Reviewer's report

Title: SNP-SNP Interactions in Breast Cancer Susceptibility

Version: 2 Date: 16 January 2006

Reviewer: Thomas A Sellers

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General
The report by Onay and colleagues summarizes results from a case-control study of 19 SNPs hypothesized to influence susceptibility to breast cancer. None of the SNPs were individually associated with risk, but a polygenic model that explored gene x gene interaction terms revealed three that were significant based on false discovery rate principles (although they were not statistically significant). This is an interesting study, but there are some issues that should be addressed.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The article has a significant number of statements that need to be supported with citations. Probably half of the statements in the background are undocumented, yet are stated with conviction of fact rather than opinion. Each sentence needs to be reviewed throughout the manuscript.
2. The thesis presented would be much more compelling if the introduction chose to focus more on the genes and SNPs selected for investigation than the lengthy discourse on polygenic models. Indeed, interpretation of the results is difficult without such a background.
3. The sampling strategy, subselection of participants from the larger study, and the control sampling is difficult to follow. It would be helpful to have Table 4 presented earlier, and with more information on the study subjects (demographics, clinical characteristics, more non-genetic risk factor data).
4. Table 3 results are impossible to interpret as presented. The significance tests do not permit interpretation of the nature of the interactions. Two rows include age interactions, which is not consistent with the title of the table. I don't understand the two ER SNP interaction. Are they in linkage disequilibrium? A haplotype approach should be applied.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. pg 4, line 1: Change “Genetic epidemiological” to “Genetic association” (traditional genetic epidemiology is gene mapping without consideration of function or relevance of the marker).
2. A careful distinction between a mutation and a polymorphism must be made. Geneticists use differences in frequency, but the authors sometimes confuse that with functional effects of the DNA alteration.
3. pg 4, line 14. I would have expected this statement to be supported with references to BRCA variants. I don’t understand the point as intended.
4. pg 4, line 8. Do we really know this to be true?
5. pg 5, line 2 from bottom. A brief description of the genetic risk criteria is necessary for the reader to interpret the results.
6. pg 8. More detail is needed on the "control" SNPs. This is an unusual approach.
7. pg 11. SNPs don’t show evidence for HWE. It’s their distribution that is being tested.
8. Table 1. The column heading “Interacting SNPs” is unclear. Does this relate to the author’s
reference to “control” SNPs (the “no’s” in the column)?

9. Table 2. Epidemiologic risk factors for breast cancer should be explored, and included when significant in the model. This is critical given the uncertainty as to the appropriateness of the various selection and matching algorithms that were applied.

Discretionary Revisions (which the author can choose to ignore)

1. pg 3, line 3 from bottom: “Although the majority of SNPS are ^silent and thought to be^ harmless, a considerable…” (unless a citation is included otherwise).
2. pg 7, line 4. This sentence should be broken into separate sentences.
3. pg 8, line 3 from bottom. Delete (it is redundant with first sentence in the section).
4. pg 8, last sentence: “The ^reliability of the^ results were ^determined^…” (this isn’t really a validation).
5. Table 2. One could just give the additive model results for the three genotypes. The p-value isn’t important since the 95% CI’s are presented, but it would be nice to have the number of cases and controls in the table.
6. pg 12. Rather than talk about modes of transmission (which is appropriate to segregation of a trait), consider genetic risk model.
7. pg 16, last paragraph. The point of this was lost upon this reader.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes

Declaration of competing interests:

I have no competing interests.