Is Primary Prevention of Breast Cancer Achievable?

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Abstract:

Breast cancer is the number one enemy in many countries and the number two enemy, after lung cancer, in women in other countries. Statistically, the incidence of this disease varies in different parts of the world, so that in Korea, Japan, and other Asian and African countries, it is considerably lower than in Northern Europe and North America.

This is probably due to dietary habits, avoidance of smoking and alcohol, lack of physical inactivity, and being overweight. To some extent, the risk of developing the disease can be reduced by changing one's lifestyle. On the other hand, the incidence is also associated with race, a personal history of breast cancer, different ages of life, weight and height, heredity, family history, and genetic risk factors. These factors cannot be changed, but there are strategies that, with knowledge of them and by using them, can help identify the disease at an early stage, treat it, or significantly increase the patient's lifespan.

By studying these factors, we realize that this disease is not as frightening and uncontrollable as it is perceived by many women. Even through genetic testing and identifying individuals who have genetic mutations caused by genetic alterations, it is also possible to help these patients achieve longer-term recovery.

Keywords: ***Breast Neoplasms, Disease Prevention, Surveillance, Lifestyle Modification, Risk Factor***

Introduction

Epidemiological investigations consistently highlight significant geographical variations in the incidence of breast carcinoma. Western nations exhibit markedly higher age-standardized incidence rates compared to Asian and Far Eastern populations—a disparity primarily driven by distinct dietary patterns, environmental exposures, and reproductive behavior. While non-modifiable biological factors define an individual's baseline risk, modulating modifiable determinants

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represents a primary strategy for population-level risk reduction.

Primary lifestyle-based intervention rests upon four core modifiable pillars: routine physical exercise, total alcohol cessation, tobacco avoidance, and a transition toward a predominantly plant-based diet with restricted intake of red meat and high-fat dairy products. Rigorous adherence to these preventive strategies significantly attenuates lifetime risk, conferring up to a 50% risk reduction in premenopausal women (<50 years) and up to an 80% protective effect in postmenopausal cohorts.[1,3]

While all females remain susceptible to breast carcinogenesis, individual risk profiles vary considerably. Endogenous biological factors dictate this baseline risk independently of lifestyle interventions.[1,2]

Sex-Specific Susceptibility

B Biological sex remains the foremost non-modifiable determinant of breast cancer risk, driven by the presence of functional mammary epithelium and the XX chromosomal complement compared to XY in males. According to the International Agency for Research on Cancer (IARC), breast cancer is the most prevalent female malignancy globally, with approximately 1.67 million newly diagnosed cases annually, representing roughly 25% of all female cancer diagnoses. While breast cancer constitutes the leading cause of oncological mortality among women in developing nations, lung adenocarcinoma predominates in developed countries.

Global incidence exhibits substantial geographic variation, ranging from 27 per 100,000 individuals in Central Africa and East Asia to 93 per 100,000 in the United States and 112 per 100,000 in Belgium. This disparity correlates directly with differences in life expectancy, industrialization, and reproductive demographics.

Male breast carcinoma represents an uncommon entity, accounting for under 1% of all breast cancer diagnoses due to the limited development of male glandular tissue. In the United States, male incidence is approximately 0.8% of female rates (~2,470 annual cases, establishing a 120:1 female-to-male ratio), whereas European studies report an incidence between 1% and 4%. Germline mutations in BRCA2, BRCA1, TP53, and PTEN serve as primary genetic drivers in male cases. Additional predisposing factors include prior skeletal fractures, infertility/nulliparity, previous thoracic radiation exposure, diabetes mellitus, and clinical conditions inducing hyperestrogenism relative to androgens (e.g., morbid obesity, taller stature, cryptorchidism, orchiectomy, orchitis, and Klinefelter syndrome [47,XXY]). The prevalence of male gynecomastia in the United States demonstrated an upward trend, reaching 1.8% in 2000.[2,4-6]

Age & Reproductive Kinetics

Incidence increases exponentially with advancing age. Although premenopausal diagnoses (<50 years) represent a substantial burden in clinical practice, cumulative incidence rises dramatically in postmenopausal cohorts. The standard epidemiological metric stating that "1 in 8 women will develop breast cancer" reflects cumulative lifetime risk up to age 85. Age-specific risk stratification provides more refined clinical context: a 40-year-old female carries a 10-year cumulative probability of 1.5% (1 in 68).

Early menarche accelerates cumulative exposure of breast tissue to endogenous estrogens. In the United States, the mean age at menarche is 12.5 years (range: 9–16 years), reflecting a secular downward trend over the past 150 years. Menarche prior to age 10 is associated with a 23% relative increase in breast cancer risk, whereas delayed menarche (>16 years) yields a 50% risk reduction, underscoring the protective effect of shortened reproductive exposure. Early menarche also correlates with higher risks of ovarian carcinoma, obesity, metabolic syndrome, type 2 diabetes, and hyperlipoproteinemia.

Environmental endocrine-disrupting chemicals (EDCs)—such as polychlorinated biphenyls (PCBs), bisphenol A (BPA), and phthalates present in cosmetics, industrial detergents, hair treatments, and plastics—act as xenoestrogens that can induce premature estrogenic stimulation. Minimizing environmental EDC exposures, managing childhood BMI, and favoring diets

enriched in phytoestrogens (e.g., soy compounds) represent key risk-mitigation measures.[7-9]

Menopausal Status & Hormonal Exposure

Menopause is clinically defined as 12 consecutive months of spontaneous amenorrhea. The median age at natural menopause is 51 years in North America and 54 years in recent European epidemiological cohorts. Premature or iatrogenic menopause may result from bilateral oophorectomy, gonadotoxic chemotherapy, or targeted endocrine therapy. The perimenopausal transition involves complex endocrine fluctuations, manifesting as vasomotor instability, mood alterations, sleep disturbance, cognitive fluctuations, central adiposity, mastalgia, arthralgia, and urogenital atrophy.

From an epidemiological perspective, delayed menopause elevates breast cancer risk by extending the total duration of luminal cell exposure to circulating ovarian steroids. Women entering menopause prior to age 44 exhibit a 34% reduction in risk compared to those undergoing menopause after age 54. This protective mechanism is significantly stronger in non-obese women (\text {BMI} < 27 \text {kg/m}^2) than in obese cohorts. Furthermore, womenone year post-menopause exhibit a 43% lower risk relative to age-matched premenopausal controls. Hysterectomy without bilateral oophorectomy does not lower risk, as ovarian steroidogenesis remains intact.

Ethnicity & Racial Disparities

Caucasian populations demonstrate the highest overall incidence of breast carcinoma, followed by African American, Native American/Alaska Native, Asian American, Hispanic, and Indigenous groups.

Despite a lower absolute incidence, African American women experience a 30% lower overall survival rate and present more frequently with high-grade, triple-negative breast cancer (TNBC) phenotypes (22% vs. 12% in Caucasians). African American patients also present at a younger median age (58 vs. 62 years) and at advanced stages (44% vs. 33% late-stage presentation). Overall survival across non-Caucasian cohorts is roughly 52% higher than in African American cohorts. Asian populations (e.g., Chinese and Japanese women) exhibit superior long-term post-diagnosis survival. Systemic disparities in screening utilization and healthcare access further aggravate survival disparities among minoritized and immigrant populations.[10-12]

Socioeconomic Stratification

Higher socioeconomic status (SES) positively correlates with increased breast cancer incidence. This epidemiologic association is mediated by reproductive choices and lifestyle factors characteristic of higher SES brackets, including advanced maternal age at first live birth, lower parity, reduced breastfeeding rates, increased use of postmenopausal hormone replacement therapy (HRT), higher alcohol consumption, and greater average adult height and BMI. Conversely, individuals in higher SES strata benefit from enhanced healthcare access, resulting in earlier-stage detection when tumors are most responsive to curative modalities. Higher SES also facilitates adherence to targeted dietary regimens and proactive health behaviors.

Anthropometric Parameters (Stature)

Epidemiological evidence links taller adult height with elevated breast cancer risk. Women measuring \ge 175\text {cm} possess a >50\% increased risk relative to those measuring \le 160\text{cm}. Incrementally, each 5\text{cm} increase in height corresponds to an 11% relative risk increase. Taller patients also demonstrate a marginal reduction in long-term survival metrics compared to shorter cohorts.[5-8]

Bone Mineral Density & Estrogenicity

Elevated bone mineral density (BMD)—a surrogate marker for sustained lifetime estrogen exposure—is strongly correlated with increased breast cancer risk. Estrogen preserves trabecular and cortical bone mass by suppressing osteoclastogenic cytokines and promoting osteoblast activity via the

GH/IGF-1 axis; however, this same endocrine environment promotes proliferative changes within the mammary epithelium. Conversely, clinical osteoporosis correlates with a reduced incidence of breast cancer, albeit at the expense of elevated skeletal fracture risk. Maintaining optimal BMD while eliminating exogenous risk factors—avoiding alcohol and tobacco, maintaining normal body weight, engaging in routine physical exercise, and supplementing calcium and vitamin D—represents the recommended approach.

Mammographic Density Dynamics

Mammographic breast density represents the ratio of radiopaque fibroglandular tissue to radiolucent adipose tissue. Fibroglandular elements appear radiodense (white/gray) on mammograms, whereas fat appears radiolucent (dark). High density independently increases breast cancer risk and reduces mammographic sensitivity due to tissue masking. Fibroglandular tissue contains a higher concentration of epithelial ducts and lobules—the anatomical sites of malignant transformation—and hormone-responsive stroma.

Mammographic density is classified into four standard categories (BI-RADS A through D). Women in the highest density category (Category D) experience a 4- to 6-fold increase in risk compared to those in the lowest category (Category A). Extremely dense breasts (Category D) occur in ~10% of women, entirely fatty breasts (Category A) in 10%, scattered fibroglandular density (Category B) in 40%, and heterogeneously dense tissue (Category C) in 40%.

For dense or heterogeneously dense breast tissue, supplementary screening via diagnostic ultrasound or breast magnetic resonance imaging (MRI) is clinically indicated. Mammographic density decreases naturally with age due to lobular involution. Postmenopausal HRT increases parenchymal density, whereas selective estrogen receptor modulators (SERMs) like tamoxifen rapidly reduce density, conferring a significant risk reduction (\ge 60\%). Weight reduction and HRT discontinuation similarly reduce tissue density.[7,13-15]

High-Risk Proliferative Lesions

Certain benign breast lesions exhibit epithelial proliferation driven by oxidative stress, estrogenic activation, and local growth factor signaling. These lesions signify localized genomic instability and necessitate formal surveillance or surgical biopsy.

Lesions Warranting Surgical Excision & Biopsy

- Atypical ductal hyperplasia (ADH)
- Atypical lobular hyperplasia (ALH) variants
- Pleomorphic lobular carcinoma in situ (PLCIS)
- Non-classical lobular carcinoma in situ variants
- Atypical papillary or palpable lesions
- Radial scars
- Complex sclerosing lesions
- High-risk fibroepithelial lesions
- Mucocele-like lesions
- Desmoid-type fibromatosis
- Spindle cell proliferative lesions

Lesions Managed via Conservative Imaging Surveillance

- Classic atypical lobular hyperplasia (ALH)
- Classic lobular carcinoma in situ (LCIS)
- Incidental papillary lesions without atypia
- Simple fibroadenomas
- Flat epithelial atypia (FEA)
- Pseudoangiomatous stromal hyperplasia (PASH)

These histopathological entities confer a heightened long-term risk of invasive carcinoma. Non-proliferative benign lesions do not confer additional risk. Overall, an estimated 70% of solid malignancies are linked to environmental exposures, with breast cancer demonstrating high sensitivity to lifestyle and environmental risk factors.

Personal History of Primary Malignancy

A personal history of breast carcinoma indicates underlying genomic susceptibility and prior carcinogenic exposures capable of inducing driver mutations. Consequently, residual ipsilateral parenchyma and the contralateral breast remain at heightened risk for metachronous disease.

Adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors) reduces the incidence of contralateral breast cancer (CBC) by up to 50%. Local recurrence—defined as tumor reappearance within or adjacent to the primary surgical bed within 10 years—occurs in 4% to 6% of treated patients. Among breast cancer survivors, CBC constitutes the most frequent second primary malignancy, followed by ovarian carcinoma and cutaneous melanoma. Contralateral lesions represent independent primary events rather than metastases, frequently displaying distinct biomarker profiles, prognostic behavior, and therapeutic responses.[16-18]

Familial Aggregation

While physical traits display classic Mendelian inheritance, familial clustering of breast cancer does not automatically imply high-penetrance genetic inheritance. In the absence of confirmed germline mutations, absolute familial risk remains moderate.

A single first-degree relative (mother, sister, daughter) with breast cancer elevates lifetime risk to 12.4%–17.8%. Having two affected first-degree relatives increases lifetime risk to approximately 25%. Risk is further elevated if the affected relative is a sibling, particularly if diagnosed before age 50. Second-degree relatives contribute roughly half the risk weight of first-degree relatives (e.g., an affected maternal aunt confers half the relative risk increase of an affected mother). The precise risk contribution of an affected male relative (father or brother) on male offspring remains less defined.

Importantly, a woman whose mother had breast cancer retains an 82% absolute probability of not developing the disease, provided no pathogenic germline mutation is present. Shared environmental, dietary, and behavioral patterns account for a portion of observed familial clustering. However, in families with multiple early-onset cases (<50 years) or \ge 3 affected relatives across generations, relative risk increases roughly fourfold, necessitating formal genetic evaluation.[17,18,20-22]

High-Penetrance Germline Mutations (BRCA1 and BRCA2)

BRCA1 and BRCA2 are tumor suppressor genes encoding proteins essential for double-strand DNA break repair via homologous recombination. Inactivation of either allele leads to genomic instability and tumorigenesis. Pathogenic germline mutations in BRCA1 or BRCA2 account for ~10% of all breast carcinomas and ~14% of epithelial ovarian cancers, inherited in an autosomal dominant pattern.

The general population prevalence of pathogenic BRCA mutations is approximately 1 in 450. In Ashkenazi and Sephardic Jewish lineages, the prevalence of founder mutations reaches ~1 in 40 (>10-fold higher).

Carriers of pathogenic BRCA mutations face a significantly elevated lifetime risk of breast cancer—25 to 30 times higher than the baseline population—as well as markedly increased ovarian cancer risk. Cumulative lifetime risks for BRCA1 carriers reach up to 87% for breast cancer and 54% for ovarian cancer. penetrance estimates vary: conservative meta-analyses report lifetime breast cancer risks of 57% for BRCA1 and 49% for BRCA2, with ovarian cancer risks of 40% and 18%, respectively.

Approximately 70% of BRCA1-associated breast tumors display a triple-negative phenotype (ER-/PR-/HER2-), characterized by aggressive clinical behavior requiring systemic chemotherapy even in early-stage disease. BRCA1 carriers also face a 40% to 65% lifetime probability of contralateral disease, making bilateral risk-reducing mastectomy (BRRM) a standard preventive consideration.

The median age at diagnosis is 44 years for BRCA1 carriers and 47 years for BRCA2 carriers. In addition, BRCA

mutation carriers carry an elevated risk for pancreatic adenocarcinoma (2%–5% vs. <1\% baseline) and cutaneous melanoma (2%–5% in BRCA2).

Male BRCA mutation carriers also face increased oncological risk. Male breast cancer risk is higher in BRCA2 carriers than in BRCA1 (8% vs. 1.8%, compared to 0.1% baseline). BRCA2 mutations also confer a significantly higher risk of aggressive prostate cancer (25% vs. 16% in BRCA1 and 14% baseline), as well as increased risks for pancreatic cancer (3%–6%) and melanoma (6%–12%).[23-30]

Clinical Indications for Germline Genetic Testing

Due to the low prevalence of pathogenic mutations in unselected populations, universal genetic screening is not currently indicated. Targeted genetic testing provides critical risk stratification, enabling tailored screening protocols, chemoprevention, or prophylactic surgery (such as bilateral salpingo-oophorectomy or risk-reducing mastectomy). Identifying a germline variant also enables cascade testing for at-risk relatives.

Formal genetic counseling and testing are indicated for individuals meeting any of the following clinical criteria[31-35]:

- **\ge 2 first- or second-degree relatives diagnosed with breast cancer before age 50, or \ge 2 relatives diagnosed with ovarian cancer at any age.**
- **Individuals of Ashkenazi Jewish descent with \ge 1 relative with early-onset breast cancer (<50 years) or ovarian cancer at any age.**
- **Personal or familial history of male breast carcinoma.**
- **Confirmed pathogenic BRCA1/2 germline mutation in a first-degree relative (50% inheritance probability).**
- **Personal diagnosis of primary breast cancer at or before age 50.**
- **Personal diagnosis of bilateral primary breast cancer at any age.**
- **Personal diagnosis of triple-negative breast cancer at any age.**
- **Personal diagnosis of breast cancer at any age in an individual of Ashkenazi Jewish ancestry.**
- **Multi-generational family history of diverse malignancies (breast, ovarian, pancreatic, prostate, colorectal, endometrial, gastric, or cutaneous melanoma).**

In confirmed BRCA1 mutation carriers, bilateral risk-reducing mastectomy (BRRM) reduces breast cancer incidence by up to 90% and improves overall survival. Bilateral salpingo-oophorectomy (BSO) significantly lowers ovarian cancer risk while offering secondary breast cancer risk reduction in premenopausal carriers .[36-39]

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