



# Triple Negative Breast Cancer in India: What Is the Real Incidence?

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The real incidence of triple negative breast cancer (TNBC) in India has always been a topic of debate. There has been considerable heterogeneity in the reporting of TNBC rates in India. A recent meta-analysis of 34 studies done till 2019 that included 20,678 patients reported a pooled prevalence of 27% (95% confidence interval [CI]: 24–31%).<sup>1</sup> Our previous work in which we collected data from 17 studies done between 1999 and 2015 involving 7,237 patients from all four regions of India reported a TNBC rate of 31% (95% CI: 27–35%).<sup>2</sup>

In this meta-analysis, substantial heterogeneity was observed across the studies ( $I^2$  of 91.2% [95% CI: 88–94%],  $p < 0.001$ ). This was unexplained by study level characteristics like study location, definition of HER2 or estrogen receptor, age, proportion of patients who were premenopausal, grade 3 disease, or larger tumor size. We also found that the TNBC rate decreased as the quality of the study increased. Although the rates were not statistically significant, the TNBC rate of lower quality studies was higher when compared to higher quality studies (38% [95% CI: 27–48%] vs. 29% [95% CI: 25–33%]). Quality of studies were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. One point was given to each parameter if the study described the setting and study participants, reported descriptive data, provided detailed outcome data, and discussed limitations. A good quality study had a score of  $\geq 4$  and a lower quality had a score of  $< 4$  with a maximum score of 5.<sup>2</sup>

## Why Are Rates of TNBC So High in India? Is it a Precise Estimation of the Ground Reality?

Experts often cite referral bias as the reason why TNBC rates are higher in these studies. Most of the studies are done at a

large referral center. Epidemiological studies can suffer from referral bias when patients are recruited from tertiary centers. Patients with TNBC have more severe disease and will probably get selectively referred to a tertiary center, which will spuriously raise the rate of TNBC in the tertiary centers.

However, in contradiction to the theory of “referral bias,” a recent study from a tertiary referral center in Chennai, which evaluated 2,137 patients with locally advanced breast cancer, reported that the incidence of TNBC was 12%.<sup>3</sup> This study was done from 2006 to 2013. Intuitively, one would think that in a study done among patients with locally advanced disease, the number of TNBCs would be higher than what is currently reported. Could it be that only patients who had less severe disease and who could afford to go to these centers were selectively referred to these institutions? Contrast that with the original assumption for a referral bias wherein patients with more severe disease gets referred to a higher center. If that is the case, is a more realistic estimate for the rate of TNBC somewhere between 12% and 27%?

Another possible reason for higher rates of TNBC is the poor quality of the pathological examination of the specimen. For instance, Chakraborty et al in their study of 925 patients collected from a single tertiary cancer center reported a TNBC rate of around 12%. The study population underwent testing during 2011 to 2015. Although the institution was a tertiary referral center, the rate of TNBC is lower than what was reported in the meta-analysis. The authors hypothesize that it is a more accurate reflection of the reality as their pathology laboratory adhered to the established guidelines.<sup>4</sup> For this study, methods for immunohistochemistry (IHC) testing were automated, peer-reviewed with internal and external quality assurance that was done mostly on core biopsies.

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However, in contradiction to Chakraborty et al, a recent study done among 3,453 patients diagnosed with stage I, II, or III breast cancer from three different private institutions in India (two of which were in Chennai) during the years 2008 to 2014 reported that the TNBC rate was 24.2%.<sup>5</sup> All three institutions have implemented high-quality pathology reporting. Most vital factor to be noted is that the patients in this study were likely to be at a higher socioeconomic status than the patients treated in government centers.

Inconsistent IHC diagnostic methods are very prevalent in India. ► **Table 1** lists issues concerning the heterogeneity of TNBC rate in India and some suggested solutions. Improper fixation techniques, use of non-U.S. Food and Drug Administration approved assays and interpretative error due to the failure to use the revised American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines for estrogen receptor/progesterone receptor positivity can cause some of the errors in reporting.<sup>6</sup> The standardized tests are compromised for cheap nonvalidated tests that lead to nonuniformity of results nationwide.

Implementing a standardized protocol for detection can help in proper identification of TNBC. Quality-assured antibodies can improve the detection rates of estrogen and progesterone receptors. IHC should be preferably done on biopsy specimens rather than lumpectomy or mastectomy specimens.<sup>4</sup> A meta-analysis done on 27 studies has shown

high diagnostic accuracy with core needle biopsy when compared to open excision biopsy in breast cancer patients.<sup>7</sup> A retrospective study done over a period of 6 years reported a reduction in the TNBC rate from 40 to 26% with better IHC techniques and tissue handling.<sup>8</sup> Training programs for pathologists and technicians, proper implementation of the ASCO-CAP guidelines in laboratories, regular internal auditing of tests, centralized testing, and quality assurance by external boards can be beneficial.<sup>6</sup> A population-based recruitment and careful interpretation of results can prevent referral bias in future studies.<sup>9</sup> Creating a national TNBC registry can help in studying the true incidence in different regions.<sup>10</sup>

Patients with TNBC have an aggressive disease and its high incidence can contribute to poor outcomes for Indian women with breast cancer. There is an association between TNBC diagnosis and interval cancers, which are those cancers that manifest between the usual intervals of a recommended screening test.<sup>11</sup> For instance, a patient could develop an aggressive TNBC between their yearly screening mammograms. In such a case, there was no benefit for the patient with their screening mammogram as it did not help diagnose their cancer before it manifested symptomatically. If the incidence of TNBC in a region is very high, there is greater risk for such interval cancers, and no real impact for a breast cancer screening program. Knowing the real incidence of TNBC would therefore help policy makers and experts in determining the relevance of population-based breast cancer screening.

Are the TNBC rates in India truly very high or is it a reflection of the lack of population-based studies? It is time we focus our attention on this question and settle the debate once and for all.

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#### Conflicts of Interest

The authors have nothing to declare.

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**Table 1** List of issues concerning the heterogeneity of TNBC rate in India and some suggested solutions (based on Shet<sup>6</sup>)

Issues	Suggested solution
Choice of specimen <sup>4</sup>	• Biopsy tissue preferred
Improper fixation of tissue <sup>6</sup>	• Avoid delay or refrigeration before fixation • Adequate formalin fixation time • Adequate formalin to be used
Use of nonvalidated antibodies <sup>6</sup>	• Automation of IHC • Participation in EQAS • Protocol optimization
Interpretative error <sup>6</sup>	• Strict implementation of ASCO-CAP guidelines for scoring • Compare core biopsy with excised specimen • FISH confirmation for HER2neu heterogeneity
Lack of training <sup>6</sup>	• Training of pathologists and technicians • Laboratory certification
Lack of uniformity in results <sup>6</sup>	• Centralized testing • Internal auditing
Expensive tests <sup>6</sup>	• Economize or proper insurance coverage of these tests
Referral bias <sup>9</sup>	• Population-based recruitment • Careful interpretation of results

Abbreviations: ASCO-CAP, American Society of Clinical Oncology-College of American Pathologists; EQAS, external quality assurance system; FISH, fluorescence in-situ hybridization; IHC, immunohistochemistry.

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