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# Triple Negative Breast Cancer in Southeast Nigeria: A Review of 149 Cases; What is New?

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## Abstract

**Purpose:** To determine the prevalence of Triple Negative Breast Cancer (TNBC) and its features. Second highlight what is new and applicable in our setting.

**Material and methods:** Data of all immunohistochemical typed blocks for breast cancer was pulled and only those negative for Estrogen Receptor (ER), Progesterone Receptor (PgR) and Her 2 Neuro Receptor (HER-2) amplification were used.

**Results:** Of 417 breast specimens in 3-years with ER negative, PgR negative and Her-2 amplification negative, 149 (35.7%) were TNBC. 143 were females 96% and 6 were males 4%. Median age was in the 31-40 years. Most presented at a late stage as in many other cases 48 (32% presenting at stage 4 while 47 (31.5%) presented at stage 3, 43 (29%) had no clear records so were marked as unknown. Treatment applied was taxane combination chemotherapy, surgery and radiation. Baseline survival data after 5 years stood at 63.5% for stage 2, 59% for stage 3. No stage 4 was seen after 5 years follow up.

**Conclusion:** Most presented late at stage 3 or 4 as premenopausal and survival was poor at 59% of stage 3. Literature suggests some will benefit from tamoxifen despite TNBC status if they have *TP53* mutation.

**Keywords:** *ESR1*-negative breast cancer; Triple-negative breast cancer; Luminal tumors; Breast cancer; Treatment; Chemotherapy

## Introduction

Breast cancer is the most common malignancy of females in Nigeria and its global incidence increase is upbeat with most deaths occurring disproportionately in sub-Saharan Africa [1-3]. Triple-Negative Breast Cancer (TNBC) accounts for 20% of Breast Cancer (BC) cases worldwide but remains the most deadly subgroup of BCs. It is defined by the absence of therapeutically targetable (ER), (PgR) and Her-2 overexpression, TNBCs often present with more aggressive clinicopathologic features (for example, basal-like phenotype, higher grade and stage, greater proliferation) than luminal tumors. Currently there are no targeted therapies for TNBC in sub-Saharan Africa; thus, surgery, anthracycline and taxane-based chemotherapy, and radiation therapy are the primary treatment options for patients with TNBC. Despite these treatments, TNBCs run a high risk of progression, especially within the first 5 years after diagnosis [4-6].

Although Estrogen receptor alpha (*ESR1*) is now routinely used in typing breast cancers in most of Eastern Nigeria, where it is used as a major prognostic and predictive factor in treatment outcome [7-9]. *ESR1* negative breast cancer remains a significant subtype contributing to (35.7%-38.4%) and usually the predominant triple negative breast cancers. For these patients no further treatment is given after surgery and neoadjuvant taxane based combination chemotherapy and radiotherapy. A comparative study done by Nikita et al. shows that by 50 weeks after diagnosis and management survival probability of triple negative breast cancers in Nigeria; falls from 1-0.3, while in UK survival probability only falls from 1.0 to 0.6 (twice as good) [10]. By 100 weeks it has flattened to 0.1 in Nigeria and in UK 0.3510. Although the differences can be explained in part by our late presentations, poorer health care's systems and lack of good health insurance. We note that Adding Transcription factor 53 statuses as well as the estrogen receptor beta status evaluation only for triple negative breast cancers will make a significant improvement in survival.

Estrogen Receptor Beta (*ESB2*) shares structural homology at DNA and ligand binding domains (98% and 56%, respectively) with (*ESR1*) the major type of estrogen receptor in breast cancer. *ESR2* functions and expression patterns are different from *ESR1* and are widely expressed in both basal and luminal epithelial cells [11-15]. The precise role of *ESR2* in breast cancer is unclear, with both antiproliferative and proliferative roles described. The mechanisms for these opposing actions of *ESR2* in breast tumorigenesis have not been fully elucidated. Provides an explanation for the dual nature of *ESR2* function in triple-negative breast cancer (TNBC) related to its interactions with *TP53* status (wild type or mutant) [16-19]. In wild-type *TP53*-expressing cells, silencing of *ESR2* augmented apoptosis, whereas it's over expression resulted in increased proliferation. Opposite effects were observed following silencing or overexpression of *ESR2* in mutant *TP53* cells, suggesting the important role of *TP53* status in determining *ESR2*'s function. Mechanistically, *ESR2*-mutant *TP53* interaction mediates sequestration of mutant *TP53*, leading to the *TP73* activation and antiproliferative effects. Treatment with tamoxifen (4-hydroxy tamoxifen) also increases *ESR2* expression and reactivates *TP73* in mutant *TP53* cells, providing an explanation for its beneficiary effects.

Suggest that the company of *ESR2* with mutant *TP53* can prognosticate TNBC patients and more importantly help select a population for tamoxifen therapy. The beneficial effects of endocrine therapy in unselected *ESR2*-negative breast cancer and TNBC cohorts have been previously described [20,21]. The ability to selectively administer endocrine therapy should, in principle, lead to greater response rates. It is unclear what the impact of *ESR2-TP53* interactions have in *ER*-positive breast cancer, particularly because all patients are offered endocrine therapy.

In view of the above we suggest a further routine subtyping of all triple negative breast cancers in Nigeria to ascertain their *TP53* status as well as *ESR2* receptor status. Those with mutant *TP53* and prominent expression of *ESR2* should still have tamoxifen which we believe will prolong their survival and give them a better quality of life. A further study is needed and is ongoing to fully elucidate the effect of these changes in our center.

## Review of Cases

Data of all immunohistochemical typed blocks for breast cancer was pulled and only those negative for Estrogen Receptor (*ER*), Progesterone Receptor (PgR) and Her 2 neuro receptor (*HER-2*) amplification was termed triple negative and reviewed.

Out of 417 breast cancer specimens seen over a 3-year period with Estrogen Alpha receptor and progesterone as well as Her-2 immunotyping with external controls, 149 (35.7%) were triple negative. Cases with negative stages for these markers were termed triple negative breast cancer type. Of these 143 were females 96% and only 6 were males 4%. Median age was in the premenopausal group 31-40, with most clearly in that premenopausal category. Most presented at a late stage as in many other cases 48 (32% presenting at stage 4 while 47 (31.5%) presented at stage 3, 43 (29%) had no clear records so were marked as unknown. Treatment applied was basically taxane based combination chemotherapy, surgery and radiation with no further treatment given. Baseline survival data after 5 years stood at 63.5% for stage 2, 59% for stage 3. No stage 4 was seen after 5 years follow up. We found that invasive ductal carcinoma (not otherwise specified) was the predominant histological type accounting for all cases (100%).

## Discussion

There were 149 (35.7%) of cases of triple negative breast cancer seen in the three-year period from 2014 to 2017 confirmed by immunohistochemistry as negative for *ER*, PgR, and *Her-2* amplification (Table 1).

| Molecular subtype | Frequency | Percentage |
|---|---|---|
| Her-2 type | 10 | 2.4 |
| Lumina B Her-2 type | 20 | 4.8 |
| Lumina B | 238 | 57.1 |
| Tripple Neg | 149 | 35.7 |
| Total | 417 | 100 |

**Table 1:** Status of molecular subtype.

Of these 143 were females 96% and only 6 were males 4%. Median age was in the premenopausal group 31-40, with most clearly in that premenopausal category (Table 2).

| Variables | Categories | Frequency | Percentage |
|---|---|---|---|
| Tripple Neg | Female | 143 | 96% |
| | Male | 6 | 4%. |

**Table 2:** Sex distribution of triple negative breast cancer.

The mean age of these patients of 46.7% is like previous studies in our center and other centers in Nigeria [22-25] (Table 3).

| Age of patients (Years) | Tripple neg (N) | Percentage (%) |
|---|---|---|
| 20-30 | 4 | 2.70% |
| 31-40 | 76 | 51% |
| 41-50 | 27 | 18.10% |
| 51-60 | 19 | 12.80% |
| 61-70 | 17 | 11.40% |
| >70 | 6 | 4% |
| Total | 149 | 100% |

**Table 3:** Molecular subtype and age relationship.

The premenopausal preponderance has also been highlighted by other authors. Breast cancer appears earlier in Africa and African Americans.

We found that invasive ductal carcinoma (not otherwise specified) was the predominant histological type accounting for 100% of cases. This finding is corroborated by other researchers across the globe [26-28].

Our findings with regard the relative frequency of TNBC to other molecular subtypes of breast cancer are like a previous study in our center and other African reports [29,30].

Majority of the TNBC were Grade 3 tumors, a finding that is consistent with previous reports.

Most presented at a late stage as in many other cases 48 (32% presenting at stage 4 while 47 (31.5%) presented at stage 3, 43 (29%) had no clear records so were marked as unknown (Table 4).

| Stage | Number | Percentage |
|---|---|---|
| 1 | 5 | 3.50% |
| 11 | 6 | 4% |
| 111 | 47 | 31.50% |
| 1V | 48 | 32% |
| Unknown | 43 | 29% |
| Total | 149 | 100% |

**Table 4:** Manchester staging of triple negative breast cancer at presentation.

Although Treatment applied was basically taxane based combination chemotherapy, surgery and radiation with no further treatment given. Baseline survival data after 5 years stood at 63.5% for stage 2, 59% for stage 3. No stage 4 was seen after 5 years follow up (Table 5).

| Stage | Survival | | Mortality | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| 1 | 5 | 100% | 0 | 0% |
| 11 | 4 | 63% | 2 | |
| 111 | 28 | 59% | 20 | |
| 1V | None were seen | Not documented | | |

**Table 5:** Baseline data for 5 year survival of tripe negative breast cancer.

We surmise that in view with existing literature in the West better results could be obtained if we had done *TP53* status of the tumor. This antibody is currently being done but prior to 2017 it was not done in our environment.

Because In wild-type *TP53*-expressing cells, silencing of ESR2 augmented apoptosis, whereas it's over expression resulted in increased proliferation. Opposite effects were observed following silencing or overexpression of *ESR2* in mutant *TP53* cells, suggesting the important role of *TP53* status in determining *ESR2*'s function. Mechanistically, *ESR2*-mutant *TP53* interaction mediates sequestration of mutant *TP53*, leading to the *TP73* activation and antiproliferative effects. Treatment with tamoxifen (4-hydroxy tamoxifen) also increases *ESR2* expression and reactivates *TP73* in mutant *TP53* cells, providing an explanation for its beneficiary effects. Analysis of the Molecular Taxonomy of Breast Cancer International Consortium TNBC subgroup of basal-like tumors (n=259), based on *ESR2* levels and *TP53* mutation status, confirmed the impact of these interactions on survival, that is, mutant *TP53*-expressing tumors with high *ESR2* levels have better survival 9. We now add sequential use of taxmoxifen in the management of TNBC with *TP53* mutation and data is currently being collected although it clearly appears to be beneficial too.

## Conclusion

Most presented late at stage 3 or 4 with majority in the premenopausal group and survival generally was poor at 59% of stage 3 after 5 years. Literature review strongly suggests that quite a significant number will indeed ironically benefit from hormonal manipulation with tamoxifen despite being triple negative if they have Transcription factor *TP53* mutation.

## Conflict of Interest

None declared.

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