Genetics inMedicine | CORRESPONDENCE

Are women with pathogenic variants in *PMS2* and *MSH6* really at high lifetime risk of breast cancer?

We read with some concern the recent article in *Genetics in Medicine* reporting a high lifetime risk of breast cancer in pathogenic variant (PV) carriers for *PMS2* and *MSH6* (ref. [1]). Although the reported odds ratios for breast cancer were given as *MSH6* (2.11; 95% confidence interval [CI] = 1.56–2.86) and *PMS2* (2.92; 95% CI = 2.17–3.92) the cumulative risks to age 60 were given as 31.1% (95% CI, 21.9–40.7) and 37.7% (95% CI, 27.5–47.8) respectively. These are equivalent to UK National Institute for Health and Care Excellence (NICE) defined high lifetime risks. These two analyses are inaccurate given that the risk of breast cancer to the age of 60 years in the UK and United States is 5–6%. Therefore, if the risks from incidence ratios and Kaplan–Meier were equivalent, the odds ratios would be over 6-fold for *PMS2* and >5-fold for *MSH6*.

The most meaningful unbiased risks are likely to come from prospective analysis. The cumulative risk to age 70 years in 124 *PMS2* PV carriers was shown to be only 8.6% to age 70 years in the largest such analysis undertaken thus far.[2] A single case between 70 and 75 years gave a distorted nonsignificant increased risk. For *MSH6* the cumulative risk to age 75 years was 13.3% (95% CI = 2.2–24.4) odds ratio 1.4 (95% CI = 0.2–2.6). As such the upper confidence interval at age 75 years for *MSH6* rules out the cumulative risks provided by the GeneDx study.[1]

The huge discrepancy observed may be attributed to a number of issues. First is the lack of adjustment of the clear ascertainment bias in contrast with the majority of published reports of cumulative risk of breast cancer in patients with tumor suppressor gene variants. Second is the absence of information on the proportion of women who were tested who had a breast cancer diagnosis. An earlier report from this group reported 5209/9276 (56.2%) of all referred samples had breast cancer.[3] If the proportion remains constant, a huge bias is present that precludes any comparison of incidence ratios with the general population. Third, the authors "compound the felony" with the inappropriate use of Kaplan–Meier analyses for cumulative risks. Despite the fact the authors report an odds ratio of below 1 for *MLH1*, they then report a 15.5% (95% CI = 5.5–30.2) risk of breast cancer by age 60 years. This is equivalent to a threefold excess risk. It is therefore highly likely that if the authors had carried out incidence ratios for those individuals testing negative for mismatch repair (MMR) and other PVs, they would have demonstrated an increased risk with a cumulative risk to age 60 years of over 25%. Finally, the authors have not reported whether the variants segregated with disease, which would at least have provided some supportive data. Whilst the authors state that "the risks of other cancers, including breast are less clearly delineated" this ignores most of the negative evidence available.[2,4]

A more appropriate use of panel data to agnostically assess cancer risks would be to carry out a case control analysis. The largest analysis published thus far from Ambry Genetics (n = 65,057 women)[5] found an odds ratio below 1 for *PMS2* although a potential risk was seen for *MSH6* with an odds ratio of 1.93; (95% CI = 1.16–3.27). Given the likely ratio of around 50% for those tested with breast cancer to those without, a form of internal case control for *PMS2* could be carried out within the available results. Interestingly for *PMS2* this was close to a 1:1 ratio with 35.5% having breast cancer and 34.7% without breast or another cancer. If one took the 0.13% prevalence of *PMS2* PV in the Ambry report as a control, then assuming the frequency of breast cancer cases was similar to the 56% in GeneDx first report, the reported incidence would be 44/28,078 or 0.16% providing an odds ratio of only 1.2. As we were not provided with the proportion of breast cancers we cannot be certain of this figure but it is unlikely to have risen above an odds ratio of twofold. Even these case control series are limited by their use of control data.

Another important issue is that three of the panel tests provided by GeneDx exclude a real assessment of breast cancer genes and most of the *MSH2* and *MLH1* carriers (52% and 64%) were detected using the colorectal 16-gene panel or high-risk Lynch/colorectal 7-gene panel or endometrial 12-gene panel. This compared with only 18% of *PMS2* and 35% of *MSH6* ($p < 0.0001$ for difference between gene duos). Ironically it may be because *PMS2* gives such lower overall risks of cancer that it has come out giving the highest risks of breast cancer in the GeneDx analysis paper.[1]

It is crucially important that those discussing breast cancer risks with women with pathogenic *PMS2* and *MSH6* variants do not base their advice or management on the reported findings, rather on the overall evidence available, in particular that coming from prospective observations in large numbers of cases.

ACKNOWLEDGEMENTS

D.G.E. and E.R.W. are supported by the all Manchester National Institute for Health Research (NIHR) Biomedical Research Centre (IS-BRC-1215-20007).

Submitted 5 November 2018; accepted: 29 November 2018
Published online: 14 December 2018

DISCLOSURE

The authors declare no conflicts of interest.

D. G. Evans, MD[1,2], *E. R. Woodward, PhD*[1,2], *F. Lalloo, MD*[1], *P. Møller, MD*[3], *J. Sampson, MD*[4], *J. Burn, MD*[5], *G. Moeslein, MD*[6] *and G. Capella, MD*[7]

[1]Manchester Centre for Genomic Medicine and NW Laboratory Genetics Hub, Manchester University Hospitals NHS Foundation Trust, Manchester, UK; [2]Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Health Innovation Manchester, Manchester, UK; [3]The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; [4]Institute of Medical Genetics, Cardiff University School of Medicine, Cardiff, UK; [5]Biomedicine West Wing, Centre for Life, Newcastle, UK; [6]Surgical Center for Hereditary Tumors, Helios University Hospital Wuppertal, University of Witten/Herdecke Germany, Witten, Germany; [7]Hereditary Cancer Program, Institut Catal. d'Oncologia-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. Correspondence: D G. Evans (gareth.evans@mft.nhs.uk)

REFERENCES

1. Roberts ME, Jackson SA, Susswein LR, et al. MSH6 and PMS2 germ-line pathogenic variants implicated in Lynch syndrome are associated with breast cancer. Genet Med. 2018;20:1167–1174.
2. Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut. 2018;67:1306–1316.
3. Susswein LR, Marshall ML, Nussbaum R, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. Genet Med. 2016;18:823–832.
4. Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer risks for PMS2-associated Lynch syndrome. J Clin Oncol. 2018;36:2961–2968.
5. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncol. 2017;3:1190–1196.

Advance online publication 14 December 2018. doi:10.1038/s41436-018-0401-1