educational background (the majority were middle school students and lower), lack of environmental awareness, and propensity for subjective feedback may have contributed to the bias. But subjective effects such as those generated by self-report cannot be eliminated. Furthermore, rather than being exposed to a single substance at work, the majority of workers are exposed to diverse pollutants, and various kinds of pollutants may interact (36). Although the relevant evidence and OR values of different occupational exposures need to be investigated, the impact of workplace exposures on the pathogenesis of COPD should be paid attention to in any case (10).

A prior history of lung disease may increase the likelihood of developing COPD. Our research shown that in clinical regression model, a prior diagnosis of chronic bronchitis was a risk factor for COPD. Patients with chronic bronchitis and COPD have a higher chance of dying and a more severe decrease in lung function (37). According to certain research, chronic bronchitis, emphysema and asthma are three phenotypes of COPD (33, 38). In the US, the COPD Gene Study examined 10,192 adult smokers and discovered a correlation between childhood pneumonia and COPD (OR 1.40; 95%CI 1.17–1.66) (25). The univariate odds ratio was comparable to our study's, despite the clinical model's lack of significance for children pneumonia. This implies that early-life respiratory illness may have an impact on the development of COPD (39). Our research, however, does not point to a connection between COPD and pulmonary tuberculosis. Since tuberculosis is a treatable illness, we consider that the cause is recall bias—some people may not be aware of their prior infection history. Its impact on lung illnesses may be because to the oxidative stress and inflammation brought on by hyperglycemia, which can cause damage to the pulmonary arteries (40). However, there is now little direct evidence of mechanism linking one disease to the other's advancement (41, 42). In a similar vein, it's well accepted that COPD and cardiovascular illness are tightly associated (43). Common risk factors for cardiovascular disease and COPD include smoking and tobacco use (44). On the other hand, the aforementioned variables could cause cardiovascular and pulmonary illnesses to appear simultaneously. It is still up to us to discover and verify the mechanism (43, 45).

This investigation has some shortcomings. Due to the respondents' cultural background and other limitations, the inquiry contains some recall bias, which could cause a partial variation in the results. The inclusion factors in the clinical model are still up for debate, and there may be potential elements that influence the outcome. Due to missing data from the survey and our use of PSM for data processing, fewer individuals were included in the two groups even though our overall population cohort size exceeded 40,000. We employ strict inclusion criteria in the hopes that the results from the interference of bias, but the objects may be too little.

Data availability statement

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

Ethics statement

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

YX: Writing – original draft, Writing – review & editing. HZ: Writing – original draft, Writing – review & editing. CY: Writing –

original draft. YW: Writing – original draft. HX: Writing – original draft. ZW: Writing – original draft. CC: Writing – review & editing. HM: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the following fundings: The National Key Research and Development Program of China grants 2016YFC1304000 (CC); The National Natural Scientific Foundation of China 82170017 (CC); Zhejiang Provincial Key Research and Development Program 2020C03067 (CC). Health Industry Scientific Research Project of Gansu Province grants GSWSKY2018-18 (HZ).

Conflict of interest

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

Publisher's note

References

1. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet*. (2012) 379:1341–51. doi: 10.1016/s0140-6736(11)60968-9

2. Ma L, Huo X, Yang A, Yu S, Ke H, Zhang M, et al. Metal exposure, smoking, and the risk of COPD: a nested case-control study in a Chinese occupational population. *Int J Environ Res Public Health*. (2022) 19. doi: 10.3390/ijerph191710896 [Epub ahead of print].

3. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S, et al. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. *Am J Respir Crit Care Med*. (2007) 176:753–60. doi: 10.1164/rccm.200612-1749OC

4. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China pulmonary health [CPH] study): a national cross-sectional study. *Lancet*. (2018) 391:1706–17. doi: 10.1016/s0140-6736(18)30841-9

5. Yin P, Wu J, Wang L, Luo C, Ouyang L, Tang X, et al. The burden of COPD in China and its provinces: findings from the global burden of disease study 2019. *Front Public Health*. (2022) 10:859499. doi: 10.3389/fpubh.2022.859499

6. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med*. (2017) 195:557–82. doi: 10.1164/rccm.201701-0218PP

7. Tønnesen P. Smoking cessation and COPD. *Europ Respirat Rev*. (2013) 22:37–43. doi: 10.1183/09059180.00007212

8. Qin R, Liu Z, Zhou X, Cheng A, Cui Z, Li J, et al. Adherence and efficacy of smoking cessation treatment among patients with COPD in China. *Int J Chron Obstruct Pulmon Dis*. (2021) 16:1203–14. doi: 10.2147/copd.S301579

9. Kim C, Seow WJ, Shu XO, Bassig BA, Rothman N, Chen BE, et al. Cooking coal use and all-cause and cause-specific mortality in a prospective cohort study of women in Shanghai. *China Environ Health Persp*. (2016) 124:1384–9. doi: 10.1289/ehp236

10. Grahn K, Gustavsson P, Andersson T, Lindén A, Hemmingsson T, Selander J, et al. Occupational exposure to particles and increased risk of developing chronic obstructive pulmonary disease (COPD): a population-based cohort study in Stockholm, Sweden. *Environ Res*. (2021) 200:111739. doi: 10.1016/j.envres.2021.111739

11. Zhou Y, Zou Y, Li X, Chen S, Zhao Z, He F, et al. Lung function and incidence of chronic obstructive pulmonary disease after improved cooking fuels and kitchen ventilation: a 9-year prospective cohort study. *PLoS Med*. (2014) 11:e1001621. doi: 10.1371/journal.pmed.1001621

12. Torén K, Järvholm B. Effect of occupational exposure to vapors, gases, dusts, and fumes on COPD mortality risk among Swedish construction workers: a longitudinal cohort study. *Chest*. (2014) 145:992–7. doi: 10.1378/chest.13-1429

13. Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, et al. The burden of obstructive lung disease initiative (BOLD): rationale and design. *COPD*. (2005) 2:277–83. doi: 10.1081/COPD-57610

14. Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. *Lancet Respir Med*. (2018) 6:421–30. doi: 10.1016/s2213-2600(18)30103-6

15. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. *Am J Respir Crit Care Med*. (2019) 200:e70–88. doi: 10.1164/rccm.201908-1590ST

16. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. *Eur Respir J*. (2023) 61. doi: 10.1183/13993003.00239-2023

17. Global Strategy for Prevention, Diagnosis and Management of COPD (2023). Report. [2022]. Available at: https://goldcopd.org/ (Accessed November 5, 2023).

18. Schermer TR, Robberts B, Crockett AJ, Thoonen BP, Lucas A, Grootens J, et al. Should the diagnosis of COPD be based on a single spirometry test? *NPJ Primary Care Respirat Med*. (2016) 26:16059. doi: 10.1038/npjpcrm.2016.59

19. van Schayck CP, Halbert RJ, Nordyke RJ, Isonaka S, Maroni J, Nonikov D. Comparison of existing symptom-based questionnaires for identifying COPD in the general practice setting. *Respirology*. (2005) 10:323–33. doi: 10.1111/j.1440-1843.2005.00720.x

20. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, et al. Symptom-based questionnaire for identifying COPD in smokers. *Respiration*. (2006) 73:285–95. doi: 10.1159/000090142

21. Cherian M, Jensen D, Tan WC, Mursleen S, Goodall EC, Nadeau GA, et al. Dyspnoea and symptom burden in mild-moderate COPD: the Canadian cohort obstructive lung disease study. *ERJ Open Res*. (2021) 7:00960–2020. doi: 10.1183/23120541.00960-2020

22. Bai JW, Chen XX, Liu S, Yu L, Xu JF. Smoking cessation affects the natural history of COPD. *Int J Chron Obstruct Pulmon Dis*. (2017) 12:3323–8. doi: 10.2147/copd.S150243

23. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. *Lancet Respir Med*. (2022) 10:497–511. doi: 10.1016/s2213-2600(21)00506-3

24. He Y, Jiang B, Li LS, Li LS, Ko L, Wu L, et al. Secondhand smoke exposure predicted COPD and other tobacco-related mortality in a 17-year cohort study in China. *Chest*. (2012) 142:909–18. doi: 10.1378/chest.11-2884

25. Hayden LP, Hobbs BD, Cohen RT, Wise RA, Checkley W, Crapo JD, et al. Childhood pneumonia increases risk for chronic obstructive pulmonary disease: the COPDGene study. *Respir Res*. (2015) 16:115. doi: 10.1186/s12931-015-0273-8

26. Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. *Int J Chron Obstruct Pulmon Dis*. (2018) 13:1353–64. doi: 10.2147/copd.S161555

27. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. *Lancet Respir Med*. (2022) 10:447–58. doi: 10.1016/s2213-2600(21)00511-7

28. Shen H, Luo Z, Xiong R, Liu X, Zhang L, Li Y, et al. A critical review of pollutant emission factors from fuel combustion in home stoves. *Environ Int*. (2021) 157:106841. doi: 10.1016/j.envint.2021.106841

29. Chapman RS, He X, Blair AE, Lan Q. Improvement in household stoves and risk of chronic obstructive pulmonary disease in Xuanwei, China: retrospective cohort study. *BMJ*. (2005) 331:1050. doi: 10.1136/bmj.38628.676088.55

30. Li J, Qin C, Lv J, Guo Y, Bian Z, Zhou W, et al. Solid fuel use and incident COPD in Chinese adults: findings from the China Kadoorie biobank. *Environ Health Perspect*. (2019) 127:57008. doi: 10.1289/ehp2856

31. Qiu S, Chen X, Chen X, Luo G, Guo Y, Bian Z, et al. Solid fuel use, socioeconomic indicators and risk of cardiovascular diseases and all-cause mortality: a prospective

cohort study in a rural area of Sichuan. *China Int J Epidemiol*. (2022) 51:501–13. doi: 10.1093/ije/dyab191

32. Zhang JJ, Smith KR. Household air pollution from coal and biomass fuels in China: measurements, health impacts, and interventions. *Environ Health Perspect*. (2007) 115:848–55. doi: 10.1289/ehp.9479

33. Murgia N, Gambelunghe A. Occupational COPD-the most under-recognized occupational lung disease? *Respirology*. (2022) 27:399–410. doi: 10.1111/resp.14272

34. Poole JA, Romberger DJ. Immunological and inflammatory responses to organic dust in agriculture. *Curr Opin Allergy Clin Immunol*. (2012) 12:126–32. doi: 10.1097/ACI.0b013e3283511d0e

35. Sigsgaard T, Basinas I, Doekes G, de Blay F, Folletti I, Heederik D, et al. Respiratory diseases and allergy in farmers working with livestock: a EAACI position paper. *Clin Transl Allergy*. (2020) 10:29. doi: 10.1186/s13601-020-00334-x

36. Sadhra S, Kurmi OP, Sadhra SS, Lam KB, Ayres JG. Occupational COPD and job exposure matrices: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. (2017) 12:725–34. doi: 10.2147/copd.S125980

37. Lahousse L, Seys LJM, Joos GF, Franco OH, Stricker BH, Brusselle GG. Epidemiology and impact of chronic bronchitis in chronic obstructive pulmonary disease. *Eur Respir J*. (2017) 50:1602470. doi: 10.1183/13993003.02470-2016

38. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. (2013) 187:228–37. doi: 10.1164/rccm.201210-1843CI

39. Savran O, Ulrik CS. Early life insults as determinants of chronic obstructive pulmonary disease in adult life. *Int J Chron Obstruct Pulmon Dis*. (2018) 13:683–93. doi: 10.2147/copd.S153555

40. Ramalho SHR, Shah AM. Lung function and cardiovascular disease: a link. *Trends Cardiovasc Med*. (2021) 31:93–8. doi: 10.1016/j.tcm.2019.12.009

41. Khateeb J, Fuchs E, Khamaisi M. Diabetes and lung disease: a neglected relationship. *Rev Diabet Stud*. (2019) 15:1–15. doi: 10.1900/rds.2019.15.1

42. Park SS, Perez Perez JL, Perez Gandara B, Agudelo CW, Rodriguez Ortega R, Ahmed H, et al. Mechanisms linking COPD to type 1 and 2 diabetes mellitus: Is there a relationship between diabetes and COPD? *Medicina*. (2022) 58:1030. doi: 10.3390/medicina58081030

43. Serban KA, Pratte KA, Bowler RP. Protein biomarkers for COPD outcomes. *Chest*. (2021) 159:2244–53. doi: 10.1016/j.chest.2021.01.004

44. Cascio WE. Wildland fire smoke and human health. *Sci Total Environ*. (2018) 624:586–95. doi: 10.1016/j.scitotenv.2017.12.086

45. Casselbrant A, Fedorowski A, Frantz S, Engström G, Wollmer P, Hamrefors V. Common physiologic and proteomic biomarkers in pulmonary and coronary artery disease. *PLoS One*. (2022) 17:e0264376. doi: 10.1371/journal.pone.0264376

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 14 December 2023
DOI 10.3389/fonc.2023.1308897

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Aditya Yashwant Sarode,
Columbia University, United States
Nidhi Kumari,
University of California, Los Angeles, United States
Nisha Gautam,
Rutgers University, Newark, United States

*CORRESPONDENCE
Lijalem Melie Tesfaw
lijalemmelie@gmail.com

RECEIVED 07 October 2023
ACCEPTED 28 November 2023
PUBLISHED 14 December 2023

CITATION
Tesfaw LM, Dessie ZG and Mekonnen Fenta H (2023) Lung cancer mortality and associated predictors: systematic review using 32 scientific research findings. *Front. Oncol.* 13:1308897. doi: 10.3389/fonc.2023.1308897

Lung cancer mortality and associated predictors: systematic review using 32 scientific research findings

Lijalem Melie Tesfaw[1,2*], Zelalem G. Dessie[1,3] and Haile Mekonnen Fenta[1]

[1]Departement of Statistics, Bahir Dar University, Bahir Dar, Ethiopia, [2]Epidemiology and Biostatistics Division, School of Public Health, Queensland University, Brisbane, QLD, Australia, [3]School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, Durban, South Africa

Background: Cancer is a chronic disease brought on by mutations to the genes that control our cells' functions and become the most common cause of mortality and comorbidities. Thus, this study aimed to assess the comprehensive and common mortality-related risk factors of lung cancer using more than thirty scientific research papers.

Methods: Possible risk factors contributing to lung cancer mortality were assessed across 201 studies sourced from electronic databases, including Google Scholar, Cochrane Library, Web of Science (WOS), EMBASE, Medline/PubMed, the Lung Cancer Open Research Dataset Challenge, and Scopus. Out of these, 32 studies meeting the eligibility criteria for meta-analysis were included. Due to the heterogeneous nature of the studies, a random-effects model was applied to estimate the pooled effects of covariates.

Results: The overall prevalence of mortality rate was 10% with a 95% confidence interval of 6 and 16%. Twenty studies (62.50%) studies included in this study considered the ages of lung cancer patients as the risk factors for mortality. Whereas, eighteen (56.25%) and thirteen (40.63%) studies incorporated the gender and smoking status of patients respectively. The comorbidities of lung cancer mortality such as cardiovascular disease, hypertension, diabetes, and pneumonia were also involved in 7 (21.90%), 6 (18.75%), 5 (15.63%), and 2 (6.25%) studies, respectively. Patients of older age are more likely to die as compared to patients of younger age. Similarly, lung patients who had smoking practice were more likely to die as compared to patients who hadn't practiced smoking

Conclusion: The mortality rate of lung cancer patients is considerably high. Older age, gender, stage, and comorbidities such as cardiovascular, hypertension, and diabetes have a significant positive effect on lung cancer mortality. The study results will contribute to future research, management, and prevention strategies for lung cancer.

KEYWORDS

lung cancer, mortality, predictors, systematic review, global

Introduction

Cancer is a chronic disease brought on by mutations to the genes that control our cells' functions, particularly their growth and division, which results in uncontrolled cell growth and division that forms malignant tumors and spreads to nearby organs (1). In 2015, the Global Burden of Disease Cancer study found that, with 8 million deaths, cancer was the second greatest cause of death worldwide, with cardiovascular illnesses taking the top spot (2).

According to 2018 World Cancer statistics, there were an estimated 18 million cancer cases around the world, of which 9.5 million cases were males and 8.5 million in females (3). Recently National Cancer Institute showed that there are more than 100 types of cancer which are usually named for the organs or tissues where the cancers form (2, 4). With 2,093,876 cases or 12.3% of the total, lung cancer is the first and most often diagnosed cancer worldwide. Among the top five most frequently diagnosed cancers, breast (2,088,849 cases, 12.2% of the total), colorectal (1,800,977 cases, 10% of the total), prostate (1,276,106 cases, 9.8% of the total), and stomach (1,033,701 cases, 5% of the total) are ranked second, third, fourth, and fifth, respectively (2). As a result, this study was focused on a meta-analysis of mortality-related risk factors of lung cancer.

Lung cancer is a malignancy that typically develops in the cells lining the airways of the lung. It remained the leading cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers (4, 5). Lung cancer has already become a threat to public health around the world with nearly 2 million cases and deaths in 2020. The cases of lung cancer annually are anticipated to reach 3.8 million in 2050, even with current risk levels and age-specific rates (6). Several studies reported that socioeconomic, demographic, biological, and behavioral factors are important determinants of lung cancer mortality (5). Among these age (7–10), sex (11–14), cigarette smoking (8, 9, 12, 13), stage (10, 14–16), infectious lung disease (ILD) (7, 17, 18), body mass index (BMI) (12, 13, 19, 20), diabetes (13, 15, 19, 21), and hypertension (12, 17, 19) are the most common factors associated with lung cancer mortality.

In regards to gender, following prostate and colorectal cancer, lung cancer is the most common cancer and the main cause of cancer death in men. The lung cancer death rates among women whose husbands had ever smoked during the current marriage were 20% higher than those among those who were married to never-smokers. Cigarette smoking is the most important preventable risk factor for lung cancer, which is the leading cause of cancer mortality (6). Lung cancer risk is higher in people with low BMI. When the analysis was limited to lifetime nonsmokers, an increased risk of lung cancer associated with a family history of the disease was found, though this did not reach statistical significance (11, 22).

Despite, the lung cancer mortality rates are increasing and numerous studies conducted (8, 17, 18, 21, 23, 24) to identify the potential risk factors, still a lack of studies that show common causes of mortality due to lung cancer. Several studies were done on lung cancer to identify associated factors of it. However, they are limited to some specific locations, cases, and attributes. Thus, this study aimed to assess the comprehensive and common mortality-related risk factors of lung cancer using more than thirty scientific research papers. In this study, we provide a comprehensive and comparable investigation of mortality-related risk factors of lung cancer global level.

Materials and methods

Study protocol

To evaluate the association between lung cancer mortality and comorbidities, as well as other socioeconomic, demographic, and biological factors. The study implemented and followed PRISMA procedures to execute the meta-analysis of the articles identified through our systematic reviews.

Search strategy

We systematically searched electronic databases up until 10 December 2022, including Google Scholar, Cochrane Library, Web of Sciences (WOS), EMBASE, Medline/PubMed, lung cancer Open Research Dataset Challenge, and Scopus. The search strategy was as follows: (lung cancer mortality OR lung neoplasms mortality OR cancer death rate) AND (risk factors OR predictors OR determinants) AND (adult patients OR lung cancer patients OR lung cancer survivors). The search was also narrowed down to articles that examined laboratory data, pre-existing comorbidities, clinical status, and demographic traits as potential indicators of lung cancer's fatal outcome. The time and language of publications were not subject to any limitations. We downloaded the literature results into EndNote X9 to speed up the screening procedure.

Eligibility criteria

After duplicates were eliminated, the initial search results were checked for relevance by both authors using titles and abstracts. The eligibility requirements were examined in the complete texts (Figure 1). Excluded from the analysis were studies without an abstract or full text, correspondence, studies on infants only, editorials, reviews, qualitative studies, books, theses, expert opinion papers, and review articles. We also used studies that only provided odds ratios (ORs), hazard ratios (HRs), or relative risks (RR) along with 95% confidence intervals (CI) for the association between demographic, epidemiological, or clinical characteristics and fatal outcomes of lung cancer among the eligible studies. The overall studies included in this study was presented in Table 1.

Data extraction and assessment for study quality

The downloaded EndNote X9 search outputs were independently reviewed for inclusion by each author. Discussion

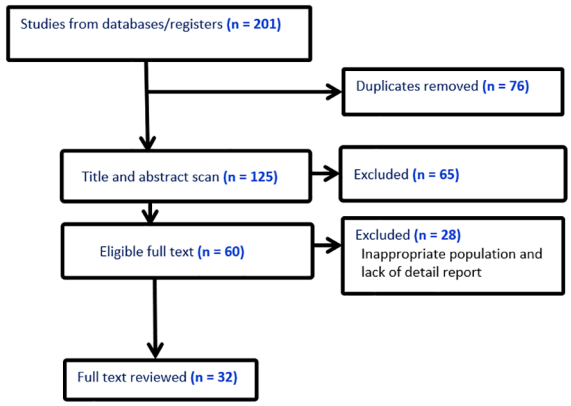


FIGURE 1
Literature screening flow chart.

and consensus among the authors were used to settle any differences. The first author's name, country, assessment techniques, sample size, study design, publication year, demographic and clinical variables (such as gender, age, and comorbidities), outcome (mortality), exposure (risk factors), and adjusted odds ratios or hazard ratios or relative risks were all extracted by all authors.

Using the Newcastle-Ottawa method, the authors independently assessed the articles' quality methodological approach. This method relied on three main elements to evaluate the quality of the papers: evaluation of the results, comparability of the study groups, and patient selection methods. The seven domains in the Newcastle-Ottawa technique were scored from 3 to 0 (i.e., from low to high bias), and their average score was taken.

Statistical analysis

To determine the relationship between risk factors and the likelihood that lung cancer will be fatal, we used ORs, RRs, or HRs (and their 95%CI) that were peer-reviewed and published. The expected between-study heterogeneity has been taken into consideration when computing a mixed-effect model. Cochran's Q test was used to determine whether there was heterogeneity in effect sizes; a significant Q value suggests that there is heterogeneity rather than homogeneity. The I^2 statistic was used to calculate the percentage of the total variance that could be attributed to study heterogeneity (39). The I^2 values between 60% and 90%, 40% and 59%, and 0% and 39% were regarded as severe, moderate, and mild, respectively. For evaluating publication bias, funnel plots with an Egger-weighted regression test were used (40). The pooled odds ratio, relative risk, and hazard ratio were calculated and publication bias was examined using STATA version 17 and R-4.0.2 statistical software, respectively.

Results

In this study, a total of 201 publications on the mortality of lung cancer were identified using so many sites such as Google Scholar, Cochrane Library, Web of Sciences (WOS), EMBASE, Medline/PubMed, cancer research database (WHO), lung cancer open research dataset challenge, and Scopus database, of which, 15 studies that did not have numbers of hospital death, 35 reviews, 15 non-English, and 76 duplicates were excluded. Among the remaining 60 studies, 28 did not report cross-tabulation with ORs or HRs, or RRs. Consequently, we got only 32 studies that satisfied all the eligibility criteria (see Figure 1). The studies considered in this meta-analysis consists of numerous mortality-related risk factor of lung cancer diseases (6, 8, 10, 11, 16, 18, 25, 26, 29, 30, 32) (see Table 1). The effect of each risk factor on mortality of lung cancer was measured and estimated using adjusted odds ratio (OR), relative risk (RR), or hazard ratio (HR).

The estimate of each risk factor was the pooled of OR, RR, and HR. This was done using a forest plot in Figures 1–4 for risk factors age, BMI; sex, smoking; cardiovascular, stage; hypertension, diabetes; and Interstitial Lung Disease (ILD), Pneumonia, respectively. Out of the 32 studies, ten, fourteen, and eight studies provided the effect of risk factors were estimated using HR, OR, and RR respectively. The Meta-analysis included studies with retrospective and prospective study designs. The mortality rate noticed in retrospective studies was lower as compared to prospective studies. For instance, in the retrospective study conducted by Zhang et al. the mortality rate was 106 to 49165 which is almost null, whereas, in the prospective study conducted by Mansfield et al, the mortality rate was 568 to 759 which is almost 75 percent of the total. The overall prevalence of mortality rate was 10% with a 95% confidence interval of 6 and 16% (see Figure 2).

Twenty studies (62.50%) studies included in this study considered the ages of lung cancer patients as the risk factors for mortality. Whereas, eighteen (56.25%) and thirteen (40.63%) studies were incorporate the gender and smoking status of patients respectively. The comorbidities of lung cancer mortality such as cardiovascular disease, hypertension, diabetes, and pneumonia were also involved in 7 (21.90%), 6 (18.75%), 5 (15.63%), and 2 (6.25%) studies, respectively (see Table 2).

Besides, Table 2 depicted the overall effect size demographic and clinical variables associated with lung cancer mortality. Except for the BMI of the patient determinants such as patient age, gender, smoking, cardiovascular, stage of cancer metastasis, diabetes and pneumonia has a significant positive effect on lung cancer mortality. For instance, patients of older age are more likely to die as compared to patients of younger age. Similarly, lung patients who had smoking practice were more likely to die as compared to patients who hadn't practiced smoking. The estimated effects of covariates for each study separately and aggregate/overall estimated effect were also presented using a forest plot in Figures 3–6.

Despite this, only one single study on the effect of anemia, residence, and receiving systematic anti-cancer treatment (SACT) on lung cancer mortality was included in this study (see Figure 7). Patients who had and lived in rural areas were more likely to die. In contrast, patients who took SACT were less likely to die.

The goodness of the meta-analysis for each factor was considered using a funnel plot in Figure 8. The points within the funnel line indicate the systematic review analysis for the corresponding variable is a good fit.

TABLE 1 Characteristics of studies included in the systematic review and meta-analysis on lung cancer mortality.

Authors (year)	Country	Sample size	Death	RR/OR or HR (95%CI)
Zhang, B., et al. (8)	Canada	49,165	106	Smoking: Yes: HR=14.04 (7.56-26.07) Age: Old (>50):HR=1.74(1.45-1.87)
Chiyo, M. et al. (7)	Japan	931	293	Gender: male: HR =1.766 (1.304-2.401) Age: HR=1.015 (1.008-1.027) ILD: Yes: HR=1.903(1.012-3.236)
Frostad, A. (23)	Norway	19,998	6710	Age: Old: aOR=1.04 (1.01-1.06)
Kabat, G.C., et al. (25)	China	1590	131	Duration of HRT use: Yes: aHR=1.51 (1.14–1.99). Contraceptive use: Yes: HR=0.91 (0.78–1.06)
Yang, L., et al. (11)	China	225, 721	2145	Follow up: higher: HR=0.75(0.63-0.93) Residence: Urban: HR=2.28 (2.06-2.52) Sex: Male: HR=1.57 (1.47-1.67) Smoking: Yes: HR=1.77 (1.67-1.87)
Roth, K., et al. (10)	Norway	148	40	Age: >=70=HR= 1.93 (1.14, 3.28) Stage: HR=Stage IB= 1.63 (0.92, 2.89) HR=Stage II-IV=4.16 (1.92, 9.05)
Chae, K.J et al. (9)	Korea	612	220	Age: in yr=HR= 1.03 (1.01–1.05) Smoke: yes=HR= 1.68 (1.22–2.32) History: yes=HR= 1.44 (1.00–2.06)
Kuderer, N.M (12).	Canada	1998	472	Age: a year=HR=1.013 (1.003–1.023) Sex: male=HR=1.183 (0.979–1.430) BMI: <35 kg/m2=HR=0.968 (0.611–1.531) Smoke: Yes=HR=1.551 (1.185–2.030) HPT: Yes=HR=1.131 (0.937–1.365) Anaemia: Yes=HR=1.471 (1.185–1.826)
Duran, A.O (13)	Turkey	330	125	Age: year=1.008 (0.990-1.027) Sex: Male=0.863 (0.479-1.554) BMI: 0.967 (0.924-1.012) Smoking: 1.518 (0.890-2.589) Diabetes: 1.200 (0.655-2.199) HPT: Yes=1.076 (0.627-1.847) Cardiac disease: Yes=1.330 (0.656-2.695)
Adair, T (22).	Australia	2480	249	Tobacco: Yes: OR=1.066 (1.002-1.090)
Matakidou, A., et al. (26)	UK	2561	191	Smoker: Yes: RR= 7.15 (5.70–8.96) Age: 60+: RR=2.02 (1.22–3.34) Relatives: Yes: RR=1.90 (1.30–4.25)
Stukenborg, G.J (17).	USA	14,456	519	Liver disease: Yes=RR=2.60 (1.16-5.87) Pneumonia: Yes=RR= 1.73 (1.24-2.42) Hypertension: Yes=RR=1.83 (1.19-2.81)
Licker, M.J., et al. (27)	Switzerland	1222	36	Respiratory complication: Yes=RR=1.9 (1.9-6.6)
Lauritsen, J.M (28).	Danish	439	60	Smoking=Yes=2.02 (0.80, 6.78)
Powell, H.A. et al. (14)	UK	10991	981	Sex=Male=OR= 1.62(1.17 to 2.25) Age=85+=OR= 2.35(1.12 to 9.01) Stage=IIIA/IA= 2.18 (1.25 to 3.81)
Kirkland, R.S (18).	USA	882	67	interstitial lung disease=Yes=OR=6.14(1.9-19.4) pulmonary HT=Yes=OR=3.1(1.6-6.2) diabetes mellitus=Yes=OR=2.0(1.1-3.3)
Thomas, P.A (29).	France	4498	351	Age: >65=OR=2.1(1.5-2.9) BMI: Underweight: OR=2.2(1.2-4.0) Overweight: OR=0.60(0.4-0.9)
Rosen, J.E (30).	USA	119,146	4051	Age: 5-yr increase=OR=1.5(1.25, 1.77) Sex: Male=OR=1.8 (1.3, 3.28) Race: Non-white=OR=1.10(0.8, 1.56)

(Continued)

10.3389/fonc.2023.1308897

TABLE 1 Continued

Authors (year)	Country	Sample size	Death	RR/OR or HR (95%CI)
Gibson, A.J (31).	Canada	1044	233	Sex: Male=OR=1.48 (1.12–1.95) never-smokers=OR=0.62 (0.41–0.95) Advanced disease at diagnosis=OR=1.85 (1.19–2.88) Receiving systemic anti-cancer therapies (SACT)=OR=0.65 (0.49–0.86)
Kozower, B.D (19)	USA	18,800	413	Age: 10-year increase=OR=1.84 (1.58, 2.15) Sex: Male=OR=1.36 (1.07, 1.73) BMI: 10KG/M2 increase=OR=0.74 (0.58, 0.94) HPT: Yes:=OR=1.10 (0.85, 1.43) Diabetes: Yes:=OR=1.15 (0.82, 1.59) Cardiovascular: Yes=OR=1.09 (0.78, 1.51) Dialysis: Yes=OR=3.97 (1.48,10.64)
Jean, R.A (32)	USA/Vreginia	6435	120	Age: year=OR=1.03(1.013-1.056) Sex: male=OR=1.83 (1.199-2.789) DM: Yes=OR=2.57(1.379-4.808)
Romano, P.S (21).	USA/California	12,439	441	Sex: male=OR=1.5 (1.2,1.8) Age: >79=OR=5.4 (3.5,8.4) Heart: Yes=OR=1.8 (1.5,2.2) Diabetes: Yes=OR=1.5 (1.1,2.2)
Kates, M., et al. (15)	USA/NewYork	1844	655	Sex: male=OR= 1.45 (1.22–1.72) Age: 80-80=OR=2.09 (1.60–2.75) Stage: III vs I=OR=1.27 (1.02–1.59) Heart Failure: Yes=OR=1.54 (1.24–1.93) Cardiovascular: Yes=OR=1.75 (1.39–2.22) Diabetes: Yes=OR=1.70 (1.18–2.45)
Breslow, R.A (33).	USA	20195	158	Smoking: Yes= RR=1.2 (0.8-1.8)
Bessö, A., et al. (34)	Sweden	316	92	Sex: male=RR=1.3(0.76–2.62) Smoking: Yes=3.32 (1.35–8.20)
Borsoi, L (35).	Austria	1000000	503/10-6	Sex: Female=RR= 1.12 (0.81-1.66) Age: RR=0.77(0.29-1.22)
Cardenas, V.M (36).	USA	508,576	5,469	Smoke: Yes=RR= 1.2(0.8-1.8) Sex: Female=RR=1.45 (0.74-2.55)
Chow, W.H., et al. (37)	USA	5263	219	Smoking: Yes=RR=3.5 (1.0-12.6) Beer: Yes=RR=1.8 (1.10-3.30) Meat: Yes=RR=1.3(0.7-2.3) Vitamin C: high=RR=0.8(0.5-1.2)
Stoelben, E.,et al. (16)	Germany	1281	131	Sex: Female=RR=0.56(0.30–1.06) Age: >75=RR=2.46 (1.17–5.16) Stage: I vs II 5.58 1.83–17.07 I vs IIIa 9.01 3.52–23.04 I vs IIIb 17.41 6.62–45.80 I vs IV 21.81 8.29–57.38
Sokolnikov, M.E (38).	Russia	17,740	681	Sex: Male: RR=7.1 (4.9–10) Age: 75+=RR=4.1 (0.9–10)
Kuehnl, A (20).	Germany	31	22	Sex: male=RR=2.08 0.478–9.025 Age: <65 vs>65=RR=0.98 0.934–1.035 BMI: <25 vs >25= RR=0.95 0.856–1.057 Grade: G1/G2 vs G3/G4=RR=0.32 0.110–0.909
Mansfield, A.S, et al. (24)	USA	759	568	Surgery= HR, 0.35; 95% CI, 0.18–0.68 Chemotherapy=HR, 2.2; 95% CI, 1.2–4.3 Radiation (ref.) KRS (yes vs no)=HR, 1.7; 95% CI, 1.4–2.2 Age: >76= HR, 1.45: 95% CI, 1.12-2.66 Sex: male=HR, 1.32: 95% CI, 1.06-3.10

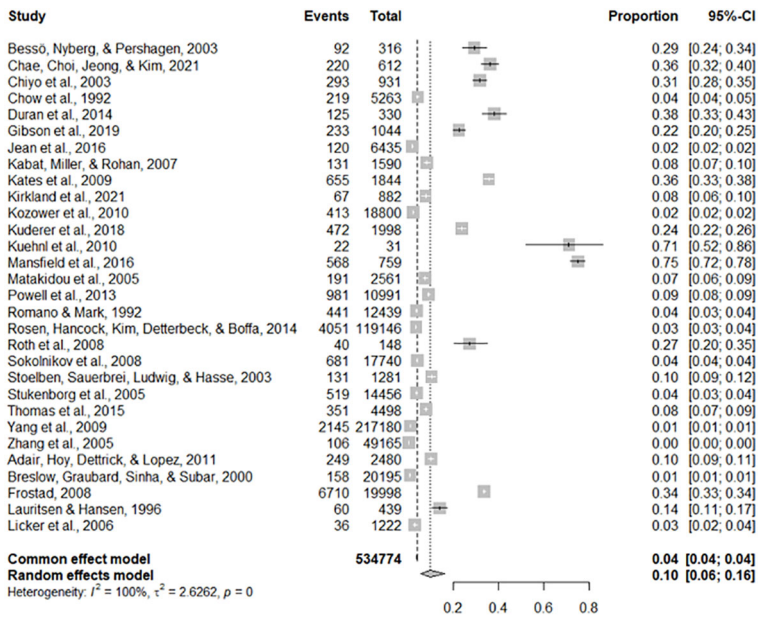


FIGURE 2
The overall mortality rate of lung cancer.

Discussion

This study presents a comprehensive systematic review examining the risk factors associated with lung cancer mortality. The objective was to comprehensively explore potential risk factors, including demographic, biological, behavioral, and socioeconomic determinants associated with lung cancer mortality, and to estimate the overall prevalence of lung cancer mortality. We delved into a

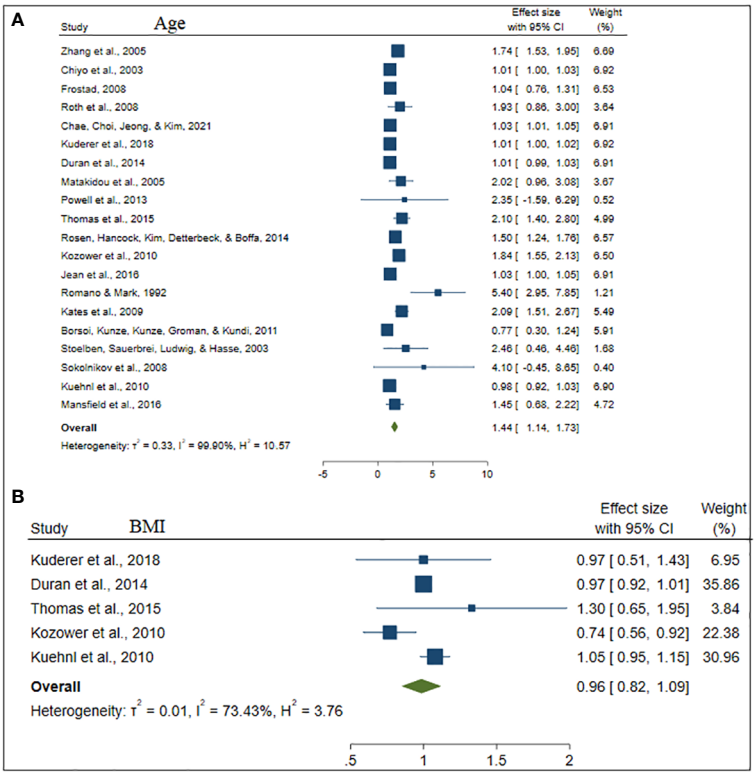


FIGURE 3
The forest plot of the effect size age **(A)** and BMI **(B)**.

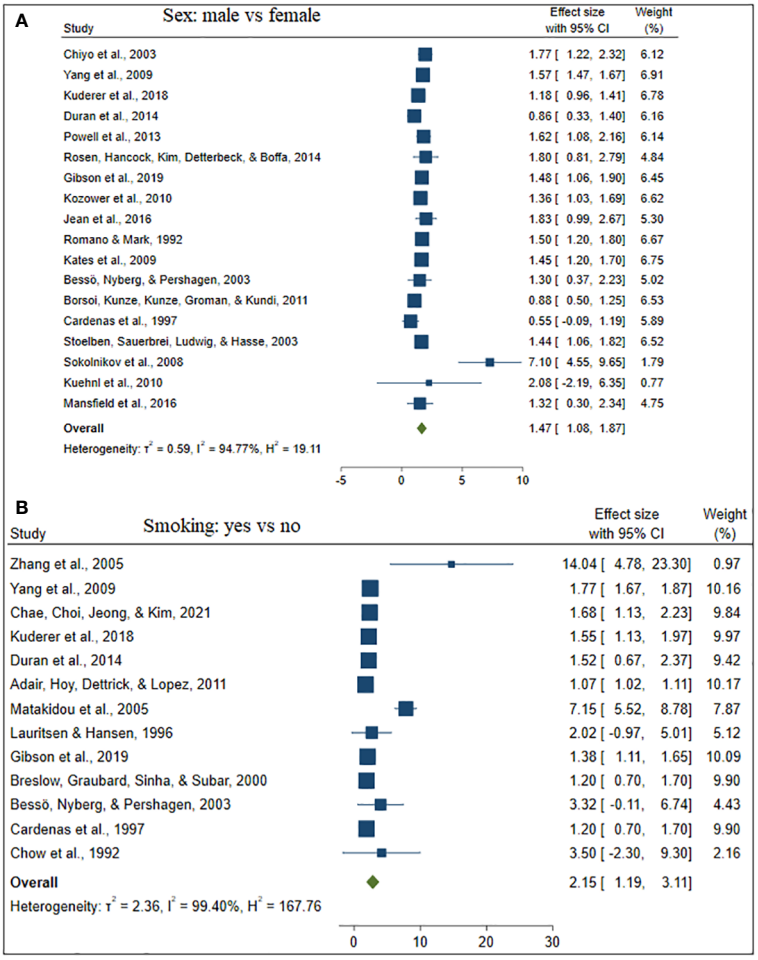


FIGURE 4
The forest plot of the effect size sex **(A)** and smoking **(B)**.

TABLE 2 Results of meta-analysis based on demographic and clinical variables associated with lung cancer mortality.

Risk factors	Numbers of studies (%)	Effect size (95% CI)	Heterogeneity	
			I^2	P-value
Older age	20 (62.50)	2.61(1.75-3.47)	99.97	0.000
BMI	5 (15.63)	0.96(0.82-1.09)	73.43	0.064
Gender: Male vs Female	18 (56.25)	1.47(1.08-1.87)	94.77	0.000
Smoking status: Yes vs No	13 (40.63)	2.15(1.19-3.11)	99.40	0.000
Cardiovascular: Yes vs No	7 (21.90)	1.57(1.28-1.86)	48.34	0.000
Stage: Yes vs No	6 (18.75)	1.60(1.21-1.99)	32.55	0.020
Hypertension: Yes vs No	6 (18.75)	1.19(1.04-1.34)	0.00	0.000
Diabetes: Yes vs No	5 (15.63)	1.43(1.14-1.72)	15.23	0.000
ILD	2 (6.25)	1.97(0.86-3.08)	0.00	0.000
Pneumonia	2 (6.25)	1.80(1.23-2.37)	0.00	0.000

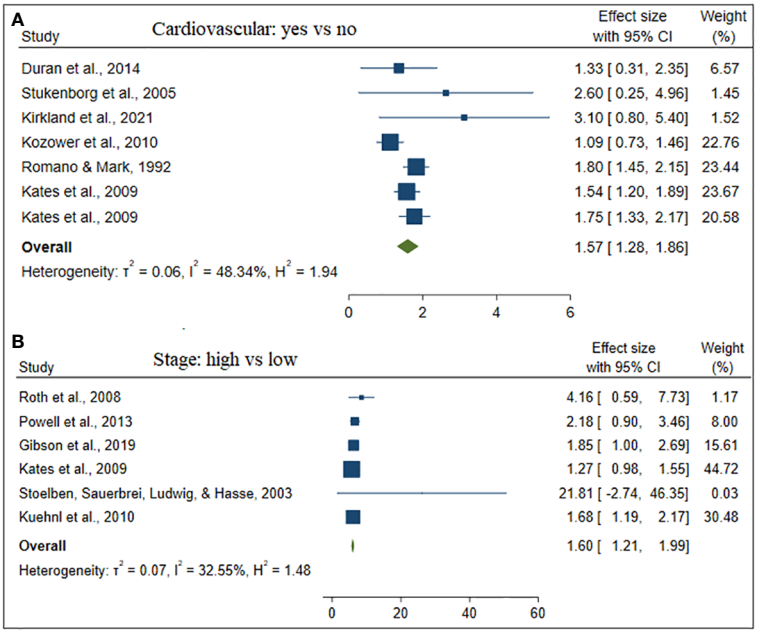


FIGURE 5
The forest plot of the effect size cardiovascular **(A)** and stage **(B)**.

total of 201 lung cancer studies sourced from diverse electronic databases, including Google Scholar, Cochrane Library, Web of Sciences (WOS), EMBASE, Medline/PubMed, the Lung Cancer Open Research Dataset Challenge, and Scopus. In the meantime, 32 studies that satisfy the eligibility criteria of the Meta-analysis were involved in this study. The majority of the studies consist of patients' age, gender, and smoking status (7–15, 21, 24, 26, 29, 31).

Despite reports indicating a decline in the mortality rate of patients with lung cancer, it remains substantial. The overall mortality rate stands at 10%, signifying that, on average, ten out of every hundred lung cancer patients succumb to the disease. Put differently, there is a one in ten likelihood that a lung cancer patient will die. In 2012, an estimated 1.8 million new cases, accounting for 12.9% of the total, were recorded (41). In 2012, the regions with the highest lung cancer mortality rates per 100,000 were Central and Eastern Europe and Eastern Asia for males, and Northern America and Northern Europe for females. Conversely, the lowest rates were observed in sub-Saharan Africa for both males and females (42).

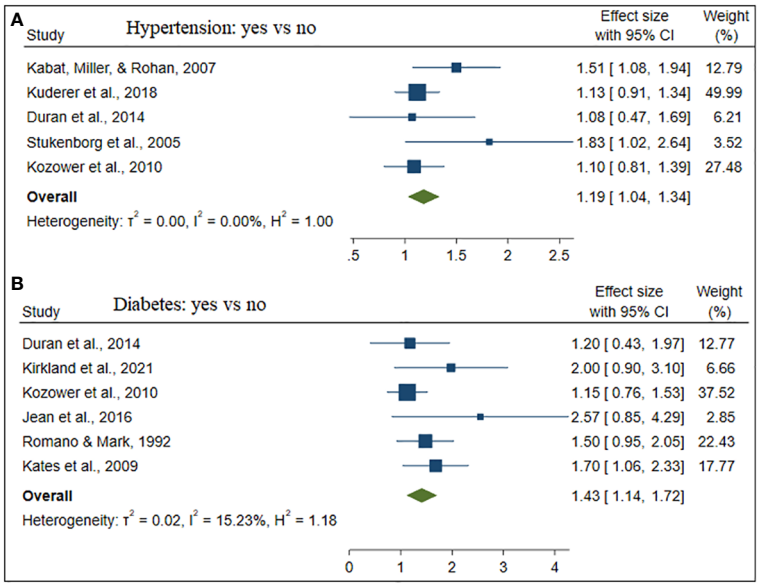


FIGURE 6
The forest plot of the effect size hypertension **(A)** and diabetes **(B)**.

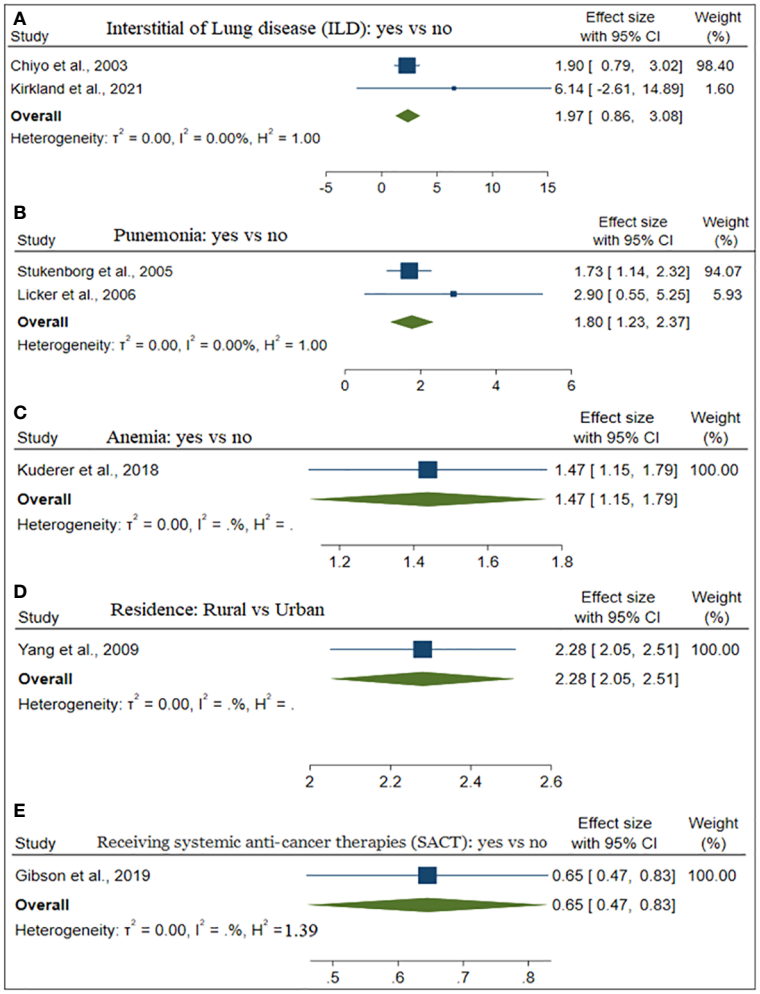


FIGURE 7
The forest plot of the effect size ILD **(A)**, Pneumonia **(B)**, Anemia **(C)**, and Residence **(D)**.

This study depicted that older age, gender, stage, and comorbidities such as cardiovascular, hypertension, and diabetes have a significant positive effect on lung cancer mortality. A study conducted on global trends of lung mortality revealed that the overall trend of lung cancer mortality among females is higher than among males (42), which contradicts the findings of this study states that males have a higher likelihood to be died as compared to females. The probability that an individual is affected by lung cancer increases as age does. This was in line with studies in (43, 44), which reported that lung cancer incidence and mortality rates steadily rise after the age of 30, reaching a peak between the ages of 75 and 79 for men and 70 to 74 for women. Due to less concomitant illness, younger individuals may be able to tolerate more rigorous multimodal therapy. Various factors, including higher prevalence of occupational hazards like asbestos exposure and common settings such as kitchens, where staff are exposed to smoke, may contribute to increased lung cancer risk among females in the population.

The majority of patients visit the hospital during the advanced stage (III/IV) of cancer, which leads to having an effective prescription or treatment. Thus, the stage of the cancer diseases affected the survival time of the patient (43). Communities who are living in rural areas had more vulnerability to death. This is common because of poor health facilities and leads unable to take treatment in time in rural areas as compared to the urban. If lung cancer is detected early and the right treatment is available, it may be curable. The place of residence of patients interrelates with lifestyle, which is a considerable risk factor for cancer (45). A potential obstacle to the effective management of future changes in incidence and mortality rate is the lack of or limited access to health care services in rural areas, particularly in developing nations.

The most frequent factor in both lung cancer incidence and mortality is smoking which is in line with studies (8, 46) state that lung cancer is directly caused by tobacco use, particularly cigarette smoking. Thus, an essential behavioral strategy for preventing lung cancer is quitting smoking. However, since this risk never goes back to normal, former smokers continue to have heightened risk compared to never smokers. Former smokers account for over 50% of instances of diagnosed lung cancer. About 58 percent of these occurrences happened in less developed areas, which is

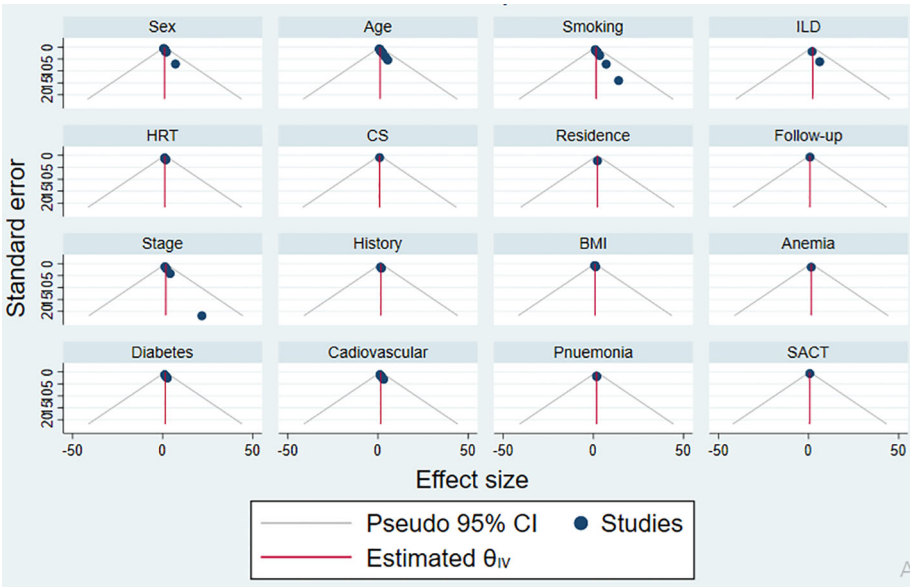


FIGURE 8
The funnel plot of each risk factors publication bias.

probably a reflection of the rising cigarette usage in these nations. Lung cancer is the most frequent kind of cancer death globally, accounting for 1.59 million projected deaths in 2012, even though exposure to tobacco smoke is avoidable (47, 48). In the last, this review synthesizes evidence from multiple studies, offering a more robust and reliable overview than individual studies. This helps in drawing more accurate conclusions. It provides a comprehensive understanding of the current state of knowledge regarding factors influencing lung cancer mortality. This is valuable for researchers, healthcare professionals, and policymakers.

Despite providing pooled estimates from 32 studies across 13 geographical locations, which may be seen as broadly representative of the pandemic, our systematic review has several limitations. Firstly, there is high heterogeneity, potentially due to substantial variations in sample sizes among studies and differences in study designs. Secondly, even with careful statistical adjustments, confounding variables can affect the validity of the results, as not all factors influencing lung cancer mortality are incorporated. Thirdly, it's important to note that this study did not consider covariates related to treatment outcomes, survival rates, and disease progression in cancer patients. Lastly, some included studies had very small sample sizes, possibly limiting the identification of factors influencing lung cancer mortality.

Conclusion

The mortality rate among lung cancer patients is notably elevated. Several factors contribute significantly to lung cancer mortality, including older age, gender, disease stage, and the presence of comorbidities such as cardiovascular conditions, hypertension, and diabetes. These findings hold substantial implications for the field of lung cancer research, management, and future prevention strategies. By shedding light on the influential factors behind lung cancer mortality, this study offers valuable insights that can inform more effective approaches to Comprehensive tobacco control policies, public awareness campaigns highlighting the dangers of smoking, and measures to improve air quality and regulate occupational exposures are essential. Access to healthcare services needs enhancement, focusing on early detection and treatment. Supporting smoking cessation efforts, promoting a healthy lifestyle, and integrating preventive measures into primary healthcare systems are vital components. International collaboration for knowledge sharing and resource allocation further strengthens the global fight against lung cancer combatting this deadly disease, ultimately leading to improved patient outcomes and reduced mortality rates.

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

LT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ZD: Data curation, Investigation, Methodology, Software,

Supervision, Validation, Writing – review & editing. HF: Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to thank the School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, South Africa for providing their guidance and support.

Conflict of interest

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

Publisher's note

References

1. Meyerson M, Gabriel S, Getz G. Advances in understanding cancer genomes through second-generation sequencing. *Nat Rev Genet* (2010) 11(10):685–96. doi: 10.1038/nrg2841

2. Tesfaw LM, Muluneh EK. Modeling the spatial distribution of cancer and determining the associated risk factors. *Cancer Inf* (2020) 19:1176935120939898. doi: 10.1177/1176935120939898

3. Torre L, Siegel R, Jemal A. Global cancer facts & figures. *Atlanta: Am Cancer Soc* (2015) 2.

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* (2018) 68(6):394–424. doi: 10.3322/caac.21492

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

6. Sharma R. Mapping of global, regional and national incidence, mortality and mortality-to-incidence ratio of lung cancer in 2020 and 2050. *Int J Clin Oncol* (2022) 27 (4):665–75. doi: 10.1007/s10147-021-02108-2

7. Chiyo M, Sekine Y, Iwata T, Tatsumi K, Yasufuku K, Iyoda A, et al. Impact of interstitial lung disease on surgical morbidity and mortality for lung cancer: analyses of short-term and long-term outcomes. *J Thorac Cardiovasc Surg* (2003) 126(4):1141–6. doi: 10.1016/S0022-5223(03)00791-8

8. Zhang B, Ferrence R, Cohen J, Bondy S, Ashley MJ, Rehm J, et al. Smoking cessation and lung cancer mortality in a cohort of middle-aged Canadian women. *Ann Epidemiol* (2005) 15(4):302–9. doi: 10.1016/j.annepidem.2004.08.013

9. Chae KJ, Choi H, Jeong WG, Kim J. The value of the illness-death model for predicting outcomes in patients with non–small cell lung cancer. *Cancer Res Treat* (2021). doi: 10.4143/crt.2021.902

10. Roth K, Nilsen TIL, Hatlen E, Sørensen KS, Hole T, Haaverstad R. Predictors of long time survival after lung cancer surgery: a retrospective cohort study. *BMC pulmonary Med* (2008) 8(1):1–8. doi: 10.1186/1471-2466-8-22

11. Yang L, Yang G, Zhou M, Smith M, Ge H, Boreham J, et al. Body mass index and mortality from lung cancer in smokers and nonsmokers: a nationally representative prospective study of 220,000 men in China. *Int J Cancer* (2009) 125(9):2136–43. doi: 10.1002/ijc.24527

12. Kuderer NM, Poniewierski MS, Culakova E, Lyman GH, Khorana AA, Pabinger I, et al. Predictors of venous thromboembolism and early mortality in lung cancer: results from a global prospective study (CANTARISK). *Oncologist* (2018) 23(2):247–55. doi: 10.1634/theoncologist.2017-0205

13. Duran AO, Inanc M, Karaca H, Dogan I, Berk VBozkurt, et al. Albumin-globulin ratio for prediction of long-term mortality in lung adenocarcinoma patients. *Asian Pacific J Cancer Prev* (2014) 15(15):6449–53. doi: 10.7314/APJCP.2014.15.15.6449

14. Powell HA, Tata LJ, Baldwin DR, Stanley RA, Khakwani A, Hubbard RB. Early mortality after surgical resection for lung cancer: an analysis of the English National Lung cancer audit. *Thorax* (2013) 68(9):826–34. doi: 10.1136/thoraxjnl-2012-203123

15. Kates M, Perez X, Gribetz J, Swanson SJ, McGinn T, Wisnivesky JP. Validation of a model to predict perioperative mortality from lung cancer resection in the elderly. *Am J Respir Crit Care Med* (2009) 179(5):390–5. doi: 10.1164/rccm.200808-1342OC

16. Stoelben E, Sauerbrei W, Ludwig C, Hasse J. Tumor stage and early mortality for surgical resections in lung cancer. *Langenbeck's Arch Surg* (2003) 388(2):116–21. doi: 10.1007/s00423-003-0354-x

17. Stukenborg GJ, Kilbridge KL, Wagner DP, Harrell FE Jr, Oliver MN, Lyman JA, et al. Present-at-admission diagnoses improve mortality risk adjustment and allow more accurate assessment of the relationship between volume of lung cancer operations and mortality risk. *Surgery* (2005) 138(3):498–507. doi: 10.1016/j.surg.2005.04.004

18. Kirkland RS, Kole AJ, Batra H, Boggs DH, Spencer SA, Dobelbower MC, et al. Predictors of in-hospital death in patients with lung cancer admitted for acute radiation pneumonitis: A healthcare cost and utilization project (HCUP) analysis. *Clin Lung Cancer* (2021) 22(5):e716–22. doi: 10.1016/j.cllc.2021.01.016

19. Kozower BD, Sheng S, O'Brien SM, Liptay MJ, Lau CL, Jones , et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. *Ann Thorac Surg* (2010) 90(3):875–83. doi: 10.1016/j.athoracsur.2010.03.115

20. Kuehnl A, Lindner M, Hornung HM, Winter H, Jauch KW, et al. Atrial resection for lung cancer: morbidity, mortality, and long-term follow-up. *World J Surg* (2010) 34 (9):2233–9. doi: 10.1007/s00268-010-0596-z

21. Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* (1992) 101(5):1332–7. doi: 10.1378/chest.101.5.1332

22. Adair T, Hoy D, Dettrick Z, Lopez AD. Reconstruction of long-term tobacco consumption trends in Australia and their relationship to lung cancer mortality. *Cancer Causes Control* (2011) 22(7):1047–53. doi: 10.1007/s10552-011-9781-0

23. Frostad A. Association between respiratory symptom score and 30-year cause-specific mortality and lung cancer incidence. *Clin Respir J* (2008) 2:53–8. doi: 10.1111/j.1752-699X.2008.00084.x

24. Mansfield A, Tafur AJ, Wang CE, Kourelis TV, Wysokinska EM, Yang P. Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemostasis* (2016) 14(9):1773–8. doi: 10.1111/jth.13378

25. Kabat GC, Miller AB, Rohan TE. Reproductive and hormonal factors and risk of lung cancer in women: a prospective cohort study. *Int J Cancer* (2007) 120(10):2214–20. doi: 10.1002/ijc.22543

26. Matakidou A, Eisen T, Bridle H, O'Brien M, Mutch R, Houlston RS, et al. Case-control study of familial lung cancer risks in UK women. *Int J Cancer* (2005) 116 (3):445–50. doi: 10.1002/ijc.21012

27. Licker MJ, Widikker I, Robert J, Frey JG, Spiliopoulos A, Ellenberger C, et al. Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg* (2006) 81(5):1830–7. doi: 10.1016/j.athoracsur.2005.11.048

28. Lauritsen JM, Hansen KS. Lung cancer mortality in stainless steel and mild steel welders: A nested case-referent study. *Am J Ind Med* (1996) 30(4):383–91. doi: 10.1002/(SICI)1097-0274(199610)30:4<383::AID-AJIM2>3.0.CO;2-X

29. Thomas PA, Berbis J, Baste JM, Le Pimpec-Barthes F, Tronc F, Falcoz PE, et al. Pneumonectomy for lung cancer: contemporary national early morbidity and mortality outcomes. *J Thorac Cardiovasc Surg* (2015) 149(1):73–83. doi: 10.1016/j.jtcvs.2014.09.063

30. Rosen JE, Hancock JG, Kim AW, Detterbeck FC, Boffa DJ. Predictors of mortality after surgical management of lung cancer in the National Cancer Database. *Ann Thorac Surg* (2014) 98(6):1953–60. doi: 10.1016/j.athoracsur.2014.07.007

31. Gibson AJ, Li H, D'Silva A, Elegbede AA, Tudor RA, Otsuka S, Bebb DG, et al. Factors associated with early mortality in non-small cell lung cancer patients following systemic anti-cancer therapy: a 10 year population-based study. *Lung Cancer* (2019) 134:141–6. doi: 10.1016/j.lungcan.2019.06.003

32. Jean RA, DeLuzio MR, Kraev AI, Wang G, Boffa DJ, Detterbeck FC, et al. Analyzing risk factors for morbidity and mortality after lung resection for lung cancer using the NSQIP database. *J Am Coll Surgeons* (2016) 222(6):992–1000.e1. doi: 10.1016/j.jamcollsurg.2016.02.020

33. Breslow RA, et al. Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. *Cancer Causes Control* (2000) 11(5):419–31. doi: 10.1023/A:1008996208313

34. Bessö A, Nyberg F, Pershagen G. Air pollution and lung cancer mortality in the vicinity of a nonferrous metal smelter in Sweden. *Int J Cancer* (2003) 107(3):448–52. doi: 10.1002/ijc.11412

35. Borsoi L, Kunze U, Kunze M, Groman E, Kundi M. Trends in mortality and mean age at death from lung cancer in Austria (1975–2007). *Cancer Epidemiol* (2011) 35(2):120–5. doi: 10.1016/j.canep.2010.06.018

36. Cardenas VM, Thun MJ, Austin H, Lally CA, Clark WS, Greenberg RS, et al. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study II. *Cancer Causes Control* (1997) 8(1):57–64. doi: 10.1023/A:1018483121625

37. Chow W-H, Schuman LM, McLaughlin JK, Bjelke E, Gridley G, Wacholder S, et al. A cohort study of tobacco use, diet, occupation, and lung cancer mortality. *Cancer Causes Control* (1992) 3(3):247–54. doi: 10.1007/BF00124258

38. Sokolnikov ME, Gilbert ES, Preston DL, Ron E, Shilnikova NS, Khokhryakov VV, et al. Lung, liver and bone cancer mortality in Mayak workers. *Int J Cancer* (2008) 123(4):905–11. doi: 10.1002/ijc.23581

39. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

40. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* (2006) 295(6):676–80. doi: 10.1001/jama.295.6.676

41. Grewal AS, Padera RF, Boukedes S, Divo M, Rosas IO, Camp PC, et al. Prevalence and outcome of lung cancer in lung transplant recipients. *Respir Med* (2015) 109(3):427–33. doi: 10.1016/j.rmed.2014.12.013

42. Islami F, Torre LA, Jemal A. Global trends of lung cancer mortality and smoking prevalence. *Trans Lung Cancer Res* (2015) 4(4):327.

43. Skarin AT, Herbst RS, Leong TL, Bailey A, Sugarbaker D. Lung cancer in patients under age 40. *Lung Cancer* (2001) 32(3):255–64. doi: 10.1016/S0169-5002(00)00233-6

44. O'Rourke MA, Feussner JR, Feigl P, Laszlo J. Age trends of lung cancer stage at diagnosis: implications for lung cancer screening in the elderly. *Jama* (1987) 258 (7):921–6. doi: 10.1001/jama.1987.03400070059035

45. Khaltaev N, Axelrod S. Global lung cancer mortality trends and lifestyle modifications: preliminary analysis. *Chin Med J* (2020) 133(13):1526–32. doi: 10.1097/CM9.0000000000000918

46. Rahal Z, El Nemr S, Sinjab A, Chami H, Tfayli A, Kadara H. Smoking and lung cancer: a geo-regional perspective. *Front Oncol* (2017) 7:194. doi: 10.3389/fonc.2017.00194

47. Loeb LA, Emster VL, Warner KE, Abbotts J, Laszlo J. Smoking and lung cancer: an overview. *Cancer Res* (1984) 44(12_Part_1):5940–58.

48. Ozlü T, Bülbül Y. Smoking and lung cancer. *Tuberkuloz ve toraks* (2005) 53 (2):200–9.

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 04 January 2024
DOI 10.3389/fonc.2023.1261041

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Dinesh Pendharkar,
Sarvodaya Hospital and Research Centre, India
Justina Ucheojor Onwuka,
International Agency For Research On Cancer (IARC), France
André Luiz Monezi Andrade,
Pontifical Catholic University of Campinas, Brazil
Aditya Yashwant Sarode,
Columbia University, United States

*CORRESPONDENCE
JoséIgnacio Nolazco
jnolazco@bwh.harvard.edu
jose.nolazco@fulbrightmail.org

RECEIVED 18 July 2023
ACCEPTED 23 November 2023
PUBLISHED 04 January 2024

CITATION
Nolazco JI, Rosner BA, Roebuck EH, Bergerot CD, Rammant E, Iyer GS, Tang Y, Al-Faouri R, Filipas DK, Leapman MS, Mossanen M and Chang SL (2024) Impact of smoking status on health-related quality of life (HRQoL) in cancer survivors. *Front. Oncol.* 13:1261041. doi: 10.3389/fonc.2023.1261041

Impact of smoking status on health-related quality of life (HRQoL) in cancer survivors

José Ignacio Nolazco[1,2*], Bernard A. Rosner[3], Emily H. Roebuck[4], Cristiane Decat Bergerot[5], Elke Rammant[6], Geetha S. Iyer[7], Yuzhe Tang[8], Ra'ad Al-Faouri[9], Dejan K. Filipas[1,10], Michael S. Leapman[11], Matthew Mossanen[1,12] and Steven Lee Chang[1,13]

[1]Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [2]Servicio de Urología, Hospital Universitario Austral, Universidad Austral, Pilar, Argentina, [3]Channing Division of Network Medicine, Department of Medicine, Harvard Medical School, Boston, MA, United States, [4]Department of Urology, Carolinas Medical Center/Atrium Health, Charlotte, NC, United States, [5]Centro de Câncer de Brasília, Instituto Unity de Ensino e Pesquisa, Grupo Oncoclinicas, Brasília, DF, Brazil, [6]Department of Human Structure and Repair, Ghent University, Ghent, Belgium, [7]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States, [8]Urology Department, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [9]Department of Surgery, Division of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States, [10]Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [11]Yale School of Medicine, Department of Urology, New Haven, CT, United States, [12]Department of Radiation Oncology, Brigham and Women's Hospital, Boston, MA, United States, [13]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, United States

Introduction: The Health-Related Quality of Life (HRQoL) often declines among cancer survivors due to many factors. Some cancer patients who smoke before the cancer diagnosis continue this harmful habit, potentially contributing to a more significant decline in their HRQoL. Therefore, this study investigates the association between smoking status and HRQoL in cancer survivors.

Methods: We conducted a cross-sectional study utilizing self-reported cancer history from 39,578 participants of the Behavioral Risk Factor Surveillance System (BRFSS) database, leveraging 2016 and 2020 year questionaries. A multidimensional composite outcome was created to assess HRQoL, integrating four distinct dimensions - general health, mental health, physical health, and activity limitations. After accounting for the complex survey design, logistic regression models were used to analyze the association between smoking status and poor HRQoL, adjusting for demographic, socioeconomic, and health-related confounders.

Results: Our study found that, after adjusting for potential confounders, current smokers exhibited a significantly poorer HRQoL than never smokers (OR 1.65, 95%CI 1.40-1.93). Furthermore, former smokers showed a poorer HRQoL than never smokers; however, this association was not as strong as current smokers (OR 1.22, 95%CI 1.09-1.38).

Conclusion: Our findings highlight the adverse association of smoking with poor HRQoL in cancer survivors, underscoring the importance of healthcare professionals prioritizing smoking cessation and providing tailored interventions to support this goal.

KEYWORDS

smoking, tobacco, health-related quality of life, cancer survivors, behavioral risk factors surveillance system (BRFSS)

Introduction

Cancer is a leading cause of death globally, with well-established physical and psychological ramifications for affected individuals (1). The importance of assessing health-related quality of life (HRQoL) in oncological research is gaining recognition. HRQoL is a multidimensional, comprehensive, and complex concept that includes diverse factors that collectively contribute to an individual overall well-being (2, 3). Numerous studies have established a strong association between increased HRQoL and enhanced survival outcomes in cancer patients (4–6). Interestingly, a significant number of patients perceive heightened HRQoL as preferable to an extended survival period (7). However, despite its significance, HRQoL often declines among cancer survivors due to a variety of factors, including physical symptoms like pain, fatigue, nausea, psychological distress, and social isolation (8).

According to a recent study utilizing the National Health Interview Survey (NHIS) dataset, the general population's smoking prevalence in 2020 was 12.5% (9). In contrast, an investigation encompassing 32,244 cancer survivors from the Population Assessment of Tobacco and Health (PATH) dataset indicated a disconcerting 17.2% smoking prevalence within this cohort (10). It is important to consider that certain malignancies demonstrate a more robust correlation with tobacco consumption relative to others, underscoring the complex relationship between smoking and cancer (11). Smoking persists as a prevalent behavior among cancer survivors and is associated with unfavorable treatment outcomes, including reduced treatment effectiveness, increased risk of recurrence, complications, toxicity, and lower survival rates (12–14).

Nevertheless, there remains a limited understanding of the specific factors influencing health-related quality of life (HRQoL) in cancer survivors, particularly in relation to smoking status. Although prior studies have demonstrated an association between smoking and poor HRQoL in diverse populations (15, 16), few have investigated the association between smoking and HRQoL among cancer patients. Uncovering this relationship is essential to improve the overall HRQoL of these individuals. Consequently, this study aimed to examine the relationship between smoking status and HRQoL in cancer survivors.

Abbreviations: ASCO, American Society of Clinical Oncology; BMI, Body Mass Index; BRFSS, Behavioral Risk Factor Surveillance System; CDC, Centers for Disease Control and Prevention; CI, Confidence Interval; CVD, Cardiovascular Disease; HRQoL, Health-Related Quality of Life; NHIS, National Health Interview Survey; NCCN, National Comprehensive Cancer Network; Non-TRC, Non-Tobacco-Related Cancers; OR, Odds Ratio; PATH, Population Assessment of Tobacco and Health; TRC, Tobacco-Related Cancers; USPSTF, U.S. Preventive Services Task Force.

Methods

Study population

This study utilized data from the Centers for Disease Control and Prevention's (CDC) Behavioral Risk Factor Surveillance System (BRFSS) for the years 2016-2020, a cross-sectional, state-based telephone survey of non-institutionalized individuals aged 18 years or older residing in the United States (17). The questionnaire contained sections addressing demographics, healthcare access, and health-related behaviors. Cancer survivors were identified through a self-reported history of cancer and those without cancer were excluded from further analyses. The resulting cohort comprised 39,578 adult cancer survivors living in the U.S. with at least one self-reported HRQoL proxy (general health, mental health, physical health, and activity limitations). The included cancers were brain, bladder, bone, breast, colon, cervical, endometrial, esophageal, gastric, Hodgkin's lymphoma, leukemia, liver, lung, melanoma, non-Hodgkin's lymphoma, oral, ovarian, pharyngeal, pancreatic, prostate, rectal, renal, testicular, thyroid, and other skin cancers. Due to the small sample size (fewer than 100 cases), laryngeal, heart, and neuroblastomas were excluded from the study.

Exposure variable

The exposure variable was defined as smoking status. Exposure to smoking status was defined into three distinct categories: never smokers, former smokers, and current smokers, based on participants' responses to two survey questions. (a) "Have you smoked at least 100 cigarettes in your entire life?" Respondents who answered "no" were classified as never smokers. Those who answered "yes" to this question were further divided based on their response to a second question: (b) "Do you now smoke cigarettes every day, some days, or not at all?" Participants who replied "not at

all" were classified as former smokers, while those who answered "every day or some days" were designated as current smokers.

Outcome and variables

The primary composite outcome measure was the HRQoL. The participants' self-reported HRQoL was assessed using the core section of the survey, which included questions on four domains: general health, mental health, physical health, and activity limitations (Supplementary Table 1). These validated questions have previously been used to provide reliable HRQoL estimates (18). The self-assessed general health status was dichotomized into "fair/poor" and "excellent/very good/good." The other three HRQoL variables were dichotomized based on their frequency of occurrence in the preceding 30 days, with those reporting fewer than 14 (good) and 14 days or more (poor) following the approach used in earlier studies on this topic (19, 20).

The composite outcome was created by first evaluating the validity and reliability of the measurement instrument using Cronbach's alpha coefficient (21). An alpha score > 0.6 was considered indicative of a valid instrument for measuring HRQoL (22). The resulting Cronbach's alpha was 0.658, suggesting that the composite outcome was appropriate for the HRQoL assessment. To create the composite outcome "HRQoL," we computed the row mean of the four dichotomized domains. In assessing HRQoL, participants were partitioned into two distinct groups based on their HRQoL scores. Individuals with an HRQoL score below 0.5 were assigned to the "poor HRQoL" category (HRQoL < 0.5), while those who scored 0.5 or higher were assigned to the "good HRQoL" category (HRQoL ≥ 0.5). This cut-off value was chosen to better identify patients with poorer quality of life, following the approach of dichotomizing the composite outcome into better and poorer halves, as employed by other researchers (23).

The explanatory variables included smoking status, demographic factors (age, gender, race/ethnicity, and marital status), socioeconomic factors (healthcare insurance, employment status, education level, and income), and comorbidities [body mass index (BMI), cardiovascular disease (myocardial infarction, stroke, or coronary heart disease), diabetes, asthma, and type of cancer]. All of these variables were considered during the analysis to assess HRQoL outcomes among cancer survivors.

Statistical analysis

Descriptive statistics, including frequencies and percentages, were used to present the categorical variables, and chi-square tests were employed to examine the differences between the two groups by evaluating the distribution of these variables. A complex survey design was considered by adjusting for stratification and clustering at the primary sampling unit, using sampling weights to compute nationwide representative frequencies and proportions. Multiple imputations were conducted using the predictive mean-matching method to address missing values, with k = 5 imputations.

A logistic regression model was used to calculate the odds of having poor HRQoL among cancer survivors based on their smoking status (never, former, and current smokers), adjusting for multiple potential confounders based on the aforementioned covariates. The predictive probability of poor HRQoL for each smoking exposure group was calculated. Secondary analyses explored the effects of tobacco-related cancers (TRC) and non-TRC on HRQoL, as well as potential interactions between HRQoL, age, and gender. Statistical significance was determined at $\alpha < 0.05$, with the data analyzed using STATA/BE version 17.0.

Sensitivity analysis

Several sensitivity analyses were performed to ensure robustness of the findings. First, an analysis excluding missing data was conducted to evaluate the potential influence of incomplete information on the results. Subsequently, two alternative HRQoL dichotomizations were examined. The first dichotomization classified participants as having "good health" if they scored 1 in all self-reported dimensions, while those with a score lower than 1 were considered "poor HRQoL." The second dichotomization categorized participants with an HRQoL score of 0 as having "poor HRQoL" (Table 1).

Results

Study population

The sample consisted of 2,193,981 participants surveyed between 2016 and 2020, of whom 39,578 were cancer survivors.

TABLE 1 Multivariate analysis of the association between smoking status and health-related quality of life at different cut-off points.

	HRQoL = 0/HRQoL > 0			HRQoL <0.5/HRQoL ≥ 0.5			HRQoL < 1/HRqoL = 1		
	OR	*CI*	p-value	OR	*CI*	p-value	OR	*CI*	p-value
Smoking Status									
Never Smoker	*Ref*			*Ref*			*Ref*		
Former Smoker	**1.22**	1.07 -1.39	< 0.001	**1.22**	1.09 -1.38	< 0.001	**1.22**	1.10 - 1.33	< 0.001
Current Smoker	**1.65**	1.39 -1.96	< 0.001	**1.65**	1.40 -1.92	< 0.001	**1.73**	1.51 - 1.98	< 0.001

Multivariate analysis of the association between smoking status and health-related quality of life (HRQoL) at different cut-off points. HRQoL cut-offs: HRQoL = 0 or HRQoL > 0, HRQoL < 0.5 or HRQoL ≥ 0.5, HRQoL < 1 or HRQoL = 1.
CI, confidence interval.
OR, odds ratio.

The weight of this sample was estimated to represent 13,836,840 cancer survivors. Regarding the exposure status, 9.76% were current smokers, 36.64% were former smokers, and 53.60% had never smoked. Table 2 shows the differences between groups according to their demographic and health-related characteristics. Compared to never smokers, current smokers were, on average, younger, more likely to be single, have a lower education level, and have a lower income. A significant racial disparity in smoking status among cancer survivors was observed. Specifically, a greater proportion of White survivors were never or former smokers, compared to higher rates of current smoking observed in Black, Hispanic, and other racial groups. Furthermore, current smokers had a higher prevalence of comorbidities such as cardiovascular disease (CVD), diabetes, and asthma.

Additional details regarding participant characteristics are presented in Table 2. Multiple imputations were used to address missing values, representing 16.80% for the income variable, 2.80% for diabetes, 1.80% for CVD, and less than 0.40% for employment status, asthma, insurance, education, gender, and marital status.

TABLE 2 Baseline Characteristics of Cancer Survivors by Smoking Status (n=39,578).

Cancer Survivors Characteristics	Never Smokers (n=20,733) No. Column %		Former Smokers (n=14,756) No. Column %		Current Smokers (n=4,089) No. Column %		p-value
Age							**<0.001**
< 40	497	2.4	225	1.5	324	7.9	
40 - 49	982	4.7	464	3.1	406	9.9	
50 -59	2904	14.0	1423	9.6	865	21.2	
60 -69	5958	28.7	3909	26.5	1385	33.9	
70 -79	6324	30.5	5538	37.5	907	22.2	
≥ 80	4068	19.6	3197	21.7	202	4.9	
Gender							**<0.001**
Female	13276	64.0	7491	50.8	2558	62.6	
Male	7454	36.0	7262	49.2	1530	37.4	
Race							**<0.001**
White	18616	89.8	13249	89.8	3384	82.8	
Black	778	3.8	518	3.5	237	5.8	
Hispanic	257	1.2	209	1.4	125	3.1	
Other†	1082	5.2	780	5.3	343	8.4	
Marital Status							**<0.001**
Single	8063	38.9	6242	42.3	2322	56.8	
Married or Partner	12669	61.1	8514	57.7	1767	43.2	
Education Level							**<0.001**
< High School Diploma	659	3.2	816	5.5	434	10.6	
High School Diploma	10085	48.7	8451	57.4	2866	70.2	
College Graduate	9963	48.1	5461	37.1	781	19.1	
Employment status							**<0.001**
Yes	7860	38.1	4074	27.7	1474	36.2	
No	12793	61.9	10633	72.3	2603	63.8	
Income (USD)							**<0.001**
< 25.000	3105	18.3	2667	21.5	1522	42.8	
25.000 - 50.000	4325	25.5	3658	29.5	995	28.0	
> 50.000	9527	56.2	6084	49.0	1037	29.2	

(Continued)

TABLE 2 Continued

Cancer Survivors Characteristics	Never Smokers (n=20,733) No. Column %		Former Smokers (n=14,756) No. Column %		Current Smokers (n=4,089) No. Column %		p-value
Insurance							**<0.001**
Yes	20284	98.0	14469	98.2	3788	92.9	
No	410	2.0	268	1.8	291	7.1	
Body mass index							**<0.001**
Underweight (< 18.5)	274	1.3	178	1.2	175	4.3	
Normal (≥ 18.5 < 25)	6126	29.5	4001	27.1	1433	35.0	
Overweight (≥ 25 < 30)	7346	35.4	5426	36.8	1276	31.2	
Obese (≥ 30)	6987	33.7	5151	34.9	1205	29.5	
CVD‡							**<0.001**
Yes	114	0.6	188	1.3	70	1.8	
No	20310	99.4	14272	98.7	3917	98.2	
Diabetes							**<0.001**
Yes	3569	17.7	2975	20.8	707	17.9	
No	16613	82.3	11359	79.2	3252	82.1	
Asthma							**<0.001**
Yes	2806	13.6	2091	14.2	796	19.6	
No	17883	86.4	12628	85.8	3275	80.4	

HRQoL, Health-Related Quality of Life.
† Consists of Asian, Alaskan, and Native Americans.
‡ Self-reported cardiovascular disease (CVD), including (myocardial infarction, stroke, or coronary heart disease).

Smoking status and HRQoL

In our multivariate analysis, we found that smoking status was an independent predictor of HRQoL in cancer survivors. Our results indicated that being a current or former smoker was significantly associated with reduced HRQoL compared to never smokers. Furthermore, the relationship between smoking and HRQoL was even stronger among current smokers, who had 65% higher odds of having a poor HRQoL than never-smokers OR of 1.65 (95% CI 1.40-1.93). Moreover, former smokers also exhibited a higher probability of poor HRQoL compared to never smokers, with an OR of 1.22 (95% CI 1.09-1.38). (Table 3) The predictive probabilities of poor HRQoL were 11,55%, 15.52%, and 21.43% for never, former, and current smokers, respectively (Figure 1).

Impact of type of cancer: tobacco-related cancers (TRC) vs. non-tobacco-related cancers (non-TRC) on HRQoL.

We investigated the relationship between HRQoL and the TRC and non-TRC groups. (Supplementary Table 2) We found that

TABLE 3 Association between Smoking Status and Poor HRQoL: Univariate and Multivariate Analysis.

	Univariate			Multivariate*		
Smoking Status	OR	*CI*	p-value	OR	*CI*	p-value
Never Smoker	*Ref*			*Ref*		
Former Smoker	**1.43**	1.27 -1.60	< 0.001	**1.22**	1.09 -1.38	< 0.001
Current Smoker	**2.54**	2.19 - 2.94	< 0.001	**1.65**	1.40 -1.93	< 0.001

*Multivariate analysis adjusted by: age, gender, race/ethnicity, marital status, healthcare insurance, employment status, education level, income, and comorbidities [body mass index (BMI) cardiovascular disease (myocardial infarction, stroke or coronary heart disease), diabetes, asthma, and type of cancer].
CI = confidence interval.
OR = odds ratio.
Poor HRQoL was defined as a composite outcome of HRQoL with a score below 0.5, based on a validated measurement instrument using self-assessed general health status, mental health, physical health, and activity limitation domains.

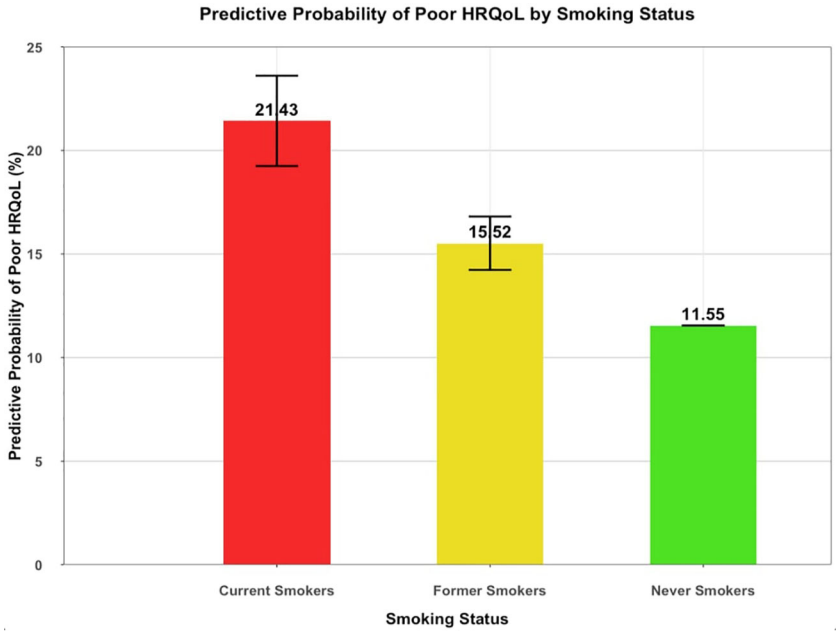


FIGURE 1
Predictive Probability of Poor HRQoL by Smoking Status Among Cancer Survivors. (n=39,578). Predictive probability of Poor HRQoL among cancer survivors according to smoking status after adjusting for covariates (age, gender, race/ethnicity, marital status, healthcare insurance, employment status, education level, income, and comorbidities [body mass index (BMI) cardiovascular disease (myocardial infarction, stroke or coronary heart disease), diabetes, asthma, and type of cancer). HRQoL encompasses General Health, Mental Health, Physical Health, and Activity Limitations.

patients with a TRC had significantly greater odds of having a poor HRQoL than those with non-TRC, with an OR of 1.51 (95%CI:1.32-1.72; $p < 0.001$).

Interactions

We evaluated the interactions between smoking status and tobacco-related cancers in predicting the HRQoL. The results indicated no significant interaction between the two variables. Additionally, we examined potential interactions between gender and age; however, none were significant predictors of HRQoL.

Sensitivity analysis

In the sensitivity analysis, we excluded all missing data and discovered that the outcomes were consistent with the initial analysis after multiple imputations. The odds of poor HRQoL were 80% higher for current smokers than never smokers, with an OR of 1.80 (95% CI 1.46-2.22). Former smokers exhibited a tendency toward lower HRQoL compared to never smokers, with an OR of 1.14 (95% CI 0.98-1.33), although this relationship was not statistically significant ($p = 0.082$). In our second sensitivity analysis, we dichotomized HRQoL into two alternative categories. The first one defined good HRQoL as those participants with a score of 1 (representing those who had self-reported good health across all self-reported dimensions) and participants with a score lower than 1 (representing those with at least one of these dimensions affected). This first alternate dichotomization was consistent with previous findings that former and current smokers had higher odds of poorer HRQoL than non-smokers, as evidenced by the ORs being 1.21 (95% CI:1.10 -1.33) for former smokers and 1.73 (95% CI:1.51 -1.98) for current smokers. We also explored an alternative classification, segregating participants with a score of 0, which typified the poorest HRQoL, from those with a score higher than 0. Comparable results emerged, as smoking was associated with a decline in HRQoL. This connection was evidenced by an OR of 1.22 (95% CI 1.07-1.39) for former smokers and an OR of 1.65 (95% CI 1.39-1.96) for current smokers ($p < 0.001$) (Table 1).

Discussion

This study found that smoking is strongly associated with poor HRQoL among cancer survivors. The prevalence of current smoking was approximately 10%, and that of former smokers was 37%, indicating that one-fourth of cancer survivors were currently smoking after cancer diagnosis. The results demonstrated that smoking status is an independent predictor of HRQoL in cancer survivors. After adjusting for demographic, socioeconomic, and health-related aspects, our study determined that current smokers had a 65% heightened risk of poor HRQoL, whereas former smokers had a 22% increased likelihood of poor HRQoL compared to never smokers within the cancer survivor population.

Considering that HRQoL is an essential element in cancer care and has a strong association with survival rates and treatment results (24–27), discerning the factors affecting HRQoL among

cancer survivors is indispensable for enhancing their overall welfare and sustained health (28, 29). Previous studies established an association between smoking and reduced HRQoL in the general population and patients with diverse medical conditions (30–32). (33, 34) However, few studies have addressed the impact of smoking on cancer survivors' HRQoL. Our study adds to the literature by specifically examining the effect of smoking on HRQoL in a large sample representative of the U.S. cancer survivor population.

The interplay between smoking and Health-Related Quality of Life (HRQoL) among oncology patients warrants meticulous investigation to elucidate the complex pathways through which tobacco consumption exerts deleterious effects on individual well-being. One potential reason for the harmful impact of smoking on HRQoL is its connection to other unhealthy habits like not being physically active, having poor sleep habits, consuming excessive alcohol, and making suboptimal dietary choices. These modifiable risk factors have consistently demonstrated associations with heightened morbidity and mortality rates (35). Moreover, there is accumulating evidence to suggest that tobacco attenuates the efficacy and tolerability of cancer therapies, potentially *via* mechanisms involving oxidative stress and modulation of drug-metabolizing enzymes, thus leading to a higher risk of cancer recurrence and progression (36, 37). Concomitantly, the burden of comorbidities attributable to smoking can profoundly influence the aggregate morbidity and mortality experienced by this patient population.

Our study also found that current smokers had a significantly higher likelihood of experiencing poor HRQoL than never smokers, with a predictive probability of 21.43% versus 11.55%, respectively. Moreover, former smokers had poorer HRQoL than those who never smoked but were not as bad as current smokers. These results highlight the significance of providing smoking cessation education to cancer survivors and emphasize that quitting is never too late. Given the increased risk of cancer progression, recurrence, second primary malignancies, and inferior treatment outcomes, smoking cessation should be a top priority in managing cancer patients who smoke (38, 39).

While several factors like comorbidities, education, and income level are non-modifiable, smoking is a modifiable risk factor that offers a tangible area for supportive care interventions (40). Therefore, healthcare professionals must prioritize smoking cessation counseling for all cancer patients regardless of whether their cancer is tobacco-related or not, based on the significant potential impact of quitting smoking on HRQoL, cancer outcomes, and overall health in cancer patients (41). Notably, tailored smoking cessation interventions are recommended for cancer patients as an integral component of their cancer care by multiple organizations, such as the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), US Preventive Services Task Force (USPSTF), and Centers for Disease Control and Prevention (CDC) (42–44). (45) These institutions advocate that healthcare professionals evaluate tobacco use among all cancer patients and administer evidence-based strategies, including pharmacotherapy and behavioral counseling, to enhance overall health outcomes and quality of life.

A thorough understanding of the association between smoking and its impact on HRQoL in cancer survivors, and an evaluation of the socioeconomic burden associated with smoking-related health costs and loss of productivity can provide a comprehensive understanding of the detrimental effects of smoking on society and the healthcare system. This valuable insight can be utilized to create effective strategies and health policies to lessen this considerable burden, consequently improving HRQoL for cancer survivors and potentially abating the economic strain on the healthcare system (46, 47).

Our study has notable strengths, including its large sample size of 39,578 cancer survivors and its use of the world's largest continuously conducted health survey by the CDC (48). Additionally, we employed a composite outcome to analyze the multidimensional concept of HRQoL and conducted a Cronbach's test to ensure instrument measure validity and reliability. However, as with any other study our study has some limitations. First, the cross-sectional design precluded the ability to establish a causal relationship between smoking status and HRQoL. It is necessary to conduct longitudinal investigations to obtain a more profound comprehension of this association. Second, our reliance on self-reported data was subject to potential misclassification due to participants' memory recall. Third, we must recognize that while our logistic regression model accounts for numerous demographic, socioeconomic, and health-related aspects, HRQoL remains a nuanced and multifarious notion. In this context, additional unmeasured confounders may influence the outcome. Fourth, our investigation is susceptible to right censoring, as excluding the most severe cancer cases, possibly attributable to mortality, may introduce a bias to the findings. Fifth, it is essential to recognize the restricted generalizability of our findings, given that our investigation concentrated on a cohort of cancer survivors residing in the United States. Consequently, the outcomes may not be seamlessly applicabble to cancer survivor populations in other countries. Sixth, our research did not consider temporality, thus rendering it impossible to determine whether cancer survivors had ceased smoking before or after their diagnosis.

In this age of precision medicine, the imperative need to integrate patient-reported outcomes, socio-environmental determinants of health, life quality assessments, nutritional considerations, and behavioral data into oncological research is increasingly evident. With a multitude of diverse and competing treatment strategies available, it is imperative to tailor indications to reflect the personalized needs of patients. Integrating these non-clinical data into the treatment decision-making process is crucial for achieving this objective. In light of this, healthcare providers must diligently evaluate and track HRQoL at an early stage and longitudinally. Further research should encompass a broader spectrum of HRQoL factors, including pain and social and emotional support, to gain deeper insights into their influence on treatment outcomes. Other investigators have sought to understand and address the HRQoL of patients in clinical practice. For example, the National Comprehensive Cancer Network (NCCN) advises incorporating distress management and HRQOL interventions into routine practice. This suggests using the "Distress

Thermometer tool" to screen for distress in every medical encounter. This instrument evaluates various domains, including physical symptoms, emotional well-being, family or interpersonal issues, spiritual concerns, financial distress, and functional limitations (49, 50).

In conclusion, our study showed a robust association between smoking status and a negative impact on cancer survivors' HRQoL. The practical implications of our findings cannot be understated, as it calls for prompt interventions to help cancer survivors quit smoking and improve their HRQoL. As such, healthcare providers must acknowledge the detrimental effects of smoking on HRQoL and take proactive steps to facilitate smoking cessation in this population. Nonetheless, the intricate relationship between smoking status and HRQoL among cancer survivors warrants further investigation, and the onus remains on the research community to unravel this intricate association.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/brfss/annual_data/annual_data.htm.

Author contributions

JN: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft. BR: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Writing – review & editing. ER: Visualization, Writing – original draft, Writing – review & editing. CB: Visualization, Writing – original draft, Writing – review & editing. ER: Visualization, Writing – original draft, Writing – review & editing. GI: Investigation, Methodology, Writing – review & editing. YT: Conceptualization, Data curation, Formal Analysis, Software, Writing – original draft. RA: Software, Writing – review & editing. DF: Data curation, Investigation, Software, Visualization, Writing – original draft, Writing – review & editing. ML: Supervision, Validation, Visualization, Writing – review & editing. MM: Investigation, Supervision, Validation, Writing – review & editing. SC: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1261041/full#supplementary-material

References

1. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer* (2008) 112(11 Suppl):2577–92. doi: 10.1002/cncr.23448

2. Yin S, Njai R, Barker L, Siegel PZ, Liao Y. Summarizing health-related quality of life (HRQOL): development and testing of a one-factor model. *Popul Health Metr* (2016) 14:22. doi: 10.1186/s12963-016-0091-3

3. Allart-Vorelli P, Porro B, Baguet F, Michel A, Cousson-Gélie F. Haematological cancer and quality of life: a systematic literature review. *Blood Cancer J* (2015) 5(4):e305. doi: 10.1038/bcj.2015.29

4. Epplein M, Zheng Y, Zheng W, Chen Z, Gu K, Penson D, et al. Quality of life after breast cancer diagnosis and survival. *J Clin Oncol* (2011) 29(4):406–12. doi: 10.1200/JCO.2010.30.6951

5. Braun DP, Gupta D, Staren ED. Quality of life assessment as a predictor of survival in non-small cell lung cancer. *BMC Cancer* (2011) 11:353. doi: 10.1186/1471-2407-11-353

6. McKernan M, McMillan DC, Anderson JR, Angerson WJ, Stuart RC. The relationship between quality of life (EORTC QLQ-C30) and survival in patients with gastro-oesophageal cancer. *Br J Cancer* (2008) 98(5):888–93. doi: 10.1038/sj.bjc.6604248

7. Shrestha A, Martin C, Burton M, Walters S, Collins K, Wyld L. Quality of life versus length of life considerations in cancer patients: A systematic literature review. *Psychooncology* (2019) 28(7):1367–80. doi: 10.1002/pon.5054

8. Schmidt ME, Goldschmidt S, Hermann S, Steindorf K. Late effects, long-term problems and unmet needs of cancer survivors. *Int J Cancer* (2022) 151(8):1280–90. doi: 10.1002/ijc.34152

9. Cornelius ME, Loretan CG, Wang TW, Jamal A, Homa DM. Tobacco product use among adults - United States, 2020. *MMWR Morb Mortal Wkly Rep* (2022) 71(11):397–405. doi: 10.15585/mmwr.mm7111a1

10. Salloum RG, Huo J, Lee JH, Lee J, Dallery J, George T, et al. Tobacco and E-cigarette use among cancer survivors in the United States. *PloS One* (2019) 14(12):e0226110. doi: 10.1371/journal.pone.0226110

11. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin* (2018) 68(1):31–54. doi: 10.3322/caac.21440

12. Warren GW, Cummings KM. Tobacco and lung cancer: risks, trends, and outcomes in patients with cancer. *Am Soc Clin Oncol Educ Book* (2013) 2013:359–64. doi: 10.14694/EdBook_AM.2013.33.359

13. Sitas F, Weber MF, Egger S, Yap S, Chiew M, O'Connell D. Smoking cessation after cancer. *J Clin Oncol* (2014) 32(32):3593–5. doi: 10.1200/JCO.2014.55.9666

14. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ* (2010) 340:b5569. doi: 10.1136/bmj.b5569

15. Dube SR, Thompson W, Homa DM, Zack MM. Smoking and health-related quality of life among U.S. *Adolescents Nicotine Tob Res* (2013) 15(2):492–500. doi: 10.1093/ntr/nts163

16. McClave AK, Dube SR, Strine TW, Mokdad AH. Associations between health-related quality of life and smoking status among a large sample of U.S. adults. *Prev Med* (2009) 48(2):173–9. doi: 10.1016/j.ypmed.2008.11.012

17. CDC. *BRFSS* (2023). Available at: https://www.cdc.gov/brfss/index.html.

18. Centers for Disease Control and Prevention (CDC). Health-related quality of life among persons with epilepsy–Texas, 1998. *MMWR Morb Mortal Wkly Rep* (2001) 50(2):24–6, 35.

19. Rohan EA, Townsend JS, Fairley TL, Stewart SL. Health behaviors and quality of life among colorectal cancer survivors. *J Natl Compr Canc Netw* (2015) 13(3):297–302. doi: 10.6004/jnccn.2015.0041

20. Secinti E, Lewson AB, Wu W, Kent EE, Mosher CE. Health-related quality of life: A comparative analysis of caregivers of people with dementia, cancer, COPD/emphysema, and diabetes and noncaregivers, 2015-2018 BRFSS. *Ann Behav Med* (2021) 55(11):1130–43. doi: 10.1093/abm/kaab007

21. Tavakol M, Dennick R. Making sense of Cronbach's alpha. *J Int Assoc Med Sci Educ* (2011) 2:53–5. doi: 10.5116/ijme.4dfb.8dfd

22. Woudstra AJ, Smets EMA, Galenkamp H, Fransen MP. Validation of health literacy domains for informed decision making about colorectal cancer screening using classical test theory and item response theory. *Patient Educ Couns* (2019) 102 (12):2335–43. doi: 10.1016/j.pec.2019.09.016

23. Dumas SE, Dongchung TY, Sanderson ML, Bartley K, Levanon Seligson A. A comparison of the four healthy days measures (HRQOL-4) with a single measure of self-rated general health in a population-based health survey in New York City. *Health Qual Life Outcomes* (2020) 18(1):315. doi: 10.1186/s12955-020-01560-4

24. Klein J, Livergant J, Ringash J. Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: a systematic review. *Oral Oncol* (2014) 50(4):254–62. doi: 10.1016/j.oraloncology.2014.01.015

25. Steel JL, Geller DA, Robinson TL, Savkova AY, Brower DS, Marsh JW, et al. Health-related quality of life as a prognostic factor in patients with advanced cancer. *Cancer* (2014) 120(23):3717–21. doi: 10.1002/cncr.28902

26. Efficace F, Biganzoli L, Piccart M, Coens C, Van Steen K, Cufer T, et al. Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. *Eur J Cancer* (2004) 40(7):1021–30. doi: 10.1016/j.ejca.2004.01.014

27. Montazeri A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health Qual Life Outcomes* (2009) 7:102. doi: 10.1186/1477-7525-7-102

28. Vissers PAJ, Thong MSY, Pouwer F, Zanders MMJ, Coebergh JWW, van de Poll-Franse LV. The impact of comorbidity on Health-Related Quality of Life among cancer survivors: analyses of data from the PROFILES registry. *J Cancer Surviv* (2013) 7 (4):602–13. doi: 10.1007/s11764-013-0299-1

29. Elliott BA, Renier CM, Haller IV, Elliott TE. Health-related quality of life (HRQoL) in patients with cancer and other concurrent illnesses. *Qual Life Res* (2004) 13(2):457–62. doi: 10.1023/B:QURE.0000018476.11278.35

30. Coste J, Quinquis L, D'Almeida S, Audureau E. Smoking and health-related quality of life in the general population. Independent relationships and large differences according to patterns and quantity of smoking and to gender. *PloS One* (2014) 9(3): e91562. doi: 10.1371/journal.pone.0091562

31. Turner J, Page-Shafer K, Chin DP, Osmond D, Mossar M, Markstein L, et al. Adverse impact of cigarette smoking on dimensions of health-related quality of life in persons with HIV infection. *AIDS Patient Care STDS* (2001) 15(12):615–24. doi: 10.1089/108729101753354617

32. Xue C, Bian L, Xie YS, Yin ZF, Xu ZJ, Chen QZ, et al. Impact of smoking on health-related quality of Life after percutaneous coronary intervention treated with drug-eluting stents: a longitudinal observational study. *Health Qual Life Outcomes* (2017) 15(1):1. doi: 10.1186/s12955-016-0578-4

33. Rezaei S, Karami Matin B, Kazemi Karyani A, Woldemichael A, Khosravi F, Khosravipour M, et al. Impact of smoking on health-related quality of life: A general population survey in West Iran. *Asian Pac J Cancer Prev* (2017) 18(11):3179–85. doi: 10.22034/APJCP.2017.18.11.3179

34. Mody RR, Smith MJ. Smoking status and health-related quality of life: as findings from the 2001 Behavioral Risk Factor Surveillance System data. *Am J Health Promot* (2006) 20(4):251–8. doi: 10.4278/0890-1171-20.4.251

35. Strine TW, Okoro CA, Chapman DP, Balluz LS, Ford ES, Ajani UA, et al. Health-related quality of life and health risk behaviors among smokers. *Am J Prev Med* (2005) 28(2):182–7. doi: 10.1016/j.amepre.2004.10.002

36. Condoluci A, Mazzara C, Zoccoli A, Pezzuto A, Tonini G. Impact of smoking on lung cancer treatment effectiveness: a review. *Future Oncol* (2016) 12(18):2149–61. doi: 10.2217/fon-2015-0055

37. Hecht SS. Progress and challenges in selected areas of tobacco carcinogenesis. *Chem Res Toxicol* (2008) 21(1):160–71. doi: 10.1021/tx7002068

38. Fiore MC, Baker TB, Nolan MB, Emamekhoo H. Providing cessation treatment to every oncology patient who smokes: An essential component of cancer care. *Cancer Wiley* (2022) 128(6):1162–4. doi: 10.1002/cncr.34052

39. Florou AN, Gkiozos ICH, Tsagouli SK, Souliotis KN, Syrigos KN. Clinical significance of smoking cessation in subjects with cancer: a 30-year review. *Respir Care* (2014) 59(12):1924–36. doi: 10.4187/respcare.02559

40. Han X, Robinson LA, Jensen RE, Smith TG, Yabroff KR. Factors associated with health-related quality of life among cancer survivors in the United States. *JNCI Cancer Spectr* (2021) 5(1):pkaa123. doi: 10.1093/jncics/pkaa123

41. Nolazco JI, Mucci LA, Sosnowski R, Przewoźniak K, Chang SL, De Nunzio C. Relationship between cigarette use and prostate cancer risk: what do we know and what should we do? *Prostate Cancer Prostatic Dis* (2023) 26(3):516–8. doi: 10.1038/s41391-023-00671-5

42. Siu AL USPreventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive services task force recommendation statement. *Ann Intern Med* (2015) 163 (8):622–34. doi: 10.7326/M15-2023

43. Shields PG, Herbst RS, Arenberg D, Benowitz NL, Bierut L, Luckart JB, et al. Smoking cessation, version 1.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* (2016) 14(11):1430–68. doi: 10.6004/jnccn.2016.0152

44. Hanna N, Mulshine J, Wollins DS, Tyne C, Dresler C. Tobacco cessation and control a decade later: American society of clinical oncology policy statement update. *J Clin Oncol* (2013) 31(25):3147–57. doi: 10.1200/JCO.2013.48.8932

45. CDCTobaccoFree. *Cancer Care Settings and Smoking Cessation*. Centers for Disease Control and Prevention (2022). Available at: https://www.cdc.gov/tobacco/patient-care/care-settings/cancer/index.htm.

46. Islami F, Marlow EC, Zhao J, Wiese D, Asare S, Bandi P, et al. Person-years of life lost and lost earnings from cigarette smoking-attributable cancer deaths, United States, 2019. *Int J Cancer* (2022) 151(12):2095–106. doi: 10.1002/ijc.34217

47. Nolazco JI. Tobacco cessation counseling in urology: Time to take the lead. *Explor Res Hypothesis Med* (2023) 000(000):000–0. doi: 10.14218/ERHM.2022.00103

48. Website. *CDC - BRFSS* (2022). Available at: https://www.cdc.gov/brfss/index.html (Accessed February 25, 2022).

49. Frost GW, Zevon MA, Gruber M, Scrivani RA. Use of distress thermometers in an outpatient oncology setting. *Health Soc Work* (2011) 36(4):293–7. doi: 10.1093/hsw/36.4.293

50. Ownby KK. Use of the distress thermometer in clinical practice. *J Adv Pract Oncol* (2019) 10(2):175–9. doi: 10.6004/jadpro.2019.10.2.7

frontiers | Frontiers in Public Health

TYPE Brief Research Report
PUBLISHED 05 January 2024
DOI 10.3389/fpubh.2023.1280316

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Priyanka Banerjee,
Texas A&M Health Science Center, United States
Richa Kapoor,
Children's Hospital of Philadelphia, United States

*CORRESPONDENCE
Shudong Zhu
✉ 1125537080@qq.com

†These authors have contributed equally to this work

RECEIVED 21 August 2023
ACCEPTED 29 November 2023
PUBLISHED 05 January 2024

CITATION
Xiao J, Li S, Zhu S, Ranjan K and Zhang D (2024) Incidence of lung cancer among healthcare workers in Hunan Province and analysis of related risk factors. *Front. Public Health* 11:1280316. doi: 10.3389/fpubh.2023.1280316

Incidence of lung cancer among healthcare workers in Hunan Province and analysis of related risk factors

Jinzhang Xiao[1†], Sishi Li[2†], Shudong Zhu[1,2,3,4*†], Kamakshi Ranjan[5] and Dianzheng Zhang[5]

[1]Nantong Tumor Hospital, Nantong, Jiangsu, China, [2]School of Medicine, Central South University, Changsha, China, [3]School of Medicine, Nantong University, Nantong, Jiangsu, China, [4]Argus Pharmaceuticals, Changsha, China, [5]Department of Bio-Medical Sciences, Philadelphia College of Osteopathic Medicine, Philadelphia, PA, United States

Background: The prevalence of lung cancer, a major type of malignant tumor, has been increasing over the years greatly impacting the health of Chinese residents. This study investigates the epidemiological characteristics of lung cancer among healthcare workers in the Hunan Province, as well as the occupational risk factors.

Methods: The data analyzed in this study was collected from the largest tumor hospital in the province: the Hunan Provincial Tumor Hospital affiliated with Central South University, School of Medicine. The data collected encompasses input collected between the years of 2004 to 2013 of the population of healthcare workers who were hospitalized for lung cancer treatments. Information was obtained through statistical analysis and telephonic interviews.

Results: The prevalence of lung cancer among healthcare workers was much higher than that of the general population, as revealed by the difference between number of healthcare worker cases per 1,000 cases and number of healthcare workers per 1,000 population in the decade from 2004 to 2013. Analysis of the data further demonstrates that lung cancer prevalence among healthcare workers increases exponentially with age. Although smoking has been shown to increase the incidence of lung cancer to some extent, it is most likely not the main cause of lung cancer. In addition, it appears that the highest rates of lung cancer incidence occurs in mainly in primary general practitioners, medical radiologists, and nurses. The lack of awareness of personal safety measures may place healthcare workers at a greater risk of lung cancer.

KEYWORDS

lung cancer, healthcare worker, risk factor, incidence, occupation

Introduction

In 2013, there were approximately 3.682 million new cases of malignant tumors nationwide, and 2.229 million deaths (1). The morbidity rate of malignant tumors is 190.17/100,000 and the mortality rate is 109.95/100,000 in the Chinese population (1), indicating malignant tumors are a great threat to human health and society. The incidence of malignant tumors is predominantly concentrated among individuals aged over 45 years. Lung cancer ranks as the most common cancer among males and the second most among women (1). Lung cancer is also the leading cause of death in both males and females (1). Between 2007 and 2013, lung cancer has also been the leading cause of both morbidity and mortality in China (1–7). Within the span of 3 years, between 2010 and 2013, the number of new cases of lung cancer in China increased by 133,000 reaching a total of 733,000 cases. Simultaneously, in 2013, the incidence of lung cancer-related deaths reached 591,000, due to a surge in an additional 101,000 deaths between 2010 to 2013 (1–7). These alarming trends underscore the importance of lung cancer study in regional and global health.

Healthcare workers are a broad group of professions including practicing doctors, physician assistants, registered nurses, pharmacists, laboratory technologists, imaging technologists, health supervisors, and trainee doctors. Due to the nature and setting of their work, healthcare workers are more likely to be exposed to various carcinogens that can adversely affect the lung than the general population.

Formaldehyde

Formalin (containing 35–40% formaldehyde) is widely used in the fixation and preservation of specimens, particularly in the preparation and preservation of human medical specimens (8). Formaldehyde has a very low boiling point at 19 °C causing it easily evaporate at room temperature. The International Agency for Research on Cancer (IARC) has classified formaldehyde as a Group 1 human carcinogen, primarily associated with nasopharyngeal carcinoma but also potentially associated with lung cancer and leukemia (8). The carcinogenicity of formaldehyde is primarily attributed to its ability to fragment DNA and cross-link DNA and protein structures (9–12). Moreover, formaldehyde, as a potent oxidant that can generate reactive oxygen radicals resulting in cellular and tissue damage (13–15). Research by Liu et al. demonstrated a higher rate of tumor death in groups exposed to formaldehyde in comparison to groups not exposed to formaldehyde, in a formaldehyde plant (16). Cui et al. showed an increased incidence of malignant tumors, especially gastric cancer, liver cancer, and lung cancer among formaldehyde plant workers (17). Worldwide studies had also reported elevated cancer mortality among workers with industrial formaldehyde exposure (18, 19). A recent systematic evaluation exhibits that various well-designed, high-quality studies also support the association between the lung cancer risk and formaldehyde exposure (20). In a hospital setting, healthcare workers, particularly those working in dissection and pathology rooms, are at risk of formaldehyde exposure during specimen preparation and preservation.

Radiation

Radiation exposure in hospitals primarily arises from tumor radiation therapy and X-ray procedures conducted in the laboratory department. Radiation causes DNA damage and genetic alterations (21). While fast growing tumor cells are more susceptible to radiation, normal cells may also accumulate DNA damages. Prolonged low-dose radiation exposure, spanning many years or even decades, may result in skin cancer, lung cancer, leukemia, and bone cancer (22). During radiation therapy or diagnosis, patients are often administered treatment by medical professionals, including doctors and nurses, who also might be exposed to radiation.

Anticancer drugs (ADs)

Anticancer drugs, particularly cytotoxic drugs, form the backbone of cancer treatment. These drugs, while effective against tumors, can also impact on normal cells. Patients undergoing anticancer drug treatment often experience various adverse reactions, with myelosuppression and gastrointestinal issues being the most common (23). Additional side effects include alopecia, liver toxicity, lung toxicity, kidney toxicity, and neurotoxicity. Long-term exposure to anticancer drugs, especially for healthcare workers such as oncology nurses, may be detrimental to health. Studies have indicated that anticancer drugs can be detected in the air during the preparation and administration of these drugs (24–27). The turbulence generated during preparation can lead to the formation of aerosols, allowing drug particles to enter human bodies through the respiratory tract and skin (28–30). Several studies have detected the presence of anticancer drug molecules in the urine of healthcare workers exposed to these drugs (31, 32). These compounds can harm the immune system, disrupt hormone secretion, damage DNA, and even lead to cancer (33). Many general hospitals and chemotherapy units lack comprehensive protective equipment and do not supply sufficient safety education. Nurses in China, in particular, often do not prioritize their own safety (34). A survey of nurses in 78 city and county-level hospitals in the southwestern provinces in China revealed gaps in awareness and protection norms (35).

Bodily secretion

Healthcare workers often encounter bodily secretions including vomit, excrement, and saliva, in hospital environments where patients are closely confined. These professionals are exposed to a dense population with a diverse range of patients leading them to be at a higher risk of contracting an infection compared to the general population. Studies have identified a higher risk of tuberculosis (TB) among healthcare workers in respiratory departments. Among the different health professionals, doctors working in departments related to the respiratory tract are at an even greater risk than others (36). Healthcare workers are found to be 10–20 times more likely to contract TB in hospital settings compared to the general population. Research in Tianjin indicated that a significant portion of medical staff did not consistently wear masks when in contact with suspected TB patients, contributing to increased risk of exposure to the infection (37). The coexistence of pulmonary tuberculosis and lung cancer is

very common with studies indicating an increased risk of lung cancer among TB patients (38–40).

Other risk factors such as clinical trauma due sharp instrument injury or needle stab injury are also common in the medical practice of healthcare workers. The infection after clinical trauma may transmit infectious diseases like TB and viral infection, which may potentially be cancerous.

In summary, occupational hazards including exposure to formaldehyde, radiation, anticancer drugs, and infectious diseases, may place healthcare workers at significant risk for negative health outcomes. Determining whether the health of healthcare workers is indeed affected and the extent to which it is affected is the objective of this study. Addressing these risks and therefore promoting corresponding safety measures will protect the well-being of healthcare professionals and reduce the incidence of occupational diseases such as lung cancer. We report herewith that the prevalence of lung cancer among healthcare workers is much higher than that of the general population. Increasing awareness and compliance of proper safety precautions and protocols will reduce the occupational risks healthcare workers face and ultimately improve their health outcomes.

Methods

This study collected data of lung cancer patients who were hospitalized in the Thoracic Surgery Department of the Hunan Provincial Tumor Hospital Affiliated to School of Medicine, Central South University between 2004 and 2013. The study collected personal information of the patients who were healthcare workers, including gender, age, occupation, home address, telephone number, discharge records, past medical history, marriage and childbirth history, and family history. A total of 16,514 cases were reviewed, including 237 cases of healthcare workers.

The home address information of the 16,514 cases were collected and assigned to each city according to the administrative division of Hunan Province (Table 1; Figure 1). The number of healthcare workers per 1,000 lung cancer patients and the number of healthcare workers per 1,000 normal population were calculated and compared (Table 2). Statistical analysis was performed using paired, one-tailed *t* test.

The study also conducted telephone interviews with the 237 cases of lung cancer patients who were healthcare workers. The survey consisted of a questionnaire on their occupation, working age, working time, and related occupational risk factors. The survey also assessed the duration and frequency of exposure to formalin, radiation, anticancer drugs, infectious secretions, risk factors involved in their scientific research, the number of workplace injuries and safety practices. Patients were also asked to describe/identify the likely cause of their lung cancer for verification. Data was collected on 57 patients (those patients who had died or refused to answer questions were not included). The occupations of the 57 patients were classified and counted. These are reflected in Tables 3–5.

TABLE 1 2006–2013 distribution of lung cancer patients in Hunan Province in different cities.

City	Cases	LCP (%)	NP (%)*
All Hunan Cities	13,324	100	100
Changsha	3,072	23.06	10.72
Zhuzhou	694	5.21	5.87
Xiangtan	501	3.76	4.18
Hengyang	850	6.38	10.87
Shaoyang	1,203	9.03	10.77
Yueyang	1,067	8.01	8.34
Changde	1,151	8.64	8.70
Zhangjiajie	265	1.99	2.25
Yiyang	1,005	7.54	6.57
Chenzhou	450	3.38	6.98
Yongzhou	1,000	7.51	7.89
Huaihua	588	4.41	7.22
Loudi	1,180	8.86	5.76
Xiangxi	297	2.23	3.88

LCP (%): Percentage of lung cancer patients of each city in the province. NP (%): Percentage of population of each city in the province. *From the Sixth National Population Census of Hunan Province.

Results

Regional distribution of lung cancer

Regions with a total of 13,965 cases were recorded at Hunan Provincial Tumor Hospital during the eight-year period spanning from 2006 to 2013. These data are organized in Table 1. Within this dataset, 415 cases were found to be missing, resulting in a missing rate of 3.00%. Furthermore, 227 cases were from other provinces, while only 13,324 cases originated from Hunan Province. Unfortunately, regional information regarding lung cancer patients for the years 2004 and 2005 is not available.

Table 1 and its associated Figure 1 shows that the lung cancer cases are relatively concentrated in the city of Changsha. There is a similar distribution of lung cancer to the distribution of normal population among most cities with the exception of Changsha.

Prevalence of lung cancer in healthcare workers

Table 2 shows that the number of healthcare workers per 1,000 lung cancer cases within the decade of 2004–2013 was approximately 4 fold that of the number of healthcare workers per 1,000 normal population, which is statistically significant ($p < 0.001$). This implies that the probability of healthcare workers contracting lung cancer is much higher than that of the general population.

Basic information of healthcare workers contracting lung cancer

Table 3 shows that as age increases, the prevalence of lung cancer among healthcare workers also rises. In the 25–34 age group, healthcare workers account for 35.6% of the total number of healthcare workers, whereas in this age group, cancer-contracting healthcare

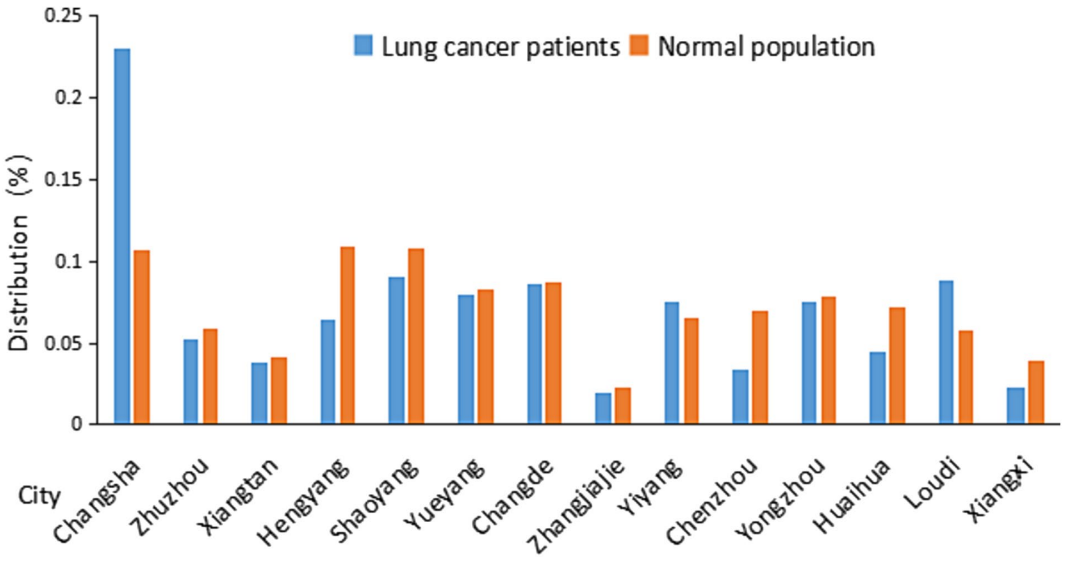


FIGURE 1
Distribution of lung cancer patients and normal population in Hunan Province in different cities. Distribution data were from Table 1.

TABLE 2 2004–2013 the number of healthcare workers per 1,000 lung cancer patients and the number of healthcare workers per 1,000 normal population.

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Average	*p* value
Total	1,163	1,218	1,048	1,058	1,259	1,428	1717	2,207	2,405	2,793		
Case*	11	19	22	19	17	21	25	28	32	43		
A**	3.15	3.18	3	3.21	3.34	3.62	3.81	3.96	4.47	4.56	3.63	
B***	9.46	15.6	20.99	17.96	13.5	14.71	14.56	12.73	13.05	15.41	14.80	
Ratio#	3.00	4.91	7.00	5.60	4.04	4.06	3.82	3.21	2.92	3.38	4.19	<0.001

*Number of lung cancer cases among healthcare workers. **Number of healthcare workers per 1,000 population in Hunan Province, from 2005–2014 China Health Statistics Yearbook. ***Number of healthcare workers per 1,000 lung cancer cases in Hunan Province (number of cases of sick doctors/total number of cases×1,000). #Ratio of B/A. *P* value: paired, one-tailed *t* test.

workers account for only 0.8% of the total number of cancer-contracting healthcare workers, making the percentage of cancer-contracting healthcare workers 0.023 fold of that of healthcare workers (0.8%/35.6%) (Figure 2). In contrast, for those aged over 60, healthcare workers represent only 4% of the total number of healthcare workers of all ages, while cancer-contracting healthcare workers account for 56.1% of the total number of cancer-contracting healthcare workers of all ages, making the percentage of cancer-contracting healthcare workers 14.025 fold that of healthcare workers (56.1%/4%) (also see Figure 2). This stark increase from 0.023 to 14.025 indicates that lung cancer predominantly affects healthcare workers over the age of 60. The data obtained from all age groups also demonstrates an overall positive correlation between age and incidence of lung cancer (Figure 2).

Among the cancer-contracting healthcare workers, 52.7% (100–47.3%) have a history of smoking cigarettes (Table 3). In contrast, only 25% (100–75%) of all healthcare workers have a history of smoking cigarettes (Table 3). Moreover, the prevalence of lung cancer increases with the intensity of smoking, with over 20 cigarettes per day accounting for 47.2% (27.0% + 20.2%) of all cancer-contracting healthcare worker, in contrast to only 3.8, 1.7% or 0% in groups smoking 10–20, <10, and 0 cigarettes/day. This suggests that smoking may indeed influence the incidence of lung cancer among healthcare workers to an extent, although it is likely not the primary cause of lung cancer among this population.

Interestingly, the prevalence of lung cancer among healthcare workers appears to have little correlation with alcohol consumption.

Occupational distribution of lung cancer patients

Follow-up visits of the 57 healthcare workers that were diagnosed with lung cancer (Table 4) reveals that lung cancer is most prevalent in Departments of General Practice (29.3%) and Interna Medicine (22.0%). Considering the relative low number of staff in the Departments of General Practice (7.6%) and Medical Imaging Departments (9.6%), it appears that workers in the Departments of General Practice and Medical Imaging Departments are most likely to contract lung cancer among all the healthcare workers, with the ratio of LCP/NP of 3.875 and 1.025, respectively (Table 4).

10.3389/fpubh.2023.1280316

TABLE 3 Age and consumption of cigarettes or alcohol by healthcare workers contracting lung cancer.

	Cases	LCP (%)	NP (%)	Ratio (LCP/NP)**
Total	237	100	100*	
Age				
0–25	0	0	8.7	0
25–34	2	0.8	35.6	0.023
35–44	17	7.2	29.2	0.247
45–54	42	17.7	17.3	1.023
55–59	43	18.2	5.2	3.5
60-	133	56.1	4.0	14.025
Smoking history				
None	112	47.3	75***	
Occasionally	1	0.4		
<20 year	0	0		
20 ~ 30 year	20	8.4		
30 ~ 40 year	48	20.3		
≥40 year	56	23.6		
Drinking alcohol				
never	164	69.2		
<Once/month	24	10.1		
≥Once/month	49	20.7		
Smoking intensity				
Never	112	47.3		
Occasionally	0	0		
<10/d	4	1.7	13.4****	12.7
10 ~ 20/d	9	3.8	28.7	13.3
20 ~ 30/d	64	27	35.6–58	46.6–75.8
≥30/d	48	20.2	<22.4	>90.2

*From "2013 China Health Statistics Yearbook." **Ratio of percentage of lung cancer population (LCP, 3rd column) to that of normal population (NP, 4th column) of healthcare workers. ***References [41–43]. ****References [44].

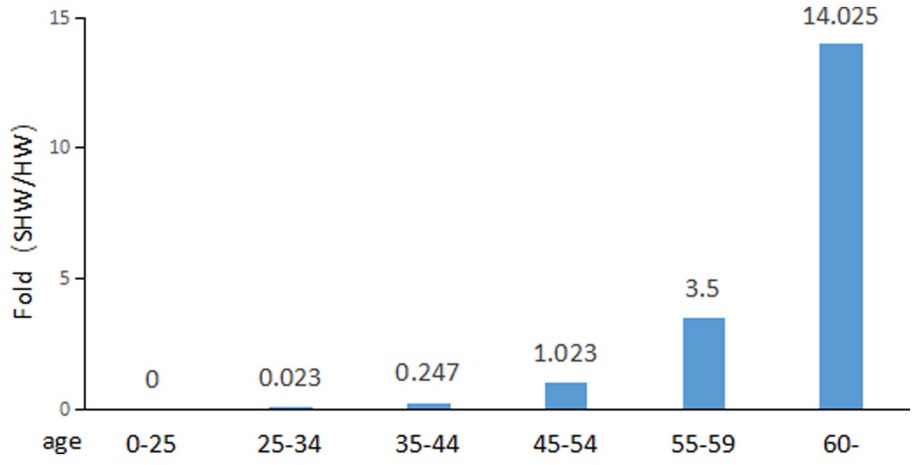


FIGURE 2
Fold change of percentage of sick healthcare workers (SHW) to that of healthcare workers (HW).

10.3389/fpubh.2023.1280316

TABLE 4 Occupational distribution of lung cancer patients among healthcare workers.

Occupation/Working years	Cases	LCP (%)	NP (%*)	Ratio (LCP/NP)
Total	57	100 (41cases**)	100****	100
General practice				
Total	12	29.3	7.6	3.875
0–30	0			
30–40	4			
40–50	8			
Internal medicine				
Total	9	22.0	32.5	0.676
0–30	2			
30–40	1			
40–50	6			
Surgery (Including orthopedics)				
Total	6	14.6	19.1	0.764
0–30	0			
30–40	4			
40–50	2			
Obstetrics & Gynecology				
Total	5	12.2	13.8	0.882
0–30	2			
30–40	1			
40–50	2			
Medical imaging				
Total	4	9.8	9.6	1.025
0–30	0			
30–40	2			
40–50	2			
Traditional Chinese medicine				
Total	5	12.2	17.4	0.701
0–30	0			
30–40	3			
40–50	2			
Total	57	100 (57cases***)		
Pharmacist				
Total	3	5.3		
0–30	2			
30–40	0			
40–50	1			
Nurse				
Total	9	15.8		
0–30	1			
30–40	7			
40–50	1			
Rural medical doctor				
Total	4	7.0		
0–30	0			

(Continued)

TABLE 4 (Continued)

Occupation/Working years	Cases	LCP (%)	NP (%*)	Ratio (LCP/NP)
30–40	1			
40–50	3			

*Composition of subspecialty practicing physicians in the five-year health statistics yearbook from 2009 to 2014 excluding physicians practicing in village clinics. Since the composition has remained stable over the years, the representative composition of 2009 is listed for comparison. **The numbers of village clinics, nurses and pharmacists (3 + 9 + 4 = 16) are not included in the total for side-by-side comparison of percentages (LCP% versus NP%). ***The proportion of pharmacists, nurses, and rural doctors in the total number of cases (57 cases) obtained in the follow-up visit. ****Information on the composition ratio of nurses, pharmacists, and rural doctors among the total healthcare workers was absent in the five-year health statistics yearbook. Current 100% including cases in General Practice, Internal Medicine, Surgery, Obstetrics & Gynecology, Medical Imaging, Traditional Chinese Medicine is only part (70.1%) of all departments (cases) of healthcare workers in the 2009 health statistics yearbook. Ratio (LCP/NP): Ratio of percentage of lung cancer population (LCP, 3rd column) to that of normal population (NP, 4th column) of healthcare workers.

TABLE 5 Occupational risk factor: exposure information in lung cancer cases of healthcare workers.

Risk factor	Cases (57)
Radiation	
0 year	49
1–5 year	4
30–35 year	4
Trauma	
None or very few	52
Yes and more than a few	5
Anticancer drugs	
None or very few	56
Yes and more than a few	1
Exposure to secretions	
None or very few	37
Occasionally	7
Often	13
Self-protection awareness	
Low	13
General	10
High	23

Occupational risk factors

Questions and answers pertaining to formalin, radiation, anticancer drugs, exposure to saliva and other secretions, frequency and duration of exposure to risk factors in scientific research, the number of traumatic incidents, and adherence to safe guidelines are crucial aspects of our investigation. Due to the limited size of our dataset, we have not been able to compile a comprehensive table of occupational risk factors. However, Table 5 listed the most reliable records of risk factors involved in the follow-up visits. Table 5 shows that either of the exposure to radiation, traumatic incidents, anticancer drugs is not an important contributing factors to the development of lung cancer in the healthcare workers. However, a lack of self-protection awareness and exposure to saliva and other secretions may contribute to the increased incidence of lung cancer in healthcare workers.

In conclusion, our study found that the incidence of lung cancer in Changsha, the provincial capital, is significantly higher than the incidence in other cities. We also observed a consistently higher number of healthcare workers per 1,000 lung cancer cases in our study compared to the number of healthcare workers per 1,000 in the general population from 2004 to 2013. Additionally, age and smoking are associated with prevalence of lung cancer in healthcare workers. We have also characterized risks associated with occupational subspecialties, as well the potential exposure risk factors associated with the high incidence of lung cancer among healthcare workers.

Discussion

It is interesting that lung cancer patients are relatively higher in Changsha than the other cities of Hunan Province (Figure 1; Table 1). Several factors may contribute to this observation: 1. Air Quality: Provincial capital cities, due to their larger populations, industrial activities, and traffic congestion, often experience poorer air quality. Changsha is one of the cities with heaviest air pollution in the middle triangle urban agglomerations (45). Research has shown a strong correlation between PM2.5 and the incidence rate of male lung cancer in urban areas. In urban areas, if PM2.5 levels change by 10 $\mu g/m^3$, the shift in incidence rate relative to its mean increases significantly by 3.97% (95% CI: 2.18, 4.96%, $p = 0.000$) compared to rural areas (46). 2. Smoking: Smoking is a significant cause of lung cancer (3), and in many cases, capital cities have higher smoking rates due to various factors such as stress, lifestyle, and greater accessibility to tobacco products. 3. Healthcare Facilities: Provincial capitals often own better healthcare facilities, which might lead to higher rates of diagnosis and reporting of lung cancer cases.

Our study was focused on the healthcare workers in the province. It is surprising that the number of healthcare workers per 1,000 lung cancer cases in the decade 2004–2013 was approximately 4 fold that of the number of healthcare workers per 1,000 normal population. This stunning revelation implies that the chance of healthcare workers contracting lung cancer is much higher than that of the general population.

This survey underscores the significant relationship between lung cancer incidence with both age and smoking. It shows that when age is increased, or when the duration or intensity of smoking is increased, there is a notable rise in the incidence of lung cancer, suggesting DNA damage either accumulated naturally with age or caused by smoking may be a significant contributor to lung cancer morbidity (1–7). Notably, although not included in the results section, our survey also demonstrates that the male-to-female ratio among healthcare workers

with lung cancer is 166:71; among male healthcare workers who had developed lung cancer, the ratio of smokers to non-smokers is 125:41, while only 0:71 for females. These extra lines of evidence are not only in consensus with the tumorigenic effects of smoking, but also indicates that smoking is not a prominent factor in the development of lung cancer among women. Indeed, our telephone interview survey revealed that most women patients and their families attributed their lung cancer to non-smoking risk factors such as exposure to (cooking) oil fumes and life stressors.

Occupationally, the highest prevalence of lung cancer is observed among general practitioners and medical imaging technicians. This pattern can be attributed to the substantial workload faced by professionals in these roles, along with prolonged patient interactions. Furthermore, grassroots hospitals where these professionals work often suffer from understaffing and inadequate equipment resources. Issues with accessibility along with a lack of understanding and indifference for self-protection and the use of personal protective equipment may contribute to this outcome. Importantly, there is a notable absence of a comprehensive occupational exposure reporting system within grassroots hospitals. An earlier survey by Zhu Lihong et al. in 2008 indicated that awareness of hand hygiene among medical staff was generally weak, with an implementation rate ranging from 50 to 70% (47). Additionally, radiologists are exposed to the causes of radiation emitted by imaging equipment (48).

Given the limited number of healthcare worker cases in this survey, it is also important to recognize the potential errors and limitations of our report. In conclusion, effective mitigation of occupational risks for healthcare workers requires collaboration among government bodies, medical units, and individuals. Governments should establish and enforce standardized regulations to address various occupational risk factors, while medical units should provide healthcare workers with comprehensive safety operation guidelines, a secure working environment, and ongoing safety awareness training. This collective effort is vital for safeguarding the health and well-being of healthcare professionals. Through this study, we hope to raise awareness of the additional risks healthcare workers face and encourage the implementation of protocols that can help decrease the disproportionately higher rate with which healthcare workers develop lung cancer.

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.

Ethics statement

Ethical review and approval was not required for the current study in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JX: Formal analysis, Writing – original draft, Data curation, Investigation, Methodology, Validation. SL: Formal analysis, Investigation, Methodology, Writing – original draft. SZ: Supervision, Writing – review & editing, Conceptualization, Funding acquisition. KR: Formal analysis, Writing – review & editing. DZ: Formal analysis, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported in part by NTU University (SZ, NTU03083068), CSU University (SZ, CSU996010197), and Hunan Province BRJH Foundation (SZ, HNBRJH2015ZSD).

Acknowledgments

We thank Drs. H Wang and Y Zhao for providing relevant data.

Conflict of interest

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

Publisher's note

References

1. Chen W, Zheng R, Zhang S, Zeng H, Zou X, Hao J. Report of cancer incidence and mortality in China, 2013, *China Cancer*. (2017) 26:1–7. Chinese. doi: 10.11735/j.issn.1004-0242.2017.01.A001

2. Chen W, Zheng R, Zhang S, Zeng H, Zuo T, Jia M, et al. Report of cancer incidence and mortality in China, 2012. *China Cancer*. (2016) 25:1–8. Chinese. doi: 10.11735/j.issn.1004-0242.2016.01.A001

3. Chen W, Zheng R, Zeng H, Zou X, Zhang S, Hao J. Report of cancer incidence and mortality in China, 2011. *China Cancer*. (2015) 24:1–10. Chinese. doi: 10.11735/j.issn.1004-0242.2015.01.A001

4. Chen W, Zhang S, Zeng H, Zheng R, Zou X, Zhao P, et al. Report of cancer incidence and mortality in China, 2010. *China Cancer*. (2014) 23:1–10. Chinese. doi: 10.11735/j.issn.1004-0242.2014.01.A001

5. Chen W, Zhang S, Zheng R, Zeng H, Zou X, Zhao P, et al. Report of cancer incidence and mortality in China, 2009. *China Cancer*. (2013) 22:2–12. Chinese. doi: 10.11735/j.issn.1004-0242.2013.01.A001

6. Zheng R, Zhang S, Wu L, Li G, Zhao P, Hao J, et al. Report of Incidence and Mortality from China Cancer Registries in 2008. *China Cancer*. (2012) 21:1–12. Chinese. doi: 10.11735/j.issn.1004-0242.2012.1.2012001

7. Chen W, Zhang S, Zheng R, Lei Z, Li G, Zou X, et al. A Report of Cancer Incidence and Mortality from 38 Cancer Registries in China, 2007. *China Cancer*. (2011) 20:162–9. Chinese.

8. Jiang L, Li Y, Cheng J, Chen Y. How to prevent formaldehyde hazards for technicians in anatomical laboratories. *China Continuing Med Educ*. (2014) 3:121-2. Chinese. doi: 10.3969/J.ISSN.1674-9308.2014.03.077

9. Wang M, Cheng G, Balbo S, Carmella SG, Villalta PW, Hecht SS. Clear differences in levels of a formaldehyde-DNA adduct in leukocytes of smokers and nonsmokers. *Cancer Res*. (2009) 69:7170–4. doi: 10.1158/0008-5472.CAN-09-1571

10. Shaham J, Gurvich R, Kaufman Z. Sister chromatid exchange in pathology staff occupationally exposed to formaldehyde. *Mutat Res*. (2002) 514:115–23. doi: 10.1016/S1383-5718(01)00334-5

11. Ladeira C, Viegas S, Carolino E, Prista J, Gomes MC, Brito M. Genotoxicity biomarkers in occupational exposure to formaldehyde--the case of histopathology laboratories. *Mutat Res*. (2011) 721:15–20. doi: 10.1016/j.mrgentox.2010.11.015

12. Jiang S, Yu L, Cheng J, Leng S, Dai Y, Zhang Y, et al. Genomic damages in peripheral blood lymphocytes and association with polymorphisms of three glutathione s-transferases in workers exposed to formaldehyde. *Mutat Res*. (2010) 695:9–15. doi: 10.1016/j.mrgentox.2009.09.011

13. Duong A, Steinmaus C, McHale CM, Vaughan CP, Zhang L. Reproductive and developmental toxicity of formaldehyde: a systematic review. *Mutat Res*. (2011) 728:118–38. doi: 10.1016/j.mrrev.2011.07.003

14. Wang HX, Wang XY, Zhou DX, Zheng LR, Zhang J, Huo YW, et al. Effects of low-dose, long-term formaldehyde exposure on the structure and functions of the ovary in rats. *Toxicol Ind Health*. (2013) 29:609–15. doi: 10.1177/0748233711430983

15. Lino-dos-Santos-Franco A, Correa-Costa M, dos Santos Durão ACC, Ligeiro de Oliveira AP, Breithaupt-Faloppa AC, Bertoni JA, et al. Formaldehyde induces lung inflammation by an oxidant and antioxidant enzymes mediated mechanism in the lung tissue. *Toxicol Lett*. (2011) 207:278–85. doi: 10.1016/j.toxlet.2011.09.026

16. Liu J, Cui Y, Jia C, Yang S, Liang L, Lu C, et al. A Relationship between Occupational Exposure to Formaldehyde and Cancer Mortality. *Chin J Public Health*. (1998) 14:712–3. Chinese.

17. Yi C, Liu J, Jia C. Epidemiological investigation and study of malignant tumors in people exposed to formaldehyde. *Chem Labor Protect*. (1997) 5:21–2. Chinese.

18. Blair A, Stewart P, O'Berg M, Gaffey W, Walrath J, Ward J, et al. Mortality among industrial workers exposed to formaldehyde. *J Natl Cancer Inst*. (1986) 76:1071–84.

19. Bertazzi PA, Pesatori AC, Radice L, Zocchetti C, Vai T. Exposure to formaldehyde and cancer mortality in a cohort of workers producing resins. *Scand J Work Environ Health*. (1986) 12:461–8. doi: 10.5271/sjweh.2111

20. Kwak K, Paek D, Park JT. Occupational exposure to formaldehyde and risk of lung cancer: a systematic review and meta-analysis[J/OL]. *Am J Ind Med*. (2020) 63:312–27. doi: 10.1002/ajim.23093

21. Huang X, Fu H, Xu S, Yang J, Ran Z, Hu Y. Discuss the harm and safety protection of x-rays to the human body. *Biotechworld*. (2013) 6:73. Chinese.

22. Chen R. Harm and protection of rays. *Fujian Quality Management*. (2008) Z2:56–7. Chinese.

23. Song X. *Investigation and analysis of adverse reactions of antitumor drugs*. Shandong: Shandong University (2008).

24. Hirst M, Mills DG, Tse S, Levin L, White DF. Occupational exposure to cyclophosphamide. *Lancet*. (1984) 323:186–8. doi: 10.1016/s0140-6736(84)92111-1

25. Schulz H, Bigelow S, Dobish R, Chambers CR. Antineoplastic agent workplace contamination study: the Alberta cancer board pharmacy perspective. *J Oncol Pharm Pract*. (2005) 11:101–9. doi: 10.1191/1078155205jp152oa

26. Hedmer M, Georgiadi A, Bremberg ER, Jönsson BA, Eksborg S. Surface contamination of cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in Sweden. *Ann Occup Hyg*. (2005) 49:629–37. doi: 10.1093/annhyg/mei042

27. Acampora A, Castiglia L, Miraglia N, Pieri M, Soave C, Liotti F, et al. A case study: surface contamination of cyclophosphamide due to working practices and cleaning procedures in two Italian hospitals. *Ann Occup Hyg*. (2005) 49:611–8. doi: 10.1093/annhyg/mei029

28. Bos RP, Sessink PJ. Biomonitoring of occupational exposures to cytostatic anticancer drugs. *Rev Environ Health*. (1997) 12:43–58. doi: 10.1515/reveh.1997.12.1.43

29. Mason HJ, Blair S, Sams C, Jones K, Garfitt SJ, Cuschieri MJ, et al. Exposure to antineoplastic drugs in two UK hospital pharmacy units. *Ann Occup Hyg*. (2005) 49:603–10. doi: 10.1093/annhyg/mei023

30. Hedmer M, Jonsson BA, Nygren O. Development and validation of methods for environmental monitoring of cyclophosphamide in workplaces. *J Environ Monit*. (2004) 6:979–84. doi: 10.1039/B409277E

31. Favier B, Gilles L, Desage M, Latour JF. Analysis of cyclophosphamide in the urine of antineoplastic drugs handlers. *Bull Cancer*. (2003) 90:905–9.

32. Burgaz S, Karahalıl B, Bayrak P, Taşkın L, Yavuzaslan F, Bökesoy I, et al. Urinary cyclophosphamide excretion and micronuclei frequencies in peripheral lymphocytes and in exfoliated buccal epithelial cells of nurses handling antineoplastics. *Mutat Res*. (1999) 439:97–104. doi: 10.1016/S1383-5718(98)00180-6

33. Yanagawa C. Measures for the disposal of non-regulated alternative medical wastes--safe handling of cytotoxic drugs. *Rinsho Byori*. (2000) 112:120–8.

34. Xu B. Investigation on Knowledge of Protection in Nursers Occupational Exposure to Cytostatic Drugs. *China Cancer*. (2001) 10:665–6. Chinese. doi: 10.3969/j.issn.1004-0242.2001.11.022

35. Diao Y, Luo T, Tan Q, Ma D. Survey of Nurse's Recognition of Self-protection for Antitumor Drug Contacting. *West China Med J*. (2008) 5:1165–6. Chinese.

36. Li J, Lu W, Li H, Liu F, Wang C. Investigation on the risk of tuberculosis infection among medical staff. *Chin J Public Health*. (2006) 22:488. Chinese.

37. Zhang H, Dong Y. Investigation and analysis of tuberculosis infection control awareness among medical staff in primary hospitals in Tianjin. *J Med Theo Prac*. (2014) 9:1240–1. Chinese.

38. Zheng W, Blot WJ, Liao ML, Wang ZX, Levin LI, Zhao JJ, et al. Lung cancer and prior tuberculosis infection in shanghai. *Br J Cancer*. (1987) 56:501–4. doi: 10.1038/bjc.1987.233

39. Campbell AH. The association of lung cancer and tuberculosis. *Australas Ann Med*. (1961) 10:129–36. doi: 10.1111/imj.1961.10.2.129

40. Steinitz R. Pulmonary tuberculosis and carcinoma of the lung. A survey from two population-based disease registers. *Am Rev Respir Dis*. (1965) 92:758–66. doi: 10.1164/arrd.1965.92.5.758

41. Jiang Y, Li X, Wu X, Li Q, Yang Y, Nan Y. Smoking and smoking cessation behavior of Chinese doctors. *Prevent Control Chronic Dis China*. (2009) 3:224–7. Chinese.

42. Peng J, Chen M, Bu P. Survey on Current Status of Smoking and Smoking-related Knowledge Among Medical Staff Members of a Hospital in Hunan. *Pract Prevent Med*. (2011) 18:831–2. Chinese. doi: 10.3969/j.issn.1006-3110.2011.05.018

43. Zhu J, Hu J, Zhou W, Zhang X. Survey on Smoking Status and Smoking Related Knowledge Among Medical Staff in Hospitals of Changsha in 2011. *Pract Prevent Med*. (2012) 19:1478–80. Chinese. doi: 10.3969/j.issn.1006-3110.2012.10.011

44. Gonghuan Y. *2010 global adult tobacco survey-China report*. Beijing: China Three Gorges Publishing House (2011).

45. Li T, Wei P, Cheng S, Wang W, Xie P, Chen Z, et al. Air pollution characteristic and variation trend of Central Triangle urban agglomeration from 2005 to 2014. *Chin J Environ Eng*. (2017) 11:2977–84. Chinese. doi: 10.12030/j.cjee.201601185

46. Guo H, Chang Z, Wu J, Li W. Air pollution and lung cancer incidence in China: Who are faced with a greater effect? *Environ Int*. (2019) 132:105077. doi: 10.1016/j.envint.2019.105077

47. Zhu L, Shen Y, Zhang S, Shen G, Jiang S, Pan X, et al. Hand Hygiene Rates among Medical Personnel and Intervention Methods. *Chin J of Nosocomiol*. (2008) 18:542–4. Chinese. doi: 10.3321/j.issn:1005-4529.2008.04.034

48. Liu S, Zou J, Zhang Y, Zou B, He X, Wang Q, et al. Meta-analysis on risk factors of cigarette smoking among Chinese medical workers. *Chin J Pract Internal Med*. (2010) 8:708–10. Chinese.

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 08 January 2024
DOI 10.3389/fpubh.2023.1310823

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, Stony Brook,
United States

REVIEWED BY
Aditya Yashwant Sarode,
Columbia University, New York City,
United States
Raksha Rao,
University of Texas Health Science Center at Houston, Houston, United States
Ronak Loonawat,
Wuxi Advanced Therapeutics, Inc., Philadelphia,
United States

*CORRESPONDENCE
Orazio Valerio Giannico
✉ oraziovaleriogiannico@gmail.com

RECEIVED 09 October 2023
ACCEPTED 17 November 2023
PUBLISHED 08 January 2024

CITATION
Giannico OV, Carone S, Tanzarella M, Galluzzo C, Bruni A, Lagravinese GM, Rashid I, Bisceglia L, Sardone R, Addabbo F, Minerba S and Mincuzzi A (2024) Environmental pressures, tumor characteristics, and death rate in a female breast cancer cohort: a seven-years Bayesian survival analysis using cancer registry data from a contaminated area in Italy.
Front. Public Health 11:1310823.
doi: 10.3389/fpubh.2023.1310823

Environmental pressures, tumor characteristics, and death rate in a female breast cancer cohort: a seven-years Bayesian survival analysis using cancer registry data from a contaminated area in Italy

Orazio Valerio Giannico[1]*, Simona Carone[1], Margherita Tanzarella[1], Claudia Galluzzo[1], Antonella Bruni[1], Giovanna Maria Lagravinese[1], Ivan Rashid[2], Lucia Bisceglia[2], Rodolfo Sardone[1], Francesco Addabbo[1], Sante Minerba[3] and Antonia Mincuzzi[1]

[1]Unit of Statistics and Epidemiology, Local Health Authority of Taranto, Taranto, Italy, [2]Coordination Center of the Apulia Cancer Registry, Strategic Regional Agency for Health and Social Care of Apulia, Bari, Italy, [3]Healthcare Management, Local Health Authority of Taranto, Taranto, Italy

Introduction: In Taranto, Southern Italy, adverse impacts on the environment and human health due to industrial installations have been studied. In the literature, few associations have been reported between environmental factors and breast cancer mortality in women. The aim of this study was to investigate the relationships between residence in areas with high environmental pressures, female breast cancer characteristics, and death rate.

Methods: Data from the Taranto Cancer Registry were used, including all women with invasive breast cancer diagnosed between 01 January 2015 and 31 December 2020 and with follow-up to 31 December 2021. Bayesian mixed effects logistic and Cox regression models were fitted with the approach of integrated nested Laplace approximation, adjusting for patients and disease characteristics.

Results: A total of 10,445 person-years were observed. Variables associated with higher death rate were residence in the contaminated site of national interest (SIN) (HR 1.22, 95% CrI 1.01–1.48), pathological/clinical stage III (HR 2.77, 95% CrI 1.93–3.97) and IV (HR 17.05, 95% CrI 11.94–24.34), histological grade 3 (HR 2.50, 95% CrI 1.20–5.23), Ki-67 proliferation index of 21–50% (HR 1.42, 95% CrI 1.10–1.83) and >50% (HR 1.81, 95% CrI 1.29–2.55), and bilateral localization (HR 1.65, 95% CrI 1.01–2.68). Variables associated with lower death rate were estrogen and/or progesterone receptor positivity (HR 0.61, 95% CrI 0.45–0.81) and HER2/neu oncogene positivity (HR 0.59, 95% CrI 0.44–0.79).

Discussion: The findings confirmed the independent prognostic values of different female breast cancer characteristics. Even after adjusting for patients and disease characteristics, residence in the SIN of Taranto appeared to be associated with an increased death rate.

KEYWORDS

breast cancer, female breast cancer, cancer survival, environmental contamination, environmental pollution, cancer epidemiology

Introduction

Female breast cancer is a leading cause of cancer incidence and mortality worldwide, with a global estimate of 2.3 million incident cases, 7.8 million prevalent cases, and 685,000 deaths in 2020. It is a global phenomenon affecting individuals of any age after puberty. Among all types of cancer, it causes the most disability-adjusted life years (DALYs) among women (1, 2).

Early cancer detection (screening) and treatment (surgery, radiation, and medical therapy) have proven to be effective, achieving survival probabilities up to 90% or higher (1). Specifically, the treatment of breast cancer is based on the tumor's biological subtyping. Numerous disease characteristics, such as TNM staging, histological grading, proliferation activity (Ki-67%), estrogen receptor (ER), progesterone receptor (PR) and HER2/neu positivity, topography, and bilaterality, have been researched as potential prognostic indicators or as targets for specific therapies (1, 3–7). Tumor, node, and metastases (TNM) classification is a system used to describe the amount and spread of cancer in a patient's body: T describes the size of the tumor and any spread of cancer into nearby tissues, N describes the spread of cancer to nearby lymph nodes, and M describes metastasis, i.e., the spread of cancer to other parts of the body. TNM combinations are grouped into five less-detailed stages, from 0 (carcinoma *in situ*: abnormal cells are present but have not spread to nearby tissues) to I-II-III (invasive cancer: the higher the number, the larger the tumor and the more it has spread into nearby tissues) to IV (invasive, metastatic cancer: cancer has spread to distant parts of the body) (3, 8–10). In addition to TNM staging, histologic grading from 1 to 3 is an important predictor of disease outcome in breast cancer patients, with a higher tumor grade (lower differentiation) being associated with poorer prognosis (differentiation describes how much a tumor resembles the normal tissue from which it arose) (3, 5, 11). Related to grading is the expression of Ki-67, a nuclear protein present during the late G1, S, G2, and M phases of the cell cycle. It has been demonstrated that high Ki-67 expression (%), which reflects the proliferation activity of tumor cells, is associated with a higher risk of relapse and worse survival in breast cancer patients (3, 5). Hormonal receptor status is another important prognostic factor in breast cancer patients. Estrogen receptor-positive (ER+) and progesterone receptor-positive (PR+) tumors are likely to respond to endocrine therapies such as tamoxifen or aromatase inhibitors. Hormone therapy reduces the chance of recurrence by nearly half. Moreover, breast cancers may independently overexpress a molecule called the HER2/neu oncogene and these HER2/neu + tumors are amenable to treatment with targeted biological agents such as trastuzumab, with improvement of survival (1, 3, 4). Moreover, associations were reported between cancer topography, laterality, and death rate. Specifically, better survival was associated with greater tumor-nipple distance in old patients, while an increased death rate was reported for synchronous bilateral breast cancer patients (6, 7).

With regard to socio-economic and environmental factors, a shorter breast cancer-specific survival in women from disadvantaged neighborhoods has been reported (12). Evidence from a meta-analysis indicated that patients residing in rural areas were more likely to be diagnosed with more advanced breast cancer compared with patients from urban areas (13). Moreover, associations were reported between air pollutants and mortality in women with breast cancer (14, 15).

In some areas of the province of Taranto, a coastal city in the Apulia Region, Southern Italy, various industrial installations and polluting sources (a steel plant, an oil refinery, urban discharges, harbor activities, and the ship-yard of the Italian Navy) have been operating in close proximity to the resident population for decades with well-known and extensively studied adverse impacts on the environment and human health (16–30). With regard to environmental, feed, and food impacts, it is of particular importance that the area shows contamination of these matrices by metals and persistent organic pollutants, specifically dioxins and PCBs. Moreover, some of these substances have been detected in human biological samples (17, 20–25). As far as human health effects are concerned, evidence has been produced after studying the populations who resided in the contaminated site of national interest (SIN) of Taranto. In particular, cohort studies have reported an increased risk for different types of cancer incidence, including breast cancer incidence in women (16, 27). Some studies have also noted an increased risk for all-cause hospitalization; for circulatory, respiratory, digestive, and urinary diseases hospitalization; and for different types of cancer hospitalization, including breast cancer hospitalization in women (16, 29, 30). Different studies have also indicated an increased risk for all-cause mortality; for circulatory and digestive diseases mortality; and for some types of cancer mortality, with no significant evidence for breast cancer mortality in women (16, 19, 26, 29, 30).

To summarize, associations have been reported between the aforementioned factors and breast cancer mortality in women. The aim of this study was to investigate the relationships between residence in areas with high environmental pressures, female breast cancer characteristics, and death rate.

Methods

Study area and baseline epidemiological data

The study area is the province of Taranto, which consists of 29 municipalities with a total resident population of 559,892 inhabitants on 1 January 2022 (31). The SIN of Taranto consists of two municipalities, Taranto (the provincial capital) and Statte, with 189,461 and 13,136 inhabitants, respectively, on 1 January 2022 (29–31). The study area with municipalities and SIN is shown in Figure 1. The map was created with QGIS version 3.28.4.

From 2015 to 2019, Taranto Province recorded 2,446 female breast cancer (ICD10 codes C50.0 to C50.9) cases, with a directly standardized rate of 147.6 cases per 100,000 inhabitants and a median age of 61 years. In the same period, 63% of patients with breast cancer requiring hospitalization were admitted to a hospital in the Taranto Province, 25% to an extra-provincial hospital in the Apulia Region, and 12% to an extra-regional hospital. Between 2013 and 2017, the relative standardized 5-year female breast cancer survival was 85.6 (95% CI 83.1–87.7) (27).

From 2013 to 2017, in the SIN, 216 female breast cancer deaths were recorded, with a standardized mortality ratio (reference: Apulia Region) of 99 (90% CI 89–111) (29). From 2015 to 2019, in the SIN, 979 female breast cancer cases were recorded, with a directly standardized rate of 155.6 cases per 100,000 inhabitants and a

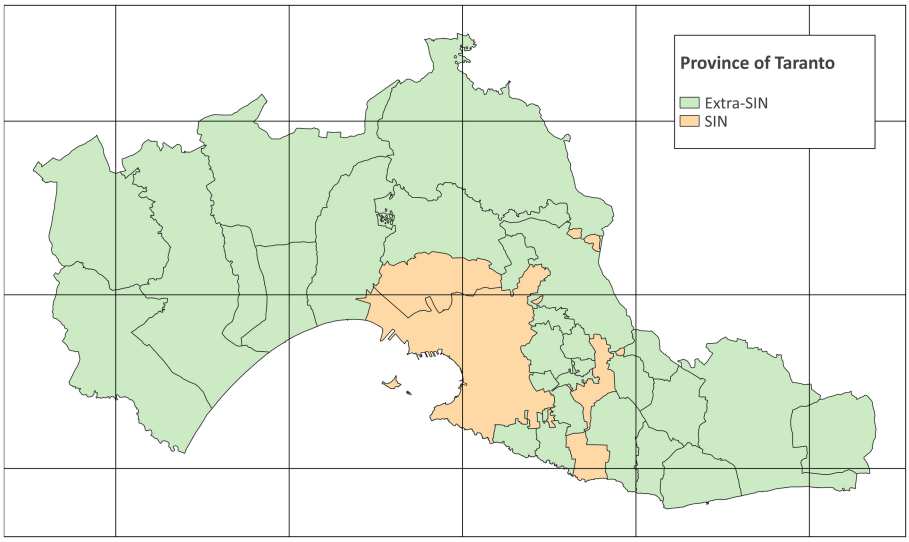


FIGURE 1
Map of the province of Taranto (grid interval: 20 km) (EPSG:32632 – WGS 84 / UTM zone 32N) (Modified from Italian National Institute of Statistics. Administrative boundaries. https://www.istat.it/it/archivio/222527).

standardized incidence ratio (reference: Taranto Province) of 109.3 (95% CI 102.5–116.3) (27).

Data source and cancer cohort

Data collected from the Taranto Cancer Registry of the Italian Association of Cancer Registries (AIRTUM) were used, including all women with invasive breast cancer (ICD10 codes C50.0 to C50.9) diagnosed between 1 January 2015 and 31 December 2020 who resided in Taranto Province at the time of diagnosis. The follow-up period considered for this study was until 31 December 2021. Death certificate only cases ($n = 29$), cases registered based on an autopsy report ($n = 1$), and patients under 30 years ($n = 12$) were excluded. As a general rule, baseline patients and disease characteristics refer to the time of diagnosis. Mortality data (all-cause mortality) relative to the follow-up period (2015–2021) were retrieved from the Taranto Province's Causes of Death and Health Registries. Patients with no mortality follow-up information due to extra-provincial transfer before 31 December 2021 (right-censoring, loss-to-follow-up) contributed to the person-time until the date of transfer ($n = 7$).

Study design and variables

This is a retrospective individual observational study with different regression analyses carried out cross-sectionally (prevalence study) and longitudinally (incidence study, survival analysis). Residence in the areas with high environmental pressures (SIN) was used as an environmental exposure proxy. Tumor characteristics at the time of diagnosis were pathological/clinical staging (TNM I to IV), histological grading (grade 1 to 3), proliferation index (Ki-67%), estrogen receptor (ER) and/or progesterone receptor (PR) status (positivity cut-off is ≥1% of positive cells), epidermal receptor (HER2/neu) status (immunohistochemistry, IHC; fluorescence *in situ* hybridization, FISH), topography (ICDO3T classification. C50.0–1: nipple and areola, central portion of breast. C50.2–5: upper-inner/lower-inner/upper-outer/lower-outer quadrant of breast. C50.6–8: axillary tail of breast, overlapping lesion of breast), and laterality (unilateral right, unilateral left, and synchronous bilateral breast cancer) (3).

In the cross-sectional study, the studied outcomes were each of the tumor characteristics (prevalence), and the studied exposure was residence in areas with high environmental pressures. The aim of this step was to assess possible associations between environmental factors and each of the tumor characteristics. In the longitudinal study, the studied outcome was all-cause death (incidence), and the studied exposures were residence in areas with high environmental pressures and tumor characteristics. The aim of this step was to assess possible associations between environmental factors, tumor characteristics, and death. Adjustment variables recorded at the time of diagnosis were age class (30–39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years), year, month, patient ID, municipality of residence, and tumor morphology (ICDO3M classification). Adjustment for the patient's ID and municipality of residence was provided to account for the heterogeneity related to possible unobserved individual or ecological level variables (e.g., genetics, heredity, tobacco use, alcohol consumption, deprivation index, and access to health services).

Statistical analysis

Data analysis was performed using R version 4.2.3. Bayesian inference was performed with package INLA version 22.12.16. Complex models could be fitted with the Bayesian approach, including generalized linear models and survival analyses. The possible non-independence and heterogeneity of observations could be taken into account by fitting mixed models with both fixed and random effects. While traditional survival analysis relies on parameter estimation based on partial likelihood, Bayesian approaches for

time-to-event data allow us to use the full likelihood to estimate all unknown elements in the model. Bayesian generalized linear models comprise Bayesian logistic regression for binary response data. However, the computation of the posterior and the other quantities of interest in these complex models is usually much more difficult than frequentist calculations. The Integrated Nested Laplace Approximation (INLA) is a deterministic method for Bayesian calculations that applies to a wide class of models called Latent Gaussian Models. INLA provides fast and accurate approximations to the posterior marginals through a clever use of Laplace approximations and advanced numerical methods taking computational advantage of sparse matrices. In most cases, INLA is both faster and more accurate than other methods for Bayesian computation (32–36).

The cross-sectional study analyzed the associations between residence in areas with high environmental pressures and tumor characteristics using a series of mixed effects binary logistic regressions. Pathological/clinical staging (TNM III-IV; TNM IV), histological grading (grade 3), proliferation index (Ki-67 > 20%), hormonal receptors status (ER+ and/or PR+), epidermal receptor status (HER2/neu+), topography (C50.0–1), and laterality (bilateral) were considered outcome measures binary variables. For each regression model, records with missing values for the analyzed outcome were excluded. Residence in areas with high environmental pressures was included as a fixed effect binary variable. Age class and year were included as fixed effects multinominal variables. Month was included as a cubic b-spline with 12 degrees of freedom. Patient ID and municipality of residence were included as random effects multinominal variables (random intercepts). Bayesian binary logistic regression models were fitted with the INLA approach for latent Gaussian models, computing odds ratios (OR) and 95% credible intervals (CrI). An independent and identically distributed random distribution was chosen for patient ID and municipality of residence (33–35).

The longitudinal study analyzed the associations between residence in areas with high environmental pressures, tumor characteristics, and death, using a mixed effects Cox proportional hazard regression. Time axis was the difference in days between the day of cancer diagnosis and the last day of follow-up (event or right censoring). All-cause death was considered as the outcome measure binary variable (event). The proportional hazard assumption was verified through the analysis of plotted survival curves between the different levels of the variables. Residence in areas with high environmental pressures, pathological/clinical staging (TNM I, II, III, IV), histological grading (grade 1, 2, 3), proliferation index (Ki-67 ≤ 20%, 21–50, >50%), hormonal receptors status (ER- and PR-, ER+ and/or PR+), epidermal receptor status (HER2/neu-, HER2/neu+), topography (C50.0–1, C50.2–5, C50.6–8), and laterality (right, left, and bilateral) were included as fixed effects binary or multinominal variables. An "NA" (not available) category was created for the records with missing values for the analyzed exposures. Age class and year were included as fixed effects multinominal variables. Month was included as a cubic b-spline with 12 degrees of freedom. Patient ID, municipality of residence, and tumor morphology were included as random effects multinominal variables (random intercepts). Bayesian Cox regression models were fitted with the INLA approach for latent Gaussian models, computing hazard ratios (HR) and 95% credible intervals (CrI). An independent and identically distributed random distribution was chosen for patient ID, municipality of residence, and tumor morphology, while a random walk model of order two was chosen for the baseline hazard function (32–36).

Generalized Variance Inflation Factors (GVIF) were calculated to test the presence of multicollinearity in the data. Sensitivity analyses were performed by examining the extent to which the results were affected by changes in methods, models, variables, influential observations, and inclusion/exclusion criteria. Different combinations of included patients and variables were tested, and for the included variables, different collapsed categories, as well as changes in the type of estimated effects (fixed or random), were also tested. The models were iteratively refitted by excluding from the dataset each age class, year, and month one at a time.

Results

Baseline patients and disease characteristics are shown in Table 1. A total of 10,445 person-years were observed, 4,068 for residents in SIN and 997 for deceased patients, with a median (IQR) age of 61.0 (50.0,72.0) years.

The results of the mixed effects Bayesian binary logistic regression models are reported in Table 2. Adjusting for baseline age class, year, month, patient ID, and municipality of residence, the fixed effect variable residence in SIN did not appear to be clearly associated with the prevalence of the investigated tumor characteristics. However, the lower limit of the 95% credible interval for TNM IV is quite close to one (OR 1.29, 95% CrI 0.96–1.73).

Survival probabilities conditional on each analyzed variable and unconditional on other variables are shown in Figure 2. The curves suggested unconditional associations between survival probability and residence in SIN, pathological/clinical staging, histological grading, proliferation index, hormonal receptors status, epidermal receptor status, topography, and laterality. The results of the mixed effects Bayesian Cox proportional hazard regression model are reported in Table 3. Mutually adjusting and adjusting for baseline age class, year, month, patient ID, municipality of residence, and tumor morphology, the fixed effects variables associated with a higher death rate were residence in SIN (HR 1.22, 95% CrI 1.01–1.48), TNM III (HR 2.77, 95% CrI 1.93–3.97), IV (HR 17.05, 95% CrI 11.94–24.34) and NA (HR 4.13, 95% CrI 2.87–5.95), grade 3 (HR 2.50, 95% CrI 1.20–5.23) and NA (HR 2.18, 95% CrI 1.02–4.66), Ki-67 21–50% (HR 1.42, 95% CrI 1.10–1.83) and > 50% (HR 1.81, 95% CrI 1.29–2.55), and bilateral localization (HR 1.65, 95% CrI 1.01–2.68). Mutually adjusting and adjusting for baseline age class, year, month, patient ID, municipality of residence, and tumor morphology, the fixed effects variables associated with lower death rate were ER+ and/or PR+ (HR 0.61, 95% CrI 0.45–0.81) and HER2/neu + (HR 0.59, 95% CrI 0.44–0.79).

Discussion

The results of the present study confirmed that TNM staging, histological grading, proliferation index, estrogen and/or progesterone positivity, HER2/neu positivity, and bilaterality are independent prognostic factors in breast cancer patients. In our cohort, only topography did not seem to be independently associated with the analyzed outcome. Of interest was the finding during the follow-up

TABLE 1 Baseline patients and disease characteristics and follow-up survival status in the female breast cancer cohort by residence in SIN and survival status.

Baseline patients and disease characteristics and follow-up survival status	Female breast cancer cohort				
	N = 2,837; person-years = 10,445				
	Extra-SIN	SIN	Survived	Deceased	Total
Age					
Age [Median(IQR)]	61.0 (50.0;72.0)	61.0 (50.0;73.0)	59.0 (49.0;69.0)	76.0 (63.5;84.0)	61.0 (50.0;72.0)
30–39 [*n* (%)]	91 (5.32%)	47 (4.17%)	129 (5.40%)	9 (2.01%)	138 (4.86%)
40–49 [*n* (%)]	314 (18.36%)	213 (18.90%)	502 (21.00%)	25 (5.59%)	527 (18.58%)
50–59 [*n* (%)]	385 (22.51%)	269 (23.87%)	601 (25.15%)	53 (11.86%)	654 (23.05%)
60–69 [*n* (%)]	427 (24.97%)	239 (21.21%)	590 (24.69%)	76 (17.00%)	666 (23.48%)
70–79 [*n* (%)]	297 (17.37%)	212 (18.81%)	398 (16.65%)	111 (24.83%)	509 (17.94%)
≥80 [*n* (%)]	196 (11.46%)	147 (13.04%)	170 (7.11%)	173 (38.70%)	343 (12.09%)
Year					
2015 [*n* (%)]	337 (19.71%)	203 (18.01%)	418 (17.49%)	122 (27.29%)	540 (19.03%)
2016 [*n* (%)]	282 (16.49%)	190 (16.86%)	373 (15.61%)	99 (22.15%)	472 (16.64%)
2017 [*n* (%)]	260 (15.20%)	190 (16.86%)	374 (15.65%)	76 (17.00%)	450 (15.86%)
2018 [*n* (%)]	278 (16.26%)	169 (15.00%)	375 (15.69%)	72 (16.11%)	447 (15.76%)
2019 [*n* (%)]	288 (16.84%)	209 (18.54%)	451 (18.87%)	46 (10.29%)	497 (17.52%)
2020 [*n* (%)]	265 (15.50%)	166 (14.73%)	399 (16.69%)	32 (7.16%)	431 (15.19%)
Pathological/clinical staging					
TNM I [*n* (%)]	646 (37.78%)	421 (37.36%)	1,012 (42.34%)	55 (12.30%)	1,067 (37.61%)
TNM II [*n* (%)]	536 (31.35%)	335 (29.72%)	793 (33.18%)	78 (17.45%)	871 (30.70%)
TNM III [*n* (%)]	234 (13.68%)	148 (13.13%)	302 (12.64%)	80 (17.90%)	382 (13.46%)
TNM IV [*n* (%)]	113 (6.61%)	92 (8.16%)	69 (2.89%)	136 (30.43%)	205 (7.23%)
NA [*n* (%)]	181 (10.58%)	131 (11.62%)	214 (8.95%)	98 (21.92%)	312 (11.00%)
Histological grading					
Grade 1 [*n* (%)]	115 (6.73%)	70 (6.21%)	177 (7.41%)	8 (1.79%)	185 (6.52%)
Grade 2 [*n* (%)]	844 (49.36%)	561 (49.78%)	1,255 (52.51%)	150 (33.56%)	1,405 (49.52%)
Grade 3 [*n* (%)]	603 (35.26%)	387 (34.34%)	795 (33.26%)	195 (43.62%)	990 (34.90%)
NA [*n* (%)]	148 (8.65%)	109 (9.67%)	163 (6.82%)	94 (21.03%)	257 (9.06%)
Proliferation index					
Ki-67 ≤ 20% [*n* (%)]	1,059 (61.93%)	710 (63.00%)	1,569 (65.65%)	200 (44.74%)	1,769 (62.35%)
Ki-67 21–50% [*n* (%)]	410 (23.98%)	256 (22.72%)	548 (22.93%)	118 (26.40%)	666 (23.48%)
Ki-67 > 50% [*n* (%)]	168 (9.82%)	110 (9.76%)	213 (8.91%)	65 (14.54%)	278 (9.80%)
NA [*n* (%)]	73 (4.27%)	51 (4.53%)	60 (2.51%)	64 (14.32%)	124 (4.37%)
Hormonal receptors status					
ER- and PR- [*n* (%)]	217 (12.69%)	144 (12.78%)	280 (11.72%)	81 (18.12%)	361 (12.72%)
ER+ and/or PR+ [*n* (%)]	1,428 (83.51%)	934 (82.87%)	2,057 (86.07%)	305 (68.23%)	2,362 (83.26%)
NA [*n* (%)]	65 (3.80%)	49 (4.35%)	53 (2.22%)	61 (13.65%)	114 (4.02%)
Epidermal receptor status					
HER2/neu- [*n* (%)]	1,326 (77.54%)	867 (76.93%)	1,888 (79.00%)	305 (68.23%)	2,193 (77.30%)
HER2/neu+ [*n* (%)]	274 (16.02%)	176 (15.62%)	388 (16.23%)	62 (13.87%)	450 (15.86%)
NA [*n* (%)]	110 (6.43%)	84 (7.45%)	114 (4.77%)	80 (17.90%)	194 (6.84%)
Topography					
C50.0–1 [*n* (%)]	172 (10.06%)	101 (8.96%)	213 (8.91%)	60 (13.42%)	273 (9.62%)

(Continued)

TABLE 1 (Continued)

Baseline patients and disease characteristics and follow-up survival status	Female breast cancer cohort				
	N = 2,837; person-years = 10,445				
	Extra-SIN	SIN	Survived	Deceased	Total
C50.2–5 [*n* (%)]	1,047 (61.23%)	695 (61.67%)	1,526 (63.85%)	216 (48.32%)	1,742 (61.40%)
C50.6–8 [*n* (%)]	337 (19.71%)	210 (18.63%)	485 (20.29%)	62 (13.87%)	547 (19.28%)
NA [*n* (%)]	154 (9.01%)	121 (10.74%)	166 (6.95%)	109 (24.38%)	275 (9.69%)
Laterality					
Right [*n* (%)]	800 (46.78%)	549 (48.71%)	1,157 (48.41%)	192 (42.95%)	1,349 (47.55%)
Left [*n* (%)]	835 (48.83%)	531 (47.12%)	1,153 (48.24%)	213 (47.65%)	1,366 (48.15%)
Bilateral [*n* (%)]	36 (2.11%)	30 (2.66%)	47 (1.97%)	19 (4.25%)	66 (2.33%)
NA [*n* (%)]	39 (2.28%)	17 (1.51%)	33 (1.38%)	23 (5.15%)	56 (1.97%)
Residence in SIN					
Extra-SIN [*n* (%)]	1,710 (100.00%)	0 (0.00%)	1,460 (61.09%)	250 (55.93%)	1,710 (60.27%)
SIN [*n* (%)]	0 (0.00%)	1,127 (100.00%)	930 (38.91%)	197 (44.07%)	1,127 (39.73%)
Survival status at the end of follow-up					
Survived [*n* (%)]	1,460 (85.38%)	930 (82.52%)	2,390 (100.00%)	0 (0.00%)	2,390 (84.24%)
Deceased [*n* (%)]	250 (14.62%)	197 (17.48%)	0 (0.00%)	447 (100.00%)	447 (15.76%)
Days of follow-up [Median (IQR)]	1,324 (795;1,972)	1,280 (758;1,903)	1,421 (889;2,025)	695 (261;1,272)	1,312 (774;1,936)
Person-years [Sum]	6,377	4,068	9,448	997	10,445

Province of Taranto, 2015–2020, follow-up to 31/12/2021. N: cohort.

TABLE 2 Results of the mixed effects Bayesian INLA binary logistic regression models in the female breast cancer cohort, adjusted for baseline age class, year, month, patient ID, and municipality of residence.

Mixed effects INLA binary logistic regressions	Female breast cancer cohort							
	TNM III-IV		TNM IV		Grade 3		Ki-67 > 20%	
	N = 2,525; *n* = 587		*N* = 2,525; *n* = 205		*N* = 2,580; *n* = 990		*N* = 2,713; *n* = 944	
Fixed effect	OR	95% CrI	OR	95% CrI	OR	95% CrI	OR	95% CrI
Residence in SIN								
Extra-SIN	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
SIN	1.09	0.88–1.42	1.29	0.96–1.73	0.98	0.83–1.16	0.95	0.81–1.13

Mixed effects INLA binary logistic regressions	Female breast cancer cohort							
	ER+ and/or PR+		HER2/neu+		C50.0–1		Bilateral	
	N = 2,723; *n* = 2,362		*N* = 2,643; *n* = 450		*N* = 2,562; *n* = 273		*N* = 2,781; *n* = 66	
Fixed effect	OR	95% CrI	OR	95% CrI	OR	95% CrI	OR	95% CrI
Residence in SIN								
Extra-SIN	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
SIN	0.97	0.77–1.22	0.99	0.80–1.22	0.86	0.66–1.12	1.25	0.76–2.05

Province of Taranto, 2015–20, follow-up to 31/12/2021. Outcome (prevalence): tumor characteristic. N: prevalent cases and non-cases. *n*: prevalent cases.

period of an overall average negative association between HER2/neu positivity and death rate in our cohort, although it may be non-constant over time. This association could be explained by the development and implementation of HER2/neu targeting treatments. In fact, patients with HER2/neu + tumors are amenable to treatment with targeted biological agents such as trastuzumab. For these reasons, the presence of this marker could be assumed as a proxy of treatment with these drugs, which is information not directly available in the cancer registry. Given this assumption, our findings could be supported by the scientific literature about the improvement of survival in the treated patients (1, 3). Another interesting result was the negative prognostic value of the presence of missing data for some variables ("NA" category) in our cohort. This could be partly explained by the fact that patients without information on some variables (e.g., grading) could correspond to poor prognosis patients who, due to a severe condition at the time of diagnosis, were unable to undergo further interventions or investigations (37).

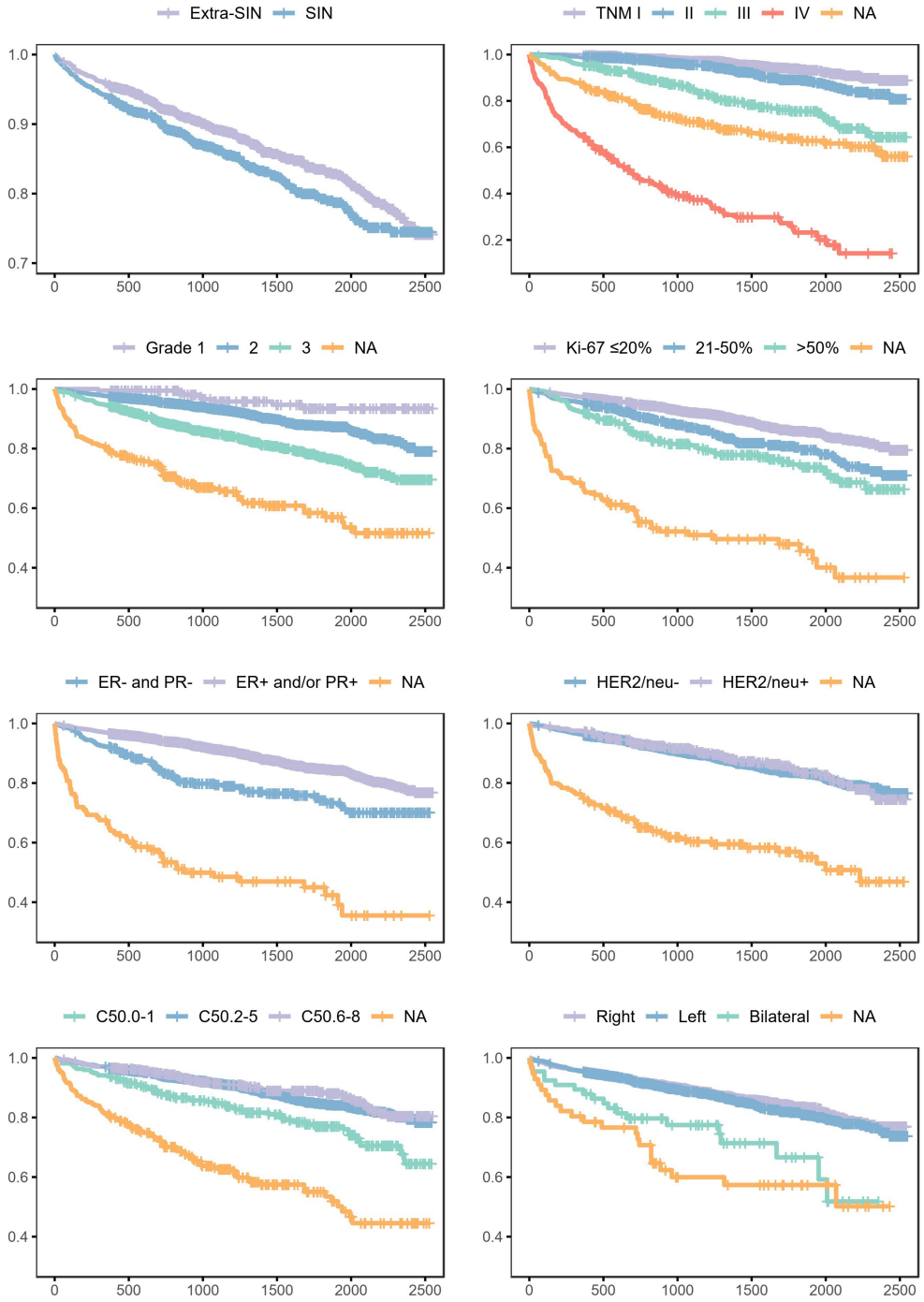


FIGURE 2
Survival probabilities in the female breast cancer cohort, conditional on each analyzed variable and unconditional on other variables. Province of Taranto, 2015–2020, follow-up to 31/12/2021. Time: days of follow-up. Outcome (incidence): all-cause death.

Regarding the impacts of environmental pressures on tumor characteristics, this study found no clear association between living in the SIN and the prevalence of the prognostic factors mentioned above. Conversely, the most important finding seems to be the association between residence in SIN and increased all-cause death rate. This result was observed independently of all other factors analyzed, as the HR was adjusted for the other variables included in the Bayesian mixed effects regression model. In summary, this suggests that the patients in the studied cohort that resided in the SIN have an adjusted excess relative risk for all-cause mortality of 22% (95% CrI 1–48%) compared to the residents in the other municipalities of the province.

The specific environmental factors that may be associated with this excess mortality could be related to some documented anthropic pressures in the SIN: harbor, discharge, oil refinery, and steel plant (29, 30). Several pieces of evidence in the study area have shown the contamination of environmental, feed, and food matrices (e.g.,

TABLE 3 Results of the mixed effects Bayesian INLA Cox proportional hazard regression model in the female breast cancer cohort, mutually adjusted and adjusted for baseline age class, year, month, patient ID, municipality of residence, and tumor morphology.

Mixed effects INLA Cox proportional hazard regression	Female breast cancer cohort	
	All-cause death	
	N = 2,837; person-years = 10,445; *n* = 447	
Fixed effects	HR	95% CrI
Residence in SIN		
Extra-SIN	1.00	(ref)
SIN	1.22	1.01–1.48
Pathological/clinical staging		
TNM I	1.00	(ref)
TNM II	1.26	0.88–1.79
TNM III	2.77	1.93–3.97
TNM IV	17.05	11.94–24.34
NA	4.13	2.87–5.95
Histological grading		
Grade 1	1.00	(ref)
Grade 2	1.93	0.94–3.96
Grade 3	2.50	1.20–5.23
NA	2.18	1.02–4.66
Proliferation index		
Ki-67 ≤ 20%	1.00	(ref)
Ki-67 21–50%	1.42	1.10–1.83
Ki-67 > 50%	1.81	1.29–2.55
NA	1.09	0.41–2.89
Hormonal receptors status		
ER- and PR-	1.00	(ref)
ER+ and/or PR+	0.61	0.45–0.81
NA	0.88	0.33–2.30
Epidermal receptor status		
HER2/neu-	1.00	(ref)
HER2/neu+	0.59	0.44–0.79
NA	1.40	0.87–2.23
Topography		
C50.0–1	1.00	(ref)
C50.2–5	0.88	0.65–1.18
C50.6–8	0.81	0.56–1.17
NA	0.95	0.67–1.34
Laterality		
Right	1.00	(ref)
Left	1.03	0.84–1.26
Bilateral	1.65	1.01–2.68
NA	1.28	0.80–2.03

Province of Taranto, 2015–2020, follow-up to 31/12/2021. Time: days of follow-up. Outcome (incidence): all-cause death. N: incident cases and non-cases. n: incident cases.

mussels and eggs) with metals and persistent organic pollutants, such as dioxins and PCBs, in relation to potential foodborne exposure. Some of these substances or their metabolites/markers have also been detected in human biological samples (17, 20–25). With regard to air pollution, studies have documented air pollution originating from the industrial area (e.g., particulate matter, sulfur dioxide, and polycyclic aromatic hydrocarbons) and the impacts on human health (16, 18, 19, 26, 28–30, 38).

Our findings confirm previous knowledge regarding the increased risk of all-cause mortality reported for women who resided in the SIN of Taranto (16, 19, 26, 29, 30). However, they also suggest that the excess relative risk in the cohort analyzed may be greater. In fact, recent epidemiological studies on all the female population residing in the area have shown an excess relative risk for all-cause mortality of 7% (90% CI 5–9%) in the SIN of Taranto compared to the Apulia Region in the years 2013–17 (29). Although we are considering different periods and methods, and the credible interval of our study fully contains the aforementioned estimate with its confidence interval, we could not discount the possibility that the excess mortality risk in the SIN of Taranto might be higher in the cohort of women with breast cancer. Therefore, our findings suggest that frail female breast cancer patients may be more vulnerable to the risks associated with a disadvantaged or polluted external environment. This could be also consistent with the findings reported in the few studies that analyzed the association between socio-economic-environmental pressures and the prognosis of female breast cancer (12, 14, 15).

These results raise possible ethical questions, if confirmed. As a matter of fact, several epidemiological studies have reported an increased risk for breast cancer incidence and hospitalization and for all-cause mortality in the entire female population that resided in the SIN of Taranto (16, 19, 26, 27, 29, 30). According to the present study, this excess relative risk for all-cause mortality might be higher in the cohort of female breast cancer patients.

However, since this study used an ecological variable (i.e., residence in the SIN of Taranto) to ascertain exposure to environmental pressures, this approach is potentially prone to ecological fallacy. In addition, there is a lack of specificity in the exposure assessment as the specific chemical pollutants could be varied and come from different sources in the studied region (37). Another limitation of the study could be the lack of information about genetics and hereditary. These data are unfortunately not available in cancer registries or health records. However, part of the influence of these factors may have been indirectly captured in the analysis using mixed models with random effects, which take into account the heterogeneity between patients and areas.

Nonetheless, regardless of these limitations, all the other evidence already available on Taranto gives a high *a priori* plausibility of the association between residence in SIN and increased mortality detected in this study, also considering that this association persists despite adjustment for all other measured patients and disease characteristics. Moreover, in addition to the well-known pressures of a strictly environmental nature, the two municipalities of Taranto and Statte present relatively high municipality-level deprivation indexes. This is a regionally referenced deprivation index that used the individual data of the general population and housing census of 2011. For the calculation of the index, five conditions were chosen by the authors to best describe the multidimensional concept of social and material deprivation: low level of education, being unemployed, living on rent, living on rent, and living in a single-parent family. The index was calculated as the sum of standardized indicators and is also available and categorized into quintiles (39). Although including the municipality of residence as a random effect in the regression models provided some ecological-level adjustment for the deprivation index, it can also be useful to consider the value of the index itself for descriptive purposes when interpreting the results. Anyhow, particular attention should be paid to the interpretation of this index both due to its ecological-level indicator nature and since the latest available index relates to the 2011 census (39). Therefore, the available deprivation index cannot be guaranteed to accurately indicate individual-level deprivation during the years covered by the present study.

However, it is important to consider that socio-economic status, deprivation, and inequalities could not only exert an effect on lifestyle harmful habits (e.g., cigarette smoking), health conditions, and mortality but also potentially affect the utilization of health services (39, 40). Furthermore, in this regard, the SIN corresponds almost completely to the provincial capital Taranto, which could potentially influence access to health services at a territorial and hospital level, and in terms of regional and extra-regional mobility. This is linked to another limitation of the study, which is the lack of available data about the diagnostic-therapeutic pathways followed by these patients, including information regarding their access to breast cancer screening services. On the other hand, the fact that both SIN and extra-SIN municipalities belong to the same Local Health Authority, and so consequentially the entire studied cohort could virtually access the same healthcare and screening services, did not lead us to suppose that there could be relevant biases in relation to these aspects (37).

To summarize, as mentioned previously, the lack of information about individual-level environmental exposures, genetics and hereditary factors, socio-cultural indicators, harmful habits, and utilization of healthcare services could represent a limitation of the present study. However, from another perspective, the same elements could also be considered starting points for what can be done in the future. Specifically, it would be interesting to update and expand upon this epidemiologic study by recovering further individual-level data about genetics and hereditary factors (BRCA1, BRCA2, PTEN, and TP53 mutations) (41), environmental exposures (distance from polluting sources, exposure to airborne pollutants through dispersion models, and biomonitoring), socio-economic factors (updated indicators of deprivation at individual or census-tract level), access to secondary prevention programs (screening path through mammography, echography, and genetic tests), and diagnostic-therapeutic-surgical paths (timing, place, and type of interventions).

In conclusion, the results confirmed the independent prognostic values of different female breast cancer characteristics. Despite the limitations discussed above, even after adjusting for patients and disease characteristics, in the cohort of women with invasive breast cancer, residence in the SIN of Taranto appeared to be associated with an increased death rate.

Data availability statement

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

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin

in accordance with the national legislation and the institutional requirements.

Author contributions

OVG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SC: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – review & editing. MT: Data curation, Writing – review & editing. CG: Data curation, Writing – review & editing. AB: Data curation, Writing – review & editing. GML: Data curation, Writing – review & editing. IR: Data curation, Software, Writing – review & editing. LB: Data curation, Resources, Writing – review & editing. RS: Funding acquisition, Methodology, Validation, Writing – review & editing. FA: Investigation, Validation, Writing – review & editing. SM: Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. AM: Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This project received funding and support from the CALLIOPE project (CUP:E53C22002800001) through the FSC Fund of the Ministry of Enterprises and Made in Italy.

Acknowledgments

We thank all the medical doctors and healthcare professionals employed in the prevention, diagnosis, and treatment of female breast cancer in the province of Taranto. Without them, this retrospective study would not have been possible. We dedicate this work to all patients who face breast cancer and to their families and friends.

Conflict of interest

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

Publisher's note

References

1. [WHO] World Health Organization. Breast Cancer. (2021). Available at: www.who.int/news-room/fact-sheets/detail/breast-cancer (Accessed June 27, 2023).

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

3. [AIOM] Italian association of medical oncology. Guidelines. Breast neoplasms. (2021). Available at: https://www.aiom.it/linee-guida-aiom-2021-neoplasie-della-mammella/ (Accessed June 27, 2023).

4. Karihtala P, Jääskeläinen A, Roininen N, Jukkola A. Prognostic factors in metastatic breast cancer: a prospective single-Centre cohort study in a Finnish university hospital. *BMJ Open*. (2020) 10:e038798. doi: 10.1136/bmjopen-2020-038798

5. Liang Q, Ma D, Gao RF, Yu KD. Effect of Ki-67 expression levels and histological grade on breast cancer early relapse in patients with different immunohistochemical-based subtypes. *Sci Rep*. (2020) 10:7648. doi: 10.1038/s41598-020-64523-1

6. Yang Q, Yang J, Xu L, Zhou C, Lv Q. Distance between tumor and nipple as a prognostic factor in breast cancers: opposite effects in young and old patients. *Medicine (Baltimore)*. (2020) 99:e21461. doi: 10.1097/MD.0000000000021461

7. Mejdahl MK, Wohlfahrt J, Holm M, Balslev E, Knoop AS, Tjønneland A, et al. Breast cancer mortality in synchronous bilateral breast cancer patients. *Br J Cancer*. (2019) 120:761–7. doi: 10.1038/s41416-019-0403-z

8. [NCI] National Cancer Institute. NCI Dictionary of Cancer Terms. TNM staging system. (n.d.). Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tnm-staging-system (Accessed June 27, 2023).

9. [NCI] National Cancer Institute. Cancer Staging. (2022). Available at: https://www.cancer.gov/about-cancer/diagnosis-staging/staging (Accessed June 27, 2023).

10. [ASCO] American Society of Clinical Oncology. (2022). Breast Cancer: Stages. Available at: https://www.cancer.net/cancer-types/breast-cancer/stages (Accessed June 27, 2023).

11. [NCI] National Cancer Institute. Code for Histologic Grading and Differentiation. (n.d). Available at: https://training.seer.cancer.gov/coding/guidelines/rule_g.html (Accessed June 27, 2023).

12. Goel N, Hernandez A, Thompson C, Choi S, Westrick A, Stoler J, et al. Neighborhood disadvantage and breast Cancer-specific survival. *JAMA Netw Open*. (2023) 6:e238908. doi: 10.1001/jamanetworkopen.2023.8908

13. Nguyen-Pham S, Leung J, McLaughlin D. Disparities in breast cancer stage at diagnosis in urban and rural adult women: a systematic review and meta-analysis. *Ann Epidemiol*. (2014) 24:228–35. doi: 10.1016/j.annepidem.2013.12.002

14. Cheng I, Yang J, Tseng C, Wu J, Conroy SM, Shariff-Marco S, et al. Outdoor ambient air pollution and breast cancer survival among California participants of the multiethnic cohort study. *Environ Int*. (2022) 161:107088. doi: 10.1016/j.envint.2022.107088

15. Tagliabue G, Borgini A, Tittarelli A, van Donkelaar A, Martin RV, Bertoldi M, et al. Atmospheric fine particulate matter and breast cancer mortality: a population-based cohort study. *BMJ Open*. (2016) 6:e012580. doi: 10.1136/bmjopen-2016-012580

16. Alessandrini ER, Leogrande S, Morabito A, Ancona C, Assennato G, Giua R, et al. Studio di coorte sugli effetti delle esposizioni ambientali ed occupazionali sulla morbosità e mortalità della popolazione residente a Taranto. (2016). Available at: https://www.sanita.puglia.it/documents/890301/896208/Relazione+Finale+Studio+di+Coorte+-+2016/ea231c81-e196-4b43-99a4-0882bd60b83b (Accessed March 24, 2023).

17. Bustaffa E, Minichilli F, Andreassi MG, Carone S, Coi A, Cori L, et al. Studi su marcatori di esposizione ed effetto precoce in aree con inquinamento da arsenico: metodi e risultati del progetto SEpiAs. Sorveglianza epidemiologica in aree interessate da inquinamento ambientale da arsenico di origine naturale o antropica (SEpiAS CCM 2010) [Studies on markers of exposure and early effect in areas with arsenic pollution: methods and results of the project SEpiAs. Epidemiological surveillance in areas with environmental pollution by natural or anthropogenic arsenic]. *Epidemiol Prev*. (2014) 38:27–94.

18. Comba P, Pirastu R, Conti S, De Santis M, Iavarone I, Marsili G, et al. Ambiente e salute a Taranto: studi epidemiologici e indicazioni di sanità pubblica [Environment and health in Taranto, Southern Italy: epidemiological studies and public health recommendations]. *Epidemiol Prev*. (2012) 36:305–20.

19. Galise I, Serinelli M, Morabito A, Pastore T, Tanzarella A, Laghezza V, et al. L'impatto ambientale e sanitario delle emissioni dell'impianto siderurgico di Taranto e della centrale termoelettrica di Brindisi [the integrated environmental health impact of emissions from a steel plant in Taranto and from a power plant in Brindisi, (Apulia Region, Southern Italy)]. *Epidemiol Prev*. (2019) 43:329–37. doi: 10.19191/EP19.5-6.P329.102

20. Giannico OV, Baldacci S, Basile FC, Pellegrino A, Desiante F, Franco E, et al. PCDD/Fs and PCBs in hen eggs from a contaminated area in Italy: a 9 years spatio-temporal monitoring study. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. (2023) 40:294–304. doi: 10.1080/19440049.2022.2157051

21. Giannico OV, Baldacci S, Desiante F, Basile FC, Franco E, Fragnelli GR, et al. PCDD/Fs and PCBs in *Mytilus galloprovincialis* from a contaminated area in Italy: the role of mussel size, temperature and meteorological factors. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. (2022) 39:1123–35. doi: 10.1080/19440049.2022.2059108

22. Giannico OV, Fragnelli GR, Baldacci S, Desiante F, Pellegrino A, Basile FC, et al. Dioxins and PCBs contamination in milk and dairy products from Province of Taranto (Puglia Region, Southern Italy): a six years spatio-temporal monitoring study. *Ann Ist Super Sanita*. (2021) 57:233–8. doi: 10.4415/ANN_21_03_06

23. Giannico OV, Desiante F, Basile FC, Franco E, Baldacci S, Fragnelli GR, et al. Dioxins and PCBs contamination in mussels from Taranto (Ionian Sea, Southern Italy): a seven years spatio-temporal monitoring study. *Ann Ist Super Sanita*. (2020) 56:452–61. doi: 10.4415/ANN_20_04_07

24. Iavarone I, De Felip E, Ingelido AM, et al. Exploratory biomonitoring study among workers of livestock farms of the Taranto Province. *Epidemiol Prev*. (2012) 36:321–31.

25. Ingelido AM, Abate V, Abballe A, Albano FL, Battista T, Carraro V, et al. Concentrations of polychlorinated dibenzodioxins, polychlorodibenzofurans, and polychlorobiphenyls in women of reproductive age in Italy: a human biomonitoring study. *Int J Hyg Environ Health*. (2017) 220:378–86. doi: 10.1016/j.ijheh.2016.11.009

26. Leogrande S, Alessandrini ER, Stafoggia M, Morabito A, Nocioni A, Ancona C, et al. Industrial air pollution and mortality in the Taranto area, Southern Italy: a difference-in-differences approach. *Environ Int*. (2019) 132:105030. doi: 10.1016/j.envint.2019.105030

27. Minerba S, Mincuzzi A, Bruni A, Carone S, Galluzzo C, Lagravinese GM, et al. ASL Taranto, AReSS Puglia. Rapporto sui tumori ASL di Taranto. (2021). Available at: https://www.sanita.puglia.it/documents/36057/232392045/2021+Report+Registro+Tumori+-+anni+2015-2019.pdf/3439fd81-2943-49a5-87e2-810ba83326ff (Accessed March 24, 2023).

28. Pirastu R, Comba P, Iavarone I, Zona A, Conti S, Minelli G, et al. Environment and health in contaminated sites: the case of Taranto, Italy. *J Environ Public Health*. (2013) 2013:753719. doi: 10.1155/2013/753719

29. Zona A, Fazzo L, Benedetti M, Bruno C, Vecchi S, Pasetto R, et al. SENTIERI – Studio epidemiologico nazionale dei territori e degli insediamenti esposti a rischio da inquinamento. Sesto Rapporto [SENTIERI – Epidemiological Study of Residents in National Priority Contaminated Sites Sixth Report]. *Epidemiol Prev*. (2023) 47:1–286. doi: 10.19191/EP23.1-2-S1.003

30. Zona A, Iavarone I, Buzzoni C, Conti S, Santoro M, Fazzo L, et al. SENTIERI: Studio epidemiologico nazionale dei territori e degli insediamenti esposti a rischio da inquinamento. Quinto Rapporto [SENTIERI: Epidemiological Study of Residents in National Priority Contaminated Sites Fifth Report]. *Epidemiol Prev*. (2019) 43:1–208. doi: 10.19191/EP19.2-3.S1.032

31. [ISTAT] National Institute of Statistics. Demo. Demography in numbers. Available at: https://demo.istat.it/ (Accessed March 25, 2023).

32. R-INLA. Cox Proportional Hazards Model. (2023). Available at: https://inla.r-inla-download.org/r-inla.org/doc/likelihood/coxph.pdf (Accessed March 25, 2023).

33. Rue H, Riebler A, Sørbye SH, Illian JB, Simpson DP, Lindgren FK. Bayesian computing with INLA: a review. *Annual Review of Statistics and Its Application*. (2017) 4:395–421. doi: 10.1146/annurev-statistics-060116-054045

34. Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. *J. R. Stat. Soc. B*. (2009) 71:319–92. doi: 10.1111/j.1467-9868.2008.00700.x

35. Wang X, Yue YR, Faraway JJ. Bayesian regression modeling with INLA. 1st ed. Boca Raton, FL: CRC Press. (2018).

36. Martino S, Akerkar R, Rue H. Approximate Bayesian inference for survival models. *Scand J Stat*. (2011) 38:514–28. doi: 10.1111/j.1467-9469.2010.00715.x

37. Mincuzzi A, Carone S, Galluzzo C, Tanzarella M, Lagravinese GM, Bruni A, et al. Gender differences, environmental pressures, tumor characteristics, and death rate in a lung cancer cohort: a seven-years Bayesian survival analysis using cancer registry data from a contaminated area in Italy. *Front Public Health*. (2023) 11:1278416. doi: 10.3389/fpubh.2023.1278416

38. Giannico OV, Baldacci S, Bisceglia L, Minerba S, Conversano M, Mincuzzi A. The mortality cost of carbon dioxide emissions from a steel plant in southern Italy: a climate change health impact assessment. *Epidemiol Prev*. (2023) 47:273–80. doi: 10.19191/EP23.4-5.A616.067

39. Rosano A, Pacelli B, Zengarini N, Costa G, Cislaghi C, Caranci N. Aggiornamento e revisione dell'indice di deprivazione italiano 2011 a livello di sezione di censimento [Update and review of the 2011 Italian deprivation index calculated at the census section level]. *Epidemiol Prev*. (2020) 44:162–70. doi: 10.19191/EP20.2-3.P162.039

40. Carstairs V. Deprivation indices: their interpretation and use in relation to health. *J Epidemiol Community Health*. (1995) 49:S3–8. doi: 10.1136/jech.49.suppl_2.s3

41. Shiovitz S, Korde LA. Genetics of breast cancer: a topic in evolution. *Ann Oncol*. (2015) 26:1291–9. doi: 10.1093/annonc/mdv022

10.3389/fpubh.2023.1310823

Glossary

AIRTUM	Italian Association of Cancer Registries
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
CI	Confidence Interval
CrI	Credible Interval
DALY	Disability-Adjusted Life Year
ER	Estrogen Receptor
FISH	Fluorescence *In Situ* Hybridization
GVIF	Generalized Variance Inflation Factor
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
ICD	International Classification of Disease
ICDO	International Classification of Disease for Oncology
ID	Identifier
IHC	Immunohistochemistry
INLA	Integrated Nested Laplace Approximation
IQR	Interquartile Range
NA	Not Available
OR	Odds Ratio
PCB	Polychlorinated Byphenyl
PR	Progesterone Receptor
PTEN	Phosphatase and Tensin Homolog
SIN	Contaminated Site of National Interest
TNM	Tumor, Node, Metastases
TP53	Tumor Protein 53

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 10 January 2024
DOI 10.3389/fpubh.2023.1278416

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, Stony Brook, United States

REVIEWED BY
Paolo Contiero,
National Cancer Institute Foundation (IRCCS), Milan, Italy
Kranthi Kiran Kishore Tanagala,
Columbia University, New York, United States
Paramita Pal,
Takeda (United States), San Diego, United States
David Hollar,
Mercer University School of Medicine, Macon, United States

*CORRESPONDENCE
Orazio Valerio Giannico
✉ oraziovaleriogiannico@gmail.com

RECEIVED 16 August 2023
ACCEPTED 09 October 2023
PUBLISHED 10 January 2024

CITATION
Mincuzzi A, Carone S, Galluzzo C, Tanzarella M, Lagravinese GM, Bruni A, Rashid I, Bisceglia L, Sardone R, Addabbo F, Minerba S and Giannico OV (2024) Gender differences, environmental pressures, tumor characteristics, and death rate in a lung cancer cohort: a seven-years Bayesian survival analysis using cancer registry data from a contaminated area in Italy.
Front. Public Health 11:1278416.
doi: 10.3389/fpubh.2023.1278416

Gender differences, environmental pressures, tumor characteristics, and death rate in a lung cancer cohort: a seven-years Bayesian survival analysis using cancer registry data from a contaminated area in Italy

Antonia Mincuzzi[1], Simona Carone[1], Claudia Galluzzo[1], Margherita Tanzarella[1], Giovanna Maria Lagravinese[1], Antonella Bruni[1], Ivan Rashid[2], Lucia Bisceglia[2], Rodolfo Sardone[1], Francesco Addabbo[1], Sante Minerba[3] and Orazio Valerio Giannico[1]*

[1]Unit of Statistics and Epidemiology, Local Health Authority of Taranto, Taranto, Italy, [2]Coordination Center of the Apulia Cancer Registry, Strategic Regional Agency for Health and Social Care of Apulia, Bari, Italy, [3]Healthcare Management, Local Health Authority of Taranto, Taranto, Italy

Introduction: In Taranto, Southern Italy, adverse impacts on the environment and human health due to industrial installations have been studied. In the literature, associations have been reported between gender, environmental factors, and lung cancer mortality in women and men. The aim of this study was to investigate the relationships between gender, residence in areas with high environmental pressures, bronchus/lung cancer characteristics, and death rate.

Methods: Data from the Taranto Cancer Registry were used, including all women and men with invasive bronchus/lung cancer diagnosed between 1 January 2016 and 31 December 2020 and with follow-up to 31 December 2022. Bayesian mixed effects logistic and Cox regression models were fitted with the approach of integrated nested Laplace approximation, adjusting for patients and disease characteristics.

Results: A total of 2,535 person-years were observed. Male gender was associated with a higher prevalence of histological grade 3 (OR 2.45, 95% CrI 1.35–4.43) and lung squamous-cell carcinoma (OR 3.04, 95% CrI 1.97–4.69). Variables associated with higher death rate were male gender (HR 1.24, 95% CrI 1.07–1.43), pathological/clinical stage II (HR 2.49, 95% CrI 1.63–3.79), III (HR 3.40, 95% CrI 2.33–4.97), and IV (HR 8.21, 95% CrI 5.95–11.34), histological grade 3 (HR 1.80, 95% CrI 1.25–2.59), lung squamous-cell carcinoma (HR 1.18, 95% CrI 1.00–1.39), and small-cell lung cancer (HR 1.62, 95% CrI 1.31–1.99). Variables associated with lower death rate were other-type lung cancer (HR 0.65, 95% CrI 0.44–0.95), high immune checkpoint ligand expression (HR 0.75, 95% CrI 0.59–0.95), lung localization (HR 0.73, 95% CrI 0.62–0.86), and left localization (HR 0.85, 95% CrI 0.75–0.95).

Discussion: The results among patients with lung cancer did not show an association between residence in the contaminated site of national interest (SIN) and the prevalence of the above mentioned prognostic factors, nor between residence in SIN and death rate. The findings confirmed the independent prognostic values of different lung cancer characteristics. Even after adjusting

for patients and disease characteristics, male gender appeared to be associated with a higher prevalence of poorly differentiated cancer and squamous-cell carcinoma, and with an increased death rate.

KEYWORDS

bronchus cancer, lung cancer, cancer survival, gender differences, environmental contamination, environmental pollution, cancer epidemiology

Introduction

Lung cancer is the second most diagnosed cancer and the leading cause of cancer death in 2020. With an estimated 2.2 million new cancer cases and 1.8 million deaths in 2020, it represents approximately one in 10 (11.4%) cancers diagnosed and one in 5 (18.0%) deaths (1, 2). The risk of developing this cancer is associated with older age combined with a history of smoking cigarettes. It is more common among men than women and among those with lower socioeconomic status. Among non-smokers, important lung cancer risk factors are exposure to second-hand smoke, exposure to ionizing radiation, and occupational exposure to lung carcinogens, such as asbestos (3).

Treatments for lung cancers are based on the biological subtyping of the tumors, and several disease characteristics, such as staging, grading, morphology, PD-L1 expression, topography, and laterality, represent prognostic factors and/or targets for therapies (4–9). Specifically, tumor, node, metastases (TNM) classification is a system used to describe the amount and spread of cancer in a patient's body. In TNM classification, T describes the size of the tumor and any spread of cancer to nearby tissues, N describes the spread of cancer to nearby lymph nodes, and M describes the metastasis, i.e., the spread of cancer to other parts of the body. TNM combinations are grouped into five less-detailed stages, from 0 (carcinoma *in situ*, where abnormal cells are present but have not spread to nearby tissues) to I-II-III (invasive cancer, where the higher the number, the larger the tumor and the more it has spread to nearby tissues) to IV (invasive, metastatic cancer, where cancer has spread to distant parts of the body) (4, 10–12). In addition to TNM staging, histologic grading is a predictor of disease outcome in lung cancer patients, with higher tumor grade (lower differentiation) being associated with a poorer prognosis (differentiation describes how much a tumor resembles the normal tissue from which it arose) (5, 13). Tumor morphology is another prognostic factor in patients with lung cancer. Non-small-cell lung cancer (NSCLC) is any type of epithelial lung cancer other than small-cell lung cancer (SCLC). The most common types of NSCLC are lung adenocarcinoma (LAC) and lung squamous-cell carcinoma (LSCC), but there are several other types that occur less frequently, and all types can occur in unusual histological variants. NSCLC is usually less sensitive to chemotherapy and radiation therapy than SCLC, but patients with resectable cancer may be cured through surgery or surgery followed by chemotherapy. Conversely, SCLC is a distinct subtype of lung cancer that presents as a proliferation of small cells. It is more responsive to chemotherapy and radiation therapy than other cell types of lung cancer; however, it is difficult to cure as SCLC has a greater tendency to spread widely even before diagnosis takes place (4, 6, 7). Programmed death-ligand 1 (PD-L1) expression is also an important prognostic factor in lung cancer. PD-L1 is a ligand of the programmed death protein 1 (PD-1) coinhibitory immune checkpoint expressed on tumor cells and infiltrating immune cells. Tumors with the expression of PD-L1 $\geq$ 50% are amenable to first-line treatment with targeted biological agents such as pembrolizumab, with improvement in survival (4, 6, 7). In previous studies, authors have also found associations between bronchus/lung cancer topography, laterality, and death rate. Specifically, increased death rates were reported in patients with cancer localization in the main bronchus or on the right side (8, 9).

As far as gender differences are concerned, higher lung cancer incidence and mortality were reported in men, even when other clinical and demographic characteristics were considered. Regarding environmental pressures, which can also be linked to gender differences in exposure patterns, air pollution is a recognized risk factor for lung cancer incidence and mortality and is a major health concern for Europeans, with more than 300,000 premature deaths each year attributed to chronic exposure to fine particulate matter alone. Part of this mortality is due to lung cancer, and the International Agency for Research on Cancer (IARC) has classified outdoor air pollution and particulate matter in outdoor air pollution as carcinogenic to humans (Group 1), with sufficient evidence for lung cancer (14–19).

In some areas of the province of Taranto, a coastal city in the Apulia region in Southern Italy, various industrial installations and polluting sources (a steel plant, an oil refinery, urban discharges, harbor activities, and the shipyard of the Italian Navy) have been operating in close proximity to the resident population for decades with well-known and extensively studied adverse impacts on the environment and human health (20–34). With regard to environmental, feed, and food impacts, it is of particular importance that the area shows contamination of these matrices by metals and persistent organic pollutants, specifically dioxins and PCBs. Moreover, some of these substances have been detected in in human biological samples (21, 24–29). As far as human health effects are concerned, evidence has been produced after studying the populations who resided in the contaminated site of national interest (SIN) of Taranto.

Abbreviations: AIRTUM, Italian Association of Cancer Registries; CI, Confidence Interval; CrI, Credible Interval; GVIF, Generalized Variance Inflation Factor; HR, Hazard Ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Disease; ICDO, International Classification of Disease for Oncology; ID, Identifier; INLA, Integrated Nested Laplace Approximation; IQR, Interquartile Range; LAC, Lung Adenocarcinoma; LSCC, Lung Squamous-Cell Carcinoma; NA, Not Available; NSCLC, Non-Small-Cell Lung Cancer; OTLC, Other-Type Lung Cancer; OR, Odds Ratio; PCB, Polychlorinated Biphenyl; PD-1, Programmed Death protein 1; PD-L1, Programmed Death-Ligand 1; SCLC, Small-Cell Lung Cancer; SIN, Contaminated Site of National Interest; TNM, Tumor, Node, Metastases.

In particular, cohort studies have reported an increased risk for different types of cancer incidence, including lung cancer incidence in women and men (20, 31). Some studies have also noted an increased risk for all-cause hospitalization; for circulatory, respiratory, digestive, and urinary diseases hospitalization; and for different types of cancer hospitalization, including lung cancer hospitalization in women and men (20, 33, 34). Different studies have also indicated an increased risk for all-cause mortality; for circulatory and digestive diseases mortality; and for some types of cancer mortality, including lung cancer mortality in women and men (20, 23, 30, 33, 34).

To summarize, associations have been reported between the aforementioned factors and lung cancer mortality in women and men. The aim of this study was to investigate the relationships between gender, residence in areas with high environmental pressures, bronchus/lung cancer characteristics, and death rate.

Methods

Study area and baseline epidemiological data

The study area is the province of Taranto, which consists of 29 municipalities with a total resident population of 555,999 on 1 January 2023 (35). The SIN of Taranto consists of two municipalities, Taranto (the provincial capital) and Statte, respectively, with a population size of 188,098 and 12,917 on 1 January 2023 (33–35). The study area with municipalities and SIN is shown in Figure 1. The map was created with QGIS version 3.28.4.

From 2015 to 2019, Taranto Province recorded 1,740 bronchus/lung cancer (ICD10 codes C34.0 to C34.9) cases, with a directly standardized rate of 21.5 cases ber 100,000 inhabitants in women and 96.8 cases per 100,000 in men, and a median age of 70 years in women and 72 years in men. In the studied period, no trachea cancer (C33) cases were recorded. In the same period, 67% of patients with bronchus/lung cancer requiring hospitalization were admitted to a hospital in the Taranto Province, 21% to an extra-provincial hospital in the Apulia region, and 12% to an extra-regional hospital. Between 2013 and 2017, the relative standardized five-years bronchus/lung cancer survival rate was 24.5 (95% CI 19.4–29.9) for women and 17.8 (95% CI 14.7–21.2) for men (31).

From 2013 to 2017, in the SIN, 121 bronchus/lung cancer deaths were recorded among women, with a standardized mortality ratio (reference: Apulia region) of 125 (90% CI 107–145); and 451 bronchus/lung cancer deaths were recorded among men, with a standardized mortality ratio (reference: Apulia region) of 118 (90% CI 109–127) (33). From 2015 to 2019, in the SIN, 202 bronchus/lung cancer cases were recorded among women, with a directly standardized rate of 30.6 cases per 100,000 inhabitants and a standardized incidence ratio (reference: Taranto Province) of 191.2 (95% CI 165.8–219.5). For the same period, in the SIN, 582 bronchus/lung cancer cases were recorded among men, with a directly standardized rate of 111.1 cases per 100.000 inhabitants and a standardized incidence ratio (reference: Taranto Province) of 125.7 (95% CI 115.7–136.4) (31).

Data source and cancer cohort

Data from the Taranto Cancer Registry of the Italian Association of Cancer Registries (AIRTUM) were used, including all women and men with invasive bronchus/lung cancer (ICD10 codes C34.0 to C34.9) diagnosed between 01 January 2016 and 31 December 2020 who resided in Taranto Province at the time of diagnosis. In the studied

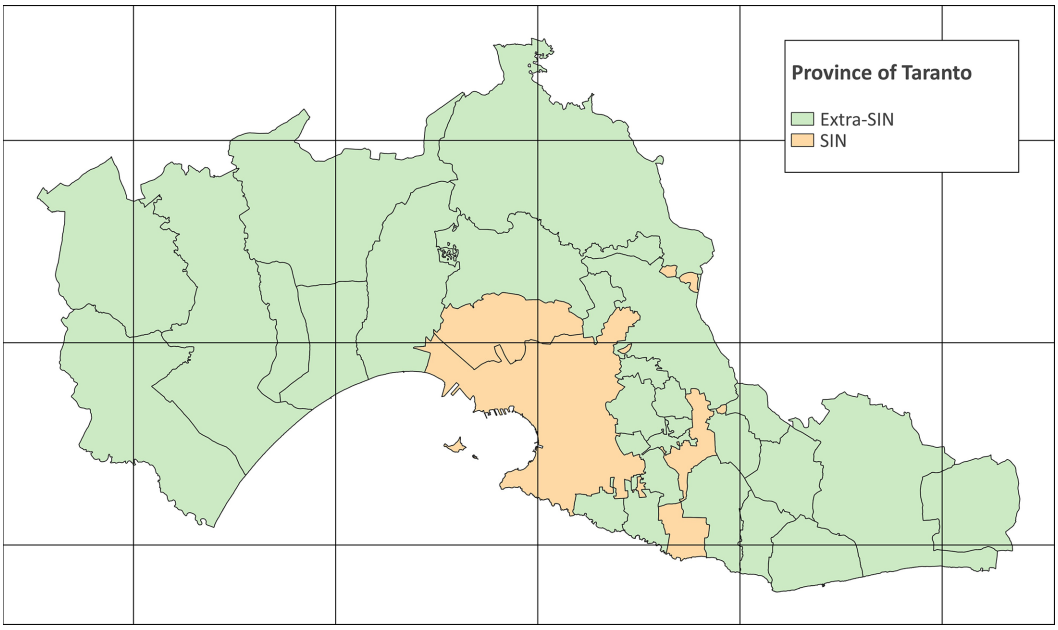


FIGURE 1
Map of the province of Taranto (grid interval: 20 km) (EPSG:32632 – WGS 84 / UTM zone 32N) (Modified from Italian National Institute of Statistics. Administrative boundaries. https://www.istat.it/it/archivio/222527).

period, no cases of trachea cancer (C33) were recorded. For simplicity reasons, in this study, we refer to main bronchus (C34.0) and lung (C34.1 to C34.8) cancers as "lung cancer." The follow-up period considered for this study was until 31 December 2022. Death certificate only cases ($n = 23$), cases registered based on an autopsy report ($n = 1$), and patients under 40 years ($n = 4$) were excluded. As a general rule, baseline patients and disease characteristics refer to the time of diagnosis. Mortality data (all-cause mortality) relative to the follow-up period (2016–2022) were retrieved from the Taranto Province's Causes of Death and Health Registries. Patients with no mortality follow-up information due to extra-provincial transfer before 31 December 2022 (right-censoring, loss-to-follow-up) contributed to the person-time until the date of transfer ($n = 8$).

Study design and variables

This is a retrospective individual observational study with different regression analyses carried out cross-sectionally (prevalence study) and longitudinally (incidence study, survival analysis). Residence in the areas with high environmental pressures (SIN) was used as an environmental exposure proxy. Tumor characteristics at the time of diagnosis were pathological/clinical staging (TNM I to IV), histological grading (grade 1 to 3), morphology (ICDO3M classification. LAC: Lung Adenocarcinoma; LSCC: Lung Squamous-Cell Carcinoma; SCLC: Small-Cell Lung Cancer; OTLC: Other-Type Lung Cancer; OTLC included morphologies with too low numbers for separate analysis and not included in previous groups, i.e., adenosquamous, large-cell neuroendocrine, lymphoepithelial, pleomorphic, mucoepidermoid, and pseudosarcomatous tumors, as well as different types of sarcoma) immune checkpoint ligand expression (PD-L1%), topography (ICDO3T classification. C34.0: main bronchus; C34.1: upper lobe, lung; C34.2: middle lobe, lung; C34.3: lower lobe, lung; and C34.8: overlapping lesion, lung), and laterality (unilateral right, unilateral left, and synchronous bilateral lung cancer).

In the cross-sectional study, the studied outcomes were each of the tumor characteristics (prevalence), and the studied exposures were gender and residence in areas with high environmental pressures. The aim of this step was to assess possible associations between gender, environmental factors, and each of the tumor characteristics. In the longitudinal study, the studied outcome was all-cause death (incidence), and the studied exposures were gender, residence in areas with high environmental pressures, and tumor characteristics. The aim of this step was to assess possible associations between gender, environmental factors, tumor characteristics, and death. Adjustment variables recorded at the time of diagnosis were age class (40–59, 60–69, 70–79, $\geq$ 80 years), year, patient ID, and municipality of residence. Adjustment for the patient's ID and municipality of residence was provided to account for the heterogeneity related to possible unobserved individual or ecological level variables (e.g., tobacco use, alcohol consumption, social and material deprivation and access to health services).

Statistical analysis

Data analysis was performed using R version 4.2.3. Bayesian inference was performed with package INLA version 22.12.16. Complex models could be fitted with the Bayesian approach, including generalized linear models and survival analyses. The possible non-independence and heterogeneity of observations could be taken into account by fitting mixed models with both fixed and random effects. While traditional survival analysis relies on parameter estimation based on partial likelihood, Bayesian approaches for time-to-event data allow us to use the full likelihood to estimate all unknown elements in the model. Bayesian generalized linear models comprise Bayesian logistic regression for binary response data. However, the computation of the posterior and other quantities of interest in these complex models is usually much more difficult than frequentist calculations. The Integrated Nested Laplace Approximation (INLA) is a deterministic method for Bayesian calculations that applies to a wide class of models called Latent Gaussian Models. INLA provides fast and accurate approximations to the posterior marginals through a clever use of Laplace approximations and advanced numerical methods, taking computational advantage of sparse matrices. In most cases, INLA is both faster and more accurate than other methods for Bayesian computation (36–40).

The cross-sectional study analyzed the associations between gender, residence in areas with high environmental pressures, and tumor characteristics using a series of mixed effects binary logistic regressions. Pathological/clinical staging (TNM III-IV; TNM IV), histological grading (grade 3), morphology (SCLC in patients with LAC, LSCC, or SCLC; LSCC in patients with LAC or LSCC), immune checkpoint ligand expression (PD-L1 $\geq$ 50%), topography (lung), and laterality (left, excluding patients with bilateral cancer) were considered as outcome measures binary variables. For each regression model, records with missing values for the analyzed outcome were excluded. Gender and residence in areas with high environmental pressures were included as fixed effects binary variables. Age class and year were included as fixed effects multinominal variables. Patient ID and municipality of residence were included as random effects multinominal variables (random intercepts). Bayesian binary logistic regression models were fitted with the INLA approach for latent Gaussian models, computing odds ratios (OR) and 95% credible intervals (CrI). An independent and identically distributed random distribution was chosen for patient ID and municipality of residence (37–39).

The longitudinal study analyzed the associations between gender, residence in areas with high environmental pressures, tumor characteristics, and death using a mixed effects Cox proportional hazard regression. The time axis was the difference in days between the day of cancer diagnosis and the last day of follow-up (event or right censoring). All-cause death was considered as the outcome measure binary variable (event). The proportional hazard assumption was verified through the analysis of plotted survival curves between the different levels of the variables. Gender, residence in areas with high environmental pressures, pathological/clinical staging (TNM I, II, III, IV), histological grading (grade 1–2, 3), morphology (LAC, LSCC, SCLC, OTLC), immune checkpoint ligand expression (PD-L1 0–49%, $\geq$ 50%), topography (main bronchus, lung), and laterality (right, left) were included as fixed effects binary or multinominal variables. An "NA" (not available) category was created for the records with missing values for the analyzed exposures. Due to low frequency, the bilateral cancer category was merged with the NA category. Age class and year were included as fixed effects multinominal variables. Patient ID and municipality of residence were included as random effects multinominal variables (random intercepts). Bayesian Cox

regression models were fitted with the INLA approach for latent Gaussian models, computing hazard ratios (HR) and 95% credible intervals (CrI). An independent and identically distributed random distribution was chosen for patient ID and municipality of residence, while a random walk model of order two was chosen for the baseline hazard function (36–40).

Generalized variance inflation factors (GVIF) were calculated to test the presence of multicollinearity in the data. Sensitivity analyses were performed by examining the extent to which the results were affected by changes in methods, models, variables, influential observations, and inclusion/exclusion criteria. Different combinations of included patients and variables were tested, and for the included variables, different collapsed categories, as well as changes in the type of estimated effects (fixed or random), were also tested. The models were iteratively refitted by excluding from the dataset each age class and year one at a time.

Results

Baseline patients and disease characteristics are shown in Table 1. A total of 2,535 person-years were observed, 1,893 for men, 1,212 for residents in SIN, and 1,118 for deceased patients, with a median (IQR) age of 72.0 (66.0;78.2) years.

The results of the mixed effects Bayesian binary logistic regression models are reported in Table 2. Mutually adjusting and adjusting for baseline age class, year, patient ID, and municipality of residence, the fixed effect variable male gender was associated with a higher prevalence of grade 3 (OR 2.45, 95% CrI 1.35–4.43) and morphology LSCC (OR 3.04, 95% CrI 1.97–4.69), while the fixed effect variable residence in SIN did not appear to be clearly associated with the prevalence of the investigated tumor characteristics.

Survival probabilities conditional on each analyzed variable and unconditional on other variables are shown in Figure 2. The curves suggested unconditional associations between survival probability and gender, TNM staging, histological grading, morphology, immune checkpoint ligand expression, topography, and laterality. The results of the mixed effects Bayesian Cox proportional hazard regression model are reported in Table 3. Mutually adjusting and adjusting for baseline age class, year, patient ID, and municipality of residence, the fixed effects variables associated with higher death rate were male gender (HR 1.24, 95% CrI 1.07–1.43), TNM II (HR 2.49, 95% CrI 1.63–3.79), III (HR 3.40, 95% CrI 2.33–4.97), IV (HR 8.21, 95% CrI 5.95–11.34) and NA (HR 5.22, 95% CrI 3.78–7.21), grade 3 (HR 1.80, 95% CrI 1.25–2.59) and NA (HR 1.79, 95% CrI 1.27–2.53), and morphologies LSCC (HR 1.18, 95% CrI 1.00–1.39), SCLC (HR 1.62, 95% CrI 1.31–1.99) and NA (HR 2.00, 95% CrI 1.71–2.33). Mutually adjusting and adjusting for baseline age class, year, patient ID, and municipality of residence, the fixed effects variables associated with lower death rate were morphology OTLC (HR 0.65, 95% CrI 0.44–0.95), PD-L1 ≥ 50% (HR 0.75, 95% CrI 0.59–0.95), lung localization (HR 0.73, 95% CrI 0.62–0.86), and left localization (HR 0.85, 95% CrI 0.75–0.95).

Discussion

The results of the present study confirmed that TNM staging, histological grading, morphology, immune checkpoint ligand expression, topography, and laterality are independent prognostic factors for mortality in lung cancer patients. Of interest was the finding during the follow-up period of an overall average negative association between PD-L1 expression and death rate in our cohort, although it may be non-constant over time. This association could be explained by the development and implementation of PD-L1 targeting drugs, such as pembrolizumab, in recent years (4, 6, 7). Pembrolizumab is a humanized monoclonal antibody that inhibits the interaction between the programmed death protein 1 (PD-1) coinhibitory immune checkpoint expressed on tumor cells and infiltrating immune cells and its ligand, PD-L1 (6). In general, patients are eligible for this first-line immunotherapy treatment if their cancer-tissue sample shows a positive expression for PD-L1 in ≥50% of neoplastic cells (4). For these reasons, the presence of PD-L1 ≥ 50% could be assumed as a proxy for treatment with immune checkpoint inhibitors, which is a piece of information not directly available in the cancer registry. Given this assumption, our findings could be supported by the scientific literature on the improvement of overall survival in the treated patients (4, 6, 7). Another interesting result was the negative prognostic value of the presence of missing data ("NA" category) for some variables in our cohort. This could be partly explained by the fact that patients without information on some variables (e.g., grading) could correspond to poor prognosis patients who, due to a severe condition at the time of diagnosis, were unable to undergo further interventions or investigations.

With regard to gender differences in tumor characteristics, according to our study, there appeared to be a lower prevalence of LAC and a higher prevalence of grade 3 tumors among men. While the former result appears to be consistent with gender differences in lung cancer characteristics reported in the literature (15), the latter result was a peculiar and interesting finding of our study. With regard to gender differences in lung cancer prognosis, an important, related result appears to be the association between male patients and increased all-cause death rate. This finding was observed independently of all other factors analyzed, as the HR was adjusted for the other variables included in the Bayesian mixed effects regression model. Specifically, this indicates that male patients in the lung cancer cohort have an excess relative risk for all-cause mortality of 24% (95% CrI 7–43%) compared to female patients. Male patients also present an excess odds ratio for grade 3 tumors of 145% (95% CrI 35–343%) compared to female patients, which is, in turn, a factor independently associated with an increased all-cause death rate. Besides, male patients in the LAC/LSCC cohort present an excess odds ratio for LSCC of 204% (95% CrI 97–369%) compared to female patients, which is also, in turn, a factor independently associated with increased all-cause death rate.

Probably, these direct and indirect effects of gender on overall survival could explain the relative standardized five-years bronchus/lung cancer survival difference between women (24.5) and men (17.8) observed in Taranto Province in the years 2013–17 (31). Moreover, the excess relative risk for mortality independently associated with male patients (direct effect) not only confirms what was already known in relation to the lower survival reported for men in the general population and among lung cancer patients, but also suggests that this excess relative risk could be different in the cohorts followed in this study (14, 16, 35). In this regard, two epidemiological studies on different lung cancer patients' cohorts reported excess relative risks

TABLE 1 Baseline patients and disease characteristics and follow-up survival status in the lung cancer cohort, by gender, residence in SIN, and survival status.

Baseline patients and disease characteristics and follow-up survival status	Lung cancer cohort						
	N = 1,696; person-years = 2,535						
	Women	Men	Extra-SIN	SIN	Survived	Deceased	Total
Age							
Age [Median (IQR)]	70.0 (62.0;76.0)	73.0 (67.0;79.0)	72.0 (66.0;79.0)	72.0 (66.0;78.0)	69.0 (63.0;74.0)	73.0 (67.0;80.0)	72.0 (66.0;78.2)
40–59 [*n* (%)]	75 (20.60%)	126 (9.46%)	102 (11.20%)	99 (12.61%)	50 (14.29%)	151 (11.22%)	201 (11.85%)
60–69 [*n* (%)]	102 (28.02%)	350 (26.28%)	248 (27.22%)	204 (25.99%)	135 (38.57%)	317 (23.55%)	452 (26.65%)
70–79 [*n* (%)]	131 (35.99%)	542 (40.69%)	349 (38.31%)	324 (41.27%)	141 (40.29%)	532 (39.52%)	673 (39.68%)
≥ 80 [*n* (%)]	56 (15.38%)	314 (23.57%)	212 (23.27%)	158 (20.13%)	24 (6.86%)	346 (25.71%)	370 (21.82%)
Year							
2016 [*n* (%)]	77 (21.15%)	249 (18.69%)	182 (19.98%)	144 (18.34%)	51 (14.57%)	275 (20.43%)	326 (19.22%)
2017 [*n* (%)]	71 (19.51%)	315 (23.65%)	198 (21.73%)	188 (23.95%)	62 (17.71%)	324 (24.07%)	386 (22.76%)
2018 [*n* (%)]	60 (16.48%)	260 (19.52%)	169 (18.55%)	151 (19.24%)	67 (19.14%)	253 (18.80%)	320 (18.87%)
2019 [*n* (%)]	81 (22.25%)	277 (20.80%)	193 (21.19%)	165 (21.02%)	90 (25.71%)	268 (19.91%)	358 (21.11%)
2020 [*n* (%)]	75 (20.60%)	231 (17.34%)	169 (18.55%)	137 (17.45%)	80 (22.86%)	226 (16.79%)	306 (18.04%)
Pathological/clinical staging							
TNM I [*n* (%)]	40 (10.99%)	134 (10.06%)	87 (9.55%)	87 (11.08%)	131 (37.43%)	43 (3.19%)	174 (10.26%)
TNM II [*n* (%)]	21 (5.77%)	69 (5.18%)	42 (4.61%)	48 (6.11%)	45 (12.86%)	45 (3.34%)	90 (5.31%)
TNM III [*n* (%)]	15 (4.12%)	97 (7.28%)	58 (6.37%)	54 (6.88%)	36 (10.29%)	76 (5.65%)	112 (6.60%)
TNM IV [*n* (%)]	149 (40.93%)	449 (33.71%)	318 (34.91%)	280 (35.67%)	40 (11.43%)	558 (41.46%)	598 (35.26%)
NA [*n* (%)]	139 (38.19%)	583 (43.77%)	406 (44.57%)	316 (40.25%)	98 (28.00%)	624 (46.36%)	722 (42.57%)
Histological grading							
Grade 1 [*n* (%)]	9 (2.47%)	5 (0.38%)	7 (0.77%)	7 (0.89%)	10 (2.86%)	4 (0.30%)	14 (0.83%)
Grade 2 [*n* (%)]	19 (5.22%)	51 (3.83%)	34 (3.73%)	36 (4.59%)	38 (10.86%)	32 (2.38%)	70 (4.13%)
Grade 3 [*n* (%)]	47 (12.91%)	207 (15.54%)	135 (14.82%)	119 (15.16%)	53 (15.14%)	201 (14.93%)	254 (14.98%)
NA [*n* (%)]	289 (79.40%)	1,069 (80.26%)	735 (80.68%)	623 (79.36%)	249 (71.14%)	1,109 (82.39%)	1,358 (80.07%)
Morphology							
LAC [*n* (%)]	183 (50.27%)	519 (38.96%)	353 (38.75%)	349 (44.46%)	211 (60.29%)	491 (36.48%)	702 (41.39%)
LSCC [*n* (%)]	28 (7.69%)	290 (21.77%)	183 (20.09%)	135 (17.20%)	79 (22.57%)	239 (17.76%)	318 (18.75%)
SCLC [*n* (%)]	33 (9.07%)	116 (8.71%)	84 (9.22%)	65 (8.28%)	8 (2.29%)	141 (10.48%)	149 (8.79%)
OTLC [*n* (%)]	25 (6.87%)	37 (2.78%)	30 (3.29%)	32 (4.08%)	34 (9.71%)	28 (2.08%)	62 (3.66%)
NA [*n* (%)]	95 (26.10%)	370 (27.78%)	261 (28.65%)	204 (25.99%)	18 (5.14%)	447 (33.21%)	465 (27.42%)
Immune checkpoint ligand expression							
PD-L1 0–49% [*n* (%)]	77 (21.15%)	274 (20.57%)	184 (20.20%)	167 (21.27%)	76 (21.71%)	275 (20.43%)	351 (20.70%)
PD-L1 ≥ 50% [*n* (%)]	32 (8.79%)	105 (7.88%)	65 (7.14%)	72 (9.17%)	40 (11.43%)	97 (7.21%)	137 (8.08%)
NA [*n* (%)]	255 (70.05%)	953 (71.55%)	662 (72.67%)	546 (69.55%)	234 (66.86%)	974 (72.36%)	1,208 (71.23%)
Topography							
Main bronchus [*n* (%)]	40 (10.99%)	164 (12.31%)	117 (12.84%)	87 (11.08%)	16 (4.57%)	188 (13.97%)	204 (12.03%)
Lung [*n* (%)]	279 (76.65%)	1,007 (75.60%)	688 (75.52%)	598 (76.18%)	320 (91.43%)	966 (71.77%)	1,286 (75.83%)
NA [*n* (%)]	45 (12.36%)	161 (12.09%)	106 (11.64%)	100 (12.74%)	14 (4.00%)	192 (14.26%)	206 (12.15%)
Laterality							
Right [*n* (%)]	179 (49.18%)	682 (51.20%)	459 (50.38%)	402 (51.21%)	176 (50.29%)	685 (50.89%)	861 (50.77%)
Left [*n* (%)]	143 (39.29%)	504 (37.84%)	352 (38.64%)	295 (37.58%)	157 (44.86%)	490 (36.40%)	647 (38.15%)
Bilateral [*n* (%)]	9 (2.47%)	33 (2.48%)	21 (2.31%)	21 (2.68%)	4 (1.14%)	38 (2.82%)	42 (2.48%)
NA [*n* (%)]	33 (9.07%)	113 (8.48%)	79 (8.67%)	67 (8.54%)	13 (3.71%)	133 (9.88%)	146 (8.61%)

(Continued)

10.3389/fpubh.2023.1278416

TABLE 1 (Continued)

Baseline patients and disease characteristics and follow-up survival status	Lung cancer cohort						
	N = 1,696; person-years = 2,535						
	Women	Men	Extra-SIN	SIN	Survived	Deceased	Total
Gender							
Women [*n* (%)]	364 (100.00%)	0 (0.00%)	157 (17.23%)	207 (26.37%)	109 (31.14%)	255 (18.95%)	364 (21.46%)
Men [*n* (%)]	0 (0.00%)	1,332 (100.00%)	754 (82.77%)	578 (73.63%)	241 (68.86%)	1,091 (81.05%)	1,332 (78.54%)
Residence in SIN							
Extra-SIN [*n* (%)]	157 (43.13%)	754 (56.61%)	911 (100.00%)	0 (0.00%)	173 (49.43%)	738 (54.83%)	911 (53.71%)
SIN [*n* (%)]	207 (56.87%)	578 (43.39%)	0 (0.00%)	785 (100.00%)	177 (50.57%)	608 (45.17%)	785 (46.29%)
Survival status at the end of follow-up							
Survived [*n* (%)]	109 (29.95%)	241 (18.09%)	173 (18.99%)	177 (22.55%)	350 (100.00%)	0 (0.00%)	350 (20.64%)
Deceased [*n* (%)]	255 (70.05%)	1,091 (81.91%)	738 (81.01%)	608 (77.45%)	0 (0.00%)	1,346 (100.00%)	1,346 (79.36%)
Days of follow-up [Median (IQR)]	360.0 (86.5;1,110.2)	224.0 (62.0;817.2)	217.0 (62.0;841.5)	294.0 (72.0;899.0)	1,424.0 (1,068.2;1,910.8)	153.0 (47.0;399.8)	248.0 (65.8;864.5)
Person-years [Sum]	642.6	1,892.7	1,323.1	1,212.2	1,417.8	1,117.5	2,535.3

Province of Taranto, 2016–20, follow-up to 31/12/2022. N: cohort.

TABLE 2 Results of the mixed effects Bayesian INLA binary logistic regression models in the lung cancer cohort, mutually adjusted and adjusted for baseline age class, year, patient ID, and municipality of residence.

Mixed effects INLA binary logistic regressions	Lung cancer cohort							
	TNM III-IV		TNM IV		Grade 3		SCLC	
	N = 974; *n* = 710		*N* = 974; *n* = 598		*N* = 338; *n* = 254		*N* = 1,169; *n* = 149	
Fixed effects	OR	95% CrI	OR	95% CrI	OR	95% CrI	OR	95% CrI
Gender								
Women	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
Men	0.96	0.68–1.36	0.74	0.54–1.03	2.45	1.35–4.43	0.91	0.59–1.40
Residence in SIN								
Extra-SIN	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
SIN	0.86	0.64–1.15	0.85	0.65–1.11	0.93	0.55–1.56	0.83	0.59–1.19

Mixed effects INLA binary logistic regressions	Lung cancer cohort							
	LSCC		PD-L1 ≥ 50%		Lung localization		Left localization	
	N = 1,020; *n* = 318		*N* = 488; *n* = 137		*N* = 1,490; *n* = 1,286		*N* = 1,508; *n* = 647	
Fixed effects	OR	95% CrI	OR	95% CrI	OR	95% CrI	OR	95% CrI
Gender								
Women	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
Men	3.04	1.97–4.69	1.03	0.63–1.69	0.86	0.59–1.26	0.89	0.69–1.15
Residence in SIN								
Extra-SIN	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
SIN	0.80	0.61–1.06	1.24	0.83–1.85	1.16	0.86–1.57	0.95	0.77–1.17

Province of Taranto, 2016–20, follow-up to 31/12/2022. Outcome (prevalence): tumor characteristic. N: prevalent cases and non-cases. n: prevalent cases.

respectively of 6% and 14% for mortality in men compared to women (14, 16). Although these differences could be attributable to random error, bias, and/or methodological differences, we could not completely rule out the hypothesis that the excess mortality risk in male patients with lung cancer compared to female patients could be different in the population residing in the province of Taranto.

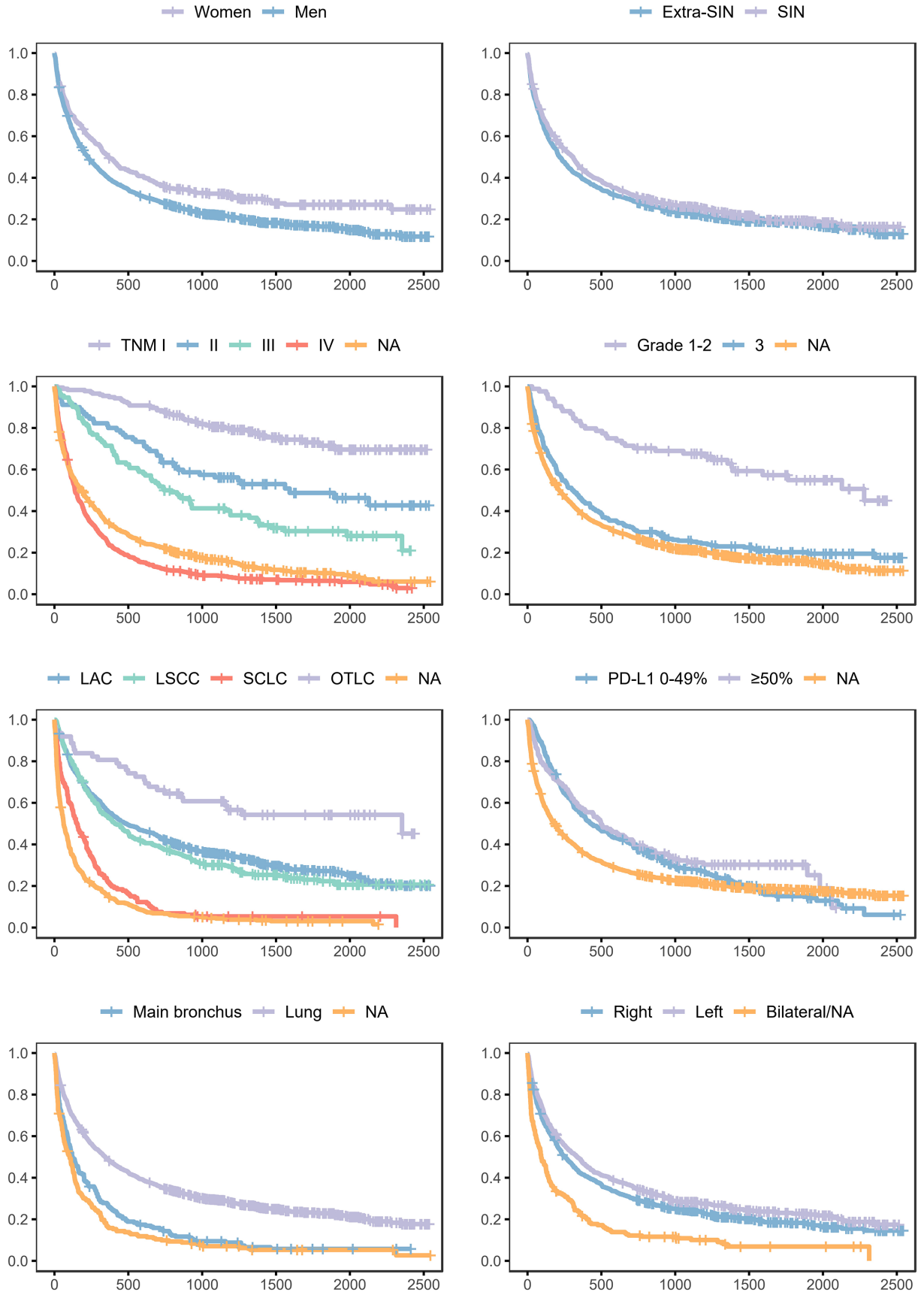


FIGURE 2
Survival probabilities in the lung cancer cohort, conditional on each analyzed variable and unconditional on other variables. Province of Taranto, 2016–20, follow-up to 31/12/2022. Time: days of follow-up. Outcome (incidence): all-cause death.

10.3389/fpubh.2023.1278416

TABLE 3 Results of the mixed effects Bayesian INLA Cox proportional hazard regression model in the lung cancer cohort, mutually adjusted and adjusted for baseline age class, year, patient ID, and municipality of residence.

Mixed effects INLA Cox proportional hazard regression	Lung cancer cohort	
	All-cause death	
	N = 1,696; person-years = 2,535; *n* = 1,346	
Fixed effects	HR	95% CrI
Gender		
Women	1.00	(ref)
Men	1.24	1.07–1.43
Residence in SIN		
Extra-SIN	1.00	(ref)
SIN	0.97	0.87–1.08
Pathological/clinical staging		
TNM I	1.00	(ref)
TNM II	2.49	1.63–3.79
TNM III	3.40	2.33–4.97
TNM IV	8.21	5.95–11.34
NA	5.22	3.78–7.21
Histological grading		
Grade 1–2	1.00	(ref)
Grade 3	1.80	1.25–2.59
NA	1.79	1.27–2.53
Morphology		
LAC	1.00	(ref)
LSCC	1.18	1.00–1.39
SCLC	1.62	1.31–1.99
OTLC	0.65	0.44–0.95
NA	2.00	1.71–2.33
Immune checkpoint ligand expression		
PD-L1 0–49%	1.00	(ref)
PD-L1 ≥ 50%	0.75	0.59–0.95
NA	1.07	0.91–1.25
Topography		
Main bronchus	1.00	(ref)
Lung	0.73	0.62–0.86
NA	0.89	0.70–1.12
Laterality		
Right	1.00	(ref)
Left	0.85	0.75–0.95
Bilateral/NA	1.04	0.85–1.27

Province of Taranto, 2016–20, follow-up to 31/12/2022. Time: days of follow-up. Outcome (incidence): all-cause death. N: incident cases and non-cases. n: incident cases.

In general, gender-based differences in women with lung cancer could be observed in terms of exogenous risk factors (tobacco use, second-hand smoke, asbestos, radon, radiation, and infections), endogenous risk factors (estrogen and genetic polymorphism), diagnosis (diagnosis at a younger age and with never-smoking history), and outcome and mortality (superior surgical outcomes, differences in response to therapies and adverse effect rates, and improved survival across stages and histologies) (15). Therefore, our findings could indicate an interaction between gender differences in lung cancer prognosis and disadvantaged and/or polluted external context, which is also linked to the second main analyzed determinant in the present study, namely the environmental pressures.

In this regard, the results of this study did not show a clear association between residence in SIN and prevalence of the above mentioned prognostic factors, and between residence in SIN and all-cause death rate. Briefly, this suggests that among the followed-up lung cancer cohort, patients who resided in SIN were supposed to have approximately the same risk of all-cause mortality compared to the patients who resided in other municipalities of the province. To evaluate how the random effect variable municipality of residence affects the association between residence and mortality, in sensitivity analysis, the model was refitted without random effects. Even in this analysis, residence in SIN was not associated with a higher death rate in patients with lung cancer (HR 0.97, 95% CrI 0.87–1.08).

These results do not seem to be consistent with what is already known in relation to the increased risk for all-cause mortality reported for women and men residing in the SIN of Taranto. In fact, the latest epidemiological studies on the resident population reported an excess relative risk for all-cause mortality of 7% (90% CI 5–9%) in women and 10% (90% CI 8–13%) in men in SIN of Taranto compared to the Apulia region for the years 2013–17 (33). A probable explanation is related to the aforementioned very low overall survival of patients with diagnosed invasive lung cancer (31). Specifically, on the one hand, we suppose that the high absolute case fatality rate in these patients is probably not significantly influenced by environmental pressures once the lung cancer has developed, and therefore, it was observed independently from their residence in SIN. On the other hand, we suggest that this high mortality rate in the lung cancer cohort could basically act as an important competing risk to the other causes of death associated with environmental pressures (e.g., cardiovascular diseases) and mask with its magnitude the excess relative risk for all-cause mortality that has been conversely reported for the general population who reside in SIN (31, 33). Besides, a lung cancer cohort is presumably largely made up of smokers or ex-smokers, and tobacco use increases mortality as well. Therefore, the selection of the cohort conditional on the diagnosis of lung cancer could also have influenced the results, preventing the adverse effect of residence in SIN on mortality from being clearly observed.

Whatever the explanations, these findings confirmed the well-known ethical questions regarding the environmental health issues in the contaminated site, as several epidemiological studies have reported an increased risk for lung cancer incidence, hospitalization, and mortality in the entire population residing in the SIN of Taranto (20, 23, 30, 31, 33, 34). In other words, even if we have not found in the present study a difference in survival related to residing in SIN in patients with diagnosed lung cancers, the development of the disease has been clearly associated with residence in SIN in the entire population. In particular, the latest epidemiological data on resident populations reported in SIN an excess relative risk (reference: Taranto Province) for lung cancer incidence of 91% (90% CI 66–120%) in

women and 26% (90% CI 16–36%) in men for the years 2015–19 (31). These data raise another point of reflection. Even if female lung cancer patients present a lower all-cause death rate compared to male patients, and even if the women in SIN present a lower absolute incidence rate for lung cancer compared to men, in the SIN of Taranto, a higher excess relative risk for lung cancer incidence was reported in women compared to men (31). This could explain why, in SIN, a higher excess relative risk (reference: Apulia Region) for lung cancer mortality in the general population for the years 2013–2017 was reported in women compared to men (25% vs. 18%) (33). As discussed above, women in our LAC/LSCC cohort also presented a higher prevalence of LAC compared to men. In this regard, it is worth pointing out the interesting finding of the seemingly higher prevalence of LAC in SIN compared to other municipalities, even if the non-effect is included in the 95% credible interval (OR 1.25, 95% CrI 0.94–1.64; given the nature of the data and models, the LAC odds ratio is the reciprocal of the LSCC odds ratio reported in Table 2). The same result was observed in the model without random effects. According to a previous meta-analysis (41), the association with particulate matter exposure was significant for LAC incidence and unclear for LSCC incidence. For these reasons, a hypothesis could be that an overall average higher population exposure to environmental pollutants in SIN could be linked to a higher prevalence of LAC.

However, since this study used an ecological variable (i.e., residence in the SIN of Taranto) to ascertain exposure to environmental pressures, this approach is potentially prone to ecological fallacy. In addition, there is a lack of specificity in the exposure assessment as the specific chemical pollutants could be varied and come from different sources in the studied region. Moreover, in addition to gender differences and the well-known pressures of a strictly environmental nature, the two municipalities of Taranto and Statte present relatively high municipality-level deprivation indexes. This metric is a regionally referenced deprivation index that uses individual data of the general population and housing census of 2011. For the calculation of the index, five conditions were chosen from the authors to best describe the multidimensional concept of social and material deprivation: low level of education, being unemployed, living on rent, living in a crowded house, and living in a single-parent family. The index was calculated as the sum of standardized indicators and is also available categorized into quintiles (42). Although the ecological-level adjustment for the deprivation index was somehow provided by including the municipality of residence in the regression models as a random effect, taking the value of the index itself into consideration with descriptive purposes can also be useful to interpret the results. Regardless, particular attention should be paid to the interpretation of this index due to its ecological-level indicator nature and because the latest available index relates to the 2011 census (42). These limits, therefore, do not guarantee that the available deprivation index represents an accurate indicator of deprivation at the individual level in the years covered by the present study.

However, it should be taken into account that gender, socioeconomic status, deprivation, and inequalities could not only exert an effect on harmful habits (e.g., cigarette smoking), health conditions, and mortality but also potentially affect the utilization of health services (42, 43). Furthermore, in this regard, the SIN corresponds almost completely to the provincial capital, Taranto, which could potentially influence access to health at territorial and hospital levels, and in terms of regional and extra-regional mobility. This is linked to another limitation of the study, which is the lack of available data about the preventive or diagnostic-therapeutic pathways followed by these patients, including information regarding their access to smoking cessation programs/services. In general, the fact that both SIN and extra-SIN municipalities belong to the same Local Health Authority, and so consequentially, the entire studied cohort could virtually access the same healthcare services, did not lead us to suppose that there could be relevant biases in relation to these aspects. However, there is the possibility that residing in the provincial capital could facilitate early cancer diagnosis due to the higher accessibility of the population to healthcare services. In the same way, residing in SIN and being conscious of the overall average higher lung cancer incidence and mortality could potentially influence access to health care services. Conversely, SIN also corresponds to an area with a high level of deprivation, a factor that could potentially exert negative effects on early diagnosis probability, therefore acting in the opposite direction with unclear overall net effects. Socioeconomic deprivation could increase the probability of tobacco use as well. In this regard, another potential limitation of the study could be the lack of information about harmful habits such as smoking or alcohol consumption. These data are unfortunately not available in cancer registries or in health records, and many other published longitudinal studies that use this kind of data lack these details (42–47). However, part of the influence of these factors may have been indirectly captured in the analysis using mixed models with random effects, which take into account the heterogeneity between patients and areas. Moreover, we expected this lack of information to not be a limitation in the strict sense, as these variables could not act as confounders, but rather as mediators between gender and residence in SIN and mortality. In a broad sense, deprivation and tobacco use could be part of a broad range of possible mediators between these factors and mortality, which could comprise socio-cultural factors, risky behaviors, diseases and treatments, and biological factors.

To summarize, as mentioned previously, the lack of information about individual-level environmental exposures, socio-cultural indicators, harmful habits, and utilization of healthcare services could represent a limitation of the present study. However, from another perspective, the same elements could also be considered starting points for what can be done in the future. Specifically, it would be interesting to update and expand upon this epidemiological study by recovering further individual-level data about specific environmental exposures (distance from the different polluting sources, exposure to airborne pollutants through dispersion models, and biomonitoring), risky behaviors (cigarette smoking, alcohol abuse, high-fat diet, and physical inactivity), gender-specific pressures and socioeconomic factors (updated indicators of deprivation at individual or census-tract level), and access to prevention programs and diagnostic-therapeutic paths (timing, place, and type of interventions).

In conclusion, the results confirmed the independent prognostic values of different lung cancer characteristics. Despite the limitations discussed above, even after adjusting for patients and disease characteristics, in the cohort of patients with invasive lung cancer, male gender appeared to be associated with a higher prevalence of poorly differentiated cancer and squamous-cell carcinoma, and with an increased death rate.

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.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

AM: Data curation, Funding acquisition, Project Administration, Resources, Supervision, Writing – review & editing. SC: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – review & editing. CG: Data curation, Writing - review & editing. MT: Data curation, Writing – review & editing. GML: Data curation, Writing – review & editing. AB: Data curation, Writing – review & editing. IR: Data curation, Methodology, Software, Validation, Writing – review & editing. LB: Data Curation, Resources, Writing – review & editing. RS: Funding acquisition, Methodology, Validation, Writing – review & editing. FA: Investigation, Validation, Writing – review & editing. SM: Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. OVG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This project receives funding and support from the CALLIOPE project (CUP: E53C22002800001) through the FSC Fund of Ministry of Enterprises and Made in Italy.

Acknowledgments

We thank all the medical doctors and healthcare professionals employed in the prevention, diagnosis, and treatment of bronchus and lung cancer in the province of Taranto. Without them, this retrospective study would not have been possible. We dedicate this work to all patients who face bronchus and lung cancer and to their families and friends.

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.

The reviewer PC declared a past co-authorship/collaboration with the author(s) AM, LB, SM to the handling editor.

Publisher's note

References

1. [WHO] World Health Organization. Cancer. (2022). Available at: https://www.who.int/news-room/fact-sheets/detail/cancer

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

3. [NCI] National Cancer Institute. Lung Cancer Prevention (PDQ®) – Health Professional Version. (2023). Available at: https://www.cancer.gov/types/lung/hp/lung-prevention-pdq (Accessed June 29, 2023).

4. [AIOM] Italian association of medical oncology. Guidelines. Lung Neoplasms. (2021). Available at: https://www.aiom.it/linee-guida-aiom-2021-neoplasie-del-polmone/ (Accessed June 29, 2023).

5. Yasukawa M, Sawabata N, Kawaguchi T, Kawai N, Nakai T, Ohbayashi C, et al. Histological grade: analysis of prognosis of non-small cell lung Cancer after complete resection. *In Vivo*. (2018) 32:1505–12. doi: 10.21873/invivo.11407

6. [NCI] National Cancer Institute. Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version. (2023). Available at: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq (Accessed June 29, 2023).

7. [NCI] National Cancer Institute. Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version. (2023). Available at: https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq (Accessed June 29, 2023).

8. Yang L, Wang S, Gerber DE, Zhou Y, Xu F, Liu J, et al. Main bronchus location is a predictor for metastasis and prognosis in lung adenocarcinoma: a large cohort analysis. *Lung Cancer*. (2018) 120:22–6. doi: 10.1016/j.lungcan.2018.03.011

9. McWilliam A, Vasquez Osorio E, Faivre-Finn C, van Herk M. Influence of tumour laterality on patient survival in non-small cell lung cancer after radiotherapy. *Radiother Oncol*. (2019) 137:71–6. doi: 10.1016/j.radonc.2019.04.022

10. [NCI] National Cancer Institute. NCI Dictionary of Cancer Terms. TNM staging system. (n.d.). Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tnm-staging-system (Accessed June 29, 2023).

11. [NCI] National Cancer Institute. Cancer Staging. (2022). Available at: https://www.cancer.gov/about-cancer/diagnosis-staging/staging (Accessed June 29, 2023).

12. Feng SH, Yang ST. The new 8th TNM staging system of lung cancer and its potential imaging interpretation pitfalls and limitations with CT image demonstrations. *Diagn Interv Radiol*. (2019) 25:270–9. doi: 10.5152/dir.2019.18458

13. [NCI] National Cancer Institute. Code for Histologic grading and differentiation. (n.d.). Available at: https://training.seer.cancer.gov/coding/guidelines/rule_g.html (Accessed June 29, 2023).

14. Yu XQ, Yap ML, Cheng ES, Ngo PJ, Vaneckova P, Karikios D. Evaluating Prognistic Factors for Sex Differences in Lung Cancer Survival: Findings from a Large Australian Cohort. *J Thorac Oncol*. (2022) 17:688–99. doi: 10.1016/j.jtho.2022.01.016

15. Ragavan M, Patel MI. The evolving landscape of sex-based differences in lung cancer: a distinct disease in women. *Eur Respir Rev*. (2022) 31:210100. doi: 10.1183/16000617.0100-2021

16. Sagerup CM, Småstuen M, Johannesen TB, Helland Å, Brustugun OT. Sex-specific trends in lung cancer incidence and survival: a population study of 40,118 cases. *Thorax*. (2011) 66:301–7. doi: 10.1136/thx.2010.151621

17. [IARC] International Agency for Research on Cancer. Outdoor Air Pollution. IARC monographs on the evaluation of carcinogenic risks to humans; volume 109. (2015). Available at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Outdoor-Air-Pollution-2015 (Accessed June 26, 2023).

18. [EEA] European Environment Agency. Air pollution. (2022). Available at: https://www.eea.europa.eu/publications/environmental-burden-of-cancer/air-pollution

19. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis. *Environ Int*. (2020) 143:105974. doi: 10.1016/j.envint.2020.105974

20. Alessandrini ER, Leogrande S, Morabito A, Ancona C, Assennato G, Giua R, et al. Studio di coorte sugli effetti delle esposizioni ambientali ed occupazionali sulla morbosità e mortalità della popolazione residente a Taranto. (2016). Available at: https://www.sanita.puglia.it/documents/890301/896208/Relazione+Finale+Studio+di+Coorte+-+2016/ea231c81-e196-4b43-99a4-0882bd60b83b (Accessed November 5, 2023).

21. Bustaffa E, Minichilli F, Andreassi MG, Carone S, Coi A, Cori L, et al. Studi su marcatori di esposizione ed effetto precoce in aree con inquinamento da arsenico: metodi e risultati del progetto SEpiAs. Sorveglianza epidemiologica in aree interessate da inquinamento ambientale da arsenico di origine naturale o antropica (SEpiAS CCM 2010) [studies on markers of exposure and early effect in areas with arsenic pollution: methods and results of the project SEpiAs. Epidemiological surveillance in areas with environmental pollution by natural or anthropogenic arsenic]. *Epidemiol Prev*. (2014) 38:27–94.

22. Comba P, Pirastu R, Conti S, De Santis M, Iavarone I, Marsili G, et al. Ambiente e salute a Taranto: studi epidemiologici e indicazioni di sanità pubblica [environment and health in Taranto, Southern Italy: epidemiological studies and public health recommendations]. *Epidemiol Prev*. (2012) 36:305–20.

23. Galise I, Serinelli M, Morabito A, Pastore T, Tanzarella A, Laghezza V, et al. L'impatto ambientale e sanitario delle emissioni dell'impianto siderurgico di Taranto e della centrale termoelettrica di Brindisi [The integrated environmental health impact of emissions from a steel plant in Taranto and from a power plant in Brindisi, (Apulia region, Southern Italy)]. *Epidemiol Prev*. (2019) 43:329–37. doi: 10.19191/EP19.5-6.P329.102

24. Giannico OV, Baldacci S, Basile FC, Pellegrino A, Desiante F, Franco E, et al. PCDD/Fs and PCBs in hen eggs from a contaminated area in Italy: a 9 years spatio-temporal monitoring study. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. (2023) 40:294–04. doi: 10.1080/19440049.2022.2157051

25. Giannico OV, Baldacci S, Desiante F, Basile FC, Franco E, Fragnelli GR, et al. PCDD/Fs and PCBs in *Mytilus galloprovincialis* from a contaminated area in Italy: the role of mussel size, temperature and meteorological factors. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. (2022) 39:1123–35. doi: 10.1080/19440049.2022.2059108

26. Giannico OV, Fragnelli GR, Baldacci S, Desiante F, Pellegrino A, Basile FC, et al. Dioxins and PCBs contamination in milk and dairy products from province of Taranto (Puglia Region, Southern Italy): a six years spatio-temporal monitoring study. *Ann Ist Super Sanita*. (2021) 57:233–8. doi: 10.4415/ANN_21_03_06

27. Giannico OV, Desiante F, Basile FC, Franco E, Baldacci S, Fragnelli GR, et al. Dioxins and PCBs contamination in mussels from Taranto (Ionian Sea, Southern Italy): a seven years spatio-temporal monitoring study. *Ann Ist Super Sanita*. (2020) 56:452–61. doi: 10.4415/ANN_20_04_07

28. Iavarone I, De Felip E, Ingelido AM, Iacovella N, Abballe A, Valentini S. Exploratory biomonitoring study among workers of livestock farms of the Taranto Province. *Epidemiol Prev*. (2012) 36:321–31.

29. Ingelido AM, Abate V, Abballe A, Albano FL, Battista T, Carraro V, et al. Concentrations of polychlorinated dibenzodioxins, polychlorodibenzofurans, and polychlorobiphenyls in women of reproductive age in Italy: a human biomonitoring study. *Int J Hyg Environ Health*. (2017) 220:378–86. doi: 10.1016/j.ijheh.2016.11.009

30. Leogrande S, Alessandrini ER, Stafoggia M, Morabito A, Nocioni A, Ancona C, et al. Industrial air pollution and mortality in the Taranto area, Southern Italy: a difference-in-differences approach. *Environ Int*. (2019) 132:105030. doi: 10.1016/j.envint.2019.105030

31. Minerba S, Mincuzzi A, Bruni A, Carone S, Galluzzo C, Lagravinese GM, et al. *ASL Taranto*, AReSS Puglia. Rapporto sui tumori ASL di Taranto (2021). Available at: https://www.sanita.puglia.it/documents/36057/232392045/2021+Report+Registro+Tumori+-+anni+2015-2019.pdf/3439fd81-2943-49a5-87e2-810ba83326ff (Accessed November 5, 2023).

32. Pirastu R, Comba P, Iavarone I, Zona A, Conti S, Minelli G, et al. Environment and health in contaminated sites: the case of Taranto, Italy. *J Environ Public Health*. (2013):753719. doi: 10.1155/2013/753719

33. Zona A, Fazzo L, Benedetti M, Bruno C, Vecchi S, Pasetto R, et al. SENTIERI - Studio epidemiologico nazionale dei territori e degli insediamenti esposti a rischio da inquinamento. Sesto Rapporto [SENTIERI - Epidemiological Study of Residents in National Priority Contaminated Sites. Sixth Report]. *Epidemiol Prev*. (2023) 47:1–286. doi: 10.19191/EP23.1-2-S1.003

34. Zona A, Iavarone I, Buzzoni C, Conti S, Santoro M, Fazzo L, et al. SENTIERI: Studio epidemiologico nazionale dei territori e degli insediamenti esposti a rischio da inquinamento. Quinto Rapporto [SENTIERI: Epidemiological Study of Residents in National Priority Contaminated Sites. Fifth Report]. *Epidemiol Prev*. (2019) 43:1–208. doi: 10.19191/EP19.2-3.S1.032

35. [ISTAT] National Institute of Statistics. Demo. Demography in numbers. (2023). Available at: https://demo.istat.it/ (Accessed July 5, 2023).

36. R-INLA. Cox proportional hazards model. (2023). Available at: https://inla.r-inla-download.org/r-inla.org/doc/likelihood/coxph.pdf (Accessed March 25, 2023).

37. Rue H, Riebler A, Sørbye SH, Illian JB, Simpson DP, Lindgren FK. Bayesian computing with INLA: a review. *Annu Rev Statist Appl*. (2017) 4:395–21. doi: 10.1146/annurev-statistics-060116-054045

38. Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent gaussian models by using integrated nested Laplace approximations. *J R Statis Soc Ser B*. (2009) 71:319–92. doi: 10.1111/j.1467-9868.2008.00700.x

39. Wang X, Yue YR, Faraway JJ. *Bayesian regression Modeling with INLA*. *1st* ed. Boca Raton: Chapman and Hall/CRC. (2018). doi: 10.1201/9781351165761

40. Martino S, Akerkar R, Rue H. Approximate Bayesian inference for survival models. *Scand J Stat*. (2011) 38:514–28. doi: 10.1111/j.1467-9469.2010.00715.x

41. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European study of cohorts for air pollution effects (ESCAPE). *Lancet Oncol*. (2013) 14:813–22. doi: 10.1016/S1470-2045(13)70279-1

42. Rosano A, Pacelli B, Zengarini N, Costa G, Cislaghi C, Caranci N. Aggiornamento e revisione dell'indice di deprivazione italiano 2011 a livello di sezione di censimento [Update and review of the 2011 Italian deprivation index calculated at the census section level]. *Epidemiol Prev*. (2020) 44:162–70. doi: 10.19191/EP20.2-3.P162.039

43. Carstairs V. Deprivation indices: their interpretation and use in relation to health. *J Epidemiol Community Health*. (1995) 49:S3–8. doi: 10.1136/jech.49.suppl_2.s3

44. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. (2018) 391:1023–75. doi: 10.1016/S0140-6736(17)33326-3

45. Dal Maso L, Panato C, Guzzinati S, Serraino D, Francisci S, Botta L. Prognosis and cure of long-term cancer survivors: a population-based estimation. *Cancer Med*. (2019) 8:4497–507. doi: 10.1002/cam4.2276

46. Coviello V, Buzzoni C, Fusco M, Barchielli A, Cuccaro F, De Angelis R, et al. Survival of cancer patients in Italy. *Epidemiol Prev*. (2017) 41:1–244. doi: 10.19191/EP17.2S1.P001.017

47. Giannico OV, Carone S, Tanzarella M, Galluzzo C, Bruni A, Lagravinese GM, et al. Environmental pressures, tumor characteristics, and death rate in a female breast cancer cohort: a seven-years Bayesian survival analysis using cancer registry data from a contaminated area in Italy. *Front Public Health*. (2023) 11:1310823. doi: 10.3389/fpubh.2023.1310823

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 09 February 2024
DOI 10.3389/fpubh.2024.1319977

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Priyanka Sharma,
Rutgers,
The State University of New Jersey,
United States
Nidhi Kumari,
University of California, Los Angeles,
United States

*CORRESPONDENCE
Ming-sheng Fu
✉ fumingsheng@fudan.edu.cn
Qin-cong Pan
✉ panqincong@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 01 November 2023
ACCEPTED 22 January 2024
PUBLISHED 09 February 2024

CITATION
Fu M-s, Pan S-x, Cai X-q and Pan Q-c (2024) Urban vs. rural: colorectal cancer survival and prognostic disparities from 2000 to 2019. *Front. Public Health* 12:1319977. doi: 10.3389/fpubh.2024.1319977

Urban vs. rural: colorectal cancer survival and prognostic disparities from 2000 to 2019

Ming-sheng Fu[1]*, Shu-xian Pan[2†], Xun-quan Cai[1†] and Qin-cong Pan[1]*

[1]Department of Gastroenterology, Shanghai Fifth People's Hospital Fudan University, Shanghai, China, [2]Department of Anesthesiology, Shanghai Fifth People's Hospital Fudan University, Shanghai, China

This study aimed to analyze the differences in colorectal cancer (CRC) survival between urban and rural areas over the past 20 years, as well as investigate potential prognostic factors for CRC survival in both populations. Using registry data from Surveillance, Epidemiology, and End Results (SEER) from 2000 to 2019, 463,827 CRC cases were identified, with 85.8% in urban and 14.2% in rural areas. The mortality of CRC surpassed its survival rate by the sixth year after diagnosis in urban areas and the fifth year in rural areas. Furthermore, the 5-year overall survival (OS) of CRC increased by 2.9–4.3 percentage points in urban and 0.6–1.5 percentage points in rural areas over the past two decades. Multivariable Cox regression models identified independent prognostic factors for OS and disease-specific survival (DSS) of CRC in urban and rural areas, including age over 40, Black ethnicity, and tumor size greater than 5 cm. In addition, household income below $75,000 was found to be an independent prognostic factor for OS and DSS of CRC in urban areas, while income below $55,000 was a significant factor for rural areas. In conclusion, this study found a notable difference in CRC survival between rural and urban areas. Independent prognostic factors shared among both rural and urban areas include age, tumor size, and race, while household income seem to be area-specific predictive variables. Collaboration between healthcare providers, patients, and communities to improve awareness and early detection of CRC may help to further advance survival rates.

KEYWORDS

colorectal cancer, survival, prognostic, urban-rural, surveillance, epidemiology, end results

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, the incidence of CRC in China is rising continuously in recent years (1). In the United States, CRC is the third most commonly diagnosed cancer and the third most common cause of cancer-related death. In 2023, It has been estimated that 106,970 cases of colon cancer and 46,050 cases of rectal cancer will be newly diagnosed in the US, and a total of 52,550 people will die from these cancers (2). We know that the risk factors that can change CRC mortality include smoking, an unhealthy diet, high alcohol consumption, lack of exercise, and overweight. In addition, regular screening, monitoring and high-quality treatment can reduce the incidence rate and mortality of CRC (3). Although the prognosis of colorectal cancer has improved over the years due to advances in diagnosis and treatment options, the mortality rate of colorectal cancer has decreased significantly since 1975 (4). However, to date, no study has compared CRC survival and prognosis trends between urban and rural areas over the past two decades, the differences

in CRC survival between urban and rural areas over the past 20 years is unclear, and the potential prognostic factors for CRC survival in urban and rural areas is unclear. To address this gap, by evaluating CRC survival data, we aimed to investigate differences in survival and prognosis between the urban and rural populations from 2000 to 2019, and investigate potential prognostic factors for CRC survival in both populations.

The objective of this study is to present an analysis of the prognostic patterns of CRC in both urban and rural regions over the past two decades, as well as exploring possible factors that could impact CRC survival rates in each location. Such findings could be vital in highlighting divergences existing in screening and treatment methods for CRC patients in urban and rural areas, ultimately helping in creating equitable access to quality cancer care, regardless of where a patient resides.

Materials and methods

Data source

The Surveillance, Epidemiology, and End Results (SEER) database, established by the National Cancer Institute (NCI), was utilized to gather patient records encompassing clinicopathological information such as occurrence, treatment, and survival data for various tumors. For this study, the SEER*Stat software (version 8.4.0.1) was implemented to obtain data from the "Incidence-SEER Research Data, 17 Registries, Nov 2021 Sub (2000–2019)" database.

Patients

Patients who were diagnosed with CRC from 2000 to 2019 were screened out from the database. Patients whom we selected met the following conditions: {Site and Morphology. Site recode ICD-O-3/WHO 2008} = "Colon and Rectum", and {Race, Sex, Year Dx. Year of diagnosis} = "2000–2019", and {Site and Morphology.ICD-O-3 Hist/behav} = "8140/3: Adenocarcinoma, NOS", and {Site and Morphology. Diagnostic Confirmation} = "Positive histology", and excluded race recode "Unknown" cases and Survival months "Unknown" cases, Finally, 463,827 colorectal adenocarcinoma cases were included in the study.

Study variables

Clinical variables including age (<40 years; 40-64 years; ≧65 years), sex (male and female), race (White W; Black B; American Indian/Alaska Native AI; Asian or Pacific Islander API), year of diagnosis (2000–2019), primary site [rectum includes rectum and rectum colon junction (RRSJ); left colon includes sigmoid colon, descending colon and splenic flexure of colon (SDS); right colon includes transverse colon, ascending colon, hepatic flexure of colon (TAH) and cecum, Appendix (CA)], stage (0, I; II; III; IV; Unknown), tumor size (<5 cm and ≧5 cm), median household income (>$75,000; $55,000–$75,000; $35,000–$55,000; <$35,000), rural (Adjacent to a metropolitan; Not adjacent to a metropolitan)-urban (1 million pop, 250,000 to 1 million pop, 250 thousand pop), Status (Alive and Dead), Cause-specific death (Dead of this cancer; Dead of other cause) were used in the current study. AJCC stage 3rd edition (1988–2003) is applicable to the stage of diagnosing CRC in 2000–2003, Derived AJCC Stage Group, 6th ed. (2004–2015) is applicable to the stage of diagnosing CRC in 2004–2015, Derived SEER Cmb Stg Grp (2016–2017) is applicable to the stage of diagnosing CRC in 2016–2017, and Derived EOD 2018 Stage Group (2018+) is applicable to the stage of diagnosing CRC in 2018–2019. EOD 10-size (1988–2003) is applicable to the Tumor size of CRC diagnosed in 2000–2003, CS Tumor size (2004–2015) is applicable to the Tumor size of CRC diagnosed in 2004–2015, and Tumor Size Summary (2016+) is applicable to the Tumor size of CRC diagnosed in 2016-2019. Both overall survival (OS) and disease-specific survival (DSS) were used to analyze the survival outcomes.

Statistical analysis

The study used descriptive statistics to summarize demographic information and performed a chi-square test to compare categorical variables between urban and rural cases as baseline clinical characteristics. The SEER cause-specific death classification was utilized to determine the time at which patients who died from cancer were censored for DSS analyses, while patients who died from any cause were also censored for OS analyses. Using Kaplan–Meier for survival analysis. GraphPad Prism 8 (GraphPad Software, La Jolla, CA, United States) survival curves were employed to analyze both OS and DSS, and these were compared using the Log-rank (Mantel-Cox) test. Moreover, the study utilized univariate and multivariable Cox proportional hazards regression models to analyze the prognostic factors of OS and DSS for CRC.

The SEER Stat (National Cancer Institute, Bethesda, MD, United States; version 8.4.0.1) was used to download data in this study. Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, United States). All analyses were double-sided, and a p value < 0.05 was deemed statistically significant.

Results

Distribution of CRC in urban and rural areas

The study analyzed a total of 463,827 cases of colorectal cancer (CRC) between 2000 and 2019, with 85.8% being reported in urban areas and 14.2% in rural areas. In the past two decades, the proportion of CRC diagnosed before the age of 40 was slightly

Abbreviations: CRC, Colorectal cancer; SEER, Surveillance, epidemiology, and end results; OS, Overall survival; DSS, Disease-specific survival; NCI, National Cancer Institute; W, White; B, Black; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; RRSJ, Rectum includes rectum and rectosigmoid junction; SDS, Left colon includes sigmoid colon, descending colon and splenic flexure of colon; TAH, Right colon includes transverse colon, ascending colon, hepatic flexure of colon; CA, Cecum, appendix; AJCC, The American Joint Committee on Cancer; SPSS, Statistical product and service solutions.

higher 0.7 percentage points in urban areas than in rural areas. Conversely, the proportion of CRC aged 65 or older was found to be 1.4 percentage points higher in rural areas than in urban areas. The proportion of women with CRC was higher 1.4 percentage points in urban areas compared to rural areas. When examining racial demographics, Black and Asian or Pacific Islander populations were, respectively, found to be higher 2.6 and 6.0 percentage points in urban areas as compared to rural areas. On the other hand, White and American Indian populations were found to be higher 7.5 and 2.1 percentage points in rural areas respectively, compared to urban areas.

Regarding clinical findings, the proportion of CRC cases diagnosed at stage III and stage IV was higher 1.6 percentage points in urban areas than in rural areas. Additionally, the proportion of tumors less than 5 cm in size was higher 0.8 percentage points in urban areas compared to rural areas. In terms of household income, 85% of households with incomes over $55,000 were located in urban areas compared to only 24.2% in rural areas. Finally, the total mortality rate of CRC was found to be higher 3.5 percentage points in rural areas compared to urban areas, while CRC-specific mortality rates were higher 1.9 percentage points in rural areas compared to urban areas (as shown in Table 1).

Kaplan–Meier survival analysis

The Kaplan Meier survival analysis revealed that the median survival months for CRC were higher in urban areas compared to

TABLE 1 Comparison between urban and rural areas.

Variable		Urban		Rural		X^2	*p*-value
		N (%)		*N* (%)			
Age	5–39 years	10,231	2.6%	1,234	1.9%	139.18	<0.0001
	40–64 years	146,274	36.8%	23,716	36.0%		
	≧65 years	241,458	60.7%	40,914	62.1%		
Sex	Female	189,501	47.6%	30,404	46.2%	48.05	<0.0001
	Male	208,462	52.4%	35,460	53.8%		
Race	White	314,470	79.0%	57,003	86.5%	7258.95	<0.0001
	Black	44,634	11.2%	5,685	8.6%		
	AI	1,765	0.4%	1,635	2.5%		
	API	37,094	9.3%	1,541	2.3%		
Primary site	RRSJ	116,198	29.2%	19,180	29.1%	9.59	0.022
	SDS	121,001	30.4%	19,760	30.0%		
	TAH	97,943	24.6%	16,249	24.7%		
	CA	62,821	15.8%	10,675	16.2%		
Stage	0	4,363	1.1%	793	1.2%	76.26	<0.0001
	I	66,039	16.6%	11,370	17.3%		
	II	109,285	27.5%	18,204	27.6%		
	III	109,385	27.5%	17,469	26.5%		
	IV	83,142	20.9%	13,397	20.3%		
	Unknown	25,749	6.5%	4,631	7.0%		
Tumor size	<5 cm	189,160	47.5%	30,740	46.7%	16.77	<0.0001
	≧5 cm	208,803	52.5%	35,124	53.3%		
Median household income	>$75,000	140,550	35.3%	2,937	4.5%	138121.15	<0.0001
	$55,000–$75,000	200,471	50.4%	12,996	19.7%		
	$35,000–$55,000	56,522	14.2%	42,329	64.3%		
	<$35,000	420	0.1%	7,602	11.5%		
Status	Dead	229,987	57.8%	40,384	61.3%	288.52	<0.0001
	Alive	167,976	42.2%	25,480	38.7%		
Cause-specific death	Dead of this cancer	143,244	36.0%	24,938	37.9%	292.82	<0.0001
	Dead of other cause	86,743	21.8%	15,446	23.5%		
	Alive	167,976	42.2%	25,480	38.7%		

AI, American Indian/Alaska Native; API, Asian or Pacific Islander; RRSJ, Rectum, Rectosigmoid junction; SDS, Sigmoid, Descending, Splenic flexure of colon; TAH, Transverse, Ascending, Hepatic flexure of colon; CA, Cecum, Appendix.

TABLE 2 Kaplan–Meier survival analysis.

Variable		Urban	Rural	X^2	*p*-value
		Median survival months (95% CI)	Median survival months (95% CI)		
Age	5–39 years	142.64 (140.31–144.97)	138.24 (131.69–144.80)	28398.51	<0.0001
	40–64 years	131.10 (130.50–131.70)	122.40 (120.97–123.84)		
	≧65 years	74.87 (74.52–75.23)	72.56 (71.73–73.39)		
Sex	Female	97.50 (97.03–97.98)	93.75 (92.60–94.90)	92.28	<0.0001
	Male	94.42 (93.97–94.87)	88.49 (87.45–89.53)		
Race	White	95.25 (94.89–95.61)	91.47 (90.64–92.29)	1299.20	<0.0001
	Black	87.83 (86.85–88.81)	82.81 (80.19–85.430)		
	AI	101.27 (95.93–106.61)	96.39 (91.09–101.70)		
	API	112.46 (111.28–11,364)	96.25 (91.19–101.31)		
Primary site	RRSJ	101.25 (100.63–101.88)	94.96 (93.51–96.42)	909.28	<0.0001
	SDS	97.22 (96.62–97.82)	91.18 (89.77–92.59)		
	TAH	93.14 (92.50–93.79)	89.48 (87.95–91.00)		
	CA	87.96 (87.17–88.74)	85.37 (83.52–87.22)		
Stage	0	123.94 (120.48–127.40)	113.07 (105.34–120.80)	134540.85	<0.0001
	I	132.99 (132.18–133.82)	124.42 (122.50–126.34)		
	II	118.04 (117.42–118.65)	113.06 (111.61–114.51)		
	III	109.08 (108.43–109.72)	102.23 (100.69–103.77)		
	IV	28.75 (28.36–29.15)	26.26 (25.35–27.16)		
	Unknown	60.12 (59.01–61.23)	62.20 (59.67–63.74)		
Tumor size	<5 cm	110.74 (110.26–111.22)	104.99 (103.85–106.13)	11972.86	<0.0001
	≧5 cm	82.34 (81.90–8,278)	78.49 (77.47–79.52)		
Median household income	>$75,000	99.96 (99.40–100.51)	95.98 (92.32–99.63)	418.96	<0.0001
	$55,000–$75,000	94.14 (93.68–94.59)	93.68 (91.97–95.39)		
	$35,000–$55,000	91.87 (90.98–92.76)	90.23 (89.27–91.18)		
	<$35,000	79.16 (71.53–86.80)	88.17 (85.72–90.60)		

rural areas. The median survival of age groups of less than 40, 40–64 and over 65 in urban areas had a higher 8.7 months, 4.4 months, and 2.3 months respectively, when compared to their rural counterparts. When analyzing the effect of household income on CRC's prognosis, The median survival of household earning more than $75,000 *per annum* had a higher 4 months in urban compared rural. Conversely, the median survival of those earning less than $35,000 annually had a lower 9 months in urban when compared to their rural counterparts (as shown in Table 2).

Comparison of the OS and DSS of CRC between urban and rural areas in 20 years

The research results show that in urban and rural areas, CRC patients under 40 years old have the worst OS, while CRC patients over 65 years old have the worst DSS. The OS of male CRC patients in urban areas is worse than that of female patients, while there is no significant difference in OS between male and female patients in rural areas. Whether in urban or rural areas, the DSS of female CRC patients is slightly lower than that of male patients, while the OS and DSS of black and family income below $35,000 CRC patients are the lowest (as shown in Figures 1, 2).

The primary site of cancer also played a significant role in survival outcomes. For instance, CRC patients diagnosed with primary site Rectum and Cecum and Appendix in urban areas had the worst OS, those with primary site Right colon and Cecum and Appendix had the worst DSS. Patients identified as Stage IV and Stage Unknown had significantly reduced OS and DSS. Interestingly, patients with tumors larger than 5 cm demonstrated significantly reduced OS and DSS rates in both urban and rural settings. Notably, the OS of urban CRC patients is slightly lower than that of rural patients, while, there was no significant difference in DSS between urban and rural CRC patients (as shown in Figures 3, 4).

Independent prognostic factors for OS and DSS of CRC

This study conducted a Cox proportional hazard model to analyze the risk factors associated with the survival of CRC

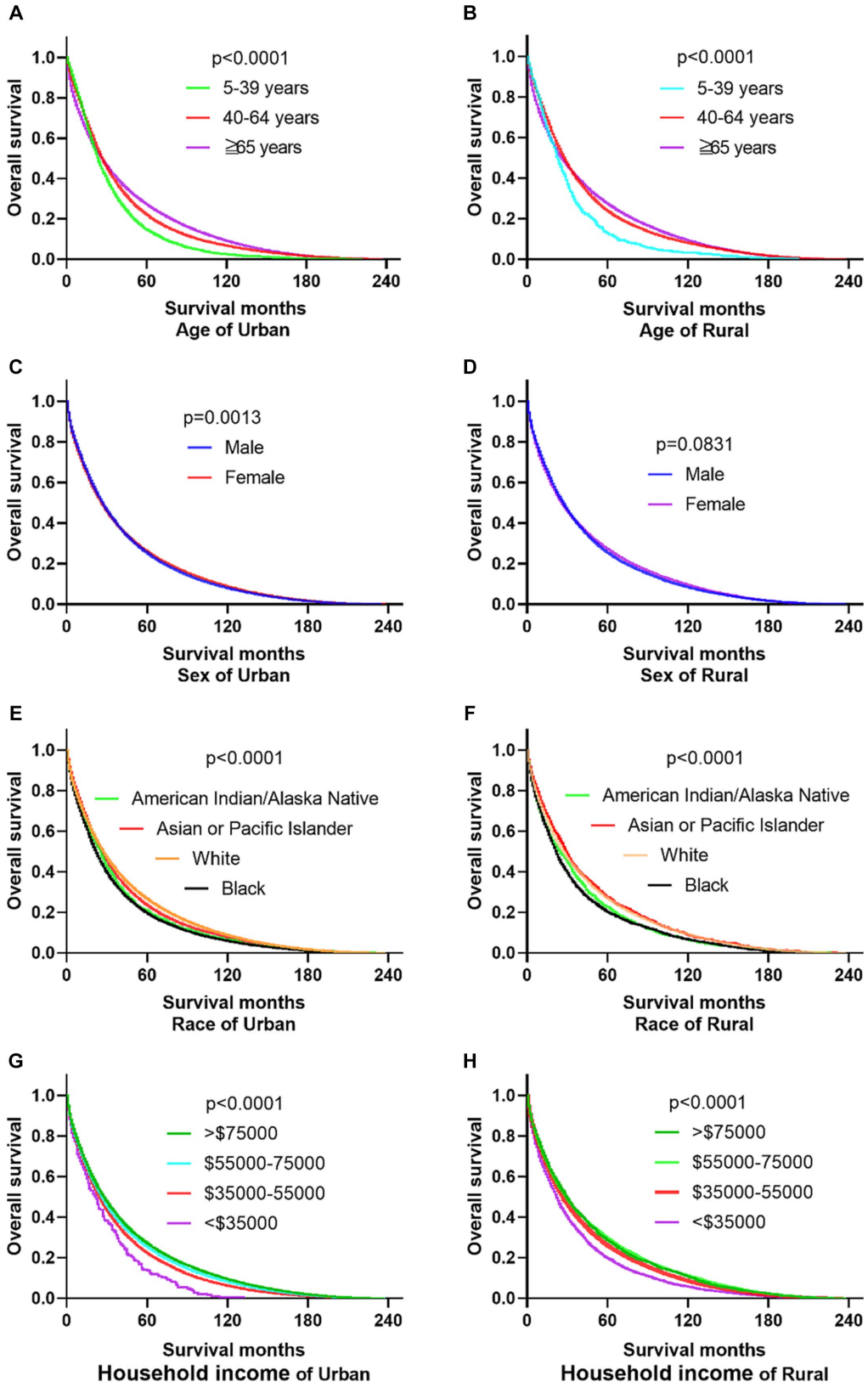


FIGURE 1
Comparative OS of CRC: age, sex, race, and household income factors in urban and rural areas. **(A,B)** In urban and rural areas, CRC patients under the age of 40 have the worst OS. **(C,D)** The OS of male CRC patients in urban areas is worse than that of female patients, while there is no significant difference OS between male and female patients in rural areas. **(E,F)** Black CRC patients have the lowest OS in urban and rural areas. **(G,H)** CRC patients with incomes exceeding $75,000 in urban and rural households have the highest OS, while CRC patients with incomes below $35,000 have the lowest OS.

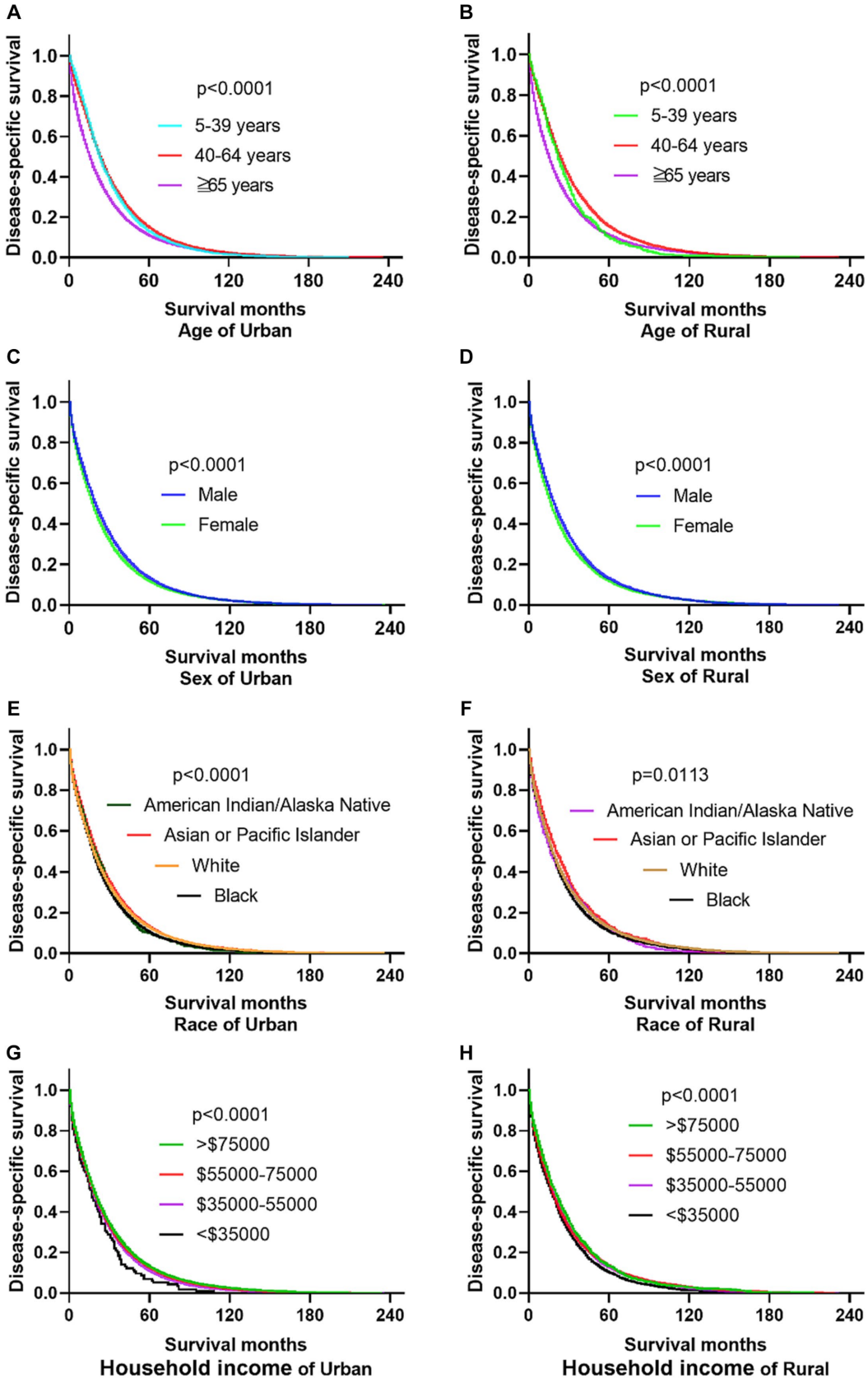


FIGURE 2
Comparative DSS of CRC: age, gender, ethnicity, and income factors in urban and rural areas. **(A,B)** Urban and rural CRC patients over 65 years old have the worst DSS. **(C,D)** The DSS of CRC women in urban and rural areas is lower than that of men. **(E,F)** The DSS of black people in urban and rural areas is the lowest. **(G,H)** CRC patients with households incomes below $35,000 in urban and rural have the lowest DSS.

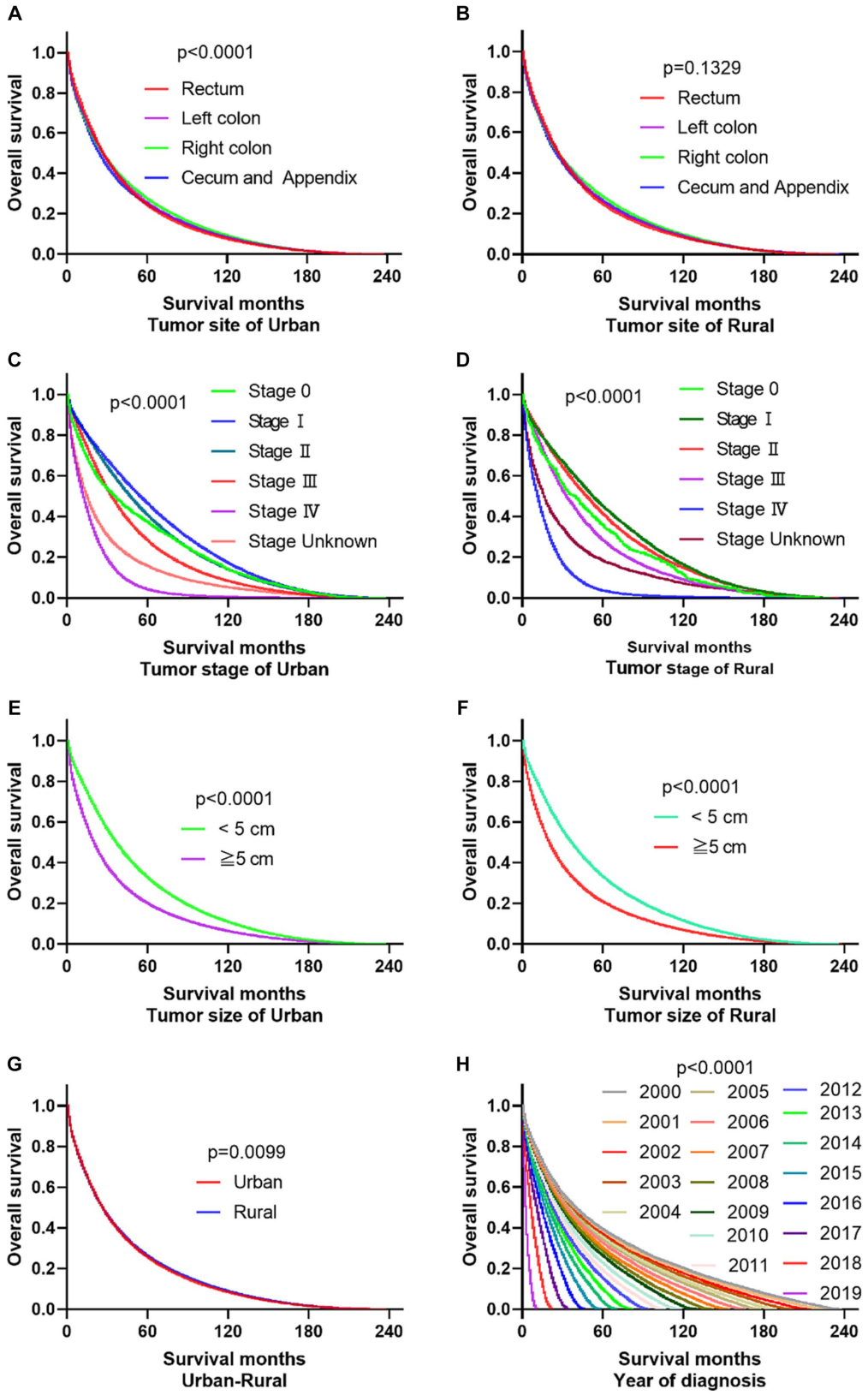


FIGURE 3
Comparative OS of CRC: primary site, stage, tumor size, urban–rural and year of diagnosis. **(A,B)** The OS of CRC patients with primary site Rectum and Cecum and Appendix was the worst in urban, it is not significantly different compared the primary site in rural. **(C,D)** Whether in urban or rural, the OS of CRC patients in Stage IV and Stage Unknown were significantly reduced. **(E,F)** No matter in urban or rural, the OS of CRC patients with tumors over 5 cm was significantly reduced. **(G)** The OS of urban CRC patients is slightly lower than that of rural patients. **(H)** Comparison of OS in CRC patients diagnosed in urban and rural areas from 2000 to 2019.

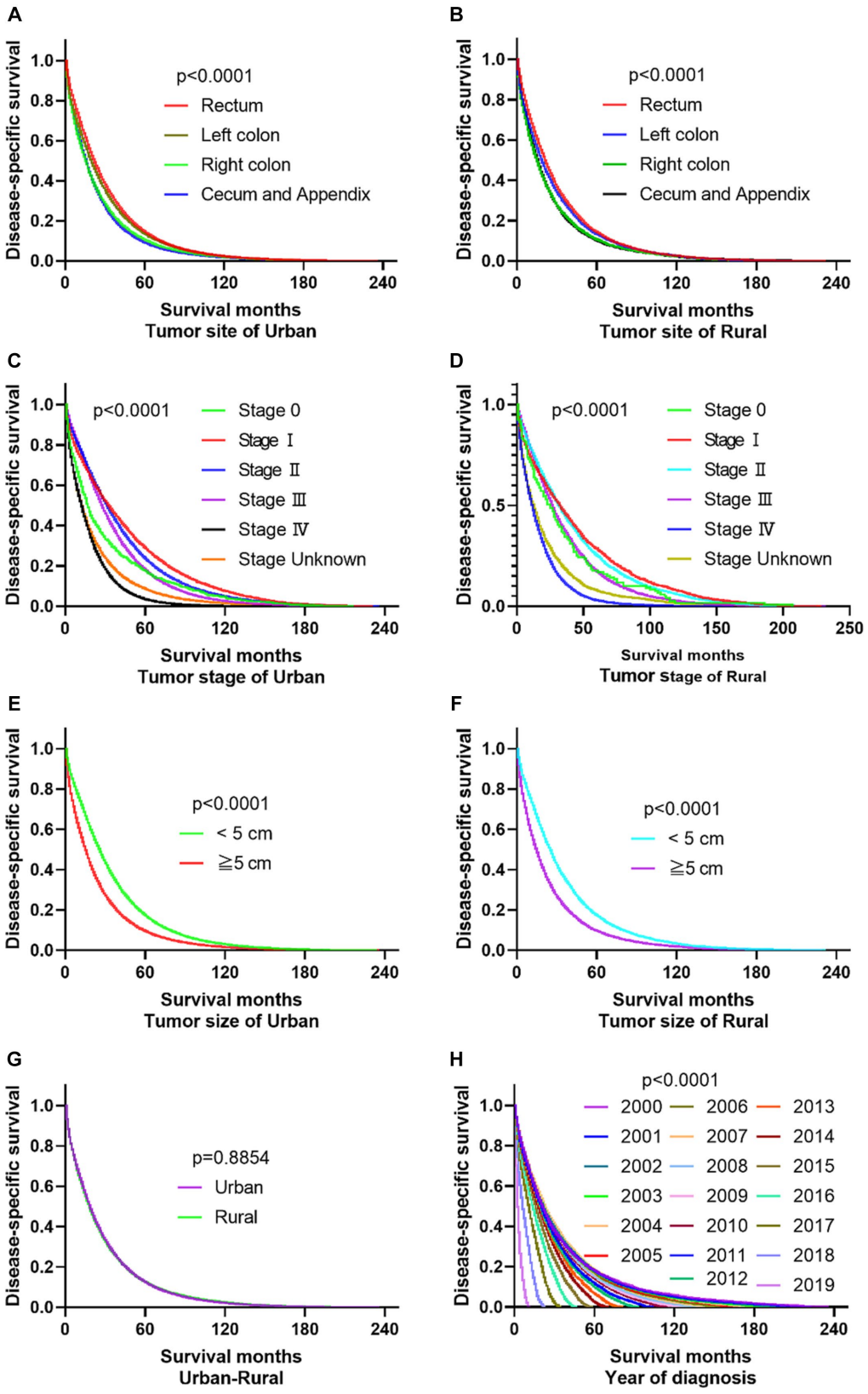


FIGURE 4
Comparative DSS of CRC: Primary Site, Stage, Tumor Size, Urban–Rural and year of diagnosis. **(A,B)** The DSS of CRC patients with primary site Right colon and Cecum and Appendix was the worst in urban and rural. **(C,D)** No matter in urban or rural, the DSS of CRC patients in Stage IV and Stage Unknown were significantly reduced. **(E,F)** The DSS of CRC patients with tumors over 5 cm was significantly reduced. **(G)** There was no significant difference in DSS between urban and rural CRC patients. **(H)** Comparison of DSS in CRC patients diagnosed in urban and rural areas from 2000 to 2019.

patients. Univariate analysis showed that several variables significantly impacted the risk of death for CRC patients. These included age over 65 years old, male gender, Black race, tumor location (ileocecal tumors had the worst prognosis compared to rectum), tumor stage (stage III, IV, and unknown), and tumor size (tumors over 5 cm had a higher risk of death). In addition, the study found that household income also had a significant impact on CRC survival, with those earning less than $55,000 having a decreased survival rate. The rural–urban divide was also examined, and it was found that the survival of CRC in rural areas was slightly lower than that in urban areas (as shown in Tables 3, 4).

Upon conducting multivariate analysis, it was found that age over 40 years, male gender, Black race, right colon tumor location, stage III or IV, and tumors over 5 cm were independent prognostic factors for OS in both urban and rural settings. Age over 40 years, Black race, and tumors over 5 cm were identified as independent prognostic factors for DSS. Household income also played a role, as income less than $75,000 and less than $55,000 were independent prognostic factors for OS and DSS of CRC in urban and rural areas, respectively (as shown in Tables 5, 6).

Trends changes of CRC cases, survival and mortality in urban and rural areas in 20 years

The registration of CRC cases remained stable in both rural and urban areas between 2000 and 2017 but significantly increased from 2018 to 2019. In urban areas, the mortality and survival rates for CRC reached a balance in the sixth year after diagnosis, meaning that during the first 6 years after diagnosis, survival was higher than mortality, but after that, mortality exceeded survival. On the other hand, in rural areas, the mortality and survival rates reached a balance in the fifth year after diagnosis. Looking at the overall survival and mortality rates, CRC patients in urban areas had higher survival rates compared to those living in rural areas, while those living in rural

TABLE 3 Univariate analysis of overall survival using Cox proportional hazards models.

Variable		*N*	HR	95% CI	*p*-value
Age	5–39 years	11,465	REF		
	40–64 years	169,990	1.152	1.117–1.189	<0.0001
	≧65 years	282,372	2.305	2.236–2.376	<0.0001
Sex	Female	219,905	REF		
	Male	243,922	1.038	1.030–1.046	<0.0001
Race	White	371,473	REF		
	Black	50,319	1.127	1.127–1.141	<0.0001
	AI	3,400	0.957	0.914–1.002	0.059
	API	38,635	0.807	0.807–0.819	<0.0001
Primary site	RRSJ	135,378	REF		
	SDS	140,761	1.068	1.058–1.079	<0.0001
	TAH	114,192	1.107	1.096–1.119	<0.0001
	CA	73,496	1.186	1.173–1.200	<0.0001
Stage	0	5,156	REF		
	I	77,409	0.855	0.818–0.893	<0.0001
	II	127,489	1.045	1.001–1.091	0.046
	III	126,854	1.209	1.158–1.263	<0.0001
	IV	96,539	4.708	4.510–4.915	<0.0001
	Unknown	30,380	2.544	2.433–2.660	<0.0001
Tumor size	<5 cm	219,900	REF		
	≧5 cm	243,927	1.523	1.511–1.534	<0.0001
Median household income	>$75,000	143,487	REF		
	$55,000–$75,000	213,467	1.081	1.071–1.090	<0.0001
	$35,000–$55,000	98,851	1.121	1.109–1.133	<0.0001
	<$35,000	8,022	1.169	1.135–1.205	<0.0001
Rural–Urban areas	Urban	397,963	REF		
	Rural	65,864	1.064	1.053–1.075	<0.0001

AI, American Indian/Alaska Native; API, Asian or Pacific Islander; RRSJ, Rectum, Rectosigmoid junction; SDS, Sigmoid, Descending, Splenic flexure of colon; TAH, Transverse, Ascending, Hepatic flexure of colon; CA, Cecum, Appendix; HR, hazard ratio; CI, confidence interval.

TABLE 4 Univariate analysis of disease-specific survival using Cox proportional hazards models.

Variable		*N*	HR	95% CI	*p*-value
Age	5–39 years	11,465	REF		
	40–64 years	169,990	1.002	0.970–1.036	0.886
	≧65 years	282,372	1.323	1.281–1.366	<0.0001
Sex	Female	219,905	REF		
	Male	243,922	1.031	1.022–1.041	<0.0001
Race	White	371,473	REF		
	Black	50,319	1.273	1.254–1.291	<0.0001
	AI	3,400	1.043	0.986–1.103	0.142
	API	38,635	0.891	0.875–0.907	<0.0001
Primary site	RRSJ	135,378	REF		
	SDS	140,761	1.018	1.006–1.031	0.003
	TAH	114,192	0.886	0.874–0.898	<0.0001
	CA	73,496	1.038	1.023–1.053	<0.0001
Stage	0	5,156	REF		
	I	77,409	0.67	0.624–0.719	<0.0001
	II	127,489	1.114	1.039–1.194	0.002
	III	126,854	1.958	1.827–2.098	<0.0001
	IV	96,539	9.568	8.930–10.251	<0.0001
	Unknown	30,380	4.056	3.780–4.352	<0.0001
Tumor size	<5 cm	219,900	REF		
	≧5 cm	243,927	1.895	1.876–1.914	<0.0001
Median household income	>$75,000	143,487	REF		
	$55,000–$75,000	213,467	1.086	1.074–1.099	<0.0001
	$35,000–$55,000	98,851	1.124	1.109–1.139	<0.0001
	<$35,000	8,022	1.179	1.136–1.224	<0.0001
Rural–Urban areas	Urban	397,963	REF		
	Rural	65,864	1.056	1.042–1.070	<0.0001

areas had higher mortality rates than those in urban areas. These findings are shown in Figure 5.

Trends changes of OS of CRC in urban and rural areas in 20 years

According to the data, the 1-year overall survival rate of CRC has improved significantly over the past 20 years, both in urban and rural areas. In 2019, the 1-year overall survival rate of CRC in a population of 1 million was 7.2 percentage points higher than that of 2000. In Not adjacent to a metropolis, this improvement was 5.8 percentage points higher. Additionally, compared to 15 years ago, there has been an increase in the 3-year and 5-year overall survival rates of CRC by 0.9–3.2 percentage points and 0.6–4.3 percentage points, respectively, in both urban and rural areas. In terms of longer-term outcomes, there was an improvement in the 10-year overall survival rate of CRC in urban areas by 2.3–3.0 percentage points in 2010, compared to 2000. In metropolitan areas, there was a larger increase of 5.4 percentage points. However, there was a decrease of 1.9 percentage points in non-metropolitan areas (as shown in Figure 6).

Discussion

The research findings indicate that there were notable differences in the characteristics and outcomes of CRC cases between urban and rural areas in the period between 2000 and 2019. Specifically, a higher proportion of CRC cases in the urban setting were female, black, diagnosed at advanced stages (stage III and stage IV), and had tumors less than 5 cm. Furthermore, a larger percentage of urban CRC cases had a higher household income of over $55,000, compared to their rural counterparts. In terms of mortality rates, both total and CRC-specific mortality rates were higher in rural compared to urban areas, with a 3.5 percentage point difference for total mortality and a 1.9 percentage point difference for CRC-specific mortality. It is worth noting that men had a significantly higher risk of developing and dying from CRC compared to women in the US (5). Men diagnosed with CRC have a 62.8% chance of surviving 5 years from the date of diagnosis compared with women's 64.7% chance of survival (6). Moreover, while CRC incidence and mortality rates have decreased in both genders in China, men remained at a higher risk throughout. Factors such as smoking, obesity, alcohol consumption, and lack of physical activity contributed more to the development of CRC in men

10.3389/fpubh.2024.1319977

TABLE 5 Multivariate analysis comparing the risk factors of overall survival in urban and rural.

Variable		Urban			Rural		
		HR	59% CI	*p*-value	HR	59% CI	*p*-value
Age	5–39 years	REF			REF		
	40–64 years	1.269	1.228–1.312	<0.0001	1.281	1.17–1.402	<0.0001
	≧65 years	3.046	2.948–3.147	<0.0001	2.831	2.589–3.095	<0.0001
Sex	Female	REF			REF		
	Male	1.056	1.048–1.065	<0.0001	1.076	1.055–1.097	<0.0001
Race	White	REF			REF		
	Black	1.123	1.108–1.138	<0.0001	1.138	1.099–1.178	<0.0001
	AI	0.970	0.909–1.035	0.356	1.114	1.036–1.197	0.003
	API	0.852	0.839–0.865	<0.0001	0.992	0.927–1.061	0.809
Primary site	RRSJ	REF			REF		
	SDS	1.008	0.997–1.019	0.147	1.026	1.0–1.053	0.047
	TAH	1.072	1.06–1.085	<0.0001	1.073	1.044–1.103	<0.0001
	CA	1.078	1.064–1.092	<0.0001	1.065	1.033–1,099	<0.0001
Stage	0	REF			REF		
	I	0.887	0.846–0.931	<0.0001	0.883	0.793–0.983	0.023
	II	1.038	0.99–1.088	0.126	0.980	0.881–1.089	0.706
	III	1.341	1.279–1.405	<0.0001	1.262	1.135–1.403	<0.0001
	IV	5.469	5.217–5.734	<0.0001	4.971	4.471–5.526	<0.0001
	Unknown	2.511	2.392–2.637	<0.0001	2.081	1.866–2.322	<0.0001
Tumor size	<5 cm	REF			REF		
	≧5 cm	1.262	1.252–1.273	<0.0001	1.272	1.246–1.298	<0.0001
Median household income	>$75,000	REF			REF		
	$55,000–$75,000	1.073	1.063–1.083	<0.0001	1.011	0.956–1.069	0.705
	$35,000–$55,000	1.098	1.084–1.113	<0.0001	1.072	1.017–1.131	0.01
	<$35,000	1.003	0.876–1.15	0.96	1.138	1.072–1.208	<0.0001

AI, American Indian/Alaska Native; API, Asian or Pacific Islander; RRSJ, Rectum, Rectosigmoid junction; SDS, Sigmoid, Descending, Splenic flexure of colon; TAH, Transverse, Ascending, Hepatic flexure of colon; CA, Cecum, Appendix; HR, hazard ratio; CI, confidence interval.

than women (7). Commonly, Chinese men smoke more frequently than women (8).

Several studies have examined the survival rates of CRC patients. One study conducted by Hashibe et al. found that rural CRC patients had lower survival rates compared to other areas (9). Additionally, statistics indicate that historically, Black men have had higher incidence and mortality rates for CRC compared to other racial and ethnic groups. The 5-year survival rate for Black individuals with CRC is reported to be 59%, while for White individuals, it is 63.8% (6). It is well-established that CRC screening can effectively prevent or detect CRC at an early stage (10). However, there are certain barriers that can hinder access to appropriate primary care services for racially minoritized populations. These barriers include lack of insurance or social support, as well as racism and discrimination (11). Studies conducted within the Veterans' Health Administration have shown that there are no differences in diagnostic follow-up testing between White and Black individuals, suggesting that access to appropriate structures and services may be crucial in ensuring appropriate post-screening follow-up for minoritized populations (12). while considering unique social and healthcare contexts, there are cultural and community-specific approaches that can be employed to promote CRC screening and follow-up care among racially minoritized populations. Here are some our suggestions: Provide culturally tailored education: Develop educational materials and campaigns that are sensitive to the cultural beliefs, values, and practices of racially minoritized populations. Use culturally appropriate language, images, and storytelling methods to communicate the importance of CRC screening and follow-up care. Enhance community engagement: Engage community leaders, organizations, and influencers to raise awareness about CRC screening. Utilize trusted community members who can act as ambassadors and share personal stories or testimonials of their experiences with CRC screening. Provide multilingual services and assistance to avoid language barriers that prevent screening and follow-up care. Respect the Faith-based initiatives of ethnic minorities, strengthen cooperation with healthcare providers, enhance their cultural abilities and awareness of the unique needs of ethnic minorities. Establish mutual trust and provide personalized care.

The findings from a Kaplan–Meier survival analysis revealed that in the CRC group with a household income less than $35,000, rural areas had a median survival time that was 9 months longer compared to urban areas. This difference may be attributed to the higher

10.3389/fpubh.2024.1319977

TABLE 6 Multivariate analysis comparing the risk factors of disease-specific survival in urban and rural.

Variable		Urban			Rural		
		HR	59% CI	*p*-value	HR	59% CI	*p*-value
Age	5–39 years	REF			REF		
	40–64 years	1.170	1.13–1.211	<0.0001	1.136	1.033–1.25	0.008
	≧65 years	2.058	1.988–2.13	<0.0001	1.868	1.7–2.053	<0.0001
Sex	Female	REF			REF		
	Male	1.002	0.991–1.012	0.718	1.012	0.986–1.037	0.371
Race	White	REF			REF		
	Black	1.179	1.161–1.198	<0.0001	1.159	1.111–1.209	<0.0001
	AI	0.999	0.924–1.08	0.982	1.126	1.031–1.231	0.009
	API	0.907	0.89–0.924	<0.0001	1.015	0.933–1.104	0.73
Primary site	RRSJ	REF			REF		
	SDS	0.965	0.953–0.978	<0.0001	0.988	0.957–1.02	0.445
	TAH	0.970	0.956–0.985	<0.0001	0.978	0.944–1.013	0.215
	CA	1.024	1.008–1.041	0.004	1.004	0.966–1.044	0.831
Stage	0	REF			REF		
	I	0.702	0.65–0.759	<0.0001	0.817	0.683–0.978	0.028
	II	1.113	1.032–1.201	0.005	1.141	0.957–1.361	0.141
	III	2.109	1.956–2.274	<0.0001	2.192	1.84–2.611	<0.0001
	IV	10.325	9.578–11.13	<0.0001	10.281	8.634–12.242	<0.0001
	Unknown	3.817	3.535–4.122	<0.0001	3.546	2.967–4.238	<0.0001
Tumor size	<5 cm	REF			REF		
	≧5 cm	1.376	1.361–1.391	<0.0001	1.385	1.349–1.423	<0.0001
Median household income	>$75,000	REF			REF		
	$55,000–$75,000	1.082	1.07–1.095	<0.0001	1.073	0.998–1.154	0.056
	$35,000–$55,000	1.092	1.074–1.11	<0.0001	1.135	1.059–1.216	<0.0001
	<$35,000	0.872	0.736–1.034	0.116	1.178	1.091–1.272	<0.0001

proportion of White individuals (88.2%) in rural areas compared to urban areas (76.6%). On the other hand, when considering variables such as age, sex, race, primary site, stage 0-stage IV, tumor size, and household income over $35,000, the median survival time of CRC in urban areas was higher than in rural areas. This observation suggests that urban areas may have an advantage in terms of CRC early detection screening. It is well-known that CRC early-detection screening plays a vital role in improving survival rates (13). However, socioeconomic factors can act as barriers that hinder both the planning and completion of CRC screening (14).

Our findings indicate that the overall survival rate of CRC patients was higher in urban areas compared to rural areas. Conversely, the mortality rate of CRC was higher in rural areas compared to urban areas. In urban areas, the survival rate of CRC patients was lower than the mortality rate at the sixth year after diagnosis, while in rural areas, this occurred at the fifth year. This study suggests that when evaluating the effectiveness of CRC treatment, it may be more appropriate to assess the 6-year survival rate in urban areas and the 5-year survival rate in rural areas. Furthermore, when comparing the data from 2000, we observed a significant improvement in the 1-year, 3-year, and 5-year overall survival rates of CRC in both urban and rural areas.

Our study identified several factors that independently influenced the prognosis for the OS of CRC. These factors included age over 40 years, male gender, Black ethnicity, tumor location in the right colon, advanced stages (stage III and stage IV), and tumor size over 5 cm. Additionally, household income below $75,000 and $55,000 were found to be independent prognostic factors for the OS and DSS of CRC in urban and rural areas, respectively. Overall, this study highlights various risk factors that impact the survival of CRC patients, including demographic characteristics like age, gender, and race, as well as medical factors such as tumor location, stage, and size. The study also emphasizes the importance of socioeconomic status, as household income was found to significantly impact CRC survival. There is a growing concern worldwide about the increasing incidence of CRC in younger adults (below 50 years old). This trend has raised clinical concerns that younger adults may present with more advanced disease, leading to a poorer prognosis compared to older cohorts due to a lack of screening (15, 16). Recent studies have reported that a younger age at diagnosis and receiving systematic therapies could potentially result in longer OS and DSS for CRC patients (17). The distribution of CRC varies significantly across different regions worldwide (18). It is predominantly observed in Australia, Europe, and North America. In general, the incidence in developed countries or regions is approximately three times higher than

10.3389/fpubh.2024.1319977

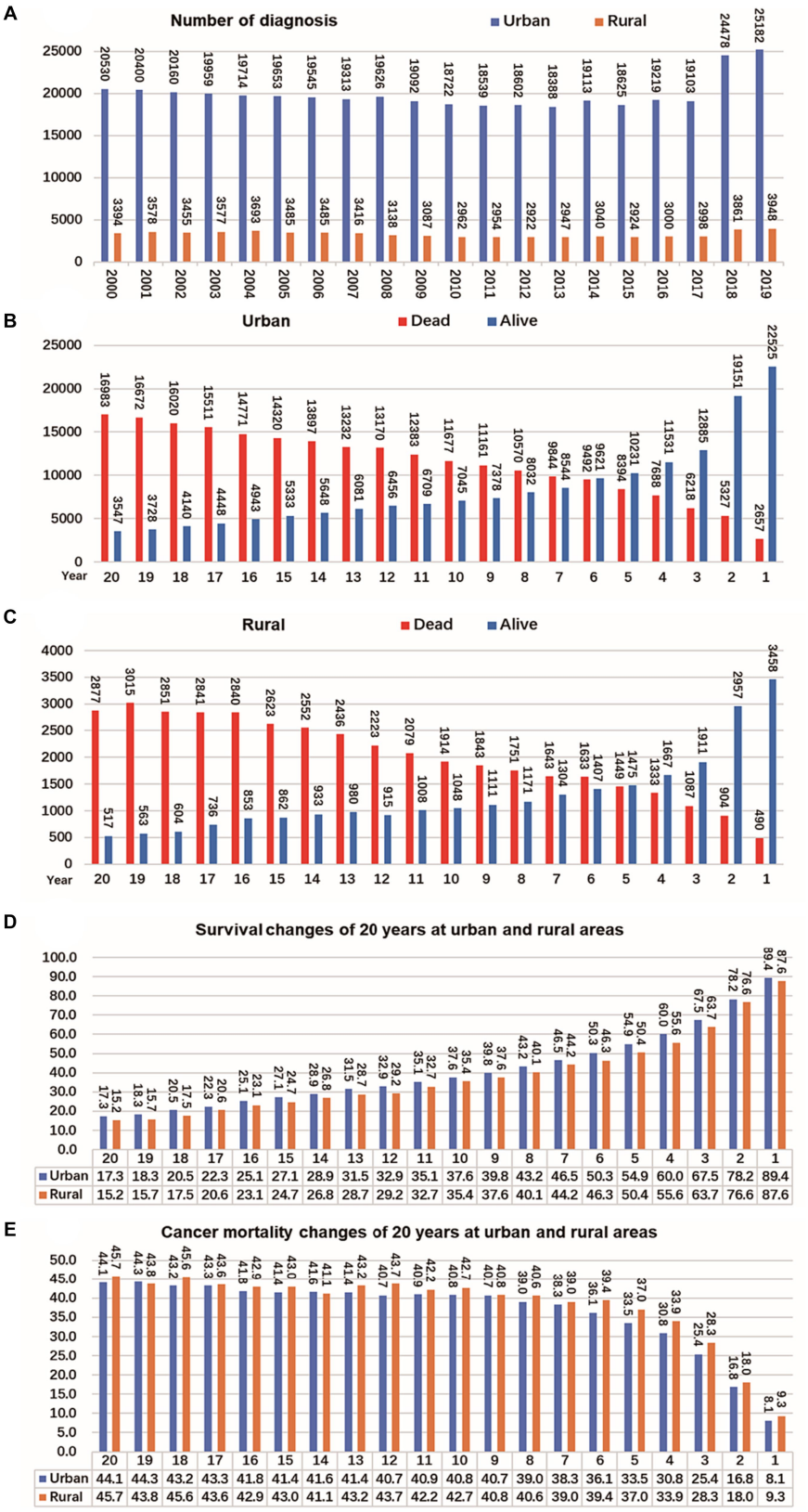


FIGURE 5
Changes of CRC cases, survival and mortality in urban and rural areas in 20 years. **(A)** Number of CRC per year from 2000 to 2019, shows that the number of cancer diagnoses in rural and urban areas remained relatively stable from 2000 to 2017, and the number of cancer diagnoses increased significantly from 2018 to 2019. **(B)** The tumor mortality rate (49.7%) and survival rate (50.3%) reached a balance in the sixth year in urban. **(C)** The tumor mortality rate (49.6%) and survival rate (50.4%) reached a balance in the fifth year in rural. **(D)** Survival of CRC changes in 20 years at urban and rural areas. **(E)** Mortality of CRC changes in 20 years at urban and rural areas.

10.3389/fpubh.2024.1319977

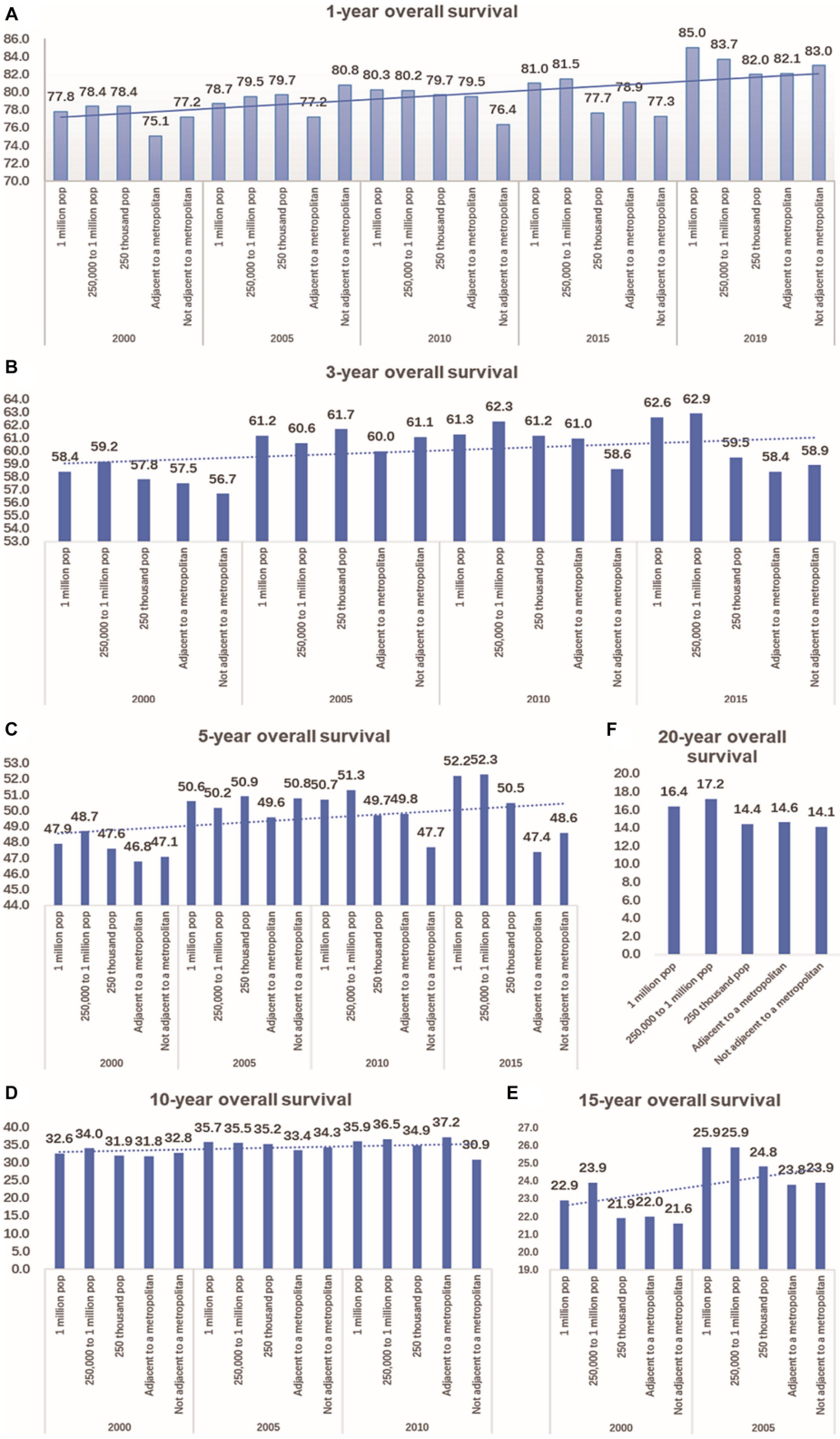


FIGURE 6
Comparison of 1-year, 3-year, 5-year, 10-year, 15-year, and 20-year OS of CRC between urban and rural in 20 years. **(A)** The change of CRC's 1-year OS in metropolitan, medium city, small city, adjacent to a metropolitan and countryside, Compared with 20 years ago, the 1-year OS of CRC in urban and rural has significantly improved. **(B)** Compared with 15 years ago, the 3-year OS of CRC in urban and rural increased by 0.9–3.2 percentage points. **(C)** Compared with 15 years ago, the 5-year OS of CRC in urban and rural increased by 0.6–4.3 percentage points. **(D)** Compared with 2000, the 10-year OS of CRC in urban increased by 2.3–3.0 percentage points in 2010,in the adjacent to a metropolitan area, it increased by 5.4 percentage points, in the not adjacent to a metropolis area, it decreased by 1.9 percentage points. **(E)** Compared with 2000, the 15-year OS of CRC in urban and rural increased by 1.8–3.0 percentage points in 2005. **(F)** Comparison of 20-year OS of CRC in urban and rural.

in less developed areas. However, there is a notable increase in the incidence of CRC in Asia that cannot be ignored (19, 20). In China, both the incidence and mortality rates of CRC have shown an upward trend over the years. According to data from the Chinese Cancer Registration in 2014, the highest incidence and mortality rates were observed in the eastern region, followed by the central region, with the lowest rates in the western region. The mortality rate of colorectal cancer in urban areas of China experienced a significant increase from 2002 to 2008, followed by a decrease from 2008 to 2015. Conversely, the mortality rate in rural areas continued to rise (21). The specific reasons for this change are not very clear, and we think it may be related to the imbalance in economic development between urban and rural areas in China. Researchers believe that it is related to the following factors, such as inequitable distribution of health care services between urban and rural areas; pilot CRC screening strategies were put into place by the Chinese government in 2012. However, these programs were conducted only in urban areas; rural areas generally lack adequate field conditions, implementation funding, and screening equipment (21). We can be learned from the lessons for future public health strategies as follow, Providing accessible healthcare services: Ensuring access to high-quality healthcare facilities and services, especially in rural areas, can promote early diagnosis and effective treatment of CRC. Develop corresponding screening plans for urban and rural areas to ensure that high-risk populations in both areas receive appropriate screening. It is recommended to conduct regular screening for individuals with moderate risk, while individuals with higher risk may require earlier or more frequent screening. Promoting a healthy lifestyle: Encouraging individuals to develop healthy habits, such as regular physical activity, maintaining a balanced diet rich in fruits and vegetables, limiting the consumption of processed foods, avoiding smoking and excessive alcohol consumption, can reduce the risk of developing CRC.

Limitations and strengths

This study has certain limitations and strengths that should be considered. One limitation is that the data used in this study is derived from the SEER database, which represents the US population. Therefore, the generalizability of the findings to other countries or regions may be limited. Additionally, the lack of treatment data in the SEER database restricts the ability to compare the impact of different treatments on prognosis in urban and rural areas. Despite these limitations, the study has notable strengths. One strength is the inclusion of 20 years of urban and rural data, allowing for an analysis of the changes in survival and prognostic factors for CRC over this period. Moreover, the study highlights the importance of considering different survival rates for urban (6-year survival) and rural (5-year survival) populations when evaluating treatment effects. Further research is needed to validate these findings in diverse settings and to explore the impact of specific treatments on the prognosis of CRC in urban and rural areas.

Conclusion

To summarize, our study revealed that the OS of urban CRC patients is slightly lower than that of rural patients, while, there was no significant difference in DSS between urban and rural CRC patients. In urban areas, the mortality rate of CRC exceeded the survival rate in the sixth year after diagnosis, while in rural areas, it was the fifth year after diagnosis. Over the past 20 years, there has been an improvement in the 5-year OS of CRC, with an increase of 2.9–4.3 percentage points in urban areas and 0.6–1.5 percentage points in rural areas. Several independent prognostic factors for OS of CRC were identified in both urban and rural settings. These factors included age over 40 years, male gender, Black ethnicity, and tumor size over 5 cm. Additionally, household income below $75,000 and below $55,000 were found to be independent prognostic factors for OS and DSS of CRC in urban and rural areas, respectively.

These findings highlight the importance of considering urban–rural disparities in CRC prognosis and the influence of socioeconomic factors on survival outcomes. Further research is needed to explore the underlying reasons for these disparities and to develop targeted interventions to improve outcomes for CRC patients in both urban and rural settings.

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.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

M-sF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. S-xP: Data curation, Project administration, Visualization, Writing – review & editing. X-qC: Formal analysis, Visualization, Data curation, Writing – review & editing. Q-cP: Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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

Publisher's note

References

1. Xia C, Dong X, Li H, Cao M, Sun D, He S, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J*. (2022) 135:584–90. doi: 10.1097/CM9.0000000000002108

2. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin*. (2023) 73:233–54. doi: 10.3322/caac.21772

3. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. (2018) 68:31–54. doi: 10.3322/caac.21440

4. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer*. (2010) 116:544–73. doi: 10.1002/cncr.24760

5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. (2019) 69:7–34. doi: 10.3322/caac.21551

6. U.S. Cancer Statistics Working Group. (2022). U.S. Cancer statistics data visualizations tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Available at: https://www.cdc.gov/cancer/dataviz.

7. Khil H, Kim SM, Hong S, Gil HM, Cheon E, Lee DH, et al. Time trends of colorectal cancer incidence and associated lifestyle factors in South Korea. *Sci Rep*. (2021) 11:2413. doi: 10.1038/s41598-021-81877-2

8. Wang M, Xu S, Liu C, Liu W, Luo X, Zhang X, et al. Trends of smoking prevalence and implications for chronic diseases in China: an analysis of data from serial national cross-sectional surveys. *Lancet*. (2018) 392:S75. doi: 10.1016/S0140-6736(18)32704-1

9. Hashibe M, Kirchhoff AC, Kepka D, Kim J, Millar M, Sweeney C, et al. Disparities in cancer survival and incidence by metropolitan versus rural residence in Utah. *Cancer Med*. (2018) 7:1490–7. doi: 10.1002/cam4.1382

10. Pan J, Xin L, Ma YF, Hu LH, Li ZS. Colonoscopy reduces colorectal Cancer incidence and mortality in patients with non-malignant findings: a Meta-analysis. *Am J Gastroenterol*. (2016) 111:355–65. doi: 10.1038/ajg.2015.418

11. Haverkamp D, English K, Jacobs-Wingo J, Tjemsland A, Espey D. Effectiveness of interventions to increase colorectal Cancer screening among American Indians and Alaska natives. *Prev Chronic Dis*. (2020) 17:E62. doi: 10.5888/pcd17.200049

12. Partin MR, Gravely AA, Burgess JF Jr, Haggstrom DA, Lillie SE, Nelson DB, et al. Contribution of patient, physician, and environmental factors to demographic and health variation in colonoscopy follow-up for abnormal colorectal cancer screening test results. *Cancer*. (2017) 123:3502–12. doi: 10.1002/cncr.30765

13. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for colorectal Cancer. *JAMA*. (2021) 325:1978–98. doi: 10.1001/jama.2021.4417

14. Hunleth JM, Steinmetz EK, McQueen A, James AS. Beyond adherence: health care disparities and the struggle to get screened for Colon Cancer. *Qual Health Res*. (2016) 26:17–31. doi: 10.1177/1049732315593549

15. Kong JC, Su WK, Ng CW, Guerra GR, Chakraborty J, Lutton N, et al. Colorectal cancer in younger adults from a bi-National Colorectal Cancer Audit registry. *ANZ J Surg*. (2021) 91:367–74. doi: 10.1111/ans.16250

16. Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. *Gastroenterology*. (2020) 158:341–53. doi: 10.1053/j.gastro.2019.07.055

17. Chen Q, He L, Li Y, Zuo C, Li M, Wu X, et al. Risk factors on the incidence and prognostic effects of colorectal Cancer with brain metastasis: a SEER-based study. *Front Oncol*. (2022) 12:758681. doi: 10.3389/fonc.2022.758681

18. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2018) 68:394–424. doi: 10.3322/caac.21492

19. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. (2017) 67:7–30. doi: 10.3322/caac.21387

20. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. (2016) 66:115–32. doi: 10.3322/caac.21338

21. Yu W, Jiang J, Xie L, Li B, Luo H, Fu Y, et al. Mortality trends in colorectal cancer in China during 2000–2015: a joinpoint regression and age-period-cohort analysis. *Prev Chronic Dis*. (2018) 15:E156. doi: 10.5888/pcd15.180329

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 23 February 2024
DOI 10.3389/fpubh.2024.1341789

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Ronak Loonawat,
Wuxi Advanced Therapeutics, Inc., United States
Priya Wadgaonkar,
City of Hope National Medical Center, United States

*CORRESPONDENCE
Xiaomin Zhong
✉ 13912074971@163.com

RECEIVED 20 November 2023
ACCEPTED 07 February 2024
PUBLISHED 23 February 2024

CITATION
Yuan Y, Chen Q, Ding X, Zhong Q and Zhong X (2024) Endocrine disrupting chemical Bisphenol A and its association with cancer mortality: a prospective cohort study of NHANES.
Front. Public Health 12:1341789.
doi: 10.3389/fpubh.2024.1341789

Endocrine disrupting chemical Bisphenol A and its association with cancer mortality: a prospective cohort study of NHANES

Ying Yuan, Qian Chen, Xiaorong Ding, Qin Zhong and Xiaomin Zhong*

Department of Oncology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huai'an, China

Introduction: There is evidence suggesting that Bisphenol A (BPA) is associated with increased all-cause mortality in adults. However, the specific nature of the relationship between BPA exposure and cancer mortality remains relatively unexplored.

Methods: The National Health and Nutrition Examination Survey (NHANES) dataset was used to recruit participants. Urinary BPA was assessed using liquid chromatography-mass spectrum (LC–MS). Through the use of multivariable Cox proportional hazard regressions and constrained cubic splines, the relationships between urine BPA and death from all causes and cancer were investigated.

Results: This study has a total of 8,035 participants, and 137 died from cancers after a 7.5-year follow-up. The median level of BPA was 2.0 g/mL. Urinary BPA levels were not independently associated with all-cause mortality. For cancer mortality, the second quartile's multivariable-adjusted hazard ratio was 0.51 (95% confidence interval: 0.30 to 0.86; $p = 0.011$) compared to the lowest quartile. The restricted cubic splines showed that the association was nonlinear (p for nonlinearity = 0.028) and the inflection point was 1.99 ng/mL.

Conclusion: Urinary BPA exposure was U-shaped associated with the risk of cancer mortality, and a lower level of BPA less than 1.99 ng/mL was associated with a higher risk of cancer mortality.

KEYWORDS

environmental phenols, Bisphenol A, cancer mortality, all-cause mortality, NHANES

Introduction

Bisphenol A (BPA) is a kind of environmental phenols utilized in baby bottles, food containers, and dentistry (1). The exposure of humans to BPA is pervasive, originating from various sources such as consumer products, food, water, and dust (2). National biological monitoring data in the United States reveals that BPA is detectable in more than 90% of urine samples in the general population (3). Currently, 12 states have enforced regulations to restrict the use of BPA in the United States. While BPA is known to undergo rapid metabolism and is primarily eliminated through urine, its cumulative exposure in everyday items could lead to

concerns regarding potential long-term health consequences (4). The potential pathways underlying BPA-induced adverse health outcomes include endocrine disruption (5), oxidative stress (6) and inflammation (7).

Exposure to bisphenol A starts very early in life, causing adverse health outcomes not only in children but also later in life (8, 9). The BPA exposure has been linked to disruptions in endocrine function and metabolism (10), which can contribute to the development of metabolic disorders (11). Some studies showed that BPA exacerbated inflammation by regulating gut physiology (12) and was involved in the development of type 2 diabetes mellitus (13), obesity (14), hypertension (15) and cardiovascular disease (16). Despite mounting evidence indicating potential toxic effects of BPA on various human cancers (17, 18), the relationship between BPA exposure and mortality remains unclear.

A study reported that BPA exposure was positively related to all-cause mortality in adults. However, nonsignificant association between BPA exposure and cancer mortality was found (19). Even so, the previous study had a lower number of sample and lacked a nonlinear analysis. Therefore, we conducted a study utilizing a comprehensive database to examine the correlation between urinary BPA levels and mortality rates related to all causes and cancer.

Methods

Study participants

Our study utilized data from NHANES, a program specifically designed to evaluate the health and nutritional status of individuals, both adults and children, in the United States. The data covered the period from 2003 to 2012. Individuals with missing data on urinary creatinine ($n = 2$) or mortality ($n = 13$) as well as those who were diagnosed with cancer ($n = 68$) were excluded from a pool of adult participants with complete records of urinary BPA ($n = 8{,}118$). Ultimately, a total of 8,035 participants were included in the study. The study was approved by the institutional review board of National Center of Health Statistics and all participants provided written informed consent.

Covariates collection

The method for measuring baseline urinary BPA levels in NHANES has been previously described (20). In brief, spot urine samples were collected from each participant and promptly transferred to specimen containers within 4 hours of collection. The determination of urinary BPA levels involved the use of online solid phase extraction, advanced liquid chromatography, and tandem mass spectrometry. It's worth noting that the limit of detection (LOD) for urinary BPA levels was 0.20 ng/mL. Urinary BPA levels that fell below the LOD were recorded as the LOD value divided by the square root of two. Creatinine levels were measured using the Jaffe rate reaction assay.

Furthermore, essential participant information through questionnaires, which encompassed sociodemographic details and lifestyle factors were collected. Sociodemographic variables included age, gender, race, and educational level. Race was categorized into four groups: Mexican-American, non-Hispanic white, non-Hispanic black, and other races. Educational level was divided into three categories: college or higher education, high school or equivalent, and less than high school. Lifestyle factors encompassed smoking, alcohol consumption, and physical activity level. Smoking status was determined by whether participants had smoked at least 100 cigarettes in their lifetime. Alcohol consumption was assessed based on the daily or yearly number of drinks consumed. Physical activity level was calculated using total metabolic equivalent of task minutes per week and classified into three groups: inactive, moderate, and vigorous. Body Mass Index (BMI) was computed by dividing weight (in kilograms) by the square of height (in meters). Diabetes was defined as a previously diagnosis, fasting glucose levels of $\geq$7.0 mmol/L, glycated hemoglobin levels of $\geq$6.5%, or the use of antidiabetic medication. Participants were also queried about their history of congestive heart failure, coronary artery disease, angina, heart attack, or stroke, and those who reported such conditions were identified as having a history of cardiovascular disease (CVD).

The study outcomes consisted of all-cause mortality and cancer mortality. Mortality status of the study participants was determined by linking to the National Death Index until 31st December 2015. Cancer diagnosis was according to ICD-10 codes C00-C97, which specifically identify malignant neoplasms.

Statistical analysis

To account for selection variations, oversampling and adjustments for non-responses, the sampling weights common to NHANES data were incorporated in our study. To evaluate the variances between groups, either Student's t-test for continuous variables or Chi-square tests for categorical variables was used. For the analysis of survival rates, univariate analysis was conducted using Kaplan–Meier analysis with the Log-rank test. Multivariable survival analysis, on the other hand, was performed using Cox proportional hazards analysis. It presented the cumulative incidence function of cancer mortality with non-cancer mortality as a competing risk. Model 1 was adjusted for urinary creatinine, Model 2 was adjusted for urinary creatinine, age, gender, and race. Model 3 was additionally adjusted for education level, BMI, drinker, smoker, activity, diabetes, and cardiovascular diseases (CVD). Restricted cubic splines with knots placed at the 5th, 50th, and 95th percentiles were used to assess potential nonlinear relationships. All statistical analyzes were carried out using R software, specifically version 3.6.

Results

The study included a sizable cohort of 8,035 individuals, predominantly middle-aged, with a slight majority being male. According to Table 1, 137 cases of cancer mortality were documented over a 7.5-year follow-up period. The measurement of urinary bisphenol A (BPA) levels revealed a median concentration of 2.0 ng/mL. Notably, individuals who succumbed to cancer during the follow-up period tended to be older ($p = 0.001$), male ($p = 0.035$), and had higher incidences of diabetes ($p = 0.001$) and cardiovascular disease ($p < 0.001$). These observations underline the importance of considering demographic and health-related factors when assessing mortality risk.

TABLE 1 Characteristics of the study population.

Variable	Overall (*n* = 8,035)	Survivors (*n* = 7,898)	Non-survivors (*n* = 137)	*p* value
Age, years	45.9 (18.7)	45.6 (18.6)	65.4 (14.9)	<0.001
Male, %	4,120 (51.3)	4,037 (51.1)	83 (60.6)	0.035
Race, %				0.142
Non-Hispanic white	3,509 (43.7)	3,447 (43.6)	62 (45.3)	
Non-Hispanic black	1828 (22.8)	1792 (22.7)	36 (26.3)	
Mexican American	1,432 (17.8)	1,405 (17.8)	27 (19.7)	
Others	1,266 (15.8)	1,254 (15.9)	12 (8.8)	
Education, %				0.001
Less than high school	2,156 (26.8)	2,109 (26.7)	52 (38.0)	
High school or equivalent	1904 (23.7)	1864 (23.6)	35 (25.5)	
College or above	3,975 (49.5)	3,925 (49.7)	50 (36.5)	
BMI, kg/m^2	28.7 (6.9)	28.7 (6.9)	29.0 (7.3)	0.567
Drinker (%)	4,635 (57.7)	4,479 (56.7)	104 (75.9)	<0.001
Smoker, %				0.507
Never	5,567 (69.3)	5,496 (69.6)	89 (65.0)	
Past	459 (5.7)	405 (5.1)	8 (5.8)	
Current	2009 (25.0)	1997 (25.3)	40 (29.2)	
Activity, %				0.001
Inactive	1702 (21.2)	1,695 (21.5)	22 (16.1)	
Moderate	3,362 (41.8)	3,295 (41.7)	79 (57.7)	
Vigorous	2,971 (37.0)	2,908 (36.8)	36 (26.3)	
Diabetes, %	1,137 (14.2)	1,104 (14.0)	33 (24.1)	0.001
CVD, %	751 (9.3)	720 (9.1)	31 (22.6)	<0.001
Urinary creatinine, mg/dL	117 [68, 175]	117 [68, 175]	105 [62, 173]	0.228
Bisphenol A, ng/mL	2.0 [0.9, 4.0]	2.0 [0.9, 4.0]	1.9 [0.7, 4.3]	0.412
Benzophenone-3, ng/mL	12.2 [3.7, 55.7]	13.2 [4.0, 60.7]	5.35 [1.6, 19.3]	<0.001
Triclosan, ng/mL	10.3 [2.5, 57.0]	10.9 [2.7, 58.7]	5.7 [1.6, 30.4]	<0.001

Kaplan–Meier analysis indicated significant associations between urinary BPA levels and both all-cause mortality and cancer mortality. The analysis suggests that lower urinary BPA levels are associated with an increased risk of all-cause mortality (log-rank $p = 0.01$) and cancer mortality (log-rank $p = 0.007$) (Figure 1). However, compared with the lowest quartile of BPA, no association of all-cause mortality was observed in any quartiles across models, which suggested that BPA was not independently associated with all-cause mortality (Table 2).

On the contrary with expectations, the risk of cancer mortality was reduced with the increase of BPA levels both in the unadjusted model and adjusted models (Table 3). Most importantly, the second quartile's multivariable-adjusted hazards ratio (HR) was 0.51 (95% CI: 0.30 to 0.86; $p = 0.011$) compared to the lowest quartile of BPA. However, these associations were not consistent across all quartiles of BPA levels, indicating a more nonlinear relationship. In order to confirm the nonlinear relationship, we used restricted cubic splines (Figure 2). We found that urinary BPA was U-shaped associated with cancer mortality (p for nonlinearity = 0.028). This suggests that the relationship is not purely linear, but rather exhibits a threshold effect. Specifically, lower levels of BPA (below approximately 1.99 ng/mL) were associated with an increased risk of cancer mortality. Beyond this threshold, higher BPA levels appeared to confer protection against cancer mortality. This nonlinear relationship highlights the complexity of BPA's impact on health outcomes and underscores the need for careful consideration of dose–response relationships. Future research should focus on elucidating the mechanisms underlying these observed associations and conducting longitudinal studies to validate these findings across diverse populations and settings.

Discussion

In this study, we found that urinary BPA was U-shaped associated with the risk of cancer mortality and a lower level less than 1.99 ng/mL increasing the risk of cancer mortality. This study provides valuable insights into the complex relationship between urinary BPA levels and cancer mortality, emphasizing the need for a nuanced understanding of dose–response dynamics and the consideration of confounding factors in epidemiological research.

BPA is a widely used raw material and is involved in the initiation and development of hormone-dependent cancers. A comparable study

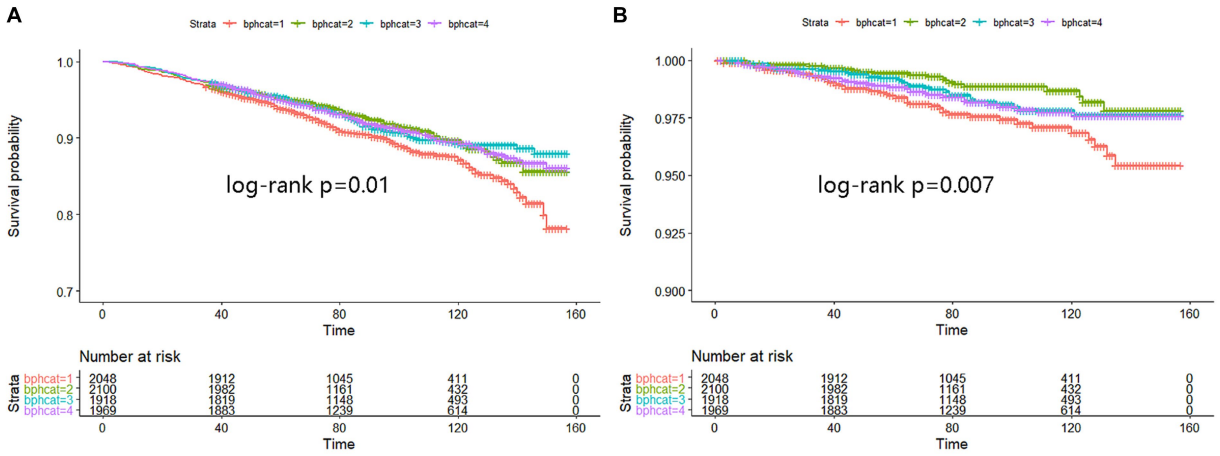


FIGURE 1
Kaplan–Meier analysis was performed to assess the relationship between urinary BPA levels and both all-cause mortality **(A)** and cancer mortality **(B)**. The X-axis represented months while Y-axis represented survival probability. Strata 1: <0.9; Strata 2: 0.9 ~ 1.9; Strata 3: 2.0 ~ 4.0; Strata 4: >4.0.

TABLE 2 Adjusted hazard ratios for associations between BPA and all-cause mortality.

Bisphenol A, ng/mL	Model 1		Model 2		Model 3	
	HR	*p*	HR	*p*	HR	*p*
<0.9	Ref	–	Ref	–	Ref	–
0.9 ~ 1.9	0.88 [0.71, 1.09]	0.254	0.88 [0.71, 1.09]	0.249	0.88 [0.71, 1.09]	0.246
2.0 ~ 4.0	0.98 [0.78, 1.23]	0.841	1.07 [0.86, 1.34]	0.536	1.07 [0.86, 1.34]	0.530
>4.0	1.11 [0.87, 1.41]	0.394	1.11 [0.88, 1.39]	0.381	1.02 [0.81, 1.28]	0.887

TABLE 3 Adjusted hazard ratios for associations between BPA and cancer mortality.

Bisphenol A, ng/mL	Model 1		Model 2		Model 3	
	HR	*p*	HR	*p*	HR	*p*
<0.9	Ref	–	Ref	–	Ref	–
0.9 ~ 1.9	0.44 [0.26, 0.74]	0.002	0.46 [0.27, 0.77]	0.003	0.51 [0.30, 0.86]	0.011
2.0 ~ 4.0	0.66 [0.40, 1.08]	0.099	0.76 [0.47, 1.23]	0.264	0.77 [0.47, 1.26]	0.304
>4.0	0.72 [0.43, 1.22]	0.221	0.79 [0.48, 1.29]	0.342	0.81 [0.48, 1.36]	0.426

discovered that higher exposure to BPA was independently related with an elevated risk of all-cause mortality but with no significant association with cancer mortality (19). They divided BPA into tertiles and did not explore the nonlinear relationship. A recent study showed that the highest tertile of urinary BPA levels corresponded to a 36% increase in all-cause mortality and a 62% increase in CVD mortality compared to the lowest tertile (21). Different from previous study, we demonstrated a U-shaped association between BPA exposure and cancer mortality using dose–response analysis and adjusting for more variables. A study also found that BPA was not significantly associated with all-cause mortality in overall population, but in the obesity, diabetes, and hypertension subgroups (22). Variations in the characteristics of the study populations, especially comorbidity, may account for the discrepancy.

BPA is an endocrine disruptor with multiple effects. BPA exhibits estrogenic properties by binding to estrogen receptors and interfering with the regular functioning of the endocrine system (23). Additionally, BPA has the potential to influence biological processes, including cell signaling, gene expression, and apoptosis, which can contribute to a range of health issues affecting the reproductive, immune, metabolic, and nervous systems (24, 25). Several studies found a U-shaped association between BPA levels and the risk of diabetes (26) and obesity (27). A higher level of BPA impacted the production of ROS (6), cancer metabolites (28), and tumoral immune microenvironment (29), contributing to the migration and invasion of cancer cells. Conversely, a lower level may be the reflection of an imbalance of endocrine-related pathways. BPA could inhibit DNA replication and cell proliferation in tumor cells (30) by modulating cell cycle-and apoptosis-related proteins and genes in cancerous cells (31). Therefore, a lower and higher level of BPA both influenced the cancer mortality. More studies are warranted to explain the dose-repose relationship.

There may be various underlying mechanisms driving the positive correlation between BPA and all-cause mortality (Figure 3). Firstly, BPA caused endocrine disruption through agonistic or antagonistic behavior at various nuclear receptors such as estrogen (ER), androgen

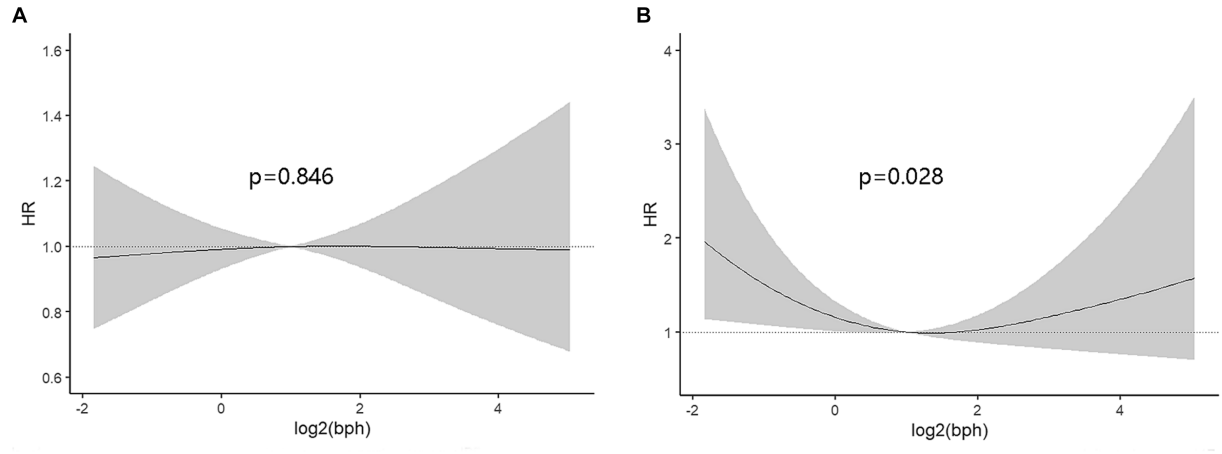


FIGURE 2
The dose–response analysis was performed to assess the relationship between urinary BPA and all-cause mortality **(A)** or cancer mortality **(B)**. The X-axis represented log-transformed BPA concentrations while Y-axis represented hazard ratio.

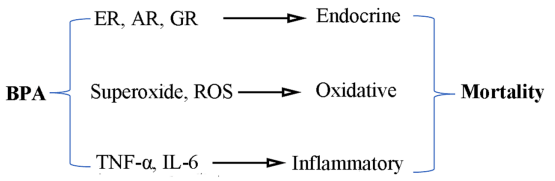


FIGURE 3
The pathophysiological mechanisms between BPA and cancer mortality. ER, estrogen; AR, androgen; GR, glucocorticoid; ROS, reactive oxidative stress.

(AR) and glucocorticoid (GR) (32). Besides, BPA exposure resulted in a strong induction of oxidative stress and inflammatory response (33, 34). However, more research is necessary to elucidate the biological mechanisms underlying this association.

This study boasts several notable strengths, including its use of a nationally representative cohort from the United States and rigorous quality control measures. Nonetheless, this study does come with certain constraints. To begin with, BPA levels were assessed solely through spot urine samples at the baseline, offering no insight into long-term BPA exposure or fluctuations in BPA concentrations within the body. Lastly, it's important to note that the generalizability of this study could be limited due to the exclusion of participants with incomplete covariate data, potentially introducing selection bias. BPA exposure is more related to hormone-associated cancers such as breast, prostate and ovarian cancers. However, the number of specific cancer type was few in the original database, which need to be verified by further large-scale cancer epidemiological investigations.

Conclusion

In conclusion, we found BPA exposure was U-shaped associated with the risk of cancer mortality, and a lower level of BPA less than 1.99 ng/mL was associated with a higher risk of cancer mortality. Our results can serve as valuable information for guiding policies related to enhanced monitoring of chemical exposures and risk assessment in cancer prevention field.

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 humans were approved by National Center of Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YY: Writing – original draft. QC: Data curation, Writing – original draft. XD: Supervision, Writing – original draft. QZ: Project administration, Writing – review & editing. XZ: Project administration, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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

Publisher's note

References

1. Jamal A, Rastkari N, Dehghaniathar R, Nodehi RN, Nasseri S, Kashani H, et al. Prenatal urinary concentrations of environmental phenols and birth outcomes in the mother-infant pairs of Tehran environment and neurodevelopmental disorders (TEND) cohort study. *Environ Res*. (2020) 184:109331. doi: 10.1016/j.envres.2020.109331

2. Dekant W, Volkel W. Human exposure to bisphenol a by biomonitoring: methods, results and assessment of environmental exposures. *Toxicol Appl Pharmacol*. (2008) 228:114–34. doi: 10.1016/j.taap.2007.12.008

3. Lehmler HJ, Liu B, Gadogbe M, Bao W. Exposure to bisphenol a, bisphenol F, and bisphenol S in U.S. adults and children: the National Health and nutrition examination survey 2013-2014. *ACS Omega*. (2018) 3:6523–32. doi: 10.1021/acsomega.8b00824

4. Stahlhut RW, Welshons WV, Swan SH. Bisphenol a data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both. *Environ Health Perspect*. (2009) 117:784–9. doi: 10.1289/ehp.0800376

5. Cimmino I, Fiory F, Perruolo G, Miele C, Beguinot F, Formisano P, et al. Potential mechanisms of bisphenol a (BPA) contributing to human disease. *Int J Mol Sci*. (2020) 21:5761. doi: 10.3390/ijms21165761

6. Xia T, Guo J, Zhang B, Song C, Zhao Q, Cui B, et al. Bisphenol a promotes the progression of Colon Cancer through dual-targeting of NADPH oxidase and mitochondrial Electron-transport chain to produce ROS and Activating HIF-1alpha/VEGF/PI3K/AKT Axis. *Front Endocrinol (Lausanne)*. (2022) 13:933051. doi: 10.3389/fendo.2022.933051

7. Hong T, Jiang X, Zou J, Yang J, Zhang H, Mai H, et al. Hepatoprotective effect of curcumin against bisphenol A-induced hepatic steatosis via modulating gut microbiota dysbiosis and related gut-liver axis activation in CD-1 mice. *J Nutr Biochem*. (2022) 109:109103. doi: 10.1016/j.jnutbio.2022.109103

8. Urbano T, Zagnoli F, Malavolti M, Halldorsson TI, Vinceti M, Filippini T. Dietary intake of potentially toxic elements and children's chemical exposure. *Curr. Opin. Environ. Sci. Health*. (2022) 30:100393. doi: 10.1016/j.coesh.2022.100393

9. Rochester JR. Bisphenol a and human health: a review of the literature. *Reprod Toxicol*. (2013) 42:132–55. doi: 10.1016/j.reprotox.2013.08.008

10. Gore AC. Endocrine-disrupting chemicals. *JAMA Intern Med*. (2016) 176:1705–6. doi: 10.1001/jamainternmed.2016.5766

11. Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, et al. Metabolism disrupting chemicals and metabolic disorders. *Reprod Toxicol*. (2017) 68:3–33. doi: 10.1016/j.reprotox.2016.10.001

12. DeLuca JA, Allred KF, Menon R, Riordan R, Weeks BR, Jayaraman A, et al. Bisphenol-a alters microbiota metabolites derived from aromatic amino acids and worsens disease activity during colitis. *Exp Biol Med (Maywood)*. (2018) 243:864–75. doi: 10.1177/1535370218782139

13. Dallio M, Masarone M, Errico S, Gravina AG, Nicolucci C, Di Sarno R, et al. Role of bisphenol a as environmental factor in the promotion of non-alcoholic fatty liver disease: in vitro and clinical study. *Aliment Pharmacol Ther*. (2018) 47:826–37. doi: 10.1111/apt.14499

14. Liu B, Lehmler HJ, Sun Y, Xu G, Liu Y, Zong G, et al. Bisphenol a substitutes and obesity in US adults: analysis of a population-based, cross-sectional study. *Lancet Planet Health*. (2017) 1:e114–22. doi: 10.1016/S2542-5196(17)30049-9

15. Bae S, Kim JH, Lim YH, Park HY, Hong YC. Associations of bisphenol a exposure with heart rate variability and blood pressure. *Hypertension*. (2012) 60:786–93. doi: 10.1161/HYPERTENSIONAHA.112.197715

16. Melzer D, Osborne NJ, Henley WE, Cipelli R, Young A, Money C, et al. Urinary bisphenol a concentration and risk of future coronary artery disease in apparently healthy men and women. *Circulation*. (2012) 125:1482–90. doi: 10.1161/CIRCULATIONAHA.111.069153

17. Hafezi SA, Abdel-Rahman WM. The endocrine disruptor bisphenol a (BPA) exerts a wide range of effects in carcinogenesis and response to therapy. *Curr Mol Pharmacol*. (2019) 12:230–8. doi: 10.2174/1874467212666190306164507

18. Pellerin E, Caneparo C, Chabaud S, Bolduc S, Pelletier M. Endocrine-disrupting effects of bisphenols on urological cancers. *Environ Res*. (2021) 195:110485. doi: 10.1016/j.envres.2020.110485

19. Bao W, Liu B, Rong S, Dai SY, Trasande L, Lehmler HJ. Association between bisphenol a exposure and risk of all-cause and cause-specific mortality in US adults. *JAMA Netw Open*. (2020) 3:e2011620. doi: 10.1001/jamanetworkopen.2020.11620

20. Granic A, Sayer AA, Robinson SM. Dietary patterns, skeletal muscle health, and sarcopenia in older adults. *Nutrients*. (2019) 11:745. doi: 10.3390/nu11040745

21. Chen YM, Liu ZY, Chen S, Lu XT, Huang ZH, Wusiman M, et al. Mitigating the impact of bisphenol a exposure on mortality: is diet the key? A cohort study based on NHANES. *Ecotoxicol Environ Saf*. (2023) 267:115629. doi: 10.1016/j.ecoenv.2023.115629

22. Chen S, Tao Y, Wang P, Li D, Shen R, Fu G, et al. Association of urinary bisphenol a with cardiovascular and all-cause mortality: National Health and nutrition examination survey (NHANES) 2003-2016. *Environ Sci Pollut Res Int*. (2023) 30:51217–27. doi: 10.1007/s11356-023-25924-7

23. Wang Z, Liu H, Liu S. Low-dose bisphenol a exposure: a seemingly instigating carcinogenic effect on breast Cancer. *Adv Sci (Weinh)*. (2017) 4:1600248. doi: 10.1002/advs.201600248

24. Aftabsavad S, Noormohammadi Z, Moini A, Karimipoor M. Effect of bisphenol a on alterations of ICAM-1 and HLA-G genes expression and DNA methylation profiles in cumulus cells of infertile women with poor response to ovarian stimulation. *Sci Rep*. (2021) 11:9595. doi: 10.1038/s41598-021-87175-1

25. Thongkorn S, Kanlayaprasit S, Panjabud P, Saeliw T, Jantheang T, Kasitipradit K, et al. Sex differences in the effects of prenatal bisphenol a exposure on autism-related genes and their relationships with the hippocampus functions. *Sci Rep*. (2021) 11:1241. doi: 10.1038/s41598-020-80390-2

26. Bi J, Wang F, Wei Y, Zhang Y, Jia C, He J, et al. Association of serum bisphenol a levels with incident overweight and obesity risk and the mediating effect of adiponectin. *Chemosphere*. (2022) 308:136287. doi: 10.1016/j.chemosphere.2022.136287

27. Wang F, Zhang Y, Zhang S, Han X, Wei Y, Guo H, et al. Combined effects of bisphenol a and diabetes genetic risk score on incident type 2 diabetes: a nested case-control study. *Environ Pollut*. (2022) 307:119581. doi: 10.1016/j.envpol.2022.119581

28. Hong X, Wang G, Liu X, Wu M, Zhang X, Hua X, et al. Lipidomic biomarkers: potential mediators of associations between urinary bisphenol a exposure and colorectal cancer. *J Hazard Mater*. (2022) 427:127863. doi: 10.1016/j.jhazmat.2021.127863

29. Palacios-Arreola MI, Moreno-Mendoza NA, Nava-Castro KE, Segovia-Mendoza M, Perez-Torres A, Garay-Canales CA, et al. The endocrine disruptor compound bisphenol-a (BPA) regulates the intra-Tumoral immune microenvironment and increases lung metastasis in an experimental model of breast Cancer. *Int J Mol Sci*. (2022) 23:2523. doi: 10.3390/ijms23052523

30. Kidani T, Yasuda R, Miyawaki J, Oshima Y, Miura H, Masuno H. Bisphenol a inhibits cell proliferation and reduces the motile potential of murine LM8 osteosarcoma cells. *Anticancer Res*. (2017) 37:1711–22. doi: 10.21873/anticanres.11503

31. Mlynarcikova A, Macho L, Fickova M. Bisphenol a alone or in combination with estradiol modulates cell cycle-and apoptosis-related proteins and genes in MCF7 cells. *Endocr Regul*. (2013) 47:189–99. doi: 10.4149/endo_2013_04_189

32. Kodila A, Franko N, Sollner DM. A review on immunomodulatory effects of BPA analogues. *Arch Toxicol*. (2023) 97:1831–46. doi: 10.1007/s00204-023-03519-y

33. Nagarajan M, Maadurshni GB, Manivannan J. Exposure to low dose of bisphenol a (BPA) intensifies kidney oxidative stress, inflammatory factors expression and modulates angiotensin II signaling under hypertensive milieu. *J Biochem Mol Toxicol*. (2023) 38:e23533. doi: 10.1002/jbt.23533

34. Nagarajan M, Maadurshni GB, Manivannan J. Bisphenol a (BPA) exposure aggravates hepatic oxidative stress and inflammatory response under hypertensive milieu – impact of low dose on hepatocytes and influence of MAPK and ER stress pathways. *Food Chem Toxicol*. (2023) 183:114197. doi: 10.1016/j.fct.2023.114197

frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 13 March 2024
DOI 10.3389/fonc.2024.1356001

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Ronak Loonawat,
Wuxi Advanced Therapeutics, Inc., United States
Priya Wadgaonkar,
City of Hope National Medical Center, United States

*CORRESPONDENCE
Dylan J. Jester
Dylan.Jester@va.gov

†These authors have contributed equally to this work

RECEIVED 14 December 2023
ACCEPTED 29 February 2024
PUBLISHED 13 March 2024

CITATION
Jester DJ, Assefa MT, Grewal DK, Ibrahim-Biangoro AM, Jennings JS and Adamson MM (2024) Military environmental exposures and risk of breast cancer in active-duty personnel and veterans: a scoping review.
Front. Oncol. 14:1356001.
doi: 10.3389/fonc.2024.1356001

Military environmental exposures and risk of breast cancer in active-duty personnel and veterans: a scoping review

Dylan J. Jester[1*], Mehret T. Assefa[1], Daya K. Grewal[1,2†], Abou M. Ibrahim-Biangoro[1,3†], Jennifer S. Jennings[1,4] and Maheen M. Adamson[1,5]

[1]Women's Operational Military Exposure Network Center of Excellence (WOMEN CoE), VA Palo Alto Health Care System, Palo Alto, CA, United States, [2]Department of Psychology, Palo Alto University, Palo Alto, CA, United States, [3]Department of Social and Behavioral Sciences, University of California, San Francisco, San Francisco, CA, United States, [4]War Related Illness and Injury Study Center (WRIISC), VA Palo Alto Health Care System, Palo Alto, CA, United States, [5]Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, United States

Background: The effects of military environmental exposures (MEE) such as volatile organic compounds (VOCs), endocrine-disrupting chemicals (EDCs), tactile herbicides, airborne hazards and open burn pits (AHOBP), and depleted uranium on health are salient concerns for service members and Veterans. However, little work has been done to investigate the relationship between MEE and risk of breast cancer.

Data sources and methods: We conducted a scoping review on MEE, military deployment/service, and risk of breast cancer among active-duty service members and Veterans. PRISMA was used. PubMed, Embase, and citations of included articles were searched, resulting in 4,364 articles to screen: 28 articles were included.

Results: Most papers on military deployment and military service found a lower/equivalent risk of breast cancer when comparing rates to those without deployment or civilians. Exposure to VOCs due to military occupation or contaminated groundwater was associated with a slightly higher risk of breast cancer. Exposure to Agent Orange was not associated with an increased risk of breast cancer. Evidence regarding EDCs was limited. No paper directly measured exposure to AHOBP or depleted uranium, but deployments with known exposures to AHOBP or depleted uranium were associated with an equivalent/lower risk of breast cancer.

Conclusions: Women are the fastest growing population within the military, and breast cancer poses a unique risk to women Veterans who were affected by MEE during their service. Unfortunately, the literature on MEE and breast cancer is mixed and limited, in part due to the Healthy Soldier Paradox and poor classification of exposure(s).

KEYWORDS

female, breast neoplasm, women veterans, war, environmental epidemiology

Introduction

The number of women Veterans served by the Department of Veterans Affairs - Veterans Health Administration (VA) more than quintupled between 2000 and 2021 (159,810 to 870,000+) (1, 2), while the number of men grew substantially slower over the same period (2, 3). In 2020, women comprised 19% of all military branches (2, 4), which highlights an ongoing need for the expansion of women-specific health services. The 2023 Office of Women's Health - State of Reproductive Health governmental report found that abnormal breast conditions were reported as one of the top five reproductive and sexual health concerns for women Veterans aged 45+ (5). As VA projects the resources needed to care for the expanding women Veteran population, clinical and educational efforts must consider the unique health concerns faced by women Veterans.

Breast cancer (BC) is the most prevalent cancer among women, with around 300,000 cases diagnosed in the United States (U.S.) annually (6). One out of every eight women will be diagnosed at least once in their lifetime (6). The incidence rate (IR) of BC peaks in the 60s and 70s for women and the mortality rate increases exponentially with age (7), with Black women having the highest risk of mortality out of all racial and ethnic groups in the U.S. While the IR of BC has increased over the past two decades, the mortality rate has lowered substantially following advancements in early detection and treatment (7). Conversely, less than 1% of all BC patients are men (8) but BC in men is deadlier than in women (8). Military men with BC tend to present at a higher stage and with a larger tumor size than military women with BC, though demographics or tumor characteristics do not fully explain the higher rate of mortality in men with BC (9). BC is of great concern to VA and is a presumptive condition under The Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics (PACT) Act of 2022. Presumptive conditions allow Veterans to receive care for ongoing health concerns that are of unknown etiology, and can be presumed to be related to service (10). Cancer of any kind remains an ongoing concern for Veterans as they age, and especially among Veterans with military environmental exposures (MEE).

The rates of cancers differ among active-duty personnel and the general U.S. population (11). Over 800 active-duty personnel receive a cancer diagnosis yearly, and tumor etiology is often correlated with service characteristics and MEE (12). These exposures include, but are not limited to, airborne hazards and open burn pits (AHOBP), asbestos, biological and chemical warfare tests, contaminated water, chemical agent resistant coating paint, embedded substances such as depleted uranium and lead, fuels, industrial solvents, ionizing radiation, mefloquine for malaria, nerve agents, noise, pesticides, perfluoroalkyl and polyfluoroalkyl substances, pyridostigmine bromide pills for sarin gas exposure, tactile herbicides, and vaccines. Cancer among current and former military personnel with known MEE persists as a complex health concern (12–15).

The current literature on MEE and cancer is limited. For example, the tactile herbicide Agent Orange was linked to an increased incidence of several cancers, including leukemia and cancers that start in soft tissues (16), and a slightly higher rate of BC was found among military personnel when compared to civilians (17). However, higher rates of BC may be tied to confounding risk factors in military personnel, such as delayed age of first childbirth or increased use of contraceptives. Additionally, military personnel often have greater access to routine screening, resulting in quicker identification of early-stage BCs (18, 19). In other words, tying BC incidence to MEE rather than characteristics associated with service (i.e., confounding factors) is a difficult task.

Combat exposure has increased from 7% to 24% when comparing pre-1990 to post-1990 women Veterans, suggesting that MEE concerns may grow among women Veterans in the coming decades (20). However, few have investigated BC in association with specific MEE. Therefore, we conducted a scoping review to determine whether deployment/military service and MEE affect the risk of BC among active-duty personnel and Veterans.

Methods

Search strategy

Unlike systematic reviews that focus on a specific research question, scoping reviews ask broad research questions to characterize and understand a developing and heterogenous area within the literature (21). Search terms were compiled using PubMed's Medical Subject Headings (MeSH) trees and through consultation with the California War Related Illness and Injury Study Center (CA WRIISC), the Women's Operational Military Exposure Network Center of Excellence (WOMEN CoE) and Advisory Board, and staff oncologists at VA Palo Alto Health Care System. Relevant articles were searched for in PubMed and Embase and terms can be found in the notes of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 1). Some articles broadly examined cancer incidence and did not mention BC in the title or abstract, but included estimates of BC within the results/tables. Therefore, four authors (AIB, DJJ, DKG, MTA) screened citations from the included articles to find these additional manuscripts.

Inclusion criteria

To be included, studies had to: (1) enroll active-duty personnel, Reservists, or Veterans, (2) measure MEE or military service/deployment, (3) concern BC risk (i.e., papers on BC mortality were excluded), and (4) have an English full-text.

Study selection

Covidence software was used to collate and screen the articles. Four authors (AIB, DJJ, DKG, MTA) screened titles/abstracts and full-texts and met weekly to resolve disagreements through discussion. The database search was conducted on June 16,

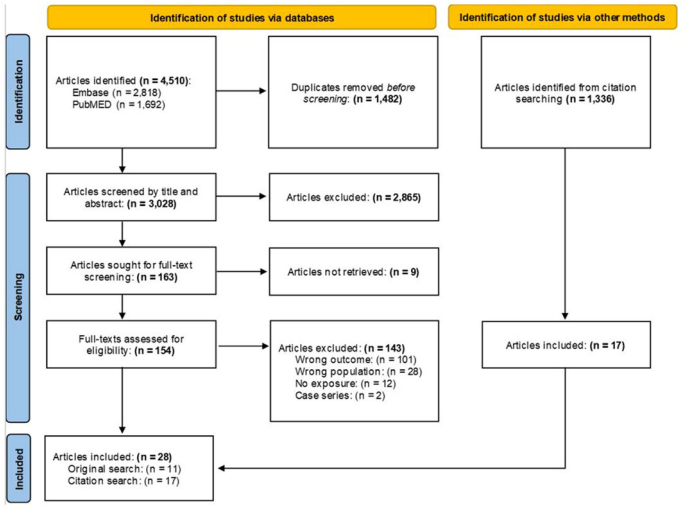


FIGURE 1
PRISMA flow chart. MeSH Trees used: Diseases Category ==> Neoplasms ==> Neoplasms by Site ==> Breast Neoplasms. Titles and abstracts were searched using the terms: ("breast cancer*" OR "breast neoplasm*" OR "breast tumor*" OR "breast metas*" OR "mammary metas*" OR "mammary cancer*" OR "malignant neoplasm* of the breast*" OR "malignant neoplasm* of breast*" OR "breast malignant neoplasm*" OR "malignant tumor* of breast*" OR "malignant tumor* of the breast*" OR "breast malignant tumor*" OR "cancer of breast*" OR "cancer of the breast*" OR "mammary carcinoma*" OR "mammary neoplasm*" OR "breast carcinoma*" OR "mastect*" OR "lumpect*" OR "mammogr*") AND (Veteran* OR military OR combat OR deploy* OR undeploy* OR soldier* OR war OR wars OR warzone OR "department of defense" OR DOD OR front-line* OR duty OR enlist*). Asterisk wildcards were used to find word endings. Terms were left purposefully broad to examine the largest possible selection of the literature. Prospective or retrospective cohort, case-control, cross-sectional, ecological, or related study designs (e.g., case-cohort) were included. Case studies, case series, reviews and meta-analyses, book chapters, theses, and dissertations were excluded.

2023, and resulted in a total of 4,510 articles. After the removal of 1,482 duplicates, 3,028 titles and abstracts were screened and 2,865 were excluded. A total of 163 full-texts were assessed, of which 11 were included. After screening an additional 1,336 citations from the included articles, 17 were retained for a final total of 28 articles.

Data extraction

Data extraction was completed by four authors (AIB, DJJ, DKG, MTA) with each paper receiving at least two checks for accuracy and included the following headings: author/publication year, sample characteristics, sample size, exposure, results, warfare era/service years, and diagnosis years. See Table 1 for the characteristics of each study.

Results

In total, 28 papers were synthesized. Sample size ranged from 64 to millions. Several military conflicts were included: Malayan Emergency, Vietnam War, Israel-Lebanon Conflicts, Persian Gulf War, Kosovo War, Bosnian War, Croatian War of Independence, and post-9/11 conflicts (Operation Enduring Freedom [OEF], Operation Iraqi Freedom [OIF], Operation New Dawn [OND]). More than half of the studies used a case-control or cohort study design. Several MEE were examined: military service/deployment, volatile organic compounds (VOCs), endocrine-disrupting chemicals (EDCs), Agent Orange, and ultraviolet B radiation (Vitamin D synthesis).

Military service/deployment

Twenty-three papers measured BC among military personnel and those deployed to specific conflicts (17, 22, 23, 25–33, 37–42, 44–48).

Risk compared to civilians & standardized rates

Nine papers compared risk of BC in military personnel compared to civilians or standardized national rates. Zhu and colleagues (2009) conducted a cohort study and compared military and civilian cancer surveillance data. They found a slightly higher IRR for Black military women 1.37 [1.21, 1.55] and for White military women 1.19 [1.09, 1.30] when compared to civilians (17). Katuwal and colleagues (2018) carried out a cohort study of nearly 7.5 million Nordic women from 1961-2005 and found roughly 375,000 cases of BC. Military personnel had the greatest SIR for BC at 1.58 [1.03, 2.32] (29). Storm and colleagues (2006) followed 460 women military personnel who deployed to the Balkans and found no significantly increased risk (Standardized Incidence Ratio [SIR]=1.5 [0.3, 4.3]) (37). Yamane and colleagues (2006) compared BC IRs among 76,477 U.S. Air Force active-duty personnel to national IRs, and found the rates to be statistically equivalent (SIR=0.88 [0.76, 1.01]) (41). Yi (42) included 185,265 male Vietnam Veterans from Korea (n=8 cases), but found a statistically equivalent rate of BC when compared to the general

TABLE 1 Characteristics of the included studies.

Study Name (Year)	Sample Characteristics (Country/ Region)	Sample Size	Exposure	Results	Era/ Service Years	Diagnosis Years
Ajene et al. (2004) (22)	Navy active-duty personnel (U.S.)	78 women	Military Service (Various Periods)	For women, breast cancer was observed at a rate of 8.5 cases per 100,000 personnel, with a rate of 56.4 cases per 100,000 personnel seen in the 40+ age group. The authors state that their rate was much lower than historical Navy rates (34.1 per 100,000) and Surveillance, Epidemiology, and End Results (SEER) rates (143.2 per 100,000), likely due to the younger age of the sample.	N/A	1998-2000
Armed Forces Health Surveillance Center (2013)	Active-duty personnel (U.S.)	All women in active component of Armed Forces with any service from 2000-2012	Military Service (Various Periods)	Between 2000 and 2012, 1,092 women were diagnosed with breast cancer. The overall crude incidence rate was 40.6 per 100,000 person-years. The annual incidence rate was lowest in 2006 at 28.6 per 100,000 person-years and highest in 2001 at 53.6 per 100,000 person-years. Active-duty women who served in the Air Force (IRR=2.4), identified as non-Hispanic Black (IRR=2.2), were older (40+) (IRR=27.1), senior officers (IRR=4.1), and women serving in healthcare roles (IRR=2.1) or administrative/supply roles (IRR = 1.6) had an increased risk of breast cancer. Women who served in the Marine Corps (reference group), identified as Hispanic (reference group), were younger women (<25) (reference group), were junior enlisted (reference group), and women with "other" duties (reference group) had a decreased risk of breast cancer. Women with combat-specific duties had a marginally increased risk of breast cancer (IRR = 1.1) when compared to women with "other" duties.	N/A	2000-2012
Bytnar et al. (2023) (23)	Active-duty personnel and civilians (U.S.)	Several million (not stated)	Military Service (Various Periods)	No significant increased risk of breast cancer was found among active-duty personnel compared to the general population, and this did not differ by race: White IRR=1.06 [0.98, 1.13]; Black IRR=1.06 [0.96, 1.16] women service members. When stratified by age, Black (IRR=0.98 [0.86, 1.12]) and White (IRR=0.96 [0.85, 1.07]) women military service members aged 20-39 had no significant increased risk of breast cancer when compared to the general population. However, Black (IRR=1.17 [1.01, 1.34]) and White (IRR=1.15 [1.04, 1.26]) women military service members aged 40-59 had a statistically increased risk of breast cancer when compared to the general population. Further stratification by cancer stage (local, regional, and distant) showed only a significant age effect for local breast cancers (confined to the breast), but not for regional (extends to the surrounding lymph nodes, organs, or tissues) or distant cancers (extends to distant organs or lymph nodes).	N/A	1990-2013
Carran et al. (2012) (24)	Adult children of Veterans (New Zealand)	76 adult children of New Zealand Veterans	Dibutylphthalate was applied daily to soldiers' clothing as an acaricide during the Malayan Emergency	Authors found a slightly increased risk of breast cancer among female adult children of New Zealand Veterans deployed to Malayasia who were exposed to the endocrine-disrupting chemical dibutylphthalate. However, results were based on 3 incident cases.	Malayan Emergency: 1948-1960	N/A
Gaffey et al. (2023) (25)	Veterans (U.S.)	576,601 women, 24.6%	Military Service (Post-9/ 11 conflicts)	Those who deployed in support of OEF/OIF were 23% [14%, 27%] less likely to receive a breast cancer diagnosis than women who did not deploy after adjusting for age, race and ethnicity, marital status,	OEF/OIF	2001-2021

(Continued)

TABLE 1 Continued

Study Name (Year)	Sample Characteristics (Country/ Region)	Sample Size	Exposure	Results	Era/ Service Years	Diagnosis Years
		(n=141,935) deployed		military service connection, smoking status, body mass index, history of alcohol use disorder, hormonal contraceptive use, and hormone replacement therapy use. IRs were 34 and 44 per 100,000 person-years for OEF/OIF-deployed Veterans and for those not deployed in support of OEF/OIF, respectively.		
Hansen et al. (2012) (26)	Military personnel (Denmark)	218 cases of breast cancer 899 age-matched controls	Military night shift work, leisure time sun exposure, and diurnal preference	Women with any history of night shift work exhibited an increased odds of breast cancer (OR: 1.4 [0.9, 2.1]) compared to those who never worked night shifts. Breast cancer risk increased with longer duration of night shift work and cumulative number of shifts, but risk was neutral for those working fewer than three-night shifts per week. Women with the highest tertile of cumulative night shift exposure had an increased odds of breast cancer (OR=2.3 [1.2, 4.6]). Women with a morning chronotype preference (natural inclination to be more active during the morning) and intense night shifts had the largest risk (OR=3.9 [1.6, 9.5]). These findings persisted after adjusting for age, hormone replacement therapy, number of childbirths, age at menarche, years of education, sunbathing frequency, and smoking status.	N/A	1990-2003
Hoiberg & Ernst (1980) (27)	Navy active-duty personnel (U.S.)	364 women officers and enlisted personnel	Military Service (Various Periods)	The overall breast cancer incidence rate among women was 34.1 per 100,000 people, with rates increasing with age. The highest rate was among women 46+ years old at 496.3 per 100,000 people. Rates by Age: 17-25: 1.0, 26-35: 33.0, 36-45: 262.2, 46+: 496.3 per 100,000	1966-1976	1965-1976
Kang et al. (2000) (28)	Veterans (U.S.)	6430 women Veterans: 3,393 Vietnam War Veterans 3,038 non-Vietnam War Veterans	Military Service (Vietnam War)	Breast cancer was reported in 5% of Vietnam Veterans and 4.1% of non-Vietnam Veterans. The crude and adjusted odds of developing breast cancer were not statistically different between the two Veteran groups (Crude OR=1.22 [0.96, 1.55]; Adjusted OR=1.18 [0.91, 1.51]) controlling for age, race, branch, pay grade, marital status, nursing occupation, smoking, alcohol consumption, family history, use of oral contraceptives, and use of postmenopausal estrogen or progestin use. Risk of breast cancer increased with age.	Vietnam War	N/A
Katuwal et al. (2018) (29)	Military personnel and civilians (Finland, Sweden, Norway, Denmark, Iceland)	7.5 million adults	Military Service (Various Periods)	26 cases of breast cancer were reported among military personnel from four out of the five Nordic countries. Of the 54 occupational categories, military personnel had the highest overall risk for breast cancer (SIR: 1.58 [1.03, 2.32]). SIR was also provided by histology (ductal and lobular breast cancer) and country, with highest SIR observed for ductal breast cancer (SIR=1.41 [0.75, 2.42]) and Denmark (SIR=2.14 [0.70, 5.01]).	1961-2005 divided into three periods: 1961-1975 1976-1990 1991-2005	1961-2005
Lee et al. (2023) (30)	Veterans (Korea)	1,301,331 Korean Vietnam War Veterans	Military Service (Vietnam War)	A total of 123 new cases of breast cancer were identified among Korean Vietnam War Veterans. The breast cancer incidence rate was 5.1 per 100,000 person-years; however, the SIR was not significantly elevated (SIR=1.05 [0.88, 1.26]).	Vietnam War	2002-2020
Lee et al. (2016) (31)	Active-duty personnel (U.S.)	All individuals in active component of Armed Forces with	Military Service (Post-9/ 11 conflicts)	652 cases of breast cancer were observed (IR=31.8 per 100,000). Active-duty women who identified as non-Hispanic Black (Risk Ratio [RR]=1.29), were officers (RR=2.73), had a healthcare occupation within the military (RR=1.52), and were older (20-24 as reference: 25-29	July 1, 2005-December 31, 2014	N/A

(Continued)

TABLE 1 Continued

Study Name (Year)	Sample Characteristics (Country/ Region)	Sample Size	Exposure	Results	Era/ Service Years	Diagnosis Years
		any service from 2005-2014		RR=3.29; 30-34 RR=9.65; 35-39 RR=22.32; 40+ RR=59.18) had an increased risk of breast cancer.		
Macfarlane et al. (2003) (32)	Veterans (United Kingdom)	51,721 Gulf War Veterans and 50,755 service personnel	Military Service (Gulf War)	Non-Gulf War service personnel were matched for age, sex, rank, service, and level of fitness. A total of 6 occurrences of breast cancer in Gulf War cohort and 10 in the non-Gulf War cohort were identified. Breast cancer risk did not differ between the cohorts (IRR=0.59 [0.21, 1.62]). There was no change in the IRR after adjusting for smoking behavior and alcohol consumption.	Gulf War	1991-2002
Mahar et al. (2022) (33)	Military Veterans and Royal Police Veterans (Canada)	30,576 Veterans 122,293 matched general population	Military Service (Gulf War & Post-9/ 11 conflicts)	The incidence rate of breast cancer in women Veterans was 30.01 [18.91, 47.63]) per 100,000 person-years, compared to the general population (25.06 [19.46, 32.27] per 100,000 person-years (matched on age, sex, residential geography, and community socioeconomic status). Women Veterans had no statistically significant increased risk of breast cancer when compared to the general population, before or after adjusting for the matching variables (Crude HR=1.20 [0.71, 2.03]; Adjusted HR=1.19 [0.70, 2.02]).	Gulf War and Post 9/ 11 conflicts: April 1, 1990- December 31, 2018	Baseline health insurance date following military service – 2019
Mohr et al. (2013) (34)	Active-duty personnel (U.S.)	600 incident cases of breast cancer 600 controls	25-hydroxyvitamin D (25(OH)D)	In the adjusted models, no statistically significant relationship was found between serum Vitamin D levels and odds of breast cancer. Inverse trends were present among women with a blood draw within 90 days of their breast cancer diagnosis, where women in the lowest quintile of 25(OH)D had a higher estimated risk of breast cancer (OR=3.3 [1.6, 7.1]) compared to women in the highest quintile. It was not made clear by the authors if Vitamin D levels were affected by fortified foods or supplements in the sample.	1994-2009	N/A
Rennix et al. (2005) (35)	Army active-duty personnel (U.S.)	274,596 women Army personnel	Volatile Organic Compounds (VOCs)	184 cases of invasive breast cancer were identified. Incidence of breast cancer was significantly elevated in women ages 17-34 years, especially among Black women, when compared to general population. Women in occupations with medium or high potential exposure to VOCs (e.g., chlorinated hydrocarbons, aromatics, alcohols, aldehydes, ketones, other solvents and distillates) had an IRR of 1.48 [1.01, 2.07], adjusting for race, age at diagnosis, and year of diagnosis. Enlisted Black women had higher IRR compared to enlisted White women (IRR=1.43 [1.01, 2.07]) and IRR increased with age at diagnosis (IRR=2.17 [1.98, 2.39]) and year of diagnosis (IRR=1.24 [1.11, 1.39]) (I.e., more recent time-periods had an increased risk compared to older time-periods).	Pre-Gulf War & Gulf War: 1980-1996	1980-1996
Ruckart et al. (2015) (36)	Marines stationed at Camp Lejeune (U.S.)	71 male breast cancer cases 373 controls	VOC-contaminated drinking water	The odds for breast cancer among ever being stationed at Camp Lejeune was 1.14 [0.65, 1.97]. Adjusted ORs for high residential cumulative exposures to tetrachloroethylene, t-1,2 dichloroethylene, and vinyl chloride were 1.20 [0.16, 5.89], 1.50 [0.30, 6.11], and 1.19 [0.16, 5.89], respectively, with a monotonic exposure response relationship for PCE only. Ever being stationed at Camp Lejeune and high cumulative exposures to VOCs were associated with an earlier age of onset for male breast cancer, but	Camp Lejeune Garrison Exposure: 1953-1987	2004-2012

(Continued)

TABLE 1 Continued

Study Name (Year)	Sample Characteristics (Country/ Region)	Sample Size	Exposure	Results	Era/ Service Years	Diagnosis Years
				confidence intervals were wide due to the small sample size.		
Storm et al. (2006) (37)	Balkan Veterans (Denmark)	460 women	Military Service (Balkan Conflicts)	Among military women, there were 3 observed cases and no statistically significant increased risk of breast cancer (SIR=1.5 [0.3, 4.3]). The authors suggested that exposure to depleted uranium was a major concern during these conflicts, though it was not directly measured.	Balkan war (January 1, 1992-December 31, 2001)	1992-2002
Strand et al. (2014) (38)	Military peacekeepers (Norway)	268 women	Military Service (Kosovo)	Of the 2 cancers observed in women, 1 was breast cancer for a combined SIR of 0.55 [0.07, 1.98].	First Gulf War and the Balkans conflict	1999-2011
Strand et al. (2015) (39)	Military peacekeepers (Norway)	21,582 military peacekeepers	Military Service (Lebanon)	No military peacekeeper was diagnosed with breast cancer (SIR=0.00 [0.00, 2.07]).	Israel-Lebanon war (1978-1998)	1978-2012
Strand et al. (2020) (40)	Military peacekeepers (Norway)	275 women	Military Service (Kosovo)	Of the 8 cancers observed in women, 3 were cases of breast cancer (all-site cancer SIR=1.10 [0.47, 2.16]). There was 1 case of breast cancer observed in men (SIR=6.00 [0.15, 33.4]).	Bosnian war/ Balkan conflict	1999-2016
Yamane et al. (2006) (41)	Air Force active-duty personnel (U.S.)	76,477 women	Military Service in the U.S. Air Force (Gulf War & Post-9/ 11 conflicts)	Breast cancer was listed as the most frequent cancer among women in the Air Force (26.7% of all cancers in women), but service members did not have a statistically increased risk (SIR=0.88 [0.76, 1.01]).	1989-2002	1989-2002
Yi (2013) (42)	Veterans (Korea)	185,265 men	Military Service (Vietnam War)	There were 8 observed cases of breast cancer, but service members did not have a statistically increased risk (SIR=1.37 [0.67, 2.83]).	Vietnam War	1992-2003
Yi & Ohrr (2014) (43)	Veterans (Korea)	180,251 Veterans	Agent Orange	Vietnam-era Veterans exposed to high levels of Agent Orange did not have an increased risk of breast cancer (Adjusted HR=0.53 [0.12, 2.26]). The authors did not specify the number of women Veterans in the study, though it is presumed to include very few, if any, given the cohort characteristics from a previous publication (Yi, 2013) (42).	Vietnam War	1992-2003
Young et al. (2010) (44)	Veterans (U.S.)	621,902 Gulf War Veterans (43,533 women)	Military Deployment	Compared to non-Gulf War Veterans, Gulf War Veterans had a statistically equivalent incidence rate of breast cancer among men (PIR=0.78 [0.39, 1.58]) and women (PIR=1.01 [0.86, 1.20]). These rates did not change appreciably when restricting the sample to Gulf War Army or Gulf War Marine Corps members.	Gulf War	1991-2006
Zhu et al. (2009) (17)	Active-duty personnel and civilians (U.S.)	Several million (not stated)	Military Service (Gulf War & Post-9/ 11 conflicts)	Breast cancer was the most common cancer among active-duty military women (n=864). The authors found a slightly higher IRR for Black military women 1.37 [1.21, 1.55] and for White military women 1.19 [1.09, 1.30] when compared to civilians. When examining diagnosis year (1990-1994 to 2000-2004), breast cancer incidence did not statistically differ for the military population.	Gulf War & Post-9/ 11 conflicts	1990-2004
Zullig et al. (2012) (45)	Veterans (U.S.)	4,875,740 Veterans 31,010 incident cancers	Military Service (Various Periods)	Among women Veterans, breast cancer was the most diagnosed cancer, accounting for 29.5% of all female cancers. Among men, breast cancer accounted for 0.2% of all male cancers.	N/A	2007

(Continued)

TABLE 1 Continued

Study Name (Year)	Sample Characteristics (Country/ Region)	Sample Size	Exposure	Results	Era/ Service Years	Diagnosis Years
Zullig et al. (2017) (46)	Veterans (U.S.)	5,894,299 Veterans 46,166 incident cancers	Military Service (Various Periods)	Among women Veterans, breast cancer was 30.23% of all female cancers. Among men, breast cancer accounted for 0.17% of all male cancers. Results did not change appreciably from the Zullig et al. (45) findings, although breast cancer became a slightly higher proportion of all cancer cases among Black (1.26%) and "Other Minority" (1.58%) Veteran groups when compared to White Veterans (0.96%). This difference could be explained by the increase of Asian, Black, Hispanic, and Native/Indigenous women in the military.	N/A	2010
Zullig et al. (2019) (47)	Veterans (U.S.)	1,330 women diagnosed with invasive cancer	Military Service (Various Periods)	Breast cancer was the most diagnosed cancer (approximately 30%) among women Veterans with an invasive cancer diagnosis. A total of 402 breast cancer cases were identified, which did not change appreciably by race. Most women Veterans presented with an early stage of breast cancer (50% Stage 1; 32% Stage 2; 14% Stage 3; 4% Stage 4), unlike women Veterans diagnosed with lung and bronchus (27% Stage 3; 35% Stage 4) and colorectal cancers (23% Stage 3; 21% Stage 4).	N/A	2010

APR, Adjusted Proportional Incidence Ratio; HR, Hazard Ratio; IRR, Incidence Rate Ratio; PIR, Proportional Incidence Rate; SIR, Standardized Incidence Ratio; OR, Odds Ratio; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; U.S., United States of America; N/A, Not Available.
The sample for which breast cancer outcomes are reported are included in the sample size column of Table 1. For papers that provided outcomes for both men and women, the full sample size was included. For papers that examined breast cancer exclusively in either men or women, only the corresponding sample size was included (vs the entire sample).

population (SIR=1.37 [0.67, 2.83]) (42). Strand and colleagues (2015) conducted a cohort study of 21,582 Norwegian male military peacekeepers deployed to Lebanon and zero cases of BC were observed (SIR=0.00 [0.00, 2.07]) (39). Mahar and colleagues (2022) published a cohort study of 30,576 Canadian Veterans and police and 122,293 matched controls. Women Veterans had no statistically significant increased risk of BC (adjusted HR=1.19 [0.70, 2.02]) (33). Bytnar and colleagues (23) reconducted the analysis from Zhu et al. (17) using military (n=1,185 cases) and civilian (n=183,042 cases) cancer surveillance data. Black (IRR=1.06 [0.96, 1.16]) and White (IRR=1.06 [0.98, 1.13]) women military personnel had no significant increased risk of BC when compared to the general population (23). Lee and colleagues (2023) compared 250,842 Vietnam-era Korean Veterans (353 women) with 1,050,489 matched Korean civilians (1,695 women) and observed 123 cases of BC (IR=5.1 [4.2, 6.0]), but found no significantly increased rate (SIR=1.05 [0.88, 1.26]) (30).

Demographics & work characteristics

Six papers provided estimates that differed by demographic or work characteristics. Hansen and Lassen (26) studied 218 women with BC and 899 age-matched controls from a nested cohort study of 18,551 women Danish military employees. Women with the highest tertile of cumulative night shift military work exposure had an increased odds of BC (OR=2.3 [1.2, 4.6]) and women with a morning chronotype preference (inclination to be more active during the morning) and intense night shifts had the largest risk (OR=3.9 [1.6, 9.5]) (26). The Armed Forces Health Surveillance Center (2013) published a cohort study and found that the IR of BC among active-duty service women was 40.6 per 100,000 from 2000-2012 (48). Non-Hispanic Black women, older women, senior officers, and women serving in healthcare or administrative roles had an increased risk of BC (48), and women with combat-specific duties had a mildly increased risk. Conversely, women who served in the U.S. Marine Corps, those who identified as Hispanic, younger women, junior enlistees, and women with "other" duties had a decreased risk of BC (48). Lee and colleagues (2016) examined all U.S. active-duty personnel from 2005-2014, of which 652 cases of BC were observed (IR=31.8 per 100,000). Active-duty women who were non-Hispanic Black, officers, healthcare workers, or older had an increased risk of BC (31). Zullig and colleagues (2012) found no major differences in BC incident diagnoses among Black, "Other," and White Veterans from the 2007 Veterans Affairs Central Cancer Registry (45). Zullig and colleagues (2017) updated their 2007 analysis (Zullig et al. (45),) with data from 2010, but results did not change appreciably (46). Zullig and colleagues (2019) conducted a cross-sectional study of 1,330 incident invasive cancer cases among women Veterans in 2010; BC was the most common invasive cancer (30.23%, n=402), but it did not differ by race (47).

Deployment characteristics

Four papers compared deployment characteristics. Kang and colleagues (2000) followed 3,392 Vietnam-era deployed women Veterans (n=170 cases) and 3,038 Vietnam-era women Veterans who never deployed to Vietnam (n=126). Both the crude (odds ratio

[OR]=1.22 [0.96, 1.55]) and adjusted ORs (OR=1.18 [0.91, 1.51] suggested that the odds of developing BC were statistically equivalent between groups (28). Macfarlane and colleagues (2003) followed a cohort of 51,721 Gulf War Veterans and 50,755 matched service personnel and found no increased risk among Veterans that deployed in support of the Gulf War (IRR=0.59 [0.21, 1.62]) (32). Young and colleagues (2010) followed 621,902 Gulf War Veterans and 746,248 non-Gulf War Veteran controls. Gulf War Veterans had a statistically equivalent IR of BC among men (Proportional IR [PIR]=0.78 [0.39, 1.58]) and women (PIR= 1.01 [0.86, 1.20]), respectively (44). Gaffey and colleagues (2023) conducted a cohort study of 576,601 women Veterans (n=141,935 OEF/OIF-deployed). Those who deployed in support of OEF/OIF were 23% [17%, 29%] less likely to be diagnosed with BC (RR=0.77; [0.71, 0.83]) (25).

General incidence rates

Four studies provided general incidence rates without a comparison group. Hoiberg & Ernst (27) conducted a cohort study of 364 active-duty Navy women (n=47 cases) and found an IR by age (overall 34.1 per 100,000) (27). Ajene and colleagues (22) conducted a cohort study of 78 women Naval personnel and found a BC IR of 8.53 per 100,000 persons (22). Strand and colleagues (2014) analyzed 268 Norwegian women military peacekeepers deployed to Kosovo, and one incident case of BC was observed (38). Strand and colleagues (2020) reanalyzed their 2014 cohort of Norwegian military peacekeepers deployed to Kosovo: 275 women were included and three BC cases were found (40).

Volatile organic compounds & endocrine-disrupting chemicals

Two papers measured exposure to VOCs. Rennix and colleagues (2005) conducted a cohort study of 274,596 enlisted Army women. Exposure to VOCs was tied to job titles, categorized as none, low, medium, or high (35). None of the top military occupational specialties were associated with BC risk. However, history of moderate or high exposure to VOCs was associated with a 48% higher incidence (IRR=1.48 [1.03, 2.12]) (35). Ruckart and colleagues (2015) led a case-control study of Marines stationed at the Camp Lejeune garrison who were exposed to contaminated groundwater (71 cases of male BC, 373 controls). Adjusted ORs for high residential cumulative exposures to tetrachloroethylene, t-1,2 dichloroethylene, and vinyl chloride were 1.20 [0.16, 5.89], 1.50 [0.30, 6.11], 1.19 [0.16, 5.89], respectively (36). Ever being stationed at Camp Lejeune and high cumulative exposures to VOCs were associated with an earlier age at onset for male BC, though it was not statistically significant (36).

Carran and Shaw (24) conducted a cohort study of 71 Veterans and 76 female adult children of Veterans. They found an increased risk of BC among female adult children of New Zealand Veterans deployed to Malaya who were exposed to the EDC dibutylphthalate (24).

Tactile herbicides (agent orange)

One paper directly measured exposure to the tactile herbicide, Agent Orange. Yi & Ohrr (43) mapped each unit's post location and tactile area of responsibility to known geographic regions of chemically treated areas. Korean Vietnam-era Veterans (n=180,251 with follow-up from 1992-2003) were given an Exposure Opportunity Index and stratified into categories (high vs. low) in a cohort study (43). Exposure to high levels of Agent Orange was not associated with an increased risk of BC (adjusted HR=0.53 [0.12, 2.26]) (43).

Serum 25-hydroxyvitamin D/ultraviolet B sunlight exposure

Mohr and colleagues (2013) examined the relationship between pre-diagnostic serum 25-hydroxyvitamin D (Vitamin D) and risk of BC among active-duty personnel using a nested case-control study with 600 incident cases and 600 controls. No statistically significant relationship was found between serum Vitamin D levels and odds of BC.

Discussion

This scoping review covered 28 papers on the relationships between military service, MEE, and BC among active-duty personnel and Veterans. Unfortunately, evidence is still needed before conclusive remarks can be made. Most papers on military service or deployment reported a decreased or statistically equivalent risk of BC, while a few larger surveillance studies found an increased risk. When considering the effects of military service and deployment on risk of BC, individual and environmental risk factors should be considered (49). If risk factors are not controlled for, findings may be biased by the Healthy Soldier Paradox (25).

The Healthy Soldier Paradox occurs when healthier personnel are deployed in support of military operations and sicker personnel are not deployed or are given different military occupations (50). This form of sampling bias can lead to inaccurate associations between deployment and health outcomes, where deployed individuals appear to have a lower risk of adverse outcomes than non-deployed personnel. Recent work has called the Healthy Soldier Paradox into question for OEF/OIF/OND-era Veterans (51), as OEF/OIF/OND-era Veterans have a higher risk of mortality when compared to the general U.S. population. However, it may be that healthy solider effects vary by outcome, such that OEF/OIF/OND-era Veterans may have a higher risk of mortality but a decreased risk of BC (25). In a study of 31,548 military healthcare

system users with BC and 63,096 controls with BC, the military healthcare system users had a significantly lower risk of mortality (24% [20%, 29%]) (52). This lower mortality risk was found across all ages, Stages II, III, and IV tumors, and for Black and White patients (52), suggesting that military personnel may also benefit from an equal-access healthcare system (18, 19).

Many studies have few years of follow-up, small sample sizes, lack accurate measurement, and suffer from misclassification bias. *Follow-Up*: Epidemiological analyses of cancer require a sufficiently long follow-up so that cases can occur. Most cases of BC occur in women aged 50+ (6), and many personnel from post-9/11 conflicts may not be in this age group yet. *Small Sample Size*: Women personnel and Veterans with MEE concerns are still a relatively small group from an epidemiological perspective. *Accurate Measurement of Exposure*: Investigators often rely on participant recall for MEE (leading to recall bias) and do not consider that most MEE are transient, may occur more than once, and may occur with varying severity. *Accurate Measurement of Outcome*: Measurement of BC has improved in recent decades due to advances in mammography screening (53) and modern classification codes (e.g., ICD-10). However, characteristics of the breast tumor (e.g., T-stage, N-stage, M-stage) and histological and molecular subtyping are not often explored. *Misclassification Bias*: Misclassification bias reflects an issue with categorizing participants by exposure/outcome status. Without accurately measuring MEE, participants may be misclassified, leading to null results (54). For many articles, exposures are generalized to entire groups, but individual-level data are needed.

Most papers in this review considered military service or military deployment as an exposure when measuring BC risk in personnel. Unlike most social and environmental exposures, military service (yes/no) is not well operationalized and leaves a lot to be desired in terms of specificity. Characteristics of military service (e.g., military occupation and job duties, deployment location, rank, military branch, number of years served, and MEE) should be measured in future studies, as these factors may improve our detection of the Healthy Soldier Paradox. Additionally, tying specific military occupations and job duties to MEE will be crucial for determining causality, and will inform policy and practice regarding the expansion of personal protective equipment and environmental toxin passive monitoring devices in the field.

With these limitations stated, several conclusions may still be found. Exposure to VOCs appears to impact the downstream risk of BC among military personnel (35, 36). Specific VOCs' effects are largely unknown, but the risk of BC appears stronger among women than among men, and the mechanism of action may be through oxidative damage, cytotoxicity, and genotoxicity (55–57). The effects of EDCs have not been sufficiently studied in military samples, but they are known to impact risk of BC in civilians (58). Vitamin D (34, 59, 60) may not be considered an environmental exposure, but ionizing radiation from the sun would be an important MEE. Future work should measure UV exposure, heat, and drought directly. No papers directly assessed the effects of AHOBP or depleted uranium, but many Veterans who deployed in support of Gulf War and OEF/OIF/OND with MEE to AHOBP and depleted uranium are now at an age where BC is a salient concern (61). One large study looked at Agent Orange and BC risk and did not find an association. Unfortunately, no studies were found on other tactile herbicides (e.g., Agents White, Blue, Purple, Pink, Green) or pesticides. Many MEE included in this review were not specific to military populations. VOCs, EDCs, and carcinogenic airborne hazards are well-known occupational exposures in the civilian sector. Too little work has been done to understand if the effects of these generic exposures are moderated by military service. Finally, it is important to recognize that a greater number of high-quality articles will be needed to draw significant conclusions that link MEE and BC, as surveillance cohort studies are insufficient to draw causal links.

Recommendations

Future studies should: 1) Measure MEE in real time (e.g., dose, duration, source, route of entry) using ecological momentary assessment or passive monitoring; 2) Study specific VOCs, EDCs, and AHOBP; 3) Compare deployed to non-deployed military personnel and include a group of civilian controls when possible; 4) Recruit a diverse group of women and gender-diverse personnel, including all military branches, races/ethnicities, ranks, occupations, and deployment locations; 5) Determine warfare theater/era effects; 6) Measure BC histological/molecular subtypes; 7) Expand years of follow-up and increase recruitment; and 8) Explore biological plausibility by tying MEE to specific carcinogenic pathways.

Findings on MEE and BC are varied, in part due to the Healthy Soldier Paradox, potential misclassification of exposure(s), and modest sample sizes. The strongest evidence with reproducible findings appears to be Veterans' increased risk of BC after being exposed to VOCs.

Author contributions

DJ: Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. MA: Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Investigation, Formal analysis, Data curation. DG: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation. AI: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation. JJ: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition. MA: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Women's Operational Military Exposure Network Center of Excellence (WOMEN CoE). The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Acknowledgments

The authors would like to thank the California War Related Illness and Injury Study Center (WRIISC) staff and the Women's Operational Military Exposure Network Center of Excellence (WOMEN CoE) staff and advisory board for their continued support of this project.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Maher N. Understanding sex differences in health and health care utilization among veterans can help guide future veterans administration health care planning and policy. *J Women's Health (2002)*. (2021) 30:916–7. doi: 10.1089/jwh.2020.9009

2. Frayne SM, Mattocks KM. Sourcebook: women veterans in the Veterans Health Administration. In: *sociodemographics and use of VHA and non-VA care (fee)*, (Washington D. C: Department of Veterans Affairs) vol. 2. (2012).

3. Bagalman E. *The number of veterans that use VA health care services: A fact sheet*. Washington (DC: Congressional Research Service (2014).

4. U.S. Department of Defense. 2021 Demographics profile of the military community(2021). Available online at: https://download.militaryonesource.mil/12038/MOS/Reports/2021-demographics-report.pdf.

5. Office of Women's Health. State of reproductive health volume II: VA reproductive health diagnoses and organization of care(2023). Available online at: https://www.womenshealth.va.gov/WOMENSHEALTH/docs/VHA-WH-Reproductive-Health-Report-2023.pdf.

6. Ban KA, Godellas CV. Epidemiology of breast cancer. *Surg Oncol Clinics*. (2014) 23:409–22. doi: 10.1016/j.soc.2014.03.011

7. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast cancer statistics, 2022. *CA: Cancer J Clin*. (2022) 72:524–41. doi: 10.3322/caac.21754

8. Konduri S, Singh M, Bobustuc G, Rovin R, Kassam A. Epidemiology of male breast cancer. *Breast*. (2020) 54:8–14. doi: 10.1016/j.breast.2020.08.010

9. Aggarwal A, Adepoju B, Yacur M, Maron D, Sharma MC. Gender disparity in breast cancer: a veteran population-based comparison. *Clin Breast Cancer*. (2021) 21: e471–8. doi: 10.1016/j.clbc.2021.01.013

10. Department of Veterans Affairs. *The PACT Act and your VA benefits* (2023). Available online at: https://www.va.gov/resources/the-pact-act-and-your-va-benefits/.

11. Byrnes A. VA launches national women veterans oncology system of excellence. *Battling Breast Cancer*. (2021). Available at: https://news.va.gov/press-room/va-creates-national-women-veterans-oncology-system-of-excellence-in-fight-against-breast-cancer/.

12. Lovejoy LA, Shriver CD, Ellsworth RE. Cancer incidence and etiology in the active duty population of US Military. *Military Med*. (2024) 189(1-2):e58–e65. doi: 10.1093/milmed/usac297

13. Ferras M, Dye J, Ayala GX, Schmied E. An examination of factors that influence receipt of reproductive health screenings among female veterans. *Military Med*. (2023) 188:42–8. doi: 10.1093/milmed/usac036

14. Braun LA, Kostas-Polston EA, Miedema J, Hoffecker L, Wilson C. A scoping review of cervical cancer risk factors, prevention, diagnosis, and treatment in US active duty military women. *Women's Health Issues*. (2021) 31:S53–65. doi: 10.1016/j.whi.2021.04.003

15. Cohen BE, Maguen S, Bertenthal D, Shi Y, Jacoby V, Seal KH. Reproductive and other health outcomes in Iraq and Afghanistan women veterans using VA health care: association with mental health diagnoses. *Women's Health Issues*. (2012) 22:e461–71. doi: 10.1016/j.whi.2012.06.005

16. American Cancer Society. *Agent Orange and Cancer Risk* (2023). Available online at: https://www.cancer.org/cancer/risk-prevention/chemicals/agent-orange-and-cancer.html.

17. Zhu K, Devesa SS, Wu H, Zahm SH, Jatoi I, Anderson WF, et al. Cancer incidence in the US military population: comparison with rates from the SEER program. *Cancer Epidemiol Biomarkers Prev*. (2009) 18:1740–5. doi: 10.1158/1055-9965.EPI-09-0041

18. Kvasnovsky CL, Kesmodel SB, Gragasin JL, Punnoose V, Johnson PA, Goel R, et al. Expansion of screening mammography in the Veterans Health Administration: implications for breast cancer treatment. *JAMA surgery*. (2013) 148:999–1004. doi: 10.1001/jamasurg.2013.3738

19. Lairson DR, Chan W, Newmark GR. Determinants of the demand for breast cancer screening among women veterans in the United States. *Soc Sci Med*. (2005) 61:1608–17. doi: 10.1016/j.socscimed.2005.03.015

20. Patten E, Parker K. *Women in the U.S. Military: Growing Share, Distinctive Profile* (2011). Available online at: https://givingtogether.org/resources/Events/Education%20Event%20Veterans%20Handouts/Pew%20Survey%20of%20Women%20Veterans%20December%202011.pdf.

21. Munn Z, Peters MD, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res methodology*. (2018) 18:1–7. doi: 10.1186/s12874-018-0611-x

22. Ajene A, Bohnker B, Malakooti MA, Riegodedios A, Sack DM. Neoplasms in the Navy, 1998–2000: a descriptive analysis of the Physical Evaluation Board database. *Military Med*. (2004) 169:707–11. doi: 10.7205/MILMED.169.9.707

23. Bytnar JA, McGlynn KA, Shriver CD, Zhu K. Cancer incidence in the US military: An updated analysis. *Cancer Res*. (2023) 82:20–0.doi: 10.1002/cncr.34978

24. Carran M, Shaw I. New Zealand Malayan war veterans' exposure to dibutylphthalate is associated with an increased incidence of cryptorchidism, hypospadias and breast cancer in their children. *New Z Med J (Online)*. (2012) 125:52–63.

25. Gaffey AE, Han L, Ramsey CM, Skanderson M, Dziura J, Driscoll M, et al. Post-9/11 deployment history and the incidence of breast cancer among women veterans. *Ann Epidemiol*. (2023) 77:98–102. doi: 10.1016/j.annepidem.2022.11.010

26. Hansen J, Lassen CF. Nested case–control study of night shift work and breast cancer risk among women in the Danish military. *Occup Environ Med*. (2012) 69:551–6. doi: 10.1136/oemed-2011-100240

27. Hoiberg A, Ernst J. Cancer among Navy personnel: incidence and mortality. *Military Med*. (1980) 145:195–200. doi: 10.1093/milmed/145.3.195

28. Kang HK, Mahan CM, Lee KY, Magee CA, Selvin S. Prevalence of gynecologic cancers among female Vietnam veterans. *J Occup Environ Med*. (2000) 42(11):1121–7. doi: 10.1097/00043764-200011000-00018

29. Katuwal S, Martinsen JI, Kjaerheim K, Sparen P, Tryggvadottir L, Lynge E, et al. Occupational variation in the risk of female breast cancer in the Nordic countries. *Cancer Causes Control*. (2018) 29:1027–38. doi: 10.1007/s10552-018-1076-2

30. Lee W, Park S, Kang SK, Ham S, Yoon JH, Choi WJ. Cancer risk in Vietnam war veterans from the Korean Vietnam war veterans' health study cohort. *Front Oncol*. (2023) 13:1048820. doi: 10.3389/fonc.2023.1048820

31. Lee T, Williams VF, Clark LL. Incident diagnoses of cancers in the active component and cancer-related deaths in the active and reserve components, US Armed Forces, 2005-2014. *Msmr*. (2016) 23:23–31.

32. Macfarlane GJ, Biggs AM, Maconochie N, Hotopf M, Doyle P, Lunt M. Incidence of cancer among UK Gulf war veterans: cohort study. *Bmj*. (2003) 327:1373. doi: 10.1136/bmj.327.7428.1373

33. Mahar AL, Aiken AB, Cramm H, Cyr KS, Shellenberger J, Kurdyak P. Cancer incidence among Canadian Veterans: A matched cohort study. *Cancer Epidemiol*. (2022) 79:102199. doi: 10.1016/j.canep.2022.102199

34. Mohr SB, Gorham ED, Alcaraz JE, Kane CI, Macera CA, Parsons JK, et al. Serum 25-hydroxyvitamin D and breast cancer in the military: a case–control study utilizing pre-diagnostic serum. *Cancer Causes Control*. (2013) 24:495–504. doi: 10.1007/s10552-012-0140-6

35. Rennix CP, Quinn MM, Amoroso PJ, Eisen EA, Wegman DH. Risk of breast cancer among enlisted Army women occupationally exposed to volatile organic compounds. *Am J Ind Med*. (2005) 48:157–67. doi: 10.1002/(ISSN)1097-0274

36. Ruckart PZ, Bove FJ, Shanley E, Maslia M. Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: a case control study. *Environ Health*. (2015) 14:1–16. doi: 10.1186/s12940-015-0061-4

37. Storm HH, Jørgensen HO, Kejs AMT, Engholm G. Depleted uranium and cancer in Danish Balkan veterans deployed 1992–2001. *Eur J Cancer*. (2006) 42:2355–8. doi: 10.1016/j.ejca.2006.01.064

38. Strand LA, Martinsen JI, Borud EK. Cancer risk and all-cause mortality among Norwegian military United Nations peacekeepers deployed to Kosovo between 1999 and 2011. *Cancer Epidemiol*. (2014) 38:364–8. doi: 10.1016/j.canep.2014.04.003

39. Strand LA, Martinsen JI, Borud EK. Cancer incidence and all-cause mortality in a cohort of 21 582 Norwegian military peacekeepers deployed to Lebanon during 1978–1998. *Cancer Epidemiol*. (2015) 39:571–7. doi: 10.1016/j.canep.2015.04.011

40. Strand LA, Martinsen JI, Borud EK. A 5-year continued follow-up of cancer risk and all-cause mortality among norwegian military peacekeepers deployed to Kosovo during 1999–2016. *Military Med*. (2020) 185:e239–43. doi: 10.1093/milmed/usz179

41. Yamane GK. Cancer incidence in the US air force: 1989-2002. *Aviation space Environ Med*. (2006) 77:789–94.

42. Yi SW. Cancer incidence in Korean Vietnam veterans during 1992-2003: the Korean veterans health study. *J Prev Med Public Health*. (2013) 46:309. doi: 10.3961/jpmph.2013.46.6.309

43. Yi SW, Ohrr H. Agent Orange exposure and cancer incidence in Korean Vietnam veterans: a prospective cohort study. *Cancer*. (2014) 120:3699–706. doi: 10.1002/cncr.28961

44. Young HA, Maillard JD, Levine PH, Simmens SJ, Mahan CM, Kang HK. Investigating the risk of cancer in 1990–1991 US Gulf War veterans with the use of state cancer registry data. *Ann Epidemiol*. (2010) 20:265–272.e1. doi: 10.1016/j.annepidem.2009.11.012

45. Zullig LL, Jackson GL, Dorn RA, Provenzale DT, McNeil R, Thomas CM, et al. Cancer incidence among patients of the US Veterans Affairs health care system. *Military Med*. (2012) 177:693–701. doi: 10.7205/MILMED-D-11-00434

46. Zullig LL, Sims KJ, McNeil R, Williams CD, Jackson GL, Provenzale D, et al. Cancer incidence among patients of the US Veterans Affairs Health Care System: 2010 update. *Military Med*. (2017) 182:e1883–91. doi: 10.7205/MILMED-D-16-00371

47. Zullig LL, Goldstein KM, Sims KJ, Williams CD, Chang M, Provenzale D, et al. Cancer among women treated in the veterans affairs healthcare system. *J Women's Health*. (2019) 28:268–75. doi: 10.1089/jwh.2018.6936

48. Center (AFHSC AFHS). Incident diagnoses of breast cancer, active component service women, US Armed Forces, 2000-2012. *Msmr*. (2013) 20(9):25–7.

49. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. *Breast Cancer: Targets Ther*. (2019) 11(9):151–64. doi: 10.2147/BCTT

50. Sullivan-Baca E, Rehman R, Haneef Z. An update on the healthy soldier effect in US Veterans. *Military Med*. (2023) 188:3199–204. doi: 10.1093/milmed/usac151

51. Bollinger MJ, Schmidt S, Pugh JA, Parsons HM, Copeland LA, Pugh MJ. Erosion of the healthy soldier effect in veterans of US military service in Iraq and Afghanistan. *Population Health metrics*. (2015) 13:1–12. doi: 10.1186/s12963-015-0040-6

52. Lin J, Hu H, Shriver CD, Zhu K. Survival among breast cancer patients: comparison of the US military health system with the surveillance, epidemiology and end results program. *Clin Breast cancer*. (2022) 22:e506–16. doi: 10.1016/j.clbc.2021.11.010

53. Bytnar JA, Byrne C, Olsen C, Witkop CT, Martin MB, Banaag A, et al. The impact of mammography screening guideline changes among women serving in the US Military. *Military Med*. (2020) 185:e2088–96. doi: 10.1093/milmed/usaa176

54. Spiegelman D. Approaches to uncertainty in exposure assessment in environmental epidemiology. *Annu Rev Public Health*. (2010) 31:149–63. doi: 10.1146/annurev.publhealth.012809.103720

55. Wang F, Li C, Liu W, Jin Y. Oxidative damage and genotoxic effect in mice caused by sub-chronic exposure to low-dose volatile organic compounds. *Inhalation toxicology*. (2013) 25:235–42. doi: 10.3109/08958378.2013.779767

56. Cavallo D, Ursini CL, Fresegna AM, Ciervo A, Maiello R, Buresti G, et al. Occupational exposure in industrial painters: sensitive and noninvasive biomarkers to evaluate early cytotoxicity, genotoxicity and oxidative stress. *Int J Environ Res Public Health*. (2021) 18:4645. doi: 10.3390/ijerph18094645

57. Cetintepe SP, Hazar M, Bilinmiş I, Dilsiz SA, Basaran N. Evaluation of genotoxicity, oxidative stress and immune parameters of auto-paint workers. *Environ Res*. (2023) 237:116970. doi: 10.1016/j.envres.2023.116970

58. Rodgers KM, Udesky JO, Rudel RA, Brody JG. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. *Environ Res*. (2018) 160:152–82. doi: 10.1016/j.envres.2017.08.045

59. Chlebowski RT. Vitamin D and breast cancer incidence and outcome. *Anti-Cancer Agents Medicinal Chem (Formerly Curr Medicinal Chemistry-Anti-Cancer Agents)*. (2013) 13:98–106. doi: 10.2174/187152013804487362

60. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. *Cancers*. (2021) 13:4287. doi: 10.3390/cancers13174287

61. National Academies of Sciences, Engineering, and Medicine. *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. (Washington, DC: The National Academies Press). (2017). doi: 10.17226/23677

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 25 March 2024
DOI 10.3389/fonc.2024.1351839

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Venkateshwar Madka,
University of Oklahoma Health Sciences Center, United States
Aditya Yashwant Sarode,
Columbia University, United States

*CORRESPONDENCE
Jia Luo
jia-luo@uiowa.edu

RECEIVED 07 December 2023
ACCEPTED 14 March 2024
PUBLISHED 25 March 2024

CITATION
Li H, Xu M, Chen D, Wen W and Luo J (2024) Pirfenidone ameliorates alcohol-induced promotion of breast cancer in mice. *Front. Oncol.* 14:1351839. doi: 10.3389/fonc.2024.1351839

Pirfenidone ameliorates alcohol-induced promotion of breast cancer in mice

Hui Li[1], Mei Xu[2], Danlei Chen[3], Wen Wen[1] and Jia Luo[1,4]*

[1]Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, IA, United States, [2]Department of Pharmacology and Nutritional Sciences, University of Kentucky College of Medicine, Lexington, KY, United States, [3]Department of Hepatobiliary Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China, [4]Iowa City VA Health Care System, Iowa City, IA, United States

Purpose: Alcohol consumption increases the risk of breast cancer and promotes cancer progression. Alcohol exposure could affect both processes of the mammary carcinogenesis, namely, the cell transformation and onset of tumorigenesis as well as cancer aggressiveness including metastasis and drug resistance/recurrence. However, the cellular and molecular mechanisms underlying alcohol tumor promotion remain unclear. There are four members of the mammalian p38 mitogen-activated protein kinase (MAPK) family, namely, p38α, p38β, p38γ and p38δ. We have previously demonstrated alcohol exposure selectively activated p38γ MAPK in breast cancer cells *in vitro* and *in vivo*. Pirfenidone (PFD), an antifibrotic compound approved for the treatment of idiopathic pulmonary fibrosis, is also a pharmacological inhibitor of p38γ MAPK. This study aimed to determine whether PFD is useful to inhibit alcohol-induced promotion of breast cancer.

Methods: Female adolescent (5 weeks) MMTV-Wnt1 mice were exposed to alcohol with a liquid diet containing 6.7% ethanol. Some mice received intraperitoneal (IP) injection of PFD (100 mg/kg) every other day. After that, the effects of alcohol and PFD on mammary tumorigenesis and metastasis were examined.

Results: Alcohol promoted the progression of mammary tumors in adolescent MMTV-Wnt1 mice. Treatment of PFD blocked tumor growth and alcohol-promoted metastasis. It also significantly inhibited alcohol-induced tumorsphere formation and cancer stem cell (CSC) population.

Conclusion: PFD inhibited mammary tumor growth and alcohol-promoted metastasis. Since PFD is an FDA-approved drug, the current findings may be helpful to re-purpose its application in treating aggressive breast cancer and alcohol-promoted mammary tumor progression.

KEYWORDS

alcohol use disorders, cancer stem cells, drug therapy, mammary tumors, metastasis

Introduction

Both epidemiological and experimental studies indicate that alcohol consumption increases the risk of breast cancer and promotes cancer progression (1–6). In addition to the promotion of the tumorigenesis, alcohol may also enhance the growth of existing breast tumors and increase the aggressiveness of breast cancer cells to invade and metastasize (5). However, the cellular and molecular mechanisms underlying alcohol tumor promotion remain unclear. We have previously demonstrated that alcohol exposure selectively activated p38γ MAPK without affecting other p38 MAPK isoforms in breast cancer cells *in vitro* and *in vivo* (7–9). p38γ MAPK is a member of p38 MAPK family which contains four isoforms p38α, p38β, p38γ, and p38δ. Although p38γ MAPK has been less investigated, it has unique functions particularly in the regulation of cell cycle progression, mobility, migration/invasion, cancer stem cells (CSCs), and epithelial-mesenchymal transition (EMT) (10, 11). The activation and over-expression of p38γ MAPK is associated with malignant tumors (11, 12). We have previously showed that alcohol activated p38γ MAPK, which may lead to increased CSCs and metastasis of breast cancer cells (7–9). Therefore, these results suggest that p38γ MAPK may play an important role in alcohol-induced promotion of breast cancers.

Pirfenidone (PFD) is a synthetic pyridone compound that is an FDA-approved drug for the treatment of idiopathic pulmonary fibrosis (IPF). IPF is a progressive and fatal lung disease of unknown etiology. The therapeutic effects of PFD may be mediated by its beneficial property of anti-TGF-β signaling, anti-inflammation and anti-oxidative stress (13). PFD has recently been identified as a pharmacological inhibitor of p38γ MAPK (14–16). Since p38γ MAPK plays an important role in the progression of breast cancer and alcohol-induced promotion of mammary tumor, we hypothesized that the inhibition of p38γ MAPK activation by PFD was able to ameliorate alcohol-induced promotion of breast cancer. To test this hypothesis, we used an animal model of spontaneous mammary tumor, MMTV-Wnt1 mice in which alcohol was shown to promote breast cancer (9). Since adolescent MMTV-Wnt1 mice are more sensitive to alcohol-induced mammary tumor promotion (9), we used adolescent mice for this study. Our results indicated PFD effectively inhibited alcohol-induced promotion of tumorsphere formation, CSC population, tumor growth, and metastasis. Since PFD is an FDA-approved drug, the current findings may be helpful to re-purpose its application.

Materials and methods

Breast cancer cell cultures

The cultures of mouse and human breast cancer cells have been previously described (10, 17). Human breast cancer cells BT474 cells were cultured in full RPMI medium with insulin and 10% fetal bovine serum (FBS). SKRB3 cells were cultured in IMEM with 10% FBS. Mice mammary adenocarcinoma cell line E0771 was provided by Dr. Enrico Mihich (Roswell Park Cancer Institute, Buffalo, NY) and maintained in DMEM media supplemented with 10% FBS, penicillin (100 U/ml)/streptomycin (100 U/ml) and 0.25 mg/ml amphotericin B at 37°C in a humidified air containing 5% CO_2. Pirfenidone (PFD) was obtained from Selleckchem (S-7701; Houston, TX). BT474, SKBR3 and E0771 cells were used for this study because they are aggressive breast cancer cell lines with high expression of p38γ MAPK and suitable for further studies of the role of p38γ MAPK in EMT and CSCs in mouse xenograft models (10, 17). The concentrations of PFD were selected based on previous studies showing effectiveness in cell cultures (18, 19).

Animals and treatment

FVB MMTV-Wnt1 [FVB.Cg-Tg (Wnt1)1Hev/J, #002934] mice were obtained from The Jackson Laboratories (Bar Harbor, ME), bred, and housed in a climate-controlled animal facility. All procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Kentucky and the University of Iowa. Only female mice were used for this study. For alcohol exposure, adolescent mice (5 weeks-old) were assigned into control and alcohol exposure groups. Adolescent mice were used for this study because our previous study indicated that adolescent MMTV-Wnt1 mice were more sensitive to alcohol-induced mammary tumor promotion than adult mice (9). Mice were exposed to alcohol by feeding with alcohol containing liquid diet (Cat #: F1258SP, Bio-Serv, Flemington, NJ), while control mice were feed with isocaloric liquid diet (Cat #: F1259SP, Bio-Serv, Flemington, NJ) in which maltose was used to substitute isocalorically for alcohol. The alcohol concentration in the diet increased as the following: week 1, 2% alcohol; week 2, 4% alcohol; weeks 3 and on: 6.7% alcohol. Diet was provided ad libitum for the experimental period. During the experimental period, body weights of mice were evaluated. No significant body weight difference was observed among these animals. To monitor tumorigenesis, mice were examined weekly after the initiation of alcohol exposure. Tumor development/growth was monitored weekly. Mice with tumors exceeding 20 mm maximum diameter were euthanized and evaluated for metastasis. Mice were euthanized by IP injection of ketamine/xylazine (≥ 160 mg/kg/20 mg/kg). Dissected mammary tumor tissues or mammary glands were either immediately dissociated or fixed for the following procedures. To determine the blood alcohol concentrations (BACs), the blood was collected one week after feeding with 6.7% alcohol diet. The BACs were determined using Alcohol Analyzer AM1 (Analox Instruments, MA), and the mean BAC was around 80 mg/dl. PFD was dissolved in DMSO at 100 mg/ml and intraperitoneal (IP) injected to animals at 100 mg/kg two days before alcohol exposure. Mice received PFD injection every other day. The concentration of PFD was selected was based on previous studies in mice showing the effectiveness in inhibiting tumor growth (18, 20). The recommended concentration of PFD for the treatment of IPF in human is 1800 mg/day (21).

Analysis of tumor volume and metastasis

The volume of the tumors was measured as previously described (22): two perpendicular dimensions of tumors were

measured with a dial caliper. The volume was calculated based on the formula: $V = 0.5a \times b^2$; a is the longest and b is the shortest dimension. Tumor metastasis was determined as previously described (9). Briefly, when tumors reached 20 mm maximum diameter, mice were sacrificed, and lung tissues were removed and fixed with 4% paraformaldehyde. The paraffin-embedded lung tissues were sectioned at a thickness of 5 µm. The Hematoxylin–Eosin (H&E)-stained sections were examined and photographed under a microscope.

Dissociation of mouse mammary tumor cells, determination of CSC population and tumorsphere formation

Dissociation of mouse mammary tumor cells was performed using reagents and procedures provided by STEMCELL Technologies Inc (Cambridge, MA). Briefly, resected mammary tumors were minced and incubated in collagenase/hyaluronidase-containing dissociation solution at 37°C for 4 hours. Pellets were washed with HBSS and Ammonium Chloride solution followed by incubations with Trypsin and then Dispase. Cells were washed by HBSS containing 2% FBS and then filtered through a 40 µm cell strainer. After centrifuging, the single-cell suspensions were collected for next experiments. The breast cancer stem cells were identified by aldehyde dehydrogenase (ALDH) activity and Thy1+/CD24+ as previously described (7, 9, 23). Briefly, dissociated mouse mammary tumor cells ($5x10^5$ cells) were incubated with ALDEFLUOR assay buffer containing ALDH substrate for 45 min at 37°C. Some cells were stained under the same condition with a specific ALDH inhibitor as a negative control. Cells were sorted using flow cytometry and analyzed using WINMDI software. ALDEFLUOR-positive cells were considered as the population of CSCs. Data were presented relative to control groups. For Thy1+/CD24+ staining, briefly, dissociated mouse mammary tumor cells were incubated with fluorescent conjugated CD24 or Thy1+ antibodies for 30 min on ice followed by 2 times of wash in PBS. Cells were then analyzed by flow cytometry. Propidium iodide (PI) was used to determine the live cells which were subjected to the analysis.

Tumor sphere formation was determined as previously described (9). Briefly, dissociated single mammary tumor cell suspension (1000 cells) from either control or alcohol-fed mice were plated on ultra-low attachment plates in full Essential 8™ basal medium without further alcohol exposure, and incubated at 37°C and 5% CO_2 for 10 days. The ability of tumor cells to form spheres was determined manually and presented relative to control groups.

Immunoblotting

Mammary tissues were collected, and proteins were extracted. Around 30–50 µg of extracted protein was used in immunoblots to examine the levels of total and phosphorylated p38γ MAPK. The nitrocellulose membranes were first probed with specific primary antibodies overnight at 4°C. The generation and usage of primary phosphospecific antibody against p38γ MAPK has been previously described (7). Anti-p38γ MAPK antibody was obtained from R & D Systems (Cat # AF1347, Minneapolis, MN). Anti-p38α MAPK antibody (Cat # 9218) and Anti-GAPDH antibody (Cat # 2118) were obtained from Cell Signaling Technology (Danvers, MA). Anti-phospho-p38α antibody (Cat # 09-272) was obtained from Sigma Aldrich (St. Louis, MO). Anti-phospho-p38γ antibody was customized synthesized as previously described (7). After washing with TBS containing 0.05% Tween-20 three times, the membranes were incubated with anti-rabbit or anti-mouse secondary antibodies (horseradish peroxidase-conjugated) for one hour at room temperature. Protein-specific signals were then detected with enhanced chemiluminescence substrate (GE Healthcare, Chalfont, Buckinghamshire, UK) using a Chemi™Doc imaging system (Bio-Rad 215 Laboratories, Hercules, CA) and then quantified with the software of Image lab 5.2 (Bio-Rad Laboratories, Hercules, CA).

MTT assay

To examine cell metabolic activity, 3-(4, 5-dimethyl-thiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay was used as previously described (8). Cells were seeded on 96-well plates at $2x10^3$ cells per well. At times indicated, MTT was added to each well at the final concentration of 500 µg/ml and incubated at 37°C for 2 hours. After the incubation, media were carefully removed and 100 µl DMSO was added to each well to dissolve the MTT formazan. Plates were read using the Beckman Coulter DTX 880 Multimode Detector plate reader (Analytical Instruments, Golden Valley, MN) at the wavelength of 595 nm.

Statistical analysis

Differences among treatment groups were analyzed using analysis of variance (ANOVA). Differences in which p was less than 0.05 were considered statistically significant. In cases where significant differences were detected, specific *post-hoc* comparisons between treatment groups were examined with Student-Newman-Keuls tests. The prevalence of metastasis between control and ethanol-treated groups was determined by the Fisher exact test.

Results

PFD inhibits p38γ MAPK activation in breast cancer cells *in vitro* and *in vivo*

It was reported that PFD is a pharmacological inhibitor of p38γ MAPK (14–16). We first wanted to determine whether PFD inhibited p38γ MAPK activation in breast cancer cells *in vitro* and *in vivo*. As shown in Figure 1A, PFD effectively decreased the phosphorylation and the expression of p38γ MAPK in cultured mouse and human breast cancer cells without affecting other p38 MAPK isoform (p38α MAPK). Consistently, PFD inhibited the

10.3389/fonc.2024.1351839

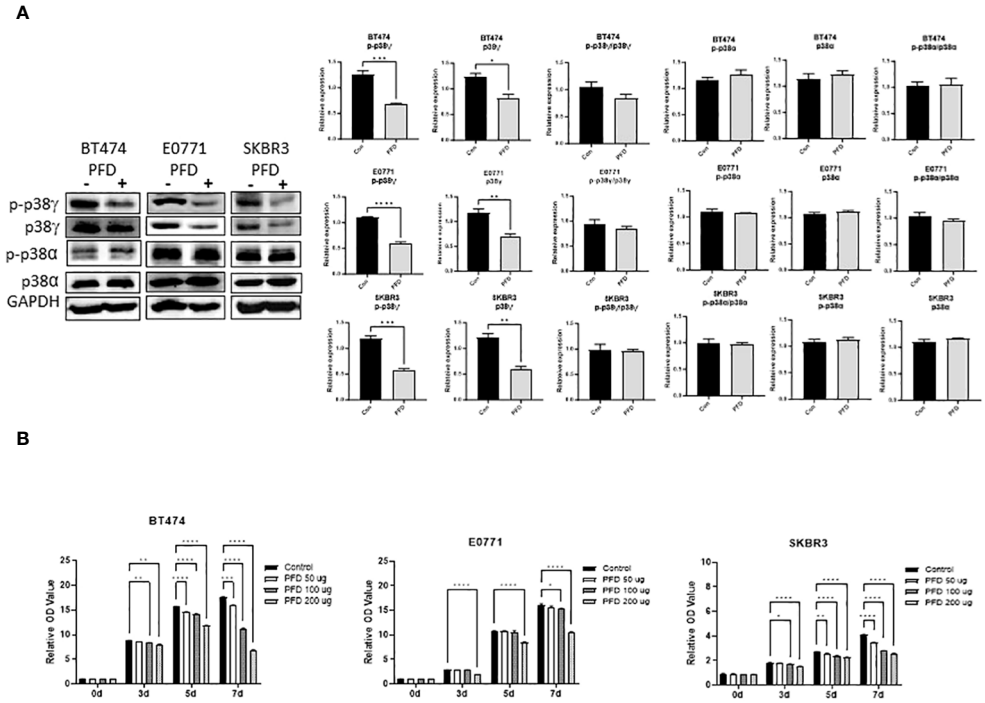


FIGURE 1
Effects of PFD on the phosphorylation of p38γ MAPK and the growth of breast cancer cells *in vitro*. **(A)** PFD specifically inhibited p38γ MAPK phosphorylation and expression in cultured breast cell lines. Mouse breast cancer cells (E0771) and human breast cancer cell lines (SKBR3 and BT474) were treated with PFD at 200 μg/ml in DMSO for three days. The controls received equal amount of DMSO only. Cell lysates were collected and subjected to immunoblotting (IB) analysis of the phosphorylation of p38γ and p38α MAPK (left panel). The expression of phosphorylated p38γ and p38α MAPK was quantified and normalized to the levels of GAPDH, p38γ or p38α MAPK, respectively (right panel). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$ denotes significant difference from controls. Each data point was the mean ± SEM of three independent experiments. **(B)** PFD inhibited growth of cultured breast cell lines. E0771, SKBR3 and BT474 cells were treated with PFD at 50, 100 or 200 μg/ml for 3-7 days (3-7d). The cell viability was determined by MTT assay as described in Materials and Methods. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ denotes significant difference from controls. Each data point was the mean ± SEM of three independent experiments.

growth of these breast cancer cells (Figure 1B). To test whether PFD was effective *in vivo*, we IP injected PFD into adolescent MMTV-Wnt1 mice. We demonstrated that PFD administration inhibited alcohol-induced expression and phosphorylation of p38γ MAPK in the mammary tissues of MMTV-Wnt1 mice without affecting p38α MAPK (Figure 2).

PFD inhibits mammary tumor growth and alcohol-stimulated metastasis

Our previous studied indicated that p38γ MAPK activation played an important role in alcohol-induced metastasis of breast cancer (7–9). We sought to determine whether PFD was able to inhibit alcohol-induced promotion of breast cancer. As shown in Figure 3A, PFD had little effect on the onset of mammary tumorigenesis. Alcohol did not significantly enhance the growth rate of mammary tumors but drastically promoted metastasis in the lung (Figures 3B, 4). PFD treatment completely abolished the growth of mammary tumors (Figure 3B). Furthermore, PFD eliminated alcohol-induced metastasis in the lung (Figure 4).

PFD inhibits alcohol-induced increase of tumorsphere formation and cancer stem cell population

Tumorsphere formation and CSC population are indicative of the aggressiveness of breast cancer (10). Our previous studied suggested that alcohol-induced activation of p38γ MAPK may be involved in regulating tumorsphere formation and CSC population (7–9). Therefore, we sought to determine whether PFD could inhibit alcohol-induced formation of tumorspheres and CSCs. As shown in Figure 5A, PFD indeed blocked alcohol-stimulated formation of tumorspheres. Using two CSC assays (ALDH activity and Thy1+/CD24+ population), we showed that PFD significantly inhibited on alcohol-stimulated CSC population (Figure 5B). These data are consistent with the findings that PFD

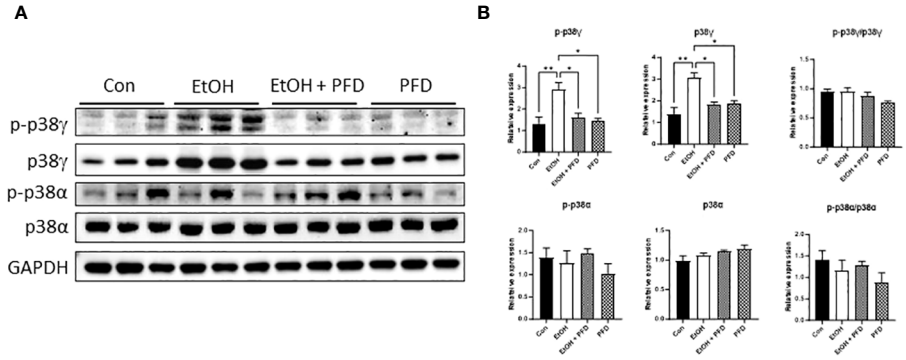


FIGURE 2
Effects of PFD on alcohol-induced expression and phosphorylation p38γ MAPK in mammary tissues of MMTV-Wnt1 mice. Adolescent MMTV-Wnt1 mice (5-weeks-old) were exposed to alcohol through liquid diet as described in Materials and Methods. PFD (100 mg/kg in DMSO) was delivered by IP injection every other day starting two days before alcohol exposure is initiated. The controls received IP injection of equal amount of DMSO. Mice were euthanized when tumors reached 20 mm maximum diameter. **(A)** Mammary tissues were collected and processed for IB analysis of phosphorylation/expression of p38γ and p38α MAPK. **(B)** The expression of phosphorylated and total p38γ and p38α MAPK was quantified and normalized to the levels of GAPDH, p38γ or p38α MAPK, respectively. *denotes significant difference from controls, * $p < 0.05$, ** $p < 0.01$, n = 3.

can block alcohol-promoted aggressiveness of breast cancer (Figures 3, 4).

Discussion

We used MMTV-Wnt1 mice to evaluate the effects of PFD on alcohol-induced tumor promotion. Transgenic expression of Wnt1 using a mouse mammary tumor virus LTR enhancer causes extensive ductal hyperplasia early in life and mammary adenocarcinomas in approximately 50% of the female transgenic (MMTV-Wnt1) mice by 6 months of age (24). In this animal model, metastasis to the lung and proximal lymph nodes is rare at the time tumors are detected but may occur at the later times (24). In our study, metastasis to the lung and proximal lymph nodes was rarely observed in the absence of alcohol exposure. This study was the first

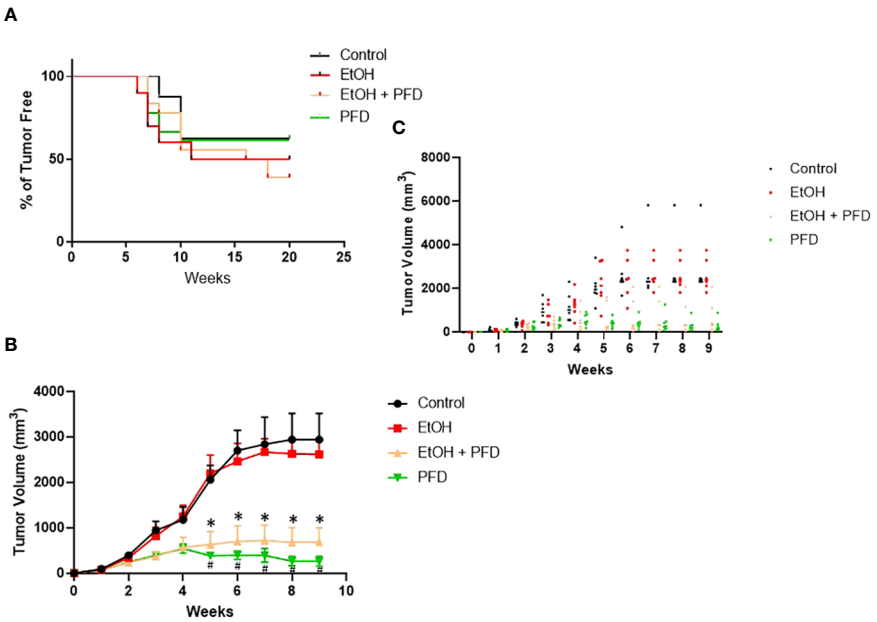


FIGURE 3
Effects of PFD on the onset of tumorigenesis and growth of mammary tumors. **(A)** Adolescent MMTV-Wnt1 mice were exposed to alcohol through liquid diet as described above. PFD (100 mg/kg) was delivered by IP injection every other day starting two days before alcohol exposure is initiated. The mice were monitored weekly for the appearance and growth of mammary tumors. The percentage of tumor-free mice was determined. n = 16 for control group; n = 20 for alcohol-exposed group (EtOH); n = 18 for the PFD; n = 18 for the PFD + EtOH group. **(B)** Adolescent MMTV-Wnt1 mice were exposed to alcohol and PFD as described above. The tumor volume was measured weekly as described in Materials and Methods. The average was calculated from tumor bearing mice only. # denote significant difference between control and PFD group; * denote significant difference between EtOH and EtOH + PFD group, $p < 0.05$; n = 6 for control group; n = 6 for EtOH group; n = 7 for PFD group; n = 6 for EtOH + PFD group. **(C)** Individual data points on tumor volumes are shown.

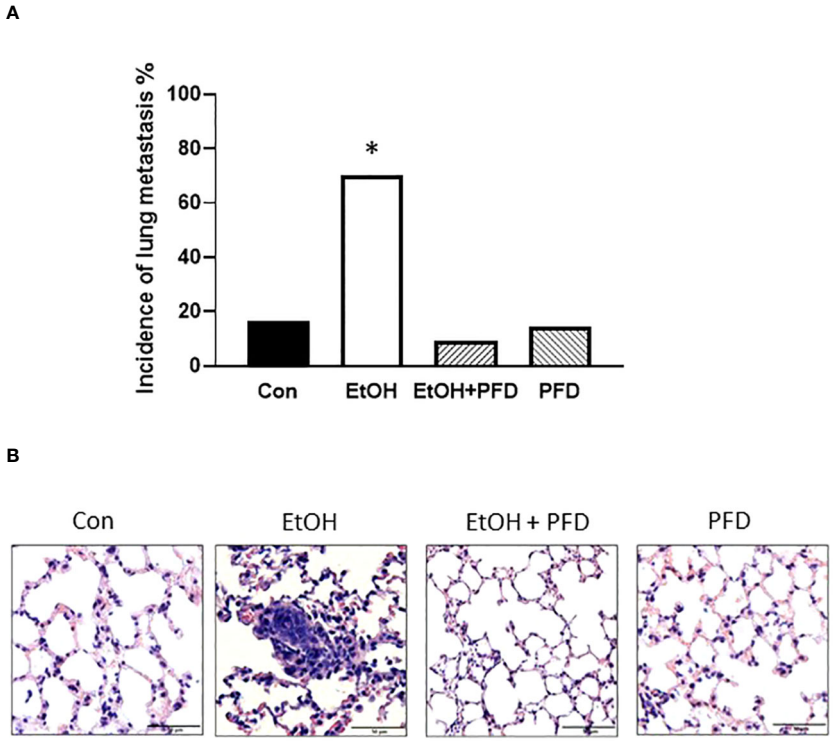


FIGURE 4
Effects of PFD on metastasis of breast cancer cells *in vivo*. Adolescent MMTV-Wnt1 mice were exposed to alcohol and PFD as described above. When tumor size reached maximal diameter of 20 mm, the mice were euthanized, and the lung metastasis was determined **(A)**. A representative image of H&E staining of lung metastasis from each group was shown **(B)**. * denote significant difference from other groups, $p < 0.05$; n = 6 for control group; n = 10 for EtOH group; n = 7 for PFD group; n = 11 for EtOH + PFD group. The incidence of lung metastases: Control: 1 out of 6; EtOH: 7 out of 10; PFD: 1 out of 7; EtOH + PFD: 1 out of 11.

to determine the effects of PFD, an inhibitor of p38γ MAPK, on alcohol-induced promotion of breast cancer. We demonstrated here PFD treatment blocked alcohol-promoted tumor growth and metastasis in adolescent MMTV-Wnt1 mice. It also significantly inhibited alcohol-induced tumorsphere formation and CSC population. Thus, PFD may be beneficial in treating aggressive breast cancer and particularly effective for ameliorating alcohol-promoted progression of breast cancer. Since PFD is an FDA-approved drug, our findings have important implication for repurposing this drug.

Drug repurposing strategy is to identify new clinical applications of drugs that are already approved for the treatment of other medical conditions. This innovative process has several advantages, as it reduces or eliminates the steps associated with early pharmacological development, such as safety, toxicity, pharmacokinetic and pharmacodynamic studies, and therefore significantly reduces the time and costs associated with traditional new drug discovery/development. PFD, an anti-fibrotic, anti-inflammatory and antioxidant drug, is approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for the treatment of idiopathic pulmonary fibrosis. It has a wide range of targets due to its ability to diffuse across membranes and is rapidly absorbed from the gastrointestinal tract (25). The main action of PFD is considered as an antagonist of TGF-β signaling. It also has anti-inflammatory effects through suppressing proinflammatory cytokines such as TGF-β, tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and several other cytokines (13). It was reported that PFD can attenuate oxidative stress (13). Due to this variety of potential targets, PFD is a valuable candidate for treating a wide range of diseases.

PFD has been tested in preclinical models and clinical trials to treat several cancers including pancreatic cancer, lung cancer, colorectal cancer, liver cancer, renal cancer and breast cancer, and the outcomes are promising (26–30). It appears that the anti-cancer property of PFD involves in different mechanisms. For example, the anti-colorectal cancer property seems mediated by PFD's effects on TGF-β signaling. PFD inhibited TGF-β-induced cell proliferation, migration, and tumor progression of colorectal cancer (25). PFD blocked alcohol-stimulated TGF-β signaling and cell migration/invasion and the epithelial-mesenchymal transition (EMT) in cultured colorectal cells (31). Similarly, PFD suppressed the metastasis triple-negative breast cancer by inhibiting TGF-β/SMAD pathway (20). PFD may inhibit cancers by mechanisms other than blocking TGF-β signaling. For instance, PFD is reported to target the tumor microenvironment and tumor-stroma interaction as a *novel* treatment for non-small cell lung cancer (NSCLC) (32). PFD can sensitize NSCLC cells to chemotherapy (33). PFD promoted miR200 expression to down-regulate ZEB1 and repress the EMT of NSCLC (34, 35). PFD attenuated cell

10.3389/fonc.2024.1351839

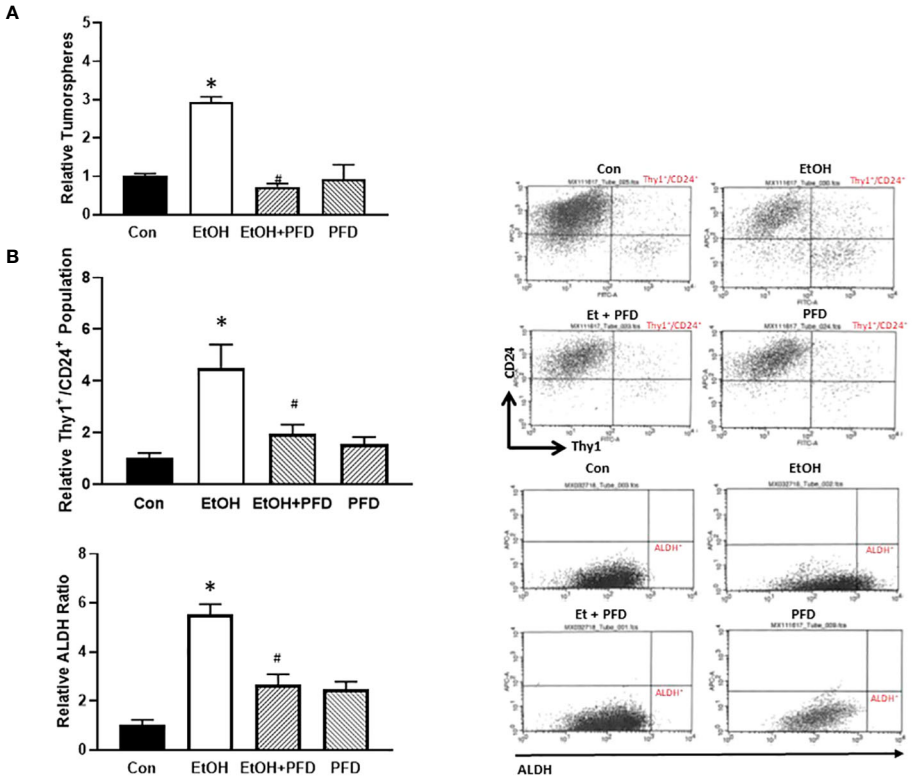


FIGURE 5
Effects of PFD on the formation of tumorsphere and cancer stem cell (CSC) population. **(A)** Adolescent MMTV-Wnt1 mice were exposed to alcohol and PFD as described above. Mice were euthanized when tumors reached 20 mm maximum diameter, mammary tumor tissues dissected and assayed for tumorsphere formation as described in Materials and Methods. *denotes significant difference from control group, $p < 0.05$. # denotes significant difference from EtOH group, $p < 0.05$. n = 6 for control group; n = 10 for EtOH group; n = 7 for PFD group; n = 6 for EtOH + PFD group. **(B)** Adolescent MMTV-Wnt1 mice were exposed to alcohol and PFD as described above. Mice were euthanized when tumors reached 20 mm maximum diameter, and mammary tumor tissues dissected, and tumor cells were isolated. The CSC population in tumor cells was determined and calculated by flow cytometry analysis of Thy1+/CD24+ (top panel) and ALDH ratio (bottom panel) as described in Materials and Methods. Representative FACS plots of Thy1/CD24 and ALDH staining were shown on the left. * denotes significant difference from controls $p < 0.05$; # denotes significant difference from alcohol-treated group, $p < 0.05$, n = 6 for control group; n = 10 for EtOH group; n = 7 for PFD group; n = 6 for EtOH + PFD group.

proliferation and promoted apoptosis of hepatocellular carcinoma cells by Inhibiting Wnt/β-Catenin signaling pathway (27).

p38γ MAPK has been shown to regulate cell cycle transition, cell mobility, metastasis, EMT, CSC population, and tumorigenesis (10, 36–39). Importantly, p38γ MAPK is overexpressed and implicated in several types of cancers including colorectal cancer, liver cancer, pancreatic cancer, and breast cancer (16, 37, 40, 41); increased p38γ MAPK expression predicts a poor clinical prognosis (18, 36). CSCs are a subpopulation of tumor cells capable of self-renewal and differentiation and involved in tumor initiation, recurrence, progression, chemoresistance and metastasis (38). Overexpression of p38γ MAPK increases CSCs and tumorspheres (38), suggesting that p38γ MAPK may regulate CSC population and cancer aggressiveness. Therefore, targeting p38γ MAPK signaling network could be an important strategy for therapeutic intervention of cancers (39). PFD is identified as a pharmacological inhibitor of p38γ MAPK (14–16). As a result, PFD has been tested for its therapeutic effects in several cancers associated p38γ MAPK activation, such as colorectal cancer, pancreatic cancer and breast cancer and demonstrated effective in inhibiting the tumorigenesis and progression (16, 18, 40, 42). Our findings that PFD can block alcohol-induced growth, CSC population, and metastasis of mammary tumors in mice support the notion that PFD may be beneficial in treating breast cancer, particularly for those of aggressive types and in the context of alcohol exposure. These results may also provide new value for PFD for the treatment of other alcohol-associate diseases. For example, alcohol is a known etiological factor for pancreatitis and pancreatic cancer (43). As a result, PFD may be a candidate drug for treating alcoholic pancreatitis and associated pancreatic cancer. Indeed, PFD is effective ameliorating chronic pancreatitis in mice (44), and inhibiting pancreatic tumorigenesis (16).

Due to the regulatory role of p38γ MAPK in tumorigenesis and progression, development of more specific p38γ MAPK inhibitors other than PFD becomes an important and exciting future research direction. There are some p38γ MAPK inhibitors with varied efficacy and specificity (39). Recently, some *novel* p38γ MAPK inhibitors with higher specificity are developed (41, 45). One of them, CSH71 which targets the lipid-binding-domain (LBD) of p38γ MAPK shows high specificity. CSH71 is selectively cytotoxic to

cutaneous T-cell lymphoma (CTCL) Hut78 cells but spares normal healthy peripheral blood mononuclear (PBMC) cells (41). These *novel* p38γ MAPK inhibitors are promising for the treatment of alcohol-stimulated cancers and other diseases. It is unclear how alcohol activates p38γ MAPK. It has been proposed that the interaction of several upstream signaling molecules, such as CD40L and CD40, may result in p38 MAPK activation which stimulates diverse cytokine profile, transcription factors and oxidative stress (46). These processes may be involved metastasis or cancer stemness. Therefore, understanding of these signaling cascades may be helpful to develop additional targets for the treatment of alcohol-induced tumor promotion.

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.

Ethics statement

Ethical approval was not required for the studies on humans in accordance with the local legislation and institutional requirements because only commercially available established cell lines were used. The animal study was approved by Institutional Animal Care and Use Committee (IACUC) of the University of Kentucky and the University of Iowa. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

HL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. MX: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. DC: Data curation, Investigation, Methodology, Writing – review & editing. WW: Methodology, Writing – review & editing. JL: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by NIH grants (AA017226 and AA015407). It was also supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development [Biomedical Laboratory Research and Development: Merit Review (BX001721)].

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1351839/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Gross image of the lung showing potential metastases. Mice were treated as described in. The lungs were dissected, and gross images were recorded. Arrow indicates a potential lung tumor.

References

1. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA*. (2011) 306:1884–90. doi: 10.1001/jama.2011.1590

2. Mostofsky E, Mukamal KJ, Giovannucci EL, Stampfer MJ, Rimm EB. Key findings on alcohol consumption and a variety of health outcomes from the nurses' Health study. *Am J Public Health*. (2016) 106:1586–91. doi: 10.2105/AJPH.2016.303336

3. Shield KD, Soerjomataram I, Rehm J. Alcohol use and breast cancer: A critical review. *Alcohol Clin Exp Res*. (2016) 40:1166–81. doi: 10.1111/acer.13071

4. Wang Y, Xu M, Ke ZJ, Luo J. Cellular and molecular mechanisms underlying alcohol-induced aggressiveness of Breast Cancer. *Pharmacol Res*. (2017) 115:299–308. doi: 10.1016/j.phrs.2016.12.005

5. Xu M, Luo J. Alcohol and cancer stem cells. *Cancers (Basel)*. (2017) 9. doi: 10.3390/cancers9110158

6. Scheideler JK, Klein WMP. Awareness of the link between alcohol consumption and cancer across the world: A review. *Cancer Epidemiol Biomarkers Prev*. (2018) 27:429–37. doi: 10.1158/1055-9965.EPI-17-0645

7. Xu M, Ren Z, Wang X, Comer A, Frank JA, Ke ZJ, et al. ErbB2 and p38gamma MAPK modulate alcohol-induced increase in breast cancer stem cells and metastasis. *Mol Cancer*. (2016) 15:12. doi: 10.1186/s12943-016-0532-4

8. Xu M, Wang S, Ren Z, Frank JA, Yang XH, Zhang Z, et al. Chronic ethanol exposure enhances the aggressiveness of breast cancer: the role of p38 gamma. *Oncotarget*. (2016) 7:3489–505. doi: 10.18632/oncotarget.v7i3

9. Xu M, Li H, Chen D, Wu H, Wen W, Xu H, et al. Adolescent- and adult-initiated alcohol exposure in mice differentially promotes tumorigenesis and metastasis of breast cancer. *Alcohol Clin Exp Res (Hoboken)*. (2023) 47:251–62. doi: 10.1111/acer.14986

10. Xu M, Wang S, Wang Y, Wu H, Frank JA, Zhang Z, et al. Role of p38gamma MAPK in regulation of EMT and cancer stem cells. *Biochim Biophys Acta Mol Base Dis*. (2018) 1864:3605–17. doi: 10.1016/j.bbadis.2018.08.024

11. Xu W, Liu R, Dai Y, Hong S, Dong H, Wang H. The Role of p38γ in Cancer: From review to outlook. *Int J Biol Sci*. (2021) 17:4036–46. doi: 10.7150/ijbs.63537

12. Qin JZ, Xin H, Qi XM, Chen G. Isoform-specific and cell/tissue-dependent effects of p38 MAPKs in regulating inflammation and inflammation-associated oncogenesis. *Front Biosci (Landmark Ed)*. (2022) 27:31. doi: 10.31083/j.fbl2701031

13. Antar SA, Saleh MA, Al-Karmalawy AA. Investigating the possible mechanisms of pirfenidone to be targeted as a promising anti-inflammatory, anti-fibrotic, anti-oxidant, anti-apoptotic, anti-tumor, and/or anti-SARS-CoV-2. *Life Sci*. (2022) 309:121048. doi: 10.1016/j.lfs.2022.121048

14. Moran N. p38 kinase inhibitor approved for idiopathic pulmonary fibrosis. *Nat Biotechnol*. (2011) 29:301. doi: 10.1038/nbt0411-301

15. King TE Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. (2014) 370:2083–92. doi: 10.1056/NEJMoa1402582

16. Wang F, Qi XM, Wertz R, Mortensen M, Hagen C, Evans J, et al. p38γ MAPK is essential for aerobic glycolysis and pancreatic tumorigenesis. *Cancer Res*. (2020) 80:3251–64. doi: 10.1158/0008-5472.CAN-19-3281

17. Wang S, Xu M, Li F, Wang X, Bower KA, Frank JA, et al. Ethanol promotes mammary tumor growth and angiogenesis: the involvement of chemoattractant factor MCP-1. *Breast Cancer Res Treat*. (2012) 133:1037–48. doi: 10.1007/s10549-011-1902-7

18. Qi X, Yin N, Ma S, Lepp A, Tang J, Jing W, et al. p38γ MAPK is a therapeutic target for triple-negative breast cancer by stimulation of cancer stem-like cell expansion. *Stem Cells*. (2015) 33:2738–47. doi: 10.1002/stem.2068

19. Wu SB, Hou TY, Kau HC, Tsai CC. Effect of pirfenidone on TGF-β1-induced myofibroblast differentiation and extracellular matrix homeostasis of human orbital fibroblasts in graves' Ophthalmopathy. *Biomolecules*. (2021) 11:1424. doi: 10.3390/biom11101424

20. Luo D, Zeng X, Zhang S, Li D, Cheng Z, Wang Y, et al. Pirfenidone suppressed triple-negative breast cancer metastasis by inhibiting the activity of the TGF-β/SMAD pathway. *J Cell Mol Med*. (2023) 27:456–69. doi: 10.1111/jcmm.17673

21. Li H, Yang J, Chen S, Wang P, Yu X, Zhou Q, et al. Analysis of the safety and efficacy of different plasma concentrations of pirfenidone in patients with idiopathic pulmonary fibrosis. *Front Pharmacol*. (2022) 13:1055702. doi: 10.3389/fphar.2022.1055702

22. Tomayko MM, Reynolds CP. Determination of subcutaneous tumor size in athymic (nude) mice. *Cancer Chemother Pharmacol*. (1989) 24:148–54. doi: 10.1007/BF00300234

23. Cho RW, Wang X, Diehn M, Shedden K, Chen GY, Sherlock G, et al. Isolation and molecular characterization of cancer stem cells in MMTV-Wnt-1 murine breast tumors. *Stem Cells*. (2008) 26(2):364–71. doi: 10.1634/stemcells

24. Li Y, Hively WP, Varmus HE. Use of MMTV-Wnt-1 transgenic mice for studying the genetic basis of breast cancer. *Oncogene*. (2000) 19:1002–9. doi: 10.1038/sj.onc.1203273

25. Jamialahmadi H, Nazari SE, TanzadehPanah H, Saburi E, Asgharzadeh F, Khojasteh-Leylakoohi F, et al. Targeting transforming growth factor beta (TGF-β) using Pirfenidone, a potential repurposing therapeutic strategy in colorectal cancer. *Sci Rep*. (2023) 13:14357. doi: 10.1038/s41598-023-41550-2

26. Kozono S, Ohuchida K, Eguchi D, Ikenaga N, Fujiwara K, Cui L, et al. Pirfenidone inhibits pancreatic cancer desmoplasia by regulating stellate cells. *Cancer Res*. (2013) 73:2345–56. doi: 10.1158/0008-5472.CAN-12-3180

27. Zou WJ, Huang Z, Jiang TP, Shen YP, Zhao AS, Zhou S, et al. Pirfenidone inhibits proliferation and promotes apoptosis of hepatocellular carcinoma cells by inhibiting the wnt/β-catenin signaling pathway. *Med Sci Monit*. (2017) 23:6107–13. doi: 10.12659/MSM.907891

28. Zhao J, Zhu Y, Li Z, Liang J, Zhang Y, Zhou S, et al. Pirfenidone-loaded exosomes derived from pancreatic ductal adenocarcinoma cells alleviate fibrosis of premetastatic niches to inhibit liver metastasis. *Biomater Sci*. (2022) 10(22):6614–26. doi: 10.1039/d2bm00770c

29. Wang G, Zhou X, Guo Z, Huang N, Li J, Lv Y, et al. The Anti-fibrosis drug Pirfenidone modifies the immunosuppressive tumor microenvironment and prevents the progression of renal cell carcinoma by inhibiting tumor autocrine TGF-β. *Cancer Biol Ther*. (2022) 23:150–62. doi: 10.1080/15384047.2022.2035629

30. Sakairi Y, Yoshino I, Iwata T, Yoshida S, Kuwano K, Azuma A, et al. A randomized controlled phase III trial protocol: perioperative pirfenidone therapy in patients with non-small cell lung cancer combined with idiopathic pulmonary fibrosis to confirm the preventative effect against postoperative acute exacerbation: the PIII-PEOPLE study (NEJ034). *Thorac Dis*. (2023) 15:1486–93. doi: 10.21037/jtd

31. Zheng K, Yu J, Chen Z, Zhou R, Lin C, Zhang Y, et al. Ethanol promotes alcohol-related colorectal cancer metastasis via the TGF-β/RUNX3/Snail axis by inducing TGF-β1 upregulation and RUNX3 cytoplasmic mislocalization. *EBioMedicine*. (2019) 50:224–37. doi: 10.1016/j.ebiom.2019.11.011

32. Fujiwara A, Funaki S, Fukui E, Kimura K, Kanou T, Ose N, et al. Effects of pirfenidone targeting the tumor microenvironment and tumor-stroma interaction as a novel treatment for non-small cell lung cancer. *Sci Rep*. (2020) 10:10900. doi: 10.1038/s41598-020-67904-8

33. Branco H, Oliveira J, Antunes C, Santos LL, Vasconcelos MH, Xavier CPR. Pirfenidone sensitizes NCI-H460 non-small cell lung cancer cells to paclitaxel and to a combination of paclitaxel with carboplatin. *Int J Mol Sci*. (2022) 23:3631. doi: 10.3390/ijms23073631

34. Fujiwara A, Shintani Y, Funaki S, Kawamura T, Kimura T, Minami M, et al. Pirfenidone plays a biphasic role in inhibition of epithelial-mesenchymal transition in non-small cell lung cancer. *Lung Cancer*. (2017) 106:8–16. doi: 10.1016/j.lungcan.2017.01.006

35. Liu J, Cao L, Li Y, Deng P, Pan P, Hu C, et al. Pirfenidone promotes the levels of exosomal miR-200 to down-regulate ZEB1 and represses the epithelial-mesenchymal transition of non-small cell lung cancer cells. *Hum Cell*. (2022) 35:1813–23. doi: 10.1007/s13577-022-00766-6

36. Rosenthal DT, Iyer H, Escudero S, Bao L, Wu Z, Ventura AC, et al. p38 promotes breast cancer motility and metastasis through regulation of RhoC GTPase, cytoskeletal architecture, and a novel leading edge behavior. *Cancer Res*. (2011) 71:6338–6349 22. doi: 10.1158/0008-5472.CAN-11-1291

37. Tomás-Loba A, Manieri E, González-Terán B, Mora A, Leiva-Vega L, Santamans AM, et al. p38γ is essential for cell cycle progression and liver tumorigenesis. *Nature*. (2019) 568:557–60. doi: 10.1038/s41586-019-1112-8

38. Kudaravalli S, den Hollander P, Mani SA. Role of p38 MAP kinase in cancer stem cells and metastasis. *Oncogene*. (2022) 41:3177–85. doi: 10.1038/s41388-022-02329-3

39. Qi XM, Chen G. p38γ MAPK inflammatory and metabolic signaling in physiology and disease. *Cells*. (2023) 12:1674. doi: 10.3390/cells12131674

40. Yin N, Lepp A, Ji Y, Mortensen M, Hou S , Qi XM, et al. The K-Ras effector p38γ MAPK confers intrinsic resistance to tyrosine kinase inhibitors by stimulating *EGFR* transcription and EGFR dephosphorylation. *J Biol Chem*. (2017) 292:15070–9. doi: 10.1074/jbc.M117.779488

41. Zhang XH, Chen CH, Li H, Hsiang J, Wu X, Hu W, et al. Targeting the non-ATP-binding pocket of the MAP kinase p38γ mediates a novel mechanism of cytotoxicity in cutaneous T-cell lymphoma (CTCL). *FEBS Lett*. (2021) 595:2570–92. doi: 10.1002/1873-3468.14186

42. Yin N, Qi X, Tsai S, Lu Y, Basir Z, Oshima K, et al. p38γ MAPK is required for inflammation-associated colon tumorigenesis. *Oncogene*. (2016) 35:1039–48. doi: 10.1038/onc.2015.158

43. Li H, Wen W, Luo J. Targeting endoplasmic reticulum stress as an effective treatment for alcoholic pancreatitis. *Biomedicines*. (2022) 10:108. doi: 10.3390/biomedicines10010108

44. Palathingal Bava E, George J, Iyer S, Sahay P, Tarique M, Jain T, et al. Pirfenidone ameliorates chronic pancreatitis in mouse models through immune and cytokine modulation. *Pancreatology*. (2022) 22:553–63. doi: 10.1016/j.pan.2022.05.002

45. Natarajan P, Manne M, Koduru SK, Bokkasam TS. 3-deazaadenosine: A promising novel p38γ antagonist with potential as a breast cancer therapeutic agent. *Cancer Treat Res Commun*. (2023) 36:100744. doi: 10.1016/j.ctarc.2023.100744

46. Sarode AY, Jha MK, Zutshi S, Ghosh SK, Mahor H, Sarma U, et al. Residue-specific message encoding in CD40-ligand. *iScience*. (2020) 23:101441. doi: 10.1016/j.isci.2020.101441

frontiers | Frontiers in Public Health

TYPE Perspective
PUBLISHED 04 April 2024
DOI 10.3389/fpubh.2024.1370108

OPEN ACCESS

EDITED BY
Uttara Saran,
University of Texas MD Anderson Cancer Center, United States

REVIEWED BY
Qian Xu,
Shandong Provincial Qianfoshan Hospital, China
Priya Wadgaonkar,
City of Hope National Medical Center, United States

*CORRESPONDENCE
Axelle Mayode Atchade
✉ Barbara.Nemesure@stonybrookmedicine.edu
Barbara Nemesure
✉ Barbara.Nemesure@stonybrook.edu

RECEIVED 13 January 2024
ACCEPTED 19 March 2024
PUBLISHED 04 April 2024

CITATION
Atchade AM, Williams JL, Mermelstein L and Nemesure B (2024) Unraveling the complexities of early-onset colorectal cancer: a perspective on dietary and microbial influences.
Front. Public Health 12:1370108.
doi: 10.3389/fpubh.2024.1370108

Unraveling the complexities of early-onset colorectal cancer: a perspective on dietary and microbial influences

Axelle Mayode Atchade[1]*, Jennie L. Williams[2], Linda Mermelstein[2] and Barbara Nemesure[1,2]*

[1]Stony Brook Medicine, Stony Brook, NY, United States, [2]Cancer Center, Stony Brook Medicine, Stony Brook, NY, United States

While advances in screening have resulted in declining rates of colorectal cancer (CRC) among adults ≥50 years of age since the mid-2000s, the incidence of early-onset CRC (EOCRC) has steadily increased over the last decade. This increase is not fully accounted for by hereditary factors, and the hypothesis that a sedentary lifestyle and obesity are the primary culprits is not fully supported by recent reports indicating that many affected individuals lead active lifestyles, maintain normal weight, and are otherwise healthy. Attention has shifted toward dietary patterns, notably the consumption of processed and ultra-processed foods found in Western diets, which are suspected of disrupting the gut microbiome balance that potentially leads to EOCRC. The impact of antibiotic use on the gut microbiome is also posited as a contributing factor, given its rising prevalence in medical and agricultural practices. We propose that a paradigm shift is necessary for EOCRC research, moving beyond metabolic factors to a broader exploration of dietary and microbial influences. Future research must prioritize understanding the relationship between dietary habits, particularly processed food intake, antibiotic exposure, and gut microbiome dynamics, to unravel the complex etiology of EOCRC. This will be crucial in developing comprehensive preventive strategies to address the increasing incidence of this malignancy in younger populations.

KEYWORDS

early onset colorectal cancer, gut microbiome, westernized diet, microbial influence, antibiotic use

1 Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosis worldwide and ranks second in cancer-related mortality in the United States (1, 2). Notably, CRC takes on a particularly alarming role as the leading cause of death among men under 50 years of age on a global scale. Even with advances in screening, a 1–2% annual increase in incidence rates has been witnessed among young adults since the mid-1990s, resulting in a shift from 11 to 20% of cases occurring in individuals under 55 years from 1995 to 2019 (2, 3).

Genetic mutations such as Lynch Syndrome and Familial Adenomatous Polyposis contribute to approximately 1/4 of CRC diagnoses (4–7), but these hereditary syndromes do not appear to explain the onset of cancer in the majority of patients under the age of 50 years (8, 9). Additionally, there has not been an indication to date that the incidence of these

10.3389/fpubh.2024.1370108

germline mutations has increased over time. While lifestyle factors and the obesity epidemic have been proposed as drivers for increases in CRC among younger patients (10–12), a striking number of cases occur in individuals lacking metabolic syndromes, or those without attributable risk factors such as smoking or consumption of alcohol. Furthermore, these cases are often diagnosed at advanced stages with poor cell differentiation (3, 7, 13). This prompts a cascade of questions surrounding the unidentified mechanisms and factors contributing to these increased incidence rates in this demographic. Herein, we explore the intricate connection between the surge in EOCRC and the factors influencing its pathogenesis, such as metabolic syndromes, processed foods, antibiotics, and the colonic microbiome.

2 The influence of metabolic syndrome

To assess the influence of metabolic factors on CRC, a retrospective study was undertaken using data obtained from the Stony Brook Cancer Registry, which records demographic, lifestyle, clinical, and other factors for all cancer cases (of any type) diagnosed at The Stony Brook University Hospital (SBUH). The evaluation included more than 900 CRC patients diagnosed at SBUH between 2010 and 2020 and evaluated factors such as gender, race, age and year at diagnosis, marital status, family history of cancer, smoking status (current, former, never), and history of alcohol consumption (current, former, never). Descriptive statistics stratified by age at diagnosis were used to quantify the distribution of all risk factors under evaluation, and statistically significant associations were defined as those with p-values <0.05. Eleven percent of patients were under the age of 50 years at the time of diagnosis, and the data indicated that most cases were not obese, nor did they have a history of diabetes, hypertension, or hyperlipidemia (Table 1). Furthermore, these prevailing metabolic factors, often implicated in CRC risk, exhibited a disparate pattern, with rates being more than four times lower in CRC cases under 50 compared to those aged 50 and above.

Similarly, in a study reported by Chen et al., including 253 early-onset CRC cases, only 3.6 and 5.5% exhibited overweight and obesity, respectively, in stark contrast to the 13.4 and 5.6% observed in cases aged 50 years and above (4). These findings further dispel the notion that obesity in younger patients serves as a primary driver for the escalating incidence rates within this demographic. Of additional note, these factors are increasing in the population as a whole, thereby making it unclear why such metabolic influences would only raise incidence among younger patients while rates continue to decline among those ≥50 years old who have a larger burden of compromised health (12).

Traditional lifestyle factors such as cigarette smoking and alcohol consumption also fail to account for the rise in early-onset CRC cases. As shown in Table 1, more than half of the cases under 50 years reported never consuming alcohol, and 65% never smoked. Additionally, the percentage of abstainers among younger patients tended to exceed that of their older counterparts. The conventional links between these lifestyle behaviors and CRC incidence appear elusive in the context of early-onset disease.

In light of these observations, the focus shifts toward the gut microbiome as a potential orchestrator of the increasing trend in CRC among those under 50 years. Alterations in the microbiota, induced by various factors such as environmental exposures, antibiotics, sedentary lifestyle, and dietary intake, emerge as plausible contributors. Given the significant changes in the American diet over the past several decades, as well as findings from a recent worldwide systematic review including 12 countries and 5 continents, which indicated that increasing CRC risk in younger adults is being driven by rising rectal cancers in North America and Australia (14), we postulate that dietary shifts may be pivotal in disrupting the gut microbiome. These disruptions, in turn, may foster adverse cellular changes in the gastrointestinal tract, providing a novel perspective on the intricate web of influences contributing to EOCRC incidence. A closer inspection of the evolution of dietary consumption patterns in the US since the 1900's may help to elucidate mechanisms responsible for noted disruptions in the gut microbiota.

TABLE 1 Characteristics of $N = 909$ patients with colorectal cancer stratified by age at diagnosis.

Characteristics	<50 Years ($n = 101$)	> = 50 Years ($n = 808$)	p-value
Gender, % Male	56.4	54.6	0.75
Race, %			0.55
Black	8.9	7.3	
White	91.1	92.7	
Family Hx Cancer, %	65.5	57.7	0.17
Smoking Status, %			<0.01
Current	21.6	15.7	
Former	13.4	44.7	
Never	65.0	39.6	
Alcohol Consumption, %			0.09
Current	45.3	45.6	
Former	2.1	8.1	
Never	52.6	46.3	
Marital Status, %			<0.01
Single	44.4	14.2	
Married	45.5	54.8	
Divorced/Separated	10.1	31.0	
Diabetes Hx, %	4.0	18.2	<0.01
Hypertension Hx, %	10.9	49.9	<0.01
Obesity Hx, %	10.9	16.6	0.15
Hyperlipidemia Hx, %	4.0	26.7	<0.01

2.1 The dietary shift

During the past century, the American diet has undergone radical changes, marked by a notable increase in the consumption of processed and ultra-processed foods, including refined carbohydrates, sugar, white flour, white rice, and industrial seed/vegetable oils (15, 16). This evolution is not merely a shift in dietary preferences but a journey into the unknown landscape of the Westernized colonic microbiome that is breeding a silent epidemic of EOCRC in young adults. The dietary evolution is characterized by a 206% surge in caloric sweeteners and has witnessed a staggering 550% increase in the availability of poultry from

1800 to 2019 (15) (Figure 1). The rise of industrial seed oils and vegetable shortening, triumphing over traditional animal fats, mirrors a broader trend in the infiltration of ultra-processed foods, such as chips, ready-to-eat meals, pre-packaged snacks, cereals, hot dogs, and energy bars, into more than 50% of the American diet.

The story unfolds further in the realm of meat processing, a domain increasingly marked by chemical preservatives and alterations in saturated fatty acid sources, resulting in colonic inflammation. Meat processing methods (i.e., curing, salting, smoking, and canning) result in high amounts of saturated fats, trans fats, and cholesterol (16). The curing process, for example, results in the release of nitrates and nitrites, endogenous N-nitroso compounds (NOCs), (16, 17) further cementing the link between dietary choices and CRC. In addition, studies show regular red meat consumption which contains heme induces toxicity and is a catalyst for epithelial damage, compensatory hyperproliferation, and eventual hyperplasia, a precursor to CRC. The repercussions extend beyond the immediate realm of meat consumption. Cooking methods, particularly at high temperatures, transform innocuous meats into carcinogenic agents, releasing polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) (16, 17). This toxic union with NOCs triggers mutations in pro-inflammatory genes, stimulates DNA damage through alkylation (16, 17), and sets the stage for tumorigenesis.

Liang et al. further cast a spotlight on the Western-style diet, reporting a culinary preference among the young compared to older individuals residing in Taiwan, who consume a more traditional Taiwanese diet (18). This dietary preference emerged as a potent force causing genetic or epigenetic alterations leading to microsatellite instability, a precursor to CRC (5, 19). Increases in EOCRC were primarily driven by distal colon and rectal tumors between 2004 and 2013 (20), and this trend was highlighted through the study by Zheng et al., revealing stronger associations between diet quality and early-onset advanced adenomas in the distal colon and rectum compared to the proximal colon (20). The intricacies of tumor progression further reveal that the proximal CRC is more likely to advance through the serrated neoplasia pathway, which contrasts with the majority of distal cancers originating from conventional adenomas. These distal cancers bear the molecular signatures of APC and TP53 mutations (20).

The molecular composition becomes a key player, as prior analyses in older cohorts expose the stronghold of the Western dietary pattern on tumors with specific molecular characteristics. These characteristics include low MSS or microsatellite instability, non-CpG island methylator phenotype, and BRAF/KRAS wild type which are representative of the molecular subtype common in EOCRC (20, 21). Collectively, the evidence points to a compelling conclusion that diet may wield a more potent influence on neoplasia originating from the traditional adenoma-carcinoma sequence (20), a stark reminder of the intricate interplay between dietary choices and the molecular landscape of colorectal cancer. However, while changes in food availability and patterns of consumption are believed to yield a significant impact on gut health, it is not likely that diet alone is responsible for the noted increases in EOCRC incidence. Additional factors such as medications, exposures and other potentially negative influences require further consideration.

2.2 Colonic microbiota and antibiotics

The colonic microbiota, a complex ecosystem profoundly influenced by factors such as diet, toxins, antibiotics, and pathogens, emerges as a critical player in the development of CRC. Among these factors, enteric pathogens pose the greatest risk of causing microbial imbalance, thus initiating or worsening tumorigenesis through mechanisms such as chronic inflammation, immune suppression, and the production of cancer-promoting metabolites (16). Dietary choices, particularly those high in meat and animal fat, have been identified as significant contributors to dysbiosis, fueling the production of genotoxic hydrogen sulfide (H_2S) and the secretion of bile acids, which metabolize into carcinogenic secondary bile acids (19, 22). Notably, distinctions between low-risk and high-risk CRC populations have

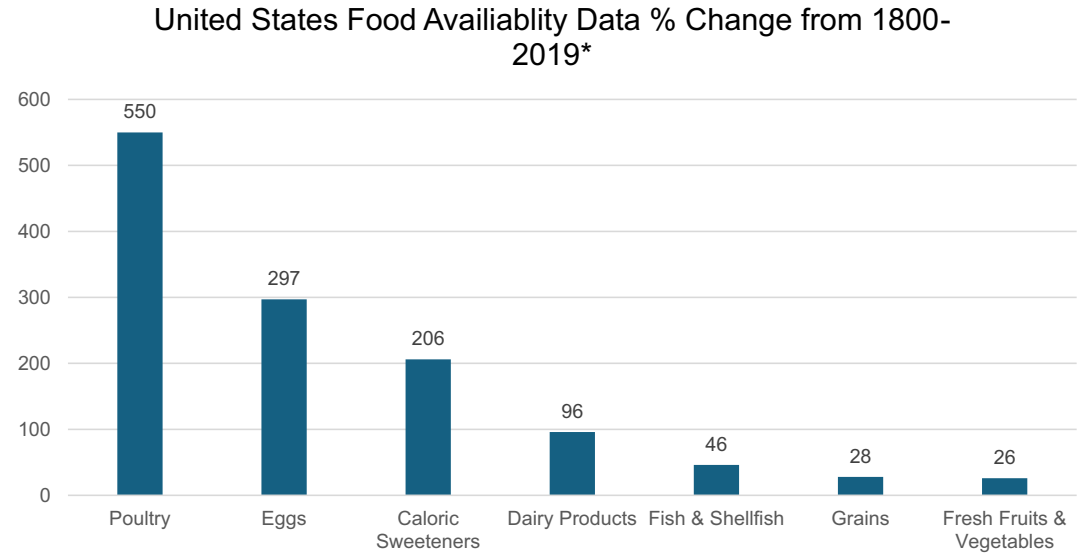


FIGURE 1
*Data extracted from Lee et al.'s study on United States Dietary Trends Since 1800 (15).

emerged, with the latter exhibiting an overabundance of proinflammatory bacteria, including *Porphyromonas, Fusobacterium, Enterococcaceae, and Bacteroides-Prevotella* genera, while beneficial and short-chain fatty acid-producing bacteria like *Faecalibacterium prausnitziin*, known for its anti-inflammatory properties, are diminished (22). Research demonstrates that the gut microbiota's sulfur metabolism, particularly influenced by Western dietary habits, plays a direct role in carcinogenesis (23). Notably, H_2S exhibits dual effects, depending on its origin and concentration. High levels can damage the mucosa by disrupting disulfide bonds in the mucus layer, allowing luminal bacteria and their byproducts to breach the epithelial lining, triggering apoptosis and inflammation (23), especially in regions where sulfur-metabolizing bacteria are abundant, such as the distal colon. Interestingly, research suggests that low concentrations of H_2S, both endogenous and from exogenous dietary sources like garlic and cruciferous vegetables, can protect and repair the colonic epithelium by promoting vasorelaxation, reducing stress, and preventing cell death (23).

Additionally, research has shown that in the United States, African Americans carry the biggest burden of CRC, and many have hypothesized that this could be due to diet-induced changes in the microbiome. Indeed, the incidence of colon cancer in rural South Africans has been reported to be substantially less than that for African Americans (24). O'Keefe et al. compared changes within the mucosal membrane of African Americans and rural South Africans following a dietary exchange. This was conducted to test the theory that Western diets contribute to increased CRC incidence (24). The rural South Africans were provided with a high-fat, low-fiber Westernized Diet for two weeks (25), whereas the African Americans ate the low-fat, high-fiber African-style diet. Alterations in colonic mucosal biomarkers, microbiota (e.g., *Fusobacterium nucleatum*), and metabolome found in the colon of South Africans were linked to increased risk of CRC (across all ages) (24, 25). The alternative, a decrease in risk factors, was observed for African Americans on the South African-style diet. Taking into account the emergence of EOCRC, one could reasonably speculate that exposure to risk factors, such as a Western diet high in ultra-processed foods during childhood and adolescence, could contribute to increased incidence rates. Since a considerable time lapse is required for normal colonic mucosa to develop into cancer, significant physiological and metabolic disturbances beginning in early life may partially account for the rising incidence of sporadic EOCRC (23, 26).

As we examine all age groups, a pattern of decreased microbial diversity and dysbiosis emerges as a common denominator in CRC risk. Pediatric studies hint at the early-life origins of dysbiosis as the setting for EOCRC development, linking it to factors like mode of delivery and antibiotic exposure during critical developmental periods (26, 27). While causative links between EOCRC and microbiota remain elusive, studies establish a positive correlation between the use of anti-anaerobic antibiotics and colorectal cancer. The gut microbiome, predominantly composed of anaerobes, appears susceptible to dysbiosis induced by anti-anaerobic antibiotic interventions, potentially fostering an environment conducive to colorectal tumor growth. The medical field's reliance on antibiotics, crucial for treating bacterial infections, introduces a paradox. The collateral damage inflicted on beneficial short-chain fatty acid-producing gut bacteria raises concerns about antibiotics' unintended consequences, particularly in the context of EOCRC. In the 1980s, the use of broad-spectrum antibiotics in the US tripled due to inappropriate prescriptions for ear and upper respiratory tract infections in children (6, 13, 27). The historical surge in antibiotic prescriptions, especially in pediatric populations, underscores the need for judicious antibiotic use to mitigate the risk of dysbiosis and its potential contribution to EOCRC. Furthermore, disparities in antibiotic prescription rates have indicated that White children received more antibiotics than Black children (27, 28), raising the question of how race factors into the colonic microbiome. Racial disparities in EOCRC incidence rates further complicate the narrative. While incidence rates for non-Hispanic Blacks have seen a marginal increase, the incidence rates for Hispanics and non-Hispanic Whites have surged to 85% within the same time span (4). The role of race and antibiotic exposure in shaping the colonic microbiome merits deeper exploration to untangle the complex web of contributing factors.

Beyond medicine, the extensive use of antibiotics in agriculture poses an additional threat to the gut microbiome. Antibiotics are employed in livestock for growth promotion and disease prevention, potentially leading to the transfer of antibiotic-resistant bacteria from animals to humans (3). The United States Food and Drug Administration (FDA) prohibited the use of antibiotics for growth promotion in 2017 and required that medically important antibiotics be prescribed by a veterinarian (29). However, these guidelines are non-binding and voluntary, and there are loopholes that allow the continued use of medically important antibiotics in agriculture. The ramifications for public health and nutrition are compounded by the conditions of livestock and factory farms. For example, the prevalent use of constricted battery cages for laying hens fosters unsanitary conditions and disease, both in poultry and potentially in their eggs (29). This is particularly disconcerting considering the staggering 550% increase in poultry food availability over the last century (Figure 1). Pesticides on fresh produce and the presence of toxic contaminants in fish-inhabited waters represent additional factors contributing to changes in the gut microbiome. Additionally, the modern diet, loaded with additives like artificial coloring and preservatives, further compounds the issue by influencing the gut microbiome. Exogenous factors, including diet and environmental exposures, intricately shape microbial diversity, consequently impacting metabolism, immune responses, and gene expression (6).

2.3 Discussion

The rising incidence of EOCRC poses a significant and alarming public health challenge. While previous research has predominantly linked metabolic syndromes to this trend, our investigation unveils a more intricate narrative, emphasizing the role of changing dietary patterns, particularly in Westernized societies. The traditional focus on factors such as obesity, diabetes, and hypertension fail to account for over half of EOCRC cases, urging a reevaluation of the multifaceted contributors to this growing issue. This realization underscores the need for a broader exploration of potential contributors, leading us to scrutinize the significant role that dietary patterns and lifestyle behaviors play in the context of EOCRC.

One pivotal aspect of this discussion revolves around the profound changes in human nutrition witnessed over the past century. The shift toward diets rich in meat, fats, oils, and added sugars, coupled with reduced consumption of vegetables and whole grains, has created an environment conducive to inflammatory processes within the intestinal microenvironment (30). While the exact mechanisms

remain elusive, the proposed link between inflammatory diets and EOCRC highlights the importance of understanding the metabolic decomposition of lipids, particularly secondary bile acids and hydrogen sulfide (16), as potential instigators of inflammation and subsequent damage to the intestinal epithelial barrier.

A notable consequence of dietary transformation is the decline in fiber intake, primarily due to increased consumption of refined grains and sugars (31, 32). This decline has been associated with an elevated risk of colon cancer, emphasizing the critical role of fiber in maintaining intestinal health. The statistical evidence of a substantial increase in the availability of caloric sweeteners and sugar-sweetened beverage consumption further underscores the urgency of addressing excessive sugar intake despite some recent declines (22, 30, 32, 33).

The protective potential of a healthy diet, characterized by a high intake of fruits, vegetables, legumes, whole grains, and low-fat dairy (22), is underscored by epidemiological studies revealing an inverse relationship between colorectal adenomas and carcinomas and fiber intake (34). Encouragingly, these findings suggest that increased fiber intake during childhood and adolescence may serve as a protective measure against EOCRC.

The evaluation of the surge in EOCRC consistently points to changes in Westernized dietary patterns in the United States as a significant contributor. These dietary alterations, in turn, impact the colonic microbiome, adding a layer of complexity to our understanding of EOCRC etiology. Importantly, these changes in the microbiome persist even in the absence of traditional metabolic syndromes. Such findings warrant further research into the intricate relationships between diet, gut microbiota, and initiation of cancer (16). A shift in focus from traditional metabolic factors to dietary patterns, coupled with efforts to regulate processed foods and promote judicious antibiotic use, is crucial. This includes targeted interventions and therapies aimed at inhibiting incidences of EOCRC. Public health campaigns and collaborative efforts among researchers, healthcare professionals, policymakers, and the public are imperative to reverse this trend and improve gastrointestinal health in younger generations. As we advance in our understanding of these relationships, we pave the way for informed strategies that can effectively mitigate the risk of EOCRC and promote better overall gastrointestinal health.

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 authors.

Ethics statement

The studies involving humans were approved by Stony Brook University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because the data were retrospective and fully de-identified.

Author contributions

AMA: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. JW: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. LM: Conceptualization, Data curation, Methodology, Writing – review & editing. BN: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. World Health Organization. (2023) Colorectal Cancer. Available at: https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer.

2. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin*. (2023) 73:233–54. doi: 10.3322/caac.21772

3. Mauri G, Russo G, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol*. (2019) 13:109–31. doi: 10.1002/1878-0261.12417

4. Pearlman R, Frankel WL, Swanson B, Zhao W, Yilmaz A, Miller K, et al. Prevalence and Spectrum of germline Cancer susceptibility gene mutations among patients with early-onset colorectal Cancer. *JAMA Oncol*. (2017) 3:464–71. doi: 10.1001/jamaoncol.2016.5194

5. Chang DT, Pai RK, Rybicki LA, Dimaio MA, Limaye M, Jayachandran P, et al. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. *Mod Pathol Off J U S Can Acad Pathol*. (2012) 25:1128–39. doi: 10.1038/modpathol.2012.61

6. Stoffel EM, Koeppe E, Everett J, Ulintz P, Kiel M, Osborne J, et al. Germline genetic features of young individuals with colorectal Cancer. *Gastroenterology*. (2018) 154:897–905.e1. doi: 10.1053/j.gastro.2017.11.004

7. Spaander MCW, Zauber AG, Syngal S, Blaser MJ, Sung JJ, You YN, et al. Young-onset colorectal cancer. *Nat Rev Dis Primers*. (2023) 9:21. doi: 10.1038/s41572-023-00432-7

8. Chen FW, Sundaram V, Chew TA, Ladabaum U. Advanced-stage colorectal Cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. (2017) 15:728–737.e3. doi: 10.1016/j.cgh.2016.10.038

9. Perea J, Rodríguez Y, Rueda D, Marín JC, Díaz-Tasende J, Álvaro E, et al. Early-onset colorectal cancer is an easy and effective tool to identify retrospectively lynch syndrome. *Ann Surg Oncol*. (2011) 18:3285–91. doi: 10.1245/s10434-011-1782-4

10. Patel SG, Ahnen DJ. Colorectal Cancer in the young. *Curr Gastroenterol Rep*. (2018) 20:15. doi: 10.1007/s11894-018-0618-9

11. Pan SY, Des Meules M. Energy intake, physical activity, energy balance, and cancer: epidemiologic evidence. *Methods Mol Biol*. (2009) 472:191–15. doi: 10.1007/978-1-60327-492-0_8

12. Zheng J, Zhao M, Li J, Lou G, Yuan Y, Bu S, et al. Obesity-associated digestive cancers: a review of mechanisms and interventions. *Tumour Biol J Int Soc Oncodevelopment Biol Med*. (2017) 39:5020. doi: 10.1177/1010428317695020

13. Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of Colon and Rectal cancers in young adults. *Gastroenterology*. (2020) 158:341–53. doi: 10.1053/j.gastro.2019.07.055

14. Saad El Din K, Loree JM, Sayre EC, Gill S, Brown CJ, Dau H, et al. Trends in the epidemiology of young-onset colorectal cancer: a worldwide systematic review. *BMC Cancer*. (2020) 20:288. doi: 10.1186/s12885-020-06766-9

15. Lee JH, Duster M, Roberts T, Devinsky O. United States dietary trends since 1800: lack of association between saturated fatty acid consumption and non-communicable diseases. *Front Nutr*. (2022) 8:748847. doi: 10.3389/fnut.2021.748847

16. Ahmad Kendong SM, Raja Ali RA, Nawawi KNM, Ahmad HF, Mokhtar NM. Gut Dysbiosis and intestinal barrier dysfunction: potential explanation for early-onset colorectal Cancer. *Front Cell Infect Microbiol*. (2021) 11:744606. doi: 10.3389/fcimb.2021.744606

17. Mehta SS, Arroyave WD, Lunn RM, Park YM, Boyd WA, Sandler DP. A prospective analysis of red and processed meat consumption and risk of colorectal Cancer in women. *Cancer Epidemiol Biomarkers Prev*. (2020) 29:141–50. doi: 10.1158/1055-9965.EPI-19-0459

18. Liang JT, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. *Br J Surg*. (2003) 90:205–14. doi: 10.1002/bjs.4015

19. Medici B, Riccò B, Caffari E, Zaniboni S, Salati M, Spallanzani A, et al. Early onset metastatic colorectal Cancer: current insights and clinical management of a rising condition. *Cancers*. (2023) 15:3509–31. doi: 10.3390/cancers15133509

20. Zheng X, Hur J, Nguyen LH, Liu J, Song M, Wu K, et al. Comprehensive assessment of diet quality and risk of precursors of early-onset colorectal Cancer. *JNCI J Natl Cancer Inst*. (2021) 113:543–52. doi: 10.1093/jnci/djaa164

21. Mehta RS, Nishihara R, Cao Y, Song M, Mima K, Qian ZR, et al. Association of Dietary Patterns with Risk of colorectal Cancer subtypes classified by *Fusobacterium nucleatum* in tumor tissue. *JAMA Oncol*. (2017) 3:921–7. doi: 10.1001/jamaoncol.2016.6374

22. Dik VK, Smeets HM, Siersema PD. Frequent use of antibiotics is associated with colorectal Cancer risk: results of a nested case–control study. *Dig Dis Sci*. (2016) 61:255–64. doi: 10.1007/s10620-015-3828-0

23. Moon JY, Kye BH, Ko SH, Yoo RN. Sulfur metabolism of the gut microbiome and colorectal Cancer: the threat to the younger generation. *Nutrients*. (2023) 15:1966. doi: 10.3390/nu1508196

24. O'Keefe SJ, Li JV, Lahti L, Ou J, Carbonero F, Mohammed K, et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nat Commun*. (2015) 6:6342. doi: 10.1038/ncomms7342

25. Dharwadkar P, Zaki TA, Murphy CC. Colorectal Cancer in younger adults. *Hematol Oncol Clin North Am*. (2022) 36:449–70. doi: 10.1016/j.hoc.2022.02.005

26. Dai R, Kelly BN, Ike A, Berger D, Chan A, Drew DA, et al. The impact of the gut microbiome, environment, and diet in early-onset colorectal Cancer development. *Cancers*. (2024) 16:676. doi: 10.3390/cancers16030676

27. Puzzono M, Mannucci A, Grannò S, Zuppardo RA, Galli A, Danese S, et al. The role of diet and lifestyle in early-onset colorectal Cancer: a systematic review. *Cancers*. (2021) 13:5933–58. doi: 10.3390/cancers13235933

28. Carson TL, Byrd DA, Smith KS, Carter D, Abaskaron M, Little RB, et al. A case-control study of the association between the gut microbiota and colorectal cancer: exploring the roles of diet, stress, and race. *Res Square*. (2023) doi: 10.21203/rs.3.rs-2475944/v1

29. Chalmers M. *How chicken antibiotics could cause the next Global Health crisis*. Sentient Media (2021).

30. Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, et al. Association of obesity with risk of early-onset colorectal cancer among women. *JAMA Oncol*. (2019) 5:37–44. doi: 10.1001/jamaoncol.2018.4280

31. Chang VC, Cotterchio M, De P, Tinmouth J. Risk factors for early-onset colorectal cancer: a population-based case-control study in Ontario, Canada. *Cancer Causes Control*. (2021) 32:1063–83. doi: 10.1007/s10552-021-01456-8

32. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. *Gut*. (2021) 70:2330–6. doi: 10.1136/gutjnl-2020-323450

33. Yue Y, Hur J, Cao Y, Tabung FK, Wang M, Wu K, et al. Prospective evaluation of dietary and lifestyle pattern indices with risk of colorectal cancer in a cohort of younger women. *Ann Oncol Off J Euro Soc Med Oncol*. (2021) 32:778–86. doi: 10.1016/j.annonc.2021.03.200

34. Thanikachalam K, Khan G. Colorectal Cancer and nutrition. *Nutrients*. (2019) 11:164–74. doi: 10.3390/nu11010164

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 28 May 2024
DOI 10.3389/fnut.2024.1375252

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Zahra Vahdat Shariatpanahi,
Shahid Beheshti University of Medical Sciences, Iran
Syed Faisal Zaidi,
King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia

*CORRESPONDENCE
Fengming Chen
✉ cfm2138@cdutcm.edu.cn

†These authors share first authorship

RECEIVED 26 January 2024
ACCEPTED 15 May 2024
PUBLISHED 28 May 2024

CITATION
Qu Y, Cheng Y and Chen F (2024) The relationship between caffeine consumption and colon cancer prevalence in a nationally representative population.
Front. Nutr. 11:1375252.
doi: 10.3389/fnut.2024.1375252

The relationship between caffeine consumption and colon cancer prevalence in a nationally representative population

Yuhua Qu[1†], Yulu Cheng[2†] and Fengming Chen[1*]

[1]Department of Anorectology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China, [2]Department of Disinfection Supply Center, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China

Aims: This study examines the correlation between caffeine consumption and the prevalence of colon cancer.

Methods: Utilizing data from the National Health and Nutrition Examination Survey (NHANES) for the years 2001 to 2014, we applied weighted logistic regression to evaluate the association between caffeine consumption and the prevalence of colon cancer. This analysis accounted for variables including age, gender, race, education, poverty income ratio, smoking status, alcohol consumption, and diabetes. The findings were expressed as weighted odds ratios (ORs) with accompanying 95% confidence intervals (CIs). The restricted cubic spline analysis was performed to exam the dose-dependent relationship.

Results: The study included 27,637 participants, of which 144 were diagnosed with colon cancer and 27,493 served as controls. Individuals in the highest quartile (Q4) of caffeine consumption (Q4) displayed a significantly increased risk of colon cancer compared to those in the lowest quartile (Q1), with a weighted OR of 2.00 (95% CI: 1.11–3.59; $p = 0.022$). Additionally, restricted cubic spline analysis indicated a significant correlation between higher caffeine intake and increased colon cancer risk, with an overall association p-value of 0.007.

Conclusion: These findings suggest a potential relationship between higher levels of caffeine consumption and an increased risk of colon cancer. The dose–response relationship suggests a notable correlation at higher caffeine intake levels. Further investigations are warranted to confirm these results and elucidate potential underlying mechanisms.

KEYWORDS

caffeine intake, colon cancer, dose–response relationship, restricted cubic spline, NHANES

1 Introduction

Coffee is one of the most commonly consumed beverages worldwide, with an estimated yearly trade of more than 10 billion dollars (1). Its global popularity stems from its distinctive flavor and stimulating properties, making it a staple in the daily routines of billions (2). On average, an American adult consumes about 1.5 standard cups of coffee daily, making caffeine a major component of their daily intake (3). Coffee contains a variety of bioactive compounds

linked to several health conditions, including diabetes (4), cardiovascular disease (5), cancer (6), and so on. These compounds include caffeine, chlorogenic acids, and various minerals, all of which can significantly impact human health (7). Among the many biological compounds, caffeine, chemically known as 1,3,7-trimethylxanthine, mirrors the molecular structure of adenosine, enabling it to block adenosine receptors and inhibit its effects (8). Notably, caffeine has been shown to exhibit antioxidant and anti-inflammatory properties, modulate the gut microbiome, and alter drug/nutrient metabolism (9). Therefore, the potential health impacts of caffeine consumption have become a focal point of extensive research.

Colon cancer, also referred to as colorectal cancer, is a malignancy originating in the colon or rectum. As the third most common cancer, colon cancer has become the second leading cause of cancer-related deaths worldwide, posing a significant public health concern (10). The causes of colon cancer are multifactorial, with lifestyle factors playing a significant role in its onset and progression (11). The impact of caffeine intake on the risk of digestive tract cancers has been extensively studied, yet the findings remain inconsistent. Some research indicates a protective effect of caffeine, suggesting it may lower the risk of certain digestive tract cancers (12, 13), while other studies have found no significant relationship (14–16). The disparity underscores the need for further research to clarify the role of caffeine consumption in the development of colon cancer.

Given the widespread consumption of coffee and caffeine among U.S. adults, this study investigates the potential association between caffeine intake and the prevalence of colon cancer in US population. We analyzed data from large-scale, population-based surveys, taking into account numerous potential confounding factors. Our findings aim to enrich the existing body of knowledge regarding the health effects of caffeine consumption and may have significant implications for public health recommendations and prevention strategies for colon cancer.

2 Methods

2.1 Study population

The National Health and Nutrition Examination Survey (NHANES) is a large, nationally representative, cross-sectional survey conducted by the Centers for Disease Control and Prevention in the United States (17). NHANES is designed to investigate the health and nutritional status of the non-institutionalized US population via interviews, questionnaires, physical examinations, and laboratory tests. The survey protocol, including study design and data collection procedures, is approved by the National Center for Health Statistics Ethics Review Board, and all the participants provided the written informed consent. The data were accessed for research purposes on 02/04/2023.

NHANES has provided nationally representative samples to explore the association between caffeine intake and colon cancer. Our study used data from seven consecutive NHANES two-year cycles, spanning from 2001 to 2014. These cycles were selected to ensure a sufficient sample size and to allow for the analysis of trends over time. The NHANES survey employs a complex, multistage probability sampling design, ensuring the representation of various demographic groups, including age, sex, race/ethnicity, and socioeconomic status. The inclusion criteria for our study population were adults aged ≥20 and < 80, and individuals with missing data on mobile examination center collected caffeine consumption or cancer status were excluded to reduce potential bias in the analysis. According to the inclusion and exclusion criteria, the final study population comprised a total of 27,637 participants. The NHANES sampling weights were utilized for the survey design to guarantee the nationally representative estimate for the US population.

2.2 The identification of colon cancer

To identify participants with a history of colon cancer, we relied on self-reported medical data from questionnaires. In the continuous NHANES questionnaire survey, participants answered the following two questions: 'Have you ever been told by a doctor or health professional that you have colon cancer?', and 'Have you ever been told by a doctor or health professional that you have rectum cancer?'. A positive response to any of these questions indicated a self-reported history of colon cancer. To minimize the potential misclassification bias, we considered participants to have a history of colon cancer only when they reported a positive diagnosis for colon or rectum cancer.

2.3 Caffeine intake assessment

Caffeine intake in our study was assessed using the Dietary Interview – Total Nutrient Intakes data from the NHANES survey. The dietary intake information was obtained through in-person 24-h dietary recall interviews, conducted by trained interviewers based on the United States Department of Agriculture's (USDA) Automated Multiple-Pass Method. This method is designed to ensure the accuracy of self-reported dietary intake by guiding respondents through a structured, detailed interview process. To estimate caffeine intake, the reported food and beverage consumption data were linked to the USDA Food and Nutrient Database for Dietary Studies (FNDDS). The FNDDS provides detailed information on the nutrient content of various food items, including caffeine levels. The daily caffeine intake for each participant was calculated by summing up the caffeine content of all consumed food and beverages during the 24-h recall period.

We utilized only the First Day Dietary Interview data to estimate caffeine intake. The First Day Dietary Interview was performed in a mobile examination center, where participants were interviewed in a controlled environment (18). This approach ensures consistency and accuracy in the data collection process. The decision to use only the first day of dietary recall was based on the assumption that it provides a reliable snapshot of the participants' habitual caffeine consumption while minimizing the potential for recall bias.

2.4 Covariates

In this study, we adjusted for several potential confounding factors that could influence the association between caffeine intake and the prevalence of colon cancer. The covariates included in our analyses were age (continuous), gender (male or female), race/ethnicity (categories), education level (categories), poverty income ratio (categories), smoking status (never smokers, former smokers, and current smokers) (19), alcohol consumption (yes/no), and diabetes

(yes/borderline/no). These covariates were incorporated into the statistical models to account for their potential effects on the relationship between caffeine intake and the prevalence of colon cancer. Education level is often used as a proxy for socioeconomic status and may be associated with cancer risk through various mechanisms, such as health behaviors and access to healthcare. We categorized education into three groups: low high school, high school, and above high school. Poverty income ratio is a measure of socioeconomic status based on the ratio of family income to the poverty threshold. It is a continuous variable that may be associated with cancer risk through factors such as access to healthcare, health behaviors, and environmental exposures. Poverty income ratio was categorized into three levels, including <1.33, 1.33 ~ 3.5, and ≥ 3.5. In this study, participants who consuming at least 12 alcohol drinks a year were defined as drinkers (20).

2.5 Statistical analysis

This study used the sample weight (WTDRD1/7) to account for the complex survey design considering stratification, clustering, and oversampling. The sample weight was divided by 7 to adjust for the use of seven consecutive two-year cycles from 2001 to 2014, ensuring that the results are representative of the US adult population. To compare the demographic, lifestyle, and dietary characteristics between cancer patients and controls, we conducted descriptive analyses. Continuous variables were presented as weighted means ± standard errors, while categorical variables were presented as weighted proportions. We performed weighted t-test for continuous variables and weighted chi-square test for categorical variables to determine the differences between the groups.

To investigate the association between caffeine intake and the prevalence of colon cancer, we utilized weighted logistic regression controlling for various potential confounders. Three distinct models were employed: Model 1 is the unadjusted model; Model 2 is adjusted for age, gender, and race; and Model 3 is the fully adjusted model, which includes adjustments for age, gender, race, education, poverty income ratio levels, smoking, drinking, and diabetes. The caffeine intake was first analyzed as a continuous variable. It was subsequently categorized into quartiles of intake for further analysis, with the groups defined as: ≤13 mg, 13 ~ 97 mg, 97 ~ 213 mg, and > 213 mg. The results were presented as weighted odds ratio (OR) with corresponding 95% confidence interval (CI). Additionally, we employed restricted cubic spline regression with four knots to further investigate the dose–response relationship between caffeine intake and colon cancer.

All statistical analyses were performed based on R software, and $p < 0.05$ was considered statistically significant.

3 Results

3.1 Participant characteristics by cancer status

27,637 participants were enrolled in the study, with 144 individuals in the colon cancer group and 27,493 individuals in the control group. The baseline characteristics by cancer status are shown in Table 1. The average age of the cancer group was significantly higher than that of the control group (64.67 ± 1.17 vs. 45.44 ± 0.24, $p < 0.001$). Caffeine intake was also significantly different between the two groups, with the cancer group having higher mean caffeine intake (241.51 ± 18.96 mg) compared to the control group (183.08 ± 3.45 mg, $p < 0.001$).

TABLE 1 Characteristics of the study population.

	Cancer group	Control group	*p*
Sample size	144	27,493	
Age (years)	64.67 ± 1.17	45.44 ± 0.24	<0.001
Caffeine intake (mg)	241.51 ± 18.96	183.08 ± 3.45	<0.001
Gender (male, %)	52.5	48.5	0.86
Race (%)			<0.001
Mexican American	1.4	8.6	
Non-Hispanic Black	9.5	11.6	
Non-Hispanic White	86.0	68.5	
Other Hispanic	1.7	4.8	
Other races	1.4	6.5	
Education (%)			0.29
Below high school	17.9	16.9	
High school	20.7	23.6	
Above high school	61.5	59.5	
PIR levels (%)			0.79
< 1.33	24.2	21.3	
1.33 ~ 3.5	30.7	32.2	
≥ 3.5	45.1	46.5	
Smoking (%)			<0.001
Current smoker	15.0	23.3	
Former smoker	49.2	22.8	
Never smoker	35.8	53.9	
Drinking (yes, %)	18.3	11.5	0.07

PIR, Poverty income ratio.

There was no significant difference in gender distribution ($p = 0.86$), with males representing 52.5% of the cancer group and 48.5% of the control group. The racial composition of the groups was significantly different ($p < 0.001$). Education levels ($p = 0.29$) and PIR levels showed no significant differences between the groups ($p = 0.79$). However, no significant difference was observed in alcohol consumption ($p = 0.07$), with 18.3% of the cancer group and 11.5% of the control group reporting alcohol consumption.

3.2 Weighted logistic regression analysis on the association between caffeine intake and colon cancer

Table 2 presents the weighted logistic regression analysis examining the association between caffeine intake and colon cancer.

TABLE 2 Weighted association between caffeine intake and colon cancer based on logistic regression.

	Model 1	*p*	Model 2	*P*	Model 3	*p*
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Caffeine (Per 50 mg)	1.04 (1.02, 1.05)	<0.001	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
Caffeine (Categories)						
Q1	Reference		Reference		Reference	
Q2	0.41 (0.21, 0.83)	0.013	0.46 (0.23, 0.92)	0.028	0.48 (0.24, 0.96)	0.039
Q3	0.71 (0.37, 1.37)	0.307	0.67 (0.35, 1.29)	0.224	0.67 (0.35, 1.30)	0.235
Q4	2.09 (1.21, 3.60)	0.009	1.97 (1.14, 3.42)	0.016	2.00 (1.11, 3.59)	0.022

Model 1 adjusted for no covariates. Model 2 adjusted for age, gender, and race. Model 3 adjusted for age, gender, race, education, poverty income ratio levels, smoking, drinking, and diabetes.

In Model 1, which was not adjusted for any covariates, the OR for colon cancer per 50 mg increase in caffeine intake was 1.04 (95% CI: 1.02–1.05, $p < 0.001$), indicating a significant positive association between caffeine intake and colon cancer risk.

In Model 2, which was adjusted for age, gender, and race, the OR for colon cancer per 50 mg increase in caffeine intake remained significant at 1.04 (95% CI: 1.02–1.06, $p < 0.001$). The analysis of caffeine intake by categories revealed a significantly lower risk of colon cancer in the second quartile (Q2) compared with the first quartile (Q1) as the reference group (OR: 0.46, 95% CI: 0.23–0.92, $p = 0.028$). The risk of colon cancer in the third quartile (Q3) was not statistically significant compared to the reference group (OR: 0.67, 95% CI: 0.35–1.29, $p = 0.224$). However, the fourth quartile (Q4) showed a significantly higher risk of colon cancer compared to the reference group (OR: 1.97, 95% CI: 1.14–3.42, $p = 0.016$).

In Model 3, which was further adjusted for education, poverty income ratio levels, smoking, drinking, and diabetes, the OR for colon cancer per 50 mg increase in caffeine intake remained significant at 1.04 (95% CI: 1.02–1.06, $p < 0.001$). The risk of colon cancer in Q2 was significantly lower compared to the reference group (OR: 0.48, 95% CI: 0.24–0.96, $p = 0.039$), while the risk in Q3 was not statistically significant (OR: 0.67, 95% CI: 0.35–1.30, $p = 0.235$). The risk of colon cancer in Q4 was significantly higher compared to the reference group (OR: 2.00, 95% CI: 1.11–3.59, $p = 0.022$).

3.3 Dose–response association analysis

To explore the dose–response association between caffeine intake and the risk of colon cancer, we conducted the restricted cubic spline analysis based on logistic regression. The caffeine intake of 0 mg was set as the reference. As shown in Figure 1, the results reveal a non-significant association between caffeine intake and the risk of colon cancer at low levels. However, at higher levels of caffeine intake, a significant association was observed. The overall *p*-value for the association was 0.007, indicating a statistically significant relationship between caffeine intake and the risk of colon cancer. This indicates that the dose–response relationship between caffeine intake and the risk of colon cancer is predominantly driven by the association observed at higher levels of caffeine intake.

4 Discussion

This study explored the association between caffeine intake and the prevalence of colon cancer utilizing data from the NHANES survey from 2001 to 2014. Our findings indicated a significant association between higher caffeine intake and an increased risk of colon cancer. This association remained significant adjusting for age, gender, race, education, poverty income ratio levels, smoking, drinking, and diabetes. Additionally, we observed a reduced risk of colon cancer at low levels of caffeine intake, suggesting that the relationship may be influenced by varying consumption levels. Moreover, our dose–response analysis using restricted cubic spline regression revealed the trend in the relationship between caffeine intake and colon cancer risk, with a significant association observed at higher levels of caffeine intake. These findings enhanced the understanding of the relationship between caffeine intake and colon cancer risk and provided valuable insights that could guide public health recommendations and risk assessment strategies.

Research on the association between coffee consumption and colon cancer risk has yielded conflicting results. A meta-analysis encompassing 26 prospective studies with a collective total of 3,308,028 subjects, revealed a protective effect of coffee against colorectal cancer in the U.S. population, with a risk ratio of 0.83 (95% CI: 0.72–0.95). However, this analysis found no significant association between coffee intake and rectal cancer (16). Caroline et al. (21) investigated the association between coffee intake and the risk of colorectal cancer in older US adults, encompassing 47,010 men and 60,051 women aged 47–96 years without prior cancer diagnosis. Their findings indicated that consuming ≥2 cups of decaffeinated coffee a day was associated with a decreased risk of colorectal cancer (hazard ratio = 0.82, 95% CI = 0.69 ~ 0.96), colon cancer (hazard ratio = 0.82, 95% CI = 0.69 ~ 0.99), and rectal cancer (hazard ratio = 0.63, 95% CI: 0.40 ~ 0.99) compared to caffeinated coffee. Giovannucci's meta-analysis, which combined data from 12 case–control studies and 5 cohort studies, demonstrated an inverse relationship, with a pooled relative risk of 0.72 (95% CI: 0.61–0.84) (22). Similarly, the NIH-AARP Diet and Health Study revealed a significant decrease in colon cancer risk among individuals consuming 4/5 cups (HR: 0.85; 95% CI: 0.75–0.96) and ≥ 6 cups (HR: 0.74; 95% CI: 0.61–0.89) of coffee daily (23). Based on 5,145 cases and 4,097 controls from the MECC study, Schmit et al. (24), found that coffee consumption reduced the risk of colorectal cancer by 26%. The HERPACC-I and II studies further supported

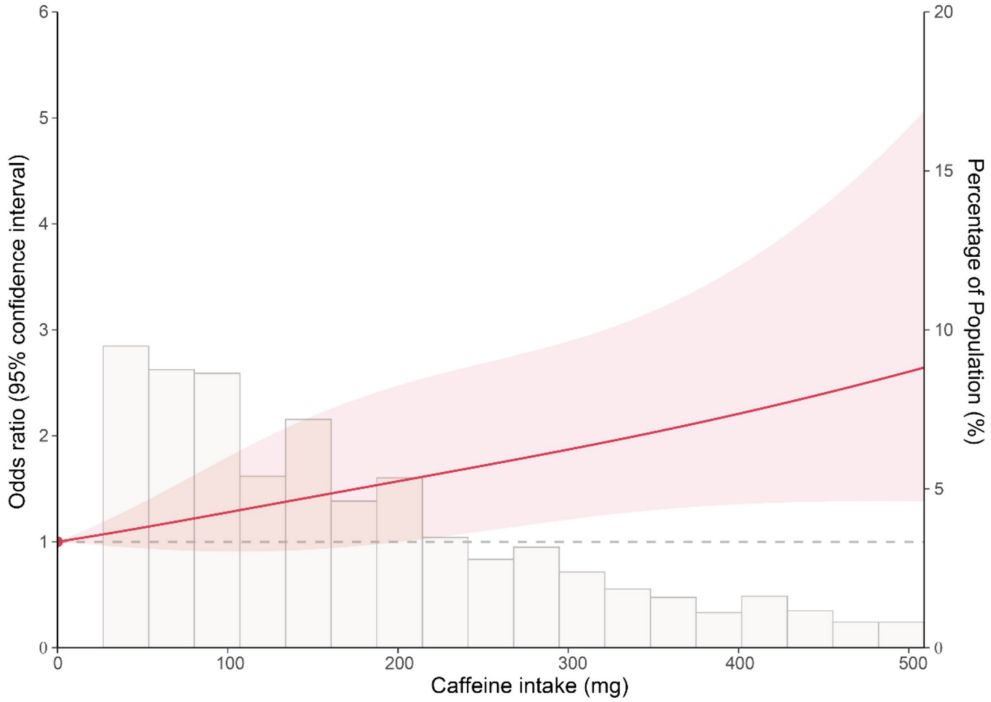


FIGURE 1
Restricted cubic spline plot of the association between caffeine intake and the risk of colon cancer. The solid line represents the OR of colon cancer for varying levels of caffeine intake, with 0 mg caffeine intake set as the reference. The shaded area represents the 95% confidence interval.

these findings, showing that consuming three or more cups of coffee daily was associated with a reduced risk of colon cancer (OR: 0.78; 95% CI: 0.65–0.92) in Asian populations (25).

In contrast, a pooled analysis of 13 prospective cohort studies indicated that consumption of more than 1,400 g of coffee daily did not increase colon cancer risk (RR: 1.07; 95% CI: 0.89–1.30) (26). Furthermore, data from the Nurses' Health Study and the Health Professionals' Follow-up Study showed no significant association between caffeinated coffee consumption and the risk of colon or rectal cancer (pooled HR: 0.99; 95% CI: 0.96–1.03) (27). A meta-analysis of 12 additional cohort studies also found no significant impact of coffee consumption on colorectal cancer risk (28). These studies highlight that it is necessary to further investigate the associations between caffeinated and decaffeinated coffee intake and colorectal cancer risk.

Our study adds to the expanding body of knowledge regarding the association between caffeine intake and colon cancer risk. Our results suggest that higher levels of caffeine consumption may be linked to an increased risk of colon cancer, underscoring the potential need for public health initiatives to curtail excessive caffeine consumption. To further delineate the causal relationship between caffeine intake and colon cancer risk, future research should employ longitudinal study designs. Additionally, exploring the biological mechanisms behind this association and how it may be modified by factors such as genetics, sex, and lifestyle habits could offer valuable insights for developing effective cancer prevention strategies.

The strengths of our study include the use of a large, nationally representative dataset, which enhances the generalizability of our findings to the US adult population. Additionally, the comprehensive adjustment for potential confounding factors minimizes the risk of residual confounding. Moreover, the application of restricted cubic spline regression in our dose–response analysis allowed for a more flexible representation of the relationship between caffeine intake and colon cancer risk. However, our study also has some limitations. First, the cross-sectional nature of NHANES data precludes any determination of causality between caffeine intake and colon cancer risk. Second, the reliance on self-reported dietary information and cancer diagnoses may have introduced recall and reporting biases. Third, despite adjusting for multiple confounders, there is still a possibility of residual confounding (such as family history of colorectal cancer in first-degree relatives, history of abdominal radiation, and inflammatory bowel disease) due to unmeasured or inadequately measured factors. Lastly, the single 24-h dietary recall used to estimate caffeine intake may not accurately represent habitual consumption patterns.

5 Conclusion

In summary, our findings provide evidence for a positive association between high levels of caffeine intake and the risk of colon cancer among US adults. The dose–response relationship analysis, utilizing restricted cubic spline regression, revealed a predominantly linear relationship, with a significant association observed at higher levels of caffeine intake. These findings suggest that excessive caffeine consumption may be a risk factor for colon cancer. Future longitudinal studies are warranted to confirm our findings and to further investigate the potential mechanisms underlying the observed association. Public health efforts to promote moderate caffeine consumption and to raise awareness of the potential risks associated with excessive intake may help to reduce the incidence of colon cancer in the population.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The survey protocol, including study design and data collection procedures, is approved by the National Center for Health Statistics Ethics Review Board, and all the participants provided the written informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YQ: Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. YC: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. FC: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Butt MS, Sultan MT. Coffee and its consumption: benefits and risks. *Crit Rev Food Sci Nutr*. (2011) 51:363–73. doi: 10.1080/10408390903586412

2. van Dam RM, Hu FB, Willett WC. Coffee, caffeine, and health. *N Engl J Med*. (2020) 383:369–78. doi: 10.1056/NEJMra1816604

3. Drewnowski A, Rehm CD. Sources of caffeine in diets of US children and adults: trends by beverage type and purchase location. *Nutrients*. (2016) 8:154. doi: 10.3390/nu8030154

4. Ding M, Bhupathiraju SN, Chen M, van Dam RM, Hu FB. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. *Diabetes Care*. (2014) 37:569–86. doi: 10.2337/dc13-1203

5. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation*. (2014) 129:643–59. doi: 10.1161/CIRCULATIONAHA.113.005925

6. Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol*. (2013) 11:1413–1421.e1. doi: 10.1016/j.cgh.2013.04.039

7. Ludwig IA, Clifford MN, Lean ME, Ashihara H, Crozier A. Coffee: biochemistry and potential impact on health. *Food Funct*. (2014) 5:1695–717. doi: 10.1039/C4FO00042K

8. Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev*. (1999) 51:83–133.

9. Nehlig A. Effects of coffee on the gastro-intestinal tract: a narrative review and literature update. *Nutrients*. (2022) 14:399. doi: 10.3390/nu14020399

10. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol*. (2021) 14:101174. doi: 10.1016/j.tranon.2021.101174

11. Marmol I, Sanchez-de-Diego C, Pradilla Dieste A, Cerrada E, Rodriguez Yoldi MJ. Colorectal carcinoma: a general overview and future perspectives in colorectal Cancer. *Int J Mol Sci*. (2017) 18:197. doi: 10.3390/ijms18010197

12. Martimianaki G, Bertuccio P, Alicandro G, Pelucchi C, Bravi F, Carioli G, et al. Coffee consumption and gastric cancer: a pooled analysis from the stomach cancer pooling project consortium. *Eur J Cancer Prev*. (2022) 31:117–27. doi: 10.1097/CEJ.0000000000000680

13. Deng W, Yang H, Wang J, Cai J, Bai Z, Song J, et al. Coffee consumption and the risk of incident gastric cancer—a meta-analysis of prospective cohort studies. *Nutr Cancer*. (2016) 68:40–7. doi: 10.1080/01635581.2016.1115093

14. Zhang J, Zhou B, Hao C. Coffee consumption and risk of esophageal cancer incidence: a meta-analysis of epidemiologic studies. *Medicine (Baltimore)*. (2018) 97:e0514. doi: 10.1097/MD.0000000000010514

15. Xie Y, Huang S, He T, Su Y. Coffee consumption and risk of gastric cancer: an updated meta-analysis. *Asia Pac J Clin Nutr*. (2016) 25:578–88. doi: 10.6133/apjcn.092015.07

16. Sartini M, Bragazzi NL, Spagnolo AM, Schinca E, Ottria G, Dupont C, et al. Coffee consumption and risk of colorectal Cancer: a systematic review and meta-analysis of prospective studies. *Nutrients*. (2019) 11:694. doi: 10.3390/nu11030694

17. Ahluwalia N, Dwyer J, Terry A, Moshfegh A, Johnson C. Update on NHANES dietary data: focus on collection, release, analytical considerations, and uses to inform public policy. *Adv Nutr*. (2016) 7:121–34. doi: 10.3945/an.115.009258

18. Gahche JJ, Bailey RL, Potischman N, Ershow AG, Herrick KA, Ahluwalia N, et al. Federal Monitoring of dietary supplement use in the resident, civilian, noninstitutionalized US population, National Health and nutrition examination survey(()). *J Nutr*. (2018) 148:1436S–44S. doi: 10.1093/jn/nxy093

19. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, et al. Life's essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. (2022) 146:e18–43. doi: 10.1161/CIR.0000000000001078

20. Chen X, Wei G, Jalili T, Metos J, Giri A, Cho ME, et al. The associations of plant protein intake with all-cause mortality in CKD. *Am J Kidney Dis*. (2016) 67:423–30. doi: 10.1053/j.ajkd.2015.10.018

21. Um CY, McCullough ML, Guinter MA, Campbell PT, Jacobs EJ, Gapstur SM. Coffee consumption and risk of colorectal cancer in the Cancer prevention study-II nutrition cohort. *Cancer Epidemiol*. (2020) 67:101730. doi: 10.1016/j.canep.2020.101730

22. Giovannucci E. Meta-analysis of coffee consumption and risk of colorectal cancer. *Am J Epidemiol*. (1998) 147:1043–52. doi: 10.1093/oxfordjournals.aje.a009398

23. Sinha R, Cross AJ, Daniel CR, Graubard BI, Wu JW, Hollenbeck AR, et al. Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study. *Am J Clin Nutr*. (2012) 96:374–81. doi: 10.3945/ajcn.111.031328

24. Schmit SL, Rennert HS, Rennert G, Gruber SB. Coffee consumption and the risk of colorectal Cancer. *Cancer Epidemiol Biomarkers Prev*. (2016) 25:634–9. doi: 10.1158/1055-9965.EPI-15-0924

25. Nakagawa-Senda H, Ito H, Hosono S, Oze I, Tanaka H, Matsuo K. Coffee consumption and the risk of colorectal cancer by anatomical subsite in Japan: results from the HERPACC studies. *Int J Cancer*. (2017) 141:298–308. doi: 10.1002/ijc.30746

26. Zhang X, Albanes D, Beeson WL, van den Brandt PA, Buring JE, Flood A, et al. Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *J Natl Cancer Inst*. (2010) 102:771–83. doi: 10.1093/jnci/djq107

27. Michels KB, Willett WC, Fuchs CS, Giovannucci E. Coffee, tea, and caffeine consumption and incidence of colon and rectal cancer. *J Natl Cancer Inst*. (2005) 97:282–92. doi: 10.1093/jnci/dji039

28. Je Y, Liu W, Giovannucci E. Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. *Int J Cancer*. (2009) 124:1662–8. doi: 10.1002/ijc.24124

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 25 July 2024
DOI 10.3389/fonc.2024.1398679

OPEN ACCESS

EDITED BY
Chitra Thakur,
Stony Brook University, United States

REVIEWED BY
Mohammad Salehi,
Golestan University of Medical Sciences, Iran
Arjun Katailiha,
University of Texas MD Anderson Cancer Center, United States

*CORRESPONDENCE
Junqi Liu
fccliujq@zzu.edu.cn
Narasimha M. Beeraka
bnmurthy24@gmail.com;
biraka_n@staff.sechenov.ru

†These authors have contributed equally to this work

RECEIVED 10 March 2024
ACCEPTED 08 July 2024
PUBLISHED 25 July 2024

CITATION
Zhao J, Ren R, Beeraka NM, PA M, Xue N, Lu P, Bai W, Mao Z, PR HV, Bulygin KV, Nikolenko VN, Fan R and Liu J (2024) Correlation of time trends of air pollutants, greenspaces and tracheal, bronchus and lung cancer incidence and mortality among the adults in United States.
Front. Oncol. 14:1398679.
doi: 10.3389/fonc.2024.1398679

Correlation of time trends of air pollutants, greenspaces and tracheal, bronchus and lung cancer incidence and mortality among the adults in United States

Jia Zhao[1†], Ruihang Ren[2†], Narasimha M. Beeraka[3,4,5*], Mahesh PA[6], Nannan Xue[7], Pengfei Lu[8], Wenhua Bai[2], Zhihan Mao[2], Hemanth Vikram PR[9], Kirill V. Bulygin[4], Vladimir N. Nikolenko[4], Ruitai Fan[2] and Junqi Liu[2*]

[1]Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [2]Department of Radiation Oncology & Cancer Center, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [3]Department of Pharmacology, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), Andhra Pradesh, Ananthapuramu, India, [4]Department of Human Anatomy and Histology, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia, [5]Herman B. Wells Center for Pediatric Research, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States, [6]Department of Pulmonary Medicine, JSS Medical College, JSS Academy of Higher Education & Research (JSS AHER), Mysuru, Karnataka, India, [7]Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO) and CIBERONC, Madrid, Spain, [8]Cancer Center of the First Affiliated Hospital of Xinjiang Medical University, Urumqi, China, [9]Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education & Research (JSS AHER), Mysuru, Karnataka, India

Background: Tracheal, Bronchus, and Lung (TBL) cancer continues to represent the majority of cancer-related incidence and mortality in United States (U.S.). While air pollutants are considered essential risk factors, both global and national average concentrations of major harmful air pollutants have significantly decreased over the decades. Green space may have a beneficial effect on human health.

Methods: We obtained data on national and state-level burden of TBL cancer, the annual average concentration of main air pollutants, and levels of green spaces in 2007, 2013, and 2019. According to generalized estimating equation (GEE), we examine the associations among incidence and mortality of TBL cancer, air pollutants, and greenspaces, represented by the Normalized Difference Vegetation Index (NDVI) in different age groups with models adjusted with meteorological, and socio-demographic. We observed additional effects of the interaction between the NDVI, Ozone, PM2.5, and other factors, which helped us to interpret and understand our results. Also, we collated states that witnessed net increments in forest coverage and conducted the same analysis separately.

Results: In our analysis, the majority of associations between NDVI and air pollutants with TBL cancer remained significantly positive, particularly noticeable among individuals aged 20 to 54. However, our findings did not

explore air pollution as a potential mediator between greenspace exposure and TBL cancer. While the associations of PM2.5 with TBL cancer remained positive, the other four pollutants showed positive but statistically insignificant associations. Our interaction analysis yielded that there were positive associations between NDVI and ozone, PM2.5, and tobacco use. Max NDVI acts as a protective factor along with high HDI. Additionally, PM2.5 and HDI also showed a negative association. In 18 states with more forest, NDVI acts as a protective factor along with higher health care coverage, better health status, and participation in physical activities.

Conclusion: In the state-level of U.S., the effects of total greenspace with TBL cancer are mixed and could be modified by various socio-economic factors. PM2.5 has a direct correlation with TBL cancer and the effects can be influenced by underlying socioeconomic conditions.

KEYWORDS

air pollutants, particulate matter, greenspace, TBL cancer, age groups

1 Introduction

Tracheal, bronchus, and lung (TBL) cancer stands as one of the significant contributors to cancer-related fatalities in U.S. as of 2023. It is projected to constitute 21% of cancer-related deaths and 12% of cancer diagnoses. Despite its profound impact on public health, TBL cancer exhibits a comparatively low survival rate (1, 2). According to the Cancer Tomorrow report by GLOBOCAN, incident cases of TBL in U.S. are forecasted to surge by approximately 38% by 2040, with mortality cases expected to rise by about 45%. Furthermore, the majority of TBL cancer cases in U.S. occur in individuals aged 50 and above. However, roughly 20% of total TBL cancer deaths are not linked to tobacco use, potentially placing it as the eighth most prevalent cause of cancer-related mortality (1, 3, 4).

According to the International Agency for Research on Cancer (IARC), outdoor air pollution is classified as a Group 1 human carcinogen and significantly contributes to the burden of diseases, including lung cancer (5). Moreover, ambient PM2.5 air pollution has been identified as a contributing factor in nearly 14.1% of lung cancer deaths globally (6). The persistence of unhealthy air pollution levels for more than one-third of Americans underscores the need for continued research and public health interventions (1, 4, 7). The evolutionary and developmental mechanisms underlying TBL cancer remain complex. Exposure to air pollution may play a role in the progression of TBL cancer through the activation of signal transduction pathways, DNA damage, inflammation, metabolism, and epigenetic regulation (8). Recent studies have revealed a mechanistic relationship between air pollution and lung cancer, both in functional mouse models and clinical cohorts (9–11).

Based on the findings from seven European cohorts participating in the "Effects of Low-level Air Pollution: a Study in Europe" (ELAPSE), researchers have discovered a significant link between long-term exposure to PM2.5 and an increased risk of lung cancer, even at concentrations below the current European Union (EU) limit values. Similarly, the Adventist Health and Smog Study-2 (AHSMOG-2) cohort study also observed significant positive associations between incident lung cancer and PM2.5 exposure, particularly among individuals who have never smoked or are past smokers, at low concentrations (12, 13). Moreover, a case study in Canada suggests that never-smoking patients have indicated relationships with air pollution exposures, and chronic exposure to home air pollution is linked to an elevated risk of lung cancer in Nepal among never-smokers (14, 15). Besides, more than half of lung cancer patients in Taiwan are individuals who have never smoked. Elevated levels of PM2.5 can influence both the occurrence and the survival of patients with adenocarcinoma lung cancer (16, 17). Similarly, in Pennsylvania and California, air pollution could affect the survival rates of lung cancer patients following diagnosis (18, 19).

Greenspace was considered to provide health benefits and higher access to greenspace is positively correlated with longer life expectancy (20–22). Exposure to green spaces is inversely associated with overall and cause-specific mortality, indicating that it provides a protective role (23–25). For TBL cancer, green spaces may act as a protective role or work as an effective tool to improve air quality. Studies in France and Belgium have reported varying associations between exposure to greenspace, cancer incidence, and mortality. However, a retrospective cohort study in Taiwan revealed that increased exposure to green space may mitigate the harmful impacts of PM2.5 and reduce the risk of lung cancer (26–28). For other cancers, including breast and prostate cancer, there might be a

protective relationship between exposure to greenspace and the development of malignancies (29).

Despite extensive studies on the health benefits of green spaces and the detrimental effects of air pollution, the specific interactions between green space, air pollution, and TBL cancer at the state level in the United States remain underexplored. This study addresses the following gaps: (1) Limited exploration of green space and cancer links: While existing research validates the general health benefits of green spaces, there is a lack of detailed exploration regarding their specific association with TBL cancer. This study aims to provide a more comprehensive understanding of how green spaces influence TBL cancer incidence and mortality. (2) Reconfirmation of PM2.5 impact: Although the link between PM2.5 air pollution and TBL cancer has been established, this study reconfirms this connection within the context of green space exposure, emphasizing the need to consider multiple environmental factors simultaneously. (3) Need for nuanced analysis: Current research often overlooks the complex interactions between green spaces, air pollution, lung cancer, and varying population demographics. This study highlights the necessity of a more nuanced and precise analysis that accounts for these interactions to better inform future research and public health policies.

By addressing these gaps, the study aims to enhance our understanding of the interplay between environmental factors and TBL cancer, ultimately providing valuable insights for the development of more effective health interventions and policies. Therefore, in this study, we conducted a comprehensive analysis to assess the interplay between green spaces, air pollutant levels, and the risk of tracheal, bronchus, and lung (TBL) cancer across different age groups (over 20 years, 20–54 years, and over 55 years) at the state level in U.S. Furthermore, we explored potential underlying mechanisms by investigating their associations with meteorological, sociodemographic, and socioeconomic factors.

2 Materials and methods

2.1 Study design and population

The contiguous U.S. spans approximately 9,834,633 square kilometers and is inhabited by nearly 330 million people. It comprises 50 states and the District of Columbia. Our analysis focused on 48 states along with the District of Columbia. The health system at the state level in U.S. holds significant authority. Alaska and Hawaii, along with overseas territories, were excluded from our research due to the non-applicability of study variables (30).

2.2 Data collection and measurements

2.2.1 Outcome: TBL cancer incidence and mortality data

The Global Burden of Diseases (GBD) data visualization tool was developed by the Institute for Health metrics and Evaluation (IHME) in U.S (31). It provides statistics on the incidence and mortality rate of TBL cancer data by state, age, and year. Using the terminology defined in the GBD research, the state-wide incidence and mortality rate of TBL cancer were calculated (32). GBD is a reliable data source in U.S., compiling and summarizing data from various national databases. For individuals aged 20 and older, 20 to 54, and over 55, we estimated the incidence and mortality rate of TBL cancer for the 48 states and the District of Columbia, spanning three specific years: 2007, 2013, and 2019. We rounded the collected epidemiological data to integers for the convenience of subsequent research.

2.2.2 Exposures and other variables

2.2.2.1 Area greenness

In accordance with the US Environment Protection Agency (EPA), "greenspace" is any vegetated land, including gardens, lawns, forests, wetlands, and agricultural land (33). Using the NDVI, green space was estimated based on land surface reflectance, NDVI is a remote sense indicator that has been extensively utilized in epidemiological studies to evaluate the association between greenness and health. The following formula was used to obtain the NDVI proportions: NDVI = (NIR − R)/(NIR + R) (34). The MODIS images, composed of surface reflectance images updated every 16 days with a spatial resolution of 1000m per pixel, were primarily employed to assess the greenness on www.gisrs.cn (accessed on 30 April 2023). This website offers annual state-level estimates of the NDVI in U.S. An NDVI value of '0' indicates the absence of vegetation, while values approaching '1' indicate the highest level of greenness (35).

2.2.2.2 Air pollution

Data sources from EPA were used to calculate the concentrations of main ambient air pollutants (36). The routine air quality monitoring stations in the U.S. gathered annual average concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and particulate matter with diameters up to 2.5 μm (PM2.5) and 10 μm (PM10) for the years 2007, 2013, and 2019. We downloaded the average annual data of different time nodes for corresponding states and calculated the average values. The data were measured in various units, including parts per billion (ppb) and parts per million (ppm), and these were converted to micrograms per cubic meter ($\mu g/m^3$).

2.2.2.3 Weather and other variables

Data from the National Centers for Environmental Information (NCEI) and the Statewide Mapping and Climate at a Glance online sources were utilized to gather meteorological information for the states across U.S. for the years 2007, 2013, and 2019 (37). We selected a time scale of 12 months to obtain the yearly average temperature(°F) and annual precipitation(in inches). Data on PD (population density) and GDP (gross domestic product) for each state were compiled from the U.S. Bureau of Economic Analysis and the U.S. Census Bureau (38, 39). In assessing educational attainment, we used the rate of college completion as an indicator of higher education levels (40). State-level tobacco use age-adjusted prevalence was sourced from the BRFSS Prevalence & Trends Data

portal (41). For the state-level HDI, we acquired the data from https://globaldatalab.org/shdi/, version v7.0 (42). Additionally, we collected potential socioeconomic factors, including healthcare coverage, health status, obesity rate, and participation in physical activities (43). We did not adjust the collected relevant factors as they met the criteria for our research. To explore the impact of different types of green spaces, We identified 18 states with increasing net forest coverage from 2000 to 2020 (44).

2.3 Statistical analysis

Utilizing state-level map charts and data visualization techniques, we depicted the variations in mean NDVI, TBL cancer incidence, and mortality across 48 states and Washington D.C. from 2007, 2013, to 2019. Two-dimensional multiple line graphs were employed to explore the relationship between TBL cancer data and mean NDVI (Y1 and Y2-axis) over the specified periods on the horizontal axis (X-axis), using R studio. The statistical software R, v.4.3.0, facilitated the plotting of multiple variables, utilizing gg-plot for bubble charts. The bubble plot, resembling a scatterplot, portrayed the average concentrations of pollutants and mean NDVI across the X-axis and Y-axis.

Initially, we assessed the correlations among air pollutants and between air pollutants and meteorological factors using Spearman's correlations. Subsequently, the association between NDVI and TBL cancer incidence and mortality for each year was examined, controlling for individual air pollutants. A Poisson regression model was applied for each year, adjusting for meteorological parameters, GDP, and population density. Then, integrating the three-time points into a single model using a Generalized Estimating Equation (GEE) with a Poisson link, we estimated the association between NDVI (as the primary exposure variable) and TBL cancer incidence and mortality across different subgroups. Additionally, we investigated how NDVI and air pollution interacted with other relevant factors over the three time periods in the GEE model. All statistical analyses were two-sided, with effect estimates and 95% confidence intervals (CI) provided for associations with a p-value less than 0.05, indicating strong evidence of association. These statistical analyses were conducted using R Studio.

3 Results

Although TBL cancer incidence and mortality in over 20 years subgroup peaked in 2019 with relatively similar numbers (86.87 in 2007; 82.33 in 2013, and 88.69 in 2019), overall trends remained consistent and declined over the three time periods. The overall incidence and mortality rates of adult TBL cancer for individuals aged 20–54 years and over 55 years decreased across the three time periods (Table 1). The East South-Central region of U.S. showed higher rates of TBL cancer incidence and mortality among individuals over 55 years (Figure 1). The overall mean NDVI values in U.S. ranged from 0.70 in 2007 to 0.71 in 2013 to 0.72 in 2019 (Figure 1). The East and East Central regions of U.S. had higher mean NDVI values in 2007, 2013, and 2019. Conversely, the Western region, including states with high altitudes such as Arizona, Nevada, Utah, New Mexico, and Wyoming, exhibited comparatively lower NDVI values.

There was a strong correlation between PM2.5 and SO_2, while the other air pollutants showed weak to moderate relationships (Supplementary Table S1). PM2.5, PM10, NO_2, and Ozone levels exhibited moderate and positive correlations with the annual average temperature. On the contrary, annual average precipitation was negatively and moderately correlated with PM10 and Ozone. Controlling for specific pollutants, NDVI was primarily associated with TBL cancer incidence and mortality in individuals over 20 years old across all three years (Supplementary Table S2). We also employed a unified model to evaluate all three years, adjusting for meteorological and socio-demographic factors. In this analysis, the associations between NDVI, air pollutants, and TBL cancer incidence and mortality remained largely positive.

The study found a significant association between the NDVI and the incidence of TBL cancer in individuals aged 20 and above. Specifically, for PM2.5, the association was quantified with a β coefficient of 0.713 (95% CI: 0.856, 1.140; $p < 0.01$). Similar significant associations were observed for other air pollutants: PM10 (β = 0.756; 95% CI: 0.590, 0.922; $p < 0.001$), SO2 (β = 0.692; 95% CI: 0.525, 0.859; $p < 0.001$), NO2 (β = 0.730; 95% CI: 0.557, 0.903; $p < 0.001$), and Ozone (β = 0.808; 95% CI: 0.626, 0.990; $p < 0.001$).

Similarly, NDVI was associated with TBL cancer mortality in the same age group. The β coefficient for PM2.5 was 0.664 (95% CI: 0.426, 0.902; $p < 0.01$). For other pollutants, the associations were: PM10 (β = 0.748; 95% CI: 0.579, 0.917; $p < 0.001$), SO2 (β = 0.669; 95% CI: 0.496, 0.842; $p < 0.001$), NO2 (β = 0.712; 95% CI: 0.540, 0.884; $p < 0.001$), and Ozone (β = 0.796; 95% CI: 0.610, 0.982; $p < 0.001$) (Table 2). Especially, more pronounced effects were observed among individuals aged 20 to 54 in terms of mortality (0.777 – 1.780) (Table 2). These findings were further supported by subgroup analyses, which demonstrated statistically significant correlations in both middle-aged individuals (20–54 years old) and older adults (55 years and above), reinforcing the overall relationship between NDVI, air pollution, and TBL cancer outcomes. The consistent significance across multiple pollutants and age groups underscores the robustness of the observed associations and suggests a broad impact of vegetation and air quality on TBL cancer incidence and mortality.

Furthermore, the associations of PM2.5 with TBL cancer remained significantly positive after adjusting for meteorological and socio-demographic variables, ranging from 0.012 to 0.080. Notably, PM2.5 was associated with TBL cancer mortality in individuals aged 20–54 years (β = 0.076; 95% CI =0.070, 0.082; $p < 0.001$) for PM10, along with SO2, NO2, and Ozone (β = 0.062; 95% CI = 0.053, 0.070; $p < 0.001$), (β = 0.079; 95% CI = 0.072, 0.085; $p < 0.001$), and (β = 0.080; 95% CI = 0.073, 0.087; $p < 0.001$), respectively (Table 3). Despite this, the associations for the other four pollutants were positive but not statistically significant (Table 3).

Our interaction analysis between NDVI and ozone revealed positive associations with all TBL cancer rates, while concentrations

TABLE 1 Summary statistics for the incidence and mortality rates of Tracheal, Bronchus, and Lung (TBL) cancers, along with other socio-demographic factors in U.S. states for the years 2007, 2013, and 2019.

Measures	2007			2013			2019		
	Mean(SD)	Median(IQR)	Max,Min	Mean(SD)	Median(IQR)	Max,Min	Mean(SD)	Median(IQR)	Max,Min
TBL cancer mortality in 20+	86.87(±18.15)	85.78(98.74-74.84)	131.45,34.84	84.23(±19.00)	82.33(97.03-72.22)	128.65,34.96	89.92(±20.66)	88.69(103.82-77.74)	138.09,36.94
TBL cancer mortality in 20-54	12.21(±3.62)	11.51(14.64-10.03)	21.28,4.91	10.26(±3.37)	9.42(12.64-8.03)	18.56,3.98	8.75(±2.77)	8.21(10.42-6.98)	15.65,3.52
TBL cancer mortality in 55+	239.14(±40.34)	237.57(264.24-217.94)	339.60,123.74	212.49(±40.17)	205.08 (238.10-188.54)	319.23,112.49	210.46(±40.99)	206.79(240.14-182.02)	318.14,11.03
TBL cancer incidence in 20+	106.01(±21.42)	108.19(119.39-93.46)	164.08,41.33	104.13(±22.80)	103.15 (118.52-92.38)	168.88,41.52	110.40(±24.55)	110.31(127.21-97.35)	175.73,42.95
TBL cancer incidence in 20-54	17.02(±4.68)	16.32(20.20-13.93)	29.15,6.74	14.58(±4.53)	13.69(17.77-11.73)	28.14,5.54	12.36(±3.68)	11.47(14.71-10.06)	23.23,4.82
TBL cancer incidence in 55+	287.49(±46.89)	291.88(318.81-262.33)	438.97,144.11	259.34(±47.09)	259.58 (288.92-228.42)	412.51,131.60	255.84(±47.21)	258.00(287.61-229.87)	403.67,127.51
Environmental factors									
MaxNDVI	0.90(±0.05)	0.92(0.93-0.89)	0.96,0.71	0.91(±0.05)	0.92(0.94-0.91)	0.98,0.73	0.92(±0.04)	0.93(0.94-0.91)	0.97,0.72
Mean NDVI	0.70(±0.17)	0.77(0.82-0.61)	0.88,0.23	0.71(±0.18)	0.80(0.83-0.60)	0.87,0.23	0.72(±0.16)	0.80(0.84-0.64)	0.89,0.29
Air pollutants									
PM2.5(μg/m^3)	10.94(±2.81)	11.52(13.09-8.20)	15.61,5.31	8.45(±1.56)	8.75(9.60-7.31)	11.25,3.90	7.00(±1.47)	7.39(8.18-5.98)	9.25,2.85
PM10(μg/m^3)	23.50(±6.64)	23.44(27.08-20.09)	52.51,10.99	19.53(±7.02)	18.17(21.27-14.89)	43.00,8.85	16.79(±5.28)	16.28(19.10-13.89)	38.33,7.18
SO2(μg/m^3)	24.88(±14.07)	23.14(36.15-13.63)	75.86,3.21	10.42(±7.10)	8.54(14.64-5.07)	38.45,2.16	6.58(±6.07)	5.07(7.64-2.97)	34.39,0.68
NO2(μg/m^3)	44.57(±20.22)	40.56(54.08-31.92)	103.13,8.49	34.85(±15.76)	31.41(42.35-25.42)	89.03,6.13	33.83(±14.26)	32.10(41.47-26.48)	75.65,6.04
OZONE(μg/m^3)	86.09(±10.22)	87.52(94.83-78.52)	104.81,63.54	79.14(±6.80)	78.35(82.64-74.42)	96.29,64.14	78.28(±6.71)	77.11(83.80-73.03)	92.18,63.75
Meterorological variables									
Annual average temperature (degree Fahrenheit)	53.00(±7.79)	52.90(59.25-46.40)	71.5,40.8	51.59(±7.60)	50.30(57.00-45.25)	70.90,38.60	52.88(±8.74)	53.00(59.20-45.65)	73.50,38.30
Average precipitation (degree Inch)	34.06(±10.77)	36.31(42.24-28.62)	50.13,8.74	37.92(±15.37)	42.76(48.01-23.64)	63.50,7.28	41.82(±14.73)	46.48(49.88-31.52)	70.61,13.19
Socio-economic variables									
Population density	436.27 (±1605.31)	108.80(242.25-49.95)	11280.00,5.90	395.75 (±1404.40)	101.20 (235.10-45.80)	9856.5,5.8	373.79 (±1336.25)	88.70(220.55-41.40)	9370.60,5.10
GDP	316943.29 (±373357.02)	189002.50 (415680.35-90324.80)	2041192.20,26226.7	331896.06 (±402848.75)	19169.80 (436805-93593.80)	2179229.00,28681.50	382161.30 (±488529.52)	219588.00 (501016.95-97940.10)	2729225.80,29940.70

This table includes data on cancer incidence and mortality rates per 100,000 population. These factors are analyzed to understand the potential socio-demographic influences on cancer trends over time. Note: age groups (over 20 years, 20–54 years, and over 55 years).

10.3389/fonc.2024.1398679

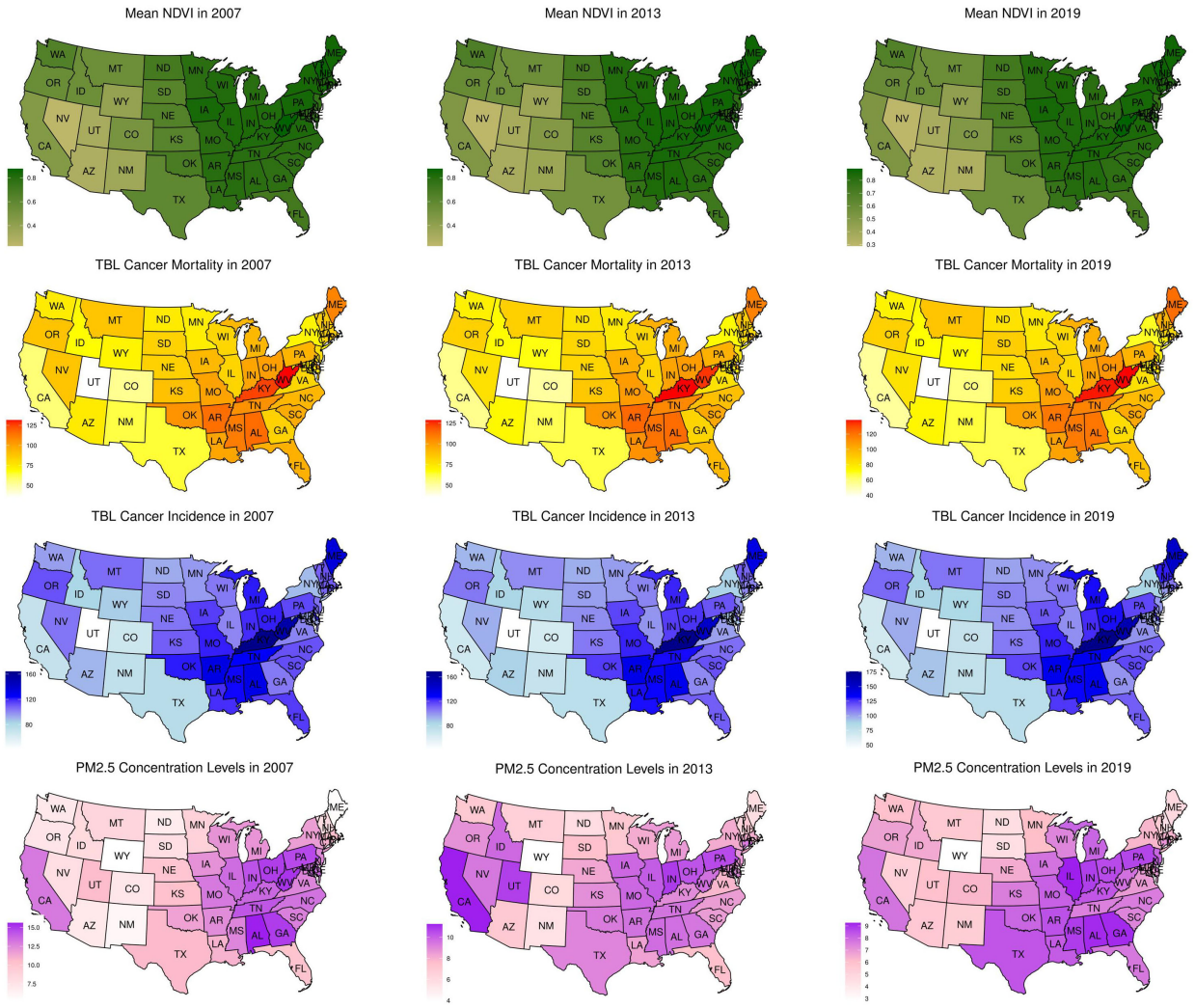


FIGURE 1
Distribution of mean NDVI, TBL cancer mortality, TBL cancer incidence, and mean PM2.5 concentration levels in ages over 20 years in the U.S. in 2007, 2013, and 2019. The normalized differential vegetation index (NDVI) values for 2007 (left), 2013 (middle), and 2019 (right), are shown on a spectrum of light green (least value) to dark green (highest value). Mean NDVI values of 0 to 0.2 are categorized as low, >0.2 to 4.0 as moderate, and >0.4 as high levels of greenspaces. Rates of TBL cancer incidence and mortality in ages over 55 years are shown on a spectrum of white (least value) to red (highest value) and dark blue (highest value).

of other air pollutants showed no significant associations. Interaction between PM2.5 and HDI showed a negative association (β = -0.324; 95% CI = -0.177, -0.471; $p < 0.05$) (β = -0.351; 95% CI = -0.484, -0.219; $p < 0.01$) with TBL cancer incidence and mortality in individuals over 20 years old. The interaction between PM2.5 and educational level was negatively associated with TBL cancer rates in all subgroups except for TBL cancer incidence in individuals aged over 55. Our interaction analysis between tobacco use and PM2.5 concentration levels indicated a positive association (β = 2.710; 95% CI = 1.510, 3.910; $p < 0.05$) (β = 2.710; 95% CI = 1.640, 3.780; $p < 0.05$) with TBL cancer incidence and mortality in individuals over 20 years old. Additionally, the interaction between max NDVI and HDI was negatively associated with TBL cancer incidence in the individuals aged 20–54 (β = -25.053; 95% CI = -13.052, -37.054; $p < 0.05$), as well as TBL cancer mortality in individuals aged 20 to 54 and those aged over 55 (β = -64.227; 95% CI = -18.502, -82.794; $p < 0.001$) (β = -25.053; 95% CI = -13.052, -37.054; $p < 0.05$) (Table 4).

In the analysis of 18 states with increasing net forest coverage from 2000 to 2020, we observed additional effects between mean NDVI and health care coverage, health status, obesity rate, and participation in physical activities, separately. (Supplementary Table S3). Regarding health care coverage, better health status, and participation in physical activities, NDVI indicated a protective role. However, when interacting with high BMI individuals, NDVI was positively associated with TBL cancer rates.

The graph depicts the TBL cancer incidence and mortality rates (per 100,000 population) among individuals aged over 55 years and the mean NDVI across 49 states in the United States for the years 2007, 2013, and 2019 (Figure 2). The lines on the graph illustrate the temporal trends of the data series, with blue lines representing cancer incidence, orange lines representing cancer mortality, and

TABLE 2 Generalized estimation equation (GEE) result coefficients (β) (95% CI, lower, upper) of NDVI for association of TBL cancer incidence, mortality and air pollutants.

NDVI continuous	TBL cancer incidence in 20+	TBL cancer mortality in 20+	TBL cancer incidence in 20-54	TBL cancer mortality in 20-54	TBL cancer incidence in 55+	TBL cancer mortality in 55+
Unadjusted	0.726(0.499,0.953) **	0.673(0.440,0.906) **	0.281(0.068,0.494)	0.840(0.533,1.147) **	0.343(0.131,0.555)	0.281(0.068,0.494)
Model 1	0.998(0.856,1.140) ***	0.930 (0.787,1.070) ***	0.558(0.431,0.684) ***	1.159(0.964,1.350) ***	0.636(0.511,0.762) ***	0.558 (0.431,0.684) ***
Model 2	0.713(0.482,0.944) **	0.664(0.426,0.902) **	0.277(0.059,0.495)	0.777(0.467,1.087) *	0.334(0.118,0.550)	0.277(0.059,0.495)
Model 3	0.756(0.590,0.922) ***	0.748 (0.579,0.917) ***	0.763(0.605,0.921) ***	1.830(1.579,2.081) ***	0.764(0.605,0.923) ***	0.763 (0.605,0.921) ***
Model 4	0.692(0.525,0.859) ***	0.669 (0.496,0.842) ***	0.559(0.401,0.717) ***	1.350(1.099,1.601) ***	0.578(0.424,0.732) ***	0.559 (0.401,0.717) ***
Model 5	0.730(0.557,0.903) ***	0.712 (0.540,0.884) ***	0.728(0.564,0.892) ***	1.780(1.530,2.030) ***	0.736(0.569,0.903) ***	0.728 (0.564,0.892) ***
Model 6	0.808(0.626,0.990) ***	0.796 (0.610,0.982) ***	0.755(0.585,0.925) ***	1.710(1.445,1.975) ***	0.765(0.595,0.935) ***	0.755 (0.585,0.925) ***

Each of the study variables was used in the GEE with the Poisson link to explore the associations between the incidence and mortality of TBL cancer and NDVI as the primary exposure variable. The unadjusted variables are reported separately. In the multivariate analysis, Model 1: Each covariate and weather parameters; further adjusted for GDP, Mean temperature, Annual precipitation and population density with each of the air pollutants in Model 2: PM2.5; Model 3: PM10; Model 4: SO_2; Model 5: NO_2; Model 6: Ozone; "*" Indicates significant p-interaction values and is reported if p-int < 0.05; "**" Indicates significant p-interaction values and is reported if p-int < 0.01; "***" Indicates significant p-interaction values and is reported if p-int < 0.001.
Note: age groups (over 20 years, 20–54 years, and over 55 years).

green lines indicating the mean NDVI. The horizontal axis (X-axis) displays the three time periods (2007, 2013, and 2019), while the Y1-axis on the left side corresponds to the cancer rates, and the Y2-axis on the right side corresponds to the mean NDVI (Figure 2). Selected states in U.S. of our study: (1) Alabama, (2) Arizona, (3) Arkansas, (4) California, (5) Colorado, (6) Connecticut, (7) Delaware, (8) District of Columbia, (9) Florida, (10) Georgia, (11) Idaho, (12) Illinois, (13) Indiana, (14) Iowa, (15) Kansas, (16) Kentucky, (17) Louisiana, (18) Maine, (19) Maryland, (20) Massachusetts, (21) Michigan, (22) Minnesota, (23) Mississippi, (24) Missouri, (25) Montana, (26) Nebraska, (27) Nevada, (28) New Hampshire,(29) New Jersey, (30) New Mexico, (31) New York, (32) North Carolina, (33) North Dakota, (34) Ohio, (35) Oklahoma, (36) Oregon, (37) Pennsylvania, (38) Rhode Island, (39) South Carolina, (40) South Dakota, (41) Tennessee, (42) Texas, (43) Utah, (44) Vermont, (45) Virginia, (46) Washington, (47) West Virginia, (48) Wisconsin, and (49) Wyoming (Figure 2).

Figure 3 presents the mean NDVI and concentrations of PM2.5 and Ozone across states for the years 2007, 2013, and 2019. In the left panel, the association between the mean NDVI (Y-axis) and the levels of PM2.5 or Ozone concentration (X-axis) is depicted. The size and color of the bubbles indicate the TBL cancer incidence and mortality for each state across the three time periods. Note: The data are represented as asthma prevalence (cases per 100,000 population), NDVI as the mean value, PM2.5 (particulate matter of diameter 2.5 μm or smaller), PM10 (particulate matter of diameter 10 μm or smaller), NO_2 (nitrogen dioxide), SO_2 (sulfur dioxide), O_3 (ozone) in $\mu g/m^3$, annual average temperature in degrees Fahrenheit, average annual precipitation in inches, GDP (gross domestic product), PD (population density) as persons/sqkm. Average values are presented as mean (± standard

TABLE 3 Generalized estimation equation (GEE) result coefficients (β) (95% CI, lower, upper) of PM2.5 for association of TBL cancer incidence, mortality and air pollutants.

PM2.5	TBL cancer incidence in 20+	TBL cancer mortality in 20+	TBL cancer incidence in 20-54	TBL cancer mortality in 20-54	TBL cancer incidence in 55+	TBL cancer mortality in 55+
Unadjusted	0.015(0.009,0.021) *	0.016(0.010,0.023) **	0.033(0.028,0.038) ***	0.067(0.058,0.076) ***	0.031(0.026,0.036) ***	0.033(0.028,0.038) ***
Model 1	0.025(0.017,0.033) **	0.029(0.020,0.038) **	0.042(0.035,0.049) ***	0.078(0.065,0.091) ***	0.037(0.031,0.044) ***	0.042(0.035,0.049) ***
Model 2	0.017(0.013,0.022) ***	0.019(0.014,0.024) ***	0.035(0.031,0.038) ***	0.076(0.070,0.082) ***	0.033(0.029,0.036) ***	0.035(0.031,0.038) ***
Model 3	0.012(0.006,0.019) *	0.014(0.007,0.050)*	0.030(0.025,0.035) ***	0.062(0.053,0.070) ***	0.028(0.023,0.033) ***	0.030(0.025,0.035) ***
Model 4	0.015(0.010,0.020) **	0.017(0.012,0.021) ***	0.035(0.031,0.039) ***	0.079(0.072,0.085) ***	0.033(0.029,0.037) ***	0.035(0.031,0.039) ***
Model 5	0.022(0.017,0.026) ***	0.023(0.019,0.028) ***	0.039(0.035,0.043) ***	0.080(0.073,0.087) ***	0.037(0.033,0.041) ***	0.039(0.035,0.043) ***

Each of the study variables was used in the GEE with the Poisson link to explore the associations between the incidence and mortality of TBL cancer and PM2.5 as the primary exposure variable. The unadjusted variables are reported separately. In the multivariate analysis, Model 1: Each covariate and weather parameters; further adjusted for GDP, PD, Mean temperature, Annual precipitation and population density with each of the air pollutants in Model 2: PM10; Model 3: SO2; Model 4: NO2; Model 5: Ozone; "*" Indicates significant p-interaction values and is reported if p-int < 0.05; "**" Indicates significant p-interaction values and is reported if p-int < 0.01; "***" Indicates significant p-interaction values and is reported if p-int < 0.001.
Note: age groups (over 20 years, 20–54 years, and over 55 years).

TABLE 4 GEE interaction analysis result (β) (95% CI, lower, upper) of related factors for association of TBL cancer incidence, mortality and air pollutants in different age groups.

	TBL cancer incidence in 20+	TBL cancer mortality in 20+	TBL cancer incidence in 20-54	TBL cancer mortality in 20-54	TBL cancer incidence in 55+	TBL cancer mortality in 55+
NDVI*OZONE	0.026(0.015,0.037)*	0.025(0.014,0.036)*	0.034(0.0260.042)***	0.039(0.024,0.055)*	0.034(0.025,0.042)***	0.034(0.026,0.042)*
PM2.5*HDI	-0.324(-0.177,-0.471)*	-0.351(-0.484,-0.219)**	-0.110(0.006,-0.226)	-0.283(-0.105,-0.461)	-0.081(0.062,-0.224)	-0.110(-0.006,0.226)
PM2.5*EDU	-0.229(-0.168,-0.289)***	-0.249(-0.193,-0.305)***	-0.108(-0.059,-0.157)*	-0.216(-0.134,-0.298)**	-0.087(-0.027,-0.147)	-0.108(-0.059,-0.157)*
PM2.5*SMOKE	2.710(1.510,3.910)*	2.710(1.640,3.780)*	0.751(-0.106,1.526)	-0.235(0.765,-1.235)	0.807(-0.333,1.947)	0.751(-0.065,1.567)
MaxNDVI*HDI	*2.067(-13.329,17.463)*	*-5.383(8.692,-19.458)*	*-25.053(-13.052,-37.054)**	*-64.227(-18.502,-82.794)****	*-24.50(12.00,37.00)*	*-25.053(-13.052,-37.054)**

Models in first four rows were adjusted for GDP, population density, mean temperature, annual precipitation, and population density. In italicized MaxNDVI with HDI, model were adjusted for Mean temperature and Annual precipitation; "*" Indicates significant p-interaction values and is reported if p-int < 0.05; "**" Indicates significant p-interaction values and is reported if p-int < 0.01; "***" Indicates significant p-interaction values and is reported if p-int < 0.001. Note: age groups (over 20 years, 20–54 years, and over 55 years).

deviation), with minimum (Min) and maximum (Max) values, and percentile measures at 25th, 50th, 75th (Figure 3).

4 Discussion

In this research, we investigated the relationship between greenspace, air pollutant concentration, and TBL cancer across different age groups at the state level in U.S. Our findings uncovered a direct relationship between the average NDVI and PM2.5 levels with TBL cancer rates across all age groups, particularly notable in the 20 to 54 age range. This study stands as the first at the state level to identify such a connection. In our examination of interactions, we noted positive correlations between ozone and NDVI, as well as between PM2.5 and tobacco consumption. Conversely, we observed negative associations between PM2.5 concentration and educational attainment as well as HDI, and between maximum NDVI and HDI in the GEE models analyzing TBL cancer data.

Several studies have investigated the impact of greenspace on TBL cancer and other types of cancer. These studies have identified variability in the observed relationships, influenced by factors such as the type of greenspace, method of exposure measurement, individual attributes, and geographic location. For instance, studies in France and Spain found different results depending on the type of greenery. In France, spending more time near farmland was positively linked to a higher chance of getting breast cancer. Meanwhile, in Spain, it was linked to a higher risk of getting any type of cancer (26, 45). While exposure to neighborhood-level greenspace in Australia is speculated to be linked to higher risks of having skin cancer (46). In addition to a cross-sectional study conducted in Philadelphia, when green parcels as tiny as 1m² are included as greenspace, there is a positive correlation between the density of greenspace and both overall and cause-specific mortality (47). A recent meta-analysis compiled data from nine papers investigating the link between greenspace exposure and lung cancer, eventually, the combined findings suggested no significant association (29). Therefore, the relationship between green space and health appears to be nuanced, potentially varying based on geographical context, study methodologies, and the techniques used to assess exposure in the studies (48).

4.1 NDVI, Ozone, and TBL cancer

In our analysis of the interaction between maximum NDVI and HDI, we observed a protective effect of high greenspace in areas with high HDI. We theorized those individuals residing in high socioeconomic status areas, compared to those in low-income regions, exhibited lower rates of TBL lung cancer and stronger health preservation. This may be attributed to the likelihood that individuals with higher incomes are more inclined to benefit from the protective effects of greenspaces (49, 50). Additionally, we observed a positive correlation between NDVI and ozone levels with all TBL cancer rates. We considered the possibility that greenspaces could emit hydrocarbons, such as isoprene and terpenes, which serve as precursors to ozone. These biogenic hydrocarbons might contribute to the development of TBL cancer (51). According to research conducted in California, there was a moderate association observed between ozone levels and patients diagnosed with either squamous cell carcinoma or adenocarcinoma, which are two subtypes of lung cancer (19).

In the analysis of 18 states with increasing net forest coverage, we observed the NDVI exhibited a protective effect with higher healthcare coverage, improved health status, and engagement in physical activities (Supplementary Table S3). This indicates that the health impacts of different types of green spaces are diverse. States with net increases in forest coverage exhibit a more significant and positive effect on health promotion compared to states with unchanged or decreasing green spaces, demonstrating a better fit between the health effects and the presence of green spaces (52).

Our study did not account for other air pollution as a possible mediator between greenspace exposure and TBL cancer. However, it is hypothesized that certain trees and plants may release pollen, exacerbating allergies, while other aspects of urban vegetation may impede air circulation, leading to the accumulation of air pollutants (51). A study conducted in Los Angeles found higher levels of

FIGURE 2
Data depicts the TBL cancer incidence and mortality (per 100,000 population) among individuals aged over 55 years, alongside the mean NDVI across 49 states in the United States for the years 2007, 2013, and 2019. Temporal trends are depicted by lines on the graph, with blue lines representing cancer incidence, orange lines representing cancer mortality, and green lines indicating the mean NDVI. The horizontal axis (X-axis) spans the three time periods of 2007, 2013, and 2019, while the Y1-axis on the left represents the cancer rate, and the Y2-axis on the right represents the mean NDVI.

PM2.5 in areas adjacent to greenspaces compared to the parks or the broader region (49). This underscores the importance of considering potential unintended consequences when increasing green space in urban areas. For instance, it may create conditions favorable for the survival of infectious pathogens, potentially contributing to the spread of diseases (53). However, despite these considerations, the evidence regarding the association between access to green space and physical activity remains inconclusive (54).

4.2 PM2.5 and TBL cancer

With regard to our analysis, there is a significant positive relation between PM2.5 with TBL cancer mortality, which was similar to mortality attributable to risk factors of ambient particular pollution in the GBD compare visualization tool and one related research (55). As an avoidable cause of TBL cancer, attention to outdoor air pollution had perhaps been distracted away owing to the dominance of tobacco smoking. It is generally accepted that

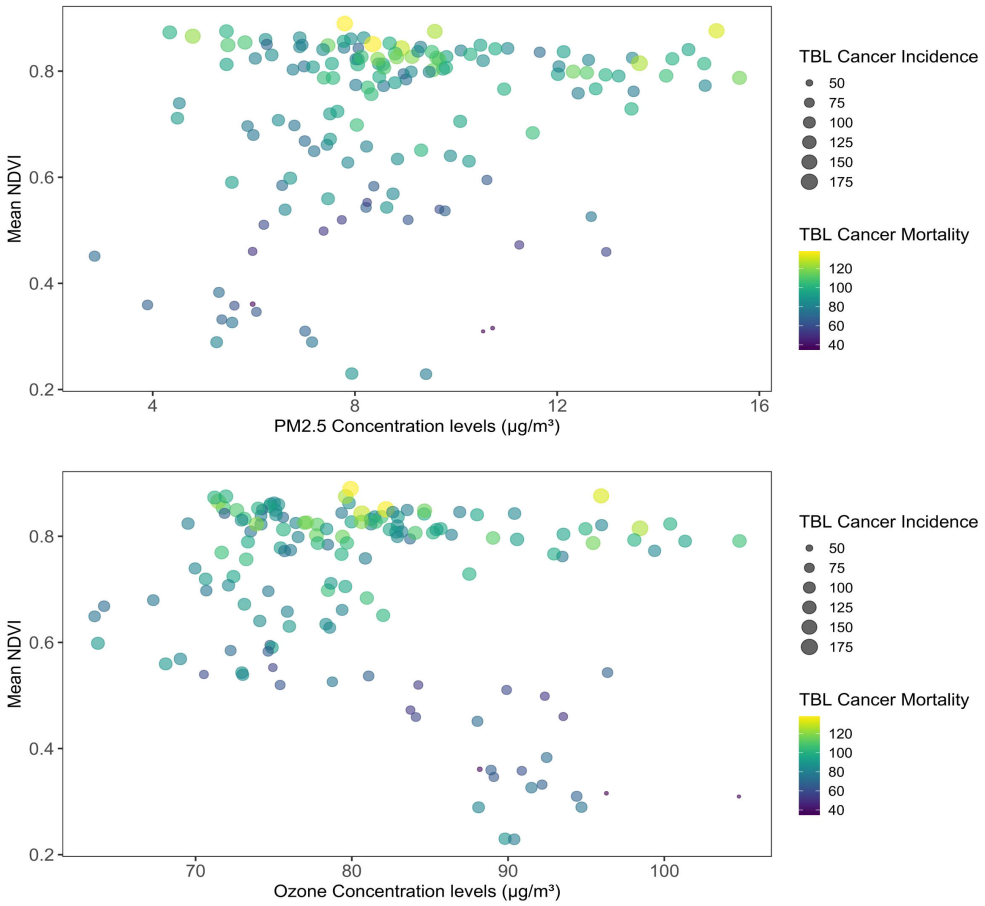


FIGURE 3
Mean NDVI and concentrations of PM2.5 and ozone across the states in the years 2007, 2013, 2019. Note: the left panel shows the association of the mean NDVI along the Y-axis and the PM2.5 or Ozone concentration levels on the X-axis. The size and colors of the bubbles measure the TBL cancer incidence and mortality of each state in the three time periods.

hazardous ambient emissions could be reduced to improve air quality, thus improving the morbidity and mortality of lung cancer (56). Interestingly, research on PM2.5 exposure in Europe, Japan, and Canada has uncovered several significant findings. Both long-term and short-term exposure to PM2.5 can contribute to lung cancer. Moreover, even exposure levels lower than the current EU limit values and possibly the WHO Air Quality Guidelines have been linked to lung cancer risk (12, 57, 58). In a population study conducted in Pennsylvania, researchers observed "U-shaped" dose-response curves, suggesting that both low and high exposures to PM10 can have a similar impact on lung cancer survival (18). In a cohort study in Canada, researchers applied a newly developed class of concentration-response models and observed sublinear associations between lung cancer incidence and PM2.5 (58). However, due to socioeconomic inequalities such as ethnicity, income level geography specificity, and so on, it is challenging to determine whether disparities in air pollution have been rising or falling in U.S (59). A study of U.S. veterans found that black individuals and those in socioeconomically deprived areas face a higher risk of PM2.5-related deaths from non-accidental and non-communicable causes, highlighting the impact of socioeconomic and racial factors (60).

In our interaction analysis, we found protective effects between PM2.5 and HDI, as well as educational level, respectively. Increased indoor PM2.5 concentrations were noted in rural U.S. households during winter, especially among those using wood stoves for heating. Additionally, urbanization overall has a notably positive impact on HDI (61, 62). Educational interventions have demonstrated efficacy in lowering indoor PM2.5 levels in specific subsets of households studied (63). It's worth noting that air pollution can impact school performance, particularly in test scores. Air pollution does affect school performance, in particular test scores (64, 65). Regarding the combined effects of air pollution and smoking, we observed significant positive associations between PM2.5 and tobacco use. Hence, it is crucial to assess the risks of air pollution-related lung cancer alongside smoking risks. Remarkably, individuals with lung cancer who have never smoked showed significant associations with ambient air pollution exposure, compared to those who have ever smoked. Hence, it is vital to consider cumulative exposure to ambient air pollutants when assessing the risk of developing lung cancer, alongside accurately quantifying traditional risk factors like smoking. As smoking prevalence continues to decrease, the lung cancer risks associated with long-term current and previous ambient air quality may become relatively more important to public health (66).

4.3 Age Subgroup analysis

Our subgroup analyses based on age revealed some evidence of effect modification by selected individual characteristics. The TBL cancer mortality of 20–54 years subgroup was found to be strongest and positively associated with all the variables. Age appeared to modify the association between TBL cancer and exposure to PM2.5, with stronger impacts among young individuals compared to the elderly. This finding is consistent with a cohort study in Canada, which also indicated a tendency for stronger associations between lung cancer incidence with PM2.5 among younger adults (58). We attributed our findings to several factors distinguishing young adults from the elderly. For instance, they exhibit varying patterns of response to negative stimuli, with older adults showing different mobility performance compared to their younger counterparts. Additionally, young adults may not experience increased self-confidence due to their greater reliance on the Internet for cancer care. Notably, there are significant differences in immune profiles between adults and the elderly among colorectal cancer patients. A study conducted in U.S. revealed that the elderly group had notably higher levels of monocyte chemoattractant protein-1 (MCP-1) and lower levels of epidermal growth factor (EGF) compared to adults (67–71).

4.4 Limitations

Our study has a few limitations, one of which is the constrained accessibility of the EPA air quality monitoring network for measuring state-level air pollutant concentrations in specific cities. For greenspace, our measure of state-wide greenness was rather crude in that it lacked specification of the space type. Annual green space may be influenced by weather and geographical characteristics. Furthermore, contact with green space is indirect, complex, and multidimensional exposure. Green space including agriculture, lawns, forests, wetlands, and gardens, may contribute differently to public health. The risk of TBL cancer is influenced by numerous factors, and our findings regarding the association between green space exposure, air pollutants, socioeconomic factors, and TBL cancer should be interpreted cautiously. The benefits offered by green space may be overshadowed by other conditions and accompanying lifestyles. Additionally, our study's findings may not apply to other regions globally due to differences in urban morphology, air quality improvement efforts, and car-oriented lifestyles, particularly in U.S. Unfortunately, we lacked information on other significant factors potentially related to cancer, which could confound our analyses. There is an urgent need for standardized methods of analysis when considering green space exposure and its various forms. Existing and future studies focusing on greenness in specific areas should be interpreted with caution (72). The characteristics such as access, biodiversity, facilities, and aesthetics would influence green spaces when exerting their health benefits to the public (73, 74). Future studies should aim to adjust for a comprehensive set of covariates, assess the quality of greenspace, and explore the association of greenspace exposure with different cancer subtypes (20, 23, 29, 75, 76).

5 Conclusion

In U.S., the distribution of greenspace and air pollution concentrations varies from east to west, with both factors being linked to TBL cancer along with distinct socioeconomic variables and other correlated risk factors. This study represents the first attempt to investigate the relationship between greenspace, air pollutants, socioeconomic factors, and TBL cancer at the state level in U.S. By correlating and contrasting with existing research on air pollution, greenspace, and various diseases, this study contributes to a better understanding of the association between the natural environment and health issues.

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 authors.

Author contributions

JZ: Conceptualization, Writing – original draft, Writing – review & editing. RR: Conceptualization, Data curation, Methodology, Validation, Writing – original draft, Writing – review & editing. NB: Conceptualization, Data curation, Formal analysis, Writing – review & editing. MP: Conceptualization, Writing – review & editing. NX: Conceptualization, Writing – original draft, Writing – review & editing. PL: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. WB: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. ZM: Conceptualization, Data curation, Writing – review & editing, Writing – original draft. HP: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. KV: Formal analysis, Writing – review & editing. VN: Writing – review & editing. RF: Conceptualization, Writing – review & editing. JL: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Henan Province Medical Science and Technology Research Program Joint Construction Project (No. LHGJ20190203). The funder has no role, if any, in the writing of the manuscript or the decision to submit it for publication.

Acknowledgments

The authors thank the supporting staff of the cancer center, The First affiliated hospital of Zhengzhou University.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1398679/full#supplementary-material

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. (2023) 73:17–48. doi: 10.3322/caac.21763

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

3. Deng Y, Zhao P, Zhou L, Xiang D, Hu J, Liu Y, et al. Epidemiological trends of tracheal, bronchus, and lung cancer at the global, regional, and national levels: a population-based study. *J Hematol Oncol*. (2020) 13:98. doi: 10.1186/s13045-020-00915-0

4. Society. AC. *Cancer facts & Figures 2023* Vol. 2023. Atlanta: American Cancer Society (2023).

5. IARC. *Outdoor air pollution. IARC monographs on the evaluation of carcinogenic risks to humans* (2016), 1–454.

6. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392:1923–94. doi: 10.1016/S0140-6736(18)32225-6

7. Zhou Z, Xinyi S, Zejun L, Xi Y, Xiaoliang B, Holmes MA, et al. Association between particulate matter (PM) 2· 5 air pollution and clinical antibiotic resistance: a global analysis. *Lancet Planet Health*. (2023) 7(8):e649–59.

8. Xue Y, Wang L, Zhang Y, Zhao Y, Liu Y. Air pollution: A culprit of lung cancer. *J Hazard Mater*. (2022) 434:128937. doi: 10.1016/j.jhazmat.2022.128937

9. Ledford H. How air pollution causes lung cancer - without harming DNA. *Nature*. (2023) 616(7957):419–20. doi: 10.1038/d41586-023-00989-z

10. Balmain A. Air pollution's role in the promotion of lung cancer. *Nature*. (2023) 35–36. doi: 10.1038/d41586-023-00929-x

11. Hill W, Lim E, Weeden C, Lee C, Augustine M, Chen K, et al. Lung adenocarcinoma promotion by air pollutants. *Nature*. (2023) 616:159–67. doi: 10.1038/s41586-023-05874-3

12. Hvidtfeldt UA, Severi G, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, et al. Long-term low-level ambient air pollution exposure and risk of lung cancer - A pooled analysis of 7 European cohorts. *Environ Int*. (2021) 146:106249. doi: 10.1016/j.envint.2020.106249

13. Gharibvand L, Shavlik D, Ghamsary M, Beeson WL, Soret S, Knutsen R, et al. The association between ambient fine particulate air pollution and lung cancer incidence: results from the AHSMOG-2 study. *Environ Health Perspect*. (2017) 125:378–84. doi: 10.1289/EHP124

14. Raspanti GA, Hashibe M, Siwakoti B, Wei M, Thakur BK, Pun CB, et al. Household air pollution and lung cancer risk among never-smokers in Nepal. *Environ Res*. (2016) 147:141–5. doi: 10.1016/j.envres.2016.02.008

15. Myers R, Brauer M, Dummer T, Atkar-Khattra S, Yee J, Melosky B, et al. High-Ambient air pollution exposure among never smokers versus ever smokers with lung cancer. *J Thorac Oncol*. (2021) 16:1850–8. doi: 10.1016/j.jtho.2021.06.015

16. Tseng CH, Tsuang BJ, Chiang CJ, Ku KC, Tseng JS, Yang TY, et al. The relationship between air pollution and lung cancer in nonsmokers in Taiwan. *J Thorac Oncol*. (2019) 14:784–92. doi: 10.1016/j.jtho.2018.12.033

17. Lo W-C, Ho C-C, Tseng E, Hwang J-S, Chan C-C, Lin H-H. Long-term exposure to ambient fine particulate matter (PM2.5) and associations with cardiopulmonary diseases and lung cancer in Taiwan: a nationwide longitudinal cohort study. *Int J Epidemiol*. (2022) 51:1230–42. doi: 10.1093/ije/dyac082

18. McKeon TP, Anil V, Penning TM, Hwang WT. Air pollution and lung cancer survival in Pennsylvania. *Lung Cancer*. (2022) 170:65–73. doi: 10.1016/j.lungcan.2022.06.004

19. Eckel SP, Cockburn M, Shu YH, Deng H, Lurmann FW, Liu L, et al. Air pollution affects lung cancer survival. *Thorax*. (2016) 71:891–8. doi: 10.1136/thoraxjnl-2015-207927

20. Nieuwenhuijsen MJ. Green infrastructure and health. *Annu Rev Public Health*. (2021) 42:317–28. doi: 10.1146/annurev-publhealth-090419-102511

21. Connolly R, Lipsitt J, Aboelata M, Yanez E, Bains J, Jerrett M. The association of green space, tree canopy and parks with life expectancy in neighborhoods of Los Angeles. *Environ Int*. (2023) 173:107785. doi: 10.1016/j.envint.2023.107785

22. Porcherie M, Linn N, Le Gall AR, Thomas MF, Faure E, Rican S, et al. Relationship between urban green spaces and cancer: A scoping review. *Int J Environ Res Public Health*. (2021) 18(4):1751. doi: 10.3390/ijerph18041751

23. Yang BY, Zhao T, Hu LX, Browning M, Heinrich J, Dharmage SC, et al. Greenspace and human health: An umbrella review. *Innovation (Camb)*. (2021) 2:100164. doi: 10.1016/j.xinn.2021.100164

24. Bereziartua A, Chen J, de Hoogh K, Rodopoulou S, Andersen ZJ, Bellander T, et al. Exposure to surrounding greenness and natural-cause and cause-specific mortality in the ELAPSE pooled cohort. *Environ Int*. (2022) 166:107341. doi: 10.1016/j.envint.2022.107341

25. Bauwelinck M, Casas L, Nawrot TS, Nemery B, Trabelsi S, Thomas I, et al. Residing in urban areas with higher green space is associated with lower mortality risk: A census-based cohort study with ten years of follow-up. *Environ Int*. (2021) 148:106365. doi: 10.1016/j.envint.2020.106365

26. Zare Sakhvidi MJ, Yang J, Siemiatycki J, Dadvand P, de Hoogh K, Vienneau D, et al. Greenspace exposure and cancer incidence: a 27-year follow-up of the French GAZEL cohort. *Sci Total Environ*. (2021) 787:147553. doi: 10.1016/j.scitotenv.2021.147553

27. Rodriguez-Loureiro L, Verdoodt F, Lefebvre W, Vanpoucke C, Casas L, Gadeyne S. Long-term exposure to residential green spaces and site-specific cancer mortality in urban Belgium: A 13-year follow-up cohort study. *Environ Int*. (2022) 170:107571. doi: 10.1016/j.envint.2022.107571

28. Huang YJ, Lee PH, Chen LC, Lin BC, Lin C, Chan TC. Relationships among green space, ambient fine particulate matter, and cancer incidence in Taiwan: A 16-year retrospective cohort study. *Environ Res*. (2022) 212:113416. doi: 10.1016/j.envres.2022.113416

29. Zare Sakhvidi MJ, Yang J, Mehrparvar AH, Dzhambov AM, Ebrahimi A, Dadvand P, et al. Exposure to greenspace and cancer incidence, prevalence, and mortality: A systematic review and meta-analyses. *Sci Total Environ*. (2022) 838(Pt 2):15618. doi: 10.1016/j.scitotenv.2022.156180

30. Thomas R, Rosenau P, Unruh LY, Barnes AJ. "United States: Health System Review." *Health systems in transition* (2020) 22(2):1–441.

31. Global burden of disease study 2019 (GBD 2019) results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME (2020). Available at: https://vizhub.healthdata.org/gbd-results/.

32. Diseases GBD and Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9

33. Pilant A, Endres K, Rosenbaum D, Gundersen G. US EPA EnviroAtlas meter-scale urban land cover (MULC): 1-m pixel land cover class definitions and guidance. *Remote Sens*. (2020) 12:1909.

34. Tucker CJ. *Red and photographic infrared linear combinations for monitoring vegetation*. United States: NASA Center for Aerospace Information (CASI (1978).

35. Savtchenko A, Ouzounov D, Ahmad S, Acker J, Leptoukh G, Koziana J, et al. Aqua MODIS products available from NASA GES DAAC. *Adv Space Res*. (2004) 34(4):710–4. doi: 10.1016/j.asr.2004.03.012

36. *Download daily data* . US EPA (Accessed May 8th, 2023).

37. NOAA National Centers for Environmental information. Climate at Glance: Statewide Mapping (2023). Available online at: https://www.ncei.noaa.gov/access/monitoring/climate-at-a-glance/statewide/mapping.

38. U.S. Bureau of Economic Analysis. *"SASUMMARY State annual summary statistics: personal income, GDP, consumer spending, price indexes, and employment"* (Accessed September 14, 2023).

39. Available online at: https://www.census.gov/data/tables/time-series/dec/density-data-text.html.

40. Dobkin F, Kerr G. Demographic disparities in United States Clean Air Act PM2. 5 attainment counties: assessing population living in nonattainment conditions. *J Environ Stud Sci*. (2024) 1–12.

41. Smoke Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion. Division of population health. BRFSS prevalence & Trends data (2015). Available online at: https://www.cdc.gov/brfss/brfssprevalence/.

42. Data retrieved from the Subnational HDI Database of the Global Data Lab . Available online at: https://globaldatalab.org/shdi/.

43. Wang C, Zheng W, Yongjie X, Yadi Z, Zilin L, Wei C, et al. Disparities in the global burden of tracheal, bronchus, and lung cancer from 1990 to 2019. *Chinese Medical Journal Pulmonary and Critical Care Medicine*. (2023) 1:36–45. doi: 10.1016/j.pccm.2023.02.001

44. Accessed through global forest watch on 04/10/2022 . Available online at: www.globalforestwatch.org.

45. O'Callaghan-Gordo C, Kogevinas M, Cirach M, Castano-Vinyals G, Aragones N, Delfrade J, et al. Residential proximity to green spaces and breast cancer risk: The multicase-control study in Spain (MCC-Spain). *Int J Hyg Environ Health*. (2018) 221:1097–106. doi: 10.1016/j.ijheh.2018.07.014

46. Astell-Burt T, Feng X, Kolt GS. Neighbourhood green space and the odds of having skin cancer: multilevel evidence of survey data from 267072 Australians. *J Epidemiol Community Health*. (2014) 68:370–4. doi: 10.1136/jech-2013-203043

47. Wang H, Tassinary LG. Effects of greenspace morphology on mortality at the neighbourhood level: a cross-sectional ecological study. *Lancet Planet Health*. (2019) 3: e460–8. doi: 10.1016/S2542-5196(19)30217-7

48. Mueller W, Milner J, Loh M, Vardoulakis S, Wilkinson P. Exposure to urban greenspace and pathways to respiratory health: An exploratory systematic review. *Sci Total Environ*. (2022) 829:154447. doi: 10.1016/j.scitotenv.2022.154447

49. Su JG, Jerrett M, de Nazelle A, Wolch J. Does exposure to air pollution in urban parks have socioeconomic, racial or ethnic gradients? *Environ Res*. (2011) 111:319–28. doi: 10.1016/j.envres.2011.01.002

50. The trust for public land, in: *2018 city park facts* (2018). Available online at: www.tpl.org/cityparkfacts (Accessed 3 Sepetember 2023).

51. Hartig T, Mitchell R, de Vries S, Frumkin H. Nature and health. *Annu Rev Public Health*. (2014) 35:207–28. doi: 10.1146/annurev-publhealth-032013-182443

52. Watson JEM, Evans T, Venter O, Watson JEM, Evans T, Venter O, et al. The exceptional value of intact forest ecosystems. *Nat Ecol Evol*. (2018) 2:599–610. doi: 10.1038/s41559-018-0490-x

53. Lohmus M, Balbus J. Making green infrastructure healthier infrastructure. *Infect Ecol Epidemiol*. (2015) 5:30082. doi: 10.3402/iee.v5.30082

54. Lachowycz K, Jones AP. Greenspace and obesity: a systematic review of the evidence. *Obes Rev*. (2011) 12:e183–189. doi: 10.1111/j.1467-789X.2010.00827.x

55. Safiri S, Sohrabi MR, Carson-Chahhoud K, Bettampadi D, Taghizadieh A, Almasi-Hashiani A, et al. Burden of tracheal, bronchus, and lung cancer and its attributable risk factors in 204 countries and territories, 1990 to 2019. *J Thorac Oncol*. (2021) 16(6):945–59.

56. Kamis A, Cao R, He Y, Tian Y, Wu C. Predicting lung cancer in the United States: A multiple model examination of public health factors. *Int J Environ Res Public Health*. (2021) 18(11):6127. doi: 10.3390/ijerph18116127

57. Ma C, Jung CR, Nakayama SF, Tabuchi T, Nishihama Y, Kudo H, et al. Short-term association of air pollution with lung cancer mortality in Osaka, Japan. *Environ Res*. (2023) 224:115503. doi: 10.1016/j.envres.2023.115503

58. Bai L, Shin S, Burnett RT, Kwong JC, Hystad P, van Donkelaar A, et al. Exposure to ambient air pollution and the incidence of lung cancer and breast cancer in the Ontario Population Health and Environment Cohort. *Int J Cancer*. (2020) 146:2450–9. doi: 10.1002/ijc.32575

59. Jbaily A, Zhou X, Liu J, Lee TH, Kamareddine L, Verguet S, et al. Air pollution exposure disparities across US population and income groups. *Nature*. (2022) 601:228–33. doi: 10.1038/s41586-021-04190-y

60. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of cause-specific mortality associated with PM2.5 air pollution in the United States. *JAMA Netw Open*. (2019) 2:e1915834. doi: 10.1001/jamanetworkopen.2019.15834

61. Tripathi S. How does urbanization affect the human development index? A cross-country analysis. *Asia-Pacific J Regional Sci*. (2021) 5:1053–80. doi: 10.1007/s41685-021-00211-w

62. Walker ES, Noonan CW, Semmens EO, Ware D, Smith P, Boyer BB, et al. Indoor fine particulate matter and demographic, household, and wood stove characteristics among rural US homes heated with wood fuel. *Indoor Air*. (2021) 31:1109–24. doi: 10.1111/ina.12808

63. Walker ES, Noonan CW, Belcourt A, Boulafentis J, Garcia C, Graham J, et al. Efficacy of air filtration and education interventions on fine particulate matter among rural Native American homes heated with wood stoves: Results from the EldersAIR randomized trial. *Sci Total Environ*. (2022) 843:157029. doi: 10.1016/j.scitotenv.2022.157029

64. Miller SJ, Vela MA. *The effects of air pollution on educational outcomes: evidence from Chile*. IDB Publications (Working Papers) 4756, Inter-American Development Bank (2013).

65. Balakrishnan U, Tsaneva M. Air pollution and academic performance: Evidence from India. *World Dev*. (2021) 146:105553. doi: 10.1016/j.worlddev.2021.105553

66. Lipfert FW, Wyzga RE. Longitudinal relationships between lung cancer mortality rates, smoking, and ambient air quality: a comprehensive review and analysis. *Crit Rev Toxicol*. (2019) 49:790–818. doi: 10.1080/10408444.2019.1700210

67. Fernandez-Aguilar L, Latorre JM, Martinez-Rodrigo A, Moncho-Bogani JV, Ros L, Latorre P, et al. Differences between young and older adults in physiological and subjective responses to emotion induction using films. *Sci Rep*. (2020) 10:14548. doi: 10.1038/s41598-020-71430-y

68. van der Kruk E, Strutton P, Koizia LJ, Fertleman M, Reilly P, Bull AMJ. Why do older adults stand-up differently to young adults?: investigation of compensatory movement strategies in sit-to-walk. *NPJ Aging*. (2022) 8:13. doi: 10.1038/s41514-022-00094-x

69. Eng L, Bender J, Hueniken K, Kassirian S, Yang D, Mitchell L, et al. et al: Cancer care-related social media (SM) and internet usage differences between adolescents and young adults (AYA), adults and elderly patients with cancer. *Ann Oncol*. (2018) 29 (Suppl 8):VIII624. doi: 10.1093/annonc/mdy300.065

70. Budhi IB, Bagus MI, Ayu SI, Darmawan I, Widyanti S, Kristanto YY. The immune profiles in young, adult and elderly of advanced stage colorectal cancer patients. *Ann Oncol*. (2019) 30(Suppl 11):XI6. doi: 10.1093/annonc/mdz447.018

71. Valiathan R, Ashman M, Asthana D. Effects of ageing on the immune system: infants to elderly. *Scand J Immunol*. (2016) 83:255–66. doi: 10.1111/sji.12413

72. Fuertes E, Markevych I, von Berg A, Bauer CP, Berdel D, Koletzko S, et al. Greenness and allergies: evidence of differential associations in two areas in Germany. *J Epidemiol Community Health*. (2014) 68:787–90. doi: 10.1136/jech-2014-203903

73. Knobel P, Dadvand P, Alonso L, Costa L, Español M, Maneja R. Development of the urban green space quality assessment tool (RECITAL). *Urban Forestry Urban Greening*. (2021) 57(126895). doi: 10.1016/j.ufug.2020.126895

74. Knobel P, Dadvand P, Maneja-Zaragoza R. A systematic review of multi-dimensional quality assessment tools for urban green spaces. *Health Place*. (2019) 59 (102198). doi: 10.1016/j.healthplace.2019.102198

75. Nguyen PY, Astell-Burt T, Rahimi-Ardabili H, Feng X. Green space quality and health: A systematic review. *Int J Environ Res Public Health*. (2021) 18(21):11028. doi: 10.3390/ijerph182111028

76. Weber KA, Lyons E, Yang W, Stevenson C, Stevenson DK, Shaw GM. Residential proximity to green space and preeclampsia in California. *Environ Epidemiol*. (2020) 4:e120. doi: 10.1097/EE9.0000000000000120

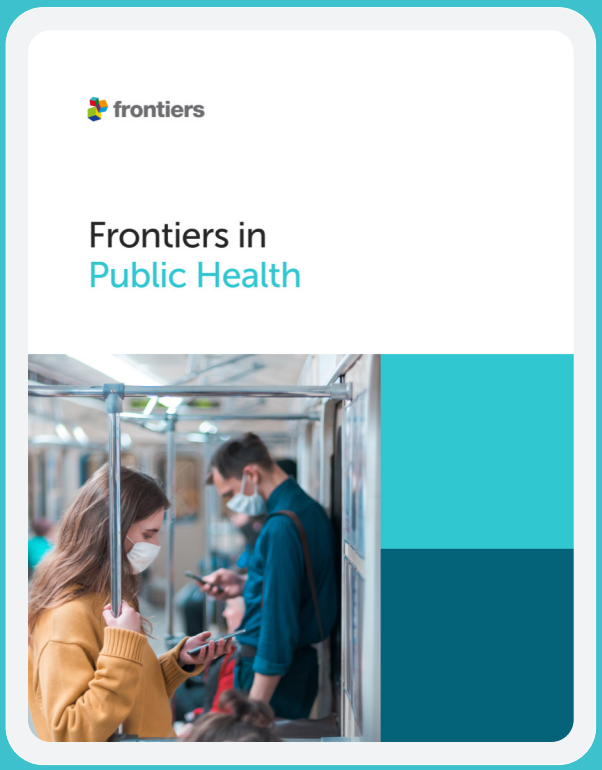
Frontiers in Public Health

Explores and addresses today's fast-moving healthcare challenges

One of the most cited journals in its field, which promotes discussion around inter-sectoral public health challenges spanning health promotion to climate change, transportation, environmental change and even species diversity.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact