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REVIEW

Breast cancer genetics and risk assessment: an overview for the clinician

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ABSTRACT

Breast cancer is the most common cancer in women globally with enormous associated morbidity, mortality and economic impact. Prevention of breast cancer is a global public health imperative. To date, most of our global efforts have been directed at expanding population breast cancer screening programs for early cancer detection and not at breast cancer prevention efforts. It is imperative that we change the paradigm. As with other diseases, prevention of breast cancer starts with identification of individuals at high risk, and for breast cancer this requires improved identification of individuals who carry a hereditary cancer mutation associated with an elevated risk of breast cancer, and identification of others who are at high risk due to non-genetic, established modifiable and non-modifiable factors. This article will review basic breast cancer genetics and the most common hereditary breast cancer mutations associated with increased risk. We will also discuss the other non-genetic modifiable and non-modifiable breast cancer risk factors, available risk assessment models and an approach to incorporating screening for genetic mutation carriers and identifying high-risk women in clinical practice. A discussion of guidelines for enhanced screening, chemoprevention and surgical management of high-risk women is beyond the scope of this review.

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The scope of the problem

All women are at substantial risk for breast cancer. Breast cancer is the second most common cancer globally, accounting for 12.5% of all cancers and 26% of cancers in women, with 2.2 million cases annually worldwide [1–3]. Across the globe, the incidence of breast cancer ranges between 8 cases per 100,000 in Africa and other developing countries to >100 cases per 100,000 in some western European countries. The incidence is highest in Belgium and the Netherlands where the population lifetime breast cancer risk is approximately 14% (>100 cases per 100,000), compared to the USA and Canada where the population lifetime breast cancer risk is approximately 12% (90 cases per 100,000), compared to a much lower lifetime risk of 3–4% in low-income and developing countries [2,4]. Despite substantial improvements in breast cancer treatments and an overall reduction in breast cancer mortality globally, breast cancer is the fifth most common cause of cancer death worldwide and accounts for 6.6% of global cancer deaths [1,5], and 15% of all female cancer deaths, with 5-year survival rates ranging from approximately 40% in low-income countries to 80% or above in developed countries [2,6].

With breast cancer prevention as a public health priority, efforts to improve identification of women at elevated risk are critical. To date, global efforts in the fight against breast cancer have centered on implementation of screening programs and early detection with mammography. Although mammography is the principal modality for early detection for average-risk women and a critical tool in our fight against breast cancer because tumor size and stage at diagnosis correlates with survival [5–10], it is not a prevention tool. In addition, all breast cancer screening guidelines across the globe are limited in that they are based on age alone and are not risk based. This 'one size fits all' approach, does not meet the needs of high-risk women. Although most women, even in countries where the breast cancer prevalence is very high, are at average risk, defined as a lifetime risk of <15%, current age-based screening guidelines do not consider the approximately 25% of women in developed countries who are at high risk as defined by a lifetime risk of more than 20%. Clinicians are failing to identify most of these high-risk women and continue to recommend screening at the frequency for average-risk women, despite screening guidelines supporting enhanced screening for women at high risk. Risk stratification, and identification of high-risk women, allows for implementation of individualized risk-reducing strategies and enhanced screening based on risk and is critical to breast cancer primary prevention efforts.

Breast cancer genetics

Hereditary cancer mutations are germline mutations that are inherited and associated with familial cancer whereas somatic mutations are non-inherited genetic mutations

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associated with the development of cancer, but the mutation is found only in the tumor. Hereditary breast cancer (HBC) mutations are specific germ-line mutations associated with breast cancer. Individuals who carry an HBC mutation have a lifetime risk of breast cancer that is variable depending on the mutation, but substantially higher than the general population, and the cancers often occur in younger individuals.

Across the globe, genetics and hereditary factors account for approximately 25% of new breast cancer while 75% are sporadic (not inherited) [11]. In the USA and other developed countries, estimates are that 12–14% of new breast cancer is associated with a single-gene hereditary cancer mutation, with the remaining approximately 15% associated with family clusters without an identifiable mutation [11]. In the USA approximately 1 in 500 (0.2%) women carry a hereditary cancer mutation, with a much higher prevalence of 1 in 40 (2–3%) Ashkenazi Jewish individuals. The prevalence of single-gene mutations, specifically BRCA1, BRCA2, TP53 and CHEK2, increases with early age of diagnosis, and in a study of 379 women with breast cancer before age 30 years the prevalence of a pathogenic variant was nearly 20% [12].

All HBC gene carriers are at substantially elevated risk for breast cancer, with some mutations associated with an 80% lifetime risk. Based on the known 12–14% prevalence of single gene actionable mutations, estimates are that 40,000 cases of breast cancer per year in the USA, out of the total of 275,000 new breast cancer cases per year, could be prevented by identification of all women who carry an HBC mutation. Despite widely available and much lower cost genetic testing in developed countries, estimates are that only 10% of women who carry a hereditary cancer mutation have been identified [11].

Approximately 5–10% of breast cancer in developed countries is associated with BRCA1 and BRCA2 [11–13], the most common single hereditary gene mutations associated with breast cancer. BRCA1 and BRCA2 are very highly penetrant genes associated with a lifetime risk of developing breast cancer approaching 80%. Approximately 5–15% of women who are negative for BRCA1 and BRCA2 will be found to carry one of the other highly penetrant genes or moderately penetrant genes associated with HBC [13–15] Highly penetrant genes associated with a lifetime risk of breast cancer of >30% include TP53, PTEN, CDH1, STK11 and PALB2. Moderately penetrant genes associated with a 17–30% lifetime risk include CHEK2, ATM, BARD1, BRIP1, NBN, NF1, RAD51D and MSH6 [16]. Breast cancer risk and recommendations for screening and risk reduction vary by gene. In general, screening breast magnetic resonance imaging is recommended for women at >20% lifetime risk, which includes women with mutations in highly penetrant genes and the majority (but not all) of moderately penetrant genes. Consideration of chemoprevention is recommended for women with mutations in high and moderately penetrant genes [13].

Risk factors beyond genetics

In addition to the women who carry an HBC mutation, a larger cohort of women is at elevated risk due to established modifiable (lifestyle) and non-modifiable (genetics, family history, breast density) risk factors. These women, like HBC mutation carriers, are also being missed. In the USA, physicians and women know the statistic that 'one in eight' women will develop breast cancer in her lifetime. That statistic represents the population risk in the USA, but for an individual woman is almost meaningless, as her risk may be substantially higher or substantially lower than population risk due to her own individual risk factors.

Approximately half of new sporadic breast cancer cases can be explained by non-modifiable factors such as advancing age, reproductive factors including early puberty and late menopause, advanced age at first live birth, increased breast density and proliferative breast lesions [17]. In developed countries, modifiable factors account for approximately 33% of all new breast cancer cases and 40% of sporadic cases each year (approximately 66,000 cases in the USA). Modifiable factors are associated with lifestyle factors and include poor diet, lack of exercise, alcohol, smoking and obesity [17–20].

Notably, these lifestyle-related risk factors for breast cancer are identical to the risk factors for CVD [21], although a minority of women recognize lifestyle as a factor in breast cancer risk. Globally, the incidence of sporadic breast cancer is increasing due to a shift in both modifiable and non-modifiable risk factors associated with breast cancer, such as earlier menarche, older maternal age at first live birth, higher rates of nulliparity, higher rates of obesity and adoption of westernized lifestyle including less exercise and a higher-fat diet [1,5]. It is notable that in the Women's Health Initiative (WHI) dietary modification trial [22] of nearly 50,000 women, a low-fat diet was associated with a reduction in both breast cancer incidence and mortality compared to controls. Additional large studies and meta-analyses suggest that a largely plant-based diet, or a diet high in cruciferous vegetables, is associated with a 15% reduction in breast cancer incidence [3,19,20,22].

After advancing age, increased breast density is the most important single non-genetic risk factor for breast cancer for an individual woman [3,17,23,24]. Breast density reflects the amount of glandular breast tissue compared to adipose tissue within the breast. Breast density is a largely inherited trait, cannot be determined by physical examination and decreases with age. Mammographic breast density, as measured using the Breast Imaging Reporting and Data System (BI-RADS) classification system, defines four categories of breast density: 1 = almost entirely fat, 2 = scattered fibroglandular, 3 = heterogeneously dense, 4 = extremely dense. Both heterogeneously dense and extremely dense breasts are considered high density categories and increase breast cancer risk. Approximately 48% of women of screening age have heterogeneously dense or extremely dense breasts [25–27].

Dense breasts are associated with breast cancer in two ways. First, increased breast density decreases the sensitivity of mammography to detect small cancers. In women with fatty breasts the sensitivity of mammography is 88% compared to 62% sensitivity in women with extremely dense

breasts. In younger women, increased breast density makes mammography less sensitive with estimates of detecting only 73% of breast cancers in women in their early 40s compared with 85% of breast cancers in women in their early 60s [20,23–30]. Elevated breast density is separately associated with an increased risk of developing breast cancer [3,20,23,31], with increasing risk with increasing density. As the percent of glandular breast tissue compared to fat increases from <10% to more than 75%, the relative risk of developing breast cancer increases in women with dense breasts from 1.2 to 5.3 [3,23–27,29].

Breast density is an important risk factor but does not explain all risk. Notably, black women have a higher likelihood of having fatty, less dense breasts compared to white women, but have a higher risk for developing aggressive breast cancers, especially triple negative, suggesting differences in the tumor biology [28,29]. Additionally, Asian women have higher breast density, but a lower than average incidence of breast cancer compared to white women [29,30,32]. Although increased breast density is the most important risk factor outside family history, increased breast density alone does not establish a woman as high risk and all guidelines support that breast density alone should not be used as the sole factor in determining the need for supplemental screening [3,23,33,34].

Defining high risk

Estimates of an individual woman's lifetime risk of developing breast cancer due to genetic or non-genetic reasons determine her risk category. Although there are no uniform society or guideline-defined risk categories, expert consensus defines average risk as a lifetime risk of <15%, moderate risk as a lifetime risk between 15% and 20%, and high risk as a lifetime risk above 20%. Women identified to be at high risk of developing breast cancer are a heterogeneous group of women that includes women who carry a deleterious genetic mutation associated with an increased risk of breast cancer and those who are at high risk due to other established modifiable and non-modifiable risk factors.

HBC genetic mutations are associated with variable risk. Highly penetrant HBC genes are associated with a lifetime risk above 30% and include BRCA1 and BRCA2, mutations associated with a relative risk of 10 and a lifetime risk of nearly 80%. Other high-penetrance mutations with lifetime risk >30% include TP53 (Li Fraumeni syndrome, 27–54%), PTEN (Cowden syndrome 67–85%), CDH1 (42–53%), STK11 (31–54%) and PALB2 (33–58%). Moderately penetrant genes are associated with a lifetime risk of 17–30% and include CHEK2 (29–37%), ATM (17–52%), NF1 (26%) and BARD, BRIP1, RAD51 and MSH6 (<20%) [13,16].

For women without a hereditary cancer mutation, most women's risk category can be determined by family history alone and falls into the average risk category, although approximately 25% of women in developed countries have a calculated lifetime risk, using a validated risk assessment tool, of above 20% and are considered high risk. Across the globe, risk assessment is rarely done outside high-risk clinics. Barriers to broad adoption of risk assessment are numerous and complex and include: a lack of guidelines supporting universal risk assessment; a lack of training and education of clinicians about the importance of risk assessment; a lack of technology to implement risk assessment tools into clinical practice; and a lack of validation in non-white individuals. Improvement in risk assessment tools, clinician education and broad implementation of risk assessment is necessary to reduce the incidence of breast cancer.

Identification of HBC mutation carriers in clinical practice

In the USA, and in several other developed countries, the National Comprehensive Cancer Network (NCCN) guidelines for identifying patients who may have a heritable genetic cancer mutation inform who should be referred for consultation and genetic testing [16,35]. Most primary care providers in the USA lack education about these guidelines, and the prevalence of and importance of identification of mutation carriers. The NCCN guidelines are also difficult to implement in clinical practice for most clinicians and contribute to our failure to identify most mutation carriers. Data from a large outpatient gynecology practice of 3811 women screened with a family history screener to identify those who met NCCN criteria for genetic testing identified 903 women, or nearly 24%. Of the 903 women who met the NCCN guidelines, only 165 completed testing and nine (4.4%) were identified to have an actionable pathogenic mutation [36]. Applying a 4.4% prevalence rate to the 903 women meeting the NCCN guidelines, it is likely that 40 women in the original cohort had an actionable mutation and 31 of those women were missed. Similarly, data from a community-based education program of 91 women attending one of four community breast cancer education events found that 25% of women met NCCN criteria for genetic testing [37]. In France, the Eisinger score (a six-question screener) is recommended by the French National Institute for Cancer to identify individuals who should be referred for hereditary genetic cancer testing [38,39]. Unfortunately, data from recent studies confirm that even with broad application of the NCCN guidelines, a significant number of individuals with an HBC mutation will be missed [40–42]. A recent review found that family history to screen for genetic mutation carriers is resource intensive, misses more than 50% of carriers and is associated with underutilization of genetic testing services and delays in carrier identification [43,44].

These data have led some to support population testing of all individuals, with some data supporting cost-effectiveness. Other data support genetic testing for all women with breast cancer. A study of nearly 1000 new breast cancer patients who had not undergone genetic testing previously had an 80-gene hereditary cancer panel test. Of those patients nearly 50% met the NCCN guidelines for testing, while the other 50% did not. Of the patients who met the NCCN guidelines, 9.39% had a pathogenic mutation compared to 7.9% in the group that did not meet NCCN criteria [40]. The difference between the groups was not statistically

significant and highlights the high prevalence of mutations missed by application of the NCCN guidelines. The conclusion of the authors states "guidelines should be expanded immediately to include genetic testing of all patients with breast cancer" [40,p.458].

To prevent HBC mutation carriers from developing breast cancer, we must identify them. Currently, we are missing approximately 90% of HBC mutation carriers and the opportunity to prevent breast cancer in these women. All women's health clinicians should incorporate family history screening into clinical practice to improve identification of individuals who carry an HBC mutation and use the NCCN guidelines or the Eisinger score to refer for consultation and testing. For all women of Ashkenazi Jewish descent and for all women with a new diagnosis of breast cancer, genetic testing should be considered through shared decision-making. Now, as we consider population testing, it is reasonable to consider genetic testing for women with a strong family history of cancer, even if they do not meet the NCCN guidelines for testing.

Risk assessment beyond genetics in clinical practice

There are several widely available, easy to use and validated breast cancer risk assessment tools for women who do not carry an HBC mutation that estimate an individual woman's 5-year, 10-year and lifetime risk of breast cancer. The most widely used are the Gail model [45], the Breast Cancer Surveillance Consortium (BCSC) [46], BRCAPRO [47] and Tyrer–Cuzick [48,49].

These validated prediction tools stratify a patient's lifetime risk into average (<15%), intermediate (15–20%) or high (>20%). These tools consider multiple concurrent risk factors (family history, breast density, prior breast biopsy or history of high-risk lesions and others), although each risk prediction tool incorporates different risk factors weighted differently. The Gail model only considers first-degree relatives as part of family history [45], while the Tyrer–Cuzick considers three generations [48,49]. Only the current version of the Tyrer–Cuzick (version 8) incorporates breast density [48,49]. These risk assessment tools are all available online, and several are also available as apps supported by iOS and Google Play. Specifically, the BCSC has two available risk calculators available as apps. The original validated BCSC Risk Calculator estimates a women's 5-year and 10-year risk of developing invasive breast cancer [46,50]. A recently released second BCSC Advanced Breast Cancer Risk Calculator and app estimates the 6-year cumulative risk of developing advanced breast cancer, defined as prognostic pathologic stage 2 or higher [51].

Although a clinical breast examination is part of the standard well woman examination in the USA, model-calculated breast cancer risk assessment is not standard, and there are no guidelines to support risk assessment as part of an annual preventative visit. In the USA, the American College of Radiology (ACR) issued a recommendation in 2018 that all women be evaluated for breast cancer risk by age 30 years, especially black women and those of Ashkenazi Jewish descent, to identify high-risk women who would benefit from supplemental screening before age 40 years [52]. The ACR recommendations include a review of the available risk assessment tools but do not specify the risk assessment tool to be used to assess risk. In 2019 the American Society of Breast Surgeons (ASBS) updated their mammography screening guidelines to include breast cancer risk assessment [53], stating that 'all women aged 25 and older should have a formal risk assessment for breast cancer'. The ASBS defined risk assessment to include family history, screening for prior chest radiation and screening for the need for genetic testing based on the NCCN guidelines. For women aged 30 years or above, the ASBS added risk assessment using the Tyrer–Cuzick model version 8 that incorporates breast density [53]. Without clear guidelines recommending risk assessment for all women, broad adoption is unlikely. However, when risk assessment tools are generally applied to women in developed countries between age 40 and 60 years, nearly 25% of women will be identified to be at 'high risk', as defined by a lifetime risk over 20%. Without guidelines and broad adoption of risk assessment, most high-risk women will remain undetected; for women at calculated high risk, defined as a risk calculated lifetime risk of more than 20%, US guidelines (U.S. Preventative Services Task Force (USPSTF), NCCN, American Cancer Society (ACS), ACR ASBS) [54] and guidelines of the European Society of Breast Imaging (EUSOBI) [54] and European Society of Breast Cancer Specialists (EUSOMA) [54] recommend supplemental screening with breast magnetic resonance imaging regardless of breast density, and the opportunity to educate them about lifestyle for risk reduction, enhanced screening, genetic testing and chemoprevention when appropriate is missed.

A great deal of science is currently being devoted to improving risk assessment tools because the accuracy and predictive value of current risk assessment tools are variable and, in many cases, modest because not all important risk factors are incorporated into the models, and not all risk factors that are incorporated are strongly predictive of risk. Additionally, these risk models are further limited by validation in largely white populations, making accuracy in prediction uncertain in other ethnic groups [55]. For these reasons, the predictive value of risk assessment using current models may be small for some women, and for these reasons leads some to question their broad application in clinical practice.

However, available risk assessment models are what we have currently to identify women at high risk. Unfortunately, these risk assessment tools are rarely utilized in clinical practice outside high-risk breast clinics. In addition, women themselves are largely unaware of available risk assessment tools to calculate risk and are largely uninformed about modifiable risk factors they could implement to reduce their personal risk, enhanced screening recommendations or the availability of chemoprevention. As a result, women are not self-advocating or asking their health-care providers to give them information about their personal risk, and most women at high risk for non-genetic reasons remain unidentified.

Incorporation of single nucleotide polymorphisms into current risk prediction models for women at non-genetic

elevated risk in addition to established risk factors, and artificial intelligence-based risk models using data from screening mammography, are under investigation and appear to improve the accuracy of existing risk assessment models [56–60]. Future development of risk prediction tools that are generalizable, more accurate, simpler to use and incorporated into electronic health records are needed for widespread risk assessment adoption which will allow us to move to risk-based screening.

Conclusion

Despite decades of advances in science and large bodies of laboratory, epidemiological and clinical research, the breast cancer incidence continues to rise. Breast cancer remains the leading cancer-related cause of disease burden for women, affecting 1 in 20 globally and as many as one in eight in high-income countries. Reducing breast cancer incidence will likely require both a population-based approach of reducing exposure to modifiable risk factors and a precision-prevention approach of identifying women at increased risk and targeting them for specific interventions. It is only through identification of high-risk women that we can prevent breast cancer, not just screen for it.

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