Genetics inMedicine | CORRESPONDENCE

Response to Roberts et al. 2018: is breast cancer truly caused by *MSH6* and *PMS2* variants or is it simply due to a high prevalence of these variants in the population?

To the editor:

We have read the recent paper by Roberts et al. in *Genetics in Medicine* with great interest.[1] In this paper the authors claim that *MSH6* and *PMS2* germline pathogenic variants are associated with increased breast cancer risk. The authors are to be commended for analyzing all MMR genes in a single study and performing gene-stratified analyses. They report a strong increase in cumulative risk of breast cancer for *MSH6*- and *PMS2*-associated Lynch syndrome patients (31.1 and 37.7% at age 60 respectively). If confirmed this would have major consequences for surveillance policy in this subset of Lynch patients. Nonetheless, we would like to place some notes on the interpretation of the results.

Risk analyses in clinically selected cohorts should be interpreted with caution because they are influenced by ascertainment and testing bias. We have previously reported on the cancer spectrum in *PMS2* families as well and we too found an increased standardized incidence ratio (SIR) for breast cancer of 3.8 (95% CI: 1.9–6.8).[2] However, although we corrected colorectal cancer and endometrial cancer risk estimates for ascertainment bias using modified segregation analyses, event rates were too low to apply the same corrections for other cancers, including breast cancer. Therefore, SIR analyses were presented, but with appropriate skepticism. Roberts et al. suggest that ascertainment bias in their study is counteracted by inclusion of patients not only selected due to a clinical suspicion of Lynch syndrome, but also because of other cancer prevalence in the proband or family. However, the inclusion of these patients might have actually resulted in overestimation of the breast cancer association.

We believe that the identified association might be explained by the relatively high prevalence of *MSH6* and *PMS2* variants in the general population. Indeed, Win et al. estimated that the prevalence of pathogenic variants in these genes is much higher (*MSH6*: 1 in 758, *PMS2*: 1 in 714) when compared with *MLH1* (1 in 1946) and *MSH2* (1 in 2841).[3] Consequently, just by chance alone, one would expect to find more *MSH6*- and *PMS2*- pathogenic variant carriers than *MLH1*- and *MSH2*- pathogenic variant carriers in this large cohort. This could explain why Roberts et al. only find an association of breast cancer with *MSH6* and *PMS2*, but not with *MLH1* and *MSH2*. In other words, the identified association in this cohort containing relatively many breast cancers (107/423, 25.3%) could be based on a higher a priori chance of finding these variants and performing risk analyses without correcting for ascertainment bias. Roberts et al. also report that breast cancer in absence of other Lynch-associated cancers was reported more frequently in *MSH6*/*PMS2* when compared with carriers of pathogenic variants in *MLH1*/*MSH2*. We believe this could be explained by the relatively low penetrance of *PMS2* and *MHS6*. For this reason it would be interesting to know how the initial cohort of 50,000 analyzed patients was composed, i.e., how many probands or families fulfilled hereditary breast and ovarian cancer (HBOC) or Lynch syndrome criteria.

In their discussion of the results, the authors refer to Engel et al., who published a paper in 2012 with a similar study design and reported a SIR of 1.9, but included no *PMS2* carriers and only 16.4% *MSH6* carriers. This SIR is very similar to the SIR of 1.96 for the combined MMR genes as reported by Roberts et al. However, if indeed only *MSH6* and *PMS2* confer an increased risk than this similar SIR is strange in light of the very different proportion of these variants in the current report (264/423, 62%). If results would truly be similar the overall SIR would have to be markedly higher in the current study.

Lastly, a prospective project that is currently ongoing (Prospective Lynch Syndrome Database, PLSD) did not confirm increased breast cancer risk for any of the MMR genes. Unfortunately, results from this study were not commented on by the authors in their discussion of available literature. This project will hopefully, in time, provide definitive answers to the association of breast cancer and pathogenic germline variants in the MMR genes.

In conclusion, the combination of a high *MSH6* and *PMS2* variant prevalence in the general population and the high incidence of breast cancer in the analyzed cohort without correction for ascertainment bias suggest an alternative explanation for the identified association in this study. We believe that this possibility should be investigated further before breast cancer is accepted as part of the tumor spectrum and changes in clinical guidelines are suggested.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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