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Breast Cancer Epidemiology and Risk Factors: A Comprehensive Review

Ahmed Abdelhalim Yameny[1,2]

[1]Society of Pathological Biochemistry and Hematology, Egypt.

[2]Molecular Biology Department, Genetic Engineering and Biotechnology Research Institute (GEBRI), University of Sadat City, Egypt.

Corresponding author: Ahmed A. Yameny. Email: dr.ahmedyameny@yahoo.com

Tel: (002)01002112248, ORCID number: 0000-0002-0194-9010

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Abstract:

Breast cancer remains the most commonly diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality. Despite advances in screening and therapy, its global burden continues to rise, particularly in low- and middle-income countries, highlighting rising incidence in Asia and persistently high mortality in sub-Saharan Africa. The disease's incidence reflects a complex interplay between genetic, hormonal, environmental, and lifestyle determinants. Established risk factors include age, family history, reproductive behavior, hormonal exposure, obesity, alcohol consumption, and radiation exposure. Strong evidence supports associations between breast cancer risk and high mammographic breast density, hormonal exposures (hormone replacement therapy and oral contraceptives), early menarche, late menopause, delayed first childbirth, and limited breastfeeding duration. Genetic factors, notably BRCA1 and BRCA2 mutations, contribute to 5–10% of cases, predominantly in younger women and those with family history. Emerging evidence implicates atrial fibrillation, metabolic syndrome, and microbiome alterations in modulating breast cancer susceptibility. Meanwhile, protective factors such as physical activity, breastfeeding, and healthy dietary patterns have shown potential to mitigate risk. This review synthesizes current epidemiological trends and evidence-based risk factors contributing to breast cancer development, highlighting regional disparities, modifiable exposures, and emerging genetic insights. Understanding these determinants is essential to guide preventive strategies, early detection, and tailored public health interventions.

Keywords: breast cancer, epidemiology, risk factors, genetics, prevention, global health

1. Introduction:

Breast cancer (BC) is the most prevalent cancer among women globally and a major public health concern, representing nearly one in four cancer diagnoses in females (1). According to GLOBOCAN 2020 estimates, approximately 2.3 million new cases and 685,000 deaths were attributed to breast cancer worldwide (2). While incidence rates are higher in high-income regions such as North America and Western Europe, mortality remains disproportionately elevated in low- and middle-income countries due to limited access to screening, early diagnosis, and effective treatment (3,4).

The epidemiology of breast cancer reflects multifactorial etiologies that encompass both **non-modifiable** and **modifiable** risk determinants. Non-modifiable factors include **age**, **genetic predisposition**, and **reproductive history**, notably

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mutations in the *BRCA1* and *BRCA2* genes, which confer a lifetime risk as high as 70% (5). **Modifiable risk factors**, such as obesity, physical inactivity, alcohol intake, and hormone replacement therapy, also play crucial roles in disease pathogenesis through hormonal and metabolic pathways (6,7).

Epidemiological trends indicate shifting patterns in incidence linked to reproductive transitions, urbanization, and lifestyle westernization in developing regions (8). Furthermore, molecular and genomic studies have advanced understanding of disease heterogeneity, emphasizing that breast cancer comprises biologically distinct subtypes with variable risk profiles and outcomes (9).

This review aims to summarize contemporary knowledge on the **epidemiology and risk factors of breast cancer**, integrating global data to delineate trends, identify modifiable exposures, and support evidence-based prevention strategies.

I. Global Epidemiological Trends

Incidence and Burden:

Breast cancer represents a substantial global public health burden, constituting the most frequently diagnosed cancer among women worldwide. In 2022, breast cancer accounted for approximately 2.3 million new cases globally, representing 11.6% of all cancer diagnoses and 31% of all cancer diagnoses in women. The disease is now the most common cancer among women in 157 out of 185 countries, with incidence rates continuing to rise despite medical advances (10).

Global age-standardized incidence rates (ASR) demonstrate striking geographical variation. Developed regions, including Europe, North America, Australia, and New Zealand, report the highest incidence rates, exceeding 80 per 100,000 women annually, while developing countries report substantially lower rates below 40 per 100,000, though underreporting in resource-limited settings remains a significant concern. More specifically, very high human development index (HDI) countries demonstrate ASRs of 70.9 per 100,000, compared to high HDI countries at 44.4 per 100,000, and middle to low HDI countries at 32.5-33.6 per 100,000 (11).

Mortality and Global Disparities:

Breast cancer caused approximately 670,000 deaths globally in 2022, accounting for roughly 7% of all cancer-related deaths worldwide and representing the leading cause of cancer death among women. However, mortality patterns reveal profound inequalities across global regions. Africa demonstrates the highest mortality-to-incidence slope values, indicating disproportionately high mortality relative to incidence, particularly in younger women (ages 0-39). This disparity reflects limited screening infrastructure, delayed diagnoses at advanced stages, and restricted access to effective treatment options (12).

Conversely, developed nations such as North America exhibit negative slope values between mortality and incidence, indicating lower mortality despite higher incidence rates, reflecting the benefits of early detection programs and advanced therapeutic interventions. In 2050, breast cancer is projected to represent a substantially increased global burden, with projections indicating significant increases across continents and HDI levels, with Asia maintaining the highest absolute number of cases (13).

International Perspectives: Regional Variations

China

China reported 385,837 new breast cancer cases in 2021, representing a 103% increase in age-standardized incidence rates from 1990 to 2021. Rapid increases reflect urbanization, reproductive pattern changes (delayed childbearing, reduced parity, decreased breastfeeding), increasing obesity rates, and improved cancer detection through expanding screening programs (14).

Asia

Asia accounted for 985.4 thousand new breast cancer cases and 315.1 thousand deaths in 2022, with age-standardized incidence and mortality rates of 34.3 and 10.5 per 100,000, respectively. Substantial regional variation exists within Asia, with Eastern Asia, South Central Asia, and South-Eastern Asia demonstrating divergent trends and projections for 2050 (13).

Africa

Africa demonstrates concerning epidemiological patterns with the highest mortality-to-incidence slope values globally. A cohort study in Ghana revealed that only 10.3% of diagnosed patients presented with early-stage (stages I-II) disease, while 50% presented with stage III and 39.3% with stage IV breast cancer, reflecting late-stage presentation patterns common across sub-Saharan Africa. Genetic factors, including high prevalence of triple-negative breast cancer subtypes and BRCA1 mutations among African populations, contribute to aggressive disease phenotypes (15).

II. Breast Cancer Risk Factors

1. Non-Genetic Risk Factors and Epidemiological Evidence

Methodological Framework

Recent systematic reviews and meta-analyses have synthesized extensive literature on breast cancer risk factors. An umbrella review analyzing 281 meta-analyses of cohort studies identified only five (1.8%) associations meeting criteria for strong evidence, eight (2.8%) demonstrating highly suggestive evidence, 23 (8.2%) showing suggestive evidence, and 55 (19.6%) providing weak evidence. This limited consensus reflects heterogeneous study designs, varying population characteristics, and methodological variations across studies (16).

Established Protective and Risk Factors with Strong Evidence

The strongest epidemiological evidence supports the following associations with breast cancer risk:

A. Breast Density:

High breast density demonstrates the strongest association with increased breast cancer risk, with summary relative risks ranging from 2.57 to 3.25, representing nearly a threefold increased risk in women with the highest compared to the lowest breast density categories. Breast density reflects the proportion of fibroglandular tissue and is influenced by age, menopausal status, and body mass index (16).

B. Pre-existing Medical Conditions:

Atrial fibrillation (AF) history and use of cardiac glycosides (particularly digoxin) emerged as strong risk factors, with AF associated with an 18% increased risk (95% CI: 1.14-1.22) and cardiac glycoside use with a 39% increased risk (95% CI: 1.33-1.45). The mechanisms linking AF and digoxin use to breast cancer remain incompletely understood but may involve estrogenic properties of cardiac glycosides and shared systemic inflammatory pathways (16).

C. Protective Factors:

Postmenopausal women with body mass index (BMI) ≥25 demonstrate a 14% reduced breast cancer risk compared to those with BMI <25, yielding a protective association with a relative risk of 0.86 (95% CI: 0.81-0.91). Additionally, adherence to vegetable-fruit-soybean dietary patterns showed strong protective associations with a relative risk of 0.87 (95% CI: 0.83-0.92) (16).

2. Reproductive Factors

Reproductive factors represent major modifiable influences on breast cancer risk and demonstrate complex, often bidirectional associations with breast cancer susceptibility.

Age at Menarche:

Early age at menarche is consistently associated with increased breast cancer risk across multiple

epidemiological studies. Women with early menarche (before age 12) experience greater cumulative estrogen exposure during critical periods of breast tissue development and differentiation, resulting in elevated relative risks compared to women with late menarche. The protective effect of late menarche reflects reduced years of ovulatory cycles and diminished cumulative hormone exposure during vulnerable developmental windows (17).

Age at Menopause:

Later age at menopause substantially increases breast cancer risk, with relative risks increasing approximately 3% per year of delayed menopause. The extended duration of ovulatory cycles and endogenous estrogen production in women experiencing late menopause confers increased cumulative hormonal exposure to the breast epithelium. Natural menopause after age 55 is associated with substantially elevated risk compared to menopause before age 45 (18).

Pregnancy and Age at First Birth:

The relationship between pregnancy and breast cancer demonstrates temporal complexity. While parity (having children) generally exerts a protective effect on lifetime breast cancer risk, this protection is not immediate. The age at first full-term pregnancy significantly influences risk patterns: earlier first pregnancies confer greater long-term protection, while later first pregnancies substantially increase risk. Women with their first full-term pregnancy after age 35 demonstrate substantially elevated relative risks compared to nulliparous women, whereas those with their first birth before age 20 show reduced risks (19).

Notably, following childbirth, an elevated temporary risk period persists for up to 20-25 years, particularly for hormone receptor-positive breast cancers, particularly in women with later first pregnancies. This transient elevation reflects pregnancy-induced proliferation of breast epithelium and increased systemic estrogen levels during pregnancy and lactation (20).

Parity and Number of Births

Higher parity exerts substantial protective effects against breast cancer development. The protective association strengthens with an increasing number of births, with pooled analyses indicating relative risk reductions of 5-10% per birth. However, evidence suggests this protective effect has weakened in younger birth cohorts, potentially reflecting changing reproductive patterns, increased hormone replacement therapy use, and altered lifestyle factors across generations (21).

Breastfeeding:

Breastfeeding duration demonstrates dose-dependent protective associations with breast cancer risk. Each month of breastfeeding is associated with approximately 2% reduction in breast cancer risk (RR=0.98 per month, 95% CI 0.97-1.00). Women who have breastfed for 12 months or longer demonstrate substantially reduced risk compared to never-breastfeeding women. The protective mechanisms involve lactation-induced epithelial differentiation, reduced ovulatory cycles, and altered endocrine function (17).

3. Exogenous Hormonal Exposures:

Hormone Replacement Therapy:

Current and recent use of hormone replacement therapy (HRT), particularly estrogen-progestin combinations, is associated with increased breast cancer risk. The Women's Health Initiative and numerous observational cohort studies demonstrate that HRT use is associated with elevated relative risks ranging from 1.2 to 1.5, depending on formulation, duration, and hormone type. Risk increases with duration of use and decreases following cessation, with residual risk persisting for approximately 10 years post-discontinuation. The

risk is particularly elevated for hormone receptor-positive cancers in postmenopausal women (22).

Oral Contraceptive Use:

Current and recent oral contraceptive (OC) use is associated with modestly elevated breast cancer risk, with meta-analyses demonstrating relative risk increases of approximately 20-25% during current use. Risk appears to decline following cessation of OC use, approaching baseline risk within 10 years. The timing of initiation appears important, with earlier use potentially conferring differential risk compared to later initiation (17).

4. Obesity and Anthropometric Factors

The relationship between body mass index and breast cancer demonstrates striking heterogeneity according to menopausal status, with opposite associations observed in premenopausal versus postmenopausal women (23).

Premenopausal Women:

In premenopausal women, obesity (BMI ≥30) is associated with increased breast cancer risk, likely reflecting elevated circulating androgen levels and reduced sex hormone-binding globulin (SHBG) concentrations, resulting in increased bioavailable estrogens. Relative risks range from 1.3 to 1.7 for obese compared to normal-weight premenopausal women, with stronger associations observed for triple-negative and estrogen receptor-negative subtypes (24).

Postmenopausal Women:

Conversely, in postmenopausal women, obesity demonstrates a protective association with breast cancer risk, paradoxically contrary to the premenopausal pattern. BMI ≥30 in postmenopausal women is associated with a 10-40% reduced breast cancer risk compared to normal weight, particularly for hormone receptor-positive subtypes. This paradoxical association likely reflects competing mechanisms: while obesity increases circulating estrogens through peripheral aromatization in adipose tissue, it simultaneously reduces mammographic breast density (a strong breast cancer risk factor), achieves lower BMI in younger life before obesity develops, and creates metabolic alterations unfavorable for hormone-sensitive cancer development (23).

5. Lifestyle and Dietary Factors

Physical Activity:

Consistent epidemiological evidence demonstrates that higher physical activity levels confer protective associations with breast cancer risk. Vigorous physical activity demonstrated protective associations with relative risks of 0.79 in premenopausal women (95% CI: 0.79; $I^2 = 6\%$) and 0.90 in postmenopausal women. The protective mechanisms involve reduced body weight, improved insulin sensitivity, altered sex hormone levels, and reduced systemic inflammation (22).

Alcohol Consumption:

While frequently cited as a risk factor, meta-analyses reveal conflicting evidence regarding alcohol consumption and breast cancer risk. Some meta-analyses report positive associations with relative risks of 1.28 for the highest versus lowest alcohol intake categories, while others report insufficient evidence for association. High heterogeneity and inconsistent adjustment for confounding variables limit definitive conclusions. The proposed mechanism involves alcohol's effects on estrogen metabolism and hepatic function (22).

Dietary Patterns:

Strong evidence supports protective associations of vegetable-fruit-soybean dietary patterns (RR=0.87; 95% CI: 0.83-0.92), while weaker associations exist for individual dietary components. Meta-analyses examining red and processed meat consumption demonstrate inconsistent results, with some finding positive associations in premenopausal women and others reporting no significant association. Dietary calcium demonstrates protective associations, while

high glycemic index and ultra-processed food consumption show positive associations with increased breast cancer risk(25).

6. Genetic and Familial Factors

BRCA1/BRCA2 Mutations:

Hereditary breast cancer accounts for approximately 5-10% of all breast cancer cases, with germline mutations in BRCA1 and BRCA2 genes conferring lifetime breast cancer risks of 45-87% depending on mutation type, family history, and modifying factors. BRCA1 mutations are particularly associated with triple-negative and estrogen receptor-negative cancers, often presenting at earlier ages, while BRCA2-associated cancers demonstrate more heterogeneous phenotypes. Other high-penetrance genes, including TP53, PTEN, and PALB2, account for smaller proportions of hereditary breast cancer (26).

Family History and Genetic Risk Assessment:

Women with a positive family history of breast cancer, particularly those with affected first-degree relatives, demonstrate substantially elevated risk. The Breast Cancer Risk Prediction Project, analyzing data from over 1.8 million women across 20 prospective cohorts, is developing comprehensive risk prediction tools incorporating reproductive history, anthropometry, smoking, alcohol intake, and emerging genetic markers to predict breast cancer risk across racial and ethnic groups and by tumor subtypes (26).

7. Age-Related Patterns and Birth Cohort Effects

Breast cancer incidence demonstrates strong age-related patterns, with incidence rates increasing exponentially with advancing age, particularly beyond age 50. However, younger women diagnosed with breast cancer (ages <40) often present with more aggressive subtypes, including triple-negative and BRCA1-associated cancers (27).

Birth cohort analyses reveal important temporal trends in breast cancer epidemiology. Protective associations of parity diminish in younger birth cohorts compared to older cohorts (hazard ratios of 0.86 in 1950s cohort versus 0.60-0.73 in earlier cohorts), while lifestyle factors including smoking and alcohol consumption show stronger associations with breast cancer risk in more recent birth cohorts (21).

8. Occupational and Environmental Exposures

Flight Attendants:

Flight attendants demonstrate elevated breast cancer risk, likely due to combined occupational exposures including circadian disruption, cosmic radiation, and potential chemical exposures. Relative risks for flight attendants compared to the general population range from 1.3 to 1.7 across studies (22).

Shift Work and Circadian Disruption:

Night shift work and circadian disruption are associated with elevated breast cancer risk through mechanisms involving melatonin suppression, altered cortisol rhythms, and disrupted circadian regulation of cell cycle control. Meta-analyses demonstrate relative risk increases of 1.15-1.25 for night shift workers compared to day workers (22).

Environmental Chemical Exposures:

Occupational exposure to organic solvents and polychlorinated biphenyls (PCBs) has been associated with increased breast cancer risk in some studies, though evidence remains limited and potentially confounded by other occupational exposures and lifestyle factors (22).

9. Socioeconomic Factors and Health Disparities

Breast cancer epidemiology demonstrates an unusual inverse socioeconomic gradient compared to most chronic diseases. Women with higher education and socioeconomic status experience higher breast cancer incidence rates, likely reflecting adoption of identified risk factors, including delayed childbearing, reduced breastfeeding, increased hormone replacement therapy use, and higher alcohol consumption. Conversely, women with

lower socioeconomic status experience higher mortality rates despite lower incidence, reflecting disparities in screening access, diagnostic delay, and treatment quality (15).

10. Emerging Risk Factors and Biomarkers

Circulating Biomarkers:

Meta-analyses identified several circulating biomarkers associated with breast cancer risk meeting criteria for strong to highly suggestive evidence. High insulin-like growth factor-1 (IGF-1) levels demonstrate causal associations with increased breast cancer risk through Mendelian randomization analysis (RR=1.08; 95% CI: 1.02-1.14). Sex hormone-binding globulin (SHBG), the primary binding protein for estrogens and androgens, demonstrates strong protective associations (RR=0.64; 95% CI: 0.58-0.73), with lower SHBG levels associated with increased breast cancer risk across subtypes (16).

Atrial Fibrillation and Metabolic Syndrome:

Beyond traditional cardiovascular disease associations, atrial fibrillation independently associates with increased breast cancer risk (RR=1.18; 95% CI: 1.14-1.22), suggesting shared etiological pathways or unmeasured confounding. Metabolic syndrome components, including elevated triglycerides and dysglycemia, demonstrate positive associations with breast cancer incidence (16,28).

Microbiome Alterations:

Emerging research suggests breast tissue and gut microbiome composition may influence breast cancer risk through altered estrogen metabolism (the "estrobolome") and systemic immune regulation, though clinical translation remains preliminary (29).

Conclusion

Breast cancer epidemiology reflects a complex interplay of genetic predisposition, reproductive factors, endocrine exposures, lifestyle choices, occupational exposures, and socioeconomic determinants. While only five associations met criteria for strong epidemiological evidence in recent meta-analyses, convergent findings across multiple studies and biological plausibility support the established risk factors. The global burden of breast cancer continues rising, with particularly concerning trends in developing regions where limited healthcare infrastructure results in late-stage presentation and high mortality despite lower incidence rates. Future epidemiological research must prioritize inclusion of diverse populations, mechanistic investigation of identified associations, and implementation of evidence-based prevention strategies tailored to population-specific risk factor distributions and healthcare system capacity.

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