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BREAST CANCER DISPARITIES (LA NEWMAN, SECTION EDITOR)

Breast Cancer Disparities Related to Young Age at Diagnosis

Leticia Varella[1] · **Shoshana Rosenberg**[1]

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Abstract

Purpose of Review Despite being uncommon, breast cancer at a young age correlates with worse outcomes. Several aspects of a breast cancer diagnosis may affect young and older patients differently, including biology, genetic predisposition, fertility concerns, and psychosocial outcomes. Understanding these differences is critical to providing tailored, high-quality care to young patients.

Recent Findings Young women with breast cancer are less likely to have early stage at presentation and more likely to have tumors with aggressive characteristics. Genetic mutations predisposing to breast cancer are more common. Due to their life stage, young women face concerns regarding fertility and pregnancy and are at higher risk for psychosocial distress.

Summary Recent clinical trials in the adjuvant setting have provided insight on the optimal treatment for young patients. Multiple other studies have outlined the psychosocial impact of breast cancer in young patients, helping to understand their unique challenges. However, there is still need for further research, including around interventions, to address clinical and social concerns specific to young patients.

Keywords Breast Cancer · Young Age · Disparities

Introduction

Approximately 13,000 women aged 40 years or younger are diagnosed with breast cancer every year in the USA. While relatively uncommon, 1 in 65 women will develop breast cancer by age 40 [1]. Moreover, breast cancer is the leading cause of cancer-related death in women between the ages of 20 and 39 [2]. Importantly, young age at diagnosis correlates with worse prognosis, increased risk of recurrence, and inferior survival compared to older patients [3]. Notably, Black women have a higher incidence of breast cancer at a young age [4] and young Black women have a higher mortality than White women [5].

Numerous studies have demonstrated that several breast cancer aspects are different or affect young women more acutely compared to older patients. These include tumor biology differences, genetic predisposition, and issues such as fertility concerns, sexual health, and psychosocial health. In this review, we will summarize key disparities between young and older women with breast cancer (Table 1).

Disease Presentation and Tumor Characteristics

Young women diagnosed with breast cancer are less likely to have early stage disease at presentation. Data from a prospective observational cohort study of young women with breast cancer in the UK revealed that 98% of the breast cancers were clinically detected, as opposed to screen-detected [6]. A retrospective study with more than 8000 women with breast cancer found that the median tumor size was larger at the time of diagnosis in young vs. older women [7]. Although previous evidence has suggested diagnosis delays in young patients, a large study inclusive of women treated at several National Comprehensive Cancer Network centers did not find a correlation of age and delay in diagnosis (defined as > 60 days) [8]. However, the vast majority of that patient population was White. Recent data from the National Cancer Database (NCDB) showed that Black women experienced treatment

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✉ Leticia Varella
lev9027@med.cornell.edu

[1] Weill Cornell Medicine, New York, NY, USA

Table 1 Considerations in treatment of young women with breast cancer

Stage and tumor characteristics	Tumors are more likely to be grade 3, ER-negative, HER2-positive, and lymph node–positive
Genetics	Higher frequency of mutations in genes associated with hereditary breast cancer
Treatment	Impact of ovarian function/suppression on treatment outcomes in the adjuvant setting
Fertility and pregnancy	Need to discuss fertility preservation options at the time of diagnosis Safety of pregnancy after breast cancer diagnosis
Supportive/psychosocial care	Life stage–specific challenges such as early menopause, quality of life, and financial impact

delays more frequently than White women, suggesting racial disparities in access to care [9•]. Further research inclusive of more diverse young patients is needed to elucidate whether young age may exacerbate these disparities in access to care.

Studies have demonstrated that breast cancer in young women is more likely to be grade 3, estrogen receptor (ER)–negative, human epidermal growth factor receptor 2 (HER2)–positive, have positive lymph nodes, and high-risk gene expression profiling [6, 10•]. The Young Women's Breast Cancer Study (YWBCS) prospective cohort evaluated pathologic features and molecular phenotype in young patients diagnosed with breast cancer. ER-negative and HER2-positive tumors were present in 27% and 28% of women, respectively, a different distribution comparing to published studies in the general population. In that study, immunohistochemistry was used as a surrogate for molecular subtype, and there was a higher proportion of luminal B tumors [10•]. In the UK cohort, there was a lower frequency of T1 tumors ($\leq$2 cm) and a higher frequency of positive lymph nodes (50%) than previously reported data from unselected UK patients. In that cohort, 34% of patients had ER-negative and 24% had HER2-positive tumors [6].

Genetic Predisposition

Mutations in a known breast cancer predisposition gene are more common among young women with breast cancer. Nonetheless, most young patients do not have family history of breast cancer or carry an associated germline mutation [6, 10•]. As an example, a family history of breast cancer in first- and second-degree relatives was present in only 33% of patients in the UK cohort [6]. In the YWBCS, 16% of patients had a first-degree relative with breast or ovarian cancer, and only 11% of patients had a BRCA mutation detected. Importantly, the largest proportion of BRCA mutations were found in the very young population ($\leq$30 years) [10•].

Although BRCA 1 and BRCA 2 pathogenic mutations are responsible for the majority of familial high-risk predisposition to breast cancer, recent data demonstrate the association between other genes and breast cancer [11]. Multi-gene panels allow for testing of less frequent genes as TP53, ATM, PALB2, CHEK2, PTEN, CDH1, and RAD51C, among others. The National Comprehensive Cancer Network (NCCN) Guidelines currently recommend considering genetic testing for every woman diagnosed up to the age of 45 [12].

Treatment

Treatment of young women with breast cancer is generally based on the same clinical and pathological features than in older women. However, specific characteristics including the hormonal status of young patients have potential treatment implications.

Large randomized clinical trials published in the last few years have helped to shed light on the use of genomic assays to help guide clinicians regarding the use of adjuvant chemotherapy in premenopausal patients.

In the TAILORx trial, there was no benefit from adjuvant chemotherapy in women with early stage breast cancer that had a low or intermediate recurrence score of a 21-gene breast cancer assay. However, subgroup analysis demonstrated a benefit in prevention of recurrence from chemotherapy in women up to 50 years old with an intermediate recurrence score [13]. The MINDACT trial was also a prospective trial integrating a gene-expression assay to estimate the benefit from adjuvant chemotherapy in patients with breast cancer. Exploratory analysis by age in patients with a high clinical risk and low genomic risk in the 70-gene panel demonstrated a 5% benefit in prevention of metastasis in women 50 years or younger with the addition of chemotherapy, whereas the benefit was only 0.2% in women older than 50 [14••]. In the RxPONDER trial, women with hormone receptor–positive, HER2-negative breast cancer, one to three positive axillary lymph nodes, and a recurrence score of 25 or lower on the 21-gene panel were randomized to endocrine therapy alone or endocrine therapy with the addition of chemotherapy. Premenopausal women who received chemotherapy had a benefit in prevention of invasive disease and distant recurrence [15••]. It remains unclear how much of the benefit from chemotherapy in young women derives from ovarian suppression caused by the treatment.

Adjuvant endocrine therapy recommendations for ER-positive breast cancer differ between pre- and post-menopausal women. Although tamoxifen remains the standard of care for premenopausal women with a low risk of recurrence, young patients with a higher risk may benefit from the addition of ovarian suppression. The results of the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT) showed superior disease outcomes in premenopausal patients with a high clinicopathological risk that received ovarian suppression during adjuvant therapy for early-stage ER-positive breast cancer [16]. In these trials, women younger than 35 years had the largest magnitude of improvement in outcomes with ovarian suppression, but also had a higher rate of nonadherence to treatment, suggesting that the toxicity of endocrine therapy may be more burdensome to very young women [17]. Moreover, in the metastatic setting, the use of ovarian suppression allows pre-menopausal patients to receive similar endocrine therapies to post-menopausal women.

Disease Outcomes

Data from the Surveillance, Epidemiology, and End Results (SEER) registry from 1975 through 2015 demonstrated an increase in breast cancer incidence rates among young women diagnosed at ages 20 to 39 years. There was also an improvement in survival that interestingly reached a plateau in 2005. However, survival in patients with metastatic disease continued to improve after 2005, possibly reflecting an improvement in cancer therapy for advanced disease [18]. There are well-documented racial disparities in disease outcomes, with mortality higher in young Black women than White women [5]. Factors that contribute to a higher mortality include later stages at diagnosis, barriers to high-quality treatment, and aggressive tumor characteristics, including a higher incidence of inflammatory and triple-negative breast cancer [5].

The prognostic impact of age in patients diagnosed with breast cancer seems to depend on tumor factors and stage. Analyzing SEER cancer registry data between 2010 and 2015, Kim et al. found that there was no increased risk of mortality among women < 40 years of age with triple-negative disease or HER2-positive disease, after controlling for tumor and treatment factors. However, in that same analysis, young women with HR-positive, low-grade breast cancer had higher breast cancer–specific mortality compared to women ages 40–60 years [19]. In a cohort of patients from the NCCN Database, women ≤ 40 years with luminal A or B tumors had a higher mortality than women ages 51 to 60, but age was not associated with worse mortality in young women with HER2-positive disease [20]. Interestingly, a retrospective analysis of a French cohort of patients with metastatic breast cancer showed that women younger than 40 years had a lower risk of death than older patients [21].

Fertility and Pregnancy

Chemotherapy can affect fertility by directly impacting the ovaries, and the impairment may be permanent. In addition, endocrine therapy can cause delays in childbearing because of the need to complete treatment prior to attempting pregnancy. In the YWBCS, 51% of women indicated some degree of concern about becoming infertile post-treatment. Despite that, only 10% of patients reported that they utilized fertility preservation strategies [22]. The potential impact of breast cancer treatment on future fertility must be discussed with patients. In accordance with current guidelines, referral to reproductive specialists for consideration of cryopreservation should be offered as early as possible after the diagnosis time of breast cancer [23].

Despite a historical concern by clinicians and patients that pregnancy after breast cancer could increase the chances of recurrence, to date, studies have demonstrated the safety of pregnancy following a breast cancer diagnosis. A meta-analysis including 39 studies demonstrated that women with prior breast cancer had a 60% decreased chance of becoming pregnant following their diagnosis. Pregnancy after breast cancer diagnosis correlated with a higher risk of cesarean delivery, low birth weight, preterm birth, and small for gestational age. However, patients who became pregnant after diagnosis of breast cancer had improved disease-free survival relative to patients who did not have a post-diagnosis pregnancy [24••]. In a multicentric retrospective cohort with patients that became pregnant at any time after a diagnosis of breast cancer, Lambertini et al. found no negative impact in disease outcomes, including in patients with a history of ER-positive breast cancer [25].

Administration of a gonadotropin-releasing hormone (GnRH) agonist during chemotherapy for breast cancer has been associated with ovarian function protection, but the possible mechanism of action of this effect is not well understood [26].

The best timing of pregnancy after diagnosis of breast cancer remains unclear. Women with a history of ER-positive breast cancer who are taking endocrine therapy for prevention of recurrence must interrupt therapy before attempting pregnancy. The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial is investigating if temporary interruption of endocrine therapy to allow pregnancy is associated with a higher risk of breast cancer recurrence. This study also aims to provide information on pregnancy and offspring outcomes [27].

Diagnosis of breast cancer during pregnancy is an uncommon occurrence, but pregnant women face unique challenges. Although treatment during pregnancy has the same goals as in non-pregnant women, adjustments are usually made in order to protect the fetus. Moreover, pregnant women with cancer experience high levels of distress [28]. In addition to the usual difficulties of being diagnosed at young age, pregnant women face challenges regarding possible pregnancy termination, future fertility, need for surgery during pregnancy, and breastfeeding challenges. Importantly, distress can have persistent effects [28].

Psychosocial Outcomes

Young women with breast cancer face challenges regarding quality of life, fertility, early menopause, sexual life, and financial impact.

Young women may experience a higher emotional burden after breast cancer diagnosis due to their life stage, when they might be starting their families and careers. In a review of 28 articles including 8 large cohorts that included patients aged 50 or younger with breast cancer, Howard-Anderson et al. found that young women were more likely to have clinical depression, more severe symptoms of depression, higher levels of stress, and poorer quality of life compared to older women with breast cancer [29].

Breast cancer treatment not only impacts fertility but can also cause permanent cessation of menstrual periods. Symptoms of early menopause including fatigue, difficulty sleeping, weight gain, decreased libido, and cognitive dysfunction have a negative impact in quality of life [30].

Sexual health in young patients with breast cancer can be affected by emotional distress as well as by the side effects from treatment. Estrogen depletion from chemotherapy and endocrine therapy can lead to decreased libido, vaginal dryness, and consequent dyspareunia. In a survey with young women previously diagnosed with breast cancer, Ljungman et al. found that up to 68% of women reported sexual dysfunction in at least one area, including vaginal lubrication and satisfaction with sex life [31].

Given younger women experience poorer disease outcomes, adherence to adjuvant endocrine therapy is especially essential for young women with hormone receptor–positive breast cancer. In one analysis that included over 8000 patients with breast cancer, age younger than 40 years was associated with both non-adherence and early discontinuation of adjuvant endocrine therapy [32]. In one study inclusive of pre-menopausal breast cancer survivors younger than 45, concern regarding fertility was found to be associated with tamoxifen non-initiation and non-adherence [33]. In addition to fertility, participants in this study also cited side effect concerns as a factor influencing their starting and adhering to tamoxifen, demonstrating how hormonal side effects from cancer treatment may also affect adherence to endocrine treatment.

A breast cancer diagnosis in young women has also been associated with employment disruption and financial impairment. In a population of 830 young women with breast cancer in the USA, Tangka et al. found that 47% of them experienced financial diminishment due to costs corresponding to treatment, and 55% required paid leaves of absence. In that study, 10% of patients reported paying a greater amount than expected for insurance coverage [34]. In a study of adolescents and young adult survivors, treatment with chemotherapy was associated with higher odds of self-reported mental impairment in job-related tasks and higher odds of taking unpaid time off of a job [35].

Conclusions and Future Directions

Breast cancer at young age correlates with more aggressive tumor features and worse prognosis. However, in the past two decades, there have been impactful clinical trials in the adjuvant setting that were specifically designed for young women diagnosed with breast cancer, advancing treatment to optimize outcomes in this population. However, significant clinical questions remain, including a need to better quantify the contribution of ovarian suppression to the benefit from chemotherapy for prevention of recurrence in pre-menopausal patients. This would allow clinicians to better tailor recommendations regarding adjuvant therapy in young women. With the advent of newer targeted therapies in both the adjuvant and metastatic settings, better characterization of the effect of these therapies in young patients would be informative. Regarding genetics and genetic testing, as the understanding of the role of genes beyond BRCA1 and BRCA2 on hereditary breast cancer continues to evolve, it will be necessary to determine how to best integrate multigene testing into the care of young patients as well as inform screening strategies and possible preventive interventions for those at high-risk due to a deleterious mutation.

With multiple observational studies characterizing the complex and prevalent psychosocial challenges faced by young breast cancer survivors, future research should continue to focus on the development and testing of interventions that aim to improve psychosocial health for young women with early-stage as well as advanced cancer. Furthermore, recognizing caregivers and addressing their needs are also critical: patients as well as their family members should be supported beginning with diagnosis, through active treatment and survivorship, and at the end of life. The partners of young breast cancer patients may be parenting young children while also serving as the primary caregiver for a patient undergoing treatment. Finally, given documented racial disparities in the outcomes of young Black women,

ensuring that women from minority groups that have been historically underrepresented in research should be prioritized to ensure that results from these studies are generalizable to all young breast cancer patients. At the systems level, barriers to receipt of timely cancer care and treatment, which can often be more acutely felt in adolescent and young adult patients who may have less stability due to their life stage, have generally been inadequately addressed. Continued focus on these challenging issues is essential in order to meaningfully address both age and racial disparities in breast cancer care and outcomes.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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