Author's response to reviews

Title: A study of 0.5 Tesla dedicated magnetic resonance imaging for the detection of breast cancer in young, high risk women

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Author's response to reviews: see over
To the Editor,

Please find attached our second revision of our manuscript entitled “Prospective screening study of 0.5 Tesla dedicated magnetic resonance imaging for the detection of breast cancer in young, high risk women,” your manuscript ID 1136980822868118. In order to respond to Dr. Causer’s question concerning patient follow up we needed to submit an amendment to the University of Pittsburgh Institutional Review Board, as well as to retrieve records from remote storage. This contributed to a significant delay in our response to the reviewers, for which we apologize.

Response to reviewers:

Reviewer 1 (Dr. Kimler):

General comments I: The reviewer is correct in stating that we wish to make two “major” points with this study; one, determining the utility of 0.5 T MRI was the major goal of the radiologist (JHS), and the other, demonstrating the utility of combined or multiple quantitative risk assessment for definition of the high-risk screening population, was the goal of the geneticist (WSR). It is easy to understand why both should want to contribute to the study design, but it does present a problem for publication, since the study is of potential interest to more than one audience. Reviewer 1 now seems satisfied with the former point, but is uncomfortable with the latter. Specifically, he cites Kriege (2004) as an example of study enrollment by “quantitative risk assessment” that renders our example obsolete. There are two problems with this comparison. First, our study was, to our knowledge (and as corroborated by our recruitment dates) the first to use quantitative risk assessment as part of selection criteria, but we are not the first to publish. Second, the Kriege report still used only genetic risk (as determined by the Claus model, which is not as accurate as the BRCAPRO model, as discussed in the first paragraph of the Discussion) as the basis for its quantitative risk assessment, whereas we have taken pains to elucidate the fact that the Gail model incorporates other factors, particularly lifestyle factors potentially associated with hormonal effects, and previous breast pathologies suspicious enough to have required investigation. The BRCAPRO model overlaps, to a degree, the “family history” aspect of the Gail model, but instead of looking for any possible genetic factor it specifically targets the BRCA1 and BRCA2 genes, using our knowledge of the unusual features of the syndromes associated with mutations in these genes. Thus, we “improve” on the Gail model by using our more comprehensive knowledge of one source of breast cancer risk to more efficiently identify the carriers of these genes than the Gail model can accomplish alone. Since this is not as intuitive as we had thought based on the reviewers comments, we have added two sentences to this effect to the first paragraph of the Discussion.

General comments II: The second problem the reviewer is having with the genetic aspects of the study seem to be based on a misconception. The reviewer’s comments on “consecutive recruitment, etc.) seem to refer to a genetic screening of an incident population in order to recruit our test population. Although we did ascertain a very small number of patients through a general mammography clinic, the vast majority of our high
risk population were already part of our high risk clinic, and were offered a chance at a new type of tumor detection technology. By the term "consecutively recruited", we mean that all subjects that met eligibility criteria (e.g. age, risk level) were recruited in order of 1 to 30, none were left out for reasons that went unstated, and none declined enrollment, i.e. we are not extracting data from a larger study. Since the term "consecutively recruited" is objected to we will remove it, but it should be reiterated that the “screening” referred to in this paper is the MRI analysis for tumor detection, not population screening for high risk individuals. It is our contention that the selective application of the MRI screening to a previously identified high risk population produces a greater risk to benefit ratio than universal application under the present circumstances, and is also useful as a means of demonstrating utility and feasibility of the screening technology.

Minor essential revisions:

Page 4; para 2; last line: “surveillance” has been replaced with “screening” as requested.

Page 7; para 1; lines 5 and 10: the interval between mammography and MRI has been corrected to 3 months in agreement with the rest of the manuscript.

Page 17: the contribution of JHS to the study has been amended to “was responsible for the performance and interpretation” of the MRI

Figure 2B: the point of the paper is that there is no mammographically visible lesion! This has been reiterated in the figure legend.

Reviewer 2 (Dr. Causer)

Major compulsory revisions:

1a) The purpose of the study is stated well by the reviewer: Is screening high risk women with a low magnetic field strength (0.5T) unit feasible, i.e. can it offer a higher sensitivity over conventional surveillance? This purpose has been clarified by the addition of a sentence to this effect at the end of the background section of the abstract.

1b) As mentioned in response to Reviewer 1, we believe that our unique definition of a high risk population contributed to the success of the study, particularly in allowing for the detection of an occult lesion in such a small screening population. This contribution of the geneticist to the study design is, in fact, put into context in the discussion, and, as described in response to Reviewer 1, the uniqueness of our approach has now been further delineated in the discussion. This aspect of the study was downplayed in the original manuscript in favor of the radiological results, but has been brought into greater prominence in succeeding drafts, mostly in response to the concerns of Reviewer 1. Essentially, to sum up Reviewer 1’s arguments, the idea of “screening” a population of only 30 individuals is not credible unless this population is very different from those that have been previously described in the literature, hence the required expansion of our criteria for defining “high risk”. More than simply defining patient eligibility, our criteria
attempt to define a population where application of MRI screening in addition to mammography is feasible and beneficial under current circumstances. The reviewer is correct that it is the combined use of both models that is unique to our work, and besides the expanded discussion mentioned earlier we have added “combined” to the text in several places. As described in the Materials and Methods, however, we mean this to mean a risk of $\geq 3.5\%$ over the next 5 years by either model or both, not a risk of $\geq 3.5\%$ achieved through some combination of the risks calculated by the two models.

2a) The statement that ultrasound added no new information was added in response to Reviewer 1’s previous question of the role of ultrasound in the assessment of these patients. In attempting to clarify this point we found that it was moot; i.e. that ultrasound, which was applied to all BIRADS 3 patients, always confirmed the results of the MRI. Thus, other than patient 006, all showed no lesions and remained BIRADS 3, and the final category assessment was not affected by the ultrasound results. There were no BIRADS 3 lesions without corresponding ultrasound lesions. Although ultrasound results might have been a factor in this study worthy of discussion, in practice they were not, and we would prefer to make this one aspect of the study that we don’t belabor in the manuscript.

2b) Clinical follow up was done as requested for all 29 subjects in our study who did not have breast cancer detected as part of the study, and was available on all 29 subjects at least one year beyond the conduct of the study MRI, which is the standard length of follow up to exclude occult cancer (in most cases follow up was available for several years). No subjects developed breast carcinoma. Thus, the patients in BIRADS categories 2 and 3 likely did not harbor occult disease. This information has been added to the end of the Results section.

2c) The description has been amended to agree with the patients’ BIRADS category in all cases.

2d) The patient also had a benign lesion of the right breast that is discussed in the published case report (ref 41), but is not otherwise mentioned in this manuscript. We have added this reference to the figure caption, but, in the interest of keeping this manuscript focused on the screening study, we prefer not to mention in the text (it’s importance to the screening study is clearly subordinate to the discovery of invasive cancer in the other breast). In the description of the tumor, we have substituted “delineated” for “demarcated” and “mass” for “lesion”. The description of the enhancement parameters, which again paraphrases a more extensive description from the case report is meant to indicate that the mass accumulates contrast quickly, but that it also loses contrast quickly, characteristic of malignant masses. The figure legend has been simplified and can no longer be construed as contradictory.

3) We have included a reference to the updated BIRADS atlas, with the first edition of the MRI guidelines, in this discussion.

4) The comment about specificity has been removed.
Minor essential revisions:

1) The typo has been corrected.

2) “Radiographer” has been changed to “radiologist.”

3) The space has been removed from “subtraction.”

4) As discussed previously, the lesion in panel B is not germane to the point of this report and we do not want to confuse the reader by making it too prominent. The arrow in panel C is already referred to in the legend.

Thank you for the opportunity to respond to the reviewer’s comments and to make further improvements to the manuscript.

Wendy S. Rubinstein, MD, PhD