Translational Oncology 60 (2025) 102473

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Global, regional, and national estimates of burden and risk factors of female cancers in child-bearing age: A systematic analysis for Global Burden of Disease Study and Bayesian projection to 2030

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ARTICLE INFO

Keywords:
Female cancers in child-bearing age
GBD 2021
Incidence
Risk factor
DALYs
AAPC

ABSTRACT

Background: The prevention, management, and treatment of female cancers among women of childbearing age (WCBA) are crucial strategies for achieving the objectives outlined in the World Health Organization (WHO) Global Breast Cancer Initiative and Cervical Cancer Elimination Initiative. This review aims to provide comprehensive global, regional, and national estimates of the burden of female cancers in women of childbearing age, as well as their attributable risk factors, from 1990 to 2021.

Methods: According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 methodology, we estimated the incidence, disability-adjusted life-years (DALYs), and mortality of breast, cervical, ovarian, and uterine cancer among women of childbearing age. Temporal trends were assessed using the age-adjusted percentage change (AAPC). Risk factors were estimated using the population attributable fraction, stratified by socio-demographic index (SDI). Projections to 2030 were generated using a Bayesian model.

Results: In 2021, the global incidence of breast, uterine, cervical, and ovarian cancer among WCBA was 561,438 (95 % Uncertainty Interval [UI]: 523,147–602,978), 58,860 (95 % UI: 50,765–65,452), 307,428 (95 % UI: 280,667–335,692), and 85,749 (95 % UI: 75,169–95,090), respectively, corresponding to age-standardized rates per 100,000 population of 28.1 (95 % Confidence Interval [CI]: 28.0–28.1), 2.9 (95 % CI: 2.9–3.0), 15.4 (95 % CI: 15.4–15.5), and 4.3 (95 % CI: 4.3–4.4). Breast cancer accounted for the highest number of DALYs at 6659,460 (95 % UI: 6192,226–7145,549), followed by cervical cancer at 4184,314 (95 % UI: 3779,640–4629,604). Diets high in red meat, smoking, and alcohol consumption contributed to 11.2 %, 2.5 %, and 2.6 % of breast cancer deaths, respectively, while unprotected sex accounted for majority of cervical cancer deaths. Obesity was responsible for 30.2 % of both ovarian and uterine cancer deaths. Bayesian projection models indicated that by 2030, the global age-standardized incidence rates of breast and ovarian cancers among WCBA will reach 31.5 and 4.7 per 100,000 population, respectively.

Conclusion: Globally, the number of breast, uterine, and ovarian cancer cases among WCBA has increased over the past decade, accompanied by a steady rise in age-standardized incidence rates. In contrast, while the absolute number of cervical cancer cases has risen, its age-standardized incidence rate has declined. Mortality rates for both breast and cervical cancers have generally decreased worldwide; however, in countries within the lower SDI

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https://doi.org/10.1016/j.tranon.2025.102473
Received 22 April 2025; Received in revised form 11 July 2025; Accepted 15 July 2025
Available online 20 July 2025

quintile, mortality rates for these cancers continue to rise. Therefore, priority should be given to initiatives such as smoking cessation programs, alcohol reduction strategies, HPV vaccination campaigns, and safe sex education, particularly in lower SDI countries.

Introduction

Breast, cervical, ovarian, and uterine cancers significantly impact fertility and represent a growing global health challenge, largely driven by diverse socioeconomic changes [1]. Breast cancer remains the most common cancer among women, accounting for 11.6 % of all cancers worldwide, while cervical cancer is one of the leading causes of cancer-related mortality in 37 countries [2,3]. Although ovarian cancer has a comparatively lower incidence, it is associated with a poor prognosis, in part because it is frequently diagnosed at an advanced stage [4]. Treatments for gynecological cancers (ovarian, cervical, and uterine) can have a profound negative effect on reproductive potential, as standard therapies such as hysterectomy and bilateral salpingo-oophorectomy render women infertile. While fertility-sparing treatment options exist, they are generally limited to those with early-stage and less aggressive disease [4]. Alarmingly, approximately 20 % of gynecological cancers are diagnosed in women under 40 years of age, often before their first pregnancy [4]. Consequently, addressing female cancers in women of childbearing age (WCBA) is important.

According to *GLOBOCAN* data from 2022, the incidence rates of female cancers vary four- to five-fold across global regions, ranging from 410.5 per 100,000 in Australia/New Zealand to 103.3 per 100,000 in South-Central Asia, illustrating a striking disparities across countries and regions [5]. In low- and middle-income countries, limited medical resources and inadequate healthcare services impede early cancer screening, risk factor management, and timely treatment, resulting in pronounced disparities in both incidence and mortality [6]. These findings suggest that the socio-demographic index (SDI) may be a key effect modifier underlying regional differences in cancer incidence and mortality. Therefore, a comprehensive analysis of the disease burdens of female cancers in different nations and regions is essential for both global health organizations and local governments to develop tailored cancer prevention and management strategies.

Oral contraceptive use, first pregnancy after the age of 30, alcohol consumption, obesity and lack of physical exercise are modifiable risk factors for breast cancer [7]. Similarly, obesity, tamoxifen use, and nulliparity are common risk factors for uterine cancer [8]. By contrast, human papillomavirus (HPV) infection is the most important risk factor for cervical cancer, highlighting the importance of HPV vaccination as a key preventive measure [9]. For ovarian cancer, a history of endometriosis, nulliparity, and subfertility are recognized risk factors [10]. Accordingly, targeted approaches are needed to effectively address the distinct risk factors associated with each type of female cancers (breast, cervical, ovarian, and uterine cancer) and to consider the differing needs of women in reproductive versus non-reproductive age groups.

To foster a nuanced understanding of policy-making aimed at preventing female cancers among women of childbearing age, it is essential to identify high-risk populations by geographic location and to elucidate region-specific risk factors, utilizing data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 (GBD 2021). Although previous studies have assessed the overall disease burden of female cancers and identified risk factors for breast cancer, a comprehensive understanding of disease burden trends over time, as well as the complex and distinct risk factors for various types of female cancers, remains limited. Therefore, this review aims to estimate the burdens of breast, cervical, ovarian, and uterine cancer among women of reproductive age from 1990 to 2030, and to evaluate attributable risk factors stratified by SDI, in order to inform targeted public health prevention strategies.

Methods

Overview of study design

The GBD 2021, published by the Institute for Health Metrics and Evaluation, provided comprehensive and comparable global health estimates for incidence, prevalence, mortality, years of life lost (YLLs), disability-adjusted life years (DALYs), and associated risk factors. The dataset encompasses 459 causes of death and disability and 88 risk factors and risk factor groups across global, regional, and national levels for 204 countries and territories [11]. All estimates are presented with 95 % uncertainty intervals (UIs), calculated using the 2.5th and 97.5th percentiles of 1000 samples drawn from the uncertainty distribution [12]. Detailed methodological information has been published previously [13]. GBD 2021 is the most recent iteration of the database, offering extensive data on both fatal and non-fatal outcomes, accessible at https://vizhub.healthdata.org/gbd-results/ [14]. The methodologies used in GBD 2021, including burden estimation processes and risk factor quantification, have been described in detail in prior publications [15]. This review was reported in accordance with the Strengthening the Reporting of Cohort, Cross-sectional and Case-control Studies in Surgery (STROCSS) criteria [16].

Incidence, mortality, and DALYs estimation

We estimated the prevalence, mortality, and DALYs associated with female cancers among WCBA using data from GBD 2021. Although women may be affected by a range of female cancers—including breast, cervical, ovarian, endometrial, uterine, vulvar, and vaginal cancers—the GBD 2021 provides burden estimates for only the four major types: breast, cervical, ovarian, and uterine cancers. Notably, according to GBD definitions, fallopian tube cancer is not included under ovarian cancer. The International Classification of Diseases (ICD) codes corresponding to these four cancers are detailed in Supplementary Appendix 1. In general, the ICD classifies breast, cervical, uterine, and ovarian cancers as malignant neoplasms of the respective organs, with each assigned a specific code based on tumor location and histology. WCBA were defined as those aged 15–49 years, in accordance with the World Health Organization (WHO)'s definition [17].

Risk factor estimation

The burden attributable to risk factors for the four major female cancers—breast, cervical, ovarian, and uterine cancers—among women aged 15–49 years from 1990 to 2021, was estimated using the population attributable fraction (PAF) of deaths and DALYs [18–20]. Risk factors were classified into four hierarchical levels, ranging from the most general (Level 1) to the most specific (Level 4) [21]. It should be noted that the crude sum of PAFs may exceed 100 % due to the partial or complete mediation of effects by other risk factors [22]. Data were extracted from GBD 2021 using the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool), provided by the Institute for Health Metrics and Evaluation. An overview of the GBD data collection, modeling, analysis, and dissemination processes is provided in Supplementary Appendix 2, while detailed descriptions of the disease models for the four female cancers are available in the GBD 2021 Methods Appendix (https://www.healthdata.org/gbd/methods-appendices-2021/cancers). The SDI, a composite measure of development status that is strongly correlated with health outcomes, was utilized for stratification and subgroup analysis. GBD 2021 classifies

204 countries into five quintiles—low, lower-middle, middle, upper-middle, and high—based on their 2021 country-level SDI estimates. Urban and rural classifications were obtained from the original data sources, using definitions provided by national statistical agencies or census bureaus [23].

Statistical analysis

To estimate the incidence, mortality, and DALYs of these cancers among women of reproductive age, we retrieved corresponding population data from the Population Division of the United Nations Department of Economic and Social Affairs (https://population.un.org/wpp/Download/Standard/Population/). These data were stratified by year (1990–2030), sex (female), and age (seven five-year age groups from 15–49 years). Incidence was reported as the number of cases with corresponding 95 % uncertainty intervals (UIs). The age-standardized rate (ASR) per 100,000 person-years for the year 2030 was calculated using WHO world standard population distribution for the period 2000–2025 [24]. Data analysis was completed on August 5, 2024. We calculated the ASR per 100,000 in WCBA, using the standard age-standardization formula: [25]

$$\frac{\sum_{i=1}^{N}\alpha_i W_i}{\sum_{i=1}^{N} W_i}$$

Age standardization was performed using the GBD 2021 standard population, where N represents the total number of age groups. The 95 % confidence intervals (CIs) were calculated using the "ageadjust.direct" function from the "epitools" package in R software [26]. To assess the temporal trends of rates, we used the Estimated Annual Percentage Change (EAPC) indicator, which quantifies the average rate of change over a specified time interval. EAPC was calculated by fitting a regression model to the natural logarithm of the rates: [27,28]

$$\ln(ASR) = \alpha + \beta x + \varepsilon$$

EAPC is defined as: $EPAC = 100 \times (e^{\beta} - 1)$. An ASR was considered to exhibit a statistically significant increasing or decreasing trend over time if both the estimated annual percentage change (EAPC) and its 95 % CI were entirely above or below zero, respectively. Conversely, if the 95 % CI included zero, the change in ASR was considered statistically non-significant [29,30].

In this review, we used the age-adjusted percentage change (AAPC) to evaluate long-term trends in disease incidence. The AAPC represents a weighted average of the estimated annual percentage changes (EAPCs) over a specified time period and was calculated using the *Joinpoint* regression model: [31]

$$AAPC = \frac{\sum_{i=1}^{m} w_i \times EAPC_i}{\sum_{i=1}^{m} w_i}$$

We utilized the BAPC package in R (version 4.3.2; R Core Team, R Foundation for Statistical Computing, Vienna, Austria) to perform full Bayesian inference using the Integrated Nested Laplace Approximation (INLA) for predicting mortality and morbidity outcomes. Age-standardized death and DALY rates were calculated to assess temporal trends for the cancers among WCBA. Age, period, and cohort effects were analysed using a second-order random walk (RW2) model with an inverse gamma prior distribution. As the time periods were provided annually while the age groups were in five-year intervals, the grid factor was set to 5 [31].

Raw data were extracted from the GBD 2021 database (https://vizhub.healthdata.org/gbd-results/). All visualizations in this review were generated originally using *R* software (Version 4.3.2) and trend analyses were conducted using *Joinpoint Trend Analysis* Software (Version 5.0.2), developed by the National Cancer Institute's Surveillance Research Program, Statistical Methods and Applications Branch (https://surveillance.cancer.gov/joinpoint/). A two-sided P-value of <0.05 was considered statistically significant.

Results

Incidence, mortality, and DALYs of cancers among WCBA stratified by SDI

Both global and SDI-stratified incidence, mortality, and DALYs for WCBA were reported in Table 1. Globally, the incidence of breast cancer in 2021 was 561,438 cases (95 % UI: 523,147–602,978), with an ASR of 28.1 (95 % CI: 28.0–28.1) per 100,000, representing a 50.1 % increase in the number of cases and a 17.8 % increase in the ASR since 1990 (AAPC = 0.659, 95 % CI: 0.627–0.688, $p < 0.001$) (Table 1). Uterine cancer had 58,860 (95 % UI: 50,765–65,452) cases and an ASR of 2.9 (95 % CI: 2.9–3.0), with a 44.9 % increase in cases and a 14.8 % increase in the ASR (AAPC = 0.502, 95 % CI: 0.447–0.549, $p < 0.001$). Cervical cancer had 307,428 (95 % UI: 280,667–335,692) cases with an ASR of 15.4 (95 % CI: 15.4–15.5), showing a 3.2 % increase in cases but a 13.2 % decrease in the ASR (AAPC = −0.404, 95 % CI: −0.443 to −0.378, $p < 0.001$). Ovarian cancer reported 85,749 (95 % UI: 75,169–95,090) cases with an ASR of 4.3 (95 % CI: 4.3–4.4), with a 22.6 % increase in cases and a 6.1 % increase in the ASR (AAPC = 0.224, 95 % CI: 0.198–0.256, $p < 0.001$).

In the high SDI quintile, breast cancer incidence in 2021 was 125,313 cases (95 % UI: 119,245–131,419), with an ASR of 43.3 (95 % CI: 43.3–43.4) per 100,000, representing a 6.3 % increase in case numbers but an 8.8 % decrease in ASR (AAPC = −0.198, $p < 0.001$). Uterine cancer had a 91.6 % increase in cases and a 39.6 % increase in ASR (AAPC = 1.535, $p < 0.001$), while cervical and ovarian cancers showed significant declines in ASR by 60.6 % and 44 %, respectively. In the high-middle SDI quintile, breast cancer incidence increased by 80.5 % and ASR by 22.1 % (AAPC = 0.858, $p < 0.001$). From 1999 to 2021, uterine and cervical cancers had moderate increases in ASR, while ovarian cancer showed a slight decline. Within the middle SDI quintile, breast cancer incidence rose by 151 % and ASR by 44.5 % (AAPC = 1.944, $p < 0.001$), with ovarian cancer also showing significant increases. In the low-middle SDI quintile, breast and ovarian cancers showed substantial increases in ASR, whereas cervical cancer demonstrated a significant decline. In the low SDI quintile, breast cancer incidence increased by 67.7 % and ASR by 37.9 % (AAPC = 1.527, $p < 0.001$), with moderate increases for uterine and ovarian cancers, and a significant decline in cervical cancer.

In 2021, breast cancer accounted for the highest global DALYs, totaling 6659,460 (95 % UI: 6192,226–7145,549), with ASR of 333.1 per 100,000 (95 % CI: 332.9–333.4), representing a 6.0 % decrease since 1990 (AAPC = −0.188, $p < 0.001$) (Table 2). Cervical cancer contributed 4184,314 DALYs (95 % UI: 3779,640–4629,604) with an ASR of 209.9 (95 % CI: 209.8–209.9), reflecting a significant 44.8 % reduction over the same period (AAPC = −1.206, $p < 0.001$).

In 2021, breast cancer accounted for 129,405 deaths globally (95 % UI: 120,298–139,008), with an ASR of 6.4 per 100,000 (95 % CI: 6.4–6.5), representing a 9.0 % decrease in ASR since 1990 (AAPC = −0.266, $p < 0.001$). Cervical cancer resulted in 81,640 deaths (95 % UI: 73,783–90,476) with ASR of 4.08 (95 % CI: 4.08–4.10), reflecting a significant 47.3 % reduction in ASR (AAPC = −1.261, $p < 0.001$). In the high SDI quintile, breast cancer deaths decreased by 76.9 % (AAPC = −1.829, $p < 0.001$), while uterine cancer deaths showed minimal change. In comparison, countries in the low SDI quintile experienced a significant 65.2 % reduction in cervical cancer deaths (AAPC = −1.609, $p < 0.001$), but deaths from breast and ovarian cancers increased significantly, highlighting disparities in cancer outcomes based on socioeconomic status.

Leading risk factors of cancers among WCBA stratified by SDI

In 2021, overall risk factor exposures accounted for an estimated

Table 1
Incidence and age-standardized incidence rates from 1999 to 2021 for breast, cervical, ovarian, and uterine cancers among women of child-bearing age.

	Incidence in 2021 Number of cases (child-bearing age, UI)	Age-standardized rate (per 100,000, 95 % CI) population	Percentage change in number of incident cases, 1990–2021 (%)	Percentage change in age-standardized rate, 1990–2021 (%)	AAPC (Annual Age-standardized rate, 95 % CI)	P-value
Global						
Breast cancer	561,438 (523,147–602,978)	28.1 (28.0–28.1)	50.1 %	17.8 %	0.659 (0.627–0.688)	< 0.001
Uterine cancer	58,860 (50,765–65,452)	2.9 (2.9–3.0)	44.9 %	14.8 %	0.502 (0.447–0.549)	< 0.001
Cervical cancer	307,428 (280,667–335,692)	15.4 (15.4–15.5)	3.2 %	−13.2 %	−0.404 (−0.443 to −0.378)	< 0.001
Ovarian cancer	85,749 (75,169–95,090)	4.3 (4.3–4.4)	22.6 %	6.1 %	0.224 (0.198–0.256)	< 0.001
High SDI quintile						
Breast cancer	125,313 (119,245–131,419)	43.3 (43.3–43.4)	6.3 %	−8.8 %	−0.198 (−0.275 to −0.142)	< 0.001
Uterine cancer	15,500 (14,853–16,143)	5.3 (5.3–5.4)	91.6 %	39.6 %	1.535 (1.379–1.661)	< 0.001
Cervical cancer	32,703 (31,624–33,777)	11.8 (11.8–11.9)	−32.4 %	−60.6 %	−1.505 (−1.544 to −1.473)	< 0.001
Ovarian cancer	12,259 (11,637–12,755)	4.4 (4.4–4.6)	−22.7 %	−44 %	−1.138 (−1.193 to −1.082)	< 0.001
High-middle SDI quintile						
Breast cancer	124,150 (109,355–141,573)	33 (33–33.1)	80.5 %	22.1 %	0.858 (0.732–0.938)	< 0.001
Uterine cancer	18,263 (15,728–21,188)	4.8 (4.8–4.9)	63 %	12.8 %	0.502 (0.353–0.616)	< 0.001
Cervical cancer	50,551 (43,557–57,901)	13.9 (13.9–14)	44.3 %	10.8 %	0.374 (0.282–0.452)	< 0.001
Ovarian cancer	15,917 (13,917–18,073)	5 (5–5.1)	11.23 %	−1.7 %	−0.386 (−0.457 to −0.306)	< 0.001
Middle SDI quintile						
Breast cancer	183,590 (166,447–201,982)	27.4 (27.4–27.5)	151 %	44.5 %	1.944 (1.887–2.005)	< 0.001
Uterine cancer	16,726 (12,538–19,916)	2.5 (2.5–2.6)	64 %	15.7 %	0.487 (0.419–0.539)	< 0.001
Cervical cancer	100,530 (90,898–111,723)	15.1 (15.1–15.2)	41.6 %	−6.3 %	−0.169 (−0.219 to −0.125)	< 0.001
Ovarian cancer	30,147 (25,272–34,070)	4.6 (4.6–4.7)	73.2 %	30.4 %	1.183 (1.163–1.202)	< 0.001
Low-middle SDI quintile						
Breast cancer	95,123 (85,516–104,880)	20.6 (20.6–20.7)	122 %	48 %	2.103 (2.077–2.125)	< 0.001
Uterine cancer	6301 (5162–7482)	1.38 (1.38–1.39)	62.8 %	35 %	1.064 (1.029–1.089)	< 0.001
Cervical cancer	76,193 (67,245–85,724)	16.2 (16.2–16.3)	−6.7 %	−22.9 %	−0.712 (−0.789 to −0.660)	< 0.001
Ovarian cancer	19,912 (16,608–23,214)	4.1 (4.1–4.2)	88.5 %	41.7 %	1.782 (1.756–1.808)	< 0.001
Low SDI quintile						
Breast cancer	32,752 (28,071–37,902)	15.3 (15.3–15.4)	67.7 %	37.9 %	1.527 (1.497–1.557)	< 0.001
Uterine cancer	1996 (1499–2644)	0.9 (0.9–1)	27.1 %	19 %	0.682 (0.652–0.713)	< 0.001
Cervical cancer	47,151 (39,338–57,046)	21.1 (21.1–21.2)	−21.6 %	−32.6 %	−0.912 (−0.945 to −0.886)	< 0.001
Ovarian cancer	7430 (5377–9085)	3.1 (3.1–3.2)	65.3 %	37.2 %	1.524 (1.500–1.554)	< 0.001

UI: uncertainty intervals. SDI: Socio-demographic Index; CI: confidence interval.

15.83 % of breast cancer deaths and 15.74 % of DALYs among women of childbearing age. Among the related risk factors, diet high in red meat emerged as the leading specific risk factor, contributing to 11.24 % of total breast cancer deaths in this population. In addition, smoking and alcohol consumption also had significant impacts: smoking was attributable to 2.59 % of deaths and 2.56 % of DALYs, whereas alcohol consumption was responsible for 2.60 % of deaths and 2.64 % of DALYs, respectively (Fig. 1).

Another important risk factor, unprotected sex, was the leading global risk factor for cervical cancer deaths and DALYs, accounting for 100 % of cases in 2021 (Supplementary Appendix 3, Figure S1). Moreover, high body mass index (BMI) significantly contributed to ovarian and uterine cancer mortality and DALYs among women of childbearing age. Specifically, elevated BMI was responsible for 30.21 % of ovarian

Table 2
Age-standardized DLAYs and deaths for breast, cervical, ovarian, and uterine cancers among women of child-bearing age.

	DALYs					Death				
	Number of DALYs, 2021 (95 % UI)	Age-standardized rate per 100, 000, 2021 (95 % CI)	Percentage change in age-standardized rate, 1990–2021 (%)	AAPC (Age-standardized rate, 95 % CI)	P-value	Number of Deaths, 2021 (95 % UI)	Age-standardized rate per 100, 000, 2021 (95 % CI)	Percentage change in age-standardized rate, 1990–2021 (%)	AAPC (Annual Age-standardized rate, 95 % CI)	P-value
Global										
Breast cancer	6659,460 (6192,226–7145,549)	333.1 (332.9–333.4)	−6 %	−0.188 (−0.210 to −0.165)	< 0.001	129,405 (120,298–139,008)	6.4 (6.4–6.5)	−9 %	−0.266 (−0.289 to −0.243)	< 0.001
Uterine cancer	373,682 (308,997–423,441)	18.7 (18.6–18.7)	−38.6 %	−1.017 (−1.058 to −0.968)	< 0.001	7163 (5983–8042)	0.357 (0.356–0.359)	−42.8 %	−1.115 (−1.147 to −1.075)	< 0.001
Cervical cancer	4184,314 (3779,640–4629,604)	209.9 (209.8–209.9)	−44.8 %	−1.206 (−1.242 to −1.180)	< 0.001	81,640 (73,783–90,476)	4.08 (4.08–4.1)	−47.3 %	−1.261 (−1.298 to −1.235)	< 0.001
Ovarian cancer	1294,995 (1139,826–1431,298)	65.1 (65.1–65.2)	−6.9 %	−0.202 (−0.220 to −0.180)	< 0.001	25,258 (22,277–27,861)	1.2 (1.2–1.3)	−8.9 %	−0.263 (−0.283 to −0.238)	< 0.001
High SDI quintile										
Breast cancer	791,735 (753,852–835,670)	274.5 (274.4–274.6)	−68.2 %	−1.666 (−1.724 to −1.631)	< 0.001	14,780 (14,308–15,226)	5.1 (5–5.1)	−76.9 %	−1.829 (−1.900 to −1.783)	< 0.001
Uterine cancer	55,090 (51,921–58,769)	19 (18.9–19)	6.1 %	0.205 (0.133–0.268)	< 0.001	999 (954–1041)	0.34 (0.33–0.34)	0.63 %	0.021 (−0.061–0.102)	0.594
Cervical cancer	216,589 (208,518–226,283)	76.8 (76.7–76.8)	−90.3 %	−2.074 (−2.109 to −2.044)	< 0.001	4096 (3962–4236)	1.4 (1.4–1.44)	−92 %	−2.103 (−2.164 to −2.064)	< 0.001
Ovarian cancer	169,609 160,459–177,637)	59.9 (59.8–59.9)	−68.6 %	−1.694 (−1.740 to −1.648)	< 0.001	3389 (3217–3528)	1.1 (1.1–1.2)	−71.2 %	−1.749 (−1.796 to −1.704)	< 0.001
High-middle SDI quintile										
Breast cancer	1049,179 (943,000–1176,900)	280.1 (280–280.1)	−39.9 %	−1.050 (−1.132 to −0.976)	< 0.001	20,261 (18,104–22,581)	5.3 (5.3–5.4)	−46.1 %	−1.711 (−1.255 to −1.113)	< 0.001
Uterine cancer	87,315 (74,443–102,200)	23.3 (23.2–23.3)	−63.2 %	−1.512 (−1.647 to −1.389)	< 0.001	1640 (1417–1929)	0.43 (0.43–0.434)	−72.4 %	−1.673 (−1.808 to −1.548)	< 0.001
Cervical cancer	501,525 (437,267–570,234)	136.5 (136.4–136.5)	−42.3 %	−1.058 (−1.140 to −0.989)	< 0.001	9816 (8565–11,107)	2.6 (2.6–2.64)	−45.2 %	−1.121 (−1.207 to −1.057)	< 0.001
Ovarian cancer	244,570 (213,355–277,876)	66.9 (66.9–67)	−34 %	−0.891 (−0.960 to −0.812)	< 0.001	4915 (4286–5584)	1.3 (1.3–1.32)	−35.3 %	−0.974 (−1.050 to −0.891)	< 0.001
Middle SDI quintile										
Breast cancer	2202,113 (1999,760–2415,548)	329.7 (329.6–329.8)	5.9 %	0.197 (0.162–0.236)	< 0.001	43,251 (39,298–47,605)	6.4 (6.4–6.5)	3.7 %	0.119 (0.084–0.157)	< 0.001
Uterine cancer	128,113 (95,573–150,991)	19.1 (19.1–19.2)	−63.5 %	−1.589 (−1.623 to −1.558)	< 0.001	2498 (1890–2930)	0.37 (0.37–0.373)	−68.1 %	−1.682 (−1.717 to −1.650)	< 0.001

(*continued on next page*)

Table 2 (*continued*)

	DALYs Number of DALYs, 2021 (95 % UI)	Age-standardized rate per 100, 000, 2021 (95 % CI)	Percentage change in age-standardized rate, 1990–2021 (%)	AAPC (Age-standardized rate, 95 % CI)	P-value	Death Number of Deaths, 2021 (95 % UI)	Age-standardized rate per 100, 000, 2021 (95 % CI)	Percentage change in age-standardized rate, 1990–2021 (%)	AAPC (Annual Age-standardized rate, 95 % CI)	P-value
Cervical cancer	1233,604 (1123,809–1357,817)	185.7 (185.7–185.8)	−59.8 %	−1.503 (−1.537 to −1.474)	< 0.001	24,282 (22,070–26,621)	3.6 (3.6–3.64)	−62.4 %	−1.551 (−1.585 to −1.522)	< 0.001
Ovarian cancer	432,908 (367,025–485,032)	66 (65.9–66)	15.3 %	0.539 (0.513–0.568)	< 0.001	8438 (7178–9490)	1.2 (1.2–1.3)	14.5 %	0.511 (0.471–0.564)	< 0.001
Low-middle SDI quintile										
Breast cancer	1818,680 (1616,101–2022,813)	392.1 (392–392.2)	27.5 %	1.045 (1.004–1.073)	< 0.001	35,573 (31,850–39,392)	7.7 (7.7–7.8)	26.2 %	0.988 (0.951–1.015)	< 0.001
Uterine cancer	72,135 (59,003–87,763)	15.7 (15.7–15.8)	0.1 %	−0.006 (−0.023–0.010)	0.455	1416 (1159–1720)	0.31 (0.3–0.312)	−1.2 %	−0.050 (−0.068 to −0.035)	< 0.001
Cervical cancer	1270,707 (1116,265–1443,059)	272.7 (272.6–272.8)	−66 %	−1.658 (−1.724 to −1.609)	< 0.001	24,832 (21,862–28,223)	5.3 (5.3–5.4)	−68.9 %	−1.714 (−1.772 to −1.668)	< 0.001
Ovarian cancer	316,111 (266,518–370,145)	67.2 (67.2–67.3)	33.6 %	1.333 (1.304–1.361)	< 0.001	6031 (5087–7039)	1.3 (1.29–1.3)	32.5 %	1.273 (1.244–1.301)	< 0.001
Low SDI quintile										
Breast cancer	791,378 (674,721–922,524)	366.8 (366.7–366.9)	21.7 %	0.790 (0.766–0.819)	< 0.001	15,414 (13,180–17,932)	7.3 (7.29–7.31)	20.5 %	0.737 (0.713–0.765)	< 0.001
Uterine cancer	30,463 (22,837–40,846)	14.4 (14.4–14.5)	−5.6 %	−0.174 (−0.191 to −0.155)	< 0.001	598 (444–803)	0.29 (0.28–0.29)	−6.9 %	−0.215 (−0.234 to −0.194)	< 0.001
Cervical cancer	957,580 (799,604–1159,582)	436.8 (436.7–436.9)	−62.9 %	−1.567 (−1.601 to −1.540)	< 0.001	18,529 (15,504–22,399)	8.6 (8.6–8.7)	−65.2 %	−1.609 (−1.644 to −1.581)	< 0.001
Ovarian cancer	130,530 (95,190–159,501)	58 (58–58.1)	29.3 %	1.137 (1.113–1.168)	< 0.001	2458 (1787–2976)	1.13 (1.13–1.14)	28.2 %	1.082 (1.059–1.110)	< 0.001

DLAYs: age-standardized disability-adjusted life years; UI: uncertainty intervals; SDI: Socio-demographic Index; CI: confidence interval.

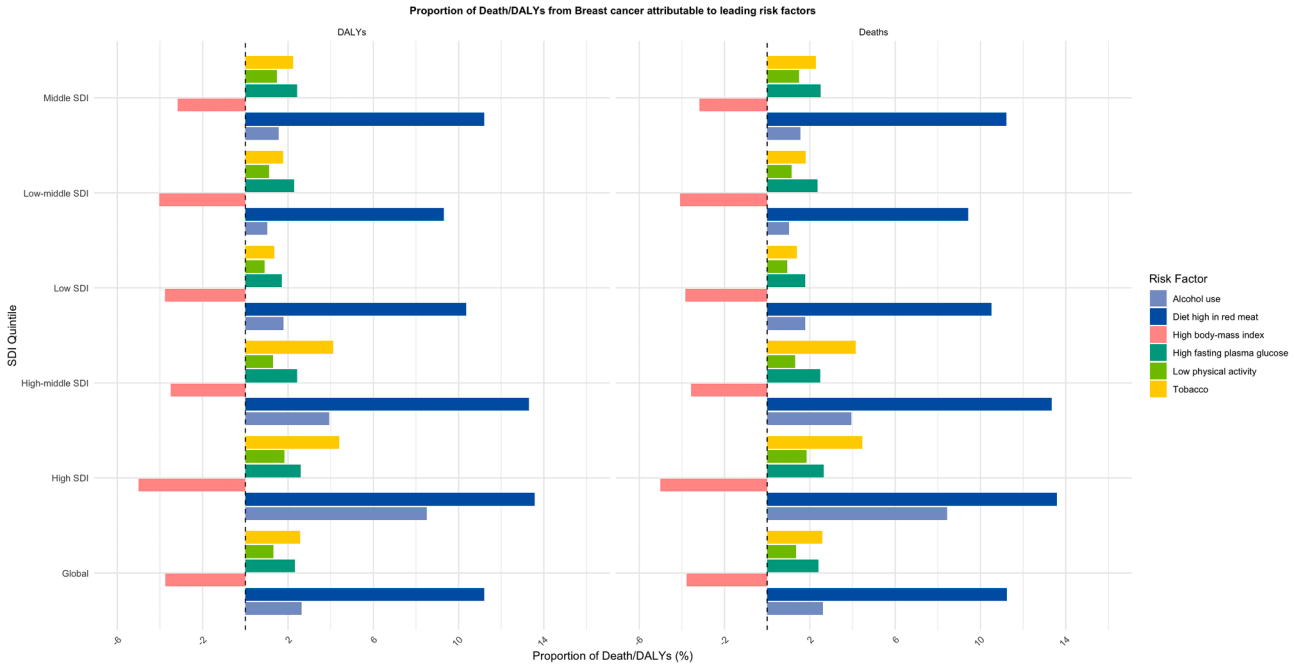

Fig. 1. Proportion of deaths and DALYs attributable to leading specific risk factors among WCBA for breast cancer, by SDI quintile, 2021.

cancer deaths and 30.18 % of ovarian cancer DALYs (Supplementary Appendix 3, Figure S2), as well as 8.01 % of uterine cancer deaths and 7.72 % of uterine cancer DALYs (Supplementary Appendix 3, Figure S3). Additionally, occupational exposure to asbestos was identified as a risk factor for uterine cancer, although its impact was minimal, accounting for only 0.15 % of deaths and 0.14 % of DALYs.

Each row represents the proportion of death or DALY attributable to a specific risk or protective factor. A bar to the right of 0 represents a risk factor while a bar to the left of 0 represents a protective factor. SDI: socio-demographic index; DALYs: disability-adjusted life years; WCBA: women of child-bearing age.

Based on the stratification by SDI, age-standardized death rates from breast cancer attributable to smoking increased significantly in certain regions, particularly in North African countries such as Morocco and Egypt; Southwestern African nations including Gabon and the Republic of the Congo; Southeast Asian countries like Vietnam and Indonesia; and Middle Eastern nations such as the United Arab Emirates and Iran from 1990 to 2021 (Fig. 2). Conversely, many countries with previously high

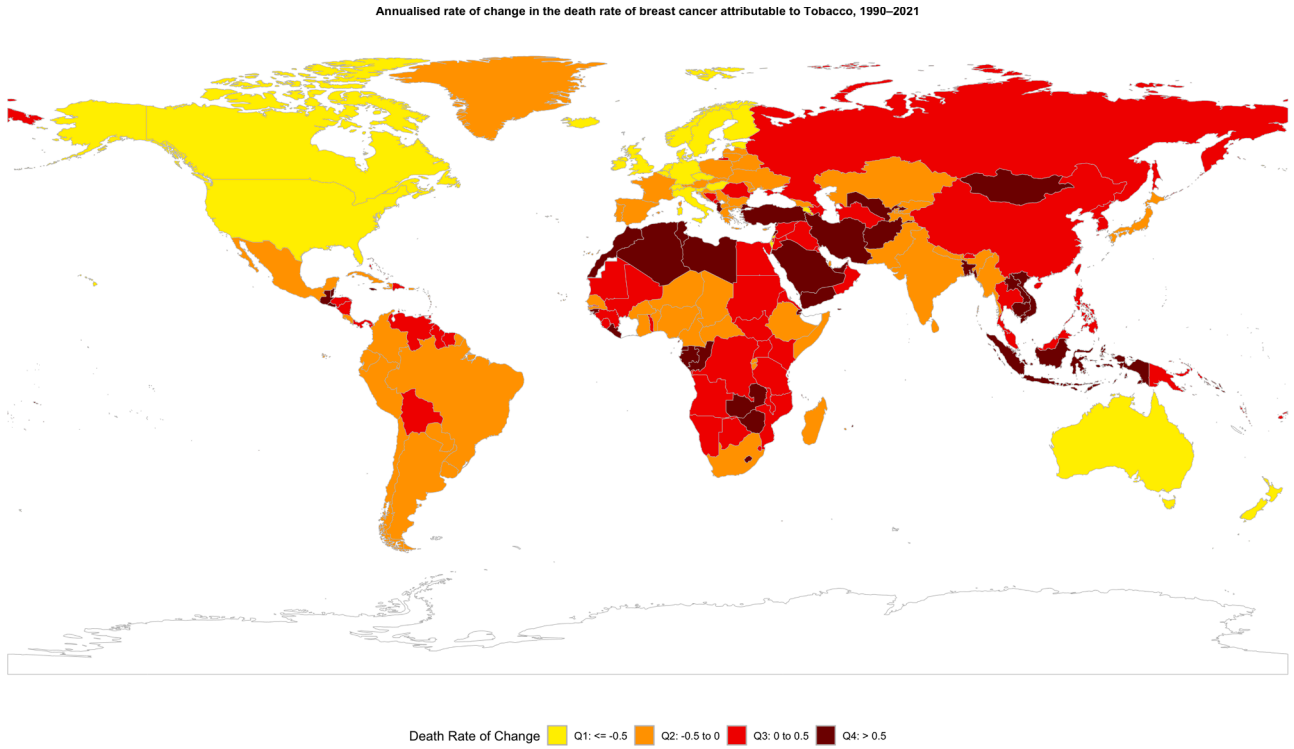

Fig. 2. Annual percentage of change in age-standardized mortality rate of breast cancer attributable to smoking, 1999–2021.

smoking-attributable death rates—such as Canada, Australia, Germany, and Norway—demonstrated steady declines during the same period (Fig. 2). Additionally, increases in the age-standardized mortality rates of breast cancer attributable to alcohol were widespread across most countries and regions. Only a handful countries—including European countries such as Switzerland, Italy, Belgium, and the Netherlands, as well as Sudan and Bhutan—recorded declines exceeding 50 % during this period (Supplementary Appendix 4, Figure S4).

Remarkably in specific region, Russia exhibited the highest age-standardized death rates for cervical cancer, attributable to smoking and unprotected sexual practices (Supplementary, Appendix 4, Figures S5 and S6). For uterine cancer, mortality rates associated with obesity (high BMI) demonstrated significant increases in most countries and regions globally, with notable exceptions in North Korea and Vietnam, where mortality rates continued to decline consistently (Supplementary, Appendix 4, Figure S7). The age-standardized death rates for ovarian cancer linked to high BMI generally decreased worldwide; however, specific increases were observed in countries such as Russia, Mongolia, China, and Japan (Supplementary, Appendix 4, Figure S8).

Annual percentage changes from 1999 to 2021 were estimated used age-standardized mortality rate data for breast cancer attributable to smoking. Different colors are used to label each country. Yellow and orange indicate negative change, meaning a decrease in age-standardized mortality rate; red and dark red indicate positive change, meaning an increase in age-standardized mortality rate.

Regional disparities were apparent in the risk-attributable burden of breast cancer among women of reproductive age. Across all regions, diet high in red meat emerged as the leading specific risk factor for age-standardized breast cancer mortality per 100,000 population. High BMI ranked as the second most significant risk factor in most regions; however, its contribution varied, particularly in high SDI and East Asian regions, where its ranking fluctuated between second and sixth place. Alcohol consumption, tobacco use, and elevated fasting plasma glucose showed considerable regional variability in their rankings, reflecting differences in lifestyle and health behaviors influencing breast cancer mortality across regions. Low physical activity generally ranked lower compared to other risk factors, suggesting a relatively smaller, albeit still notable, impact on breast cancer mortality (Fig. 3).

For each region and SDI quintile, risk factors are ranked by attributable deaths from left (first) to right (sixth). Each cell is colored according to the ranks of risk factors for each region in 2021. WCBA: women of child-bearing age; SDI: socio-demographic index.

Predictions of cancer burden among WCBA from 2022 to 2030

The age-standardized death rate of breast and ovarian cancers are projected to reach 31.5 and 4.7 per 100,000 population, respectively, by 2030, representing increases of 14.3 % and 9.3 % from 2021 levels (Fig. 4). Furthermore, age-standardized DALY and mortality rates for breast and ovarian cancers in this population are expected to rise after 2021. In contrast, while the age-standardized death rate for cervical and uterine cancers have stabilized, their corresponding DALY and mortality rates are projected to decline following 2021. By 2030, the age-standardized DALY rates for cervical and uterine cancers are anticipated to decrease to approximately 194.5 and 17.8 per 100,000 populations, respectively, while mortality rates are expected to decline to about 3.7 and 0.41 per 100,000 populations, respectively (Supplementary, Appendix 5, Figure S9 and Figure S10). Model accuracy metrics for the projected incidence, mortality, and DAILYs for female cancers at child-bearing age were reported in Appendix 6, Table S1, S2, and S3.

The open dots represent the observed values, while the shaded fan-shaped area denotes the predictive distribution between the 2.5th and 97.5th percentiles (the 95 % predictive interval). The predictive mean value is shown as a solid line. The vertical dashed line indicates where the prediction starts. A: breast cancer; B: cervical cancer; C: ovarian cancer; D: uterine cancer. WCBA: women of child-bearing age.

Discussion

The summary figure illustrating the major modifiable risk factors and their relationships to the four types of female cancers was shown in Fig. 5. The primary risk factors contributing to mortality include diet high in red meat, tobacco use, and alcohol intake for breast cancer, unprotected sex for cervical cancer, obesity for ovarian, and occupational exposure to asbestos for uterine cancers. The summary figure integrating incidence, mortality, and DALY trends for all four types of

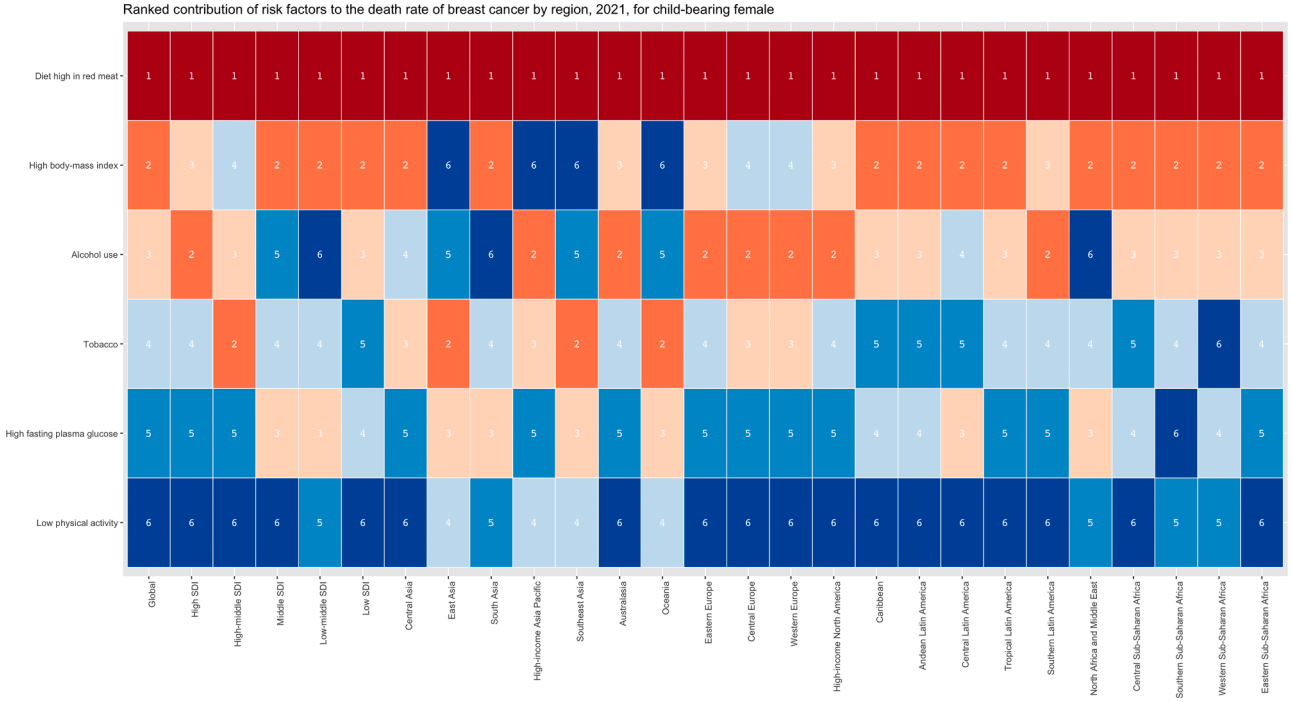

Fig. 3. Ranked contribution of risk factors to the age-standardized death rate of breast cancer among WCBA by region and SDI, 2021.

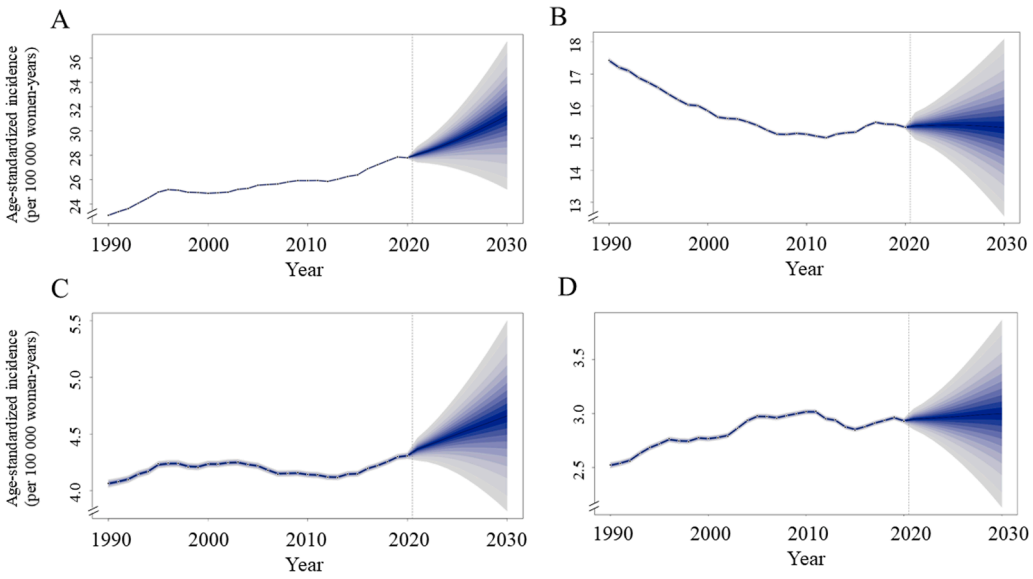

Fig. 4. The projections of age-standardized death rate in total incident for breast, cervical, ovarian, and uterine cancers among WCBA from 2022 to 2030 globally.

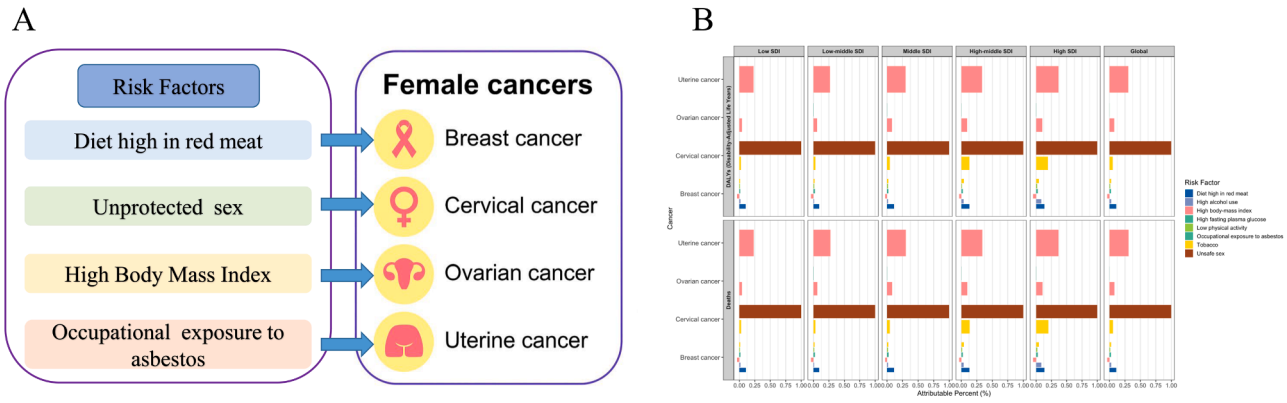

Fig. 5. Summary of major modifiable risk factors for all four types of female cancers among WCBA.

female cancers over time was shown in Fig. 6. Globally, the incidence of breast, uterine, and ovarian cancer among WCBA has increased over the past decade, with ASR exhibiting a consistent upward trend. On the other hand, although the crude incidence of cervical cancer has increased, its ASR has declined. Although breast, cervical, and ovarian cancer demonstrated significant decreases in DALYs, DALYs for ovarian cancer increased in countries classified within low-middle and low SDI quintiles. Similarly, global mortality rates for breast and cervical cancers have declined, yet mortality in low SDI quintile countries for these cancers continues to rise. Bayesian prediction models indicate that the ASR of breast and ovarian cancer among WCBA are projected to reach 31.5 and 4.7 per 100,000 population, respectively, by 2030.

A: Conceptual diagram illustrating the major modifiable risk factors for each type of female cancers among WCBA. B: Modifiable risk factors for each type of female cancers among WCBA stratified by SDI. WCBA: women of child-bearing age; SDI: socio-demographic index.

This summary figure shows the trends of both incidence, mortality, and DALY for each type of female cancers among WCBA. WCBA: women of child-bearing age.

The burden of female cancers among WCBA can be alleviated by addressing related risk factors. Increasing the consumption of fresh vegetables and fruits, while reducing the intake of red meat intake, is particularly important for the prevention of breast cancer in this population. Consistent with our findings, previous studies have demonstrated that unhealthy dietary patterns—characterized by high intake of red and processed meats, sugar-sweetened beverages, and refined carbohydrates—are associated with an increased risk of breast cancer [32]. Dietary pattern analyses further indicate that the consumption of red meat, processed meat, fried eggs, butter, sweets, and animal fats can increase the risk of breast cancer, whereas the intake of green vegetables, fruits, fresh fish, and dairy products exerts a protective effect [33].

Limiting alcohol consumption is also recommended, as evidence suggests that long-term intake exceeding 15 g per day (approximately one glass of wine) can increase risk of breast cancer. High levels of alcohol consumption not only increase circulating estrogen concentrations but also enhance cell membrane permeability to carcinogens, thereby further increasing breast cancer risk [33]. Studies have demonstrated that consuming 35 to 44 g per day of alcohol is associated with 32 % increased risk of breast cancer [34–35]. Epidemiological data indicate that, compared to non-drinkers, individuals who consume alcohol have a 40 % higher risk of developing estrogen receptor-positive/progesterone receptor-positive (ER+/PR+) breast cancer, a 39 % higher risk of ER+/PR− breast cancer, and a 21 % higher risk of ER−/PR− breast cancer. Furthermore, each additional 10 g per day of alcohol intake is associated with a 10.5 % increase in overall breast cancer risk [36].

Smoking cessation is critical for reducing breast cancer risk. A 2017 population-based epidemiological survey conducted across 28 countries in the European Union demonstrated that, compared to non-smokers, individuals who smoke or are exposed to second-hand smoke have a

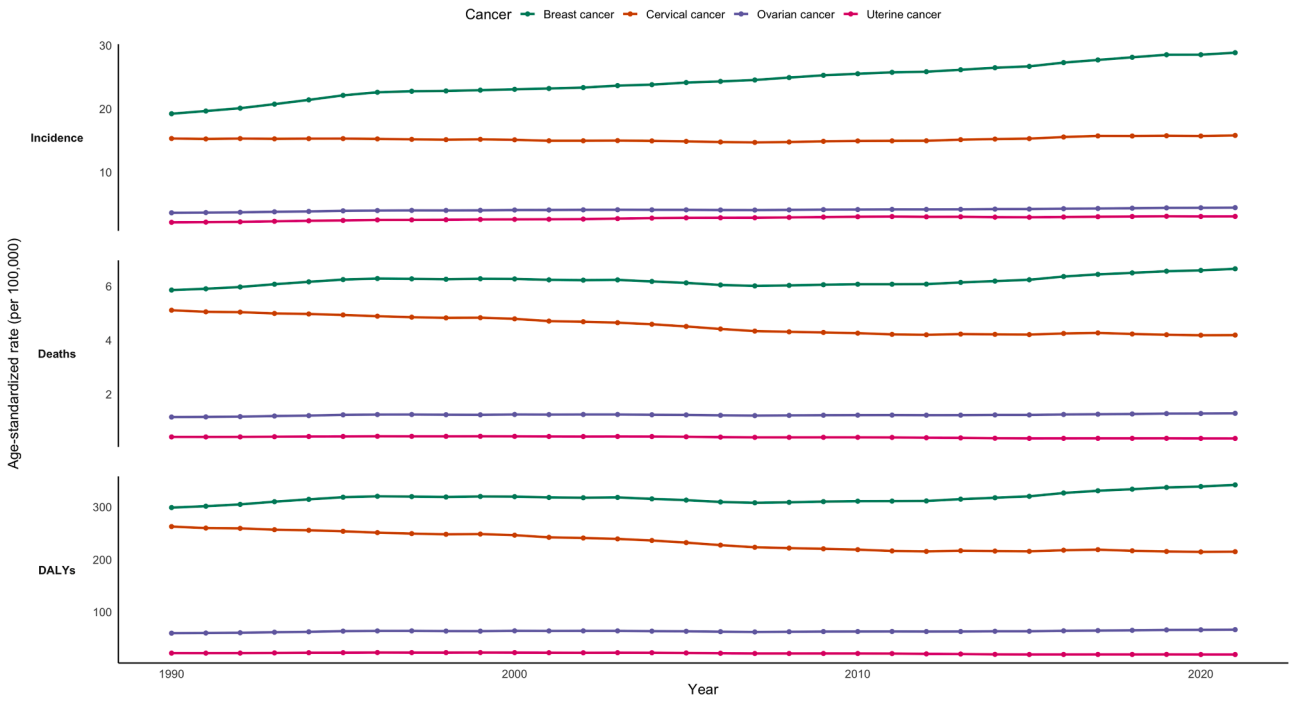

Fig. 6. Summary of incidence, mortality, and DALY trends for all four types of female cancers among WCBA from 1990 to 2021.

10 % and 7 % increased 10-year risk of developing breast cancer, respectively [37]. Moreover, both smoking and alcohol consumption are associated with an elevated risk of contralateral breast cancer, particularly among heavy smokers who consume >10 cigarettes per day [38].

Sexual behaviors are closely associated with the incidence of cervical cancer. Women who initiate sexual activity at an early age are at a higher risk of developing cervical cancer [39]. Unprotected sexual behavior constitutes an additional significant risk factor. Epidemiological surveys indicate that having first sexual intercourse before the age of 15 and having two or more sexual partners markedly increase the risk of cervical cancer [40]. Accordingly, strengthening health education and public awareness—emphasizing the importance of delaying sexual initiation, maintaining monogamous relationships, and promoting sexual health—can contribute to reducing the incidence and burden of cervical cancer. Persistent infection of high-risk HPV types is recognized as the primary cause of cervical cancer and its precancerous lesions [41]. Sexually active women have a 70 % likelihood of acquiring high-risk HPV, although most infections are transient, with <10 % progressing to cervical intraepithelial neoplasia. Progression from high-risk HPV infection to intraepithelial neoplasia and subsequently to cervical cancer typically occurs over several years or even decades. HPV vaccination represents a critical strategy for cervical cancer prevention. Real-world studies in Denmark, Sweden, the United Kingdom and other countries have demonstrated that the protective effects of HPV vaccination are greater when administered at younger ages. Large-scale vaccination programs can effectively reduce the incidence of precancerous lesions and cervical cancer, while also generating substantial herd immunity [42–44]. Recent research further suggests that HPV vaccination can reduce HPV infections by >80 % before the age of 24, significantly alleviating the global burden of cervical cancer [45].

BMI is a widely utilized metric for assessing body fat composition, thinness, and overall health status. Research has demonstrated a positive association between increasing BMI and the risk of ovarian cancer [46]. In a study involving 12,390 ovarian cancer patients, elevated BMI was found to be correlated with poorer progression-free survival, overall survival, and ovarian cancer-specific survival [47]. This relationship may be attributable to the secretion of pro-inflammatory cytokines, adipokines, pro-angiogenic factors, and other signaling molecules by adipose tissue, which collectively promote tumor growth and metastasis. Moreover, obesity serves as an important independent risk factor for uterine cancers. A cohort study of 68,253 women reported that t women with a BMI ≥30 kg/m^2 had a 5.34-fold increased risk of developing uterine cancers compared to those with normal BMI [48]. Similarly, it was also found that for every 5 kg/m^2 increase in BMI, the risk of uterine cancers increased by 1.39 to 1.50 times [49].

According to the Human Development Index (HDI), which categorizes countries and regions based on socioeconomic development levels, the three cancer types with the highest ASR in higher HDI areas are breast cancer, lung cancer, and thyroid cancer, with respective ASR of 54.1 per 100,000, 20.7 per 100,000, and 20.2 per 100,000. Conversely, in areas with lower HDI, the most prevalent cancers are breast cancer, cervical cancer, and ovarian cancer, with ASR of 30.8 per 100,000, 19.3 per 100,000, and 6.0 per 100,000, respectively [50]. The higher cancer incidence observed in high-HDI regions is likely attributable to improved detection and diagnostic capabilities, as well as lifestyle-related risk factors.

With respect to breast cancer among women of reproductive age, high-income countries with elevated incidence rates have experienced a decline in mortality since the 1990s, primarily attributable to advances in therapeutic interventions and the implementation of effective screening programs [51]. Conversely, both the incidence and mortality rates of breast cancer are rapidly increasing in developing countries across Asia, Africa, and Latin America, [52–53] as well as in developed Asian nations such as Japan and South Korea [54]. Sub-Saharan African countries exhibit the highest breast cancer mortality rates globally and poor prognoses, [55] a situation that largely reflects limited access to healthcare resources and services [56].

The incidence and mortality rates of cervical cancer are significantly higher in developing countries compared to developed nations, primarily due to limited access to screening and HPV vaccination. Improvements in protected sexual practices, reduced parity, and a lower prevalence of sexually transmitted infections have contributed to a progressive decline in the risk of persistent high-risk HPV infection, resulting in a general decrease in cervical cancer incidence across many regions [57]. Furthermore, the implementation of organized cervical cancer screening programs in Europe, Oceania, and North America has

played a substantial role in reducing both incidence and mortality rates. Nonetheless, an increase in cervical cancer risk among young women has been observed in certain countries, [58,59] highlighting the limitations of screening alone in fully mitigating the risks associated with HPV transmission [60]. Recent studies have reported a slight rise in cervical cancer incidence in Japan and China between 2007 and 2017, as well as increased incidence in the Baltic region of Europe, Eastern Africa, and Southern African countries [61].

Identifying high-risk factors for ovarian cancer and implementing targeted screening or prevention strategies are essential for reducing the disease burden in women. According to 2022 statistics, over 200, 000 women worldwide died from ovarian cancers, [50] with 70 % of cases diagnosed at advanced stages and a comparable proportion experiencing recurrence within two years. Additionally, nearly 70 % of ovarian cancer patients have a survival period of less than five years [62]. The early symptoms of ovarian cancer are nonspecific, contributing to a high rate of misdiagnosis [63]. Pathogenic variants in the BRCA1/2 genes account for approximately 15 % to 20 % of ovarian cancer cases. For individuals with a family history of hereditary susceptibility genes, BRCA1/2 genetic testing has become the standard for early ovarian cancer screening [64–65]. Mutations in these genes confer substantial genetic susceptibility, with carriers facing a markedly increased lifetime risk of developing ovarian cancer [66]. Genetic testing also enables personalized tailoring of maintenance therapies and chemotherapy regimens, thereby reducing unnecessary drug toxicities [67–68]. Furthermore, a population-based study of over 450,000 women in Utah, USA, found that women with endometriosis had a 3.2-fold increased risk of developing ovarian cancer compared to women without endometriosis. Importantly, those with deep infiltrating and/or ovarian endometriosis exhibited an 8.7-fold increased risk, and the risk of developing type I ovarian cancer was nearly 1.8 times higher in this population [69].

The strengths of this review include its utilization the GBD 2021 dataset, which represents the largest and most recent prospective cohort available. Compared to the Global Cancer Incidence, Mortality and Prevalence *GLOBOCAN* 2018 study, the GBD 2021 encompasses a greater number of participants, partly due to the inclusion of data from 19 additional countries. Furthermore, the GBD 2021 study integrates data from multiple cancer registry databases, such as the Surveillance, Epidemiology, and End Results (SEER) program in the United States, Cancer Incidence in Five Continents (CI5), the European Cancer Registry (EUREG), and the Nordic cancer database (NORDCAN), thereby enhancing the comprehensiveness and robustness of the dataset [70–72].

This review also has several limitations. First, data from countries with lower SDI may be less reliable due to limited access to cancer diagnostic tools, which could potentially bias cancer incidence estimates. Second, significant variation in incidence, DALYs, and mortality may exist across different subtypes of female cancers; however, granularity was not available for analysis in this review. Third, while this analysis focused on female cancers—including breast, uterine, and ovarian cancers—subtype-specific information for these malignancies was not captured due to limitations in the GBD dataset. Forth, estimation bias exits due to the inherent limitations of GBD, such as sparse or incomplete cancer registry data in some countries. Fifth, there may be significant heterogeneity arising from variability in national definitions of urban and rural classifications, which can reduce the robustness of between-country comparisons. Finally, although genetic risk factors are known to influence the epidemiology of female cancers in women of reproductive age, the GBD 2021 dataset does not provide genetic information, precluding an assessment of the contribution of genetic risk factors to these cancers.

In conclusion, the global incidence of breast, uterine, and ovarian cancers among WCBA has increased over the past decade, with age-standardized rates also demonstrating an upward trend. While the incidence of cervical cancer increased, its ASR declined. Interestingly, DALYs associated with breast, cervical, and ovarian cancers exhibited significant decreases overall; however, DALYs attributable to ovarian cancer increased in countries within the low-middle and low SDI quintiles. Similarly, although mortality rates for breast and cervical cancers declined globally, mortality in low SDI countries for these cancers continued to rise. Consequently, the implementation of policies targeting smoking cessation, alcohol control, HPV vaccination, and safe sex education holds considerable promise for reducing the incidence and mortality of female cancers among women of reproductive age, particularly in lower SDI countries. Advancing preventive and screening strategies for female cancers remains essential to further improve women's health during the childbearing years.

Author contributions

G.C.: study concept and design, data analysis, write the paper. S.Z.: data analysis and interpretation. Q.S.: write the paper. Y.X.: data analysis. T.F.: data analysis. R.X.: data analysis. Y.X.S.: methodologies. J.L.: methodologies, write the paper. Y.L.: methodologies. Z.L.: write the paper. G.Z.: write the paper. Y.W.: revise the paper. Y.Z.: data analysis. Y.F.: study concept and design, supervision. K.C.: study concept and design, write and revise the paper, supervision.

CRediT authorship contribution statement

Guang Chen: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Shichen Zhou:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Qiaoxin Shi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Yunqing Xun:** Investigation. **Tung-Leong Fong:** Investigation. **Ruogu Xiong:** Investigation. **Ya Xuan Sun:** Methodology. **Junjie Lu:** Methodology. **Yige Li:** Methodology. **Zheng Li:** Writing – original draft. **Guanghui Zhu:** Writing – original draft. **Ying Wu:** Supervision. **Yang Zhou:** Writing – original draft, Investigation. **Yibin Feng:** Writing – review & editing, Validation, Supervision, Conceptualization. **Karen K. L. CHAN:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing interests that could influence the work reported in this article.

Acknowledgments

All authors would like to thank the participants and research groups used in this article for providing publicly available data from GBD 2021.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2025.102473.

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