Author's response to reviews

Title: Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort.

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Author's response to reviews: see over
Dr. Louis A. Chodosh  
Editor-in-Chief, Breast Cancer Research  
http://breast-cancer-research.com

Re: MS. 8662431722064164

Dear Dr. Chodosh:

We are pleased to submit a revised version of our manuscript, "Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial Cohort." We modified our manuscript based on the helpful peer-reviewers’ comments. Individual responses to each comment and suggestion are below.

Comments from the Editor:

- **Ethics** - Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

  **Response:** This research meets all of the usual requirements for research on human subjects. During our pre-submission editing, we accidentally deleted the standard text about this, but we have since added that text to the manuscript.

- **Informed consent must also be documented. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.**

  **Response:** We documented the informed consent for all participants.

- **Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.**

  **Response:** We re-formatted the manuscript accordingly.

Comments from Reviewer #1:
- **Abstract/introduction sections**: these do not provide enough discussion of the relevance of the research question for risk prediction (e.g., the Gail model). This relevance is discussed in the discussion section but also belongs in the abstract and introduction.

Response: We revised the Abstract and Introduction to incorporate these issues early in the manuscript. We tried to incorporate tight text in order to maintain the current word count for the manuscript.

- **Methods section**: could benefit from some more detail regarding questionnaire content and detail as relevant to risk factors included in analysis. For example, was menopausal hormone therapy use ascertained with detail regarding formulation?

Response: We added details about these aspects of our questionnaire.

We note that the baseline questionnaire did not differentiate the two main menopausal hormone therapy (MHT) formulations. A follow-up questionnaire, administered approximately from 2004 to 2006, collected extensive details about MHT use. We are currently in the process of cleaning those data and hope to incorporate them into future PLCO study analyses.

- **Results section**: first three sentences of text could stand to have percentages included in addition to absolute numbers to provide a better sense of the prevalence of these characteristics in this population...these are available in the table.

Response: We added these percentages.

- **Citations in discussion section**: The sentence describing risk factors not addressed by the survey questionnaire cites one paper documenting associations with breast feeding but not alcohol consumption (could use Beral et al. meta-analysis here as well) or physical activity. These references should be added.

Response: We added references for both factors.

- **Uncontrolled confounders in this analysis**: It is mentioned in the methods section that the PLCO trial initially excluded women with bilateral oophorectomy or who were taking tamoxifen but later allowed these women to enroll. Were these women included in the present analysis? Were these characteristics adjusted for in the present regressions? The authors should clarify if these women were excluded and if not, the characteristics added to the tables as established risk factors for breast cancer and appropriate hazard ratios calculated. It is also mentioned in the discussion section that the study questionnaire did NOT include information regarding alcohol consumption, physical activity, or lactation history but there is no critical commentary provided to understand how the exclusion of these factors might have influenced the reported hazard ratios. Lastly, menopausal hormone therapy is not separated in these analyses by progestin-containing formulation, which is relevant because only estrogen/progestin (EP)-containing therapies are definitively associated with risk at this time. It is unclear from the methods whether grouping together all hormone therapies represents a analytic choice of the authors or not. If possible, the data should be reanalyzed to separate EP use from other forms of use.

Response: The changes in PLCO Trial eligibility criteria that allowed women with
oophorectomy and prior tamoxifen use to enroll were made in response to concerns that these key subgroups of women who (based on these exposures and other factors) were likely at elevated risk of hereditary breast or ovarian cancer (HBOC). These women comprise a small (although important) portion of the overall study population, so we included them in this analysis. Their analytic size makes it extremely unlikely that these exposures introduce any meaningful residual confounding. This is why we chose not to directly address this issue in the Discussion section.

The reviewer’s point about estrogen-alone vs. estrogen-plus-progestin is correct, and this factor seems statistically much more likely than tamoxifen or oophorectomy to present a threat to the validity of our results. We therefore expanded the discussion of this issue and directly address the potential for residual confounding due to misclassified exposure.

We are not comfortable, however, going as far as the reviewer does when entirely discounting the potential increased breast cancer risk among women taking estrogen-only formulations. The age range of our study population and the timing of the data collection (1993-2001) make it likely that many of these women took estrogen-only a) for long durations and b) before estrogen-only use was limited to women with hysterectomy. Both factors mean that estrogen-only use is likely to increase breast cancer risk (albeit not to the degree that estrogen-plus-progestin does) in our study population, just as it did in the Collaborative Group on Hormonal Factors in Breast Cancer analysis, which we cite in our paper.

- **Discussion of risk prediction for breast cancer as a single entity:** Breast cancer is increasingly recognized as a group of etiologically heterogeneous subtypes. I am unsure how the cutting edge risk prediction work is incorporating this essential observation into future models (for example, are new models being developed to predict estrogen-sensitive breast cancers only?). The discussion section does not address breast cancer etiologic heterogeneity and its implications for the study findings or relevance. It should do so.
  
  **Response:** The reviewer is entirely correct on this point. We and others are attempting to revise current risk prediction models to incorporate the clinic heterogeneity of breast cancers. We added a reference to a recent paper on this topic and added a brief phrase to our Discussion section.

- **Discussion of study population selection bias as explanation for findings:** Table 1 shows distributions of many demographic factors in this study population...do these distributions differ dramatically from the prior studies which detected different associations with the lifestyle risk factors that are likely associated with participation in this cohort? Like many contemporary research endeavors, it would be reasonable that this cohort over-represents white and college-educated women, who may be more likely to agree to participate in research. Wouldn’t a corresponding reduction in the distribution of several key risk factors also be an explanation for some of the attenuated hazard ratios observed? This possibility should be discussed as an alternative interpretation of the reasons for the changing risk factor profiles suggested by this study.
  
  **Response:** We also agree with the reviewer on the potential for selection bias based on the
“healthy-lifestyle” effect, whereby better-educated and better-off persons are more likely to participate in medical research, especially cancer screening studies. However, a close comparison of our Table 1 data to U.S. Census Bureau data shows minimal differences on two key metrics: race/ethnicity and education.

Our table 1 shows that 88.5% of our participants were white, 5.8% were African-American, and 3.9% were Asian/Pacific Islander. Based on year 2000 U.S. Census Bureau data, 85.3% of women ages 55-74 were white, 10.2% were African-American, and 3.3% were Asian/Pacific Islander.

Our table 1 shows that 53% of women between ages 55-74 reported receiving some formal education beyond the high school level. According to 2003 data from the U.S. Census Bureau, 46% of women between ages 55 and 74 reported receiving some formal education beyond the high school level.

We don’t consider these differences to be substantial enough to generate significant bias, but we did add a statement about this issue to the Discussion section.

Comments from Reviewer #2:
- **Case ascertainment:** need to clear description on case identification, follow up methods, and validity of ‘self-reported’ cases. And difference in the characteristics of breast cancer cases from trial and control arms.  
  **Response:** The current version of the manuscript describes these details on p. 7. The entire study population was contacted annually to ascertain study endpoints, which were adjudicated and reviewed according to the protocols published in the 2000 issue of *Controlled Clinical Trials* devoted to the PLCO study (e.g., the Prorok et al. reference in our paper).

  We currently state that breast cancer endpoints did not differ between the two study arms. Because this is an active clinical trial, we are prohibited from presenting any cancer endpoint data according to clinical trial arm until after the main clinical trial endpoints are published.

- **Results should be presented according to menopausal status.**  
  **Response:** All women in our study were post-menopausal at enrollment.

- **Discussion should include the potential limitation of the study (short follow up duration, self-reported cases, etc.) and be more concise and shortened.**  
  **Response:** The second-to-last paragraph in the discussion addresses these issues. We tried to balance the need to be concise (with which we certainly agree) with the need to address the additional issues raised by Reviewer #1. We would be happy to work with the Journal to further reduce the length of the paper if the Editor(s) felt that any of these areas could be omitted.

- **Rationale of the statistical methods used (Epicure versus Cox model)**  
  **Response:** We note that Epicure is a statistical package, not a modeling technique. But we
did use Poisson regression instead of Cox proportional hazards assumption because we preferred not to make the proportional hazards assumption for this analysis. Other breast cancer analyses using the PLCO data have used Cox regression, and our in-house work confirmed to us that—as is almost always the case—the proportional hazards and Poisson regressions generate nearly identical RR estimates in our data.

- **In Statistical analysis, the bottom of page 5, “(see Table 1)” should be “(see Table 2)”**
  
  **Response:** We corrected this mistake.

Please note that we also identified a few minor quantitative errors in the tables that were previously submitted; somehow, the updated study analytic numbers (e.g., a slightly larger number of breast cancers) made their way into some, but not all, of the manuscript and tables. We have corrected those numbers throughout and updated the tables—especially table 2—accordingly. None of the changes was substantial, nor did these corrections affect the interpretation of our results.

We welcome any additional questions you may have about our manuscript and we look forward to hearing from you in due course.

Respectfully,

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