

Female breast cancer: an updated review of epidemiology, risk factors and prevention

Đekić Malbaša J^{1,2}, Tomas Petrović A^{1,3}, Radovanović D^{1,4}, Dugandžija T^{1,4}

¹Faculty of Medicine, University of Novi Sad, Novi Sad

²Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica

³Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Novi Sad, Novi Sad

⁴Oncology Institute of Vojvodina, Sremska Kamenica
Serbia

Abstract

Background: This narrative review focuses on the main risk factors and the available prevention measures for female breast cancer (BC), which is the most common malignancy in women worldwide.

Methods: We conducted a review of epidemiological studies and analysis of incidence, mortality, risk factors, and preventive measures for BC in studies published from 1999 to 2024 identified by searching the databases Web of Science, PubMed, and Google Scholar with key search terms “breast cancer”, “incidence”, “mortality”, “epidemiology”, “risk factors”, and “prevention.”

Results: Risk factors for BC include age, genetic predisposition, hormonal factors (early menarche and late menopause), and lifestyle habits such as alcohol consumption, tobacco smoking, physical inactivity, and poor diet. Although BC represents a growing global health problem, significant risk reduction can be achieved through modifying risk factors such as physical activity, a healthy diet, limiting alcohol consumption, maintaining a healthy weight, and cessation of tobacco smoking. Implementing organized prevention and screening programs for BC and timely application of appropriate treatment has led to a decrease in mortality from this disease in most developed countries.

Conclusion: Education and support for women in adopting healthy habits are crucial. Building sustainable infrastructure for disseminating preventive measures and treatment in low and middle-income countries is crucial for global BC control. HIPPOKRATIA 2024, 28 (4):135-142.

Keywords: Breast cancer, risk factors, healthy lifestyles, genetic predisposition, screening

Corresponding author: Jelena Đekić Malbaša, MD, PhD, Institute for Pulmonary Diseases of Vojvodina, Put doktora Goldmana 4, Sremska Kamenica 21204, Serbia, e-mail: jelena.djekic-malbasa@mf.uns.ac.rs

Introduction

Breast cancer (BC) is the most common malignancy in women worldwide, accounting for approximately 23.8 % of all malignant diseases and 15.4 % of all deaths in 2022¹. The incidence and mortality rates of female BC vary significantly worldwide. Variations in the availability and use of screening programs, socioeconomic disparities, and differences in lifestyle and hereditary factors can explain observed discrepancies. BC incidence is rising at distinct rates in different regions, while mortality rates have been decreasing in many high Human Development Index (HDI) countries, in contrast to increasing rates in low HDI countries. Additionally, mammography utilization varies among countries and correlates with the HDI, with lower HDI countries exhibiting lower rates of mammography use. These findings emphasize the importance of initiatives to improve mammography utilization in Europe, particularly in countries with lower levels of development where BC mortality rates are also among the highest in the region². Future studies assessing the combined contribution of environmental and hereditary

factors and socioeconomic statuses may explain global variations in BC incidence and mortality^{2,3}.

Meta-analyses have extensively described several factors significantly associated with the occurrence of BC. Specifically, risk factors include alcohol consumption, tobacco smoking, physical inactivity, overweight/obesity in both premenopausal and postmenopausal women, nulliparity, late pregnancy, breastfeeding, use of oral contraceptives (progesterone, estrogen/progesterone combination, and hormone replacement therapy), poor diet, and a history of radiation therapy⁴. Additionally, age at first childbirth is a significant factor influencing BC risk, with younger age at childbirth associated with reduced risk of estrogen receptor-positive/progesterone receptor-positive BC (ER+PR+), while it does not significantly affect the risk of estrogen receptor-negative/progesterone receptor-negative BC (ER-PR-)⁵. These findings provide important insights for prioritizing modifiable risk factors and designing effective prevention strategies. Despite this knowledge, measures concerning primary prevention of BC are limited, with the main emphasis on early detec-

tion and reducing mortality from BC (with a significant reduction ranging from 22 % to 33 %)⁶. By implementing organized prevention and screening programs for BC and timely administration of appropriate treatment, most developed countries have seen a decline in mortality from this disease, ranging from 12 % to 58 %⁷.

However, the high incidence rate, high mortality, and the economic burden that this disease imposes on national health services make it the greatest public health challenge in both developed and developing countries. The economic burden extends beyond direct costs, encompassing indirect expenses, lost years of life, and work productivity, affecting society as a whole⁸.

In this updated review, we explore the key risk factors for BC identified in women over the past two decades and evaluate the available prevention measures. Our aim is to understand the global trend of increasing incidence rates and underscore the importance of implementing effective prevention programs across all three levels of prevention.

Methods

This report provides detailed descriptions of BC incidence, mortality, key considerations surrounding risk factors, and opportunities for preventive measures, drawing from a thorough literature review of epidemiological studies. We conducted a literature review utilizing Web of Science, PubMed, and Google Scholar databases covering 1999 to 2024. The search keywords included “breast cancer”, “incidence”, “epidemiology”, “mortality”, “risk factors”, and “prevention.” This literature encompassed various types of studies, including systematic reviews, meta-analyses, controlled randomized studies, double-blind randomized studies, narrative reviews, monographs, guidelines, and texts from official websites.

Epidemiology of BC

The International Agency for Research on Cancer portrays BC as a significant global public health challenge, with around 2.3 million incidental cases and 666,103 deaths in 2022. By 2045, the number of newly diagnosed BC cases worldwide is anticipated to increase by more than 46.5 %, or over four million incidental cases annually. In 2022, the highest number of newly diagnosed BC cases was observed in Asia, while the lowest number was reported in Oceania (Figure 1 and Figure 2)¹.

One in twenty women have a chance to develop BC during their lifetime. BC among women contributes to increasing cancer-related morbidity and mortality globally, with 15.1 million disability-adjusted life years (DALYs)⁹.

BC incidence rates are increasing in most countries worldwide, attributed to socioeconomic and demographic changes. BC mortality rates vary among countries, depending on the level of economic development. High-income countries reported a decline in mortality rates for several decades due to improved survival, while an increasing trend is still observed in many low-income countries¹⁰,¹¹. The worldwide average BC incidence rate in women is 46.8 per 100,000, with significant differ-

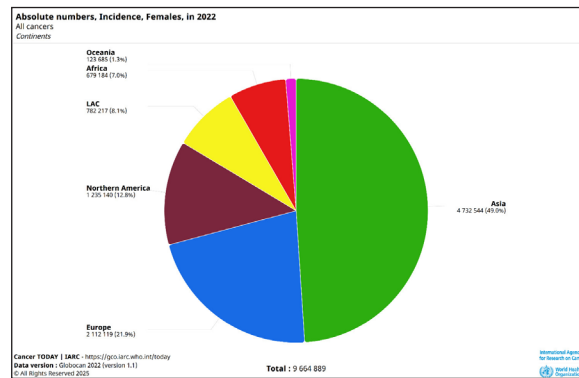


Figure 1: Distribution of breast cancer cases by world area in 2022. Figure was obtained from Reference 1 with permission from IARC/WHO for this specific publication. Copyright of this Licensed Materials remains vested in IARC/WHO.

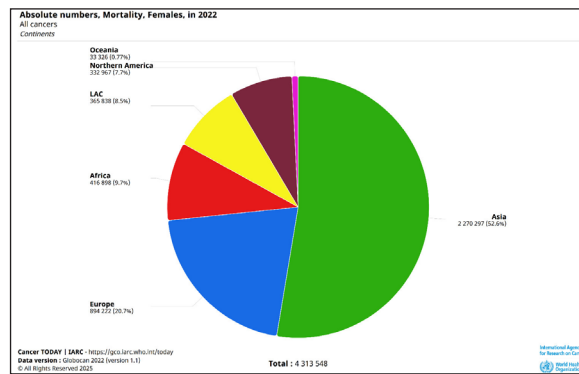


Figure 2: Distribution of breast cancer deaths by world area in 2022. Figure was obtained from Reference 1 with permission from IARC/WHO for this specific publication. Copyright of this Licensed Materials remains vested in IARC/WHO.

ences between the highest rate registered in North America (95.1 per 100,000) and the lowest in Asia (34.3 per 100,000). The global mortality rate is 12.7 per 100,000, with the highest rate registered in Africa (19.2 per 100,000) and the lowest in Asia (10.5 per 100,000). Europe ranks third globally in both BC incidence (75.6 per 100,000) and BC mortality in women (14.6 per 100,000) (Figure 3 and Figure 4)¹.

As the global burden is highest among women over 50 years of age, more than 70 % of all new cases and 81 % of all deaths occur in this age group¹².

From 1990 to 2013, the standardized BC incidence rate worldwide increased by 16.4 % (from 44.4 to 51.7 /100,000), particularly among women over 50. The increase in BC incidence rate results from earlier disease detection due to the implementation of organized BC screening and changes in the population’s age structure (demographic transition). During the observed period, the increase in BC incidence was significantly higher in developing countries (from 27.7 to 40.4 /100,000) than in developed countries (from 69.8 to 75.0 /100,000)¹¹. BC mortality rates in 2020 were significantly higher in transitional countries compared to developed (15 vs 12.8 /100,000)¹²,¹³.

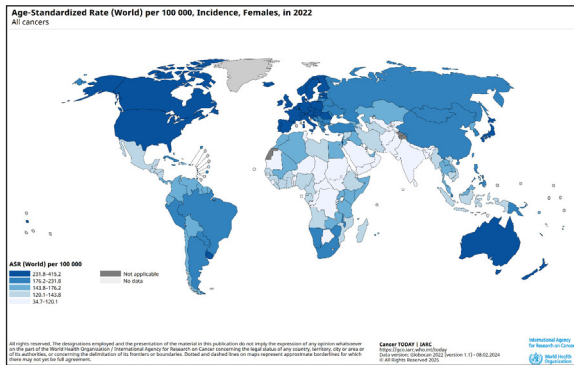


Figure 3: Age-standardized breast cancer incidence rates per 100,000 females. Figure was obtained from Reference 1 with permission from IARC/WHO for this specific publication. Copyright of this Licensed Materials remains vested in IARC/WHO.

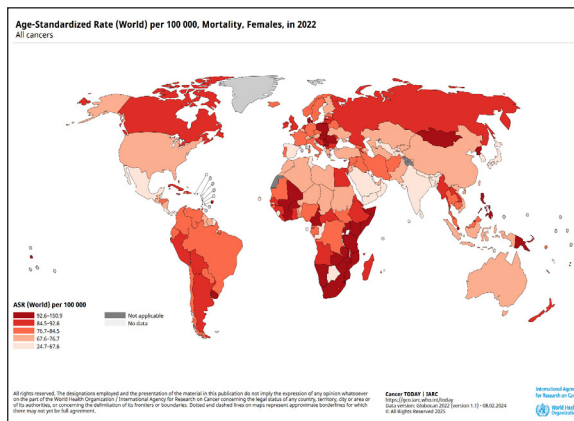


Figure 4: Age-standardized breast cancer mortality rates per 100,000 females. Figure was obtained from Reference 1 with permission from IARC/WHO for this specific publication. Copyright of this Licensed Materials remains vested in IARC/WHO.

Risk factors for BC

The primary causes of BC remain unknown despite numerous predisposing factors recognized. BC risk factors can be divided into modifiable and nonmodifiable, with 20 to 30 % of BC cases estimated to be attributable to modifiable factors and 5 to 10 % linked to genetic mutations and family history¹⁴. An individual's risk for developing BC depends on the presence and combination of these factors on an individual case basis. According to the BC risk factors' categorization, factors carrying high or moderate risk include previous BC, benign breast changes, dense breasts, high doses of radiation before the age of 30, and BC in first-degree relatives. In contrast, lower risk factors include reproductive factors (early menarche, late menopause, age at first birth, parity, not breastfeeding), hormone use (menopausal hormone therapy and oral contraceptives), poor diet, obesity, physical inactivity, alcohol consumption, tobacco smoking, and other less commonly mentioned factors^{4,15-17}. Each birth reduced the risk of ER+PR+ BC by 11 %, while women in the highest age at first birth group had a 27 % higher

risk than the youngest group. Neither age at first birth nor parity were associated with ER-PR- BC risk, whereas late menarche and breastfeeding decreased the risk of both receptor subtypes, with the protective effect of late menarche significantly greater for ER+PR+ compared to ER-PR- ($p=0.006$)⁵.

Sex and age as risk factors for BC

BC occurs 100 times less frequently in men than in women, while the risk among females increases after 50 years of age^{3,11}.

Genetic predisposition as risk factor for BC

According to research findings, *BRCA1* and *BRCA2* gene mutations account for at least $\frac{1}{3}$ to $\frac{1}{2}$ of inherited factors of BC. Alongside these genes, DNA sequencing advancements, such as next-generation sequencing, identified additional genes involved in BC susceptibility, including *TP53*, *PALB2*, *CDH1*, and *PTEN*. Also, an increased risk of BC development has been associated with various rare gene variants¹⁸. Despite this, eight out of nine women who develop BC do not have a mother, sister, or daughter who has had the disease. Although women with a close relative with a BC history are at increased risk of developing the disease, most will never develop BC, and those who do will be over 50 years old at the time of diagnosis. In regions with a high prevalence of BC, women who have one first-degree relative affected by the disease experience a lifetime increase in the incidence of 5.5 %, whereas those with two affected relatives have a 13.3 % increased risk^{19,20}.

Ionizing radiation as a risk factor for BC

The likelihood of developing BC is impacted by both the level of radiation exposure and the age at which exposure occurs, with the highest risk seen during puberty. Research findings suggest a decreased risk of BC with advancing age at radiation exposure while also highlighting a significant correlation between higher radiation doses and an elevated risk of developing the disease²¹. A meta-analysis showed that prior radiation therapy had no significant impact on BC risk, with a relative risk of 1.31 [95 % confidence interval (CI): 0.87-1.98]⁴. Although study findings are contradictory, BC screening and prevention programs should be established for long-term cancer survivors who have undergone chest radiotherapy.

Breast density on mammography as a risk factor for BC

Breast density on mammography, especially in premenopausal women, shows an increased risk of developing BC. Premenopausal women with breast density of 50 % or more had a 3.8 times higher risk compared to women with lower breast density^{22, 23}. Meta-analysis results showed that the risk of BC increased by 1.73 for every 25 % increase in breast density in postmenopausal women²⁴. Breast density seen during mammography may be a useful predictive tool for assessing BC occurrence in certain populations, aiding in the early identification of patients at increased risk.

Reproductive factors as risk factors for BC

Numerous epidemiological studies have examined the influence of various reproductive factors on BC development risk. Reproductive risk factors include early menarche (before 12 years of age), late menopause (after 50 years), age at first birth, and not breastfeeding^{5,16,20,24,25}. Also, nulliparous women had a six-fold higher risk of developing BC compared to those who had one or more children²⁵. A meta-analysis demonstrates a relative risk of 0.72 (95 % CI: 0.58-0.90) for exclusive breastfeeding compared to never breastfeeding. Exclusive breastfeeding is associated with a reduced risk of BC in parous women compared to those who do not breastfeed²⁴. Breastfeeding for six months or longer is a protective factor²⁰.

The latest research confirms that the risk of BC is associated with both endogenous (produced by the ovaries) and exogenous estrogens [such as hormone replacement therapy (HRT) and oral contraceptives]²⁶. Although oral contraceptives have been improved since the 1960s to reduce side effects, the risk of BC remains high for Iranian and African American women. However, after ten years of discontinuing oral contraceptives, there is no increased risk of BC^{27,28}. Numerous studies have shown that HRT, commonly used in menopausal women, may increase the risk of BC, with a significant decrease in risk observed after discontinuation, although recurrence rates remain high among previous HRT users with BC. Since the negative effects of HRT were discovered in 2003, the incidence rate of BC in America has decreased by 7 %¹⁴. The distinction between estrogen-only and combined hormone replacement therapies is crucial, as estrogen-only therapy has been associated with a reduced risk of BC, whereas combined therapy has shown an increased risk²⁹. A prospective nationwide cohort study of 15-34 years of age Swedish women found an increased risk of developing BC among users of combined hormonal contraceptives and a smaller risk associated with the current use of progestogen-only methods³⁰.

Obesity as a risk factor for BC

Evidence regarding the association between body excess weight and BC exists primarily for women in the postmenopausal period of life³¹. Overweight postmenopausal women [body mass index (BMI): 25-29.9] have an increased risk of BC by 12-13 %, while obesity (BMI: 30 and above) increases it by 16-20 % compared to women of normal or reduced weight (BMI below 25)³²⁻³⁴.

The differential impact of obesity on BC risk might help to explain why the incidence of estrogen receptor-negative tumors has decreased when excess body weight or obesity prevalence has increased, particularly among women with estrogen receptor-positive BC³³. Zhao et al further explored the impact of obesity on gene expression in breast tissue among premenopausal and postmenopausal women, revealing differing patterns between these groups. In premenopausal women with obesity, genes linked to breast cell proliferation, such as *RPS6KB1* and

estrogen receptor α (*ESR1*), showed decreased expression, while postmenopausal women with obesity exhibited increased expression of genes such as *PTGS2*, cyclin D1 (*CCND1*), and *TFF1*. These results imply that obesity's effect on breast cell proliferation may vary based on hormonal status, potentially influencing disparate BC risks in premenopausal and postmenopausal women with excess body weight³².

Sedentary lifestyle as a risk factor for BC

Physical activity reduces the level of sex hormones progesterone and estrogen, as demonstrated by a meta-analysis showing a 13-25 % reduction in BC risk in physically active compared to insufficiently active women. The risk of BC decreases by 5 % every two hours of increased moderate and vigorous physical activity per week. The protective effect of physical activity is most effective when regular exercise begins at a younger age^{16,35,36}.

Alcohol consumption as a risk factor for BC

Alcohol consumption, binge drinking included, is associated with a dose-response relationship with increased BC risk. The risk increases by 7-12 % for women who consume alcohol daily compared to those who do not consume alcohol^{16,37}.

Dietary risk factor for BC

Research on the influence of diet on the onset of BC is not entirely consistent. The European Prospective Investigation into Cancer and Nutrition (EPIC), a prospective multicenter study, was conducted across 10 European countries in 23 centers. This study's results align with the most recent evidence from the leading authorities on cancer prevention, suggesting that protective factors include regular consumption of fruits and vegetables, higher intake of fatty fish, and adherence to the Mediterranean diet principles. Conversely, alcohol consumption has been linked to increased BC risk³⁸. These findings underscore the importance of dietary and lifestyle modification in reducing risk among premenopausal women.

Tobacco smoking as a risk factor for BC

A meta-analysis revealed a moderate risk of BC in both active smokers [summary relative risk (SRR): 1.10, 95 % CI: 1.09-1.12] and passive smokers women (SRR: 1.07, 95 % CI: 1.02-1.13)³⁹. Results from a cohort study involving 102,927 women from 2003 to 2013 indicated that tobacco smoking is associated with an increased BC risk, particularly among women who started smoking during adolescence or pre-menarcheal period, as well as those with a family history of the disease⁴⁰. However, the International Agency for Research on Cancer has not yet accepted smoking as a definitive risk factor for BC due to inconsistencies among studies assessing its impact. Despite numerous studies indicating a potential increase in BC risk associated with tobacco smoking, a review spanning the last three decades reveals significant divergence

in opinions among clinical researchers. Furthermore, published meta-analyses have failed to reach consistent conclusions^{41,42}.

Prevention of BC

It has been shown that 20 to 30 % of BC cases may be attributable to modifiable factors¹⁴. However, a significant proportion of women developing BC have no known risk factors, and most known risk factors, such as sex, age, genetic mutations, family history, or previous BC, cannot be influenced.

Primary Prevention of Breast Cancer

In women with a hereditary predisposition to BC, chemoprevention and prophylactic surgical interventions are applied. The effects of prophylactic bilateral mastectomy in women at high risk for BC included in a retrospective cohort study indicated a 90 % reduction in disease incidence risk⁴³. Mastectomy with nipple preservation is considered the gold standard of surgical technique, providing superior cosmetic benefits without compromising oncological effectiveness. However, surgical procedures involve residual risks, surgical morbidity, potential consequences, and body image concerns. Despite the benefits, international guidelines emphasize that prophylactic mastectomy should be carefully considered⁴⁴. An analysis of ten studies showed a significant BC risk reduction in *BRCA1/2* mutation carriers following risk-reducing salpingo-oophorectomy (RRSO). The operation was associated with reduced BC risk in *BRCA1/2* mutation carriers [hazard ratio (HR): 0.49, 95 % CI: 0.37-0.65], *BRCA1* mutation carriers (HR: 0.47, 95 % CI: 0.35-0.64), and *BRCA2* mutation carriers (HR: 0.47, 95 % CI: 0.26-0.84)⁴⁵. These results confirm RRSO as an effective measure for reducing the risk of BC in women with *BRCA1/2* mutations, providing important guidelines for planning risk-reduction strategies⁴⁶. While this procedure can decrease estrogen production, it also entails the risk of inducing menopause and other health implications. The decision to undergo such surgery necessitates a thorough evaluation of benefits and risks, in consultation with a healthcare professional.

Chemoprevention in postmenopausal women, such as vitamins, selective estrogen receptor modulators (tamoxifen, raloxifene)⁴⁷, aromatase inhibitors and inactivators (anastrozole, exemestane, and letrozole)⁴⁸, and nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen)⁴⁹, has shown promising results in BC prevention. However, due to adverse effects, they continue to be investigated as potential preventive options.

Encouraging breastfeeding for its protective effects against BC is crucial. Genetic counseling and testing are essential for individuals with known genetic mutations or positive family history to assess risks and thus make informed decisions regarding preventive measures. Comprehending the specific hormone therapies' associated risks, particularly for managing menopausal symptoms, and healthcare providers' discussions on alternatives are

also vital components of BC prevention¹⁴.

Secondary prevention of BC

Previous research indicates that options for primary prevention of BC are still limited. Therefore, detecting the disease early by recognizing BC's early symptoms and signs is of tremendous importance.

Although some professional associations recommend breast self-examination (BSE) solely as a measure to raise awareness of the importance of breast examination, conducted studies have not confirmed its influence on reducing BC mortality. It has been confirmed that the frequency of biopsies due to benign changes increases, so BSE is not recommended as a screening test^{15,50}. The Commission of Senology of the Collège National de Gynécologie et Obstétrique Français conducted a study and adhered to the grading of recommendations assessment, development, and evaluation method to estimate the quality of evidence underlying the recommendations. The recommendation emerging from this research is that BSE should not be advised for women in the general population, given that they already benefit from clinical breast examination by practitioners from the age of 25, as well as organized screening from 50 to 74⁵¹.

Organized BC screening with mammography for women aged 40-75 years yields the best results in early detection of BC⁵². Adoption of BC screening programs through organized BC screening with mammography has reduced BC mortality, and the positive effects of organized screening were quickly established^{6,7}. The Swedish National Board of Health and Welfare study, conducted over 29 years, involved 133,065 women aged 40-74, randomized into screening and control groups. The analysis unveiled a significant decrease in BC mortality among women invited to screening. However, a comprehensive evaluation of the screening's effectiveness necessitates follow-up periods exceeding 20 years, as the observed reduction in BC deaths continues to increase over time⁵³. Results of a study conducted in the Netherlands show up to a 65 % reduction in BC mortality over time due to organized mammographic screening. Study findings indicate that the BC mortality rate detected through organized screening throughout the entire period was 35 % lower than that of women not included in the screening program [odds ratio (OR): 0.65, 95 % CI: 0.49-0.87]. Yearly analysis demonstrated increasing effectiveness, ranging from a 28 % reduction in BC mortality in the years 1975 to 1991 (OR: 0.72, 95 % CI: 0.47-1.09) to 65 % in the years 1992 to 2008 (OR: 0.35, 95 % CI: 0.19-0.64)⁵⁴. A similar study conducted in Norway showed a 28 % reduction in mortality in women participating in the screening program aged 50-79 years, undergoing mammography every two years⁵⁵. A cohort study examined the effectiveness of BC mammographic screening programs in the Friuli Venezia Giulia region in Italy, comparing the incidence of advanced stages of BC between women aged 50-69 who participated in the screening program and those who were not covered by screening. Women included in the

organized screening program had 13 % lower rates of positive lymph nodes of BC, 22 % lower rates of stage II+ BC, and 32 % lower rates of mastectomy compared to women not included in the organized screening program⁵⁶. The debate on whether BC preventive screenings cause more harm than good has long been present. It is crucial to provide women with transparent and objective information regarding the benefits and detriments of BC screenings so they can make informed decisions about participating in screening programs. This includes understanding that screenings can reduce BC mortality but can also result in overdiagnosis, meaning the detection of tumors that would not cause problems during a woman's lifetime. Therefore, it is important to support women in making informed decisions in consultation with their healthcare provider^{15,57}. Despite some potential biases, all studies consistently have shown the effectiveness of screening in reducing BC mortality.

However, the influence of socioeconomic factors on BC screening in Serbia highlights significant disparities in participation among women of varying socioeconomic backgrounds. Research findings suggest that women with moderate levels of education are more inclined to undergo screening than those with higher education levels voluntarily. Furthermore, women from higher socioeconomic backgrounds are more likely to initiate mammography screenings themselves compared to those experiencing financial difficulties⁵⁸. Mubarik et al point out significant disparities in the burden of BC across different regions, emphasizing the need to alleviate this health burden, particularly in less developed and underdeveloped countries facing disproportionate health-related challenges⁵⁹. The latest research suggests a significant association between the incidence and mortality of BC and country-level gender inequality, as measured by the gender development and gender inequality indexes (GDI and GII, respectively). While both GII and GDI show notable associations with BC incidence, GDI's association with BC mortality is weaker. However, there are direct relationships between GII and BC mortality. These findings emphasize the importance of addressing gender inequalities, especially in less developed countries, to potentially reduce the burden of breast cancer on a global scale⁶⁰.

These disparities underscore the necessity for customized interventions and support for individuals encountering socioeconomic obstacles to enhance participation in BC screening and facilitate access to preventive programs. Furthermore, there are notable differences in screening programs and mammography use between countries, particularly concerning the timing of program implementation. Moreover, variations in the timing and use of BC screening programs between countries are significant. Mammography utilization varies among countries, correlating with the HDI, particularly in Europe, where countries with lower levels of development exhibit lower rates of mammography use, aligning with higher breast cancer mortality rates in those regions². Public health managers should implement targeted and

cost-effective screening and treatment interventions to reduce BC-related mortality, particularly in middle and low Socio-Demographic Index countries with limited healthcare resources.

Conclusion

Among all cancer types, BC remains a leading cause of cancer morbidity and mortality in the female population worldwide. Although BS is a multi-factorial disease, its risk can be reduced through behavioral and lifestyle changes. However, measures concerning the primary prevention of BC remain limited. Providing accessible and comprehensive education regarding BC risks and symptoms can motivate individuals to take proactive measures and seek timely medical attention. Early detection and novel treatment options can decrease mortality and improve disease survival. To achieve better global BC control, and reduce inequalities in BC care, efforts should be made to develop sustainable infrastructure for organized BC screening and access to preventive measures in transitioning countries.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. World Health Organization. International Agency for Research on Cancer. Cancer Today. Available at: <https://gco.iarc.fr/today>, date accessed: 15/2/2024.
2. Cardoso R, Hoffmeister M, Brenner H. Breast cancer screening programmes and self-reported mammography use in European countries. *Int J Cancer*. 2023; 152: 2512-2527.
3. Fakhri N, Chad MA, Lahkim M, Houari A, Dehbi H, Belmouden A, et al Risk factors for breast cancer in women: an update review. *Med Oncol*. 2022; 39: 197.
4. Poorolajal J, Heidaramoghis F, Karami M, Cheraghi Z, Gohari-Ensaf F, Shahbazi F, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. *J Res Health Sci*. 2021; 21: e00520.
5. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res*. 2006; 8: R43.
6. Dibden A, Offman J, Duffy SW, Gabe R. Worldwide Review and Meta-Analysis of Cohort Studies Measuring the Effect of Mam-

- mography Screening Programmes on Incidence-Based Breast Cancer Mortality. *Cancers (Basel)*. 2020; 12: 976.
7. Zielonke N, Gini A, Jansen EEL, Anttila A, Segnan N, Ponti A, et al. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. *Eur J Cancer*. 2020; 127: 191-206.
 8. Milovic M, Tamas T, Crnobrnja V, Paut Kusturica M. Economic burden of breast cancer in northern Serbia. *Front Public Health*. 2023; 11: 1265301.
 9. GBD 2016 SDG Collaborators. Measuring progress and projecting attainment on the basis of past trends of the health-related Sustainable Development Goals in 188 countries: an analysis from the Global Burden of Disease Study 2016. *Lancet*. 2017; 390: 1423-1459.
 10. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136: E359-E386.
 11. Weedon-Fekjær H, Romundstad PR, Vatten LJ. Modern mammography screening and breast cancer mortality: population study. *BMJ*. 2014; 348: g3701.
 12. Arnold M, Morgan A, Rungay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. *Breast*. 2022; 66:15-23.
 13. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021; 71: 209-249.
 14. Obeagu EI, Obeagu GU. Breast cancer: A review of risk factors and diagnosis. *Medicine (Baltimore)*. 2024; 103: e36905.
 15. Moon HJ, Kim MJ, Kwak JY, Kim EK. Probably benign breast lesions on ultrasonography: a retrospective review of ultrasonographic features and clinical factors affecting the BI-RADS categorization. *Acta Radiol*. 2010; 51: 375-382.
 16. Nkondjock A, Ghadirian P. Facteurs de risque du cancer du sein [Risk factors and risk reduction of breast cancer]. *Med Sci (Paris)*. 2005; 21: 175-180.
 17. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. *Cancers (Basel)*. 2021; 13: 4287.
 18. Subaşıoğlu A, Güç ZG, Gür EÖ, Tekindal MA, Atahan MK. Genetic, Surgical and Oncological Approach to Breast Cancer, with *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN* and *TP53* Variants. *Eur J Breast Health*. 2023; 19: 55-69.
 19. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet*. 2001; 358: 1389-1399.
 20. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis*. 2018; 5(2): 77-106.
 21. Ng AK, Travis LB. Radiation therapy and breast cancer risk. *J Natl Compr Canc Netw*. 2009; 7: 1121-1128.
 22. Attam A, Kaur N, Saha S, Bhargava SK. Mammographic density as a risk factor for breast cancer in a low risk population. *Indian J Cancer*. 2008; 45: 50-53.
 23. Bai S, Song D, Chen M, Lai X, Xu J, Dong F. The association between mammographic density and breast cancer risk in Chinese women: a systematic review and meta-analysis. *BMC Womens Health*. 2024; 24: 131.
 24. Bae JM, Kim EH. Breast Density and Risk of Breast Cancer in Asian Women: A Meta-analysis of Observational Studies. *J Prev Med Public Health*. 2016; 49: 367-375.
 25. Unar-Munguía M, Torres-Mejía G, Colchero MA, González de Cosío T. Breastfeeding Mode and Risk of Breast Cancer: A Dose-Response Meta-Analysis. *J Hum Lact*. 2017; 33: 422-434.
 26. El Sharif N, Khatib I. Reproductive factors and breast cancer risk in Palestine: A case control study. *Cancer Epidemiol*. 2021; 74: 102019.
 27. Bethea TN, Rosenberg L, Hong CC, Troester MA, Lunetta KL, Bandera EV, et al. A case-control analysis of oral contraceptive use and breast cancer subtypes in the African American Breast Cancer Epidemiology and Risk Consortium. *Breast Cancer Res*. 2015; 17: 22.
 28. Soroush A, Farshchian N, Komasi S, Izadi N, Amirifard N, Shahmohammadi A. The Role of Oral Contraceptive Pills on Increased Risk of Breast Cancer in Iranian Populations: A Meta-analysis. *J Cancer Prev*. 2016; 21: 294-301.
 29. Manyonda I, Sinai Talaulikar V, Pirhadi R, Ward J, Banerjee D, Onwude J. Could Perimenopausal Estrogen Prevent Breast Cancer? Exploring the Differential Effects of Estrogen-Only Versus Combined Hormone Replacement Therapy. *J Clin Med Res*. 2022; 14: 1-7.
 30. Niemeyer Hultstrand J, Gemzell-Danielsson K, Kallner HK, Lindman H, Wikman P, Sundström-Poromaa I. Hormonal contraception and risk of breast cancer and breast cancer in situ among Swedish women 15-34 years of age: A nationwide register-based study. *Lancet Reg Health Eur*. 2022; 21: 100470.
 31. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, et al. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol*. 2015; 1: 611-621.
 32. Zhao H, Wang J, Fang D, Lee O, Chatterton RT, Stearns V, et al. Adiposity Results in Metabolic and Inflammation Differences in Premenopausal and Postmenopausal Women Consistent with the Difference in Breast Cancer Risk. *Horm Cancer*. 2018; 9: 229-239.
 33. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev*. 2014; 36: 114-136.
 34. Benn M, Tybjærg-Hansen A, Smith GD, Nordestgaard BG. High body mass index and cancer risk-a Mendelian randomisation study. *Eur J Epidemiol*. 2016; 31: 879-892.
 35. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer*. 2010; 46: 2593-2604.
 36. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat*. 2013; 137: 869-882.
 37. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015; 112: 580-593.
 38. Ubago-Guisado E, Rodríguez-Barranco M, Ching-López A, Petrova D, Molina-Montes E, Amiano P, et al. Evidence Update on the Relationship between Diet and the Most Common Cancers from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: A Systematic Review. *Nutrients*. 2021; 13: 3582.
 39. Macacu A, Autier P, Boniol M, Boyle P. Active and passive smoking and risk of breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2015; 154: 213-224.
 40. Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ. Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res*. 2017; 19: 118.
 41. Duan W, Li S, Meng X, Sun Y, Jia C. Smoking and survival of breast cancer patients: A meta-analysis of cohort studies. *Breast*. 2017; 33: 117-124.
 42. He Y, Si Y, Li X, Hong J, Yu C, He N. The relationship between tobacco and breast cancer incidence: A systematic review and meta-analysis of observational studies. *Front Oncol*. 2022; 12: 961970.
 43. Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Ar-

- nold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med*. 1999; 340: 77-84.
44. Franceschini G, Di Leone A, Terribile D, Sanchez MA, Masetti R. Bilateral prophylactic mastectomy in BRCA mutation carriers: what surgeons need to know. *Ann Ital Chir*. 2019; 90: 1-2.
45. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst*. 2009; 101: 80-87.
46. Bertozzi S, Londero AP, Xholli A, Azioni G, Di Vora R, Paudice M, et al. Risk-Reducing Breast and Gynecological Surgery for BRCA Mutation Carriers: A Narrative Review. *J Clin Med*. 2023; 12: 1422.
47. Lee WL, Cheng MH, Chao HT, Wang PH. The role of selective estrogen receptor modulators on breast cancer: from tamoxifen to raloxifene. *Taiwan J Obstet Gynecol*. 2008; 47: 24-31.
48. Mokbel K. The evolving role of aromatase inhibitors in breast cancer. *Int J Clin Oncol*. 2002; 7: 279-283.
49. Moris D, Kontos M, Spartalis E, Fentiman IS. The Role of NSAIDs in Breast Cancer Prevention and Relapse: Current Evidence and Future Perspectives. *Breast Care (Basel)*. 2016; 11: 339-344.
50. Dagne AH, Ayele AD, Assefa EM. Assessment of breast self-examination practice and associated factors among female workers in Debre Tabor Town public health facilities, North West Ethiopia, 2018: Cross-sectional study. *PLoS One*. 2019; 14: e0221356.
51. Lavoue V, Favier A, Franck S, Boutet G, Azuar AS, Brousse S, et al. French college of gynecologists and obstetricians (CNGOF) recommendations for clinical practice: Place of breast self-examination in screening strategies. *Breast*. 2024; 75: 103619.
52. Monticciolo DL, Malak SF, Friedewald SM, Eby PR, Newell MS, Moy L, et al. Breast Cancer Screening Recommendations Inclusive of All Women at Average Risk: Update from the ACR and Society of Breast Imaging. *J Am Coll Radiol*. 2021; 18: 1280-1288.
53. Tabár L, Vitak B, Chen TH, Yen AM, Cohen A, Tot T, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology*. 2011; 260: 658-663.
54. van Schoor G, Moss SM, Otten JD, Donders R, Paap E, den Heeten GJ, et al. Increasingly strong reduction in breast cancer mortality due to screening. *Br J Cancer*. 2011; 104: 910-914.
55. Weedon-Fekjær H, Romundstad PR, Vatten LJ. Modern mammography screening and breast cancer mortality: population study. *BMJ*. 2014; 348: g3701.
56. Giudici F, Bortul M, Clagnan E, Del Zotto S, Franzo A, Giordano L, et al. Effetti precoci dell'adesione al programma di screening mammografico della Regione Friuli Venezia Giulia sull'incidenza del cancro della mammella in stadio avanzato: uno studio di coorte [Early effects of attendance to the Friuli Venezia Giulia (Northern Italy) mammography screening programme on the incidence of advanced-stage breast cancer: a cohort study]. *Epidemiol Prev*. 2020; 44: 145-153.
57. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet*. 2012; 380: 1778-1786.
58. Djordjević S, Dimitrijević I, Boričić K, Radovanović S, Vukomanović IS, Mihaljević O, et al. Sociodemographic Factors Associated with Breast Cancer Screening among Women in Serbia, National Health Survey. *Iran J Public Health*. 2024; 53: 387-396.
59. Mubarik S, Yu Y, Wang F, Malik SS, Liu X, Fawad M, et al. Epidemiological and sociodemographic transitions of female breast cancer incidence, death, case fatality and DALYs in 21 world regions and globally, from 1990 to 2017: An Age-Period-Cohort Analysis. *J Adv Res*. 2021; 37: 185-196.
60. Kavousi S, Maharlouei N, Rezvani A, Akbari Aliabad H, Molavi Vardanjani H. Worldwide association of the gender inequality with the incidence and mortality of cervical, ovarian, endometrial, and breast cancers. *SSM Popul Health*. 2024; 25: 101613.