Author’s response to reviews

Title: Body mass index and participation in organized mammographic screening: a prospective cohort study

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Version: 2 Date: 19 March 2014

Author’s response to reviews: see over
March 18, 2014

Dear Editor,

We were encouraged by Breast Cancer Research to submit enclosed manuscript for consideration in BMC Cancer. We have addressed point-by-point all comments in reviewers’ reports, to further improve our manuscript for publication in BMC Cancer. We hope that you will find the comments addressed to your satisfaction, and our article acceptable for publication.

We present results from a study on BMI as predictor for participation in organized mammographic screening, accounting for effect modification by menopausal status, hormone replacement therapy, morbidities, and previous screening participation, adding novel information to current evidence on the field. Furthermore, we address this hypothesis in a prospective cohort design, which is first study to our knowledge, in contrast to available mainly US cross-sectional studies.

In our study, we find that BMI is an important predictor for participation in mammographic screening. Underweight and obese women had a significantly higher risk of abstaining from mammographic screening. We furthermore found that obese women with diabetes or previous screening participation had enhanced risk of nonparticipation in mammographic screening, whereas underweight women abstained from mammographic screening altogether.

We hope that you will find our manuscript relevant for publication, as we address an important topic within mammographic screening to further understand determinants for participation among invited women. Copenhagen has a high quality mammographic screening program with universal access, free of charge, however still, a high proportion of invited women do not attend mammographic screening. Socioeconomic determinants for mammographic screening have shown U-shaped associations in Denmark, with both women of low and high socioeconomic classes abstaining from screening. However, a personal characteristic such as BMI have has before been explored as a determinant for mammographic screening in Denmark. With increasing obesity and diabetes, both associated with higher breast cancer risk, we find the results of our study highly relevant for targeting the efforts to increase participation in mammographic screening.

Yours sincerely,

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Point-by-point response to Reviewers’ reports appointed by the Journal of Breast Cancer Research
Title: Body mass index and participation in organized mammographic screening: a prospective cohort study.
Version: 1 Date: 19 March 2014

Reviewer #1:
Abstract
1. **Malignant disease = cancer?**
   **Answer:** We have changed malignant disease to cancer.
2. **Age 50-69 or 50-64 as described in Methods?**
   **Answer:** Women were 50-64 years at inclusion defined by entry to the Danish Diet, Cancer, and Health Cohort. Women were 50-69 years at time of invitation to mammographic screening. This is now made consistent throughout the manuscript.
3. **Please include the fact that the screening program is population based.**
   **Answer:** We have added the fact that the screening program is population based in the Abstract line 31.
4. **Was BMI from 1993-97 used as a proxy for BMI when a woman was invited in 2008 – a max of 15 years later?**
   **Answer:** We used the Diet, Cancer, and Health Cohort baseline information form 1993-97, since women’s height and weight were measured objectively at this time, and there were no later assessments of height and weight available in this cohort. Average time between measured BMI and screening participation was 1.3 (SD 1.5) years. We present available data, ensuring temporality of exposure preceding outcome. Women by far gained weight in our cohort, when we estimated self-reported weight change over the life course at age 20 to 50, for which we have self-reported data, majority 83% reported a weight gain, and only 6% and 11% reported either no change in their weight or a weight loss, respectively. We therefore find that our measure for BMI is robust, at best an underestimate of women’s weight later in life, since a weight loss in females of age 50-69 seems very unlikely, of women’s BMI as predictor for participation in mammographic screening. If BMC Cancer decides, we can provide the numbers for self-reported weight change from age 20 to 50 in the manuscript.
5. **Please consider the last sentence of the Conclusion to be deleted.**
   **Answer:** We have omitted the sentence “Non-participation in obese women might possibly be explained by diabetes.” in the last sentence of Conclusion in the Abstract as suggested by the reviewer. We have instead rephrased the sentence, now saying in line 48: “Effect of BMI on mammographic screening participation was not significantly modified by HT, previous screening participation, or morbidities.”.

Introduction:
6. **The first and last paragraphs are fine. The two paragraphs in between are dealing with topics that are not discussed further, e.g. body perception.**
Answer: We find that it is important in the introduction to give an overall overview of the field and to put our hypothesis into context of evidence on the field. Body perception is discussed as a possible explanation for BMI as predictor for mammographic screening participation among Caucasian women, as discussed in the referenced reviews (ref 8-10). We have therefore kept the paragraphs unchanged, however, if further changes are suggested by the BMC Cancer, we will conduct the requested changes.

7. One major difference between the U.S and the Danish screening program is the organization and the inclusion of all women in Denmark – please promote this important difference. Further, the difference between self-reported BMI and self-assessed is important to underscore.

Answer: We have stated in the manuscript that the Danish mammographic screening program is population-based, universal, and free of charge in Abstract line 31, Introduction line 73-74, Methods line 101-102 Discussion line 186-193.

We have added a discussion about the difference between measured and self-reported BMI, with reference to Rothman (ref 11) in Introduction line 69-71, Discussion line 201-202. We hope that these changes address reviewer’s proposal.

8. Please include a clear rationale of the study.

Answer: We have in the Introduction, line 66-77, in our opinion clearly outlined the basis for our study. We state, that “Current evidence on the relationship between body mass index (BMI) and participation in mammographic screening comes predominantly from US, with high rates of opportunistic screening and profound socio-economic and health care access disparities that might confound the findings, since obesity is more prevalent among women with low socio-economic status [11]. Furthermore, existing studies mostly evaluated risk of non-participation based on self-reports of BMI and screening behavior, potentially masking effects due to recall and differential misclassification bias.

We studied the association between BMI and mammographic screening participation in a cohort of Danish women with measured BMI and objectively assessed screening participation and with equal and free access to organized non-profit mammographic screening. We furthermore assessed whether menopausal status, hormone replacement therapy (HT) use, previous screening participation, or morbid conditions including stroke, myocardial infarction (MI), hypertension, hypercholesterolemia, or diabetes confounded or modified this association.”.

We hope that the rationale for the study is clear for BMC Cancer.

9. Hormonal treatment (HT) is a more common term as hormonal replacement treatment (HRT)

Answer: We have changed HRT to HT throughout the manuscript.

10. Consider stratification into pre-and postmenopausal status in the aim of the study.

Answer: In the introduction line 74-75 we present stratified analysis by menopausal status as a clear aim of our study: “We furthermore assessed whether menopausal status, hormone replacement therapy (HT) use,
previous screening participation, or morbid conditions including stroke, myocardial infarction (MI), hypertension, hypercholesterolemia, or diabetes confounded or modified this association.”. We furthermore present the stratified analysis by menopausal status in Table 3 of the study, and discuss results for pre- and postmenopausal separately throughout the manuscript, and hope BMC Cancer will find the interaction with menopausal status clearly described.

Methods:

11. Pt 4 in the Abstract need to be clarified.
Answer: We have now included mean time between BMI measurement and mammographic screening in the Results, line 146-147, as suggested by the reviewer. Please also find our response to Reviewer #1, question 4.

12. What is the mean time from measurement of BMI to invitation to screening?
Answer: We have added this estimate to Results, line 146-147.

13. How is the screening history taken care of – e.g. a woman was invited in 1991, 1993…2001. She participated in 1995 and 2001. Is every response to invitation in screening included?
Answer: yes, we have included women’s whole screening history. At baseline (1993-97), we defined women as previously or never screened before baseline. If women were defined as previously screened at any time before baseline (1993-97) they were encoded (2) and if women were not screened before baseline but had a screening at any first time after baseline (1993-97) they were encoded firstly screened (1). Thus we had defined a binary variable for women’s screening history denoting previously screened (1) or firstly screened (2). We have now elaborated more on this variable to clearly define this variable as dichotomous indicator of women’s previous screening history at cohort baseline (1993-97). In in the Methods section line 117-120 we have added the sentence: “Furthermore, we defined dichotomous indicator of previous screening history at cohort baseline (1993-97), defining previously screened (1) as women who participated in mammographic screening at any time before cohort baseline (1993-97), and firstly screened (2) as women who participated in mammographic screening for their first time ever after cohort baseline (1993-97”).”.
We find that the definition of women’s mammographic screening history is stated very clearly in the manuscript now, and hope that the change in the manuscript is approvable for the BMC Cancer.

Results:

14. The last part of the Results is somewhat messy with lack of structure.
Answer: We have changed and made Results section little shorter, and hopefully more clear to read, but without taking any content or results out.

15. Consider presentation of results from the large number of analyzes-particularly when the confidence interval goes from 1.37-604.02. Also, consider use of decimals.
We have addressed our opinion regarding improvements of result section in #14, and will be awaiting response from the BMC Cancer, and are willing to improve the Results as further requested by BMC Cancer.

**Discussion:**

16. The Discussion should be rewritten in a tighter format without any repetitions. Discussions about different attitudes to BMI in the U.S and in Denmark, and the different health care systems should be included in the Discussion.

**Answer:** We have added more discussion about differences in health care between DK and USA, in Discussion, second paragraph, line 188-192. ‘In Denmark, health care is free to all citizens, and mammographic screening is recommended by health authorities, and offered free of charge, with a personal invitation, to all women in age 50-69. In contrast, in US, health care is largely privatized and access and cost of mammographic screening differs by health insurance package a woman has, and if has health insurance. Thus, access to mammographic screening is different in Denmark and USA.’

We do not have comparable data available on differences in body perception between Denmark and the U.S., but have added this discussion of perception of obesity difference in two countries in Discussion line 271-273, as suggested by reviewer: ‘Cultural differences in the perception of obesity may also have an impact on women’s body-perception and compliance with organized mammographic screening⁸⁹. Obesity rates are higher in USA than Denmark, and thus, perhaps general perception and acceptance of obesity, is higher in US, including health care system, which is likely more used to and prepared for dealing with obese persons.’

17. The last part of the conclusion should be deleted.

**Answer:** We have deleted these last sentence from the conclusion, as requested: “Postmenopausal underweight (≤18.5 kg/m²) and very obese (>35 kg/m²) women, and possibly women with diabetes, might benefit from more tailored information from health professionals to enhance participation rates in mammographic screening.”

**References**

18. The number of references should be reduced with careful rereading.

**Answer:** We have carefully included relevant references and found a number of cross-sectional studies on this topic, and we find it relevant to include all, to increase accessibility for coming readers. We have reduced number of references by deleting references, which are not crucial to background or discussion of the study results: ref 6 and 13.

19. Table 1 is very heavy. Consider deleting some information or split into two.

**Answer:** We thank reviewer for this comment, but we have, for transparency, presented descriptive data for all relevant outcome and confounder variables into Table 1. We have changed the table by presenting only
one category when presenting a binary variable to reduce table size, but chose to keep all information in the table. We hope that this reduction is sufficient.

20. Table 3: Small numbers in the obese groups – merging the three groups together?

**Answer:** We would prefer to keep the WHO classification as presented in our manuscript, as this was our original hypothesis and plan for analyses before results were made, and we would like to keep analyses according to a priori analyses plan. We have, however, done analyses as suggested by reviewer, to answer his comment but since effects of obesity on nonparticipation was strongest among most obese, we find that treating obese women with BMI above 30 would be a simplification of the data and our study hypothesis. However, if BMI Cancer would prefer data presented as one large group of obese, we are willing to proceed with such a presentation of results. In such a case, we would merge Obese class II and III into one group, since they present with same pattern of risk among both pre- and postmenopausal women, respectively. The results of an analysis of obese class II and III merged is shown in table 2, on cover letter page 7.
Table 2. Association of BMI with mammographic screening non-participation in the Diet, Cancer, and Health Cohort.

<table>
<thead>
<tr>
<th>BMI</th>
<th>BMI value</th>
<th>N (%)</th>
<th>Model 1&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Model 4&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>74 (1.4)</td>
<td>2.19 (1.26-3.82)</td>
<td>2.39 (1.37-4.18)</td>
<td>2.23 (1.27-3.95)</td>
<td>2.24 (1.26-3.96)</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5-24.9</td>
<td>2,381 (46.4)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>1,772 (34.5)</td>
<td>0.69 (0.56-0.85)</td>
<td>0.71 (0.58-0.87)</td>
<td>0.74 (0.60-0.92)</td>
<td>0.75 (0.61-0.93)</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.0-34.9</td>
<td>657 (12.8)</td>
<td>0.77 (0.57-1.02)</td>
<td>0.79 (0.59-1.06)</td>
<td>0.83 (0.62-1.12)</td>
<td>0.85 (0.63-1.15)</td>
</tr>
<tr>
<td>Obese class II-III</td>
<td>≥35.0</td>
<td>250 (4.9)</td>
<td>1.44 (1.01-2.06)</td>
<td>1.50 (1.05-2.15)</td>
<td>1.55 (1.07-2.25)</td>
<td>1.61 (1.10-2.35)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Model 1: Crude.  
<sup>2</sup>Model 2: Adjusted for age and birth cohort.  
<sup>3</sup>Model 3: Adjusted for age, birth cohort, education, menarche age, menopausal status, menopausal age, hormone replacement therapy use, oral contraceptives use, parity, age first childbirth, breastfeeding, smoking, alcohol, and sports.  
<sup>4</sup>Model 4: Adjusted for model 3+comorbidity.
Reviewer #2:

Major Comments

1. Additional details regarding selection of the study population and overlap between the Copenhagen mammographic screening register is needed. It is unclear if everyone in the DCH population was invited to participate in mammographic screening or not. Also, in the Methods sections the authors note that data from the screening register for 1991 through 2008 were used, but elsewhere in the Results section the time frame given is 2001-2008. Please explain this inconsistency.

Answer: In accordance with reviewer #1, we have added the mean time from participation in the Danish Diet, Cancer, and Health Cohort and invitation to mammographic screening. Furthermore in Methods, we describe the selection of our study population of women participating in the Danish Diet, Cancer, and Health study and in the Danish mammographic screening program, as two separate. We have furthermore in the Results, line 139-141, clearly stated how we reached the analytic cohort of our study: “Of 29,875 women in the DCH cohort, 7,507 were invited to Copenhagen mammographic screening between 2001 and 2008. Of these, 547 women were excluded as they were invited to screening before DCH baseline and 1,826 due to missing information on covariates”. We hope that BMC cancer will find the analytic study population clearly defined in our manuscript, but we can conduct further changes if requested by BMC Cancer.

We thank the reviewer for pointing out the inconsistency in the time intervals described in our manuscript. This has now been corrected in Results line 139-140: “Of 29,875 women in the DCH cohort, 7,507 were invited to Copenhagen mammographic screening between 1991 and 2008.”

2. Was there a time frame following the invitation to mammography during which a mammogram had to be obtained to count as participation? In other words, would a mammogram received 5 years after the invitation have been counted as “participation”? I would argue that it should not, and that a time frame of 1-2 years following the invitation should be used to determine participation.

Answer: We have addressed this question in our reply to reviewer #1, comment #4, and hope that this is addressed to satisfaction. We find that the design of the study with measured baseline BMI is the best available proxy for BMI as predictor for mammographic screening among invited women in our cohort of women aged 50-65 years at time of measured BMI. We explore women’s BMI at ages 50-64 years as predictor for later mammographic screening. Women’s weight in mature ages rarely change to a lower weight at later ages, and will most likely increase at higher ages, confirmed in our cohort. In our cohort, we found that majority of women had a weight gain from the age of 20 to 50, and it seems highly unlikely that women’s weight distribution would be a different pattern at older ages. Therefore, we find that the BMI measure available for current analysis is a very good and best available proxy for women’s body build at
time of mammographic screening in our cohort, as is further clarified in our response to Reviewer #1, question 4.

The mammographic screening database was built as one record per woman by a longitudinal individual sequence of mammographic screenings. For each invitation to mammographic screening it was recorded on an individual level if a woman attended or not for that specific invitation to mammographic screening as defined by the biennial invitation dates. Therefore participation was recorded specifically by biennial invitation, and a mix of invitation dates and actual participation pattern across biennial invitations is not likely in our mammographic screening register.

3. It would be preferable to employ a model building approach to arrive at a parasimonious logistic regression model rather than adjusting for a pre-determined set of covariates.

Answer: We agree with reviewer that an alternative method to ours of choosing a priori a set of confounder to adjust for, would be a selection of included covariates based on p-values. We have however, decided on this analytic strategy a priori by a protocol for PhD study, which this paper is part of, and which is also used in related articles in PhD and in our research group using mammographic screening participation and outcome data. Thus, for comparability of results and consistency in analytic strategy among related papers, we prefer to keep analyses as it is, and according to a priori decided protocol. To answer reviewer comment, however, we have done this analyses, and significant predictors based on a backward elimination strategy included birthyear (p=0.0006), screening age (p=0.0006), parity (p=0.03, smoking (p=0.003), and education (p=<0.001). Adjustment for only significant predictors would enhance the odds ratio estimates for the association of BMI with nonparticipation in mammographic screening in our cohort, as depicted below in Table 2 for the main association of BMI with mammographic screening participation. For clarity in context of cover letter, we present only results for the main association in fully adjusted Model 4 for significant predictors. These enhanced ORs may indicate that there is some confounding by others factors that we include in our main analyses, which is not accounted for in the analyses with only confounders which reach statistical significance.

Table 2. Association of BMI with mammographic screening non-participation in the Diet, Cancer, and Health Cohort.

<table>
<thead>
<tr>
<th>BMI</th>
<th>BMI value</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>74 (1.4)</td>
<td>2.29 (1.30-4.02)</td>
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</tr>
</tbody>
</table>
Obese class I 30.0-34.9 657 (12.8) 0.85 (0.63-1.14)
Obese class II 35.0-39.9 182 (3.6) 1.58 (1.03-2.43)
Obese class III >40.0 68 (1.3) 1.96 (1.05-3.67)

Adjusted for birthyear, screening age, education, parity, and smoking.

Thus, we would prefer to keep our initial modeling approach, since also previous studies use adjustment for breast cancer covariates in our study. However, if requested by BMC Cancer, we can provide an analysis adjusted for only significant predictors.

4. The number of observations dropped due to missing information is of great concern. The authors note that one-third of the eligible population was excluded due to missing information on covariates. In the Discussion they note that the excluded women did not substantially differ from the included, but these results need to be described in the Results section. Also, the analyses described in the Discussion section note comparisons on the primary exposure and outcome as well as many other covariates. So, it is not clear to me what data they were missing.

Answer: We believe that we have addressed the issue of missing value with a thorough discussion in the Discussion of a possible impact of missing values on selection of our study population. Only few women (n=15) in our cohort had missing values on objectively measured BMI. We find that, as also addressed by reviewer #1, Table 1 is clearly heavy enough since we have presented our data thoroughly. If we had also to add a column for missing values for all variables, we find that Table 1 would become far to heavy. It is clearly addressed in our manuscript, totals excluded due to missing values.

Fortunately, in this prospective cohort, the information on covariates, which have largest number of missing values, were collected at cohort baseline, before and independently from data on mammographic screening participation, which was collected later. Similarly, data on BMI were measured at baseline, also before assessment of mammographic screening participation. Thus, missing values were non-differential, and has most likely not biased our results.

As reviewer suggests, we have moved the following sentence from the Discussion to the Results, line 141-144: ‘Excluded 2,373 women did not differ from participating 5,134 women with respect to screening attendance, screening age, educational level, BMI, and smoking status, but were significantly more likely postmenopausal, parous, ever users of oral contraceptives and hormone replacement therapy, and heavy drinkers (data not shown).’

5. In the Abstract, the conclusion that non-participation in obese women might possibly be explained by diabetes”, is not appropriate based on the data. The interaction term was not statistically
significant \( (p=0.34) \), and the individual CIs are extremely wide. The Discussion of this result should be toned down and also removed from the Abstract.

**Answer:** We have omitted the sentence “Non-participation in obese women might possibly be explained by diabetes.” in the last sentence of Conclusion in the Abstract as suggested by the reviewer. We have instead, line 48-49, rephrased the sentence to: “Effect of BMI on mammographic screening participation was not significantly modified by HT, previous screening participation, or morbidities.”

We think that we throughout the manuscript clearly state “possibly” and that interaction with diabetes is hypothesis-generating, so we have toned this finding down in our manuscript, and will be awaiting the response from BMC Cancer, and we are willing to conduct further changes, if suggested by BMC Cancer.

6. **The Discussion, on page 12, describes longitudinal results regarding obese women participating in one screening but not in subsequent ones and surmising that this could be due to negative experience. The results do not appear to have been presented in the Results section.**

**Answer:** In Results section page 8, line 166-173, we present the results requested by the reviewer:

“Interaction with previous screening participation was not statistically significant \( (p=0.15) \), but indicated that non-participation in obese women was limited to those who previously participated in screening (overweight: 0.70; 0.54-0.91, obese class I: 1.01; 0.71-1.42, obese class II: 1.86; 1.14-3.04, and obese class III: 1.90; 0.91-3.96, all compared to normal weight), as compared to obese women participating in their first screening (overweight: 0.89; 0.60-1.30, obese class I: 0.47; 0.23-0.94, obese class II: 0.74; 0.24-2.34, and obese class III: 1.11; 0.29-4.35, all compared to normal weight). However, underweight women had high risk of non-participation in both, their first screening invitation (2.09; 0.61-7.17) and subsequent screening (2.30; 1.19-4.45).”

7. **In the discussion (page 12) the authors say that increased participation in screening would reduce breast cancer morbidity. As screening is secondary prevention, morbidity would actually be increased by increased screening utilization, since cases would be detected that may otherwise gone unnoticed. Breast cancer mortality would certainly be decreased through earlier detection, as the authors state.**

**Answer:** We have deleted the part about reduced morbidity in Discussion. We have rephrased the sentence:

“Increased participation rates in mammographic screening among obese women, and possibly diabetic women, may therefore be expected to result in reduced morbidity and mortality in this population.” to:

“Increased participation rates in mammographic screening among obese women, and possibly diabetic women, may therefore possibly result in reduced mortality in this population.” on page 14, line 290-292.
Furthermore in Discussion, we have altered the sentence from “The higher probability of non-participation among underweight and obese women, and possibly in particular obese women with diabetes, could implicate later diagnosis, more advanced clinical stages of disease at diagnosis, and poorer morbidity and mortality [3] to:” The higher probability of non-participation among underweight and obese women, and possibly in particular obese women with diabetes, could implicate later diagnosis, more advanced clinical stages of disease at diagnosis, and poorer mortality [3].” on page 15, line 308-310.

Minor comments

1. Were data on family history of breast cancer available? This can be an important predictor of mammography utilization

**Answer:** No, unfortunately we did not have available data on family history of breast cancer, as this was not assessed in DCH cohort. Most confounders did not have great impact on the main association studied, and therefore we would expect, that further adjustment for family history would probably not change the results or conclusions of our study.

2. Please clarify what is meant by the term “opportunistic screening”.

**Answer:** We find that this is a common term used within screening for women seeking mammography themselves outside an organized screening program. Opportunistic screening is very limited in Denmark.

3. The paragraph on page 11 beginning “Most of available evidence on association….” Seems repetitive and could be omitted.

**Answer:** We agree that it has been mentioned before that most evidence on BMI is self-reported. However in the context on page 13, line 258-263, this information is discussed against single study having prospective information on BMI, and therefore it seems relevantly discussed here. However, if BMC Cancer prefers that this sentence is omitted, we will conduct this change.