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Cancer Progress and Priorities: Breast Cancer

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Breast cancer; risk factors; prognosis; survival rate; heterogeneity

Introduction

Breast cancer is the most commonly diagnosed invasive cancer among women both globally and within the United States and the number one cause of cancer-related death among women globally [1, 2]. Less than one percent of diagnosed breast cancers occur in men [2] and, therefore, male breast cancer is not included in this report. Breast cancer is an etiologically and clinically heterogeneous disease. Many risk factors, primarily hormone related, have been identified and these associations can vary by breast cancer subtype. Survival has increased over the past few decades, with the introduction of screening mammography and improved treatments. However, progress has not been seen equally among all ethnicities/ races or with all breast cancer subtypes (e.g., triple-negative).

Descriptive Epidemiology

Incidence

Breast cancer accounts for 25% of new cancer cases in women globally, with an estimated 2,088,849 female breast cancer cancers occurring worldwide in 2018 (46.3 per 100,000 women) [1, 3]. Based on available data, incidence rates are highest in Australia, New Zealand, much of Europe, and North America, intermediate in South America and Eastern Europe, and lowest in the majority of Asia and Africa (Figure 1) [3]. Within the United States, breast cancer accounts for 30% of female cancer diagnoses with an estimated 268,600 new invasive breast cancers and an additional 62,930 cases of in situ breast cancer documented in 2019 (124.7 per 100,000 women) [2]. One in eight women will be diagnosed with breast cancer during their lifetime [2]. Diagnosis is rare before the age of 40 (probability <1%), after which incidence rates increase until about age 70 (median age at diagnosis: 62 years), before decreasing (Figure 2) [2, 4].

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In many westernized countries including the United States (Figure 3), breast cancer incidence rates increased during the 1980s and 1990s due to changes in reproductive patterns, hormone therapy use, and increased mammographic screening [1, 5]. Incidence rates then dropped in the early 2000s, particularly among women over 45 and for estrogen receptor-positive (ER) breast tumors, following a decline in hormone therapy use after the publication of the Women's Health Initiative findings and declines in mammography screening rates [1, 5-9]. Since 2004, incidence rates in the US have been increasing slowly (0.3% per year), potentially due to increasing obesity and declining birth rates [4, 5]. Increases in ER+ tumors, particularly in situ, and decreases in ER− tumors are projected to continue according to forecasting models [9-11]. However, incidence rates have continued to decline or stabilize in multiple other westernized countries (e.g., Canada, UK, France, Australia) [1, 8]. In contrast, incidence rates have been rapidly increasing in historically lower risk areas (e.g., Latin America, Africa, Asia) likely from increased life expectancy due to reductions in infectious diseases, increasing prevalence of overweight and obesity, changes in reproductive patterns, and increased breast cancer screening [1, 8].

Mortality

Breast cancer is the most common cancer death in women globally, accounting for 15% of cancer deaths, with an estimated 626,700 breast cancer deaths among women in 2018 (13.0 per 100,000 women) [1, 3]. Mortality rates are lowest in Eastern Asia (8.6 per 100,000 women) and highest in Fiji (36.9 per 100,000 women) (Figure 4) [3, 12]. In the US, where the lifetime risk of dying from breast cancer is 1 in 39 women, an estimated 41,760 women will die from breast cancer in 2019 (12.7 per 100,000 women) [5, 12]. Mortality rates in the US increased between 1975 and 1989, then decreased through 2017 due to improvements in detection and treatment (Figure 3) [5, 13]. Similar trends have been observed in Canada and European countries [1, 8], whereas mortality rates have increased in Asia, Africa, and Latin America [1, 8].

Survival among women with breast cancer

In the US, the 5-year relative survival is 91%, and after 10 and 15 years, the survival rates are 84% and 80%, respectively, for all stages combined [5]. The 5-year survival rate is 99% when the tumor is diagnosed at a local stage, 86% at a regional stage, and 17% when metastatic [5]. Survival rates by stage and subtype are shown in Figure 5. Survival rates in the US have been increasing over time (74.8% in 1975 vs. 91.3% in 2015) likely due to earlier detection through mammographic screening and improved treatments such as the use of more targeted therapies [4, 5, 13-16].

Etiologic Heterogeneity

Breast cancer is a heterogeneous disease with considerable genetic and clinical heterogeneity [17]. Breast cancers, the majority of which are adenocarcinomas, are often classified by invasiveness (i.e., in situ or invasive), morphology, expression of immunohistochemical markers, and more recently through genetic panels. In turn, these features have been associated with differing responsiveness to treatment and prognosis [18]. In situ breast cancers are confined to the ducts or lobules [17, 19]. Ductal carcinoma in situ

(DCIS) is more common than lobular carcinoma in situ (LCIS), and while both are considered risk factors for invasive breast cancer, LCIS is not considered to be a lesion capable of becoming malignant [19, 20]. However, the etiology and natural history of in situ tumors is not well known.

Invasive breast cancer is classified by histology, to guide clinical treatment, into invasive ductal (70-80% of breast cancer), invasive lobular (5-15% of breast cancer), and other less common types such as papillary tumors [17, 19]. Immunohistochemical (IHC) staining for the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) guide the use of targeted therapies. The use of other tests such as gene array profiling or other IHC markers are not as commonly used clinically [17, 21-23]. Several main intrinsic molecular subtypes have been identified using gene micro-arrays: Luminal A, Luminal B, HER2-enriched, Basal Like, and Normal Like [17, 24-26]. Further classifications of primarily triple negative tumors have identified the Claudin-low subtype and six triple-negative molecular subtypes [27, 28]. Several gene panels (e.g., PAM50) have been developed as less expensive options with a similar ability to classify tumors into molecular subtypes [17, 29, 30]. In 2013, the St. Gallen consensus agreed on surrogate definitions of the intrinsic subtypes that could be approximated by IHC staining of ER, PR, and HER2 as well as grade and proliferation [31] (Table 1), though several studies have noted that the agreement may be low [18, 32].

Disparities in the United States

Prior to age 40, US Black women have the highest breast cancer incidence rates, after which rates are highest among White women (Figure 2). American Indian/ Alaska Native women have the lowest rates until age 74. Asian/ Pacific Islander women have similar incidence rates as White and Black women until age 45, after which they have the lowest incidence rates. Black women have the highest mortality rates at all ages followed by White women (e.g., 68.2 per 100,000 in Blacks vs 46.5 per 100,000 in Whites at age 60-64). Mortality rates for American Indian/ Alaska Native and Asian/ Pacific Islander women are similar until about age 60, at which point Asian/ Pacific Islander women have the lowest mortality rates (e.g., 30.0 per 100,000 in Asian/ Pacific Islander vs 33.2 per 100,000 in American Indian/ Alaska Native at age 60-64).

While breast cancer incidence rates have either declined or remained stable since the early 2000s among White women, incidence rates among Black women have continued to increase (Figure 3) [33]. In 2016, the age-standardized incidence rate was 128.2 per 100,000 among Black women versus 132.7 per 100,000 among White women [4]. While incidence rates are lower, Black women experience higher breast cancer mortality than White women; further, that gap has continued to widen even as survival has increased overall (Figure 3) [33]. The 2016 age-standardized mortality rate was 27.3 per 100,000 Black women versus 19.6 per 100,000 White women [4]. Compared to White women, Black women also have a higher incidence of the more aggressive triple-negative (ER−/PR−/HER2−) tumor subtype (Figure 6) and, among those with ER+ tumors, Black women are more likely to be diagnosed at a later stage, potentially due to lower screening rates and barriers to health care access [33-35]. Further, disparities are still present within a similar stage and subtype of

breast cancer [33]. For example, among women with ER+/HER2− tumors, Black women have lower survival at local (98.7% vs. 100.0%) and regional (82.2% vs. 90.6%) stages than White women, suggesting that racial disparities in treatment may play a role [4, 33]. Studies have shown that Black women are more likely to experience delayed or inadequate surgery, radiation therapy, chemotherapy, and targeted therapies [33, 35-37].

Familial and genetic factors

Having a first-degree relative with breast cancer increases a woman's risk of developing breast cancer two to three-fold [38, 39]. Approximately 10-15% of breast cancers are thought to be hereditary, though a known pathogenic mutation is identified in only about 30% of those with hereditary breast cancer [40]. It is estimated that 5-10% of breast cancer is associated with a highly penetrant germ-line mutation, including in the BRCA1 and BRCA2 genes [41]. Those of Ashkenazi heritage (vs. without this heritage) have a higher prevalence of BRCA1/2 founder mutations (2.0-2.5% vs. 0.1-0.2%) [42-44]. A higher prevalence of BRCA1 mutations are found in women with early onset or triple-negative/basal-like tumors ([45]). Additional genes with moderately and highly penetrant mutations associated with breast cancer are shown in Table 2. Other similar genes that have been less consistently associated with breast cancer include BRIP1, BARD1, NBN, NF1, and RAD50 [46-51]. Several hundred common gene polymorphisms have been identified through genome-wide association studies (GWAS), which, cumulatively, currently explain about 18% of the two-fold familial relative risk [52].

Risk Factors

Breast cancer etiology is influenced by multiple exposures occurring over the life course, including early life factors during childhood and adolescence that can affect risk later in adulthood. Many of the risk factors identified, and some that still need to be elucidated by additional well-conducted research are shown in Table 3. The approximate magnitude of risk associated with each of the established risk factors is presented in Figure 7. Further, research has suggested that associations between breast cancer risk factors and breast cancer may vary by breast cancer subtype (Table 4).

Anthropometrics

The relationship between adiposity and breast cancer risk is complex and varies by the timing of body size assessment over the life course. Greater birthweight is associated with modestly higher risk of breast cancer in adulthood [53, 54]. In contrast, a higher body mass index (BMI), indicating greater adiposity, measured in childhood or in early adulthood (18-30 years) is associated with decreased risk of breast cancer [55-63]. Premenopausal adult BMI is inversely associated with risk [61, 63-66], while postmenopausal BMI is positively associated [63-66], particularly among never hormone therapy users and ER+ tumors [64, 67-69]. The differing associations by menopausal status have been hypothesized to be due to the differences in estrogen levels and its primary sources (i.e., ovary vs. adipose tissue). In a large Mendelian randomization study using data from two breast cancer consortia, a polygenic risk score (PRS) of adult BMI was inversely associated with breast cancer risk regardless of menopausal status, suggesting the PRS may reflect early life

obesity [70]. Larger central adiposity (e.g., waist circumference, waist-to-hip ratio) is associated with higher postmenopausal breast cancer risk and possibly greater risk of premenopausal breast cancer, though premenopausal studies have been limited and may be influenced by additional BMI-adjustment [63, 71]. Adult weight gain is positively associated with postmenopausal breast cancer risk [63, 72, 73].

Other non-modifiable anthropometrics that increase breast cancer risk, particularly ER+ tumors, includes taller height [66, 74, 75] and larger birth lengths [53, 76]. Having dense breasts, as assessed radiologically (e.g., digital mammogram), substantially increases risk regardless of menopausal status or hormone receptor status of the tumor [77-79]. For this reason, 38 states require breast density notifications after a mammogram, though language varies by state and may only state that there is an association in general and not contextualize the individual woman's risk [80]. In March 2019, the FDA proposed a rule to extend this to all mammograms [80]. Associations have been much less consistent for bone mineral density. Early case-control studies observed increased risk; however, more recent meta-analyses of prospective studies do not see a significant association [81, 82].

Reproductive factors

The associations of multiple reproductive factors with breast cancer risk have been well established. Younger age at menarche [83] and older age at menopause [83] are associated with increased breast cancer risk, potentially reflecting the number of ovulatory cycles over a woman's lifetime and estrogen exposure. Parous women initially have a higher risk of breast cancer after delivery compared to nulliparous women which peaks about 5 years after birth and remains elevated for approximately 20 years. Overall, women with greater parity have a lower risk of breast cancer long-term, and risk is further reduced with each subsequent birth [84, 85]. However, this relationship does appear to vary by ER status [68, 86, 87]. Additionally, the younger age at which a woman has her first child [88] and longer durations of breastfeeding [84] further reduces breast cancer risk independent of parity.

Endogenous hormones and other circulating biomarkers

Sex hormones are integral in the etiology of breast cancer, supported by laboratory studies, epidemiologic evidence (e.g., reproductive risk factors and postmenopausal BMI) and the use of selective estrogen receptor modulators (e.g., Tamoxifen) to prevent breast cancer [89, 90]. Higher circulating levels of estrogens [91-93], androgens [91-93], and prolactin [94], primarily in postmenopausal women, are established to increase breast cancer risk. Estrogen metabolites may also play a role [95-97] though evidence remains limited. Higher anti-mullerian hormone (AMH), measured premenopausally, is positively associated with breast cancer [98], though it is also strongly and directly related to age at menopause. Higher sex hormone binding globulin (SHBG) may decrease breast cancer risk [91, 92, 99]. Progesterone levels are not related to premenopausal breast cancer [91], possibly due to challenges in characterizing long-term hormone levels, and only one prospective study has examined postmenopausal progesterone levels, finding no association [100]. Circulating concentrations of insulin-like growth factor-1 are modestly positively associated with risk of ER+ breast cancer [101], which is further supported by a mendelian randomization study [102].

Other circulating biomarkers also may play a role in breast cancer etiology. Studies examining insulin or c-peptide, a byproduct of insulin, have suggested an increased risk among postmenopausal women only [103-107]. Potentially, chronic low levels of inflammation indicated by c-reactive protein may increase risk [108-110]. There is a suggestive increase in breast cancer risk for greater leptin and lower adiponectin levels [111, 112]. Studies examining melatonin levels, which may be affected by light at night or shiftwork, have been relatively inconsistent perhaps due to differences in sample collection and timing, showing either inverse or null associations between the main melatonin metabolite, 6-sulfatoxymelatonin (aMT6s) in urine and breast cancer [113, 114].

Exogenous hormones

Use of oral contraceptives increases breast cancer risk for up to 10 years after stopping use, and this is most consistently observed among current and recent users [115-117]. However, as oral contraceptive use occurs during the reproductive years, at ages when breast cancer incidence is low, the impact on population rates of breast cancer is minimal. Levonorgestrel-releasing intrauterine devices, also are suggestively associated with increased risk [118]. Other forms of hormonal contraceptives have been less studied.

The use of postmenopausal hormone therapy has been evaluated in multiple observational studies and randomized trials [119]. Combined estrogen and progestin use substantially increases risk, and associations are strongest for current/recent use and among those with the longest durations of use [119]. Long duration use of estrogen only is associated with more modest increases in risk; the major clinical trial did not observe increases in risk with estrogen only use, though timing of treatment (i.e. years after menopause) likely played a role [119, 120]. Relatively few studies have examined doses, formulations, and changing use patterns.

Dietary

There has been an interest in diet as a risk factor for breast cancer since early ecologic studies of fat and breast cancer mortality. Dietary fat has had considerable interest and controversy; however, most studies indicate no association overall with total fat [121-126]. Studies of carbohydrate intake have been inconsistent [127], though glycemic index/load may be associated with increased risk [127, 128], and soluble fiber with decreased risk [129-131].

Assessments of specific foods have suggested an increased risk with processed meats [132-136] and decreases in risk with low-fat dairy [136-138] and fruit and vegetable intake [139-141]. Coffee and tea associations have been inconsistent, but there may be associations in subgroups [142-146]. Several nutrients have also been assessed as potential risk factors. Nutrients with suggestive decreased risk include calcium [147-149], vitamin D [150-153], and carotenoids, particularly β-carotene [154-157]. Higher heme-iron intake and plasma iron levels may increase risk [158]. However, most other nutrients are inconsistent or have not been found to be associated with breast cancer, including vitamin A [159], B-vitamins [160, 161], vitamin C [159, 162, 163], vitamin E [159], folate [164-168], selenium [169, 170], phytoestrogens [171, 172], and isoflavones [173-176]. Additionally, multivitamins have not

been associated with breast cancer risk [177]. Alcohol is the dietary factor most consistently associated with breast cancer, conferring a moderate increase in risk [178-183].

As foods and nutrients are not eaten in isolation and interactions between nutrients and foods are likely (e.g., folate and alcohol), the examination of dietary patterns is important. Some studies have suggested that dietary patterns such as the “prudent”, “western”, and Mediterranean may be associated with breast cancer [184-188]. Apart from the Mediterranean pattern, including olive oil, decreasing risk [189], studies are inconsistent or weakly associated, and there may be substantial confounding with other lifestyle risk factors.

Environmental

Although many environmental factors have been evaluated, most have limited or inconsistent evidence linking them to breast cancer, leading to some controversy. Obtaining valid exposure measures during susceptible periods of life continues to be a challenge. Exposure to secondhand smoke has been suggestively associated with increases in breast cancer risk [190-193]. Others, such as air pollution [194, 195], electromagnetic fields [196-198], organochlorines (e.g., DDT/DDE, PCBs) [199-202], and acrylamides in food [203] have been inconsistent. Non-medical radiation exposure (e.g., atomic bombs) has been associated with increased breast cancer risk, particularly among those exposed at younger ages [204, 205].

Lifestyle factors

Higher levels of physical activity have been consistently linked with decreases in breast cancer risk [63, 206-210] and greater sedentary behavior or physical inactivity may be associated with increased risk [63, 211, 212]. Smoking has recently become quite well established to increase breast cancer risk, particularly if initiated prior to first pregnancy and for long durations [182, 190, 213, 214]. The use of hair dye or relaxers may possibly be associated with increased risk among Black women in particular [215, 216]. Exposure to light at night or shift work has been suggested to be positively associated with breast cancer, but the mechanism is unclear [217-221]. Sleeping duration is unlikely to be associated with risk [220, 222, 223]. Stressful life events may also be associated with increased risk, though definitions of stress or stressful life events have varied widely [224].

Medications/ other health conditions

The association of many medications with breast cancer risk (e.g., antibiotics [225], antidepressants [226], aspirin/NSAIDs [227-229], bisphosphonates [230-232], infertility drugs [233, 234], statins [235]) has been inconsistent or null, and likely limited by confounding or ascertainment biases. Diethylstilbestrol (DES) has been found to increase breast cancer risk among women who took the drug during pregnancy [236-240], and associations among the daughters exposed *in utero* are less consistent but also may be positive [76, 239, 241-244]. Early case-control studies on abortion reported an increased risk; however, prospective studies have overall observed no association [245-248]. Prior history of breast conditions such as proliferative benign breast disease [249, 250] or *in situ* tumors [251-260] has been established to substantially increase breast cancer. Obesity-

related disorders, such as diabetes [261-265] and metabolic syndrome [266], have been generally inconsistent. Migraine headaches are likely not related, as observed associations have been limited to case-control studies [267, 268]. Lastly, ionizing radiation for medical reasons (e.g., for lymphoma) has been established to increase breast cancer risk, which increases with greater doses and the highest risk occurs among those exposed before puberty similar to those exposed due to radiation from atomic bombs [204, 205, 269].

Other factors

Additional risk factors not included in Table 3 with very limited or insufficient evidence include a number of chemical or biologic agents (i.e., polycyclic aromatic hydrocarbons [270], parabens [271], BPA [272, 273], phthalates [274-276], perfluorocarbons[277-279], human papillomavirus [280], Epstein–Barr virus [281]), breast size [282], blood pressure [283-287], under-wire bras [288, 289], breast implants [290], cellphone use [291], deodorant/ antiperspirant use [292-294], and trauma to the breast [295, 296].

Risk Prediction Models

Multiple risk prediction models have been developed to predict future risk of breast cancer (e.g., Gail/ Breast Cancer Risk Assessment Tool [BCRAT], Breast Cancer Surveillance Consortium [BCSC], Rosner-Colditz, Claus, BRCAPRO, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA], Tyrer-Cuszik/ International Breast Cancer Study [IBIS]), some of which can also predict BRCA carrier status (e.g., BRCAPRO, BOADICEA, IBIS) [297, 298]. Risk prediction models are increasingly being used clinically to help guide decisions related to screening and prevention (e.g., timing and frequency of screening, use of chemoprevention) [299-301]. Risk prediction models vary in terms of factors included, with several including hormonal, environmental, or pathologic factors, high-risk genetic mutations, and more recently mammographic density [297, 298]. While all models include family history assessment, the level of detail varies widely ranging from only first-degree relatives with breast cancer to all relatives with breast, ovarian, pancreas, and prostate cancers and their ages of onset [297, 298]. The risk prediction models also vary in terms of type of population the model is suitable for (i.e., general screening population, women with a family history of breast or ovarian cancer) [297, 298].

The Gail, Rosner-Colditz, Claus, BCSC, BRCAPRO, BOADICEA, and IBIS models have all been validated in external datasets [298, 302, 303]. A recent comparison of several of the most commonly used clinical models (i.e., Gail, BRCAPRO, BCSC, Claus, IBIS) in a large, predominantly White US screening population indicated that the models were generally well-calibrated (O/E range: 0.78-0.97) but with only moderate discrimination (AUC range: 0.61-0.64) [304]. Expansion of these models to include multiple biomarkers (e.g., mammographic density and/or other imaging features, polygenic risk scores, endogenous hormones, epigenetics, metabolomics), and the development and validation of models across race/ethnicity and by tumor subtype is ongoing, and likely to lead to model improvement [305-316].

Prevention

Modifiable risk factors often targeted for breast cancer prevention include maintaining a healthy weight, participating in regular physical activity, moderating or avoiding alcohol intake, and minimizing or avoiding postmenopausal hormone therapy [317]. Women who most adhered to the American Cancer Society prevention guidelines had a 22% lower risk of breast cancer compared to women with the lowest adherence [318]. Other risk factors that could be targeted for prevention include healthy eating (e.g., increased intake of fruits and vegetables) [319] and, when possible, breastfeeding [320]. For example, among African American women, who often have lower rates of breastfeeding and higher rates of triple-negative breast cancer [317, 321], facilitating increased breastfeeding may importantly lower the risk of triple-negative breast cancers [86, 322-324]. Additionally, prevention programs (e.g., avoidance of smoking) in adolescents and young adults, particularly prior to first pregnancy, may be important, as these have been shown to be etiologically important periods.

For high-risk women, the American Society of Clinical Oncology recommends the use of selective estrogen receptor modulators (e.g., Tamoxifen, Raloxifene) or aromatase inhibitors (Exemestane, Anastrozole) [300]. While no single threshold for being high risk has been defined, women who are most likely to benefit from endocrine therapy are those with one or more of the following: diagnosis of atypical hyperplasia or LCIS, an estimated 5-year risk ≥3% (BCRAT) or 10-year risk ≥5% (IBIS), or a relative risk ≥4 times the population risk for ages 40-44 years or ≥2 times the population risk for ages 45-69 years. Tamoxifen can be used regardless of menopausal status, whereas Raloxifene, Exemestane, and Anastrozole can only be used by postmenopausal women [300]. Trials of Tamoxifen and Raloxifene have shown a 50% reduction in breast cancer risk, primarily due to a reduction of hormone receptor-positive breast cancers [317, 325-327] and trials of aromatase inhibitors have shown similar reductions [328, 329]. However, less than 10% of women eligible for chemoprevention use these drugs [330], primarily due to lack of provider recommendations and concerns about potential side effects. In the future, better targeting of women who may benefit, the use of newer selective estrogen receptor modulators, or low-dose of topical Tamoxifen may help mitigate these issues [331-333].

Additionally, in recent years there has been an increase in women electing to undergo surgical prevention for breast cancer [334]. The NCCN recommends prophylactic salpingo-oophorectomy for women with a known BRCA1/2 mutation between the ages of 35-40 that have completed childbearing and that prophylactic mastectomy should be discussed as an option for risk reduction (NCCN guidelines high risk). Bilateral prophylactic mastectomy has been shown to reduce breast cancer risk and increase survival [335]. Contralateral prophylactic mastectomy after the diagnosis of cancer in the other breast, has also been shown to reduce the breast cancer risk in the other breast; however, evidence for increased survival remains limited [335]. Prophylactic bilateral oophorectomy, the removal of both ovaries (generally with bilateral salpingectomy) reduces the risk of ovarian cancer and may also reduce the risk of breast cancer, though this is less clear [336].

Screening and Early Detection

Mammography is the most common modality for breast cancer screening in the United States; however, organizations vary in the recommended screening age range and frequency of mammograms. For example, for average-risk women, the US Preventive Services Task Force and the American Academy of Family Physicians now recommend biennial screening for women 50-74 years. In contrast, the American College of Radiology and the National Comprehensive Cancer Network recommend annual screening starting at age 40 [337-339]. In other high-income countries, the screening age range is most commonly 50 to 69 or 70 with a two-year screening interval [337, 340]. However, in 2018 only 58-74% of women ages 50-74 had at least one screening mammogram in the prior two years [341]. Mammographic screening can identify breast cancer at earlier, more treatable stages, and thus reduce breast cancer mortality [337, 342, 343]. However, evidence has been inconsistent on whether this has occurred in all age groups, and concerns exist that screening increases the number of false positives, and may lead to the over detection of breast cancer [342, 344]. Due to the difficulty of defining and estimating over detection, estimates have ranged widely from 1 to 60% in trials and 1–12% in studies with a low risk of bias [342]. While several studies have suggested that breast cancer mortality rates and advanced breast cancer diagnoses have been reduced with screening mammography [343], others have suggested that other factors are additionally responsible (e.g., better treatments) [344]. Among women with a 20% or greater lifetime risk of breast cancer, several organizations recommend annual supplemental MRIs [337]. Additionally, as mammography is less sensitive for women with dense breasts [345], alternative and supplemental screenings have been proposed including more frequent mammograms, supplemental ultrasound, MRI, and digital breast tomosynthesis (i.e., 3D mammography) [337, 345]. Several trials are currently underway examining breast cancer screening intervals and start ages (i.e., WISDOM) and the use of digital breast tomosynthesis or ultrasound (i.e., TMIST, DBTUST, ASTOUND) [346-349].

Future Directions

While earlier detection and improved treatments have reduced breast cancer mortality, breast cancer continues to be the most common cancer among women, and incidence is projected to continue to increase in the next few decades. To combat this, multiple strategies are needed. Further research into etiologic heterogeneity should be conducted, such as risk factors among different ethnicities and tumor subtypes, particularly for ER-negative/ basal-like tumors where fewer effective treatments are currently available. Underlying mechanisms of known risk factors should be examined, including reasons for heterogeneity by menopausal status or tumor subtype, potentially using emerging technologies (e.g., metabolomics, proteomics) to assess local and systemic biomarkers and tumor heterogeneity. Further improvement in and validation of risk prediction models is needed, for example, by the addition of both biomarkers (e.g., breast imaging, genetics, hormones) and lifestyle factors and further development of models that better model risk at both the youngest and oldest ages, among different ethnicities, and for subtypes particularly ER−, for which models perform less well. Finally, additional efforts to determine how to successfully

implement known (e.g., weight maintenance or reduction) and future preventive strategies, during susceptible periods, is critical.

Continued research on alternative screening modalities that may increase adherence or be more effective (e.g., more sensitive and specific) is needed. In addition to increasing prevention activities and awareness, further development or trials of chemopreventives with lower doses or better side effect profiles to increase adherence or uptake when appropriate and chemopreventives for ER-negative breast cancers may be beneficial. In addition to improvements in screening and treatments, research on improving access and equity in cancer care is needed to address existing disparities. Lastly, with the observed increases in breast cancer survival rates over time, additional research is needed regarding survivorship to improve quality of life.

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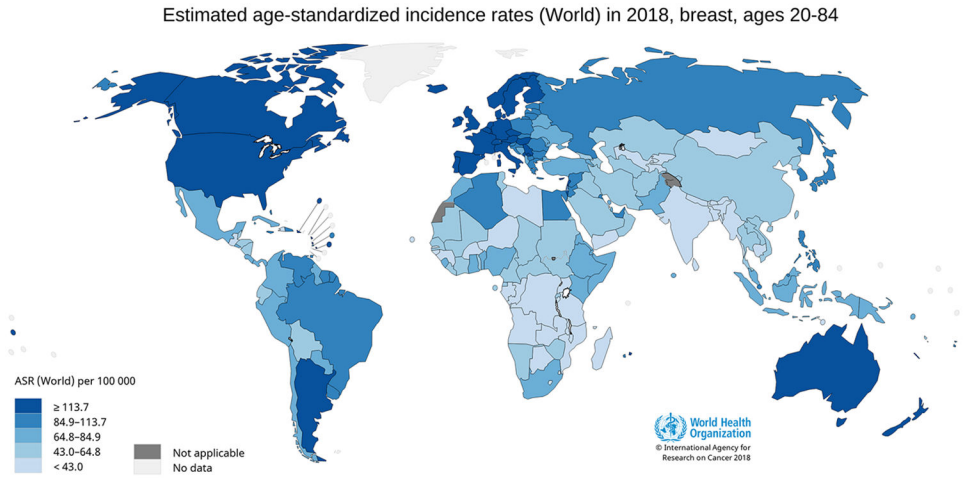

Figure 1.

World age-standardized female breast cancer incidence rates for ages 20-84. Figure 1 shows age-standardized incidence rates for female breast cancer worldwide using data from GLOBOCAN, 2018. Breast cancer incidence is highest in Australia, New Zealand, Northern Europe, and North America, intermediate in Central and South America and Eastern Europe, and lowest in the majority of Asia and Africa. Data source: GLOBOCAN, 2018; Graph production: IARC (http://gco.iarc.fr/today) World Health Organization.

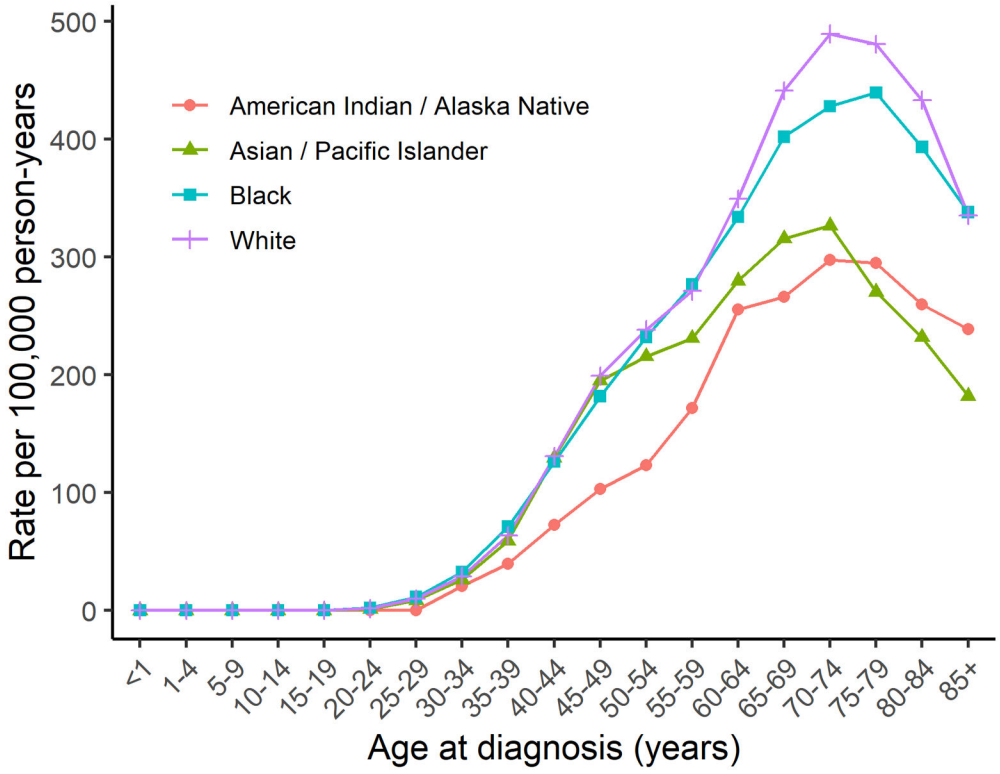

Figure 2.

United States female breast cancer incidence rates by age of diagnosis and race/ethnicity. Figure 2 shows breast cancer incidence rates by age of diagnosis in the United States among White, Black, American Indian/ Alaskan Native, and Asian/ Pacific Islander women using data from the SEER program (SEER 21, 2013-2017).

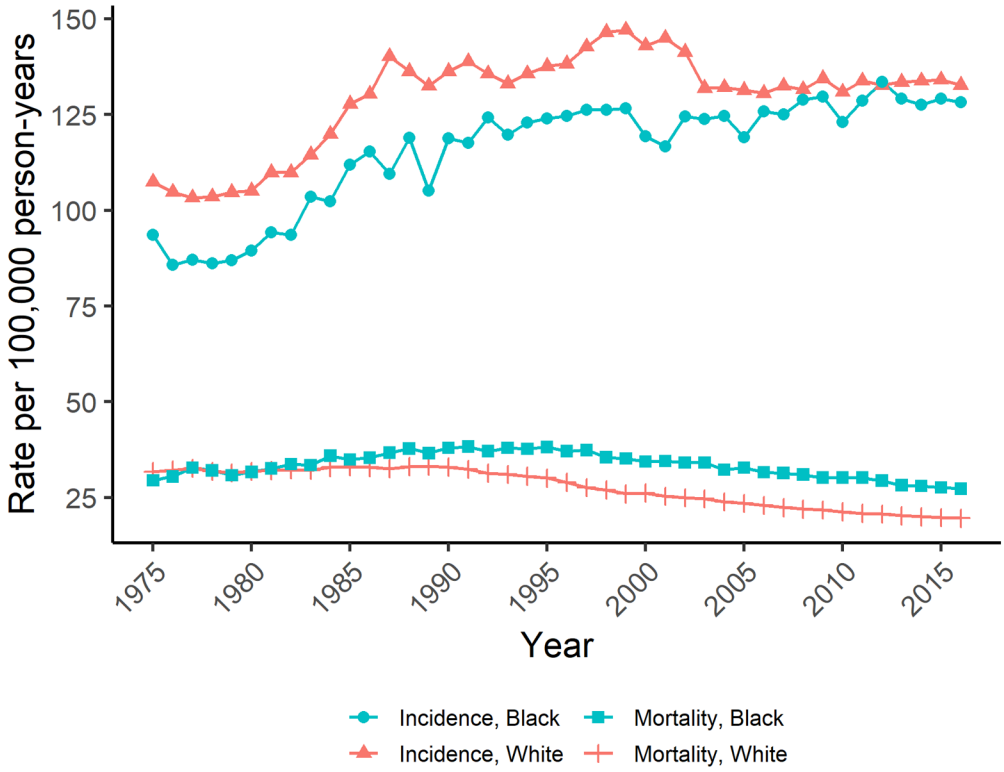

Figure 3.

United States trends in age-adjusted female breast cancer incidence and mortality. Figure 3 shows trends in age-adjusted breast cancer incidence and mortality among White and Black United States women using data from the SEER program (SEER 9, 1975-2016).

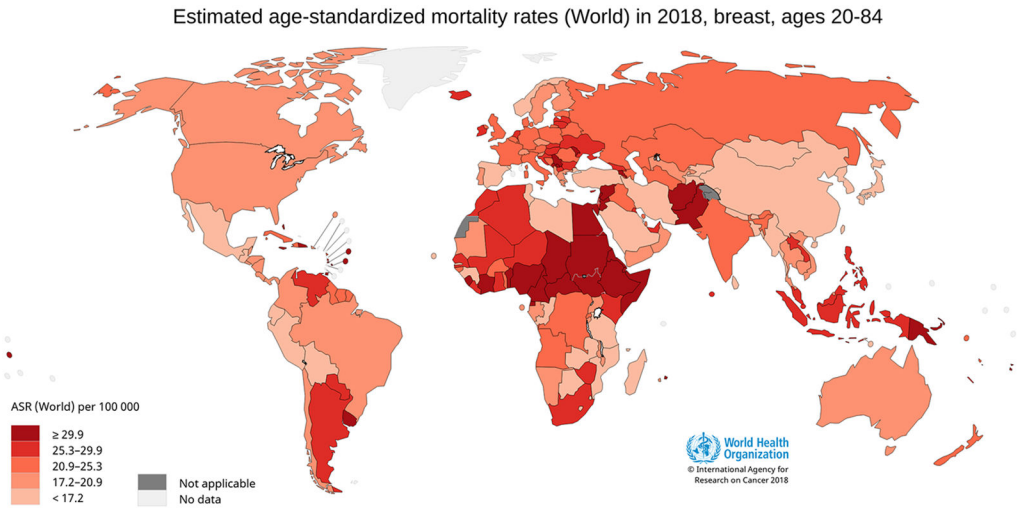

Figure 4.

World age-standardized female breast cancer mortality rates for ages 20-84. Figure 4 shows age-standardized mortality rates for female breast cancer worldwide using data from GLOBOCAN, 2018. Breast cancer mortality is highest in parts of Africa and South-Eastern Asia, intermediate in Europe, and lowest in Eastern Asia. Data source: GLOBOCAN, 2018; Graph production: IARC (http://gco.iarc.fr/today) World Health Organization.

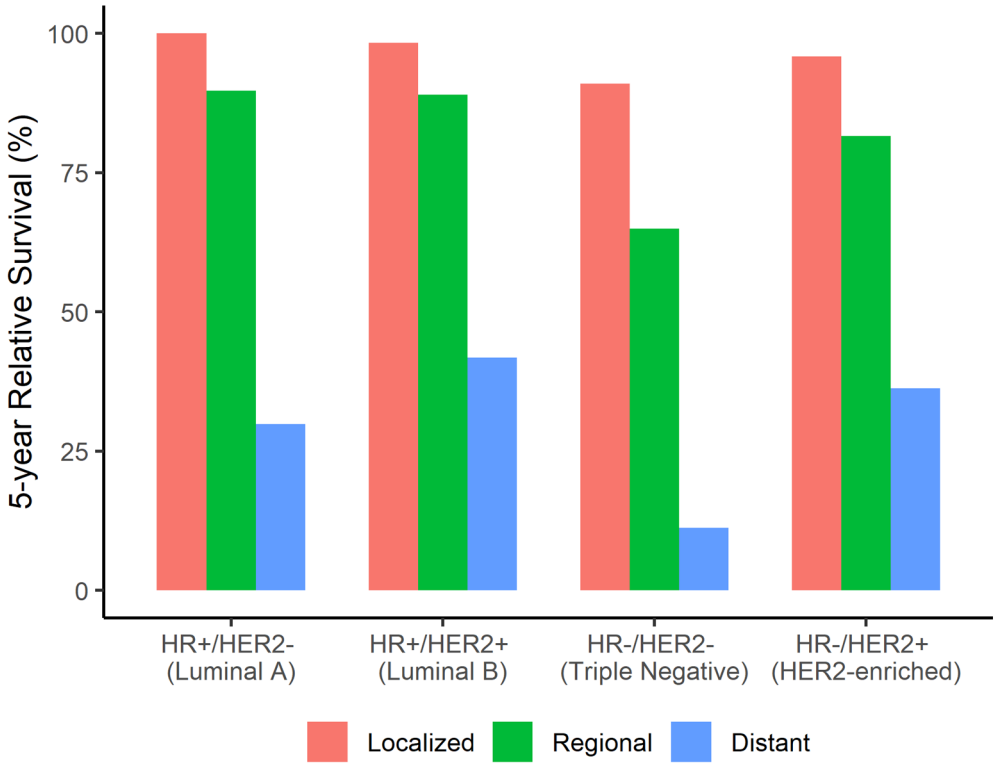

Figure 5.

United States five-year relative female breast cancer subtype survival rates by stage at diagnosis. Figure 5 shows female breast cancer five-year relative survival rates for women at local, regional, and distant stages for each breast cancer subtype using data from the SEER program (SEER 18, 2000-2015).

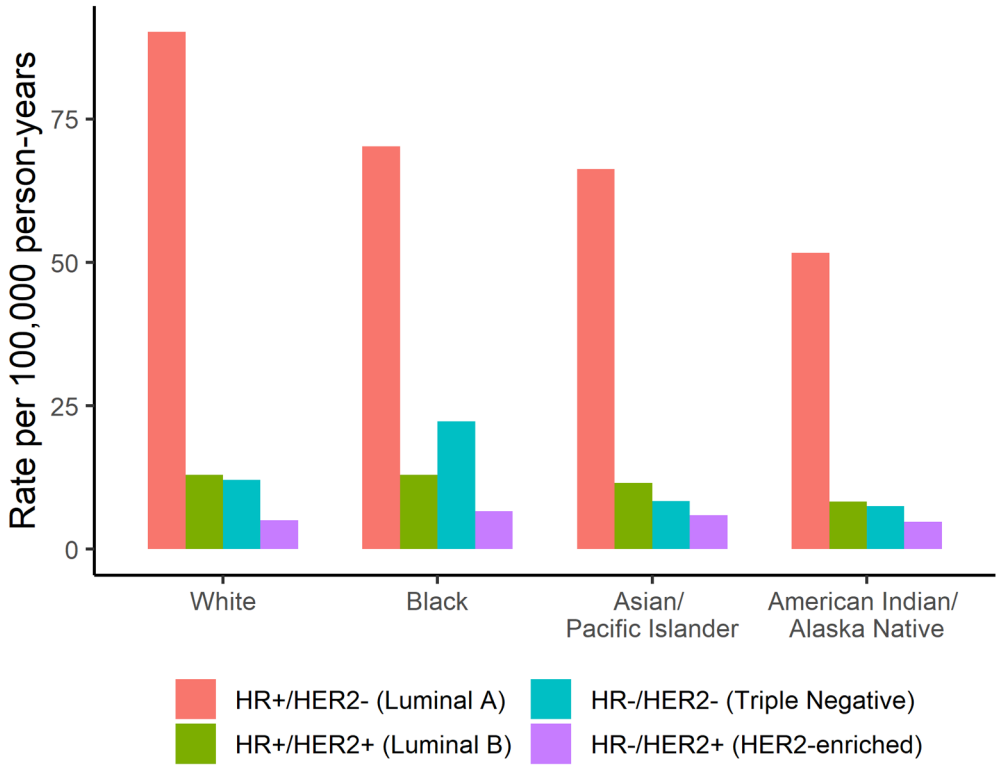

Figure 6.

United States five-year age-adjusted female breast cancer incidence rates for each breast cancer subtype by race/ethnicity. Figure 6 shows five-year age-adjusted female breast cancer incidence rates by breast cancer subtype for White, Black, American Indian/ Alaskan Native, and Asian/ Pacific Islander women using data from the SEER program (SEER 21, 2012-2016).

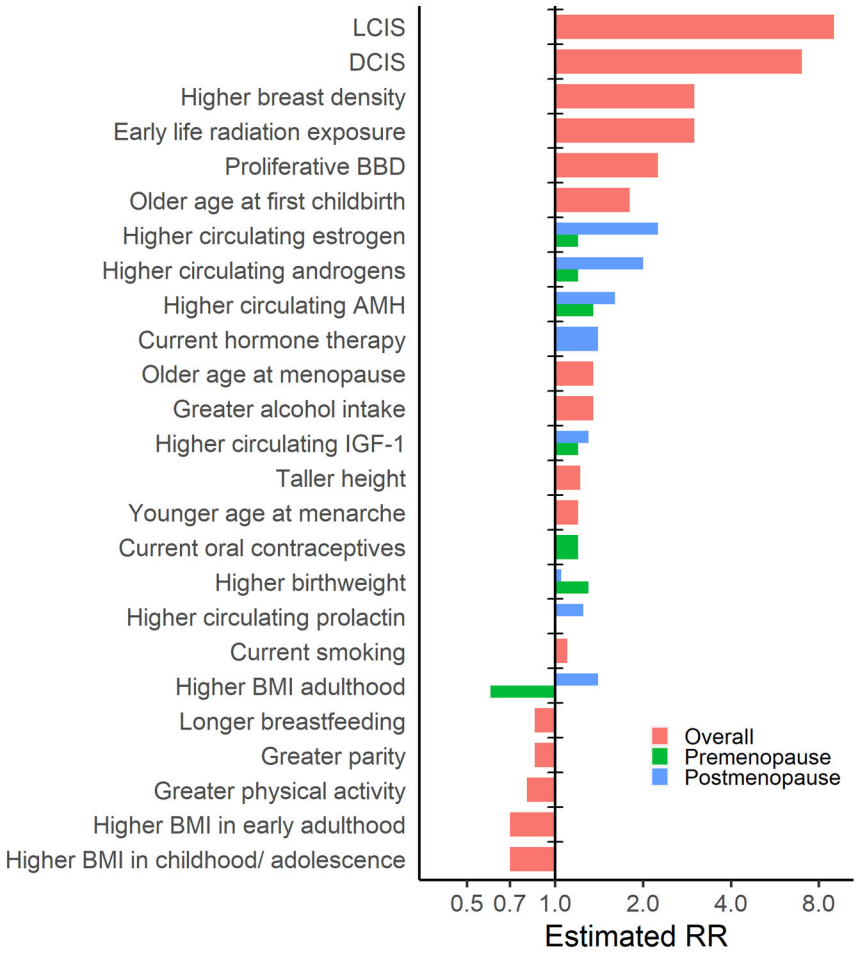

Figure 7.

Magnitude of association for established breast cancer risk factors. Figure 7 shows the magnitude of association for each established breast cancer risk factor; if the association has been shown to consistently vary by menopause status both the premenopausal and postmenopausal associations are shown. Risks are approximate and can vary depending on the extent of exposure, breast cancer subtype, and menopause status.

Table 1.

Breast cancer intrinsic molecular subtypes

Intrinsic Molecular Subtype	St. Gallen Surrogate classification	% of breast cancer	Grade	Proliferation	Prognosis
Luminal A	ER+/PR+/HER2− and low Ki-67	50%	Low	Low	Good
Luminal B	1.ER+/HER2− and high Ki-67 or PR− 2.ER+/HER2+ and any Ki67 or any PR	20%	Higher than Luminal A	Low, but higher than Luminal A	Good, but slightly worse than Luminal A
HER2-enriched	ER−/PR−HER2+	15%	High	High	Moderate
Basal-like	ER−/PR−/HER2−	15%	High	High	Moderate, but worse than other subtypes

Sources: [17-19, 31]

Table 2.

Moderate to high penetrance genes associated with breast cancer

Penetrance	Gene	Gene Function	RR of BRCA
High	BRCA1	Tumor suppressor, DNA Repair	>10
	BRCA2	Tumor suppressor, DNA Repair	>10
	TP53	Tumor suppressor, Cell cycle regulation	5 to >10
Moderate	PALB2	Tumor suppressor	2 to >10
	CDH1	Tumor suppressor, Cell adhesion	2 to >10 *
	PTEN	Tumor suppressor, Apoptosis	2 to 10
	STK11	Tumor suppressor, Apoptosis	2 to 10
	ATM	DNA Repair, Cell cycle regulation,	2 to 7
	CHEK2	Tumor suppressor, DNA Repair, Cell cycle regulation	2 to 5

* lobular breast cancer

Sources: [46-48, 350-354]

Table 3.

Summary of risk factors and serum biomarkers with breast cancer risk

Domain	Risk Factor	BRCA Association	Heterogeneity of risk	Comments	Highest level of evidence	Refs.
Anthropometrics	Birthweight, high	+	Association stronger for premenopausal; Association possibly stronger for ER+		PL	[53, 54, 355-357]
	Birth length, longer	+	Limited assessment of heterogeneity		PL	[53, 76]
	Height, taller	+	Association stronger for ER+		PL Prospective	[66, 74, 75]
	Childhood & adolescent BMI/ somatotype, heavier	−	Limited assessment of heterogeneity		Cohort Prospective	[55-60]
	Early adult (18-30) body mass index (BMI)/ weight, heavier	−	No substantial heterogeneity observed		PL Prospective	[61-63, 358]
	Premenopausal body mass index (BMI)/ weight, heavier	−	Association may vary by ethnicity; No heterogeneity observed by ER		MA Prospective	[61, 63-69]
	Postmenopausal body mass index (BMI)/ weight, heavier	+	Association may vary by ethnicity; Association stronger for never users of hormone therapy; Association stronger for ER+		MA Prospective	[63-69]
	Waist circumference/ waist-to-hip ratio, greater	+	Association stronger for never users of hormone therapy; Limited assessment of ER heterogeneity	Potential confounding by BMI	MA Prospective	[63, 71]
	Weight gain	+	Association possibly limited to postmenopausal; Association stronger for ER+		MA	[63, 72, 73, 359]
	Breast density, high	+ +	Association possibly stronger for premenopausal (percent density); Association possibly stronger for ER− (premenopausal only)	Association stronger for percent density vs. dense area	PL	[77-79, 360, 361]
	Bone mineral density (BMD), high		N/A	Association observed in several studies but not seen in prospective meta-analysis; Potential confounding by BMI, HT use, estrogen levels	MA Prospective	[81, 82]
Reproductive	Age at menarche, younger	+	Association stronger for ER+		PL Prospective	[67, 68, 83, 87, 362]
	Age at menopause, older	+	Association stronger for ER+		PL Prospective	[67, 83, 363]
	Parity, greater	−	Association consistent for ER+ and inconsistent for ER− (probable positive association)	Initial increased risk for up to 10-15 years, but inverse association long term	PL Prospective	[67, 68, 84-87, 363]

Domain	Risk Factor	BRCA Association	Heterogeneity of risk	Comments	Highest level of evidence	Refs.
	Age at first childbirth, younger	−	Association limited to ER+		MA	[67, 68, 86-88, 362, 363]
	Breastfeeding, longer duration	−	Association consistent for ER− and suggestive for ER+; No substantial heterogeneity by menopause		PL Prospective	[84, 86, 87, 364]
Endogenous hormones and other circulating biomarkers	Estrogens, high	+/+ +	Association stronger for postmenopausal; Association stronger for ER+; Association stronger for never users of hormone therapy		PL Prospective	[91-93]
	Androgens, high	+/+ +	Association possibly stronger for ER+		PL Prospective	[91-93]
	Prolactin, high	+	Association possibly limited to postmenopausal; Association possibly limited to ER+		MA	[94]
	Anti-Mullerian hormone (AMH), high	+	Association possibly stronger for ER+; No substantial heterogeneity observed by menopause at diagnosis		PL Prospective	[98]
	Sex hormone binding globulin (SHBG), high	−	No association observed for premenopausal, inverse association for postmenopausal; Association possibly stronger for ER+ (postmenopausal)		PL Prospective (Premenopausal); MA Prospective (Postmenopausal)	[91, 92, 99]
	Progesterone, high (premenopausal only)		No association observed for premenopausal; Limited assessment of postmenopausal		PL Prospective (premenopausal)	[91]
	Insulin-like growth factor 1 (IGF-1), high	+	No substantial heterogeneity observed by menopause; Association limited to ER+		PL Prospective	[101]
	Insulin/ C-peptide, high	+	Association possibly limited to postmenopausal; Limited assessment of ER heterogeneity	Null in meta-analysis, associations observed in several cohort studies published afterwards; May be mediated through BMI	MA Prospective	[103-107]
	Adipokines (low adiponectin/ high leptin)	+	Associations possibly stronger among Asian women	Possible association of lower adiponectin levels with breast cancer; Possible positive association for leptin	MA	[111, 112]
	C-reactive protein, high	+	Limited assessment of heterogeneity		MA Prospective	[108-110]
	Melatonin, high		Association possibly limited to postmenopausal; Association possibly limited to ER+	Possible inverse association for urinary aMT6s among subgroups; May vary by timing/ method of melatonin assessment	MA Prospective	[113, 114]
Exogenous Hormones	Oral contraceptives	+	Limited assessment of heterogeneity	Association stronger for current/ recent longer duration users; Limited assessment of dose/formulation	MA Prospective	[101, 115-117]

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Domain	Risk Factor	BRCA Association	Heterogeneity of risk	Comments	Highest level of evidence	Refs.
	Levonorgestrel-releasing intrauterine system	+	Limited assessment of heterogeneity	Possible positive association, may be confounded by prior OC use	MA	[118]
	Postmenopausal hormone therapy	+/+ +	Association stronger for ER+	Association stronger for estrogen and progestin vs. estrogen only; Association stronger for current vs. past users and associations increase (or become apparent for estrogen only) with increased duration of use; Limited assessment of dose/formulation	PL Prospective	[119]
Dietary	Alcohol	+	Heterogeneity by ER inconsistent;	Association possibly stronger if initiated prior to first birth	PL Prospective	[178-183]
	Carbohydrates		Association possibly limited to ER−		MA	[127]
	Carotenoids	−	Association possibly stronger for ER− (α-carotene, β-carotene, and lutein/ zeaxanthin)	Association stronger for β-carotene and lycopene; Association observed for β-carotene plasma levels but not supplement trials	PL Prospective (RCT MA for β-carotene)	[154-157]
	Coffee/ Tea/ Caffeine		N/A	Caffeine likely not associated; Associations for coffee/tea inconsistent but possible among subgroups	MA Prospective	[142-146]
	Dairy/ Calcium	−	Association stronger for premenopausal (low-fat dairy/milk, calcium); Limited assessment of ER heterogeneity	Association possible for low-fat dairy/ milk; Association observed for calcium from dietary intake and plasma levels but not in supplement trials	MA Prospective (RCT MA for calcium)	[136-138, 147-149, 365-368]
	Dietary fat		N/A		PL Prospective	[121-126]
	Dietary Inflammatory Index (DII)		N/A	Possible positive association, weak in prospective studies and may be cofounded by other lifestyle factors	MA Prospective	[369-372]
	Dietary patterns		N/A	Suggestive inverse associations for ‘Prudent’ diets or Mediterranean diets and suggestive positive for ‘Western’ diets; Associations weak in prospective studies and results may be confounded by other lifestyle factors	MA Prospective	[184-188]
	Fiber	−	Limited assessment of ER heterogeneity	Association stronger for soluble fiber	MA prospective	[129-131, 373-377]
	Folate/ folic acid		Association varies by alcohol consumption (folate intake), *MTHFR* status, and possibly menopause status; Association possibly inverse for ER− (folate intake) but may vary by dietary or supplement folate	Possible J-shaped association (folate intake); Possible differences by dietary intake (null/inverse) vs. supplemental intake (suggestive positive); No association observed in RCT (supplemental)	RCT MA	[164-168]
	Fruits/ vegetables	−	Association limited to ER−	Association possibly stronger for vegetables	PL Prospective	[139-141]

Domain	Risk Factor	BRCA Association	Heterogeneity of risk	Comments	Highest level of evidence	Refs.
	Glycemic index/ glycemic load	+	Association stronger for postmenopausal (glycemic index); Association stronger for ER− (glycemic load)		MA Prospective	[127, 128]
	Iron	+	Association possibly stronger for premenopausal (heme iron); No heterogeneity observed by ER	Possible positive association for heme iron intake and plasma iron levels	MA	[158, 378, 379]
	Meat	+	No heterogeneity observed by ER	Possible positive association for processed meat	MA Prospective	[132-136, 366, 368, 378, 380-382]
	Multivitamins		N/A		MA	[177]
	Phytoestrogens		N/A	Possible inverse association for enterolignan intake but not seen with blood/urine levels	MA	[171, 172]
	Selenium		N/A	Methods of selenium assessment heterogeneous; No association observed in RCT	MA	[169, 170]
	Soy/ Isoflavones		N/A		MA Prospective	[134, 173-176]
	Vitamin A		N/A	Possible inverse association for dietary intake (not seen in prospective and no dose-response), not seen with supplements or plasma levels	MA	[159]
	B-Vitamins (B_2, B_6, B_{12})		N/A		MA	[160, 161]
	Vitamin C		N/A	Possible inverse association for dietary intake (not seen in prospective), not seen with supplements (positive) or plasma levels	PL Prospective	[159, 162, 163]
	Vitamin D	−	No heterogeneity observed	Possible inverse association for 25(OH)D levels; Intake and supplement inconsistent	RCT MA	[150-153]
	Vitamin E		N/A	Possible inverse association for dietary intake (not seen in prospective and no dose-response) and plasma alpha-tocopherol levels	MA	[159, 383, 384]
Environmental	Air pollution		N/A	Possible positive association for NO2 and NOx, though weak and often borderline significant	MA	[194, 195]
	Acrylamides (dietary)		N/A		MA	[203]
	Electromagnetic fields		N/A	Possible positive association, though weak and often borderline significant	MA	[196-198]

Domain	Risk Factor	BRCA Association	Heterogeneity of risk	Comments	Highest level of evidence	Refs.
	Organochlorine blood levels		N/A		MA	[199-202]
	Secondhand smoke	+	Association possibly stronger for premenopausal; Limited assessment of ER heterogeneity	Possible positive association, though weak and often borderline significant	MA Prospective	[190-193, 385-388]
Lifestyle	Light at night and shift work/ Circadian rhythm disruptions	+	Association possibly stronger for premenopausal; Association possibly stronger for ER+	Possible positive association for shift work or light at night; Associations stronger in case-control studies	MA Prospective	[217-221]
	Hair dyes/ relaxers	+	Association possibly stronger for Black women	Possible positive association for hair dye/ relaxers; results mostly case-control studies and 1 cohort	MA	[215, 216]
	Physical activity	−	No substantial heterogeneity observed by menopause or ER		MA Prospective	[63, 206-210]
	Physical Inactivity/ Sedentary behavior	+	Association possibly limited to postmenopausal women	Possible increased association with greater sedentary behavior; methodology varies widely	MA	[63, 211, 212]
	Stressful life events	+	Limited assessment of heterogeneity	Possible increased association with stressful life events; methodology varies widely	MA Prospective	[224]
	Sleep duration		N/A		MA	[220, 222, 223]
	Smoking	+	Associations may vary by ethnicity; No heterogeneity observed by menopause; Associations possibly limited to ER+ among those initiated prior to first birth	Association stronger if initiated 10+ years prior to first birth	PL Prospective	[182, 190, 213, 214]
Medications	Antibiotics		N/A		MA	[225]
	Antidepressants		N/A		MA	[226]
	Aspirin/ Nonsteroidal anti-inflammatory drugs (NSAIDs)		N/A	Possible inverse association for long term, consistent aspirin use among subgroups; Associations stronger in case-control studies	MA Prospective	[227-229, 389]
	Bisphosphonates		N/A	Possible inverse association but not seen in RCT and possible confounding by indication	MA	[230-232]
	Diethylstilbestrol (DES)	+	Limited assessment of heterogeneity	Probable association among women who took DES during pregnancy; Possible association among daughters exposed in utero, but possible surveillance bias	MA (in utero); Cohorts (maternal use)	[76, 236-244]
	Fertility drugs		N/A	Issues with confounding (e.g., parity, underlying cause)	MA	[233, 234]

Domain	Risk Factor	BRCA Association	Heterogeneity of risk	Comments	Highest level of evidence	Refs.
	Statins		N/A	Heterogeneous results among various subgroups	MA	[235]
Personal Health	Abortion		N/A	N/A	MA Prospective	[245-248]
	Diabetes		N/A	Association may vary by type of diabetes	MA	[261-265]
	Ductal carcinoma in situ (DCIS)	+ +	Limited assessment of heterogeneity		MA	[251-253]
	Benign breast disease	+/+ +	Limited assessment of heterogeneity	Association varies by type of benign breast disease – strongest associations with atypical proliferation	MA	[249, 250]
	Ionizing Radiation	+ +	Limited assessment of heterogeneity	Association stronger if exposed early in life	PL Prospective	[204, 205, 269]
	Lobular carcinoma in situ (LCIS)	+ +	Limited assessment of heterogeneity		Long term follow-up studies Prospective	[254-260]
	Metabolic syndrome		Possible variation by menopause		MA	[266]
	Migraine headaches		N/A	N/A	MA Prospective	[267, 268]

ABBREVIATIONS: Refs, references; PL, pooled analysis; MA, meta-analysis; RCT, randomized trials; ER, estrogen receptor

NOTE: Color used to indicate consistency of association: Dark red, established/ probable positive association; light red, possible positive association; dark green, established/probable inverse association; light green, possible inverse association; grey, inconsistent/ no association.

Symbols used to indicate magnitude of association: + + + strong positive association (RR/OR >5); + + moderate positive association (RR/OR 2-5), + modest positive association (RR/OR <2); − − − strong inverse association (RR/OR <0.2); − − moderate inverse association (RR/OR 0.2-0.5), − modest inverse association (RR/OR >0.5).

Magnitude of association may vary by race/ethnicity, tumor subtype.

Association directions are for increasing exposure unless otherwise specified.

Table 4.

Risk factors of breast cancer by subtypes

Risk factor	Luminal A	Luminal B	HER2-enriched	Triple negative
Age at menarche, younger	+			+
Parity, greater	−	−		+
Age at 1st birth, older	+	+		
Breastfeeding, longer duration	−	−		−
Age at menopause, older	+			
Oral contraceptives use				+
Hormone therapy use	+	+		
BMI premenopausal, heavier	−			+
BMI postmenopausal, heavier				
Benign breast disease	+	+	+	+
Family history of breast cancer	+	+	+	+
Alcohol intake	+	+		

NOTE: Color used to indicate consistency of association: Dark red, established/ probable positive association; light red, possible positive association; dark green, established/probable inverse association; light green, possible inverse association; grey, inconsistent/ no association.

Symbols used to indicate magnitude of association: + + + strong positive association (RR/OR >5); + + moderate positive association (RR/OR 2-5), + modest positive association (RR/OR <2); − − − strong inverse association (RR/OR <0.2); − − moderate inverse association (RR/OR 0.2-0.5), − modest inverse association (RR/OR >0.5).

Sources [67, 86, 358, 390]