Author's response to reviews

Title: Founder mutations in BRCA1/2 are not found at higher frequency in Canadian Ashkenazi Jewish men with prostate cancer

Authors:
Nancy Hamel (nancy.hamel@staff.mcgill.ca)
Kimberley Kotar (dolphins@colba.net)
William D Foulkes (william.foulkes@mcgill.ca)

Version: 2 Date: 18 Jul 2003

Montreal, July 18, 2003

To the Editors,

We would like to thank the editors of BMC Medical Genetics as well as the reviewers for the prompt evaluation of our manuscript. The reviewer's comments were very useful and allowed us to improve our manuscript noticeably. Specifically, one major change was brought to the article in response to a query by Dr. Goldgar to better detail our definition of Ashkenazi Jewish as an inclusion criterion for the study. By revising the questions asked of participants at the time of recruitment, we became aware that 2 individuals with partial Sephardic heritage were mistakenly included among our prostate cancer cases. These 2 cases have now been removed and our data re-analyzed with only the remaining cases. We would also like to sincerely apologize to both referees for forgetting to number the pages of our manuscript.

Detailed answers to specific comments from the reviewers are provided below, along with details of how the manuscript was modified to address them.

Dr. Goldgar's comments

1. Dr. Goldgar suggested the introduction be expanded. This we have done, including, as suggested more background information on Ashkenazi Jews and the phenomenon of founder mutations in this population.

2. As Dr. Goldgar correctly pointed out, when studies of similar design examined the risk of prostate cancer in BRCA1 and BRCA2 mutation carriers independently, mutations in BRCA2 appeared to be a stronger risk factor to carriers with later-age of onset such as those from our cohort, while an excess of prostate cancer in BRCA1 carriers was of borderline significance and limited to early-onset cases. We included a sentence in our introduction which emphasizes this observation. However, since other studies also reported an excess of prostate cancer in BRCA1 mutation carriers specifically (if not necessarily in AJ cases), we still feel it is worthwhile to examine both genes for a potential contribution in our cohort.
3. We would like to apologize for not including the recent paper by Edwards et al 2003 in our list of references. As Dr. Goldgar surmised, we had meant to do so in our discussion but accidentally omitted to insert the reference at the appropriate location. Also, the series tested by Edwards et al was clearly larger than ours but did not include any AJ individuals, nor did this study identify any of the 3 AJ founder mutations. Our intention was simply to state that our series was the largest series of prostate cancer cases of Ashkenazi Jewish origin examined to date for the 3 founder mutations. We have clarified this statement in our methods section. Thank you for pointing that out.

4. In answer to Dr. Goldgar's request for a better definition of AJ as applies to our study, patients were eligible if they reported both their parents as AJ. Any patient with mixed heritage (Sephardic or other) was excluded from the study. We added a statement to that effect in our methods section.

5. As requested, we emphasized the fact that the 6174delT mutation is indeed found within the OCCR region of BRCA2, which is of course why we thought it a potential explanation for the lack of association we observed between this mutation and prostate cancer risk.

6. The heading of Table 1 has been corrected as suggested to better reflect the contents of the table.

7. Our original intention when we wrote the first version of the paper was to include whatever controls had been tested by those studies which had examined AJ founder mutation frequencies in prostate cancer cases. Of the 4 studies cited, only one group genotyped their own controls. Another group, Vazina et al, 2000, used the controls from the Washington D.C. area studied by Struewing et al, 1997, as their control references, which is why we ended up using this study as a control group as well. However, Dr. Goldgar's point regarding potential problems with this cohort was well-taken, and we decided to follow his suggestion and build a control group ourselves from all available data on population frequencies for the 3 AJ founder mutations, including data from Roa et al (1996), Struewing et al (1995) and Oddoux et al (1996). Table 1 as well as all statistical analyses were updated to reflect the new controls used.

Dr. Rennert's Comments

1. and 2. The first comments from Dr. Rennert also expressed concerns regarding our choice of controls, which we hope has already been partially answered in point 7 above. As we already indicated, not all studies studying AJ BRCA1/2 founder mutations in prostate cancer cases included controls, but all those available were included in our control population. In addition, we followed Dr. Rennert's suggestion to include more information regarding the various control groups we incorporated into our study. We added a section to our discussion describing the various control groups and comparing them to each other.

3. Dr. Rennert pointed out that because we did not examine AJ founder mutation frequencies in Canadian men without prostate cancer, our original title was misleading. We corrected our title accordingly, changing it to: Founder mutations in BRCA1/2 are not frequent in Canadian Ashkenazi Jewish men with prostate cancer.

4. As requested, we updated our methods section to include information regarding IRB approval of our study and to specify that indeed all participants in the study were offered the option of receiving genetic counseling.

5. Dr. Rennert pointed out that some numbers were accidentally deleted from the PAR% formula presented in our discussion. Thank you very much for pointing that out, we made the necessary correction. The calculations themselves had been accurate; the numbers were only deleted during editing of the text.
6. In this comment, Dr. Rennert points out that another study, Gayther et al (2000) estimated that germ-line mutations in BRCA2 may account for 5% of prostate cancer in familial clusters (with 2 probands out of 38 families being carrier of a BRCA2 mutation) and wonders at the reason why we see PAR% values of less than 1% in our study. First, familial prostate cancers represent only a subset of all prostate cancers, and the subjects in our cohorts were unselected for family history (only 13 probands out of 146 (8.9%) reported a family history). Thus, the frequency of BRCA2-related prostate cancer cases would be expected to be much lower in the general population than in the subset of cases that are familial. In addition, the 5% value reported by Gayther et al may well be an overestimate given that in both reported cases, affected siblings of the carriers were not carriers themselves, which raises a question as to whether presence of a BRCA2 germ-line mutation is truly associated with familial clustering.

As a last, discretionary revision, Dr. Rennert asked us whether we noticed an association between BRCA1/2 mutations and age of onset or disease severity, as has been previously suggested in other studies. Unfortunately, with only 2 mutation carriers among our cases, this is a difficult question to answer. As shown in our figure 1, one carrier was diagnosed at age 56 and the other at age 76 (average = 66, which is close to the average age at diagnosis of our entire cohort, 67.9 years). The carrier diagnosed at 56 had a Gleason score of 7 out 10, while the one diagnosed later at a Gleason score of 9. In our opinion, this information is not sufficient to draw conclusions.

We would like once again to thank the referees for all their helpful comments. We hope that the modifications we made to our manuscript based on their suggestions will be considered sufficient to make our work suitable for publication in BMC Medical Genetics.

Sincerely,

Nancy Hamel
on behalf of the authors