Author's response to reviews

Title: Incorporating Medical Interventions into Carrier Probability Estimation for Genetic Counseling

Authors:

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Author's response to reviews: see over
I thank the reviewers for their careful and detailed comments that have improved and clarified the points made in this manuscript. Here are my responses to the comments:

Dr. Euhus's comments:

1. “Page 3: “...women can reduce ovarian cancer risk with frequent CA-125 tests or transvaginal ultrasounds”. These tests do not reduce the risk of developing ovarian cancer and have not been shown to reduce ovarian cancer-specific mortality.”

I don't deny that CA-125 or transvaginal ultrasound have not proven themselves efficacious. The purpose of this sentence is simply to state that women concerned about their ovarian cancer mortality have tried these options. I have changed this phrase to “women have attempted to reduce their mortality from ovarian cancer with frequent CA-125 tests or transvaginal ultrasounds [12].”

2. “Page 4: “In particular, we estimate that while carriers have a reduction of 88% in the risk of ovarian or peritoneal cancer after oophorectomy (see Methods), non-carriers enjoy a 95% risk reduction[19].” Reference 19 lumped primary ovarian and primary peritoneal carcinoma together so, though the statement is accurate in that respect, I am not aware of any evidence to suggest that the risk of primary ovarian cancer after oophorectomy is different in carriers as compared to non-carriers, nor am I aware of any evidence to suggest that oophorectomy reduces the risk of primary peritoneal carcinoma. This requires clarification.”

All of the papers on oophorectomy and ovarian cancer or primary peritoneal carcinoma in BRCA carriers that I reference (references 11,15,16,19,20) combine the two cancers together for the purpose of estimating penetrance and the effect of oophorectomy, so I do the same. All I can consider is the combined endpoint, so I certainly don't mean to, or need to, suggest anything about the effects of oophorectomy on either cancer separately: all these papers say is that oophorectomy reduces the risk of the combined endpoint. To clarify this, I add the following text to the Methods section:

“Since all references combine ovarian cancer and primary peritoneal carcinoma into a single endpoint, separate effects of oophorectomy on each cancer cannot be estimated, so I combine them into a single endpoint.”

Reference [19] is the only study I'm aware of that considered the effect of oophorectomy on ovarian cancer or primary peritoneal carcinoma in BRCA mutation non-carriers. Although [19] doesn't report a p-value testing for different effects of oophorectomy in carriers vs. non-carriers, since the two estimates should be nearly independent, I can calculate a p=0.048 that the two effects are different. To clarify this, I add the following text to the Methods section:

“Although [19] doesn't report a p-value testing for different effects of oophorectomy in carriers vs. non-carriers, since their two estimates should be nearly independent, I calculate a p=0.048 that the two effects are different.”

3. “Page 8: “For example, an oophorectomy at age 40 is more likely to be too late for carriers than non-carriers because the path to cancer is accelerated in carriers and thus carriers may progress more rapidly to an advanced stage where oophorectomy cannot stop the process.” I am not sure I follow the
reasoning here. Molecular studies suggest that primary peritoneal carcinomatosis is multi-focal and multiclonal arising directly from the peritoneal lining. Oophorectomy does not stop progression at any age. It may occasionally result in the removal of an occult, localized ovarian cancer, but in this case, the relative would be classified as having had ovarian cancer. If the author is aware of data suggesting that ovarian function increases the risk of primary peritoneal carcinoma it should be cited here."

This sentence meant to refer to breast cancer, not to primary peritoneal carcinoma. Since the sentence is not critical, I have decided to remove it.

4. “Page 14: “Also, the hazard ratio for breast cancer for mutation carriers does not appear to depend on pre-oophorectomy disease history, age at oophorectomy, time since oophorectomy, or by BRCA1 vs. BRCA2.” This statement does not seem consistent with the information reported in reference 15 and the situation seems too complex to be adequately handled by a single hazard ratio. For instance, the reduction in breast cancer risk was only significant for BRCA1 mutation carriers (OR = 0.43, p = 0.00006) and not BRCA2 mutation carriers (OR = 0.57, p = 0.11), oophorectomy <= 40 years of age was associated with an OR of 0.36 as compared to 0.50 for procedures performed between 40 and 50, and oophorectomy only reduced the breast cancer risk for 15 years following the procedure but not at all after 15 years (OR = 1.32)."

I agree with the reviewer that reference 15 suggests that other factors may modify the effect of oophorectomy, but I don't believe that the above quoted effects are statistically significantly different from each other. Thus, I have modeled the oophorectomy effect on breast cancer to have a single OR=0.46 regardless of other factors. Unfortunately, reference 15 doesn't test if these effects are different, but I will consider each of the potential modifiers brought up by the reviewer in turn.

The BRCA1 OR=0.57 is close to the BRCA2 OR=0.43, and since these two estimates should be nearly independent, I can calculate a p-value of 0.50 for the difference in the two ORs. Thus the ORs are insignificantly different and I can use a common OR for the two loci. A reason for the insignificance could be that reference 15 had only 36 BRCA2 mutation carriers who underwent oophorectomy.

Similarly, for different ORs by age-at-oophorectomy (from Table 3 of ref 15, using their unadjusted estimates since BRCAPRO doesn't account for oral contraceptives):

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA 1 or 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;41</td>
<td>0.41</td>
<td>0.0004</td>
<td>(0.25,0.68)</td>
</tr>
<tr>
<td>41-50</td>
<td>0.47</td>
<td>0.005</td>
<td>(0.28,0.79)</td>
</tr>
<tr>
<td>BRCA1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;41</td>
<td>0.36</td>
<td>0.0005</td>
<td>(0.20,0.63)</td>
</tr>
<tr>
<td>51+</td>
<td>0.49</td>
<td>0.02</td>
<td>(0.27,0.91)</td>
</tr>
</tbody>
</table>

Unfortunately, I don't have enough information to calculate formal p-values to test if there is a difference between the effects of age. However, given the strong overlap of the two confidence intervals for age ranges <41 and 41-50, both for BRCA 1 or 2 and even for BRCA1 alone, it seems quite likely that the two estimates are statistically insignificantly different, justifying the use of a common OR over both age ranges.

For time since oophorectomy, for 15+ years post-oophorectomy the OR=1.30 with 95% CI (0.51, 3.30). The imprecision is caused by having only 22 mutation carriers at 15+ years post-oophorectomy. Unfortunately, the
paper doesn't test if this OR is significantly different from the overall OR=0.46 with 95% CI (0.32, 0.65). These two estimates cannot be strongly statistically significantly different since the confidence intervals do not overlap. The other two major papers on the effect of oophorectomy on breast cancer [16, 20] do not remark that their OR changes with time since oophorectomy. Even if the ORs are strongly statistically significantly different, the OR=1.30 is quite imprecisely estimated so I wonder if clinicians may be concerned about using it in clinical decision-making.

Even if there are modifiers of the effect of oophorectomy, an advantage of allowing for only a single OR for the oophorectomy effect is that this OR is more precisely estimated since all the data goes into it. This OR will be appropriate for an “average” consultand, one who would not be in a small subgroup defined by enough modifying factors to make the overall OR inappropriate, and is thus reasonable for the bulk of consultands who present for counseling.

I certainly agree that reference 15 suggests that the effect of oophorectomy may depend on other modifiers, and I think that future research will nail these effects down. Clearly, modifiers would be of great value and I stress that the methodology in my manuscript is completely general and can be used to modify BRCAPRO accordingly. I certainly look forward to more precise data about the effects of oophorectomy (especially for non-carriers) to refine the incorporation of oophorectomy into BRCAPRO.

This reasoning needs to be made more clear in my manuscript, so I have added the following statements:

“...It is critical to consider all factors that could modify the appropriate hazard ratio to use. For example, [15] estimates hazard ratios for breast cancer within groups defined by pre-oophorectomy disease history, age at oophorectomy, time since oophorectomy, and by BRCA1 vs. BRCA2. Although [15] does not formally test if the hazard ratios differ within each group, we must informally assess whether the differences they found are strongly statistically significant. For example, [15] finds that those with BRCA1 mutations have a hazard ratio of 0.43 (0.29, 0.65) and those with BRCA2 mutations a hazard ratio of 0.57 (0.28, 1.15). Since these two estimates must be nearly independent, we can calculate a p-value of 0.50 for the difference in hazard ratios between the two loci; thus we are justified in using the same hazard ratio for both loci. For age at oophorectomy, we cannot calculate a p-value, but the degree of overlap of the confidence intervals between age ranges suggests that the differences in the hazard ratio are probably statistically insignificant, and thus justifies the use of a common hazard ratio over all ages. The overall hazard ratio found by [15] was 0.46 (0.32, 0.65), but for 15 years after oophorectomy, they find a hazard ratio of 1.30 (0.51, 3.30). The two intervals overlap, but it's possible that the two are significantly different. However, neither [16] nor [20] noticed this in their data, and the 1.30 hazard ratio is estimated quite imprecisely, making us hesitant to use this in a model used in clinical decision-making. Also, if only a few modifying factors exist, using a single hazard ratio for everyone is advantageous because this overall hazard ratio would be most precisely estimated and is relevant for most consultands. Thus we use the overall hazard ratio of 0.46.”

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
5. Page 5: “...but is an increase of 40%. Percent change is useful because...” I am not sure what is meant by “useful.” Percent change may be used as a metric to measure the impact of intervention information on carrier probabilities and may highlight the multiplicativity of the effect, but in the clinic 1.4% is the same as 1%.”
My previous sentence admits that this change isn't likely to have clinical impact. Useful is meant to highlight the multiplicativity of the effect, because that is the scale on which interventions alter the carrier probability. I have changed this sentence to “Since interventions multiplicatively affect the carrier probability (detailed in Methods), percent change is a noteworthy metric.”

6. Page 5: “...then the act of a relative choosing oophorectomy (or not) does not have extra information about carrier status.” Does not significantly impact carrier probabilities?

Oophorectomy always carries information about carrier probabilities; it's only whether there is extra information in the decision to (or not to) undergo oophorectomy. I have changed this phrase to “then we do not need to model the effect of family history and carrier status on choosing to (or not to) undergo oophorectomy.” This statement is made precise by equation 7 of the Methods.

7. Page 5: “These scenarios show that interventions have more impact on the carrier probability as the benefits of intervention differ more between carriers and non-carriers.” Have more impact on carrier probability than on what?

I have changed this to “These scenarios show that the importance of accounting for interventions increases as the benefits of intervention differ more between carriers and non-carriers.”

Discretionary Revisions (which the author can choose to ignore)

I have accepted all the discretionary revisions.