Reviewer's report

Title: Association between changes in body fat and disease progression after breast cancer surgery is moderated by menopausal status

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Reviewer: Barbara Cochrane

Reviewer's report:

1. This manuscript reports on a study of increased body fat percentage following breast cancer surgery and disease progression. Strengths of the manuscript include the justification for the study (e.g., linkages made between body fat and higher levels of biomarkers associated with disease progression), the focus on change in body fat (rather than just body fat at diagnosis/study entry), adjustment of analyses for key clinical covariates, and the BIA measurement protocol. Weaknesses include confusing descriptions of eligibility criteria and the timing of data collection, inadequate a priori analyses with a high censoring rate and increased risk for type 2 error, limited analyses comparing BMI as a predictor of disease progression/mortality. More detailed comments about these and other considerations are identified below.

2. The descriptions of eligibility/sampling criteria and data collection timing are unclear at times. Specifically:

a. The abstract indicates that Stage 0-III breast cancer cases were included, but the text on page 7 (line 20) and page 9 (line 58) states that women with stage I-III breast cancer were included. Table 1 groups stage 0/I together, so it is not clear which inclusion criteria are correct (and that clarification cannot be found in the earlier publication cited (by Liu et al., 2010). Please clarify What were the numbers of pre-and post-menopausal women with stage 0 versus stage 1?

b. Were the therapies (chemo-, hormone, radio-) assessed only on study entry or also at other data collection points (i.e., was completion of these other therapies recorded or just the recommendation, order, or initiation)?

c. Women with unilateral (not bilateral) breast surgeries were included, but the extent of that unilateral surgery (e.g., lumpectomy, mastectomy, lymph node dissection) was not described or addressed as a covariate.

d. Page 7 (lines 52-57) indicates that nonrespondents were more likely to be older and not receiving chemo- or radio-therapy. Does that text mean ANY chemo- or radio-therapy or just none at the time of the 6-month assessment?
e. Page 8 (line 1) has a list of baseline characteristics that showed no difference between 6-month respondents and nonrespondents and concludes with the characteristics of distant metastasis or all-cause mortality. Presumably, these two characteristics were assessed at the final outcome assessment (7-8 years) - which should be clarified - but it's also unclear how this information was available on nonrespondents, particularly given that the text on page 15 indicates that outcomes were missing for some of the original study participants. See also #6.

3. The censoring rate is rather high and brings to question the adequacy of the sampling plan and timing of data collection. Was there any a priori power analysis done that took into consideration previous research on development of distal metastasis and mortality based on, for example, menopausal status and disease stage? Focusing sampling and subsequent response rates at follow-up on those women more likely to experience outcome events could have minimized possible type 2 errors.

4. Why weren't the analyses of disease progression also carried out with BMI as a predictor? The Conclusion on page 15 identifies the importance of measuring body fat and measuring for changes in body fat after breast cancer treatment, but such measurement (with BIA equipment) would be somewhat atypical in the clinical setting, and so comparative analyses with the more typical clinical measurement (BMI) would be important for making recommendations about clinical practice.

5. On page 5 (line 49), the text indicates that "this excess body fat rather than body weight defines obesity". However, this statement seems to overstate the claims and findings in the cited reference by Wang et al. (2010), which does identify limitations in the use of BMI for the diagnosis of obesity, but also indicates BMI might still be the best way to evaluate changes in body fat % over time and actually states that bioelectrical impedance (used in the current study) also has some limitations (i.e., overestimating body fat % in lean subjects and underestimating it in overweight and obese subjects) over dual x-ray absorptiometry (in contrast to the Thompson et al citation #30 used to support good agreement on page 8, line 36).

6. The last paragraph at the bottom of page 7 discusses details of missing data related to 6-month anthropometrics, but the 131 out of 200 participants included in this study's analysis also had to have complete 7-8 year outcome data (per lines 39-42). No information is provided on the number of participants who had incomplete final outcome data. The Discussion text at the top of page 15 indicates that 3.5-5% of outcome data were missing due to loss to follow-up, but that
information should be in the methods or results sections. In addition, the denominator for that percentage is unclear (e.g., was it the original 200, those who had 6-month data, or just those with missing outcome data who were specifically lost to follow-up).

7. Page 8 (line 17) indicates height and weight were measured with an "automatic" height and weight scale. Do you mean a digital scale (and was height also measured "automatically" or using a stadiometer attached to a digital scale)? What was the manufacturer's name (only the model number and city are identified)?

8. Although details about the BIA measurement procedure are provided on pages 8 and 9, information about the actual measures of body fat and body fat percentage is not identified. One actually has to look at Table 2 to discern that body fat is measured in kg, but I could not find a description of the denominator for body fat percentage (i.e., how the percentage was calculated) in-text or in Table 2.

9. The Results text at the top of page 13 identifies associations between ER-positive and PR-positive expression and disease metastasis in premenopausal women, but this information is not addressed in-text for postmenopausal women and probably should be, particularly given the Discussion text at the bottom of page 13 and top of page 14 regarding estrogen concentrations and menopausal status.

10. The findings at the top of page 13 seem to indicate that in postmenopausal women, changes in body fat and body fat percentage significantly predicted distal metastasis - based on p-values. However, I think it is important to note that the confidence intervals for these Hazard Ratios include 1 for both body fat predictors, such that some review/caution about these results is warranted.

11. In the interests of having tables that somewhat "stand alone," it would be helpful if the tables had more descriptive titles (e.g., identifying participants as women who had surgery for breast cancer).

12. In Table 1, I think it would be important to indicate which characteristics were recorded at study entry, at 6 months, and for final outcomes. In addition, the negative t-statistic for age is
confusing (particularly since the data show age actually is *increased* in postmenopausal women - which is to be expected). I would recommend that the t-statistic be reported as an absolute value.

13. In Table 4, the Model 1 data regarding death outcomes are not included. The Table footnotes provide no explanation for excluding this information.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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