Author's response to reviews

Title: Predicting Invasive Breast Cancer versus DCIS in Different Age Groups

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Author's response to reviews: see over
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Dafne Solera, Ph.D.
Executive Editor
BMC Cancer

RE: MS: 1396867473993617

Dear Dr. Solera:

My co-authors and I have addressed the comments from you and the reviewers. These comments are included in this letter in italics and our responses are in bold. We have detailed all the changes that we have made in the “tracked” version of our manuscript. These changes are extensive in order to address the reviewers’ comments.

My coauthors and I thank you for your careful consideration of our manuscript. We believe the review process has improved the article. Please send all correspondence concerning the manuscript to me at the address listed on the title page.

Sincerely,

Elizabeth Burnside, M.D., MPH, M.S.
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We thank the referees and the editor for their careful evaluation of our work. In the following, we respond to the referee’s comments point by point. The referee comments are provided in italics and our responses are in bold font.

Reviewer #1,
Reviewer’s report:
This is a very thorough and good study of the possibility to differentiate invasive cancer from DCIS based on mammographic variables. As written in the paper, their predictive models are limited by the unavoidable challenge of clinical data that is inherently imperfect. All of these shortcomings are though clearly stated and accounted for in their discussion.
Response: We thank the referee for the encouraging assessment.

Discretionary Revisions It would be very interesting to non American readers to know to what extend the information from this study can be used in non American settings.

Response:
We thank the reviewer for this insightful comment. The fact that we have used the BI-RADS descriptors as our mammographic features will enable non-American scientists and clinicians to replicate and/or utilize our results. The BI-RADS lexicon has been translated to many languages and should be available in most countries that provide mammography.

Reviewer #2, Steven Narod
Reviewer’s report:
The article by Ayvaci is a scholarly analysis of the ability to discriminate between DCIS and invasive cancer on the basis mammographic and clinical features.

The work is lengthy and the presentation is technical and will deter all but the most avid readers from looking at it and unfortunately the information, some of which is quite good, will be lost I fear nobody will get to the end.

Response: We thank the referee for this constructive comment. The referee has a valid concern related to the lengthy/technical presentation. To address this concern, we moved much of the statistical/technical discussion to Appendix 2. We have also removed a substantial amount of the statistical detail when the information is not critical for the broader audience.

Specific issues
The clinical justification for the study is over-wrought. Nobody is going to reassure a woman that a biopsy is not indicated just because of the high prior probability it is DCIS. Nobody is going to leave DCIS untreated outside of a clinical trial. Nobody is going to avoid treatment of a small non-palpable invasive breast cancer detected by mammography just because it has a high likelihood of being over-diagnosis. The clinical argument is an attempt to bolster the importance of the article. Why don’t the authors make specific recommendations of who not to biopsy. If they biopsy everybody what does this tell us. Which goes back to the beginning. If one is going to avoid a biopsy one wants the probability out of 35,871 diagnostic mammograms not out of 1475 cancers after the fact. There is no logic to making a clinical decision under the premise that we know it is cancer beforehand because we don’t. Nevertheless, the article of interest from a scientific point of view. The authors have missed this by and large.
Response: The referee brings up a very important point, which prompted us to revise the manuscript significantly. We now emphasize the main goals of our manuscript more succinctly and make clear that we are not proposing that our model is designed to be used in clinical practice and we now include text to this effect in the manuscript.

Our main goals are 1) to gain a better understanding of the characteristics of DCIS versus invasive cancer in women of different ages, which may someday be used for assessment of optimal management based on expected natural history of disease and 2) to discover unique features of DCIS in these same populations in order to inform prospective identification and advance the concept of personalized care.

“Nobody is going to reassure a woman that a biopsy is not indicated just because of the high prior probability it is DCIS”.

We agree. Our goal is not to create a model that will help women avoid biopsy at this time, however we were not sufficiently clear in our writing. We have clarified that our main goal is to observe differential performance and clinical/features based on age in hopes that these discoveries will provide a better understanding of natural history, clinical manifestations, and age-based differences of breast cancer.

If DCIS is a precursor of invasive cancer then why are they so different in character and not merely smaller? Could one predict which cases of DCIS might go on to invasive cancer using the same variable set? If yes then this would be wonderful.

Response: The referee has pointed to a very important research direction that is also emphasized in the NIH’s DCIS consensus conference proceedings in 2009. Such important work will likely need to look at each case of DCIS using richer and more granular data points. For example molecular subtypes, receptor status, and grade may help us understand future natural history of DCIS. However, at this time, we do not have these detailed pathologic variables or sufficient DCIS cases in our database. Thus we leave this crucially important area of research for future work.

Should be more informative in presenting statistics. P-values and AUC curves are interesting for statisticians but are pretty dry for clinicians.

Response: Following the referee’s recommendation, we removed the lengthy discussion of technical details when appropriate and move some of the statistical details to Appendix 2.

What I want to know is what is the prior probability of having dcis. 28% What is posterior probability. 5%, 20%, 50%, 90%. How will one interpret this? What decision will be made?

Response: Since we have reframed our goals, as recommended by this reviewer, to determine age based differences in the discrimination of invasive breast cancer and DCIS, we do not believe it appropriate to calculate post-test probabilities with our models. As discussed, these models are not meant to be used to support clinical decisions.

What is the justification for the three subgroups? Can there be a simple model with one subgroup?
Response: We thank the referee for this excellent comment. We now have provided an overall model (with no age-based grouping) in Appendix 1. The model suggests that age as a continuous or categorical variable is not a statistically significant predictor of DCIS vs. invasive cancer. This information is useful and included briefly in the Discussion. In the main manuscript we focus on the presentation of the models for the older vs. younger age groups, illustrating better performance in the older vs. younger age groups and unique predictive variable. However, importantly, we make sure to put our results in a more appropriate clinical context and logical presentation sequence.

I don’t understand how these are diagnosis if they are not palpable. How did they come to attention. Were any based on suspicions raised by an abnormal mammogram? Should really be two studies one for screening mammograms and one for palpable masses. This is far from clear.

Response:

We apologize for the reviewer’s confusion, likely arising from our inadequately clear description of our study design. Our study included consecutive image-guided breast biopsy patients diagnosed with invasive breast cancer or DCIS as our population of interest. We excluded women who did not have a previous diagnostic mammogram. These resultant patients, as in clinical practice, came from two distinct pools of women: the symptomatic population who went directly to diagnostic mammography and the asymptomatic population who experienced an abnormal screening mammogram. We have provided a schematic here as well as a similar figure in the manuscript to clarify our patient population. We thank the reviewer for pointing out our lack of clarity. We believe the additional figure improves the manuscript substantially.

In summary I think the article presents some interesting scientific facts but it is inappropriate to put this into a clinical context. The odds ratios are not helpful one wants to know the posterior probability of a diagnostic mammogram being DCIS or invasive cancer.

Response: We agree with the reviewer. We have substantially revised our manuscript to put our results in the appropriate context: determining whether clinical and mammographic features predictive of invasive breast cancer versus DCIS differ based on age. We have removed all of the allusions to clinical decision support and clinically relevant risk prediction. Though these are admirable goals for the far-future, we believe we are not ready to make claims beyond our main hypothesis, as the reviewer states.