



Diagnostic delays in breast cancer among young women: An emphasis on healthcare providers

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ARTICLE INFO

Keywords:

Breast cancer in young women
BCYW foundation
Diagnostic delay
Healthcare providers
Awareness
Tumor growth
Early detection

ABSTRACT

Despite advances in breast cancer care, breast cancer in young women (BCYW) faces unique challenges, diagnostic delays, and limited awareness in many countries. Here, we discuss the challenges and consequences associated with the delayed diagnosis of BCYW. The consequences of delayed diagnosis in young women - which generally varies among developed, developing, or underdeveloped countries - are severe due to a faster breast tumor growth rate than tumors in older women, also contributing to advanced cancer stages and poorer outcomes. Though there are many underlying reasons for diagnostic delays due to age, the article delves explicitly deep into the diagnostic delay of BCYW, focusing on healthcare providers, potential contributing factors, its consequences, and the urgent need to start minimizing such incidences. The article suggests several strategies to address these issues, including increasing awareness, developing educational programs for healthcare providers to identify signs and symptoms in young women, developing clear diagnostic guidelines, and improving screening strategies.

Text

Breast cancer, the number one female malignancy, is a devastating disease affecting millions worldwide. Although medical and technological advances have improved breast cancer-associated mortality and overall patient survival, the lifetime risk of breast cancer is still very

high, 8%–12%. While breast cancer (BC) is commonly associated with older women, it's crucial not to overlook that breast cancer can also strike young or very young women. The benefits of breast cancer advances have not fully percolated to young women with breast cancer, which has been steadily rising globally [1–3]. There is no universally agreed-upon age cut-off for young women with breast cancer.

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Definitions of age vary from 35 to 45 across available literature. For this manuscript, we define breast cancer in young women to be equal to or less than 40 years of age as per ESO-ESMO Fifth International Consensus Guidelines for Breast Cancer in Young Women [1].

Breast cancer at an early phase in a woman's life presents numerous unique personal, social, and medical challenges, the majority of which do not apply to women who develop breast cancer at a later age [1–3]. The outcome, curability, and prognosis of BCYW are worse, with a higher incidence of recurrence than breast cancer in older patients. This is partly due to the detection of BCYW in the late stages of the disease when it has already transitioned into more aggressive behaviors [1–3]. Breast cancer incidence and mortality rates, as well as diagnostic delays, vary significantly across developed, developing, and underdeveloped nations. The prevalence, timely detection, fatality rates, and diagnostic lags of breast cancer are influenced by several factors, including ethnicity, socioeconomic status, rural or urban residence, educational attainment, accessibility to primary healthcare, healthcare structures, insurance systems, and more. These factors significantly impact breast cancer outcomes in countries with varying Human Development Index (HDI) [4–6].

Among many underlying reasons for diagnostic delays due to age, two primary contributing factors are the lack of general awareness among young women regarding the possibility of presenting with breast cancer at a young age [7,8] and dismissing suspicious signs as unimportant findings because of their age [9–12]. This further adds to the unique challenges faced by young women with breast cancer [13]. To this effect, a quick Google search using the term “doctors missing concerns from young women” leads to numerous such reports from breast cancer survivors on different websites [14]. There are also issues linked with healthcare providers, including patient-centered issues - mainly in the context of younger women. Here, we will delve deep into the healthcare provider-linked diagnostic delay of BCYW, its consequences, and the urgent need to start minimizing such incidences.

1. Time lost, tumor growth-rate, and potential consequences

Success in treating breast cancer (and cancer, at large) largely depends on the tumor volume and biology and genomics, interactions with the host factors, and resulting responses that shape the tumor's biological behavior. Young women with breast cancer are often in the eye of the storm regarding tumor staging and behavior. Time is not on their side, as the growth rate of breast tumors in younger women is significantly faster (shorter doubling time) than in older women [15–17]. Time is vital in explaining the increase in tumor burden and allowing the undesirable interaction between aggressive tumors and the host. Hence, the consequences of diagnostic delay on worsening tumor behavior in young women are expected to differ significantly from such delays in later phases of life. Medical misses by health providers due to a lack of suspicion of malignancy in this age group have been documented as one of the most significant contributors to diagnostic delays in young women [11–14]. These patients more frequently report a lack of suspicion of cancer by the first physician they consult compared to their older counterparts [11,12]. It is also true that there is a wide range of variations in such incidences in the developed, developing, and underdeveloped countries [9–13]. Young women affected by breast cancer often say they did not receive enough attention when they “first reported the first signs to their doctors” [13,14]. In fact, in most cases, BCYW is rarely preclinical.

Moreover, young patients have been found to use different health services more than older patients. This could also reflect inadequate awareness among first-contact physicians regarding the referral pathways for prompt breast cancer diagnostic work-up. Furthermore, in specific contexts, this frequent use of different health services and the resulting delayed diagnosis might be due to fragmented health systems for younger women, a lack of clearly established guidelines and referral routes, and other variables.

Late diagnosis poses an increased risk of advanced cancer stages, which results in more limited treatment response and survival rates. Delayed diagnosis and care during a time of vulnerability can lead to severe emotional consequences and affect the physical well-being due to the disease, and even mistrust in the medical system. Therefore, understanding the factors contributing to diagnostic delays is paramount to developing and implementing strategies to address and decrease these prolonged periods and improve patient outcomes.

2. Contributing factors – examples

Although many contributing factors could lead to delayed diagnosis and inadequate treatment of young women with breast cancer, examples of significant factors include: 1) the stereotype associating breast cancer with older age groups. This misconception creates a bias that often leads healthcare providers to overlook or downplay symptoms in younger patients, assuming they are too young to develop breast cancer and minimizing their concerns at the time of first consultation; 2) The symptoms are often dismissed as benign issues, leading to a lack of proper investigation.

In addition, breast cancer screening programs for the general population typically do not include women under the age of 40, indirectly contributing to diagnostic delays in BCYW. In many countries, including the US, these women are also not covered by medical insurance companies unless they carry specific genetic alterations that are linked to a high-risk category of breast cancer in younger individuals [4–6].

Breast cancer is categorized into four subtypes, determined by the status of three therapeutic receptor targets (ER, PR, and HER2) and clinical features. These subtypes are luminal A, luminal B, HER2-positive, and triple-negative BC (TNBC) or basal-like. The distribution of these molecular subtypes varies across age groups, with luminal B, HER2-positive, and basal-like tumors being more prevalent in younger women compared to older breast cancer patients [1,2,18]. In the BCYW age group, a significant percentage (about 34%–37 %) of women have triple-negative breast cancers in different studies [19–21], which may look like homogeneous hypochoic lesions with smooth rounded borders; these can often be misreported as fibroadenomas and ignored. 3) some patients are young mothers who may be mislabeled as having galactoceles. Malignant breast lumps during pregnancy and lactation are often falsely considered an accumulation of milk or breast abscesses. Patients may be falsely reassured and ignore their symptoms; 4) limited awareness and specific guidelines for diagnosing breast cancer in young women; and 5) the absence of clear protocols leaves healthcare professionals uncertain about the appropriate steps to take when faced with potential breast cancer cases in younger patients.

3. Bridging the gap - potential way forward

The first step is not to ignore a young woman's concern when she reports unusual changes in her breast health and needs dedicated attention from a doctor or medical provider. Individualized Medicine should precede oncology (“individualized” does not mean “molecularly driven” treatment), and healthcare providers should be trained to listen to, examine, and explain new signs and symptoms. Though there are many ways to bridge the current gaps, we suggest the following-

1. Building grassroots units to sensitize community women leaders and healthcare providers about BCYW awareness to avoid delays in seeking professional medical help.
2. Developing educational programs beyond Medical Schools on correctly identifying signs and symptoms of breast cancer in young women at the first consultation, familiarity with diagnostic algorithms for breast cancer, and knowing the adequate referral routes that might be warranted for timely diagnosis and treatment.

3. Developing clear guidelines for diagnosis, prioritization programs, and tailored referral pathways are central to easing and expediting diagnostic evaluations among cases with suspicious findings.
4. In designing screening strategies, we need to improve further screening strategies that are nonrestrictive of age and factor tumor growth rate.
5. Potential partnerships among medical schools, university hospitals, and professional organizations geared towards healthcare providers, introducing early-detection modules into their curricula and continuing education programs.
6. Medical societies and governing bodies should collaborate to create evidence-based protocols for the unique challenges younger patients face, such as the higher prevalence of aggressive breast cancer subtypes and the need for alternative diagnostic techniques when mammography may not be suitable.
7. It is also essential to educate all levels of healthcare workers to include the possibility of “triple assessment,” i.e., clinical assessment, age-appropriate imaging, and histopathological assessment for young women presenting with breast-related symptoms to avoid false negative results. However, it is equally important to avoid causing unnecessary anxiety in otherwise healthy women for an event that may or may not happen. The concept of screening has been criticized for this reason. Therefore, the role of “triple assessment” should be carefully supervised to avoid too many “false positives” that add to the cost and unnecessary anxiety.
8. The mention of “appropriate imaging” refers to young women with dense breast tissue, which makes mammography a tool with poor sensitivity and radiation exposure. The recommended added imaging modalities are ultrasound or Magnetic Resonance Imaging (MRI). Ultrasound has been shown in many studies to be reasonably sensitive and specific, but it is operator-dependent and can be subjective. On the other hand, MRI is highly sensitive but not very specific and can pick up too many artifacts, leading to unnecessary investigations and anxiety. The bottom line is to make young women “breast aware” and sensitize clinicians to pick up subtle early clinical signs and to appropriately choose the right imaging modality individualized to each patient scenario.
9. Promoting targeted awareness among family doctors and primary care physicians will be necessary. They present a unique opportunity for screening, emphasizing the importance of self-breast health and care. For example, gynecologists during pre- and post-natal visits, primary care providers every time a mother visits to vaccinate newborns, etc.
10. Introducing self-breast health care as an integral part of educational programs about reproductive health, adolescent health, family planning, and pregnancy-related counseling sessions.
11. Further enhancing patient-doctor communication is vital in comprehensively breaking down the barriers that may contribute to diagnostic delays.
12. As diagnostic delay poses a significant problem for young women, undertaking forward-looking studies comparing countries with different healthcare and insurance systems will be crucial. These studies will help identify the various layers of delays in seeking medical attention, such as investigating the concerns, waiting for imaging, biopsy, pathology report, etc. By doing so, we can recognize evidence-supported shared and country- or region-specific bottlenecks and develop appropriate interventions to address them.
13. Use of more advanced scientific tools and quantitative multigene screening methods to evaluate the level of breast cancer risk awareness in healthy women. This evaluation is essential for those with and without a family history of pathogenic or likely pathogenic germline variants (PGVs) associated with breast

cancer. It is particularly pertinent because a relatively higher proportion of individuals with genetic risk factors has been observed among younger breast cancer patients (BCYW) than older ones [22]. When assessing the results from these screening panels, it is crucial to consider other risk factors. These include a family history of cancer, personal hormone-related history, past medical conditions, lifestyle choices, and breast density observed in imaging. These factors can contribute to an individual’s risk of developing breast cancer, making interpreting screening results within this broader context essential.

4. Looking into future

We should soon have more insights from artificial intelligence that allow us to identify patterns of clinical presentation and imaging changes that can more quickly lead the medical decision to an actual cure with fewer sequelae for women [23]. The current standard of care guidelines for managing breast cancer is based on historic randomized controlled trials, which did not include many women in this age group. The outcomes from these historical studies are generally extrapolated for younger patients. More recently, there has been renewed interest in BCYW, and analyses are now geared toward this age group. We are also gaining insights from clinical trials that can provide relevant information for young women with breast cancer. The recently published results of the POSITIVE trial (Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer) [22] are an excellent example of research focused on the practical needs of young women with breast cancer.

Despite identifying the relatively small (but relevant) subset of women carrying monogenic risk for breast cancer, we are far from an adequate response from Science and Medicine to prevent BCYW and to detect it “early enough” to cure it without compromising women’s future without breast cancer. Until we have moved forward in Medicine enough to prevent and detect cancer with minimal burden, we must continue to improve the strategies we know can make a difference. Again, the word ‘Time’ seems critical in BCYW: Time to live without cancer, faster Time to cure, and Time to live with the hope of fulfilling dreams. In each of these ‘Times,’ Science and Medicine offers new opportunities for advanced research, and we have a long way to go.

No less relevant, a global strategy of medical education and health and science policies defined by the needs of citizens is warranted to improve the lives of young women with breast cancer globally. The way to move the needle forward in this age group is to build bridges with similar-minded programs across the countries, continents, and the world to broaden our research base and foster support for multicenter clinical trials in this patient population, which will allow us to improve standards of care.

Funding source

None.

Declaration of competing interest

No competing financial interests exist.

Author’s contributions

Luis Costa and Rakesh Kumar: Conceptualization, integrating parts, draft writing, reviewing, and editing. *Cynthia Villarreal-Garza:* partial draft writing and reviewing. *Saket Sinha:* partial draft writing and reviewing. *Sunil Saini:* partial draft writing and reviewing. *Jayanti Semwal:* partial draft writing and reviewing. *Vartika Saxsena:* partial draft writing and reviewing. *Vaishali Zamre:* partial draft writing and reviewing. *Chintamani Chintamani:* partial draft writing and reviewing. *Mukurdipi Ray:* partial draft writing and reviewing. *Chikako Shimizu:*

partial draft writing and reviewing. *Lejla Hadzikadic Gusic*: partial draft writing and reviewing. *Masakazu Toi*: partial draft writing and reviewing. *Allan Lipton*: partial draft writing and reviewing.

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