Author's response to reviews

Title: A retrospective analysis of breast cancer subtype based on ER/PR and HER2 status in Ghanaian patients at the Korle Bu Teaching Hospital, Ghana

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Author's response to reviews: see over
Changes made

Editorial comment:

1. Heading removed from figures and figure five removed from the main manuscript
2. Table 1 and 2 included in the main main

Referee 1

1. **Please clarify the patient population, is this a random breast cancer population or a specific selection?**
   
   **Modification: Patient population:**

   Breast Cancer patients who had received and completed treatment for breast cancer at the Korle-Bu Teaching Hospital (KBTH) within the last 5-years and were being follow up constituted the study population. Data was thus collected between April 2011 and March 2012. During the period 363 consecutive patients who met the above criteria were seen and their case notes were reviewed.

   Immunohistochemistry (IHC) for Estrogen receptor (ER), Progesterone receptor (PR), and HER-2/neu, which is a prerequisite for this study, was available for 165, hence they constituted the subset for this study.

2. **Is there a bias for BRCA1 or 2 carriers? Is there data available on hereditary breast cancer in the families?**

   **Response:** That information is not available. BRCA is not done in our institution

3. **How was the IHC staining performed (please provide protocols and Antibodies used). Who did the scoring? Was there pathological revision of the slides? Are the slides and blocks available? How was the Her2 scoring interpreted (0, 1+, 2+, 3+) was there SISH performed on the HER2 2+ cases? (Approximately 30% of all HER2 ‘ 2+’ ICH turn out to be positive using SISH). This will influence the % of HER neg patients.**

   **Response:** Pathology reports from which ER, PR and Her-2/neu, were obtained came from Korle-Bu Teaching Hospital. IHC from both laboratories was performed on formalin-fixed paraffin embedded tissue sections. The ER and PR tests were scored based on an aggregate score of percentage of tumour stained and staining intensity. Aggregate score of more than 2 were considered positive. That is to say a minimum of 1-10% stained associated with minimum intensity. Her-2/neu was considered positive if an IHC 3+ result was found. Flourescence in Situ Hybridization was not available in the institution.

Referee 2

1. **Ethnicity plays an important part in this study and the authors must be consistent when they are referring to racial background. In the first sentence of the background**
section, racial backgrounds are variously described as; whites, African Americans and blacks rather than using consistent terms (e.g. black Americans and white Americans)
Modification: Line 25 and 26: But this decline is faster in white Americans compared to Black Americans in the United States of America.
Line 152, 153 and 154: patient with black American and white American reported a higher percentage of hormone negative tumours of 82.2% in Ghanaian women compared to 26.4% and 16.0% in black American and white American women respectively

2. The methods appear appropriate and are well described although the Bloom-Richardson grading system should either be referenced or briefly described
Modification: Histological grading was by the Bloom-Richardson grading system that combined scores for nuclear grade, tubule formation and mitotic rate[13]. Reference inserted.

3. A definition of T in the TNF classification system should be given (line 115).
Modification: Tumour size ranged from 0.8cm to 15cm with a mean of 4.9±2.8cm and median of 4. Eight tumours were ≥10cm. Tumour size (T in TNM classification) values were available for 155 cases. T1 (2cm across or less) tumour was present in 17/155 (11%) and T2 (more than 2cm but not more than 5cm across), T3 (bigger than5 cm across) and T4 (spread to chest wall, skin, both and inflammatory) tumours were 71 (45.8%), 42 (27.1%), and 25 (15.2%) respectively

4. It is unclear why both mean and median were included (line 107)
Modification: A total of 165 cases contributed to this study. The mean age at diagnosis was 52.5 ±12.1 years. The median has been deleted

5. Line 182 states that this study has implications for the treatment of breast cancer but it is not clear what the implications are as the current modes of treatment for each subgroup of patients, and proposed changes to these treatments are not stated.
Modification: Our findings have implication for treatment of breast cancer in Ghana. In the past, patient with breast cancer were treated blindly with Tamoxifen. However, approximately 50% of our patients may not be suitable for hormonal or targeted therapy because they are either negative for .ER/PR or do not over express HER2

6. The limitations of this study were clear, however in line 171 the use of the word inability appears inappropriate. Is it the inability to retrospectively test for basal markers, or is it that this IHC test was not done and the data is therefore not available
Modification: One limitation to our study was the non availability of retrospective data on basal markers (cytokeratin [CK]5/6 or epidermal growth factor receptor [EGFR]) as they are not routinely done in our centre.

7. There is no consensus on what pathological complete response (line 189) is and it should therefore be clearly defined within the context of this study.
Modification: Several studies using posttreatment American Joint Committee on Cancer tumor-node-metastasis staging for invasive carcinoma have documented higher complete pathological response in the core basal phenotype of triple negative breast cancer compared to all other subtypes[5, 25]

8. A large part of the discussion is dedicated to breast conservation but there is little new data for this and it is not a stated aim of the study. Similarly in the conclusions the authors promote the need for a paradigm shift in the neoadjuvant/adjuvant treatment of breast cancer patients in Ghana, but evaluating this was not one of the stated aims of this work.
Modification: For surgical treatment, 97.6% of the patients had mastectomy, a rather high rate compared to what is reported in Europe, North America and Japan (between 27.5% to 64%[26-29]. Breast conserving surgery was only done in 2.4% of our patients, a rather low rate as compared to rates of 54% to up to 70% and over elsewhere [27-31] . As many as 66% of the patients in this study presented with a T1 or 2 tumors while almost 60% had N0 or 1 lymph node staging.

9. This work would benefit from a grammar check. For example in line 172 the word will should be replaced with would
Modification: the word “will” has been replaced with “would”

10. Given the implication that basal markers are not routinely used, but would be helpful in subtyping the breast cancers in KBTH, it is surprising that including basal markers in the IHC panel is not suggested in the conclusions
Modification: Triple negative tumour is the most commonly occurring subtype in the Ghanaian breast cancer population treated at the Korle-Bu Teaching Hospital. Hence, blind hormonal therapy is not justifiable. Lack of significant association between subtypes and their clinical and pathological behaviour could be due to small sample size. We recommend the inclusion of basal makers in the IHC panel on routine basis.