Author's response to reviews

Title: Obesity is a Significant Risk Factor for Breast Cancer in Arab Women.

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Author's response to reviews: see over
Reviewer’s (1) report

Title: Obesity is a Significant Risk Factor for Breast Cancer in Arab Women.

Version: 1
Date: 4 July 2014
Reviewer: Marvella Ford

Reviewer's report:
Manuscript Title: Obesity Is a Significant Risk Factor for Breast Cancer in Arab Women

Major Compulsory Revisions

1. The research presented in this manuscript is significant. It is the first case-control study of breast cancer among women in the kingdom of Saudi Arabia (KSA). Despite the significant focus of the study, several areas in which the manuscript could be strengthened are highlighted below.

   We would like to thank the reviewer Dr. Ford for acknowledging the significance of this study. We have addressed below the issues raised by the referee and indicated the corresponding changes we have made in the manuscript point-by point.

2. The Abstract does not describe the sample with sufficient detail. The age, education, marital status, and income of the participants are not described. Among the 534 cases, the percentage of women in each breast cancer stage is not described. The geographic regions from which the sample was drawn, and the presence of any ethnic sub-groups, are not described.

   Due to the restriction on the number of words in the abstract we could not put many details of the subjects. However, we have added the following into the results section of the abstract:

   A total of 1172 women were eligible for this study, of which 281 (24.0%) were aged ≤ 35 years, 22.9% illiterate, 43.6% employed, 89.5% married, and 38.1% were obese. Grade III tumors constituted 38.4% of cases. Tumor stage I was 7.5%; II, 50.7%; II, 30.9%; IV, 11.1%.
Regarding the geographic regions from which the sample was drawn, it has been stated in the methods:

*KFSH&RC is a tertiary care facility and serves as the main referring center for the whole Kingdom of Saudi Arabia (KSA). Therefore, it is conceivable that the cancer pattern seen at KFSH&RC is a reflection to that seen in the whole country.*

3. In the Background section on page 3, information pertaining to the incidence and prevalence rates of breast cancer among women in the KSA is not presented. The authors state that women in the KSA tend to be diagnosed with breast cancer at younger ages than women in other parts of the world. However, data related to stage at age of diagnosis are not presented.

In response to the reviewer comments, we have added Figure 1 that shows the mean age at diagnosis across the stage left/right categories. The following text was inserted in results section page-6, histological features of breast cancer cases:

“Figure 1 presents the distribution of age at diagnosis of breast cancer patients according to different classes of tumor stage left/right. The results show early mean age of diagnosis with advanced stage.”

4. In Table 1, the total sample size is presented as 534. However, the number of pre-menopause cases (n=264) plus the number of post-menopause cases (n=267) that are shown in Table 1 do not add up to 534. If some cases are missing menopause status data, this should be indicated with a footnote to the table. Data on breast cancer grade also seem to be missing, as the totals for Grades I-III do not add up to 534. Data on Her_2 seem to be missing as well.

Due to missing menopause status the sum of pre- & post- menopause was smaller than the total sample by two. We have added the following footnote to the Table 1:
“Missing a pre-menopausal patient”

5. The authors’ initial analyses are interesting. However, it would be helpful if the manuscript could include a conceptual framework that would help to explain/describe the associations among the major variables of interest. For example, what is the association between education level and marital status? What is the association between BMI and education, or between BMI and income? Is marital status linked with prevalence of other types of comorbidities? Providing more information about these associations could help to explain findings such as the fact that a higher proportion of the cases vs. controls were married.

As suggested by the reviewer two more figures were added to the manuscript. Figure 2 shows the nature of relationships between BMI and each of education levels, employment, marital status, her_2, grade, ER, and PR. Figure 3 displays the associations between education and each of marital status and employment.

The following text has been added to Breast cancer sociodemographic risk factors subsection in page 6:

“Figure 2 shows significant associations between BMI and each of education, employment status and marital status. Illiterate, unemployed and married women had significantly higher mean BMI (P<0.0001). Education levels showed high association with marital status and employment in our population (P<0.0001). Among illiterate women, only 2.8% were working and 96.5% were married; whereas among highly educated women, 87.3% were employed and 80.4% were married (Figure 3).”

6. Also, as obesity is the major focus of the paper, based on the title, the relationship between obesity and other key variables could be explored further. The development of interventions to improve breast cancer outcomes could be enhanced if more were known about how these variables interact with each other.
We thank the reviewer for this comment, as we have mentioned previously; Figure 2 has been added to the manuscript to describe the relationships of BMI across the socioeconomic and pathological parameters, and interesting associations have been obtained.
- Major Compulsory Revisions

1. What was the inclusion criteria for controls?
   Just ladies who visit primary health care center could not be the subjects to be recruited as control. Please specify the inclusion criteria and exclusion criteria for control.

   **The inclusion criteria for controls were:**
   - To be Saudi women,
   - Aged 18 years or older, and
   - Were free of breast cancer.

   **The exclusion criteria for controls were:**
   - Non-Saudi female,
   - Aged less than 18 years.

2. Authors described that frequency matching by age group is used to recruit controls. But a total number of cases versus controls are quite different. Proportion of cases and controls by age 35 above and less are different. Please describe more details actual recruit for controls.

   Thank you for bringing this important point to our attention. It was clear from the Table 2 the presence of discrepancy between cases and controls in terms of age. This study was not matched case-control. The following text inserted in the revised methods subsection:

   “The study cases were female patients with histological-confirmed primary breast cancer. We started interviewing patients, in the Oncology Department at King Faisal Specialist Hospital & Research Center (KFSH&RC) Riyadh. The controls were Saudi women aged 18 years or older, who visited the primary health care and were cancer free. Volunteers were enrolled in the study during the same calendar period as cases, from all Saudi provinces. Controls were randomly selected and approached while are waiting for their doctor appointment. Nearly 96% of women approached for the study chose to participate. KFSH&RC is a
tertiary care facility and serves as the main referring center for the whole Kingdom of Saudi Arabia (KSA). Therefore, it is conceivable that the cancer pattern seen at KFSH&RC is a reflection to that seen in the whole country. This study was approved by the Research Advisory Council (Institutional Review Board) of KFSH&R.”

3. Discrepancy of menopause status of cases and controls may be also caused by uncertain frequency match.  
   We believe that the discrepancy of menopause status of cases and controls is random and not caused by uncertain frequency match. However, the effect of age was controlled for at the analysis stage.

4. Please try to frequency match explicitly and then re-analyze them.

   Please see above

- Minor Essential Revisions

The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

   The manuscript has been proofread by native English speaker, and figures labels were included.
Reviewer's (3) report

Title: Obesity is a Significant Risk Factor for Breast Cancer in Arab Women.

Version: 1 Date: 20 August 2014

Reviewer: Chelsea Catsburg

Reviewer's report:

Major Compulsory Revisions

ABSTRACT

1. Methods – Indicate what controls were matched on. Indicate statistical analysis used – “e.g. (Unconditional?) logistic regression was used to obtain odds ratios …”

As suggested the methods was revised as follows:

“Unmatched case-control study was conducted in the kingdom of Saudi Arabia using 534 cases of histologically confirmed breast cancer and 638 controls. Controls were randomly selected from primary health care visits and were free of breast cancer. Unconditional logistic regression analysis was performed to estimate odds ratios (ORs) and to examine the predictive effect of each factor on risk for BC. All study participants were interviewed by trained interviewers at hospital (cases) or at primary health care centers (controls).”

2. Results - The text seems to indicate that marriage was not an independent risk factor for breast cancer after adjustment for confounding variables, therefore do not need to mention this in abstract.

This has been removed as per the reviewer’s suggestion.

METHODS

3. Please provide information on how controls were chosen, eligibility and exclusion criteria, same for cases. Also include information on participation rates, exclusion rates for cases and controls, and if there were any differences between those who declined to participate.

To address the reviewer’s comments, the methods subsection was revised as follows:

“The study cases were female patients with histological-confirmed primary breast cancer. We started interviewing patients, in the Oncology Department at King Faisal Specialist Hospital & Research Center (KFSH&RC) Riyadh. The controls were Saudi women aged 18 years or older, who visited the primary health care
and were cancer free. Volunteers were enrolled in the study during the same calendar period as cases, from all Saudi provinces. Controls were randomly selected and approached while are waiting for their doctor appointment. Nearly 96% of women approached for the study chose to participate. KFSH&RC is a tertiary care facility and serves as the main referring center for the whole Kingdom of Saudi Arabia (KSA). Therefore, it is conceivable that the cancer pattern seen at KFSH&RC is a reflection to that seen in the whole country. This survey was carried out between June 2007 and August 2012. This study was approved by the Research Advisory Council (Institutional Review Board) of KFSH&RC.”

4. Please include dates of recruitment period

This survey was carried out between June 2007 and August 2012.

5. How were cutoffs for categorical variables other than BMI chosen? Particularly age at menarche, age at menopause

Median age at menarche and median age at menopause were chosen as cutoffs values for categorical variables.

6. What variables were tested for confounding for the multivariate regression – please indicate detailed info on variables used, cutoffs, categorical/continuous etc.

The text below has been included in the Data Analyses subsection:

“Multiple logistic regressions were fitted to adjust for age (≤ 35 years vs. > 35 years), BMI (lean, overweight, obese), marital status (single, ever married), menopause status (pre-menopause, post-menopause), HRT use (yes/no), age at menarche (< 13 years vs. ≥ 13 years), breastfeeding (yes/no), and education levels (illiterate, primary/high school, higher education). Median age at menarche and median age at menopause were chosen as cutoffs values for categorical.”

RESULTS

7. Unclear in Table 3 why some results are shown stratified by menopausal status and some are not, please show results for all.

Actually it’s Table 4 not Table 3. As shown in the title, Table 4 represents only factors independently associated with breast cancer in Saudi women, stratified by menopause status. Therefore, we did not include those variables that were not significantly associated with breast cancer.
8. Three groups of BMI (lean/overweight/obese) in Table 3 would be more informative than the two groups shown.

   BMI classes were introduced and discussed earlier, our focus here is rather on the healthy weight versus non-healthy weight (overweight/obese). Therefore, the message, being overweight or obese indicating 2.3 fold increases in breast cancer risk.

9. It seems that employment (ever/never worked) and education may be highly correlated? If so, this would be reason to not include these two variables in the same model as would skew estimates for either, what is the correlation between these two variables?

   Yes the education was significantly associated with occupation (P<0.0001), Figure 3. Therefore, occupation has been removed from the model.

10. Footnote of Table 3 needs to be much more detailed, provide cutoffs for variables adjusted for and whether they are continuous, categorical etc.

   To reflect reviewer suggestion, the footnote of Table 4 has been changed to:

   “Model adjusted for age (≤ 35 years vs. > 35 years), BMI (lean, overweight/obese), marital status (single, ever-married), menopause status (pre-menopause, post-menopause), HRT use (yes/no), age at menarche (< 13 years vs. ≥ 13 years), breastfeeding (yes/no), and education levels (illiterate, primary/high school, higher education). All these variables were categorical.”

**DISCUSSION**

11. Do the authors have any reason to explain why earlier age at menarche would be a protective factor in this population?

   No, we do not have any explanation for this phenomenon. Similar results were obtained in the Chinese population as mentioned in the discussion, with no explanation as well. Therefore, we have added in the discussion the following:

   “This may be due to genetic and/or environmental factors”

12. Please describe limitations of this study – e.g. controls were not recruited at the same centre as controls, controls were selected from across the country, where as cases were from one institution only etc. and any other biases that may arise
from the way controls and cases were recruited (once more information is provided on how this was achieved) – BMI was collected at one time point only, may have changed etc.

A paragraph describing these limitations was added in the discussion:

“Our study had limitations commonly seen in this type of studies. While cases were only from one hospital, which is a tertiary care facility that serves as the main referring center for the whole Kingdom of Saudi Arabia, cases were collected from different regions of the country. This may constitute a bias as to the origin of the patients/controls. Furthermore, controls were all recruited from hospitals. Our sample size of 534 cases and 638 controls may seem rather small for such studies. Another limitation is that BMI, which may change with time, was measured only once for both patients and controls.”

Minor Essential Revisions
13. Sentence on page 5 “Cross-tabulated and differences in participant’s characteristics…” is not clear and needs to be rewritten.

The sentence has been revised as follow:

"Tumor characteristics were cross-tabulated between pre-menopause and post-menopause patients and differences were assessed using $\chi^2$ test."

14. Page 6, sentence relating to family history beginning “Interestingly, higher proportion of cases…” – interestingly is not the correct word, as this is what we would expect to see, maybe try “As expected, higher proportion of cases…”

As suggested the word “Interestingly” was replaced by “As expected”.

Discretionary Revisions
15. Do the authors have any information on parity? If so, may want to include and consider adjusting for.

No, we do not have any information on parity.

16. Authors have great information on ER/PR/HER status and grade/stage of tumors – may be potential to analyze associations between different subgroups, i.e. is BMI more a risk factor for ER+ tumors etc.

As per the suggestion, we have shown the association between BMI and reproductive and socioeconomic risk factors in Figure 2.
17. Written English is good overall, but does have minor grammatical errors throughout, e.g., missing 'a' or 'the' - would benefit from editing.

Native speaker has proofread the manuscript and all grammatical errors were fixed.