Reviewer's report

Title: Association of common variants in mismatch repair genes and breast cancer susceptibility: a multigene study.

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Reviewer: Pavel Vodicka

Reviewer's report:

The manuscript of Conde et al. represents a potentially valuable contribution, however several important points have to be comprehensively addressed prior to the acceptance to BMC Cancer.

Major Compulsory Revisions:

Considering the content, the manuscript shortened and made more concise, it particularly concerns Introduction, Discussion and Tables on binary combinations. Authors (in the Discussion) paid the disproportional attention to the effect of interactions of MMR proteins, while very little is given to the putative effect of studied MMR SNPs on those interactions. Intro should also contain recent literature on other MMR SNPs, such as Wong et al. Fam Cancer 2008, 7, 151-155 (MSH2 gene).

It is, however, questionable, whether it is sensible to build interactions on the data from 287 individuals. The studied group is not large even for analysis of association of single polymorphism. And breast cancer is not a rare disease. I suggest to drop out all the section concerning interactions, including excessive Tables. Apart from the fact, that the population was not sufficiently described, it is composed from the histologically different cases. It is not clear, whether familial cases were included or not.

The authors studied 9 SNPs in 7 MMR genes. This is clearly a multiple comparison. Were the results corrected for multiple hypothesis testing (Bonferroni e.g.)?

MSH3 and MSH4 haplotypes: As no data on tagging are provided, one feels that the SNPs represent rather combination of polymorphisms in these genes. Clarification needed.

Discussion needs to be reformulated and focused.

Conclusions do not cover the work conducted by authors and its implications.

In general, the writing should be improved.

Minor Essential Revisions:

It is not clear, how the selection of the studied genes has been done and the nomenclature of SNPs is not given in the uniform way (e.g. page 9). How the matching has been performed (apparently not by pairing nor by two to one system).
Are 2 years after quitting the smoking sufficient to count those individuals as non-smokers?

Statistical analysis: for applying Student’s t-test, the normal distribution of data should be obtained. Were the data distributed normally or were they transformed?

Page 8: Genomic DNA was obtained from a quarter a liter of blood. Please correct.

Page 11: Deviations from HW equilibrium: Authors state that these p-values were not highly significant. The results are either significant or not, if they are, it should be commented upon in the Discussion.

Discussion, page 14: The difference across the studies is rather related to the design of the studies than to the differences in populations. Such huge differences among Caucasians are not very likely.

Discretionary Revisions:

The authors stated that MMR functional failure may also result in chemotherapy resistance. This may rather be the contrary, or depending on the drug. If the paper is not dedicated to the topic, smooth formulation would be recommended.

Author’s contribution: Who is VE?

Title in Table 2: replace by ...and analysis of associations of individual SNPs with breast cancer risk.

Level of interest: An article of importance in its field

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

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests