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Reproductive Risk Factors and Breast Cancer Subtypes: A Review of the Literature

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Abstract

Aside from age, sex, and family history, risk of developing breast cancer is largely linked to reproductive factors, which characterize exposure to sex hormones. Given that molecular testing at the tumor level is currently possible, clinical characterization of tumor subtypes is routinely conducted to guide treatment decisions. However, despite the vast amount of published data from observational studies on reproductive factor associations and breast cancer risk, relatively fewer reports have been published on associations specific to breast tumor subtypes. We conducted a review of the literature and summarized the results of associations between reproductive factors and risk or odds of three distinct tumor subtypes: estrogen receptor/progesterone receptor positive (hormone receptor positive, HR+ tumors), tumors overexpressing the human epidermal receptor 2 protein (HER2+), and triple negative breast cancer (TNBC), which lacks the three markers. Results show that the most consistent evidence for associations with reproductive risk factors exists for HR+ breast cancers, with nulliparity, current use of menopausal hormone therapy (HT), and prolonged interval between menarche and age at first birth being the strongest risk factors; increased age at first birth and decreased age at menarche were fairly consistently associated with HR+ cancers; and though less consistent, older age at menopause was also positively associated, while lactation was inversely associated with HR+ tumors. Fewer consistent associations have been reported for TNBC. The single protective factor most consistently associated with TNBC was longer duration of breastfeeding. Increased parity, younger age at first birth, older age at menarche, and oral contraceptive use were less consistently shown to be associated with TNBC. No remarkable associations for HER2+ breast cancers were evident although this was based on relatively scarce data. Findings suggest heterogeneity in reproductive risk factors for the distinct subtypes of breast tumors, which may have implications for recommended prevention strategies.

Keywords

breast tumor subtype; reproductive factors; triple negative breast cancer; tumor heterogeneity

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Conflict of Interest

The authors declare that they have no conflict of interest.

INTRODUCTION

Burden of Disease

In women, breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in both developed and developing countries [1]. Variation in incidence rates worldwide is thought to be due to differences in reproductive patterns and other hormonal factors as well as early detection [2, 3]. In the U.S., breast cancer mortality rates have been steadily decreasing over the last 2-3 decades [4]; this is largely the result of early detection as well as improved targeted therapy [1, 4]. However, despite this substantial progress, not all racial/ethnic groups have benefitted equally as differences in stage distribution, mortality, and survival by race/ethnicity are still prominent [4], [5], [6].

Defining Breast Tumor Subtypes

It is now widely recognized that breast cancer is not a single disease but one that is characterized by different subtypes determined by molecular and genetic information from tumor cells (see Table 1). Prognostic differences in patient outcomes based on estrogen receptor (ER) and progesterone receptor (PR) status, as well as the expression level of human epidermal growth factor receptor 2 (HER2) have resulted in routine clinical stratification of tumors. As a result, the American Society of Clinical Oncology and the College of American Pathologists has recommended that all invasive breast cancers be tested for ER, PR, and HER2. Up to 20% of immunohistochemistry (IHC) determinations of ER and PR testing may be inaccurate due to varying thresholds for positivity and interpretation criteria. Current recommendations regarding ER and PR status indicate that assays should be considered positive if at least 1% of tumor nuclei in the sample are reactive [7]. Previous clinical recommendations had set thresholds of <10% reactivity when identifying ER/PR negative tumors and this has frequently been the cutoff used in clinical trials; however, most recent data indicate that the best approach is to include adjuvant endocrine therapy for patients with 1-9% ER+ cells [8]. As noted in Table 1, hormone positive tumors (HR+, defined as ER+/PR+) can be further subdivided into luminal A or luminal B; the latter having a lower prevalence, yet carrying a worse prognosis. Guidelines regarding HER2 status indicate that additional confirmatory analysis with fluorescent in situ hybridization for IHC samples with equivocal HER2 status should be performed to avoid false positives and false negatives. An unequivocally positive HER2 result is defined as uniform intense membrane staining of >10% of invasive tumor cells [9]. HER2+ tumors represent 10% of all breast cancers.

Triple negative breast cancers (TNBC) are defined by the absence of ER, PR, and HER2 [8] and represent 10-20% of all breast cancer diagnoses. Gene expression data indicate that these triple negative cancers are likely comprised of a heterogeneous collection of molecular subtypes [8]. Efforts to categorize breast cancers into intrinsic subtypes with microarray techniques have shown that most (71-91%) TNBCs fall into a basal-like subtype; conversely up to 20% of basal-like breast cancers do not have a triple negative phenotype and may express ER or HER2 to some extent. The terms basal and triple negative are therefore descriptive terms for entities that overlap but are not synonymous [10]. It is unclear at this time whether a basal-like phenotype has clinical significance with regards to predicting

clinical course. Furthermore, there is no widely accepted consensus on how this molecular subtype should be defined; for example, in two recent studies, epidermal growth factor receptor (EGFR) expression was alternately treated as a marker of basal-like cancer and luminal-like cancer within categories of TNBCs [11, 12]. Given the lack of consensus on how to molecularly define basal cancers, it is not surprising that recent studies looking at whether subtypes within TNBC could predict survival have produced disparate conclusions on the prognostic implication of basal markers [11-13].

Etiology of Breast Cancer

Aside from age, sex, and family history, risk of developing breast cancer is largely related to a woman's reproductive risk factor profile [14], which is characteristic of exposure to sex hormones. Specifically, risk of developing breast cancer is increased by early menarche, late menopause, and nulliparity, whereas risk is reduced by higher parity and lactation. Furthermore, using combined hormone therapy after menopause increases breast cancer risk; the higher risk appears to apply only to recent use. Data from recent epidemiologic studies provide evidence supporting differential effects of reproductive risk factors on risk of developing HR positive or negative tumors, which provides strong rationale in support of etiologic heterogeneity among breast tumors. We present here a review and summary of the distinct associations between reproductive risk factors and breast tumor subtypes. Understanding this degree of heterogeneity is important to further our understanding of disease etiology and to provide personalized prevention and treatment regimens.

METHODS

Pubmed search using query terms “reproductive risk factors” and “hormonal risk factors” with “breast cancer subtypes”, “triple negative breast cancer”, “basal breast cancer”, “HER2 breast cancer.” Few studies prior to 2006 stratified risk factors by breast cancer subtypes, and a large meta-analysis was published in 2006 that analyzed these studies; thus, we included studies that were published subsequent to that. The reference lists of resulting hits were analyzed for studies that were not included in initial queries. We included studies that had at least 200 cases. Searches were performed January 2013 and again in January 2014. The studies included classified subtypes in a wide variety of ways. For the purpose of this review, we grouped subtypes into the following three categories: HR+ cancer (ER+/PR+ and HER2− where information about HER2 was available); HER2+ cancers regardless of HR status, which includes luminal B cancers (HR+ and HER2+) as well as HR− and HER2+ cancers; and TNBC, which in some studies were further categorized into basal-like and luminal-like.

A review of the literature included cohort, case-control, and case-only studies. To provide a summary of the evidence for assessing risk of developing each tumor subtype, we considered only cohort and case-control studies. Data on case-only studies are provided as evidence of tumor heterogeneity but not in assessment of risk.

RESULTS

Our search revealed 36 articles using the criteria noted above. After screening, 34 primary research articles and one meta-analysis were selected for this review. Of the selected articles, 10 were prospective cohort studies, 13 were case-control, and 8 were case-only studies; three studies included both case-control and case-case comparisons, and one study was a meta-analysis of both prospective cohort and case-control studies. Table 2 provides a summary of the results and Appendix Table 1 provides details of the studies and individual study results.

Hormone Receptor Positive Breast Cancers

Parity-related Factors and Breastfeeding—The strongest and most consistent relationship between reproductive risk factors and breast cancer are seen in cancers that express either estrogen or progesterone receptors (i.e., HR+). Of the 22 case-control and cohort studies that assessed parity included in this review, 19 found a statistically significant inverse association between parity and HR+ breast cancer [15-33]. In a study of premenopausal women diagnosed with breast cancer, the inverse association was only seen among women who were diagnosed at age 40 or greater [30]. Additionally, older age at first pregnancy was positively associated with HR+ breast cancers in a majority of studies [16-18, 22, 25-29, 31-35]. However, for lactation history, only 5 of 18 studies reported a statistically significant inverse association with HR+ breast cancers [21-23, 25, 30].

Menstruation History—Menstrual cycle characteristics were also correlated with HR+ breast cancer, with younger age at menarche being associated with increased odds of HR+ breast cancers in 10 of 19 studies [21, 22, 25, 26, 30-34, 36]. For one of these studies, the positive association was limited to premenopausal women diagnosed after age 40, with no association seen for those diagnosed before age 40 [30]. Older age at menopause was positively associated with HR+ breast cancer in 3 of 7 studies [21, 28, 34]. The interval between age at menarche and age at first pregnancy was examined in four studies included in this review [15, 27, 31, 32], with three finding that a short interval was significantly inversely associated with HR+ breast cancer [27, 31, 32].

Hormone Use—Current use of menopausal hormone therapy (HT) was significantly correlated with increased risk of HR+ breast cancer in all three published studies [26, 34, 37]. The relationship between HR+ tumors and prior HT use was not as strong as that for current use; a statistically significant association was found in one study [21], whereas the effect was limited to women in the lowest tertile of BMI in a second report [37]. Oral contraceptive use was only associated with a significant inverse association with HR+ tumors one of 4 studies [35].

Interactions between reproductive variables including parity, breastfeeding, and young age at first birth, have also been reported in the literature. The combination of breastfeeding and high parity, which was defined as a range from at least 2 to 4 or more births, compared to nulliparous women was inversely associated with HR+ breast cancers [30, 38, 39], as was the combination of increased parity and young age at first birth compared to nulliparous women [38, 39].

Triple Negative Breast Cancers

Parity-related Factors and Breastfeeding—Reproductive risk factors for breast cancers without expression of ER, PR, or HER2 are not as well established as those for HR+ breast cancers. Unlike the clear inverse relationship between parity and HR+ breast cancers, only a few observational studies have reported a statistically significant positive association between parity and risk of TNBC [22, 35, 38]; results of the remaining nine studies included in this review did not reach statistically significance. A significant inverse correlation between older age at first pregnancy and TNBC was reported in 2 of 12 studies included in this review [15, 25]; the remaining nine studies did not show a statistically significant relationship. Breastfeeding was inversely associated with TNBC in the majority of the 11 studies in this review [15, 20, 22, 25, 34, 38, 40]; none reported an increased risk associated with TNBC. In a recent report, Li et al., showed a 50% reduction in the odds of TNBC for younger women (less than age 45) who had breastfed greater than 12 months compared to those who had never breastfed; no association was observed for ER+ or HER2+ breast cancers [15]. These findings are consistent with those in other studies that assessed shorter breastfeeding duration [20, 34]. No statistically significant relationships with TNBC were found in a study that evaluated the combination of high parity or breastfeeding and high parity and young age at first birth [38].

Menstruation History—Associations for age at menarche and menopause with TNBC were similar to those seen with other subtypes though fewer reached statistical significance; 3 studies found an inverse relationship between age at menarche [25, 28, 38] but no study showed a statistically significant association between age at menopause and TNBC [28, 34-36, 40]. A short interval between menarche and first birth was positively associated with risk of TNBC, unlike the inverse relationship observed for HR+ breast cancers [15].

Hormone Use—The association between HT use and TNBC has only sparsely been reported. Tamimi et al., showed that only current, but not past HT use was significantly associated with risk of TNBC [34]. The relationship between oral contraceptive use and TNBC is unclear, with 4 studies in this review having evaluated this association and only one finding a statistically significant positive correlation between young age at first contraceptive use among older women with TNBC [23].

HER2 Overexpressing Breast Cancers

Few published data exist on etiology of HER2+ breast cancers. One large case-control study from China found that when compared to nulliparous women, women who had one child had a decreased risk of developing HER2+ breast cancers [22], while 11 other studies found no statistically significant association for parity. Breastfeeding was also inversely associated with HER2+ cancers in this study [22] and with HER2+/HR+ breast cancers in an Atlanta-based case-control study [25]. Older age at first birth was associated with HER2+ breast cancers in an analysis of participants in the Breast Cancer Surveillance Consortium [18]. Young age at menarche was associated with HER2+ breast cancers in two studies [20, 40] and older age at menopause was positively associated HER2+/HR+ and HER2+/HR− breast cancers in the Nurses' Health Study [34]. Data on the effect of HT and oral contraceptive

use are also not as clear as for HR+ breast cancers, with no studies reporting significant associations [23, 34, 41].

DISCUSSION

Summary of Findings

Our review of the literature regarding reproductive factors and breast tumor subtype associations suggests significant heterogeneity in reproductive risk factors for the distinct subtypes of breast tumors. However, as shown in Table 3, there is variation in strength and consistency of the associations. The strongest evidence exists for HR+ breast cancers, with nulliparity, current use of HT, and prolonged interval between menarche and age at first birth being the most robust. Increased age at first birth and increased age at menopause were consistently associated with HR+ cancers in a majority of studies; and though less consistent, younger age at menarche was also positively associated with HR+ tumors whereas longer periods of lactation and oral contraceptive use were associated with lower risk of HR+ tumors. Fewer published data exist for TNBC associations and these tend to be less consistent than those for HR+ tumors. The strongest and most consistent finding for TNBC was the inverse association with breastfeeding. Increased parity, decreased age at first birth, increased age at menarche, and oral contraceptive use were less consistently shown to be associated with TNBCs. There were no remarkable associations in the limited data available for HER2+ breast cancers.

Although much focus in the scientific community has been placed on addressing the etiology and treatment of TNBC, there is still much work to be done. What unifies TNBC tumors and separates them from other types of breast cancer is an aggressive clinical course, distinct epidemiological risk factors, and lack of chemoprevention and targeted therapy options. TNBCs often present as interval cancers, have a rapid rise in risk of recurrence following diagnosis within the first three years of surgery, progress rapidly once distal recurrence has occurred, and distal recurrence is rarely preceded by local recurrence [42]. When they metastasize, TNBCs tend to spread to the brain and lung more often than hormone receptor positive (HR+) cancers [43]. While TNBC accounts for only 10-20% of invasive cancers overall, it is more prevalent in African American and Hispanic women [44]. Using data from the California Cancer Registry, Bauer et al. reported that the prevalence of TNBC was 25% in black and 17% in Hispanic women [45]. The higher prevalence of hormone negative breast cancers among African American and Hispanic women has been hypothesized to be due to an interaction between genetic and reproductive risk factors such as increased parity [16, 46]. Findings from our review show that although risk of TNBC is associated with some reproductive factors, the results were largely inconsistent. Given the aggressive nature of this tumor subtype and the relative lack of understanding regarding etiology, much work is needed in better characterizing the molecular subtypes of these tumors that are responsive to targeted treatments [43].

Case-Only Studies

Although results of case-only studies cannot be used to estimate risk of disease, they can be a useful tool for understanding etiologic heterogeneity [47]. A summary of these studies is

found at the end of Appendix Table 1. A recent report found evidence for this heterogeneity for several reproductive factors specifically related to TNBC, including age at first full-term pregnancy, parity, interval between menarche and first pregnancy, duration of menstruation, and breastfeeding [48]. Other published studies have also shown differences in odds comparing TNBC to HR+ tumors, although the direction of the association is not always consistent across studies [25, 47-50]. Published case-case reports also exist for HER2+ tumors, including higher odds for giving birth at age less than 18 years [25] and higher odds of HER2+ breast cancers that were diagnosed within 5 years [25] or 10 years [51] from last birth. Identification of distinct breast tumor subtypes with discrete etiologic factors will continue to be helpful in identifying alternate mechanisms of etiopathogenesis for specific tumor phenotypes and in turn can aid in identifying target populations for optimal prevention.

Implications for Chemoprevention

The risk for hormone driven breast cancers can be modulated by prophylactic use of selective estrogen modulators such as tamoxifen and raloxifene or with aromatase inhibitors. One of the largest and most well-known studies of breast cancer chemoprevention was the NSABP P1 study, which found that after 7 years of follow-up, women who were taking tamoxifen benefited from a 62% reduction in the rate of ER+ invasive breast cancer but there was no reduction in risk for ER− breast cancers [52]. Other longitudinal cohort studies have confirmed a lack of benefit for prevention of hormone receptor negative breast cancer. Aromatase inhibitors are similarly ineffective chemoprevention for TNBC. A recent meta-analysis evaluated data from nine prevention trials of selective estrogen receptor modulators including 83,399 women with 306,617 patient years of follow up. The number needed to treat (NNT) to prevent one invasive case of breast cancer was 42 in the first 10 years of follow-up. The combined analysis showed a 51% reduction in risk of ER+ breast cancers but no benefit in risk reduction for ER− breast cancers [53]. The issue of lack of current chemoprevention for ER− disease is especially relevant given the high rates of this disease in women with germline variants that carry an increased risk of breast cancer. Among patients with breast cancer and a *BRCA1* mutation, up to 90% are triple negative tumors [8]. Similarly, no established targeted chemoprevention exists for women with HR−/HER2+ breast cancers.

Future Directions

Given the absence of chemoprevention options for TNBC and HER2+ breast cancer, these subtypes require additional study. Population-based studies can enrich for these subtypes by leveraging available data to enroll populations with risk factors specific to these less common subtypes, for example early childbearing and TNBC. In particular, additional data on the factors associated with HER2+ breast cancer could be extremely valuable given that oral, relatively low toxicity anti-HER2 agents, are currently available. Specifically, lapatinib was FDA approved in 2007 and will lose all patent protection by 2021. If a population of women with a relatively high risk for HER2+ breast cancer could be identified, anti-HER2 chemoprevention trials could become feasible with generic lapatinib. Biomarkers could potentially be developed by extending work being conducted in patients with HER2+ breast cancer. For example, the cleaved extracellular domain of HER2, termed soluble HER2

(sHER2), can be detected in the blood of patients with metastatic HER2+ breast cancer and is a prognostic biomarker [54].

The complex interplay between genetic susceptibility and reproductive factors will also play an important role in furthering our understanding of the cancer development and tumor heterogeneity. Prior focus has been on known high risk mutations in *BRCA1* and *BRCA2* and common reproductive risk factors, with a recent study finding that women with deleterious mutations in *BRCA1* who breastfed for at least one year had a 32% reduction in the odds of breast cancer [55]. Several studies have demonstrated a protective effect of parity among *BRCA1* mutation carriers [56-58]. However, *BRCA1/2* mutations only account for a small proportion of disease. More recently, attention is being directed to the role of common genetic variants discovered through genome-wide research in tumor development. Alone, these variants may only moderately alter risk but they may modified by established reproductive risk factors. As an example, a recent analysis of data from the Breast Cancer Association Consortium found that the breast cancer risk associated with a genetic variant in *LSP1* differed according to number of births [59]. This study was underpowered to examine the role this polymorphism played in different tumor subtypes. As genome wide germline sequencing in cancer patients becomes more accessible, the interactions between polymorphisms and reproductive risk factors within the subtypes will require additional investigation.

Additionally, for both TNBC and HER2+ breast cancer, greater understanding of etiologic factors will be critical to future chemoprevention development. The association of TNBC breast cancer with increased parity is an area that should be explored further based on our understanding of the physiologic changes during pregnancy. The relative immune suppressed state of pregnancy and the molecular changes in the breast during pregnancy are clearly worthy of study. Arguably, additional work on the inverse association between duration of lactation and both HR+ and TNBC breast cancer subtypes is also needed. Logistically, these important areas of research can be best addressed through the conduct of epidemiologic studies with clinically annotated biospecimen collection and risk factor data to enable the necessary translational studies. Furthermore, these studies need to have representation of a diverse group of racial/ethnic groups, something that is currently lacking in the scientific literature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characterization of Four Major Breast Tumor Subtypes, Population Prevalence, and Clinical Characteristics

Subtype	Molecular/genetic characteristics	Prevalence	Clinical Characteristics
Luminal A	ER+ and/or PR+, HER2−, low Ki67	40%	Slow-growing Less aggressive Low recurrence High survival Best prognosis of all subtypes Respond to endocrine therapy
Luminal B	ER+ and/or PR+, HER2+ (or HER2− with high Ki67)	10-20%	High proliferation rates Worse prognosis than Luminal A Respond to endocrine therapy
HER2 overexpressing	Positive the human epidermal growth factor receptor 2 (EGFR2) protein, ER, PR−	10%	Tend to grow and spread more aggressively More likely to be high grade and node positive Poor short-term survival Targeted therapies exist
TNBC	ER−, PR−, HER2−	10-20%	Younger age at diagnosis High histologic grade Higher rates of distant recurrence after surgery Poor short-term prognosis. Lack targeted therapy.

ER+/−, estrogen receptor positive or negative; PR+/−, progesterone receptor positive or negative; HER2+/−, human epidermal growth factor positive or negative.

Source: American Cancer Society. Breast Cancer Facts & Figures 2013-2014 [44]

Table 2

Summary of Reproductive Factors Associations by Breast Tumor Subtype from Published Case-Control and Cohort Studies*

	Hormone receptor positive	HER2+ and HR+/−	TNBC
Reproductive factor			
Increased parity	Decreased: 19/22 [15-33]	Decreased: 1/11 [22]	Increased: 3/13 [22, 35, 38]
Older age at first pregnancy	Increased: 15/22 [16] [17, 18, 22, 25-35]	Increased: 1/9 [18]	Decreased: 2/13 [15] [48]
Ever breastfeeding	Decreased: 5/18 [21-23, 25, 30]	Decreased: 2/9 [22] [25]	Decreased: 7/11 [15, 20, 22, 25, 34, 38, 40]
Younger age at menarche	Increased: 10/19 [21, 22, 25, 26, 30-34, 36]	Increased: 2/10 [20, 40]	Increased: 3/12 [25, 28, 38]
Older age at menopause	Increased: 3/7 [21, 28, 34]	Increased: 1/7 [34]	0/5 [28, 34-36, 40]
Short time from menarche to age at first pregnancy	Decreased: 3/4 [27, 31, 32]	0/1 [15]	Increased: 1/1 [15]
High parity, breastfeeding	Decreased: 3/3 [30, 38, 39]		0/1 [38]
Increased parity, young age at first birth	Decreased: 2 / 2 [38, 39]		0/1 [38]
HRT past use	Increased:1/4 [21]	0/3 [23, 34, 41]	0/1 [34]
HRT current use	Increased: 3/3 [26, 34, 37]	0/3 [23, 34, 41]	Increased: 1/1 [34]
Oral contraceptive use	Decreased: 1/5 [35]	0/2 [23],[41]	Increased: 1/4 [23]

HR+/−, hormone receptor positive or negative; HER2+, human epidermal growth factor positive; TNBC, triple negative breast cancer

*Statistically significant associations noted in numerator with listed references; denominator refers to total number of studies evaluating the association

Table 3

Summary of Evidence for Associations between Reproductive Factors and Tumor Subtypes

Evidence	Hormone Positive	TNBC	HER2+
Consistently associated with increased risk (greater than ¾ of studies)	Nulliparity or decreased parity, current HT, interval between menarche and age at first pregnancy		
Fairly consistently associated with increased risk (at least half of studies)	Increased age at first birth; younger age at menarche	Decreased lactation	
Less consistent (fewer than half of studies)	Decreased lactation, older age at menopause, oral contraceptive use	Increased parity, decreased age at first birth, decreased age at menarche, oral contraceptive use	
Too few studies			Parity, age at menarche, age at menopause, age at first birth, lactation, OC and HT use

TNBC, triple negative breast cancer; HER2+, human epidermal growth factor positive