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When Breast Cancer Strikes the Young: Understanding its Incidence, Etiologies, Challenges, and Implications

Nayanatara Swamy*, Patrick Jennings, Rachel Taylor, Scott B Harter and Gwendolyn Bryant-Smith

University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States

Abstract

In 2021, breast cancer officially overtook lung cancer as the most commonly diagnosed cancer globally, with an estimated 2.3 million new cases. The American Cancer Society estimates that 281,550 new cases of invasive breast cancer and 49,290 new cases of ductal carcinoma in situ (DCIS) will be diagnosed in the United States in 2021, and an estimated 43,600 women will die of breast cancer. Women under the age of forty represent 6-7% of the diagnosed breast cancer cases. A breast cancer diagnosis is devastating in young adults who are often ill-prepared to navigate the challenges of surgery, endocrine therapy, radiotherapy and/or chemotherapy, and long-term surveillance. In this article, this small but highly vulnerable population is highlighted in hopes of promoting improved education among health care providers. An enhanced patient-provider discussion can assist younger patients when faced with this life-changing diagnosis.

Correspondence to: Nayanatara Swamy, MD, University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States; Tel: 501-686-6912; E-mail: nswamy@uams.edu

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Introduction

The odds of receiving a breast cancer diagnosis increases with each decade (Figure 1). Given the small percentage of breast cancers diagnosed in women less than 40 years, focusing considerable resources on educating young women regarding breast cancer may seem debatable. However, young women (ages 15-39) have unique social and financial issues when diagnosed with breast cancer. Navigation of therapy decisions and the cancer journey can be especially challenging in this young group.

Discussion

Breast cancers have varying tumor biologies, and these differing tumor subtypes lead to varied personalized treatments and outcomes [1]. There are four basic molecular subtypes of breast cancer:

1. Luminal-A like [hormone receptor (HR) +, human epidermal growth factor (HER2) -]
2. Luminal-B like [HR +, HER2 +]
3. HER2 enriched [HR-, HER2 +]
4. Triple negative [HR negative, HER2 negative].

The tumor biology of breast cancers affecting young women are phenotypically more aggressive. These cancers are more likely to be a higher grade, bilateral, triple negative or HER2 positive, have a higher proliferation index, and are more likely to be diagnosed at a later stage. Later stage diagnosis is secondary to a combination of the inherently aggressive nature of these tumors, a delay in diagnosis due to a low clinical index of suspicion on the parts of both patient and health care providers, and a lack of screening in this age group.

In older women, luminal A-like tumors are more common (73%) [1]. Luminal A-like tumors are slow-growing, less aggressive, and have a favorable prognosis. In younger women, luminal B-like tumors outnumber luminal A-like tumors (42% versus 33%) [2]. Luminal B-like tumors are high grade with poorer outcomes [1]. Despite better treatments over the past few decades, the 5-year cancer-specific survival rates remain lower in women <40 years of age than in older women. The reasons are multi-factorial, including a large proportion of aggressive cancers and lower rates of treatment adherence in younger women [3-5].

Across all age groups, breast cancer has a 5-year survival rate of 99% for localized disease, 86% for regional disease, and 27% for metastatic disease [1]. A later stage at diagnosis dramatically alters the outcome. A greater proportion of younger women are diagnosed at a later stage, worsening their odds of a good outcome. The relative survival rates for women diagnosed with breast cancer are 91% at 5 years after diagnosis, 84% after 10 years, and 80% after 15 years [1]. This too portends a poor consequence in young women as they have a longer expected lifespan in comparison to older women.

What predisposes a young woman in her teens, twenties, and thirties to develop breast cancer?

Genetic inheritance is a well-known cause. Cancers are inheritable (through germline mutations) or acquired (through somatic mutations which are amassed in a person's lifetime). Figure 2 illustrates the causes

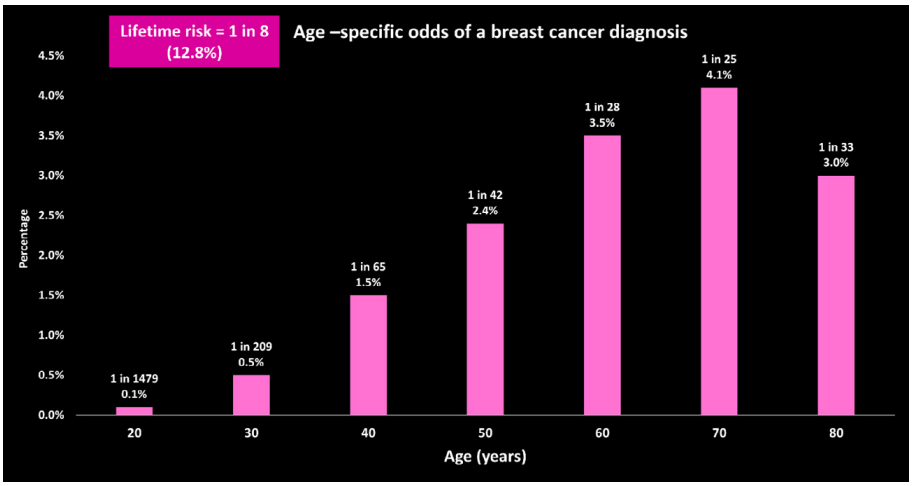

Figure 1: Histogram shows the age-specific distribution of breast cancers in 2019 as reported by the American Cancer Society [1]. 6% (13,050 out of 316,700) of all breast cancers diagnosed in the United states in 2019 were in women under the age of 40.

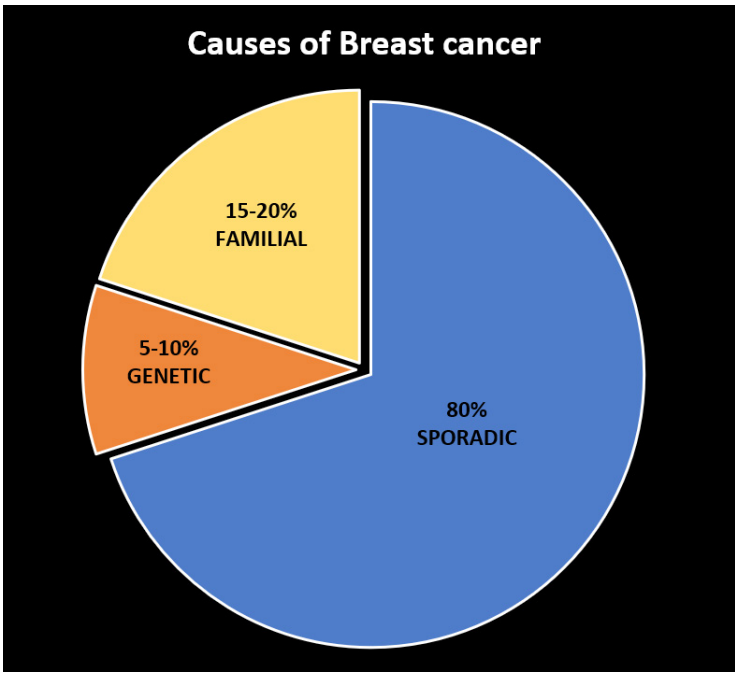

Figure 2: Causes of breast cancers.

of breast cancers [6]. 80% of breast cancers are sporadic, i.e., without any family history. 5-10% of breast cancers occur in families with known genetic mutations. The most widely known deleterious gene mutations are the BRCA1 and BRCA2 genes, who together account for 25-28% of all heritable breast cancers; BRCA1 patients have a higher proportion of triple negative cancers and BRCA2 patients, a higher proportion of luminal B-like tumors [2]. In addition, we now have a broader group of known high penetrance genetic mutations associated with breast cancer - namely TP53, PTEN, CDH1, and STK11 [7]. Moderate risk genetic mutations include ATM, CHEK2, PALB2, RAD51C, BRIP1 and mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) [7,8]. The higher penetrance genetic mutations and PALB2 genetic mutation are more likely to cause breast cancers in women in their twenties and thirties [7]. 15-20% of breast cancers occur in women with breast cancer having two or more first- or second-degree relatives with breast cancer, but without a known genetic mutation. In these patients, genes with low penetrance are thought to play a role [7]. This has led to extensive research in genome wide association studies (GWAS) [8-10]. These studies aim to identify the various single nucleotide pleomorphisms (SNPs) which are more common in women with breast cancer. While a few SNPs are insufficient to trigger breast cancer, multiple SNPs in a single person's genome, together with environmental factors add up to a significant risk [6, 9, and 10]. Ultimately, sporadic breast cancer too has a genetic basis, comprising a polygenic aggregation of somatic mutations triggering tumorigenesis. This area represents the fastest growth in our knowledge pool and may ultimately change the approach to cancer screening, from a generalized, population-based approach to a personalized, risk-based stratification model.

Breast cancer risk factors are grossly categorized into non-

modifiable and modifiable (Table 1). Understanding the role of these risk factors in the second to fourth decade of life allows individuals to make informed decisions. For example, individuals with clusters of cancers (breast, ovarian, endometrial, prostate, pancreatic, brain, gastrointestinal cancers, thyroid, melanoma, and sarcomas) in their first- and second-degree relatives should undergo genetic counseling, followed by genetic testing (if eligible) [7]. Individuals identified as high-risk for developing breast cancer are eligible to begin early screening for breast cancer by annual MRI and mammography, starting anywhere from age 25 to age 30, depending on their risk factors [12]. Patients with high-risk genetic mutations can also opt for preventive strategies to decrease their odds of developing breast cancer, like prophylactic chemotherapy or prophylactic mastectomy [1]. Additionally, with a robust knowledge of risk factors in the second to fourth decades of life, young adults can choose healthy lifestyles to offset the odds of predisposing themselves to cancers in general and systemic illness later in life [13]. Explaining the role of the different risk factors in a way that is understandable to young patients is a vital role of health care providers.

Table 1: The various risk factors of breast cancer. It is important to note that each risk factor has different degrees of risk i.e., relative risk factor [1,11].

Non-modifiable risk factors	Modifiable risk factors	Potentially modifiable risk factors
Female	Diet – fruits and vegetables are protective	Age at first birth: Age <30 years at first birth is protective
Genetic/Family history	BMI: Low BMI in premenopausal women is an increased risk, and weight gain after menopause is harmful	Age at menopause: later age on the onset of menopause has a higher risk
Race/Ethnicity	Exercise	Breastfeeding: protective
Age: older age has an increased risk	Smoking	Environmental factors: certain chemicals with estrogen-like properties are potential culprits
Height: taller women are at increased risk	Alcohol consumption	Night shift work: increased risk
Age at menarche	Hormone therapy	
Breast density: Category C and D breasts have an increased risk	Reproductive history – Nulliparity and older age at first birth are less protective	
Number of breast biopsies		
Prior biopsy diagnosis of atypical hyperplasia or lobular carcinoma in situ		
Prior radiation exposure: mantle radiation for Hodgkin lymphoma between ages 10-30 years		

How do we quantify an individual's risk for the development of breast cancer?

Risk quantification is most commonly assessed by mathematical models. Several models have been developed from different population-based data sets. These computer-based models calculate risk percentages for the development of breast cancer based on a patient's age, specific personal history, birth history, with or without an available family history. Common models include the Tyrer-Cuzick model, Gail model, Claus model, BCRAT model, BRCAPRO model, and BOADICEA model [14]. Each model incorporates a different number and types of data inputs. These models are all well calibrated, i.e., they perform well on a population level (the number of expected cancers predicted by the model is close to the number of observed cancers in the population). However, they vary in their discrimination, i.e., performance on an individual level. A model with perfect discrimination has a C-statistic of 1. A score of 0.5 signifies no discrimination or random chance. While no model can achieve perfect discrimination, the Tyrer-Cuzick model, with a C-statistic score of 0.762 has the highest discrimination and is considered the most accurate among the available risk assessment models [14]. Its biggest advantage for risk assessment in young women is that it accepts data input for all ages, from 1 to 80. Primary care providers can utilize this free online tool to calculate the risk in any young woman with a family history of breast and ovarian cancer in their first- and second-generation relatives. The lifetime risk of breast cancer is subcategorized into average risk (<15%), intermediate-risk (15-<20%), and elevated risk (> or =20%) [12]. Anyone with a 20% or greater risk qualifies for annual mammography and breast MRI from an earlier age, in hopes of improving screening methods in this population at elevated risk.

It is vital to ensure that susceptible populations at high risk are identified in time to benefit from screening at an earlier age. Accordingly, the American College of Radiology (ACR) and the Society of Breast Imaging (SBI) recommend that all women undergo a risk assessment for breast cancer at age 30 [15]. The ACR and SBI have also highlighted ethnic disparities in breast cancer care. Although the incidence rates of breast cancer are similar in non-Hispanic whites and black women (130.8 per 100,000 vs 126.7 per 100, 000), black women have higher breast cancer death rates, higher incidence rates before age 40, and a larger proportion of triple negative cases [1]. Their higher death rate is in part from the greater number of triple negative cases in these women, which are associated with poorer outcomes. Black women are also more likely than non-Hispanic whites to carry a BRCA1/2 mutation [1]. The ACR and SBI emphasize that it is especially important for African American women and women of Ashkenazi Jewish descent, to undergo breast cancer risk assessment no later than age 30, as they are more likely than the general population to carry the BRCA1/2 mutations [15].

It is worthwhile to note that a person's risk for developing breast cancer is not constant but changes continuously over time. In situations where there are interval family history changes, with more first- and second-degree relatives diagnosed with breast cancer, a person's lifetime risk can increase.

Not all young women who develop breast cancers have a positive family history. How then to identify this at-risk subgroup? The available tools are controversial, namely breast self-awareness (BSA) and clinical breast exam (CBE). Both the American Cancer Society (ACS) and the United States Preventive Services Task Force (USPSTF) do not recommend clinical breast examination (CBE) after two large-scale studies found CBE to perform no better than coincidental discovery of a mass [16,17]. They found it to cause more harm (additional testing and biopsies), than benefit. However, the American College of Obstetricians and Gynecologists (ACOG) and the National Comprehensive Cancer Network (NCCN) advocate breast self-awareness (BSA) - a woman's awareness of the normal appearance and feel of her breasts [18]. The rationale behind this decision was because 70% of breast cancer cases in younger women were incidentally detected by themselves. ACOG also recommends offering clinical breast exams to women after shared patient-provider decision making, which includes recognition of potential benefits and harms of CBE. CBE can be performed in women aged 19-39 years, every 1-3 years [18].

Treatment outcomes

The breast cancer treatment regimens are dictated by the breast cancer subtype. Better anti-HER2 therapies over the past two decades have translated to improved outcomes in this subgroup, regardless of

patient age [19]. With the rest of the breast cancer subtypes, however, age-related outcome disparities persist [1,3, and 19]. Preservation of fertility in young women further complicates matters as studies have shown that ovarian function suppression is associated with a higher 5-year breast cancer-free interval [5].

Although the prognosis is worse in younger women with breast cancer than in older women, breast cancer survival has significantly increased over the past three decades and continues to improve [1]. With access to advanced care at dedicated breast centers that provide tailored treatment regimens, these women can achieve a good outcome. Having this broad perspective at the outset will potentially decrease the mental trauma that invariably accompanies this diagnosis.

To summarize, a breast cancer diagnosis is devastating at any age, more so in young women. Although its incidence rate in young women is very low, the unfortunate few with this disease deserve an early diagnosis at an earlier stage and access to specialized care at higher centers with experience in handling these cases, in addition to adequate emotional support. With the recognition of the need to assess the lifetime risk of breast cancer at age 30 in all women and timely referral in young women who present with concerning palpable breast lumps, health care providers can protect the interests of young women in our communities. In the future, accessible wide-panel genetic testing can change the landscape of how we quantify risk in our patients.

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None.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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