International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Breast Cancer Burden in BRICS Countries Attributable to Smoking, High Alcohol Use, High Body Mass Index, and Low Physical Activity, 1990–2021: Findings from the Global Burden of Disease 2021 and Mendelian Randomization

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Background: Breast cancer remains the leading cause of cancer incidence and mortality among women globally. However, studies that not only compare the population-level burden but also interrogate the underlying causal mechanisms to explain the observed cross-national disparities are lacking. This limits the ability to translate descriptive findings into mechanistically informed prevention strategies. This study evaluates the burden of female breast cancer attributable to four modifiable risk factors: smoking, high alcohol use, high body-mass index (BMI), and low physical activity, among women of reproductive age (15 to 49 years) in BRICS countries from 1990 to 2021.

Methods: We employed a two-tiered analytical framework. First, using data from the Global Burden of Disease (GBD) 2021 study, we quantified and compared the national burden (deaths, DALYs) and temporal trends (EAPC, ARIMA projections) attributable to each risk factor. Second, to provide mechanistic insight into these population-level patterns, we conducted a two-sample Mendelian randomization (MR) analysis to assess the potential causal relationships of the same risk factors with breast cancer.

Results: Substantial heterogeneity in attributable burden was observed across BRICS nations. MR analysis supported the potential causal roles of high alcohol use, smoking, and low physical activity. Critically, the genetic evidence for causality aligned with and helped to mechanistically explain the dominant risk drivers identified in the descriptive burden analysis: the rising burden linked to high alcohol use in Brazil and India, and the increasing burden from smoking in the Russian Federation. A consistent protective association of high BMI with premenopausal breast cancer was observed in both analyses.

Conclusion: By integrating comparative burden assessment with causal inference, this study moves beyond describing disparities to offering mechanistically plausible explanations for the distinct risk factor profiles in BRICS countries. This approach provides a stronger evidence base for developing etiologically informed, targeted prevention strategies that address the specific drivers of breast cancer in different national contexts.

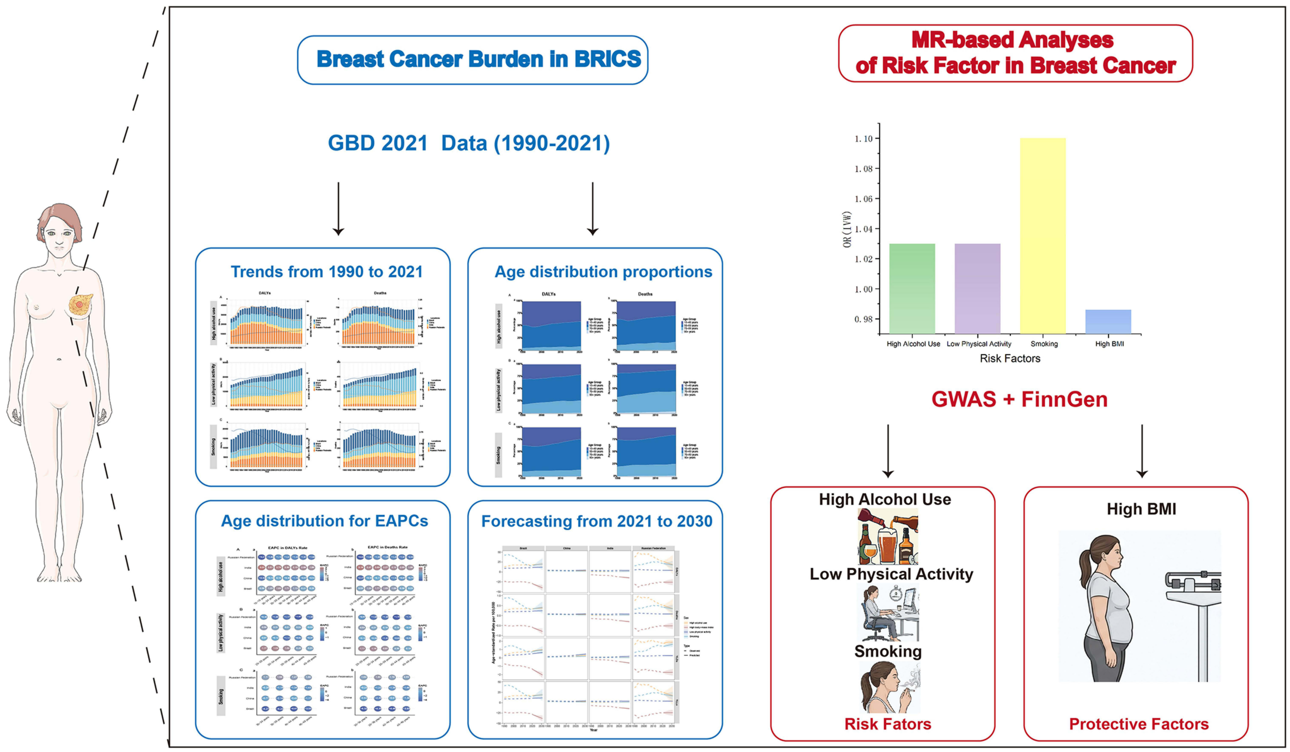
Keywords: breast cancer, BRICS countries, reproductive age women, global burden of disease, mendelian randomization

Introduction

Breast cancer pathogenesis and management have been profoundly shaped by advances in understanding its tumor biology and therapeutic landscape.[1] Decades of research have elucidated key molecular pathways, from hormonal drivers to DNA repair deficiencies, and have ushered in targeted therapies that significantly improve survival, representing

https://doi.org/10.2147/IJWH.S606547
Received: 3 March 2026
Accepted: 6 May 2026
Published: 18 May 2026

Graphical Abstract



a paradigm shift in cancer treatment.[2] However, these remarkable treatment advances address the disease after its onset. In parallel, robust epidemiological evidence confirms that a substantial proportion of breast cancer incidence is attribufgfigu to modifiable lifestyle and metabolic factors, presenting a critical opportunity for primary prevention.[3] Therefore, a comprehensive cancer control strategy rests on three intertwined pillars: deciphering tumor biology, developing effective treatments, and implementing evidence-based prevention. This study is positioned within this integrative framework, focusing on the preventive pillar by investigating modifiable risk factors, with the aim of bridging population-level patterns with biological plausibility.

In 2020, nearly 20 million new cancer cases were reported globally, with approximately 9.7 million cancer-related deaths. Among these, breast cancer emerged as the leading cause of cancer-related mortality in women, accounting for 15.4% of all cancer deaths, and was also the most commonly diagnosed cancer, representing 23.8% of all new cases.[4] This underscores that the burden of breast cancer is not only a clinical challenge but also a significant public health and health systems issue. Of the six Level 2 risk factors identified as significant contributors to breast cancer mortality—dietary risks, alcohol consumption, high BMI, high fasting plasma glucose, low physical activity, and smoking.[5] This study focuses on the modifiable ones, emphasizing that understanding their role is key to reducing the burden through prevention.

The BRICS nations represent a critical group for studying breast cancer burden transition and its modifiable risk factors, yet a systematic comparative analysis is lacking. These countries contribute substantially to the global absolute number of female breast cancer cases and deaths due to their large population sizes. These countries are experiencing swift transitions in both epidemiology and lifestyle. These changes are marked by increasing urbanization, shifts in diet, rising rates of obesity and metabolic disorders, alterations in women's reproductive patterns, declining physical activity, and evolving patterns of tobacco and alcohol use.[6] Such trends could drive faster and more distinct shifts in breast cancer risk profiles relative to high-income nations. Furthermore, significant heterogeneity exists within BRICS in terms of health system resources, screening coverage, early diagnosis, and treatment accessibility, resulting in different structures of breast cancer mortality and DALYs across these countries.[7] This internal heterogeneity, alongside their shared status as emerging economies with varying SDI levels, policies, and behavioral exposures, makes BRICS an ideal setting for comparative studies on risk factors, burden, and trend disparities.

While previous studies have analyzed various health indicators related to breast cancer, including incidence, mortality, and DALYs, and their associated risk factors, these investigations have often provided limited insights into breast cancer alone. Some studies have analyzed global data encompassing all cancer types, yet failed to provide detailed, cancer-specific insights.[5,8,9] Other research has focused on breast cancer data from specific countries or regions[10–12] or used data prior to 2021, without conducting a separate analysis of breast cancer trends within BRICS nations.[13]

Analyzing women of reproductive age separately is crucial.[14] This group shoulders significant family and societal roles, and early-onset breast cancer among them carries greater family and socio-economic impacts, reflected in higher weights of YLL and DALYs.[5] The risk profile for breast cancer in reproductive age may differ, involving factors related to metabolism, obesity, behavioral exposures, and hormones. Additionally, screening strategies and healthcare-seeking behaviors may vary, potentially leading to a different burden structure compared to the all-age population. Therefore, comparing all-age and reproductive-age women within BRICS can help identify high-risk patterns and policy priorities that might be masked by overall averages.

Our preliminary observations suggest a potential misalignment or divergence in breast cancer burden levels, temporal trends, and risk attribution structures between all-age and reproductive-age women within BRICS countries. However, existing GBD studies predominantly remain at the all-age aggregate level, lacking systematic assessment for the reproductive-age group, and, more importantly, a direct comparative framework between all-age and reproductive-age. This analysis reveals a critical knowledge gap concerning the specific countries and risk factors that disproportionately affect women of reproductive age. It underscores the necessity of systematically comparing these patterns with all-age trends and evaluating whether the disparities are widening over time. Such a misalignment between population-wide and age-specific risk profiles may signal an urgent need to refine public health strategies through age-targeted policy priorities.

This study specifically examines the impact of smoking, high alcohol use, high BMI, and low physical activity on breast cancer burden, selecting these four from the six Level 2 risk factors for methodological and practical reasons. First, policy intervenability and priority: These four represent highly modifiable behavioral and metabolic factors amenable to transnational policy implementation, making them suitable for cross-country comparison and recommendation. Second, cross-national comparability and measurement stability: Within the GBD framework, these factors have relatively consistent definitions and stronger comparability across countries. Third, methodological feasibility for causal inference: Our study further employs MR to assess potential causality. These four exposures have more established Genome-Wide Association Study (GWAS) instrumental variables available, facilitating more robust MR analyses compared to complex composite exposures like dietary risk. Thus, focusing on these four key modifiable factors allows for more stable cross-national comparable results and forms a coherent evidence chain with causal inference. Moreover, these four factors are implicated in distinct yet impactful biological pathways relevant to breast carcinogenesis, such as estrogen metabolism and oxidative stress (alcohol, smoking), chronic inflammation and insulin signaling (high BMI, low physical activity), thereby connecting population-level risk to potential mechanistic underpinnings.

To address these gaps, the present study employs data from the GBD 2021, offering, to the best of our knowledge, the first comprehensive analysis of breast cancer risk factors within the BRICS countries, with a particular focus on China, India, the Russian Federation, and Brazil. The GBD framework represents the only global methodology for estimating disease burden, providing critical metrics such as age-standardized mortality, morbidity, and DALYs for various cancers.[15] Despite its comprehensive scope, however, no in-depth GBD analysis has specifically addressed the burden of breast cancer among women of reproductive age within BRICS countries.

Through this comprehensive investigation, we aim to provide policymakers, researchers, and funding agencies with robust evidence to inform region-specific and age-targeted breast cancer prevention and treatment strategies. The findings are intended to help identify which countries, which age groups, and which risk factors should be prioritized. Ultimately, our study seeks to support the optimal allocation of limited healthcare resources, offer insights for screening and primary prevention tailored by age and country, reveal age-stratified gaps within BRICS to guide future mechanistic and intervention research, and provide projections of breast cancer trends from 2022 to 2030.

Methods

Data Acquisition

Data for this study were obtained from the GBD 2021 database, which offers comprehensive estimates of disease burden for 371 diseases and injuries across 204 countries and territories from 1990 to 2021. The GBD 2021 database integrates multiple data sources, including vital registration systems, cancer registries, epidemiological surveys, and disease surveillance reports. All disease terms were standardized using the International Classification of Diseases (ICD) codes to ensure comparability across data sets. For this analysis, we extracted data specifically on female breast cancer among women of reproductive age in the BRICS nations (Brazil, Russian Federation, India, and China). The metrics analyzed included deaths, DALYs, YLDs, and YLLs, along with their corresponding age-standardized rates (ASRs), as well as the EAPC of these indicators. These outcomes were further stratified by four modifiable risk factors: high alcohol use, smoking, high BMI, and low physical activity. The data were accessed through the GBD visualization platform (https://vizhub.healthdata.org/gbd-results).

Additionally, summary statistics for genetic associations were obtained from the FinnGen R12 and GWAS Catalog, covering the following traits: breast cancer (ukb-b-16890), breast cancer (ieu-b-4810), BMI (ieu-a-974), alcohol use disorder (finngen_R12_AUD), low physical activity (ebi-a-GCST90061421), and smoking (ukb-b-223). Detailed data sources and sample sizes are summarized in Table 1 below.

Acknowledgment of GBD Data Heterogeneity Across BRICS Nations

We acknowledge the inherent variability in the underlying data sources and quality across BRICS countries within the GBD framework. Differences in the coverage and completeness of vital registration systems, cancer registry representativeness (particularly for younger, rural, or underserved populations), and the frequency of national health surveys contribute to uncertainty intervals around the estimates. This heterogeneity is explicitly quantified and reported as 95% uncertainty intervals (UIs) in all GBD outputs. In our analysis, we consistently report these UIs and emphasize that cross-country comparisons should consider both the point estimates and their overlapping uncertainty ranges. The implications of this data variability for interpreting national-level trends and disparities are further discussed in the Limitations section.

Disease-Attributable Risk Factors

The GBD 2021 comparative risk assessment framework evaluates the impact of 88 risk factors on disease burden, which are categorized into environmental, behavioral, and metabolic domains. For this study, we focused on four Level 2 risk factors that have been linked to female breast cancer:

- High Alcohol Use: Consumption of alcoholic beverages.
- Smoking: Active and passive tobacco exposure.
- High BMI: Defined as a BMI $\geq$25 kg/m^2.
- Low Physical Activity: Insufficient metabolic equivalent (MET) minutes per week.

Table 1 Detailed Data Sources and Sample Sizes

Variables	Source	ID	Sample Size	nSNPs
Breast cancer	GWAS catalog	ukb-b-16890	462,933	9851867
Breast cancer	IEU GWAS	ieu-b-4810	212,402	12321854
Alcohol use disorder	Finngen R12	finngen_R12_AUD	500348	16380466
Low physical activity	GWAS catalog	ebi-a-GCST90061421	88,411	8489912
Smoking	GWAS catalog	ukb-b-223	462,434	9851867
BMI	IEU GWAS	ieu-a-974	171,977	2,494,613

Population attributable fractions (PAFs) were calculated to estimate the proportion of breast cancer burden attributable to each risk factor. To avoid overestimation of PAFs, mediation effects between risk factors were accounted for. The relative risks and exposure levels associated with each risk factor were derived from meta-analyses of relevant epidemiological studies.

Statistical Analysis

Temporal trends were assessed by calculating the annual percentage change (EAPC) for ASRs, including ASMR, ASDR, ASYDR, and ASYR. The formula used was:

$$Y = \alpha X + \beta \quad (1)$$

where *Y* represents the log10(ASR) value, and *X* denotes the calendar year. The EAPC was then derived using the formula:

$$EAPC = 100 \times (10^{\alpha} - 1) \quad (2)$$

Positive EAPC values, with 95% confidence intervals (CIs) excluding zero, indicated an increasing trend, while negative values indicated a decline.

Age-specific patterns were analyzed by stratifying outcomes into 5-year age groups (15–19, 20–24, 45–49 years). To forecast trends from 2022 to 2030, ARIMA models were applied, with stationarity confirmed through differencing. Model diagnostics, including residual analysis, were conducted to ensure a good model fit.

Projection Analysis and Policy Relevance

To illustrate the potential future trajectory of breast cancer burden under the assumption that recent risk factor trends and healthcare contexts persist, and to inform the timing and urgency of interventions, we projected age-standardized rates from 2022 to 2030 using Autoregressive Integrated Moving Average (ARIMA) models. Stationarity was confirmed through differencing. Model diagnostics, including residual analysis (Ljung-Box test) and inspection of ACF/PACF plots, were conducted to ensure a good fit. These projections are presented as a supplementary, policy-relevant illustration of potential outcomes, rather than as biological forecasts, and their interpretation is integrated with the discussion of country-specific public health priorities.

Mendelian Randomization

A two-sample MR analysis was performed using the "TwoSampleMR" package in R. Single nucleotide polymorphisms (SNPs) were selected as instrumental variables with a significance threshold of $P<5\times10^{-8}$. Linkage disequilibrium (LD) was addressed by applying clumping parameters of $r^2<0.001$ and a clumping distance of 10,000 kb. In cases where the number of available SNPs was insufficient, the threshold was relaxed to $P<1\times10^{-5}$.[16]

Five MR methods were employed to explore the genetic association between exposures and outcomes: inverse-variance weighted (IVW), weighted median, MR Egger regression, simple mode, and weighted mode. To assess the robustness of the findings, a leave-one-out sensitivity analysis was conducted to evaluate whether the overall results were driven by a single genetic variant. The IVW method was primarily used as the main analysis.

Sensitivity Analyses and Robustness Checks

To comprehensively assess potential horizontal pleiotropy and the robustness of our causal inferences, we conducted the following sensitivity analyses: 1. MR-Egger regression, which provides a test for directional pleiotropy (significant intercept term) and an estimate adjusted for it; 2. The weighted median method, which provides consistent estimates even if up to 50% of the instrumental variables are invalid; 3. MR-PRESSO, to detect and correct for potential outliers driven by horizontal pleiotropy; 4. Leave-one-out analysis, to evaluate if the overall result was unduly influenced by any single SNP; 5. Cochran's Q test, to quantify the heterogeneity among the instrumental variables. A significant Q statistic ($P < 0.05$) indicates the presence of substantial heterogeneity, for which we additionally report the I^2 statistic to measure the proportion of total variation due to heterogeneity rather than chance.

All statistical analyses were performed using R software (version 4.4.3). P-value of <0.05 was considered statistically significant.

https://doi.org/10.2147/IJWH.S606547

Addressing Potential Confounders

In the analysis of disease burden trends using GBD data, the estimates provided by the GBD study itself have already been adjusted for a set of known demographic and socio-economic covariates as part of its comparative risk assessment framework. For our time-series forecasting (ARIMA), we ensured model stationarity through differencing to control for underlying temporal confounders. In the Mendelian randomization analysis, the use of genetic variants as instrumental variables inherently reduces residual confounding, as genetic alleles are randomly assorted at conception and generally independent of postnatal environmental and lifestyle factors. Furthermore, we rigorously screened instrumental variables to minimize pleiotropic effects, as detailed in the MR assumptions validation below.

Patient and Public Involvement

Patients and/or the public were not involved in the study design, data interpretation, manuscript drafting or dissemination plans of this research.

Results

Overview

We analyzed the burden of breast cancer among women of reproductive age in BRICS countries from 1990 to 2021 and projected trends up to 2030, with a specific focus on four key risk factors: smoking, high alcohol use, high BMI, and low physical activity. Using data from the Global Burden of Disease Study 2021, we estimated breast cancer deaths, DALYs, YLDs, and YLLs, as well as age-standardized rates. This descriptive analysis aimed to map the heterogeneous landscape of risk-attributable burden across nations. Subsequently, risk factor analysis, supported by MR, was conducted to independently assess the potential causal underpinnings of these exposures in relation to breast cancer. Furthermore, we projected the trends of breast cancer from 2022 to 2030.

DALYs, Deaths, YLDs and YLLs of Breast Cancer in BRICS Countries

From 1990 to 2021, the DALYs attributable to high alcohol use in Brazil increased by 176%, rising from 4093 (95% uncertainty interval [UI]: 2178 to 6566) to 11,325 (95% UI: 6984 to 16,720). Similarly, DALYs related to low physical activity rose by 154%, from 1936 (95% UI: 298 to 4426) to 4926 (95% UI: 763 to 11,253). In contrast, DALYs due to smoking decreased by 19%, from 6831 (95% UI: 5039 to 8902) to 5502 (95% UI: 3755 to 7641) (Table 2). The DALYs associated with high BMI shifted from −6181 (95% UI: −13,466 to −1) to −16,218 (95% UI: −35,934 to −4).

During the same period, deaths from breast cancer attributable to high alcohol use increased by 175%, from 80 (95% UI: 42 to 129) to 220 (95% UI: 134 to 325). Deaths attributed to high BMI changed from −124 (95% UI: −270 to 0) to −323 (95% UI: −718 to 0). The number of breast cancer-related deaths due to low physical activity increased by 153%, from 39 (95% UI: 6 to 89) to 99 (95% UI: 15 to 225). Meanwhile, deaths attributable to smoking decreased by 19%, from 139 (95% UI: 103 to 182) to 112 (95% UI: 77 to 154) (Table S1).

In terms of YLDs, the most substantial increase was observed in breast cancer due to high alcohol use, which rose by 322%, whereas the smallest increase was seen for smoking-related YLDs, which rose by 23% (Table S2). Regarding YLLs, smoking's contribution to the burden of breast cancer decreased by 21% (Table S3).

In China, the DALYs for female breast cancer attributed to high alcohol use increased modestly by 31%, rising from 7525 (95% UI: 3601 to 13,232) to 9837 (95% UI: 4354 to 18,644). In contrast, DALYs linked to low physical activity experienced a more pronounced increase of 39%, from 7681 (95% UI: 956 to 19,828) to 10,692 (95% UI: 1229 to 27,019). Smoking had a relatively smaller effect, with a 29% increase in DALYs, from 3137 (95% UI: 1636 to 5511) to 4045 (95% UI: 2037 to 7488) (Table 2).

During the same period, the deaths due to female breast cancer associated with high alcohol use rose by 27%, from 148 (95% UI: 71 to 260) to 188 (95% UI: 83 to 353). Deaths related to low physical activity increased by 36%, from 151 (95% UI: 19 to 389) to 205 (95% UI: 24 to 520), while smoking-related deaths showed the smallest increase of 25%, from 63 (95% UI: 33 to 111) to 79 (95% UI: 40 to 147) (Table S1).

Table 2 The DALYs in 1990 and 2021

DALYS (95%UI)						
Region	**Risk Factors**	**1990**		**2021**		
		Number	**ASR per 100,000**	**Number**	**ASR per 100,000**	**EAPC (95% CI)**
	High Alcohol use	4093 (2178,6566)	12.515 (6.622,20.18)	11,325 (6984,16,720)	17.48 (10.792,25.779)	0.76(0.54,0.98)
Brazil	Low physical activity	1936 (298,4426)	6.127 (0.963,13.966)	4926 (763,11,253)	7.495 (1.162,17.138)	0.54(0.47,0.6)
	Smoking	6831 (5039,8902)	21.793 (16.072,28.437)	5502 (3755,7641)	8.323 (5.681,11.56)	−4(−4.32,-3.68)
	High BMI	−6181 (−13,466,-1)	−19.385 (−42.158,-0.004)	−16,218 (−35,934,-4)	−24.727 (−54.778,-0.006)	
	High Alcohol use	7525 (3601,13,232)	2.844 (1.37,4.979)	9837 (4354,18,644)	2.434 (1.081,4.633)	−0.66(−0.98,-0.35)
China	Low physical activity	7681 (956,19,828)	2.902 (0.362,7.488)	10,692 (1229,27,019)	2.629 (0.305,6.659)	−0.57(−0.72,-0.42)
	Smoking	3137 (1636,5511)	1.231 (0.642,2.157)	4045 (2037,7488)	0.974 (0.491,1.798)	−1.03(−1.13,-0.93)
	High Alcohol use	1274 (170,2640)	0.75 (0.103,1.551)	4910 (1898,9557)	1.358 (0.526,2.642)	2.09(1.91,2.26)
India	Low physical activity	3918 (568,9202)	2.36 (0.345,5.52)	9511 (1512,21,571)	2.658 (0.423,6.019)	0.14(−0.09,0.36)
	Smoking	1749 (923,3013)	1.083 (0.574,1.861)	2634 (1275,5183)	0.742 (0.359,1.459)	−1.31(−1.43,-1.18)
	High BMI	−9480 (−20,627,-6)	−5.667 (−12.32,-0.003)	−36,726 (−82,919,-22)	−10.206 (−23.052,-0.006)	
	High Alcohol use	13555 (8903,18,723)	36.014 (23.645,49.783)	11,167 (6566,16,162)	25.18 (14.864,36.386)	−1.69(−2.08,-1.29)
Russian Federation	Low physical activity	1262 (147,3113)	3.46 (0.407,8.437)	1195 (127,3130)	2.645 (0.281,6.947)	−1.28(−1.44,-1.12)
	Smoking	2941 (1903,4334)	7.911 (5.105,11.672)	4908 (3173,6936)	10.806 (6.989,15.269)	1.31(0.94,1.68)
	High BMI	−9127 (−20,228,-7)	−24.848 (−55.179,-0.018)	−9380 (−20,683,-6)	−20.778 (−45.82,-0.013)	

https://doi.org/10.2147/IJWH.S606547

Regarding YLDs, high alcohol use, low physical activity, and smoking exhibited similar growth rates, with increases of 235%, 244%, and 210%, respectively (Table S2). Similarly, the increases in YLLs under the influence of these three risk factors followed a comparable pattern, rising by 23%, 32%, and 22%, respectively (Table S3).

In India, the DALYs for female breast cancer due to high alcohol use surged by 285%, from 1274 (95% UI: 170 to 2640) to 4910 (95% UI: 1898 to 9557). In contrast, the DALYs associated with low physical activity and smoking increased by 143% and 51%, respectively, while high BMI led to a reduction of 287% (Table 2).

Over the same period, deaths from female breast cancer attributed to high alcohol use increased by 288%. Deaths linked to low physical activity climbed from 80 (95% UI: 12 to 187) to 193 (95% UI: 31 to 436), marking a 141% rise, while deaths associated with smoking grew by 49%, from 37 (95% UI: 20 to 63) to 55 (95% UI: 27 to 108). In contrast, high BMI-related deaths showed a declining trend, from −192 (95% UI: −419 to 0) to −736 (95% UI: −1658 to 0) (Table S1).

In terms of YLDs, the most significant decreases were observed for high BMI and the most significant increases were observed for high alcohol use, by 499% and 479%, respectively. YLDs associated with low physical activity and smoking increased by 291% and 123%, respectively (Table S2). Regarding YLLs, smoking had a relatively minor impact, contributing to a 49% increase in female breast cancer YLLs in India (Table S3).

Between 1990 and 2021, in the Russian Federation, the DALYs for female breast cancer attributed to high alcohol use decreased from 13,555 (95% UI: 8903 to 18,723) to 11,167 (95% UI: 6566 to 16,162), while deaths dropped from 267 (95% UI: 175 to 370) to 218 (95% UI: 129 to 316). Similarly, DALYs linked to low physical activity decreased from 1262 (95% UI: 147 to 3113) to 1195 (95% UI: 127 to 3130), with deaths declining from 26 (95% UI: 3 to 63) to 24 (95% UI: 3 to 62). Among the BRICS countries, the Russian Federation was the only nation to show a downward trend in DALYs for these two risk factors (Tables 2 and S1).

In contrast, the DALYs for female breast cancer attributable to smoking increased from 2941 (95% UI: 1903 to 4334) to 4908 (95% UI: 3173 to 6936), with deaths rising from 59 (95% UI: 38 to 87) to 97 (95% UI: 62 to 138). The DALYs linked to high BMI shifted from −9127 (95% UI: −20,228 to −7) to −9380 (95% UI: −20,683 to −6), with deaths changing from −184 (95% UI: −409 to 0) to −187 (95% UI: −413 to 0), both showing a declining trend (Tables 2 and S1).

Regarding YLDs, the influence of high alcohol use led to a 30% increase, while YLLs decreased by 20%. For high BMI, YLDs increased by 61%, and YLLs showed a minimal rise of 0.2%. Low physical activity contributed to a 48% increase in YLDs, while YLLs decreased by 8%. Smoking had the most significant impact, with YLDs surging by 163% and YLLs increasing by 63% (Tables S2 and S3).

Time Trends Between 1990 and 2021

At the national level, substantial disparities were observed in the breast cancer burden associated with four major risk factors among the BRICS countries in 2021. From 1990 to 2021, trends in ASMR exhibited distinct patterns:

For high alcohol use, India and Brazil showed an upward trend in ASMR, with India's ASMR nearly doubling, while China experienced a decline. The Russian Federation exhibited an initial increase followed by a decrease, with a particularly notable reduction exceeding 32% (Figure 1A(ii)).

In the context of low physical activity, the impact of this factor remained relatively modest across the four countries, with variations in all cases staying below 30%. The Russian Federation experienced an initial increase followed by a decline, recording the largest reduction at 25%, whereas Brazil showed an upward trend, with the highest increase reaching 19% (Figure 1B(ii)).

Regarding smoking, the Russian Federation exhibited an initial increase followed by a stabilization in its ASMR, which rose by 32%. In contrast, the other three countries showed downward trends. Brazil recorded the most pronounced decline, with its ASMR falling from 0.449 (95% UI: 0.331 to 0.588) to 0.169 (95% UI: 0.116 to 0.233), representing a 62% decrease. India and China followed, with reductions of 35% and 24%, respectively (Figure 1C(ii)).

Similarly, from 1990 to 2021, trends in the ASDR largely mirrored those of ASMR, albeit with some variations:

For high alcohol use, India experienced the highest increase in ASDR, which rose by approximately 81%, though the rise was less pronounced compared to ASMR. The Russian Federation saw the largest decline in ASDR, around 30% (Figure 1A(i)).

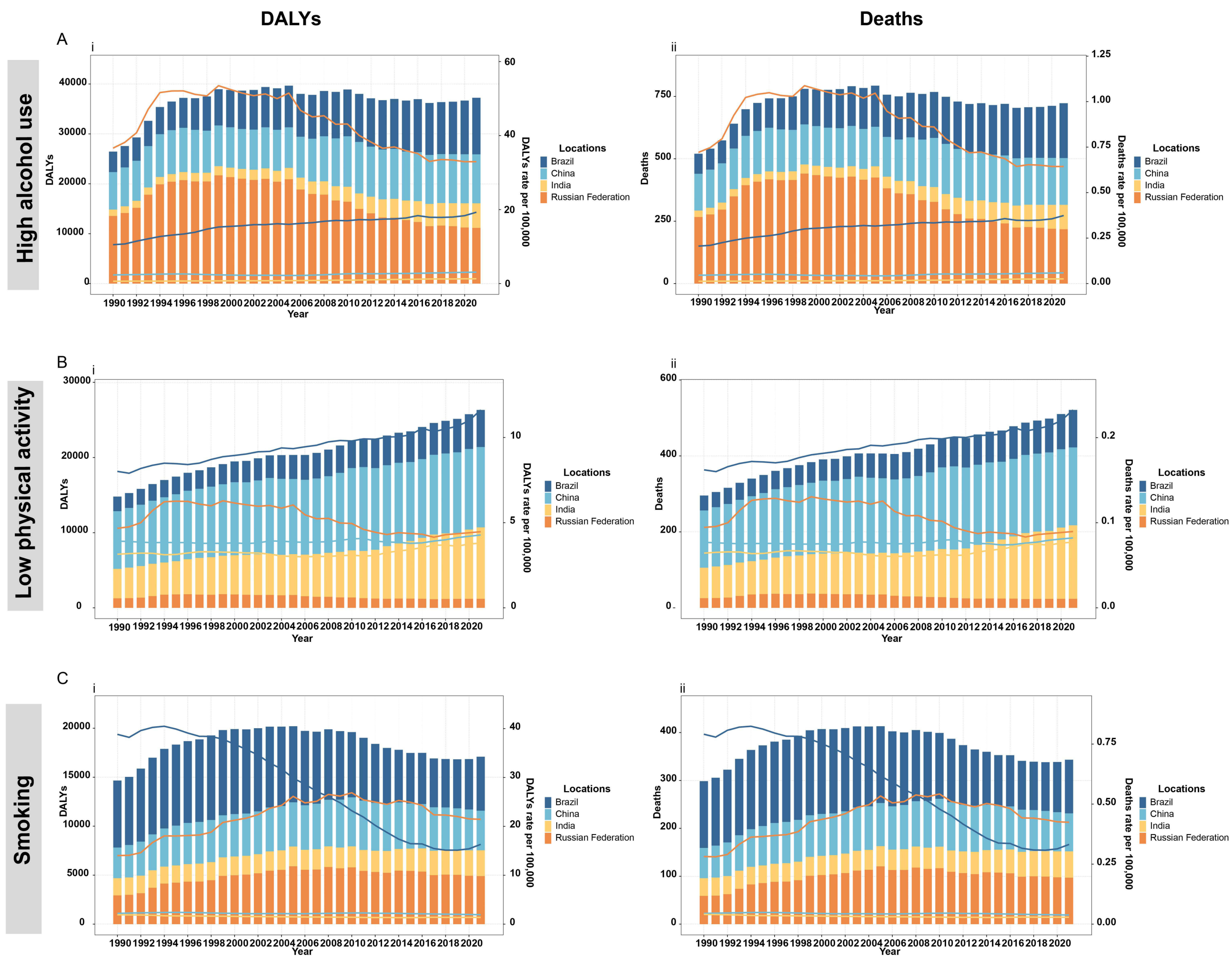


Figure 1 BRICS trends in number and age-standardized rates of DALYs, deaths, YLLs, YLDs (per 100,000, reproductive age) from 1990 to 2021. (**A**) High alcohol use (**B**) Low physical activity (**C**) Smoking i. BRICS trends in DALYs ii. BRICS trends in Deaths.

In the context of low physical activity, the impact of this factor on the ASDR in the four countries was not statistically significant overall. Brazil showed an upward trend, while the Russian Federation exhibited an initial rise followed by a decline (Figure 1B(i)).

Regarding smoking, smoking-related ASDR showed an overall increase in the Russian Federation, rising from 7.911 (95% UI: 5.105 to 11.672) to 10.806 (95% UI: 6.989 to 15.269), while the other three countries experienced declines. Brazil led with a 62% reduction (Figure 1C(i)).

From 1990 to 2021, trends in ASYR and ASYDR across the four BRICS countries showed both alignment and divergence, reflecting varied patterns of change for different risk factors. While ASYR and ASYDR often moved in the same direction within a given country for certain risks, notable exceptions emerged, with some countries exhibiting opposing trends for the same risk.

For high alcohol use, ASYR and ASYDR both increased in India and Brazil. In India, ASYR rose by 79%, from 0.733 (95% UI: 0.101 to 1.515) to 1.313 (95% UI: 0.508 to 2.555), while ASYDR surged by 165%, from 0.017 (95% UI: 0.002 to 0.036) to 0.045 (95% UI: 0.016 to 0.089). In Brazil, ASYR and ASYDR increased by 37% and 114%, respectively (Figures S1A(i) and (ii)). In contrast, China and the Russian Federation showed divergent trends: in China, ASYR decreased by 19%, from 2.74 (95% UI: 1.318 to 4.81) to 2.21 (95% UI: 0.978 to 4.188), while ASYDR more than doubled, from 0.104 (95% UI: 0.045 to 0.198) to 0.224 (95% UI: 0.093 to 0.44). In the Russian Federation, ASYR decreased by 32%, while ASYDR increased by 9% (Figures S1A(i) and (ii)).

In the context of low physical activity, this risk factor led to increased ASYDR across all four countries. China had the largest increase, more than doubling from 0.103 (95% UI: 0.013 to 0.277) to 0.229 (95% UI: 0.025 to 0.579), while Russian Federation showed the smallest, from 0.148 (95% UI: 0.017 to 0.383) to 0.177 (95% UI: 0.018 to 0.468). ASYR trends varied, with declines in China and Russian Federation, and modest increases (below 30%) in India and Brazil (Figures S1B(i) and (ii)).

Regarding smoking, the impact on ASYDR was mixed. Brazil declined from 0.664 (95% UI: 0.414 to 0.993) to 0.387 (95% UI: 0.231 to 0.604), while others increased. Russian Federation rose markedly from 0.331 (95% UI: 0.188 to 0.544) to 0.706 (95% UI: 0.4 to 1.141), and India's change was negligible from 0.024 (95% UI: 0.011 to 0.044) to 0.025 (95% UI: 0.01 to 0.05). For ASYR, only Russian Federation increased from 7.579 (95% UI: 4.886 to 11.17) to 10.1 (95% UI: 6.485 to 14.333), while others declined, with Brazil falling 62% from 21.129 (95% UI: 15.588 to 27.634) to 7.936 (95% UI: 5.429 to 10.959) (Figures S1C(i) and (ii)).

In contrast to the characteristics observed in women of reproductive age, a distinct phenomenon related to high BMI is noted across the female population of all ages. Among women of reproductive age, the ASMR, ASDR, ASYR, and ASYDR associated with high BMI are all negative, indicating a protective effect (Table 2) (Table S1–S3). Conversely, among females of all ages, the ASMR, ASDR, ASYR, and ASYDR for high BMI are all positive, with an upward trend observed across all BRICS countries. For the other three risk factors, the trends remain largely consistent, with only variations in the magnitude of effects among different countries (Figure S2).

Age Attribute

Age is a critical determinant of cancer burden. Therefore, we examined the age distribution patterns of female breast cancer among women aged 15–49 across the four BRICS nations. Among the BRICS countries, the proportion of women of reproductive age across the four health indicators showed a declining trend for all three risk factors. High alcohol consumption consistently accounted for the largest overall proportion, while low physical activity represented the smallest (Figure 2) (Figure S3).

Regarding high alcohol use, for DALYs, deaths, YLDs, and YLLs, the highest estimated annual EAPC was observed in the 25–29 age group in China and Brazil. In India, the highest EAPC for these indicators occurred in the 15–19 age group. While in the Russian Federation, the highest EAPC was observed in the 25–29 age group except YLLs. The lowest EAPC values for DALYs, deaths, YLDs, and YLLs were found in the 15–19 age group in China and the Russian Federation, with all EAPC values in the Russian Federation being negative except YLDs. In contrast, India and Brazil showed the lowest EAPC in the 45–49 age group, with positive EAPC values in both countries (Figures 3A and S4A).

In terms of low physical activity, for DALYs, deaths, YLDs, and YLLs, the highest EAPC was observed in the 25–29 age group in all countries except Brazil. In Brazil, the highest EAPC occurred in the 30–34 age group. The lowest EAPC values were found in the 45–49 age group in India and Brazil, whereas in China and the Russian Federation, the lowest EAPC was observed in the 35–39 and 40–44 age groups, respectively (Figures 3B and S4B).

Concerning smoking, the highest EAPC for DALYs, deaths, YLDs, and YLLs was observed in the 35–39 age group in the Russian Federation, 30–34 in India, 40–44 in China, and 45–49 in Brazil. In the Russian Federation, the lowest EAPC for all indicators except YLDs (which was lowest in the 30–34 age group) was found in the 45–49 age group, with all EAPC values being positive. In India, the lowest EAPC for all four indicators was in the 45–49 age group. In China, the lowest EAPC was in the 35–39 age group, and in Brazil, it was in the 40–44 age group, with all EAPC values in Brazil being negative (Figures 3C and S4C).

Although age-specific cancer distribution patterns may vary slightly from global trends, the overall trends remained largely consistent across these nations.

Forecasting ASDR, ASYR, ASYDR, and ASMR Between 2021 and 2030

In this study, data and time series were transformed and differenced to achieve stationarity. During testing, the model residuals showed no significant deviations, indicating a good fit between the selected models and the data.

From 2022 to 2030, in Brazil, DALYs, deaths, YLDs, and YLLs are projected to exhibit an upward trend under the influence of high alcohol use, low physical activity, and smoking, while a downward trend is expected for high BMI (Figure 4).

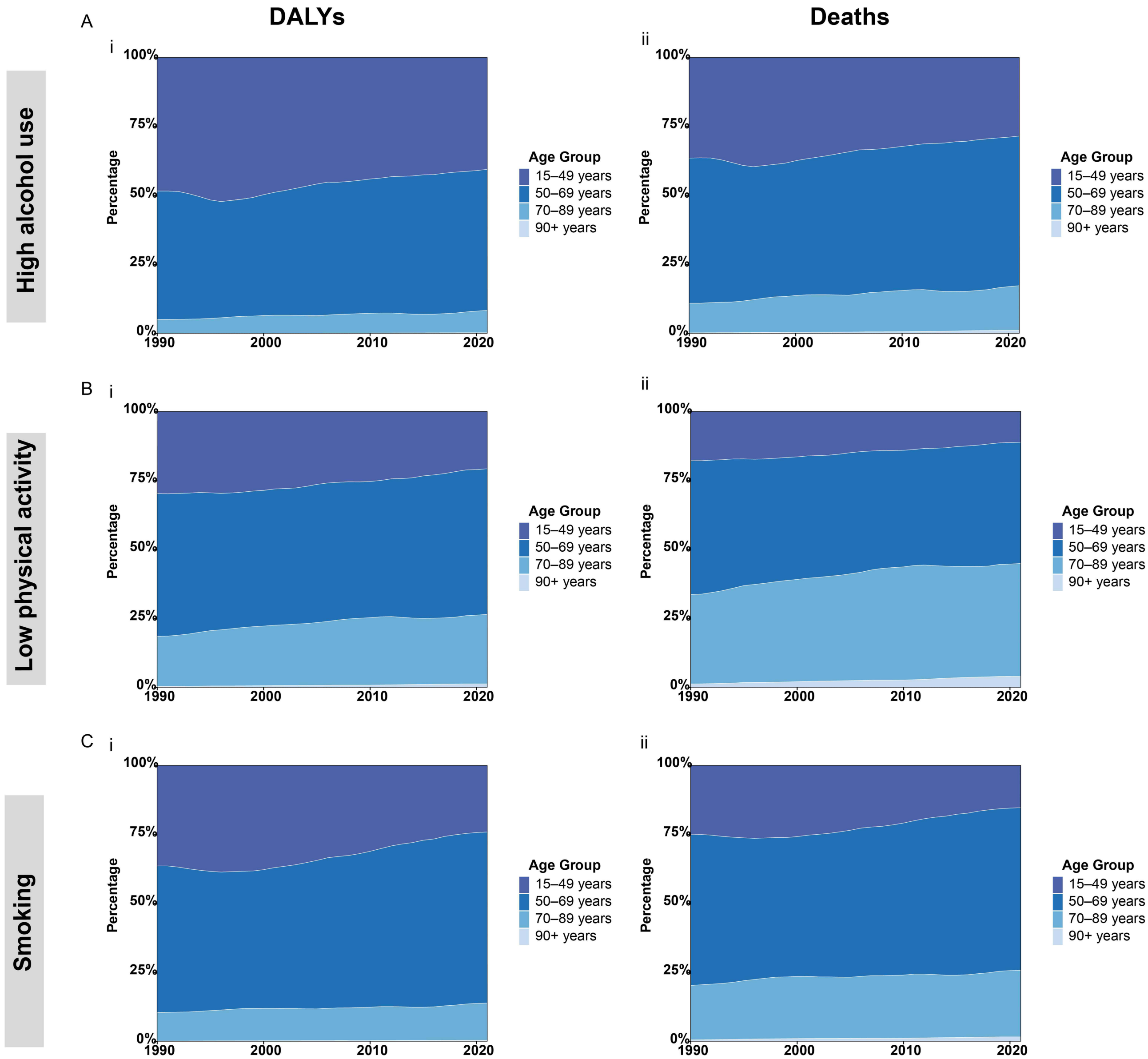


Figure 2 Age distribution proportions of age-standardized rates of DALYs, Deaths, YLLs, YLDs (per 100,000) from 1990 to 2021. (**A**) High alcohol use (**B**) Low physical activity (**C**) Smoking i. Proportions in DALYs ii. Proportions in Deaths.

In China, DALYs, deaths, and YLLs are predicted to increase under high alcohol use and low physical activity but decrease under smoking. For YLDs, all three risk factors—high alcohol use, low physical activity, and smoking—are projected to drive an upward trend (Figure 4).

In India, high BMI is projected to lead to a decline in DALYs, deaths, YLLs, and YLDs. Low physical activity is expected to result in a slight increase in YLDs, with minimal impact on DALYs, deaths, and YLLs. Smoking and high alcohol use are anticipated to have almost no effect on any of the metrics. (Figure 4).

In the Russian Federation, DALYs, deaths, and YLLs attributable to high alcohol use and smoking are projected to decline, while minimal change is anticipated for high BMI and low physical activity. Similarly, YLDs are projected to rise under high alcohol use and smoking but remain largely stable under high BMI and low physical activity (Figure 4).

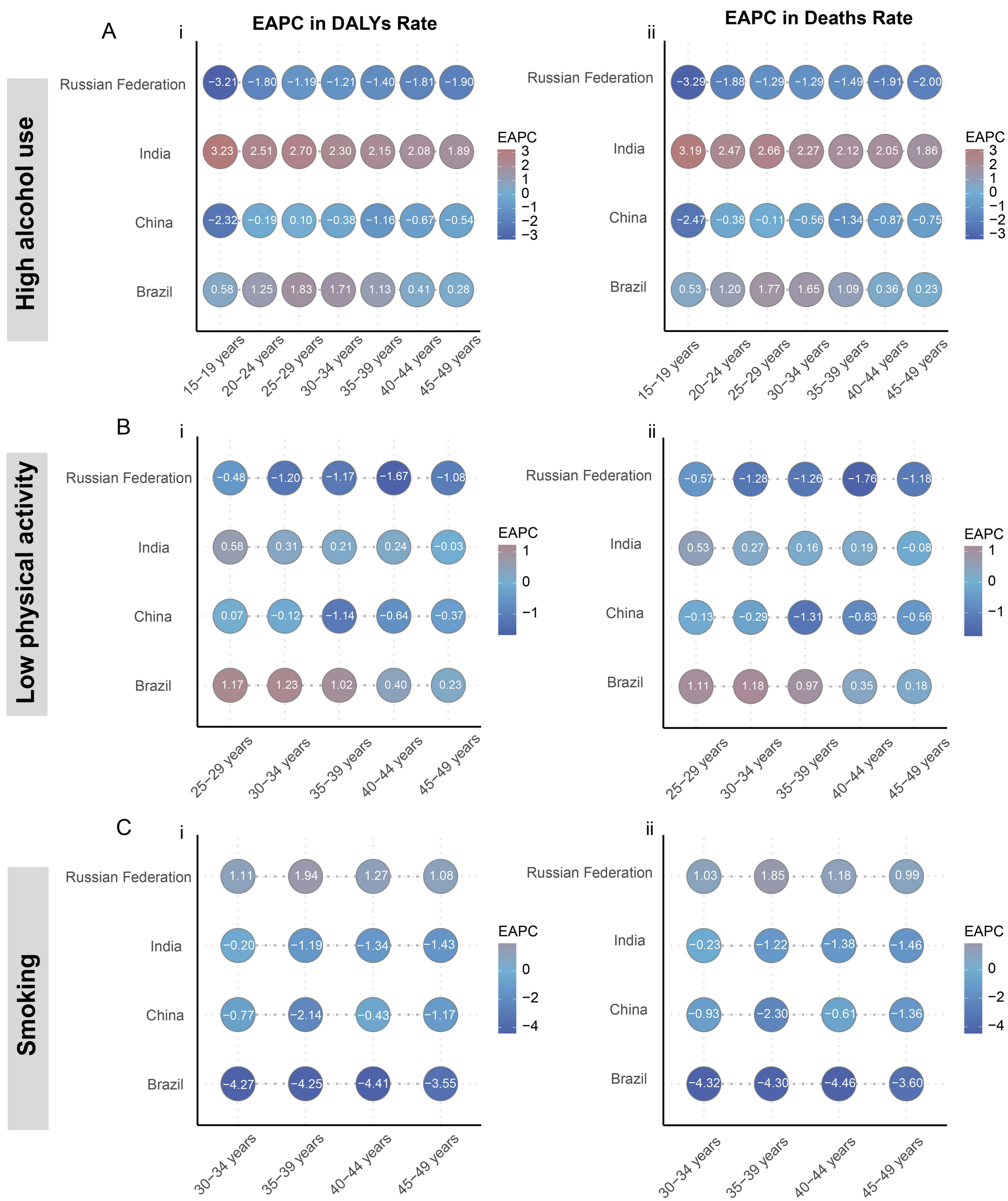


Figure 3 Age distribution for EAPCs of age-standardized rates of DALYs, Deaths, YLLs, YLDs (per 100,000, reproductive age) in 2021. (**A**) High alcohol use (**B**) Low physical activity (**C**) Smoking i. EAPC in DALYs Rate ii. EAPC in Deaths Rate.

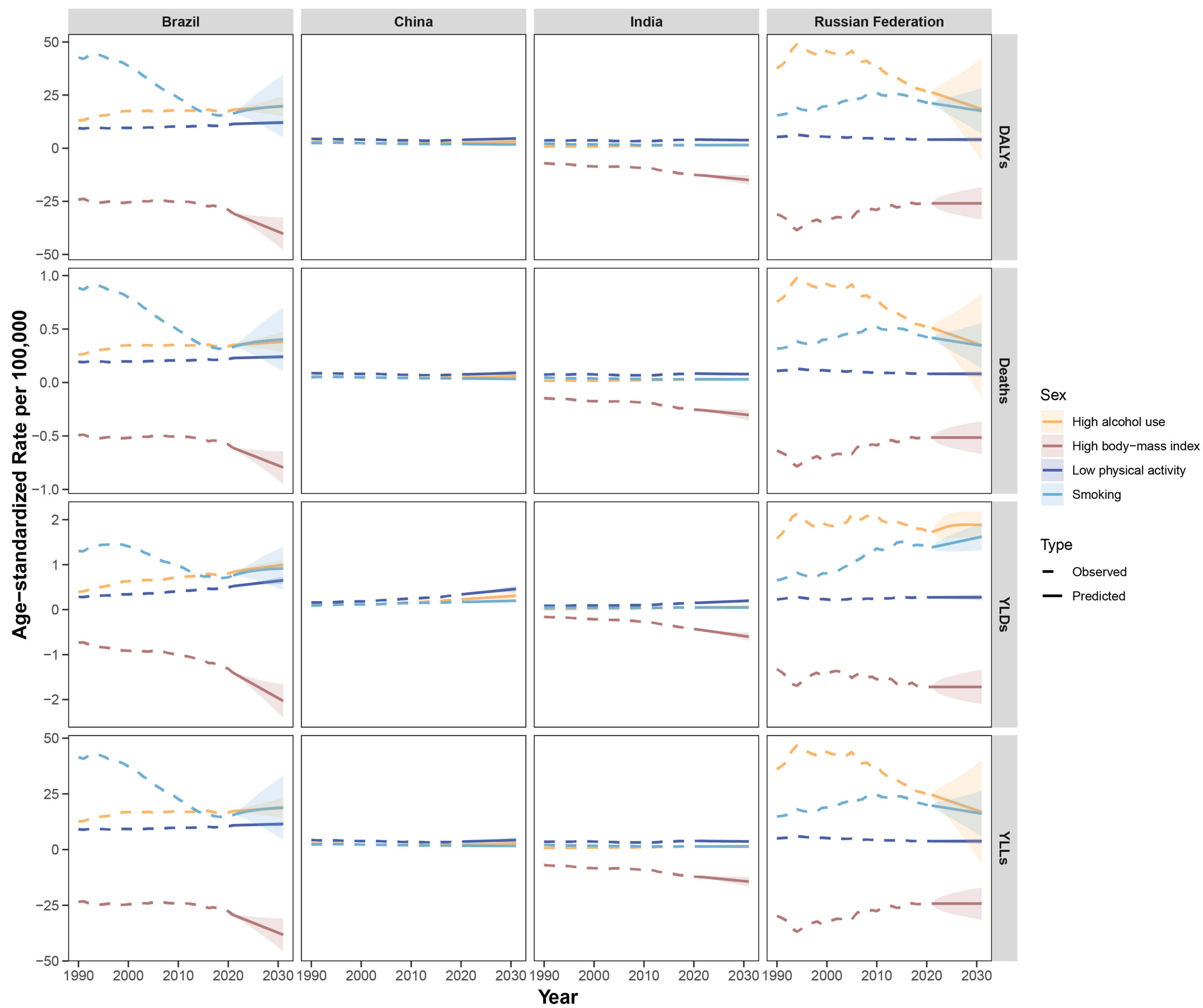


Figure 4 Age-standardized rates of Deaths, DALYs, YLLs, YLDs (per 100 000, reproductive age) in the BRICS, 1990–2030.

Causal Effects of Smoking, High Alcohol Use, and Low Physical Activity, BMI on Breast Cancer

To evaluate the potential causal relevance of the four risk factors identified in the descriptive burden analysis, we performed a two-sample MR analysis. In the MR analysis, 94 SNPs were extracted with high alcohol use as the exposure and breast cancer as the outcome. There was no evidence of heterogeneity (Q = 34.68461, p = 0.5311015) in the Cochran's Q test. No directional pleiotropy was found in the MR-Egger regression (intercept=0.001876219, se=0.001481644, p=0.208466615) and MR-PRESSO Global test (Rssobs=36.6976, p=0.548) (Table 3). The results

Table 3 Sensitivity Analysis of MR Analyses

Exposure	Heterogeneity Test		MR-Egger Pleiotropy Test		MR-PRESSO Global Pleiotropy Test	
	Q	p-value	Intercept	p-value	RSSobs	p-value
Smoking	118.9298	0.561763	−0.000429848	0.346000294	124.8055	0.491
Alcohol Use disorder	34.68461	0.531102	0.001876219	0.208466615	36.6976	0.548
Low Physical Activity	48.43276	0.169265	−0.000463666	0.789729413	50.7468	0.228
BMI	22.08181	0.055848	0.001014552	0.07595444	25.50644	0.08

demonstrated: IVW (OR=1.03, 95% CI=1.03–1.03, P<0.01), MR-egger (OR=1.00, 95% CI=0.99–1.00, P=0.809), weighted median (OR=1.03, 95% CI=1.03–1.04, P<0.01), indicating a significant association between high alcohol use and breast cancer (Figures 5A and S5A). The scatter plot of SNP effect sizes for high alcohol use and breast cancer is presented in Figure S6. Leave-one-out analysis revealed no significant outliers (Figure S10). These findings support a genetic relationship between high alcohol use and breast cancer.

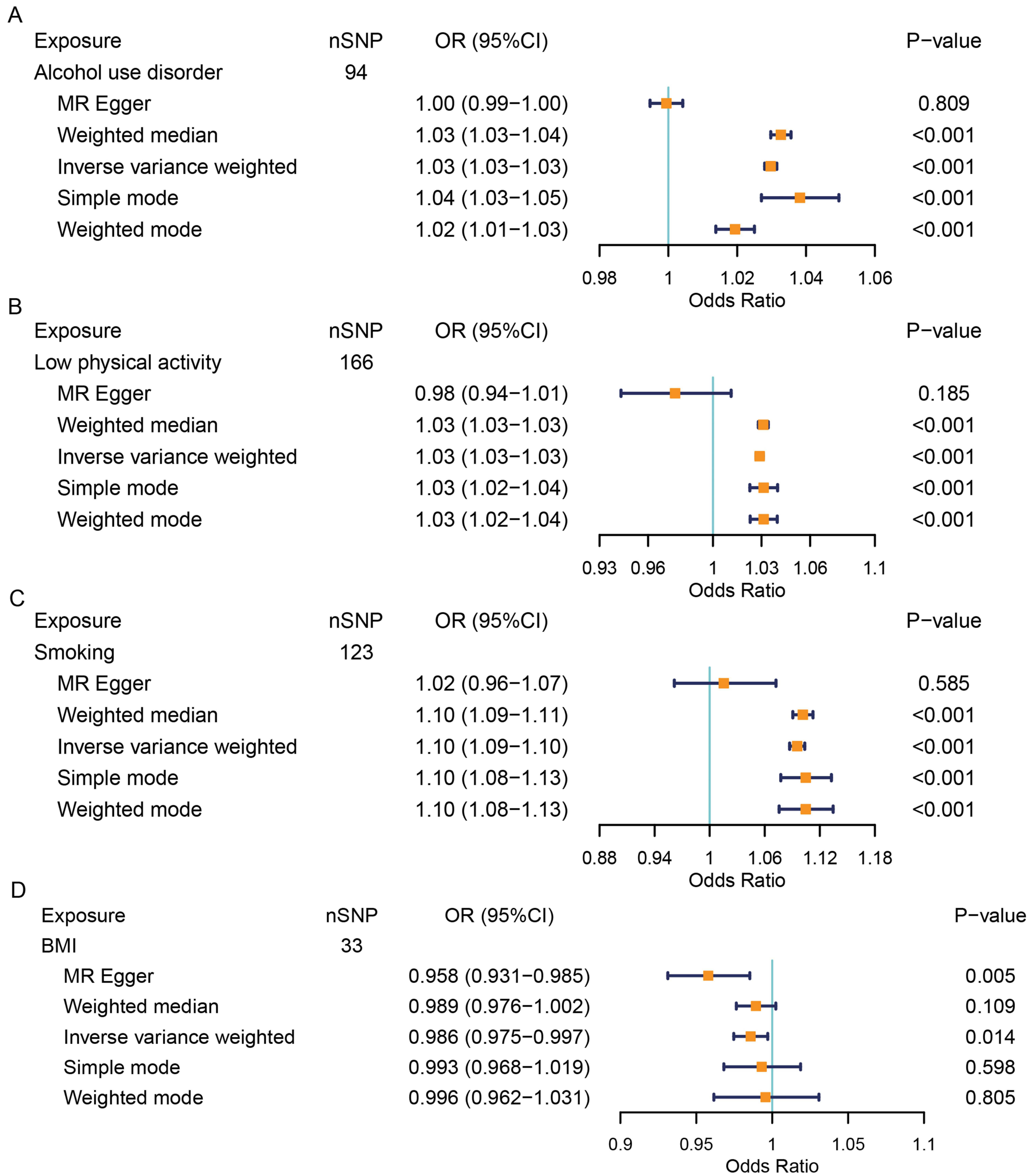


Figure 5 Presents a forest plot illustrating the MR estimates concerning the association between risk factors and breast cancer. (**A**) Alcohol use disorder (**B**) Low physical activity (**C**) Smoking (**D**) BMI.

The Mendelian randomization analysis for low physical activity extracted 166 SNPs with low physical activity as the exposure and breast cancer as the outcome. There was no evidence of heterogeneity (Q = 48.43276, p = 0.1692652) in the Cochran's Q test. No directional pleiotropy was found in the MR-Egger regression (intercept=−0.000463666, se=0.001735814, p=0.789729413) and MR-PRESSO Global test (Rssobs=50.7468, p=0.228) (Table 3). The results showed: IVW (OR=1.03, 95% CI=1.03–1.03, P<0.01), MR-egger (OR=0.98, 95% CI=0.94–1.01, P=0.185), weighted median (OR=1.03, 95% CI=1.03–1.03, P<0.01), demonstrating a significant association between low physical activity and breast cancer (Figures 5B and S5B). The scatter plot of SNP effect sizes for low physical activity and breast cancer is displayed in Figure S7. Leave-one-out analysis showed no significant outliers (Figure S11). Our findings support a genetic relationship between low physical activity and breast cancer.

For smoking, the MR analysis extracted 123 SNPs, with smoking as the exposure and breast cancer as the outcome. There was no evidence of heterogeneity (Q = 118.9298, p = 0.5617626) in the Cochran's Q test. No directional pleiotropy was found in the MR-Egger regression (intercept=−0.000429848, se=0.000454382, p=0.346000294) and MR-PRESSO Global test (Rssobs=124.8055, p=0.491) (Table 3). The results showed: IVW (OR=1.10, 95% CI=1.09–1.10, P<0.01), MR-egger (OR=1.02, 95% CI=0.96–1.07, P=0.585), weighted median (OR=1.10, 95% CI=1.09–1.11, P<0.01), demonstrating a significant correlation between smoking and breast cancer (Figure 5C) (Figure S5C). The scatter plot of SNP effect sizes for smoking and breast cancer is shown in Figure S8. Leave-one-out analysis results showed no significant outliers (Figure S12). Our findings support a genetic relationship between smoking and breast cancer.

Regarding high BMI, the MR analysis extracted 33 SNPs with high BMI as the exposure and breast cancer as the outcome. There was no evidence of heterogeneity (Q = 22.08181, p = 0.0558475) in the Cochran's Q test. No directional pleiotropy was found in the MR-Egger regression (intercept=0.001014552, se=0.000554252, p=0.07595444) and MR-PRESSO Global test (Rssobs=25.50644, p=0.08) (Table 3). The results showed: IVW (OR=0.986, 95% CI=0.975–0.997, P=0.014), MR-egger (OR=0.958, 95% CI=0.931–0.985, P<0.01), weighted median (OR=0.989, 95% CI=0.976–1.002, P=0.109), demonstrating a significant association between high BMI and breast cancer (Figures 5D and S5D). The scatter plot of SNP effect sizes for high BMI and breast cancer is displayed in Figure S9. Leave-one-out analysis showed no significant outliers (Figure S13). Our findings support a genetic relationship between high BMI and breast cancer.

Synthesis of Epidemiological Burden and Genetic Evidence

The parallel application of GBD and MR analyses provides complementary lenses on the role of modifiable risk factors. The MR findings offer genetic support for the potential causal involvement of smoking, high alcohol use, and low physical activity in breast cancer etiology. When viewed alongside the GBD-derived burden estimates, a convergent pattern emerges for specific country-risk pairs: the significant genetic association for smoking aligns with its prominent and increasing attributable burden in the Russian Federation, and the genetic signal for high alcohol use corresponds with its substantial and growing burden in Brazil and India. This convergence suggests that the population-level burden attributed to these factors in these countries is consistent with a potential causal biological mechanism.

The case of high BMI presents a more complex picture. The GBD analysis suggested a protective population-attributable fraction for high BMI in reproductive-age women. In contrast, the MR analysis yielded a negligible causal estimate (OR=0.986) with a confidence interval barely excluding the null. This discrepancy highlights the distinct perspectives of these methods: the GBD association may encapsulate complex life-course or confounding pathways, whereas the MR analysis, while controlling for confounding, may be limited in capturing age-specific effects or the relevant biological exposure window through the available genetic instruments. Therefore, the relationship between high BMI and premenopausal breast cancer risk remains an area requiring clarification and should be interpreted with caution.

Collectively, this synthesis does not posit that MR "explains" the GBD patterns, but rather that the alignment of evidence from independent methodological approaches strengthens the rationale for prioritizing specific risk factors for targeted public health intervention. The framework employed here, juxtaposing population-level attribution with genetic causal evidence, serves to triage and reinforce etiological hypotheses, particularly highlighting instances where population disease patterns are congruent with a plausible causal basis.

Discussion

Principal Findings and Global Implications

This study provides, to our knowledge, the first comprehensive analysis of the breast cancer burden attributable to four key modifiable risk factors, namely smoking, high alcohol use, high BMI, and low physical activity, among women of reproductive age in BRICS nations from 1990 to 2021, utilizing the latest data from the GBD 2021 study. Our analysis, further strengthened by MR which supports a potential causal role for high alcohol use, smoking, and low physical activity, reveals substantial heterogeneity in the breast cancer burden across these countries. This heterogeneity is closely linked to the varying prevalence and temporal trends of specific risk factors. For instance, the increasing burden in Brazil and India is primarily driven by a sharp rise in alcohol-attributable and low physical activity-related metrics, whereas the Russian Federation faces a growing threat from smoking. In contrast, China demonstrates improvements in several indicators, potentially reflecting advancements in public health interventions and healthcare systems. A notable and counterintuitive finding was the consistent inverse association observed between high BMI and breast cancer burden in this premenopausal cohort, challenging conventional wisdom and underscoring the complex, age-dependent nature of this risk factor. These population-level patterns gain further significance when considered alongside potential underlying biological mechanisms. The causal relationships suggested by MR imply that these risk factors may directly influence breast cancer pathogenesis through specific molecular pathways, such as DNA damage,[17] hormonal modulation,[18] and chronic inflammation,[19] which can interact with the individual's genetic background and tumor molecular subtype.

These findings carry significant global implications for cancer control strategies. The distinct risk factor profiles identified in each BRICS country highlight the inefficiency of a "one-size-fits-all" approach to breast cancer prevention. Instead, our results argue for a shift toward "precision public health", where limited resources are strategically allocated to target the dominant, modifiable risk factors within specific national contexts. For example, prioritizing alcohol control and promoting physical activity are likely to yield the greatest returns in Brazil and India, while intensifying tobacco control remains the most urgent priority for the Russian Federation. The projections to 2030 further underscore the necessity of these tailored interventions, as current trends are expected to persist, potentially widening the existing disparities in breast cancer burden among these major economies. By moving beyond generalized strategies to implement targeted, evidence-based policies, BRICS nations can more effectively mitigate the future impact of breast cancer and serve as a model for other regions undergoing similar epidemiological transitions.

Country-Specific Priorities Across the Development Spectrum

The significant heterogeneity in risk factor profiles revealed by our analysis underscores the critical need for tailored, country-specific public health strategies. A "one-size-fits-all" approach is inefficient; instead, resource allocation must be strategically aligned with the dominant, modifiable risk factors within each national context to maximize the cost-effectiveness of breast cancer prevention.

In Brazil and India, which are characterized by a rapidly rising breast cancer burden, public health priorities should be sharply focused on curbing the escalating trends attributable to high alcohol use and low physical activity. For these middle-income nations, evidence-based alcohol control policies are paramount; these include increasing excise taxes, restricting marketing and availability, and implementing public awareness campaigns about the link between alcohol and cancer.[20,21] Public health messaging can be enhanced by explaining the biological rationale, such as alcohol's metabolism to acetaldehyde (a mutagen)[22] and its role in elevating estrogen levels,[23] which are particularly relevant for hormone receptor-positive breast cancer subtypes. Concurrently, promoting physical activity requires creating supportive social and built environments. This can be achieved through urban planning that prioritizes walkability and access to green spaces, community-based fitness programs,[24] and integrating physical activity promotion into primary healthcare services.[25] Promoting physical activity can be framed as a strategy to mitigate chronic inflammation and insulin resistance, which are key pathways linking inactivity to cancer risk.[26] These combined efforts represent the most direct and impactful strategy to address the surge in alcohol and inactivity-related metrics.

The situation in the Russian Federation presents a distinct challenge, marked by a persistently high and increasing burden linked to smoking, even as its alcohol-attributable burden has declined. This divergence highlights tobacco control as the most urgent and immediate priority. Strengthening existing measures through comprehensive smoke-free legislation, increasing tobacco taxes, mandating plain packaging, and enhancing the accessibility and funding of smoking cessation services are essential steps.[27,28] Tobacco control efforts can be coupled with education on the direct genotoxic effects of tobacco carcinogens, which cause characteristic DNA damage and may influence tumor mutational profiles.[29] The nation's documented success in reducing alcohol-related burden could serve as a valuable model,[30] demonstrating the potential effectiveness of robust, well-enforced public health regulations when applied to tobacco.

China demonstrates a more complex, transitional burden profile, with improvements in several indicators likely reflecting advancements in its healthcare system. The policy focus here should be twofold: first, to consolidate and disseminate the successful tobacco control experiences from specific regions nationwide to ensure equitable benefits. Second, proactive measures are needed to counteract the emerging threat of population-level physical inactivity driven by rapid urbanization and lifestyle changes.[31] Furthermore, the health system must adapt to the shifting nature of the burden, as indicated by rising YLDs, by strengthening chronic disease management and survivorship care to effectively manage the increasing prevalence of women living with breast cancer.[32]

This stratified approach, moving from generalized recommendations to targeted policy packages, ensures that interventions are not only evidence-based but also contextually appropriate and feasible within the specific socio-economic and healthcare landscapes of each BRICS nation.

Towards Integrated Risk Factor Management

While the identification of country-specific priorities is crucial, our findings advocate for a paradigm shift from isolated, single-factor interventions toward an integrated, life-course approach to risk factor management. The distinct pathophysiological pathways of the four risk factors, such as alcohol's role in elevating estrogen levels and inducing oxidative stress, smoking's direct DNA damage, carcinogen exposure, hormone receptor status,[33] genetic susceptibility,[34] and hormonal levels[35] and physical inactivity's contribution to chronic inflammation[36] and insulin resistance,[37] underscore that these factors do not operate in isolation, and high BMI's protective effect before menopause[38] and increased risk after menopause through estrogen synthesis, DNA damage, and metabolic dysfunction, underscore that these factors do not operate in isolation.[39,40] Importantly, the effects of these exposures are likely modified by tumor heterogeneity.[41] For instance, the impact of alcohol and BMI may vary by hormone receptor status,[42] while smoking has been differentially associated with certain molecular subtypes.[43] Our MR findings, which reflect average population-level genetic susceptibility, themselves aggregate over a heterogeneous background of individual genetic risk, which can be shaped by gene-environment interactions and specific germline mutational profiles, as seen in subsets like triple-negative breast cancer.[44] A synergistic strategy that concurrently addresses multiple risks is likely to yield greater and more sustainable reductions in breast cancer burden.

This integrated approach should be embedded within a "life-course" framework, where breast cancer prevention is woven into health promotion activities across key stages of a woman's life. During adolescence and young adulthood, public health efforts should focus on school-based education that emphasizes the long-term cancer risks of smoking and alcohol initiation, while promoting the establishment of lifelong healthy habits, including regular physical activity.[45] For reproductive-age women, personalized risk assessment and counseling on modifiable factors should be integrated into routine healthcare touchpoints, such as prenatal and postnatal care, well-woman exams, and family planning services.[46–48] In the perimenopausal and postmenopausal periods, a critical window for risk reduction, targeted messaging and interventions can be effectively delivered within chronic disease management programs, emphasizing the compounded benefits of healthy lifestyles for both cardiovascular and cancer prevention.[49,50]

Therefore, our study supports a transition from fragmented interventions to a cohesive, life-course-oriented model of women's health. In this model, breast cancer prevention is not a standalone goal but is systematically embedded within reproductive health services, chronic disease management plans, and broader public health policies aimed at creating healthier environments. By adopting this holistic perspective, BRICS nations can move beyond merely mitigating individual risks towards fostering overall well-being and achieving sustainable, long-term cancer control.

https://doi.org/10.2147/IJWH.S606547

Future Directions

A notable and complex finding was the consistent inverse association between high BMI and breast cancer burden in premenopausal women—a result that aligns with several cohort studies[38] but contrasts with the well-established elevated risk in postmenopausal populations. This underscores the age-dependent duality of BMI's role and cautions against oversimplified public health messaging. Equity-focused strategies should emphasize lifelong weight maintenance rather than short-term reduction, and avoid inadvertently promoting weight gain in younger women.[51] At the same time, policy efforts must address the adverse metabolic and cardiovascular consequences of obesity, even as its relationship with premenopausal breast cancer appears protective.[52] Future research should investigate whether this association varies by breast cancer subtype and explore the underlying molecular mechanisms, such as differences in adipokine profiles or estrogen metabolism, that may explain the age-specific effect.[53,54]

From an equity perspective, the significant disparities in risk-factor profiles and data quality across BRICS nations reflect underlying differences in healthcare infrastructure, regulatory enforcement, and public health investment. Lower-resource settings (eg, India and Brazil) face compounded challenges from rapid urbanization, weak regulatory implementation, and limited health literacy, which amplify the burden from alcohol use and physical inactivity.[55,56] Future interventions should not only be targeted but also designed with equity at their core—ensuring that screening, counseling, and lifestyle programs reach vulnerable subgroups, including rural, low-income, and less-educated populations.[57] Furthermore, the concept of "precision public health" can be expanded in the future to include biomarker-driven risk stratification. Integrating population-level exposure data with individual molecular profiling, such as germline genetic risk scores or emerging liquid biopsy markers, could help identify high-risk subgroups within these populations for intensified prevention, moving towards a more biologically-informed tiered intervention strategy.[58]

In summary, advancing breast cancer control in these diverse economies will require a dual approach: (1) investing in robust, disaggregated data systems to address current monitoring gaps, and (2) embedding equity-focused, life-course-oriented interventions within broader primary care and health promotion platforms. By confronting these limitations directly, researchers and policymakers can collaboratively foster more resilient and inclusive cancer prevention strategies for women across the BRICS nations.

Limitations

While this study provides a comprehensive assessment of the breast cancer burden attributable to modifiable risk factors across BRICS nations, several limitations should be acknowledged. First, data availability and quality varied substantially between countries. The scarcity of high-quality, population-based cancer registries in certain regions, particularly for younger age groups, constrained the precision of our estimates. For example, data on high BMI were incomplete for adolescents (ages 15–19), and low physical activity records were sparse among women aged 15–29. Furthermore, in the case of China, relevant data pertaining to high BMI were notably lacking. Additionally, for women of reproductive age in BRICS countries, the available data related to high BMI consistently yields negative values, which precludes the calculation of the corresponding age-standardized trend, EAPC, and the proportion of cases within specific age groups. In addition, smoking-related estimates excluded individuals aged 15–20, and no GBD 2021 data were available on emerging risks such as e-cigarette use, despite growing evidence of its potential role in breast cancer progression. These gaps highlight the urgent need for strengthened cancer surveillance systems and standardized risk-factor monitoring across BRICS countries, which should be prioritized within national health information system strengthening efforts.

Second, our analysis was limited to four Level 2 risk factors within the GBD framework. While these are important modifiable exposures, we did not incorporate other clinical and socioeconomic determinants, for example, reproductive history, hormone therapy use, genetic predisposition, and access to screening. The lack of subtype-specific data, such as hormone receptor status, also prevented an investigation of how risk factors might influence distinct biological profiles of breast cancer. This limits our ability to link the observed population-level burden to specific molecular subtypes or genomic alterations, which is a key direction for connecting epidemiology with cancer biology. Future research that combines molecular characteristics with population-level burden metrics could help clarify etiological heterogeneity and support more precisely targeted prevention efforts.

Third, several methodological constraints warrant consideration. The ecological study design, which relies on aggregated population-level data, limits causal inference at the individual level and is susceptible to ecological fallacy. While our Mendelian Randomization analysis complements this by providing genetic evidence for causality at the individual level, the GBD-based comparative assessments remain correlational. Furthermore, the ARIMA projections for 2030 rely on the assumption that past trends will continue linearly, which may not hold given potential non-linear shifts in socioeconomic factors, policies, or health behaviors. Lastly, although the GBD framework applies standardized estimation methods, underlying variability in the quality, coverage, and measurement of source data across BRICS countries may affect the precision of cross-national comparisons.

Despite these limitations, our study, strengthened by MR analysis which supports a potential causal role for alcohol use, smoking, and low physical activity, provides valuable insights into the breast cancer burden among 15–49-year-old women in BRICS countries. This genetic evidence significantly bolsters the credibility of the observed epidemiological associations and establishes an important foundation for future research and policy development in breast cancer prevention and control. We explicitly acknowledge these constraints to encourage appropriate interpretation of our findings and to identify key areas for methodological improvement in subsequent studies.

Conclusion

Conclusively, our study reveals substantial heterogeneity in the breast cancer burden attributable to four modifiable risk factors among reproductive-aged women in BRICS countries from 1990 to 2021. A key finding is the consistent protective association of high BMI in this premenopausal cohort, contrasting with its established risk in postmenopausal women, highlighting the complex, age-dependent nature of this factor. MR analysis supports potential causal roles for high alcohol use, smoking, and low physical activity. The distinct risk factor profiles across nations underscore the inefficiency of a "one-size-fits-all" prevention approach. These findings advocate for a strategic shift toward "precision public health", where resource allocation is tailored to dominant national risk factors, and for integrating breast cancer prevention into a broader, life-course-oriented women's health framework to achieve sustainable cancer control.

Data Sharing Statement

Data used in the analyses can be obtained from the Global Health Data Exchange Global Burden of Disease Results Tool (https://ghdx.healthdata.org/gbd-results-tool). And the data used in this study can be downloaded from the GBD database or obtained from the corresponding author Xiaobo Zhao.

Ethics Approval and Consent to Participate

This study constitutes a secondary analysis of fully de-identified, publicly available macro-level epidemiological and genetic summary data. The research involved no direct involvement of human participants, no intervention, and no collection of new personal identifiable information. Therefore, in accordance with Items 1 and 2 of Article 32 of the "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects" (effective February 18, 2023, China), this study was exempt from requiring separate approval from an institutional review board (IRB) or ethics committee.

Acknowledgment

We highly appreciate the work of the Global Burden of Disease Study 2021 collaborators for providing the most comprehensive analysis of different diseases on a global scale.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work is financially supported by the National Natural Science Foundation of China grant number (82201853, 82201811). Natural Science Foundation of Jiangsu Province project number (BK20220172, BK20220173). Research Project of Sichuan Provincial Research Center for the Development of Primary Health Care (No: SWFZ24-W-20). Nanchong Science and Technology Project (Grant No. 22YYJCYJ0088).

Disclosure

The authors declare no competing interests in this work.

References

1. Han X, Ren C, Lu C, et al. Phosphorylation of USP27X by PIM2 promotes glycolysis and breast cancer progression via deubiquitylation of MYC. *Oncogene*. 2024;43(33):2493–2503. doi:10.1038/s41388-024-03097-y
2. Sonkin D, Thomas A, Teicher BA. Cancer treatments: past, present, and future. *Cancer Genet*. 2024;286-287:18–24. doi:10.1016/j.cancergen.2024.06.002
3. Jiang X, Pestoni G, Vinci L, et al. Cancer cases attributable to modifiable lifestyle risk factors in Switzerland between 2015 and 2019. *Int J Cancer*. 2024;154(7):1221–1234. doi:10.1002/ijc.34806
4. Bray F, Laversanne M, Sung H, 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(3):229–263. doi:10.3322/caac.21834
5. Li T, Zhang H, Lian M, et al. Global status and attributable risk factors of breast, cervical, ovarian, and uterine cancers from 1990 to 2021. *J Hematol Oncol*. 2025;18(1):5. doi:10.1186/s13045-025-01660-y
6. Rache B, Rocha R, Medeiros LAD, et al. Transition towards cancer mortality predominance over cardiovascular disease mortality in Brazil, 2000-2019: a population-based study. *Lancet Reg Health Am*. 2024;39:100904. doi:10.1016/j.lana.2024.100904
7. Mubarik S, Malik SS, Yanran Z, et al. Estimating disparities in breast cancer screening programs towards mortality, case fatality, and DALYs across BRICS-plus. *BMC Med*. 2023;21(1):299. doi:10.1186/s12916-023-03004-4
8. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol*. 2017;3(4):524–548. doi:10.1001/jamaoncol.2016.5688
9. Wu Z, Xia F, Lin R. Global burden of cancer and associated risk factors in 204 countries and territories, 1980-2021: a systematic analysis for the GBD 2021. *J Hematol Oncol*. 2024;17(1):119. doi:10.1186/s13045-024-01640-8
10. Shadmani FK, Abedi Gheshlaghi L, Jafari-Khounigh A, Rezakhani L, Khazaei M. Burden and mortality of breast cancer attributed to diabetes and smoking in women: a secondary analysis based on global burden of disease 2019 in North Africa and the Middle East. *BMJ Open*. 2025;15(1):e087178. doi:10.1136/bmjopen-2024-087178
11. Yu S, Cai X, Wang X, Lin X, Cai S. Disease burden of breast cancer and risk factors in Europe 44 countries, 1990-2019: findings of the global burden of disease study 2019. *Front Endocrinol*. 2024;15:1405204. doi:10.3389/fendo.2024.1405204
12. Igbokwe KK. Comparative examination of breast cancer burden in sub-Saharan Africa, 1990-2019: estimates from Global Burden of Disease 2019 study. *BMJ Open*. 2024;14(3):e082492. doi:10.1136/bmjopen-2023-082492
13. Guo Q, Lu Y, Liu W, Lan G, Lan T. The global, regional, and national disease burden of breast cancer attributable to tobacco from 1990 to 2019: a global burden of disease study. *BMC Public Health*. 2024;24(1):107. doi:10.1186/s12889-023-17405-w
14. Qian D, Hong W, Li S, et al. Trends in the global, national, and regional burden of breast cancer among adolescents and young adults from 1990 to 2021: analyses of the 2021 global burden of disease study. *Breast*. 2025;82:104486. doi:10.1016/j.breast.2025.104486
15. Ferrari AJ, Santomauro DF, Aali A, et al. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403(10440):2133–2161. doi:10.1016/S0140-6736(24)00757-8
16. Cai J, Li X, Wu S, et al. Assessing the causal association between human blood metabolites and the risk of epilepsy. *J Transl Med*. 2022;20(1):437. doi:10.1186/s12967-022-03648-5
17. Cybulski C, Zamani N, Kluźniak W, et al. Variants in ATRIP are associated with breast cancer susceptibility in the Polish population and UK Biobank. *Am J Hum Genet*. 2023;110(4):648–662. doi:10.1016/j.ajhg.2023.03.002
18. Nounu A, Kar SP, Relton CL, Richmond RC. Sex steroid hormones and risk of breast cancer: a two-sample Mendelian randomization study. *Breast Cancer Res*. 2022;24(1):66. doi:10.1186/s13058-022-01553-9
19. Chen Y, Zheng Z, Wang J, Huang X, Xie L. Genetically predicted Caspase 8 levels mediates the causal association between CD4+ T cell and breast cancer. *Front Immunol*. 2024;15:1410994. doi:10.3389/fimmu.2024.1410994
20. Grigg J, Manning V, Lockie D, et al. A brief intervention for improving alcohol literacy and reducing harmful alcohol use by women attending a breast screening service: a randomised controlled trial. *Med J Aust*. 2023;218(11):511–519. doi:10.5694/mja2.51991
21. Sardu C, Angius F, Contu P, et al. Raising awareness of alcohol as a modifiable risk factor for breast cancer: a randomized controlled trial comparing the efficacy of accessing an interactive website with a non-interactive website. *Breast*. 2025;79:103868. doi:10.1016/j.breast.2024.103868
22. Zhang Y, Zheng DW, Li CX, et al. Temulence therapy to orthotopic colorectal tumor via oral administration of fungi-based acetaldehyde generator. *Small Meth*. 2022;6(1):e2100951. doi:10.1002/smtd.202100951
23. Tin Tin S, Smith-Byrne K, Ferrari P, et al. Alcohol intake and endogenous sex hormones in women: meta-analysis of cohort studies and Mendelian randomization. *Cancer*. 2024;130(19):3375–3386. doi:10.1002/cncr.35391
24. Yin X, Zhang T, Zhang Y, Man J, Yang X, Lu M. The global, regional, and national disease burden of breast cancer attributable to low physical activity from 1990 to 2019: an analysis of the Global Burden of Disease Study 2019. *Int J Behav Nutr Phys Act*. 2022;19(1):42. doi:10.1186/s12966-022-01283-3
25. Zhou W, Shang S, Cho Y. Associations of wearable activity tracker use with physical activity and health outcomes in patients with cancer: findings from a population-based survey study. *J Med Internet Res*. 2024;26:e51291. doi:10.2196/51291

26. Jin Y, Yang Z, Li Z, et al. Physical activity decreases cancer burden by alleviating immunosenescence-related inflammation and improving overall immunity. *Cell Rep Med*. 2025;6(12):102484. doi:10.1016/j.xcrm.2025.102484
27. Akter S, Rahman MM, Rouyard T, Aktar S, Nsashiyi RS, Nakamura R. A systematic review and network meta-analysis of population-level interventions to tackle smoking behaviour. *Nat Hum Behav*. 2024;8(12):2367–2391. doi:10.1038/s41562-024-02002-7
28. Hebbar PB, Dsouza V, Bhojani U, et al. How do tobacco control policies work in low-income and middle-income countries? A realist synthesis. *BMJ Glob Health*. 2022;7(11). doi:10.1136/bmjgh-2022-008859
29. Tang MS, Lee HW, Weng MW, et al. DNA damage, DNA repair and carcinogenicity: tobacco smoke versus electronic cigarette aerosol. *Mutat Res Rev Mutat Res*. 2022;789:108409. doi:10.1016/j.mrrev.2021.108409
30. Neufeld M, Rehm J, Bunova A, et al. Validation of a screening test for alcohol use, the Russian Federation. *Bull World Health Organ*. 2021;99(7):496–505. doi:10.2471/BLT.20.273227
31. Sitjar PHS, Tan SY, Wong M, et al. Combined aerobic and strength exercise training on biological ageing in Singaporean breast cancer patients: protocol for the breast cancer exercise intervention (BREXINT) pilot study. *Geroscience*. 2024;46(6):6029–6038. doi:10.1007/s11357-024-01145-9
32. Jung W, Cho IY, Jung J, et al. Changes in physical activity and cardiovascular disease risk in cancer survivors: a nationwide cohort study. *JACC CardioOncol*. 2024;6(6):879–889. doi:10.1016/j.jaccao.2024.09.013
33. hua TJ, Li Z, Shi J, et al. Passive smoking exposure from partners as a risk factor for ER+/PR+ double positive breast cancer in never-smoking Chinese urban women: a hospital-based matched case control study. *PLoS One*. 2014;9(5):e97498. doi:10.1371/journal.pone.0097498
34. Slattery ML, Curtin K, Giuliano AR, et al. Active and passive smoking, IL6, ESR1, and breast cancer risk. *Breast Cancer Res Treat*. 2008;109(1):101–111. doi:10.1007/s10549-007-9629-1
35. Hanaoka T, Yamamoto S, Sobue T, Sasaki S, Tsugane S. Active and passive smoking and breast cancer risk in middle-aged Japanese women. *Int J Cancer*. 2005;114(2):317–322. doi:10.1002/ijc.20709
36. Friedenreich CM, Neilson HK, Woolcott CG, et al. Inflammatory marker changes in a yearlong randomized exercise intervention trial among postmenopausal women. *Cancer Prev Res*. 2012;5(1):98–108. doi:10.1158/1940-6207.CAPR-11-0369
37. Irwin ML, Varma K, Alvarez-Reeves M, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):306–313. doi:10.1158/1055-9965.EPI-08-0531
38. Schoemaker MJ, Nichols HB, Wright LB, et al. Association of body mass index and age with subsequent breast cancer risk in premenopausal women. *JAMA Oncol*. 2018;4(11):e181771. doi:10.1001/jamaoncol.2018.1771
39. de Azambuja E, McCaskill-Stevens W, Francis P, et al. The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial. *Breast Cancer Res Treat*. 2010;119(1):145–153. doi:10.1007/s10549-009-0512-0
40. Bhardwaj P, Iyengar NM, Zahid H, et al. Obesity promotes breast epithelium DNA damage in women carrying a germline mutation in BRCA1 or BRCA2. *Sci Transl Med*. 2023;15(684):eade1857. doi:10.1126/scitranslmed.ade1857
41. Sun X, Verma SP, Jia G, et al. Case-case genome-wide analyses identify subtype-informative variants that confer risk for breast cancer. *Cancer Res*. 2024;84(15):2533–2548. doi:10.1158/0008-5472.CAN-23-3854
42. Sudan SK, Sharma A, Vikramdeo KS, et al. Obesity and early-onset breast cancer and specific molecular subtype diagnosis in black and white women: NIMHD social epigenomics program. *JAMA Network Open*. 2024;7(7):e2421846. doi:10.1001/jamanetworkopen.2024.21846
43. John EM, Koo J, Phipps AI, et al. Reproductive characteristics, menopausal status, race and ethnicity, and risk of breast cancer subtypes defined by ER, PR and HER2 status: the breast cancer etiology in minorities study. *Breast Cancer Res*. 2024;26(1):88. doi:10.1186/s13058-024-01834-5
44. Young KL, Olshan AF, Lunetta K, et al. Influence of alcohol consumption and alcohol metabolism variants on breast cancer risk among Black women: results from the AMBER consortium. *Breast Cancer Res*. 2023;25(1):66. doi:10.1186/s13058-023-01660-1
45. Lim GH, Tan YCRS, Lee E, et al. Adolescent dietary intake and breast cancer in adulthood: a systematic review and meta-analysis. *Adv Nutr*. 2025;16(10):100503. doi:10.1016/j.advnut.2025.100503
46. Roberts E, Howell S, Evans DG. Polygenic risk scores and breast cancer risk prediction. *Breast*. 2023;67:71–77. doi:10.1016/j.breast.2023.01.003
47. Gastounioti A, Desai S, Ahluwalia VS, Conant EF, Kontos D. Artificial intelligence in mammographic phenotyping of breast cancer risk: a narrative review. *Breast Cancer Res*. 2022;24(1):14. doi:10.1186/s13058-022-01509-z
48. Farkas AH, Nattinger AB. Breast cancer screening and prevention. *Ann Intern Med*. 2023;176(11):ITC161–ITC176. doi:10.7326/AITC202311210
49. Yu D, Zhao Z, Pickering K, et al. Association between within-target risk factors and life expectancy free from cardiovascular disease, cancer, and dementia in individuals with type 2 diabetes in New Zealand between 1994 and 2018: a multi-ethnic cohort study. *BMC Med*. 2024;22(1):527. doi:10.1186/s12916-024-03743-y
50. Vasson F, Matta K, Biessy C, et al. Lifestyle changes and postmenopausal breast cancer risk in women from the European Prospective Investigation into Cancer and Nutrition. *Breast Cancer Res*. 2025;27(1):192. doi:10.1186/s13058-025-02148-w
51. Barone I, Gelsomino L, Accattatis FM, et al. Analysis of circulating extracellular vesicle derived microRNAs in breast cancer patients with obesity: a potential role for Let-7a. *J Transl Med*. 2023;21(1):232. doi:10.1186/s12967-023-04075-w
52. Nahmias-Blank D, Maimon O, Meirovitz A, Sheva K, Peretz-Yablonski T, Elkin M. Excess body weight and postmenopausal breast cancer: emerging molecular mechanisms and perspectives. *Semin Cancer Biol*. 2023;96:26–35. doi:10.1016/j.semcancer.2023.09.003
53. Tarantini S, Subramanian M, Butcher JT, et al. Revisiting adipose thermogenesis for delaying aging and age-related diseases: opportunities and challenges. *Ageing Res Rev*. 2023;87:101912. doi:10.1016/j.arr.2023.101912
54. Vieira-Potter VJ, Mishra G, Townsend KL. Health of adipose tissue: oestrogen matters. *Nat Rev Endocrinol*. 2026;22(2):76–91. doi:10.1038/s41574-025-01180-2
55. Staton CA, Vissoci JRN, El-Gabri D, et al. Patient-level interventions to reduce alcohol-related harms in low- and middle-income countries: a systematic review and meta-summary. *PLoS Med*. 2022;19(4):e1003961. doi:10.1371/journal.pmed.1003961
56. Tzelepis F, Mitchell A, Wilson L, et al. The long-term effectiveness of internet-based interventions on multiple health risk behaviors: systematic review and robust variance estimation meta-analysis. *J Med Internet Res*. 2021;23(12):e23513. doi:10.2196/23513
57. Schutte AE, Srinivasapura Venkateshmurthy N, Mohan S, Prabhakaran D. Hypertension in Low- and Middle-Income Countries. *Circ Res*. 2021;128(7):808–826. doi:10.1161/CIRCRESAHA.120.318729
58. Brunmair J, Bileck A, Stimpfl T, et al. Metabo-tip: a metabolomics platform for lifestyle monitoring supporting the development of novel strategies in predictive, preventive and personalised medicine. *EPMA J*. 2021;12(2):141–153. doi:10.1007/s13167-021-00241-6