Author's response to reviews

Title: A Population-Based Study of Kurdish Breast Cancer in Northern Iraq: Hormone Receptor and HER2 Status. A Comparison with Arabic Women and United States SEER data

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Author's response to reviews: see over
We submit the revised manuscript now entitled “A Population-Based Study of Kurdish Breast Cancer in Northern Iraq: Hormone Receptor and HER2 Status and a Comparison with Arabic Women and United States SEER data” by Runnak A Majid, Hazha A Mohammed, Hemin A Hassan, Wasan A Abdulmahdi, Rekawt M Rashid, and Michael D Hughson for further consideration for publication in BMC Women’s Health.

We have addressed all of the comments of the reviewers, I hope successfully. The changes to the comments of reviewer 2 required substantial changes to the results section, additions to the discussion, and changes in the abstract. The reviewers and editors will need to read these sections again in detail.

The number of tables is reduced to five.

Reviewer 1.
1. Background, paragraph 2: the authors should describe better the clinically relevant, IHC determined, breast cancer classification into subtypes, emphasizing also that ER+ tumors, can also be Her2 positive.

This paragraph was changed to include all of the HR/HER2 subtypes:
Breast cancer can be divided into four major subtypes on the basis of HR and HER2 testing: those that are HR+ (ER+ and/or PR+) but HER2-, those that are HR+ and HER2+, those that are HR- and HER2+, and those that are “triple negative” for ER, PR, and HER2 [7,8,10,11,12].

2. Background, paragraph 3: the authors stated “Her2 status is predictive of a better response to anthracycline or taxane-based compared to cyclophosphamide” however there is no clear evidence so this remains controversial. Please rephrase.

This statement was omitted. We do not believe it adds anything to the statement that follows regarding trastuzumab.

3. Background, paragraph 3: the authors stated incorrectly that trastuzumab improves survival when used in the neoadjuvant setting. Please rephrase.

The statement was rephrased as follows with “the neoadjuvant setting” omitted. The improvement in the adjuvant setting seems to be well substantiated:
The monoclonal antibody trastuzumab is applicable only for HER2+ tumors and improves survival when administered following anthracyclin-containing protocols that often contain a taxol [16,17,18,19].

4. Results, paragraph 2; check “encysted”
Encysted and cystic have both been used, but the WHO classification uses invasive papillary carcinoma. Encysted is changed to invasive papillary carcinoma.

Reviewer 2.
1. Although the author attempts to look at differences between Kurdish and arab women it appears that the real comparison was between women diagnosed in Iraq and those identified from the SEER database. The author thus needs to reflect this both in the title of the paper and the aim.

The title is changed to: A Population-Based Study of Kurdish Breast Cancer in Northern Iraq: Hormone Receptor and HER2 Status. A Comparison with Arabic Women and United States SEER data

In the Methods section of the abstract the following is added:
Results were compared with Egypt and with United States (US) SEER data.
The compared US SEER data are the tabulated breast cancers for the two year period 2003-2004 as published by Lund et al. for the two county area of Atlanta GA (reference 7).

This statement is repeated again in the methods section of the body of the manuscript.

In the last paragraph of the introduction it is stated:
“this study was undertaken to determine the age related distribution of the breast cancer subtypes among a sizable number of Kurdish and Arabic women treated at a Northern Iraq reference center and to compare the findings with women reported in the US SEER program.”

2. In the conclusion of the abstract the authors make a blanket statement that “frequency of non-testing is a deficiency in oncology practice that appears to be common in the Middle-East”. Although this may be true in Iraq it is certainly not true in other parts of the Middle East and it would be important that the authors revise this statement.

The reviewers comment is well taken. The statement is certainly not true for most of the Gulf states and other wealthier Middle-East countries but does apply to Iraq and many other lower income countries. This statement is omitted from the abstract and the conclusions. In the last paragraph of the discussion the statement is revised as follows:

The lack of studies for HR and HER2 in nearly 50% of Sulaimaniyah patients points to deficiencies in regional practice standards that appear to be common in many lower income countries but that should be remediable with suitably directed educational programs.

3. There should be a table 1 that summarizes the patient characteristics of both groups of patients including stage of disease and treatment if present. At present time there are too many smaller tables that can be summarized into one table of
patient and tumor characteristics.

The tables are revised and a table 1 is provided that summarizes the general characteristics of all 824 patients and comparatively the 432 patients for whom IHC was performed. The table includes tumor stage. It would be impossible to summarize treatment at this time.

4. Why was the age incidence standardized ratio only calculated for the Sulaimany patients. The authors have a cohort of over 800 patients. It would be important to look at the cohort as a whole and then subdivided into the pre identified subgroups.

Incidence could only be estimated for Sulaimany residents because that was the only group for which a defined patient population could be compared to a defined population at risk. Virtually all breast cancer patients from Sulaimaniyah are registered at Hewa Hospital. Kurdish patients outside of Sulaimaniyah represent an unknown fraction of the breast cancer population from their region. Arab patients are mainly from Baghdad but come from all of Iraq south of the Kurdish region.

5. As a whole the way the results are reported is a little confusing. It would be important to first look at the whole cohort. Report on their demographics and characteristics and then look at each subgroup separately before doing comparisons and within each subgroup and that with the SEER group.

The tables and results are revised to meet this criticism.
Table 1 summarizes the general characteristics of the total patient population and the division into patient having and not having IHC.
Table 2 summarizes and compares the mean ages, the age distributions, tumor stage, tumor grade, and HR and HER2 status of each ethnic/regional group with p-values showing the basic similarities of the groups.
Table 3 combines all groups and relates the four categories of ER and HER2 expression to patient age, tumor stage, and tumor grade. Combining all ethnic/residence groups and having the subsets of HR/HER2 expression categorized as ER/HER2 combinations provides the greatest statistical power to the observations.
The later is explained in the results as follows: ER/HER2 status succinctly summarizes HR and HER2 combinations. There are eight possible ER, PR, and HER2 interactions. Among the 432 patients in this study, there were 48 ER+/PR- tumors (11.1%) and 13 ER-/PR+ tumors (3.0%) represented in these combinations. The categories of ER+/HER2- and ER+/HER2+ tumors captures the former and omits only the 3% of tumors represented by the latter, and allows the strongest data analysis with the fewest categories of HR and HER2.
Table 4: This table shows the distribution of breast cancer in Sulaimaniyah residents by 5 year intervals. It also shows the calculation of age specific incidence and the calculation of the age standardized incidence using the WHO standardization ratio.
Table 5 consists of a comparison of Sulaimaniyah residents with a recent study from Egypt and a two county study from the SEER data base for Atlanta, Georgia (reference
7). This table emphasizes the comparisons of the frequency and incidence of the triple subtypes.

6. The authors compare results to that of information derived from SEER. The authors do not comment what years of diagnosis of the information was extracted from within SEER.

The years of the study (2003-2004) by Lund et al (7) are added to the text under methods as follows:
Incidence estimates for Sulaimaniyah and Egypt were compared with US SEER data from Atlanta, Georgia for women diagnosed with breast cancer in 2003-2004 as tabulated by Lund et al. [7]. The source of the population of white and African American women at risk by age for the two county Atlanta area was the 2000 US Census.

7. The authors have a unique dataset of information on ER/PR and HER2. Taking that information it would be important to look at the proportions of triple negative, hormone receptor positive HER2 positive and hormone receptor negative HER2 positive subgroups of the whole cohort and compare that with what's reported in the literature.

A comparison of triple subtypes is provided in Table 5. Sulaimaniyah patients are compared with white and African Americans of the Atlanta area as reported by Lund et al [7]. Only the proportion of triple negative tumors was available for Egypt.

8. It is important that the authors describe the drawbacks of this study highlighting the fact that the results are biased by which patients IHC was requested for.

The following is added at the end of the body of the manuscript:

**Limitations**
The study is observational and descriptive, and results are biased by an absence of standards for requesting IHC.