Author's response to reviews

Title: Blood spots as an alternative to whole blood collection and the effect of a small monetary incentive to increase participation in genetic association studies

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Author's response to reviews: see over
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Matthew Kaiser, PhD.
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Dear Dr. Kaiser

We thank the reviewers for the thoughtful comments on our manuscript (178115849241238) “Blood spots as an alternative to whole blood collection and the effect of a small monetary incentive to increase participation in genetic association studies”, and we appreciate the opportunity to resubmit.

As you indicated to us in your correspondence, we have responded point by point to the reviewer comments. Our reply to the comments (see below) and revised manuscript are attached with this cover letter.

Thank you again for your consideration of our manuscript.

Sincerely,

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Referee 1

Minor essential revisions

1. The years of the USRT and sub-study should be included in the Methods section.

On page 4 and 5 of the Study population section we have added the years over which the participants for the original USRT breast cancer case-control study and this study were recruited - 1999 to 2003 and 2006, respectively.

2. The first sentence of the second paragraph in the Background is not strictly correct, as the 'randomized trial' was not to determine if blood spot collection would increase participation (aim 1), but to determine whether the incentive made a difference (aim 2). The sentence is misleading as it currently stands.

We thank the referee for pointing out this error. The paragraph has been altered to read:

“To determine if offering blood spot collection would increase participation in genetic epidemiologic studies, we conducted a study of collecting dried blood spot cards by mail among 390 female USRT cohort participants selected for a nested case-control study of breast cancer who declined to provide a venipuncture blood sample. We also assessed the impact of an incentive to encourage participation by randomizing participants to receive either a $2.00 bill or no incentive with the blood spot collection kits.”

3. a. I think it is worth mentioning that blood spots appeared to be less likely to be done by smokers and younger participants (both cases and controls) (Table 1), even though these results were not ‘statistically significant’. This was the point I was trying to make in my original point 3.

We agree with the referee and have added the following sentence to the second paragraph of the Results section (page 8).

“We observed no significant differences in participation among cases and controls according to the other variables listed in Table 1, but there was a tendency for younger individuals among cases and controls and former and current smokers among cases to be less likely to participate.”

3. b. In addition, could the somewhat elevated ORs for women who had an occupational radiation dose >0.06 Gy be confounded by age (and therefore greater time exposed)? This should be mentioned, even though the numbers are small.

This is a valid point and has now been addressed in the manuscript. As outlined in the Statistical analysis section (page 6) we have adjusted for year of birth in the analyses of the radiation exposure variable:

“Mutual adjustment for the variables evaluated in this study had minimal impact on the point estimates of interest (<10%) in our logistic regression models, so we present univariate results only, except for the radiation exposure variables, for which the analyses were adjusted for year
of birth because of the potential confounding effects of age; the greater the age, the more opportunity to be exposed to occupational and personal diagnostic radiation.”

As seen in Table 1, the OR in the >0.06 Gy occupational radiation dose is now slightly attenuated (2.0 to 1.6). As such, our description in paragraph 3 of the Results section (page 7) now reads:

“After controlling for year of birth, we also observed a borderline significant difference in the distribution of occupational radiation breast dose among controls who did and did not provide a dried blood spot card, with a greater proportion of participating compared to non-participating controls being in the highest radiation dose category (>0.06 Gy) (Table 1).”

4. On the same subject, the authors say they have removed the 2 references to "statistical significance". But there are still 5 or 6 references to "significant difference", which is really the same thing. I understand this it common terminology, but it is not one that I endorse or favour (for the reasons illustrated in the previous comment). However, I will leave this to the authors to take on board and do as they wish.

We understand the referee’s opinion on this matter and thank her for allowing us to decide how to proceed. Given that “significant difference” and variants of this term are commonly used in epidemiologic literature, we have decided to leave these terms unchanged in the manuscript.

Referee 2

1. No further comments

We thank the referee for taking the time to review our manuscript.

Referee 3

Minor essential revisions

1. I have recently published a major review of the application of DBS sampling to epidemiologic/demographic studies that the authors might want to consult for additional information on the utility of DBS sampling, and on prior applications (McDade et al. 2007, Demography 44: 899-925). Joanne Mei has also published an excellent review that readers of this manuscript should be aware of (Mei et al. 2001, J Nutrition 131: 1631S-6S).

We thank the referee for directing us to these publications, as they helped to provide more insight into the use of dried blood spots for population based research. They have been added as references to the Background section (page 3).

2. a. I assume all participants in this study were women, but that should be stated explicitly.

We have now explicitly stated that all participants were women, as follows:

Abstract (page 2) – “To determine if offering blood spot collection would increase participation in genetic epidemiologic studies, we conducted a study of collecting dried blood spot cards by mail from a sample of female cancer cases (n=134) and controls (n=256) who were previously
selected for a breast cancer genetics study and declined to provide a venipuncture blood sample.”

Background (page 3, second paragraph) – “To determine if offering blood spot collection would increase participation in genetic epidemiologic studies, we conducted a study of collecting dried blood spot cards by mail among 390 female USRT cohort participants selected for a nested case-control study of breast cancer who declined to provide a venipuncture blood sample.”

Study Population (page 4, first paragraph) – “Study participants were women that were selected from eligible cases and controls identified as part of a genetic case-control study of breast cancer nested in the USRT cohort [9] conducted between 1999 and 2003 who had declined to provide a venipuncture blood sample.”

2. b. Also, limitations on generalizability to men should be noted.

We have modified the first sentence of the final paragraph of the Discussion (page 10) to read:

“Generalizability of our results to other populations, particularly men, is another limitation of this study given that participants were women that worked as medical professionals and were predominantly non-Hispanic.”

3. More details on DBS collection are needed.
   a. What lancet was used?

In the Dried blood spot kit section of the Methods (page 5), we now indicate that a BD Genie™ lancet (2.0 mm depth, 1.5 mm width) was used.

b. Was self-collection recommended, or were participants encouraged to have someone else help?

The dried blood spot kits were sent out as self-collection kits to the participants. To clarify this, the Dried blood spot kit section of the Methods (page 5), has been modified to read:

“Each subject was mailed a self-collection kit that contained a dried blood spot collection card (Whatman Protein Saver Card for five 75-80 µL blood samples), a BD Genie™ lancet (2.0 mm depth, 1.5 mm width), alcohol wipe, gauze pad, adhesive bandage, desiccant pouch, and a foil bag for the completed blood spot card. A consent form, detailed instructions for self-collection of a finger stick capillary dried blood spot sample and a questionnaire to collect updated breast cancer risk factor information were included with the kit, along with an envelope and first class mailing stamp for the subjects to return the specimens.”

4. a. How much time had passed between this study and the last contact the participants had with any study investigators?

The last contact that investigators had with the participants was when the participants failed to provide a venipuncture blood sample. In paragraph 2 of the Study population section on page 5, we indicated that 2 to 9 years (mean 4.4 years) had passed between these two points of contact. We have also now provided, in paragraph 2 of the Results on page 7, the mean
number of years that passed between the venipuncture and blood spot collection efforts separately for cases and controls:

“On average, a greater number of years passed between collection efforts for cases (mean = 5.5 years) than for controls (mean = 3.7 years).”

The distribution of cases and controls by categories of time is also now provided in Table 1.

b. Was time since last contact a significant predictor of compliance?

Previously, we had only considered time since last contact as a potential confounder of the association between incentive and participation. However, we have newly examined time since last contact as an independent predictor in Table 1. In the Results section (page 7), we have now stated:

“There was some indication in Table 1 that cases were more likely and controls were less likely to participate as a greater number of years passed between collection efforts. These results, however, were based on small numbers in the extreme categories and were not statistically significant. Furthermore, controlling for years between collection efforts in logistic regression models assessing the impact of incentive had little impact on the point estimates.”

When evaluating time since last contact as a predictor, we tried a number of different categorization schemes and also examined it as a continuous variable. None of these analyses indicated that time since last contact was a significant predictor of participation.

5. The conclusion should discuss in more detail some of the limitations of the study, including the long time frame between initial refusal and the request for DBS, the select nature of the sample, and the absence of men.

The discussion of these limitations in the final two paragraphs of the Discussion section (pages 10 to 11) has been expanded:

“In this study, two to nine years passed between the collection efforts. It is possible that blood spot recruitment following more immediately after requesting a venipuncture sample or offered in lieu of a venipuncture sample may have affected our response proportions. Nonetheless, the length of this time period was not a significant predictor of participation and adjustment for the time between collection efforts had a minimal effect on our results. The applicability of our results to other populations, particularly men, is another limitation of this study given that participants were women that worked as medical professionals and were predominantly non-Hispanic. Furthermore, we were unable to assess the quantity or quality of the genetic material obtained from the blood spot cards collected for this study; however, it has been previously demonstrated that blood spots are a stable source of high quality DNA [1] that can be effectively used to conduct genome-wide association studies [3].”

Also, the first sentence of the Conclusion section (page 11) has been modified to acknowledge these limitations:
“While the generalizability of our findings are limited due to the focus on female radiologic technologists and the time period between biospecimen collection efforts, our study does demonstrate that dried blood spots may be a feasible method for increasing participation in genetic studies.”