Author's response to reviews

Title: Mortality risk of black women and white women with invasive breast cancer by hormone receptors, HER2, and p53 status

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Author's response to reviews:

The Biomed Central Editorial Team:

Object: MS: 1688323170831939 - Mortality risk of black women and white women with invasive breast cancer by hormone receptors, HER2, and p53 status

Thank you for considering our manuscript for publication in BMC Cancer. We greatly appreciate the two reviewers’ comments. We have modified the manuscript according to the reviewers’ comments. Below, we provide a detailed response to each of the comments from the two reviewers.

Reviewer #1 (Dr. Vincent Caggiano)

Major Revisions
1) In the Abstract, under Results, the authors state "this black-white difference among older women was confined to those with Luminal A/p53- tumors (breast cancer-specific HR 1.89; 95% CI, 0.93 to 3.86; all-cause HR 2.22; 95% CI, 1.30 to 3.79)". While the all-cause HR is statistically significant, the breast cancer-specific HR is not, and should so state.

We have addressed this comment on page 3, last paragraph.

2) Under Results, Black-white differences in breast cancer-specific mortality, 2nd
paragraph, it is stated “the observed black-white differences in breast
cancer-specific mortality were attenuated after additionally controlling for tumor
stage”. This is a gentle way of saying that statistical significance disappeared. It
does not address the fact that blacks are more likely than whites to present with
advanced stage of disease (Ref. Li CI et al. Arch Intern Med 2003; 163: 49-56),
therefore the loss of statistical significance when controlling for stage.

• We have addressed this comment on page 13 as follows. “Since black women
are more likely than white women to be diagnosed with advanced stages of
breast cancer, which is associated with a higher risk of mortality [51], we
additionally controlled for tumor stage in our analysis. Then, the observed
black-white differences in breast cancer-specific mortality were attenuated.”

*Citation 51: Li CI et al. Arch Intern Med 2003; 163: 49-56.

3) Under Discussion, 4th paragraph (limitations). There is no discussion why
all-cause mortality is different from breast cancer-specific mortality. No mention
of comorbidities (Ref: Tammemagi CM et al. JAMA 2005; 294: 1765-1771). Also
there is no discussion why p53- (lack of overexpression) should have a negative
effect on mortality or survival when p53 mutations (as correlated with p53
overexpression in tumor tissue) are associated with resistance to chemotherapy,
radiation therapy, and poor prognosis, as stated in Background, 4th paragraph.

• We have added a paragraph to address this comment on page 16-17.

Minor revisions

1) Background, 3rd paragraph. It is stated that TN breast tumors account for
10-30% of all invasive breast cancer (6, 15): Most studies show that TN breast
cancer is in the range between 10-25% of the population depending upon the
demographics of the population (Ref Bauer KR Cancer 2007; 109:1721-1728;
Perou CM The Oncologist 2011;16(suppl 1):61-70). The 30% is from the LA
County component of the Women's CARE Study referred to reference 6 of the
manuscript. these were women for whom mammograms were obtained, and
once again this may not truly reflect the overall population.

• On page 6, “10-30%” has been changed into “10-25%”. Original Reference #6
has been replaced by the two references that the reviewer suggested.

2) Methods, 1st paragraph. Why were LA and Detroit selected for study, and why
were Philadelphia, Atlanta, and Seattle excluded. Was this due to funding
constraints? Would results have been different if all sites were included, or if
Atlanta, or Philadelphis, or Seattle were chosen instead of Detroit? Or instead of LA? We are left to decide if this subset analysis is valid.

• We have provided the following information:
On page 7: “Here, we determine the extent to which black-white differences in breast cancer-specific and all-cause mortality differ for TN, luminal A, luminal B, and ER-/PR-/HER+ breast cancers in a substudy conducted at two participating study sites where tumor tissue was collected.”
On page 8: “These two study sites were selected to collect tumor tissue samples based on representative case participants in the Women’s CARE Study and the ability to obtain tumor tissue samples.”

3) Methods, 1st paragraph, when discussing race. According to reference 37, Table 2, #4: white or black race (including Hispanic ethnicity). No mention at all as to if and how this categorization may affect results.

• We provided the information on page 8, first paragraph: “US-born black women and white women including those of Hispanic ethnicity”.

• We have also provided detailed information on page 11 as follows: “Since 9 black women and 73 white women reported Hispanic ethnicity, we repeated all the analyses after excluding these 82 women. Our results remained similar. Therefore, we present the results based on the analyses of all participants.”

Reviewer #2: (Dr. Keith Dookeran)

Major Compulsory Revisions:
1. The question posed by the authors is not well defined. First, in the abstract background section, the authors state that “Black women have a higher mortality risk after breast cancer diagnosis than white women and the magnitude of this disparity has been increasing in the United States.” The latter part of this statement is not clearly supported by current literature; reference #2 by Jatoi et al. reports that ‘after 1994, calendar period mortality declined for both races’ (http://jco.ascopubs.org/content/23/31/7836.short), and CDC web site data also illustrates near parallel trends for black and white breast cancer mortality between 1999-2008 (http://www.cdc.gov/cancer/breast/statistics/race.htm). This also applies to paragraph one of the introduction section and both sections require revision.

Second, also in the abstract background section, the authors state that “whether this racial disparity varies by breast cancer subtype, defined by ER, PR, HER2,
and p53 protein status, is unknown”; however, reference #22 by O’Brien et al. is a seminal population based study on race, subtype and prognosis, and what appears to be specifically unclear (and under study here) is whether the inclusion of an additional tumor marker, i.e. p53, has any influence on the race-based prognostic ability of subtype. This should be made clear.

- We have addressed the first and second comments from the reviewer on page 3 (abstract) and page 5 (introduction).
- On page 5 (introduction), we have replaced our original reference # 1 with the one suggested by the reviewer (http://www.cdc.gov/cancer/breast/statistics/race.htm).

Third, hence, it appears that the main contribution of this study is the finding that luminal A/p53- tumors influenced mortality in older black women (albeit marginally); however this point is not highlighted in either the abstract or body conclusion sections, and weakens the overall strength and presentation of the article. The authors should also make a better attempt to explain the implications of this finding; and it is not clear what proportion of women fall into this subgroup? In addition, in the discussion, although the authors admit that ‘treatment information was not available’ they should attempt to explain the possible contribution of inadequacy/heterogeneity of hormonal therapy between races. Hence, additional major revisions are required for the above issues.

- We have re-written our conclusion on page 4 (abstract) and page 19 (discussion).
- The proportion of women who fall into each subgroup defined by ER/PR/HER2/P53 has been added in Table 1.
- We have discussed the possible contribution of inadequacy/heterogeneity of therapy between races on page 18.

2. Methods questions/issues that need to be addressed. Why were only 2 of the 5 original sites used for this study? Was this a planned analysis of the larger CARE study or simply an opportunity to use an assembled dataset? What are the specific sampling details? Why is there no information on SES, comorbid disease and basic treatment, as these are important factors related to mortality? Why are baseline estimates for overall mortality by race omitted (i.e. all black vs. white women, regardless of subtype)? The authors should also provide the specific IRB approved protocol numbers.

- We have addressed why only 2 of the 5 original sites were included for this
study as follows:

On page 7: “Here, we determine the extent to which black-white differences in breast cancer-specific and all-cause mortality differ for TN, luminal A, luminal B, and ER-/PR-/HER+ breast cancers in a substudy conducted at two participating study sites where tumor tissue was collected.”

On page 8: “These two study sites were selected to collect tumor tissue samples based on representative case participants in the Women’s CARE Study and the ability to obtain tumor tissue samples.”

- We agree with the reviewer that comorbid diseases and basic treatment are important factors for mortality risk. We have discussed about comorbid diseases on page 17 and discussed about the lack of treatment information on page 18.

- We have provided overall mortality risk (black vs. white women, regardless of subtype) for all, younger, and older women in Table 2 and Table 3.

- We have provided the specific IRB approved protocol numbers on page 8.

3. The writing is not acceptable in the current form. There are major issues in the abstract, introduction and discussion sections, as noted above. In addition, in paragraph 4 of the introduction section, the authors state “to date, no studies have addressed whether the overexpression status of p53 protein impacts the black-white disparities in mortality of TN or luminal A breast cancer”; however, this assertion is not correct. Dookeran et al. recently reported on race and the influence of p53 as a marker of prognosis in breast cancer, in the context of subtype, specifically TN status (http://www.ncbi.nlm.nih.gov/pubmed/22434242). Hence, the entire manuscript requires revision for clarity and accuracy.

- We have addressed the comment on page 7 as follows: “One epidemiologic study examined the effect of p53 status on all-cause morality for black women and white women, respectively, and found that having a p53+ tumor adversely affected prognosis among black women but not white women after controlling for multiple variables including the status of ER, PR and HER2 or the subtype of breast cancer such as TN breast cancer (yes versus no) in statistical models. No analyses were reported on whether the overexpression status of p53 protein impacted the black-white disparity in mortality of TN or luminal A breast cancer [7].” Citation #7 is Dr. Dookeran’s paper (http://www.ncbi.nlm.nih.gov/pubmed/22434242).

- On page 16: “Based on our knowledge, this is the first study to examine if p53 protein overexpression impacts the black-white difference in mortality risk following invasive breast cancer diagnosis after controlling for the status of ER, PR, and HER2.” has been changed into “Based on our knowledge, this is the first study to examine if the overexpression status of p53 protein impacts the black-white disparities in mortality of TN or luminal A breast cancer.”