Author's response to reviews

Title: Obesity and Male Breast Cancer: Provocative Parallels?

Authors:

Matthew P Humphries (M.Humphries@leeds.ac.uk)
V Craig Jordan (VCJordan@mdanderson.org)
Valerie Speirs (V.Speirs@leeds.ac.uk)

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Author's response to reviews: see over
Rebuttal response

Editorial board comments

Many thanks for your helpful comments on our article.

Editor’s report:

Point 1. Because the manuscript is discussing a hypothesis rather than reviewing known findings, it is our feeling that the manuscript would be better suited to our opinion article type (http://www.biomedcentral.com/bmcmed/authors/instructions/opinion) rather than a review. I have changed the article details in our system to reflect this; please ensure the article is formatted according to opinion article format when making your revisions.

Thank you for this consideration. We have now presented the article in the form of an opinion.

Point 2. Please use subheadings to organise the manuscript, so it is clear where it is discussing etiology of male breast cancer and where it is discussing treatment. We recommend that you follow referee 3’s advice on structuring the manuscript for improved clarity.

We have used subheadings as follows: Background, Increasing incidence of male breast cancer, Obesity, Obesity and cancer, Known risk factors for male breast cancer, Survival rates and treatment for male breast cancer, Summary.


Point 4. For balance, please include a paragraph on alternate hypotheses for the increasing trend in male breast cancer

Alternative explanation for the rise in male breast cancer is now presented in the summary section. (Page 7).

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Rebuttal response

Reviewer one - Ian Fentiman

Thank you for your comments.

Reviewer's report:

“This is a generally well-written and cogently argued paper. There is one notable exception, the use of the cliche “perfect storm”. The phrase was awarded the top prize by Lake Superior State University in their 2007 list of words that deserve to be banned for overuse. This could be omitted without altering the sense while maintaining the originality of the manuscript.”

We fully accept the comment and have removed the term perfect storm from page 5. The sentence now reads.

“Thus, weight increase coupled with the fact that declining levels of hormones in the ageing male could provide a hormone environment which helps promote the genesis of MBC in obese men.”

Page 5.
**Rebuttal response**

**Reviewer two -** David B. Thomas

Thank you for your helpful comments which we believe have improved our article.

Reviewer's report:

**Point 1.** "This paper is not well organized. There are a number of redundancies in the text. Examples of these are provided below in a consideration of individual paragraphs."

We appreciate your comment. We have addressed this by introducing the following subheadings: Background, Increasing incidence of male breast cancer, Obesity, Obesity and cancer, Known risk factors for male breast cancer, Survival rates and treatment for male breast cancer, Summary.

**Point 2.** "It is unclear how the paragraphs on treatment and survival relate to the evidence for obesity as a causal agent in MBC. Either these paragraphs should be omitted, or the text revised to clearly indicate the point relevant to etiology that the authors are trying to make."

As per point 1 clear section headings have been introduced, including a separate section on obesity (Pages 3). A revised section on Survival rates and treatment for male breast cancer is included added (Pages 5).

**Point 3.** "Introduction, para 1: The last sentence is not a complete sentence."

The sentence now reads “Data *was* obtained from PubMed using the search term “male breast cancer” in titles and abstract from 01/01/2014–31/12/2014 (search performed 22/12/2014).” (Page 2).

**Point 4.** "Review, para 1: What population was used in ref 14, and is it different than the SEER population used in ref 16? In the next sentence, it would be better to simply say that rates of breast cancer are higher in black than white men, but that they are lower in black than white women. The word “contradicts” isn’t quite right. What is the relevance for your consideration of etiology that breast cancers tend to be diagnosed at a more advanced stage in black men than white men?"

The data sources are the same and the sentence structure has been changed as follows: “We have confirmed this in a more recent interrogation of the SEER dataset (Figure 1)[17].” (Page 2).

The sentence with “contradicts” referred to by the reviewer has been modified to more clearly highlight the disparity in black MBC vs. black FBC. The sentence now reads “In terms of race, the rates of breast cancer are higher in black than white men while the reverse is true in FBC patients (Figure 2)”. (Page 2)

The relevance for consideration of the etiology in later stage diagnosis in black vs. white men is to offer an explanation for the finding that black MBC has worse overall survival. An additional sentence at the end of the paragraph has been added: “Such racial disparity may be associated with biological/genetic predispositions or socioeconomic factors such as access to health care [20, 16, 21]”. (Page 2).
Point 5. “Figures 1 and 2: These show, respectively, time trends in rates of breast cancer in men and women in the US. In the corresponding text, it should be noted that the increases over time (in whites—the rates for individual years in blacks are too unstable for meaningful interpretation of time trends) are similar for white men and women from 1975-2000. The leveling off of rates in women after 2000 is due, in part, to screening which would not affect male rates. Thus, whatever is causing the increase in rates is likely not sex-specific (e.g. it could be changes in diet, but not changes in child bearing practices).”

Additional text on page 2 has been added. The added text is as follows “It should be noted from Figure 2 that the incidence rates of FBC appear to plateau which may be attributed to introduction of breast screening programs in the female population [18].” (Page 2).

The following text has been removed “Interestingly this contradicts the demographic of race in FBC patients. (Figure 2). As well as a higher incidence rate MBC in black men has worse overall survival”.


Point 7. “Review, para 5: The argument that changes in obesity seem to mirror changes in MBC rates is important. Are the two time trends correlated? In how many different populations? Also, if the increase in MBC rates is due to improvement in diagnosis, then this would negate your hypothesis that it is due to obesity. What is the evidence that the trend is not due to changes in diagnosis?”

Comparative inspection of figures 1 and 4 suggest the two time lines are related. The following text on page 3 has been added “This is also reflected by comparing data in Figures 1 and 4, where respective increases in the incidence of MBC and male obesity show parallel trends.”

This comment overlaps a point made by reviewer three and is now mentioned in the summary section

Point 8. “Fig 4: What population does this figure refer to?”

Figure 4 refers to the global population. A detailed explanation of the data sources uses are found in the cited reference “Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2014;384(9945):766-81. doi:10.1016/S0140-6736(14)60460-8.” Additional information in the figure legend has been included for clarity. Previous sentence read “Figure 4. Increase in prevalence of obesity in males and females ≥20 years old from 1980–2013. Image adapted from [21]”. The text now reads ““Figure 4. Increase in the global prevalence of obesity in males and females ≥20 years old from 1980–2013. Image adapted from [23]” Additional text has been included on page 3 which reads “...in a comprehensive study of 1769 reports from 188 countries showed a rise...”.

Point 9. “Review, para 8: The first part of this paragraph deals with hormone levels in relation to obesity, and should be moved to a previous paragraph where this is also discussed. As it is, this
seems redundant. What do you mean by the “hormonal milieu can fluctuates annually”? Do you mean that there are downward trends in hormone levels in older men over time?”

This sentence on page 5 has been restructured. It now reads “Thus, weight increase coupled with the fact that declining levels of hormones in the ageing male could provide a hormone environment which helps promote the genesis of MBC in obese men”.

Point 10. Review, para 9: How does the observation that poor survival of women with breast cancer is related to obesity relate to your hypothesis that obesity is a causal agent in MBC? I don’t follow your reasoning.

Sorry for not being clear. The point we were trying to make here was that in obese patients the microenvironment may contribute to increased proliferation due to increased estrogen concentrations from additional aromatisation in adipose tissues in ER+ females. Upon reflection the paragraph has been removed to make the article clearer.

Point 11. Review, para 10: This paragraph on the Brinton study belongs above with the rest of the evidence that risk of MBC is associated with obesity.

This paragraph has been moved to come earlier in the text (page 5).

Point 12. Review, para 11 and 12: These two paragraphs deal with treatment. It is not clear how what is presented relates to the topic of obesity as a cause of breast cancer. I suggest that either this be made clear, or that these 2 paragraphs be omitted.

A new sub-section entitled Survival rates and treatment for male breast cancer is now included on page 5.
Rebuttal response

Reviewer three - Louise Brinton

Thanks you for your helpful comments on our article.

Reviewer’s report:

Point 1. “The premise of this article is that obesity may be the explanatory factor for recent increases in the incidence of male breast cancer. Although the article provides support for rising rates of both incidence and prevalence of obesity, there are some basic nuances that are not fully discussed. This includes the possibility that the rising incidence may merely reflect increased detection (an issue that is only peripherally discussed in the article) and that studies that have assessed the relation of obesity to male breast cancer risk have found it to be only modestly related to risk (about a 30% increased risk for obese men compared with non-obese men—a magnitude of risk that is quite similar to that observed for obesity and female breast cancers). The article brings up many analogies with female breast cancers, but does not discuss the extensive attention that has focused on purported reasons for observed increases in the incidence of female breast cancers, which are much more likely to result from changes in reproductive practices and use of exogenous hormones than from changing anthropometric measures. Thus, a cautious approach is recommended in how to interpret the changing incidence of male breast cancer (notably whether it is a true increase rather than one resulting from increased detection) and whether any changes could result from a risk factor that appears to only modestly affect risk. To this end, the article would benefit from attempts to address the attributable risk of male breast cancer due to obesity. The possibility of an ecologic fallacy being the explanation for both rising incidence rates (if true) and obesity prevalence also merits further attention in the article.”

We have restructured the article in line with your comments. Under the new section Obesity and cancer we mention changes in reproductive practices, breast feeding and HRT (page 3-4) and present alternative explanations for the rise in male breast cancer in the Summary section, alongside relevant references.

Point 2. In terms of the presentation of the material, it would make more sense if the authors discussed the observed relationship between obesity and male breast cancer before discussing how obesity might explain the rising incidence of male breast cancer. Further, the contention that the number (assume this should be percent) of white men considered overweight or obese (BMI > 25) is higher than that of black men would argue against obesity being an explanation for rising incidence rates given that rates among black men are higher than those of whites. The authors follow this statement by discussing that rates of extreme obesity (BMI > 40) are higher among black than white men, but again the issue of attributable risk bears further attention, given the low prevalence of such levels of obesity in the general population. Finally, in this same paragraph, the authors argue against detection being an explanation for increased incidence given that weight gain at or around the menopause is a strong risk factor for female breast cancer—logic which is difficult to follow.

Thank you for the comment. This was raised by reviewer two, additional subheadings and restructuring has now addressed the flow of the article.

Point 3. The authors indicate that risk factors for breast cancer include increased alcohol consumption and liver cirrhosis, but provide no references for such assertions. The issue of the
relationship of alcohol consumption to risk has recently been examined in a large pooling project, which failed to observe a relation with risk (Cook et al, Cancer Epidemiol Biomarkers Prev 2015;24:520). Further, few studies have examined the relation of cirrhosis to risk, with discrepant findings. The article makes no mention of gynecomastia, a recognized risk factor for male breast cancer, and a condition that is often associated with obesity.

The risk factors have been expanded, including gynecomastia MBC and the link with gynecomastia and obesity has been expanded substantially (Page 4).

Point 4. In selected places, there is more relevant or updated literature that should be cited to support the points being made. For instance, more recent data are available regarding the incidence of male breast cancer than the articles cited. In terms of the relation of obesity to female breast cancer survival, there are many more informative studies than the small study cited (reference 65).

Thank you for pointing this out. We have added additional references. The dates we have cited are from ACS and IARC. The GLOBOCAN database was accessed 4 months ago and any citations are less than a year old with the exception of the 2013 Ly D publication. We have combined the most up to date statistics from Europe, and the US to estimate the total global incidence. We are unaware of a publication with more recent incidence statistics that relates to MBC in the global population.


Point 5. The discussion of treatment for male breast cancer would benefit from a contextual perspective. No information is provided on survival rates for male breast cancer; particularly useful would be some elaboration as to whether obesity might lead to later detection, which would then lead to a poorer survival. At the moment, the discussion regarding the effects of obesity on prognosis are entirely speculative and not entirely relevant to the focus of the article. The authors may also wish to re-consider a different title for the article (“Obesity and male breast cancer—a deadly duo?”) given trends for earlier detection of male breast cancers and its relatively good survival when detected at early stages.

These are very helpful suggestions which have been incorporated into a new section: Survival rates and treatment for male breast cancer (Page 5).

We have now revised the title which is “Obesity and male breast cancer—Provocative parallels?”