review articles

Overview of Breast Cancer and Implications of Overtreatment of Early-Stage Breast Cancer: An Indian Perspective

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abstract

The prevalence and mortality of breast cancer is increasing in Asian countries, including India. With advances in medical technology leading to better detection and characterization of the disease, it has been possible to classify breast cancer into various subtypes using markers, which helps predict the risk of distant recurrence, response to therapy, and prognosis using a combination of molecular and clinical parameters. Breast cancer and its therapy, mainly surgery, systemic therapy (anticancer chemotherapy, hormonal therapy, targeted therapy, and immunotherapy), and radiation therapy, are associated with significant adverse influences on physical and mental health, quality of life, and the economic status of the patient and her family. The fear of recurrence and its devastating effects often leads to overtreatment, with a toxic cost to the patient financially and physically in cases in which this is not required. This article discusses some aspects of a breast cancer diagnosis and its impact on the various facets of the life of the patient and her family. It further elucidates the role of prognostic factors, the currently available biomarkers and prognostic signatures, and the importance of ethnically validating biomarkers and prognostic signatures.

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BREAST CANCER PREVELANCE, SUBTYPES, AND TREATMENT

Epidemiology

Breast cancer is the most frequently diagnosed cancer and the most frequent cause for cancer-related deaths in women worldwide. Globally, breast cancer accounted for 2.08 million out of 18.08 million new cancer cases (incidence rate of 11.6%) and 626,679 out of 9.55 million cancer-related deaths (6.6% of all cancer-related deaths) in 2018.[1,2] In India, breast cancer has surpassed cancers of the cervix and the oral cavity to be the most common cancer and the leading cause of cancer deaths. In 2018, 162,468 new cases of breast cancer were diagnosed, representing 27.7% of all new cancers among Indian women and 11.1% of all cancer deaths.[3,4]

The epidemiology of breast cancer differs significantly in Indian women when compared with the Western population.[5,6] The median age of women at the time of diagnosis of breast cancer is approximately 61 years in the Western world, with the peak age being 60 to 70 years; however, in India, a higher proportion of patients with breast cancer tend to be premenopausal, and the peak age is between 40 and 50 years.[7,8] This is of concern because early-onset breast cancer is more aggressive and has a poorer prognosis than late-onset breast cancer.[9] Furthermore, 60% to 70% of all patients with breast cancer in the United States are diagnosed with stage 1 disease, whereas only approximately 1% to 8% of Indian women present with stage 1 disease. Although only approximately 10% of women in the United States present with stage IV disease, in India this number is approximately 6% to 24%, with approximately 29% to 52% of Indian women presenting at stage III.[10] Finally, although the incidence of breast cancer is rising globally, mortality associated with breast cancer is decreasing in the West but is increasing in India.[10]

Overview of Subtypes and Stages of Breast Cancer

The modern classification of breast cancer is based on immunohistochemistry (IHC), histopathologic features, and molecular characterization. The 2 most frequent histologic subtypes of invasive breast cancer are invasive ductal carcinoma and invasive lobular carcinoma (80% to 85% and 10% to 15% of all cases, respectively). Other histologic cancer subtypes compose the remaining < 1% of invasive breast cancers.[11]

IHC characterization of breast cancer is important for determining the treatment of breast cancer and for predicting prognosis. IHC characterization depends on the expression of biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and human

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CONTEXT

Key Objective

This article reviews the current status, key features, and prognostication of breast cancer and its management from the Indian viewpoint.

Knowledge Generated

Our review re-emphasizes that various key features of breast cancer in a patient from the Indian setting differ significantly from those of a patient from the Western setting, including in the molecular level, stage at presentation, prognosis, recurrence risk, and treatment options. Breast cancer overtreatment can have a significant adverse impact on the quality of life of the patient and her family. Predicting recurrence risk using prognostic biomarkers can reduce overtreatment. Although various prognostic biomarkers are available in the market for this purpose, many of them are not ethnically validated to suit Asian Indian patients with breast cancer.

Relevance

It is essential to use an ethnically validated biomarker to correctly identify patients with lower recurrence risk in whom systemic adjuvant therapy can be safely de-escalated.

epidermal growth factor receptor 2 (HER2). ER and PR expression of $\geq$ 1% is found in approximately 75% of patients with breast cancer who are considered to have hormone receptor (HR)–positive disease.[12] Furthermore, approximately 15% to 30% of breast cancer cases amplify or overexpress HER2, as measured by IHC.[13] Tumors not expressing ER and PR, and also not overexpressing HER2, termed triple-negative breast cancer (TNBC), tend to be aggressive and are associated with higher metastasis and recurrence rates than other breast cancer subtypes.[14,15] In India, the prevalence of TNBC is estimated at 31%, much higher than the Western prevalence of 12% to 17%.[16]

The staging of breast cancer into stages 0, 1, 2 and 3 is based traditionally on the TNM model. Keeping in mind the importance of molecular characterization, the American Joint Committee on Cancer's Cancer Staging Manual, 8th edition, expanded breast cancer staging in 2017 by integrating prognostic biomarkers (such as histologic tumor grade, ER, PR, HER2, and multigene test-based risk prediction) with the conventional anatomic TNM staging. This has now resulted in a large number of combinations of anatomic, clinical, and prognostic breast cancer stages.[17,18]

Breast Cancer: Current Treatment

Surgery is the mainstay of treatment of the early stages of breast cancer, and it ranges from lumpectomy to modified radical mastectomy. Surgery typically includes sentinel lymph nodes (LN) dissection for staging the extent of spread into the axilla. Adjuvant treatment using pharmacotherapy and radiotherapy is required for treating residual micrometastatic disease and reducing the recurrences rate. In 2013, the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer suggested that breast cancer may be classified into 5 subtypes: luminal A, luminal B with HER2 negative, luminal B with HER2 positive, HER2-enriched, and basal-like: triple negative (Table 1).[19]

Breast Cancer: Prognosis and Recurrence

Breast cancer prognosis largely depends on the stage at diagnosis and the HR status. Early breast cancer (stages 0 and I) generally has a favorable prognosis, and the 5-year survival rate is close to 100%. The 5-year survival rates dramatically decline with higher stages of breast cancer, with the rates for stages II, III, and IV being approximately 93%, 72%, and 22%, respectively.[7] The 5-year survival rates are the highest for ER-positive and PR-positive cases, and lowest for ER-negative and PR-negative cases, across all stages of breast cancer.[20]

Breast cancer recurrences represent a major source of cancer-related deaths.[21] On average, 8% to 10% of breast cancer cases present with locoregional recurrences after

TABLE 1. Subtypes of Breast Cancer and Suggested Pharmacotherapeutic Approaches

Subtype	Type of Therapy
Luminal A	Endocrine therapy
Luminal B with HER2 negative	Endocrine therapy; chemotherapy added for most patients
Luminal B with HER2 positive	Chemotherapy plus anti-HER2 therapy + endocrine therapy
HER2 enriched	Chemotherapy plus anti-HER2 therapy
Basal-like (triple negative)	Chemotherapy

NOTE. Data adapted from Goldhirsch A et al.[19]

Abbreviation: HER2, human epidermal growth factor receptor 2.

surgery, and approximately 11% to 30% of patients develop distant metastases.[22,23] The recurrence risk is higher in cancers that are advanced, of a high grade, HER2/neu positive, or TNBC cases.[23] During the first 5 years of diagnosis, ER-negative breast cancers have a higher recurrence risk than do ER-positive breast cancers; the risk seems to equalize between both subtypes after 15 years of diagnosis.[21] However, the recurrence risk in HR-negative cancers is confined mostly to the first 5 years after diagnosis. This is also seen in HER2-positive tumors. Conversely, HR-positive cancers generally tend to display late recurrences for at least 15 years.[24] The recurrence rates in TNBCs are generally higher than in HR-positive cancers.[25] The sites of recurrence and metastasis also depend on the type of breast cancer. Clinical factors favoring an increased relapse risk include higher tumor grade, large tumor size, axillary LN involvement, and HR-negative cancers.[22] LN involvement is the most important prognostic factor for recurrences, and axillary LN-positive disease is associated with a 4-8 times higher mortality rate than LN-negative disease.[26] Before initiating treatment of recurrent breast cancer, rebiopsy and restaging is necessary. Recurrent breast cancer treatment depends on the disease stage, the site and type of recurrence, and the time to recurrence, and it generally follows the principles of treatment of systemic therapy with or without surgery and radiation.[2]

IMPACT OF CANCER TREATMENT ON PATIENTS WITH BREAST CANCER

Breast Cancer Treatment: Adverse Effects

Breast cancer surgery and the associated sentinel LN biopsy result in transient physical discomforts such as pain and numbness in the chest wall, axilla, and breast, and arm edema. Cosmetic concerns after total mastectomy can be addressed by breast conserving surgery and breast reconstruction surgeries.[27,28] However, this is often associated with poor body image and other psychosexual problems.

Anticancer drugs are used to treat almost all patients with breast cancer. Breast cancer mortality has decreased drastically over the past few decades, and this drop in the mortality rate could be accounted for by an increased use of adjuvant chemotherapy over this period, leading to improved survival of patients with breast cancer. Adjuvant chemotherapy is thus a life-saving intervention for a patient with breast cancer. However, different subtypes and stages of breast cancer have different recurrence risks. Hormone-positive HER2-negative breast cancer that is detected early is associated with a 10% to 15% risk of distant recurrence over 10 years, and an only 2% to 3% absolute chemotherapy benefit, which is approximately the same as the risk of fatal, life-threatening, or permanently changing toxicities.[29] In such patients, because the benefits do not outweigh the risk of adjuvant chemotherapy, the associated adverse effects (AEs) and long-term consequences of anticancer treatment continue to remain a major concern for patients as well as for clinicians. The most often observed chemotherapy-related AEs are nausea and vomiting,[30] oral and GI mucositis leading to malabsorption, anorexia, weight loss, anemia and other related manifestations,[31] hypersensitivity[32], and peripheral neuropathy.[33] Approximately 90% of patients with breast cancer experience at least 1 AE.[34,35] The most frequent chemotherapy-related AEs observed in Indian patients with breast cancer include alopecia, nail discoloration, dysgeusia, and anorexia.[34] The AEs caused by breast cancer chemotherapy bring about emotional trauma, which may be augmented by a lack of proper professional support.[36]

Even though drugs are used and other approaches are taken to overcome the AEs of cancer chemotherapy, they are often incompletely effective. Furthermore, these interventions often do not address the long-term consequences of cancer treatment. Treatment of the AEs also adds to the financial burden of the disease. A study performed in a health care setting in the United States estimated that chemotherapy-related AEs resulted in a large incremental expenditure of USD 1,271 per patient annually.[37] The sum of the AEs and the additional financial burden caused by these AEs results in worsening of the quality of life (QoL) of the patient with cancer.[38]

With improvements in the technology of radiation therapy, serious complications after radiotherapy are rarely seen these days.[39] The most frequently reported AEs after radiotherapy for breast cancer include skin reactions, including edema, fibrosis, erythema, changes in pigmentation, and ulcerations, and problems caused by inflammation, including itching, warmth, dryness, and burning of skin.[40] Incidental radiation exposure of the heart, lungs, and contralateral breast may occasionally result in complications in these organs, especially in patients who receive radiotherapy after mastectomy.[39,41]

Economic Impact of Breast Cancer Treatment

Breast cancer carries a significant economic burden. The adverse economic impact of breast cancer has been reported extensively from various parts of the globe.[42-45] A 2018 systematic review of 20 studies reported that breast cancer treatment costs increased with a higher stage of cancer at diagnosis. Thus, earlier diagnosis of breast cancer can lower treatment costs.[46]

In India, although no study has accurately described the economic burden of the disease among Indian patients, the costs associated with breast cancer are expected to be high because of the high proportion of out-of-pocket (OOP) expenditure for treatment, leading to catastrophic payments, which are caused by overdependence on the private health care sector and poor health insurance uptake.[47] A 2016 study from Punjab reported that 36.23% of the total breast cancer treatment cost was for drugs (Fig 1). Obtaining treatment from the private sector was costlier than from the public sector, and the costs increased with older age and a higher stage of cancer at diagnosis.[48] In

another study, the average total OOP expenditure for breast cancer in 2014 was Indian Rupee (INR) 29,066 in public sector hospitals and INR 84,320 in private sector hospitals (USD 1715.82 and USD 4977.56 at 2014 purchasing power parity, respectively). Furthermore, nearly one half of low-income households (rural more than urban) used distressed means (defined as borrowings, sale of assets, and contribution from friends and relatives as first major source) for financing treatment expenditures caused by breast cancer. Finally, more than one half of patients from low-income households spent > 20% of their annual household expenditure on breast cancer treatment, leading to catastrophic payments.[49] An analysis of 3 public insurance schemes for anticancer treatment in India published in 2018 revealed inconsistency in the selection of reimbursed treatments. The reimbursed amount was found to be insufficient to cover the total cancer chemotherapy costs, leading to an average budget shortage of up to 43% for breast cancer treatment.[50] Thus, breast cancer can be expected to result in extreme financial hardships in Indian families.

Impact on QoL and Family

Even though breast cancer treatment is lifesaving, the physical AEs of cancer treatment and the treatment costs reduce the QoL of breast cancer survivors, which is already lowered with the diagnosis of cancer.[51] The QoL decline is worse if the patients with breast cancer have certain comorbidities (hypertension, diabetes, and arthritis), receive chemotherapy, have less social support, or have more unmet needs.[52] In the Indian scenario, a woman is conventionally expected to carry out different roles in the family, including being a wife, a mother, and a mother-in-law, each having some significant responsibility in the family; during the course of breast cancer treatment, the ability of the affected woman to completely fulfill these responsibilities may be hampered. A study from 2019 revealed that nearly 43% of patients with breast cancer had to struggle to meet the expenses associated with breast cancer. Furthermore, a male member of the family was the prime decision maker, and the caregiver was generally an immediate family member. Approximately 90% of patients admitted to facing social embarrassment because of the disease.[53]

BREAST CANCER OVERTREATMENT AND ITS PREVENTION: ROLE OF PROGNOSTIC MARKERS

Breast Cancer Overtreatment and Its Implications

A concerning issue with any cancer is the problem of cancer overtreatment and the accompanying adverse outcomes. Breast cancer overtreatment can put the recipients at the receiving end of all the AEs of cancer treatment discussed earlier. Every effort should be taken to prevent cancer overtreatment by identifying those patients in whom the administration of these risky treatment modalities can be safely avoided. Furthermore, cancer overtreatment can drain the limited health resources in developing countries.[54]

A major factor predisposing to overtreatment of cancer is fear: fear on the patient's side of dying as a result of cancer, and fear on the doctor's side of missing a serious diagnosis and its consequences.[54] However, this fear does not always warrant treatment with toxic drugs: breast cancer was detected at autopsy in up to 39% of middle-aged women in the United States who died as a result of something else.[55] Clearly, this section of asymptomatic patients with breast cancer did not require chemotherapy. However, the case might have been different had they been informed that they had breast cancer. This highlights the importance of restricting breast cancer treatment to patients who clearly need it, thereby preventing breast cancer overtreatment. At the same time, denying treatment to those who clearly need

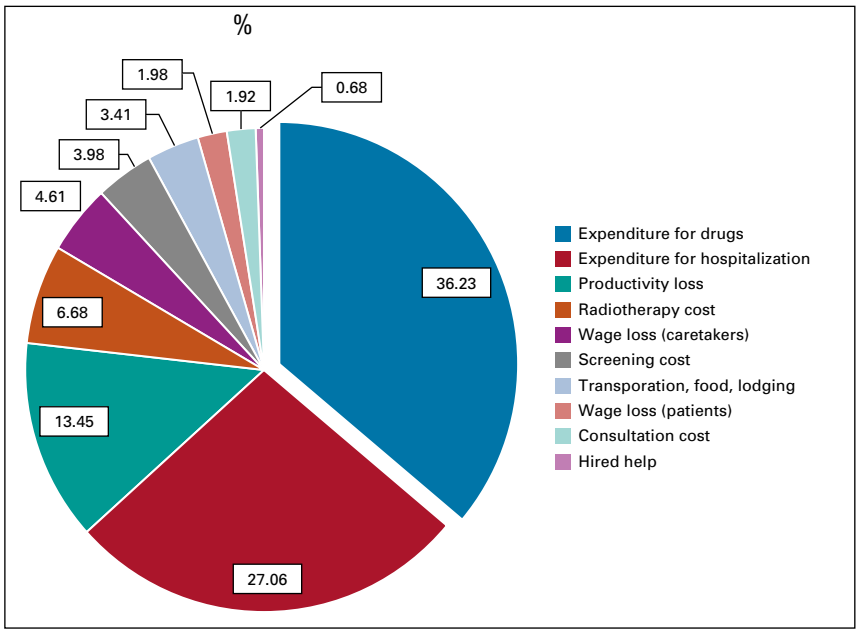

FIG 1. Major drivers of expenditure caused by breast cancer in India. Data adapted from Jain M et al.[48]

it (undertreatment) is equally devastating, and should be avoided.

Preventing Breast Cancer Overtreatment

Preventing breast cancer overtreatment can be achieved in 2 different ways. The first is by diagnosing breast cancer in its earlier stages through the screening of healthy women at a high risk of developing the disease, by using modalities such as mammography and ultrasonography. Such a diagnosis at an early stage can result in the initiation of early treatment, which avoids many of the adverse outcomes that are associated with initiating more aggressive treatment strategies at later stages of the disease. However, overenthusiastic screening can also lead to another unwanted outcome in the form of overdiagnosis. In fact, the estimated prevalence of breast cancer overdiagnosis has been up to 54% in some populations, which highlights the extent of the problem.[56] Such overdiagnosis may enhance the problem of overtreatment instead of lowering it, because of the overenthusiastic administration of treatment on demand by patients who are scared by the diagnosis of cancer.[57] Another problem documented with early screening for breast cancer is bias, such as healthy volunteer bias, length-biased sampling, and lead-time bias.[58]

The second way to prevent breast cancer overtreatment is by predicting the recurrence risk of the disease. If this can be achieved reliably, then administration of adjuvant chemotherapy can be limited to only those patients at a higher risk of developing such recurrences, thereby avoiding overtreatment in patients who might not need it. At present, the risk assessment tools that are popularly used in India include IHC4, luminal A/B subtyping, and PREDICT. Fifty-eight percent of Indian oncologists surveyed as part of a recent study reported using the online tool PREDICT to help decide on a course of adjuvant treatment.[59] Using molecular profiling and gene expression testing, it has become possible to predict the future behavior of breast cancer, thereby marking the beginning of the era of precision medicine in the disease.[57] This concept of identifying patients with breast cancer who could be safely spared chemotherapy was considered the topmost priority area in a 2007 Web-based survey of multidisciplinary cancer experts from around the world.[60]

Role of Prognostic Markers

With the increasing interest in the human genome, many genes influencing different stages of breast cancer have been identified, measured, and profiled to find out whether a correlation exists between gene expression and cancer recurrence risk. This has led to the introduction of several multigene assays for predicting prognosis and outcomes in patients with breast cancer (Table 2). The status of a patient with respect to these prognostic markers is intended to guide clinical decision making about initiating adjuvant chemotherapy and/or endocrine therapy after initial treatment of the breast cancer, depending on the risk of distant recurrence of the cancer.[61,62] In the United States, Oncotype DX is the most widely used among these breast cancer assays, followed by MammaPrint.[63] Other prognostic markers discussed in the literature include MapQuant Dx,[64] the Theros breast cancer index,[65] the Rotterdam signature,[66] and the Invasiveness gene signature.[67]

TABLE 2. Some Prognostic Markers for Breast Cancer

Prognostic Marker/Index/Assay	Nature	Details
Oncotype DX[68]	Multigene molecular tool	Using a RT-PCR–based 21-gene molecular, this tool estimates the likelihood of distant recurrence in patients with node-negative, tamoxifen-treated breast cancer
MammaPrint[69]	Multigene molecular tool	70-gene molecular assay predicting prognosis after 5 and 10 years on the basis of recurrences
Endopredict[70]	Multigene molecular tool	Quantification of mRNA levels of 8 genes by qRT-PCR to predict 10-year distant recurrence rate
Prosigna PAM50[71]	Multigene molecular tool	50-gene–based molecular assay predicting risk of recurrence of breast cancer
MD Anderson Prognostic index[72]	Multiparameter index	Using clinical nodal status, residual pathologic tumor size, pattern of residual disease, and lymphovascular space invasion, this index predicts risk of locoregional recurrence after neoadjuvant chemotherapy before breast surgery
NHS PREDICT[73]	Multiparameter online tool	Online tool using tumor size, type, LN involvement, and markers including ER, HER2, and KI67 for predicting prognosis in patients with breast cancer after surgery
Online! Adjuvant[74]	Multiparameter online tool	Online tool using patient demographics, tumor staging, and ER status for estimating prognosis in patients with breast cancer after receiving adjuvant chemotherapy

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN, lymph nodes; qRT-PCR, quantitative one-step reverse transcriptase polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction.

Many of these prognostic markers have been validated in clinical trials, predominantly in the Western world setting. The most significant clinical trials are the Trial Assigning Individualized Options for Treatment (Rx; TAILORx), performed in the United States for validating Oncotype DX,[75] and the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial, performed in the European Union for validating MammaPrint.[69] Furthermore, ASCO included some of these prognostic markers (such as Oncotype DX, MammaPrint, Endopredict, and Prosigna PAM50) in its 2017 clinical practice guidelines for predicting whether patients with breast cancer derive benefit from adjuvant chemotherapy.[76] Through pharmacoeconomic modeling studies performed around the globe, it has been proven that despite increasing the overall cost, the use of prognostic markers can significantly improve the quality-adjusted life-years and are therefore cost effective.[77-83] At the same time, there are concerns about the improper use and misinterpretation of these markers leading to breast cancer undertreatment.[84] Prognostic biomarkers commercially available in India as of March 2020 include ER, PR, HER2, Ki67, Oncotype DX, MammaPrint, Endopredict, and Prosigna.[85]

Importance of Ethnical Validation of Prognostic Markers

Breast cancer is a heterogeneous disease, and global ethnic variations in the outcomes of breast cancer are well known, as discussed earlier.[10] Even within the United States, ethnic variations are repeatedly observed wherein breast cancer incidence is lower but the outcomes are worse among Black women when compared with White women.[86,87] In a recent study, it was reported that young non-Hispanic Black women with breast cancer in the United States had significantly higher mortality and morbidity rates than did women of other ethnicities.[88] Significant ethnic variations relating to incidence, relapse-free survival, and outcomes of breast cancer have been described in the United Kingdom[89,90] and South East Asia[91] as well. Various reasons have been proposed for this difference, and the most accepted ones are differences in the levels of p53 expression and differences in the incidence of the mutated proto-oncogene HRAS1 allele.[92,93]

Although differences are noticed within the different ethnicities of a single country, it is not surprising to expect major differences with respect to epidemiology and outcomes of breast cancer among patients around the world. A 2015 study compared frozen breast cancer specimens from patients in China and Italy and concluded that the prevalence of the luminal A breast cancer subtype was significantly lower in the Chinese specimens.[94] Despite the lack of such comparative studies between patients with breast cancer from the West and from other countries, it is not unreasonable to assume that such differences in various facets of the disease may exist and that the basis for such differences may be at the genetic or molecular level. This assumption gains immense significance when we consider using prognostic markers, which are largely validated in the Western setting, for making clinical decisions for initiating or withholding treatment options in patients with breast cancer in the Indian setting.

In the recent past, Indian oncologists have had divided opinions about using prognostic markers developed in the West for making treatment decisions in breast cancer, and by far the most important reason for such resistance has been economic.[95] However, we believe that the more important question to be asked before using a prognostic marker for making a treatment decision should be whether the marker has been validated in a comparable ethnic and racial setting. Recent opinions strongly advocate validation of diagnostic and prognostic study findings to suit the population undergoing treatment, rather than blindly adopting Western findings, and this is especially needed in Asian settings where the burden of breast cancer is expected to increase tremendously in the near future.[96] In fact, some of the prognostic markers discussed earlier have fared poorly when tested in women from different ethnicities. For example, a TAILORx subgroup analysis revealed that there were ethnic differences within the study population itself, and that Black women who were participants of TAILORx study had worse clinical outcomes when compared with the non-Black women, despite similar 21-gene assay results of the Oncotype DX marker and comparable systemic therapy.[97]

Furthermore, MammaPrint was found to have a different ratio of low- to high-risk patients in Japanese and Korean cohorts compared with European cohorts. This led to the hypothesis that gene disparities between Asian and White people could be contributing to the observed differences and that a recalibration of the cutoff may be required before such prognostic tests can be used in Asian settings.[98,99] Adjuvant! Online was also found to display inaccurate results when applied to prognosticate Asian patients with breast cancer.[100-102] Thus, although prognostic markers are essential to prevent breast cancer overtreatment, using prognostic markers that are ethnically validated is equally essential. Such concerns have been raised by Indian oncologists recently as well.[59] The Asian Breast Cancer Cooperative Group 2019 consensus document advocates evidence-based yet flexible and individualized use of international treatment guidelines in Asia because these guidelines are based on data from predominantly non-Asian postmenopausal women, whereas young Asian women have distinctive clinicopathologic characteristics.[103]

None of the popularly used prognostic markers discussed previously (including Oncotype DX and MammaPrint) have been ethnically validated in Indian patients with breast cancer, and hence, using these markers to make clinical decisions for continuing or withholding chemotherapy for patients with breast cancer might not be entirely appropriate or accurate. However, an indigenously developed prognostic signature, the CanAssist Breast (CAB; Oncostem

Diagnostics, Bangalore), is now commercially available. The CAB is a machine-learning–based proteomic risk classifier. It combines 5 biomarkers (CD44, ABCC4, ABCC11, N-cadherin, and pan-cadherin) through IHC and 3 clinicopathologic parameters (tumor size, tumor grade, and node status) to calculate a "CAB risk score" that classifies Asian Indian patients with breast cancer into having a low risk or high risk of developing distant recurrence in 5 years.[104] The CAB has been validated analytically, demonstrating the robustness of the test,[105] and has been validated clinically in a retrospective cohort of primarily Asian Indian patients with breast cancer.[106] A 2019 study compared the CAB risk stratification of 455 patients with breast cancer from across India with that by Adjuvant! Online. The proportion of patients with high recurrence risk as per the CAB was nearly one half the number given by Adjuvant! Online (29% *v* 62.4%). Furthermore, the CAB categorized 36.6% of Adjuvant! Online high-risk patients into low risk, thereby enabling the treating physicians to avoid overtreating these patients with chemotherapy.[107] Even though validation in a prospective trial is pending, the CAB seems to be a reliable and cost-effective alternative to the established prognostic markers that have been developed in Western settings and have not been validated in the Indian setting, for predicting the risk of recurrence of breast cancer and for taking clinical decisions about starting or withholding chemotherapy for Indian patients with the disease.

Breast cancer has significant adverse impacts on the physical health, mental health, QoL, and economic status of the patient and her family, which are further accentuated by overtreatment. To prevent the overtreatment of breast cancer, there is a definite role for prognostic markers to identify women who are at a low risk of developing distant recurrences of the disease and thus can be safely spared the administration of chemotherapy. Despite the availability of many such prognostic markers around the world, none of them have been validated in the Indian setting, and they are expected to be inaccurate if they are relied on for taking the crucial decision of withholding chemotherapy for patients with breast cancer.[108] Prognostic markers such as the CAB, validated in Indian settings, are the need of the hour. Additional validation in prospective clinical trials can strengthen the definitive role of such prognostic markers in the treatment of breast cancer in Indian women.

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