Response to Dominguez-Valentin M et al. 2019: Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database

To the editor:

The Prospective Lynch Syndrome Database (PLSD) group has recently published in *Genetics in Medicine* the results of one of the biggest prospective studies on Lynch syndrome (LS),[1] including 6350 carriers (3480 females) of pathogenic mismatch repair (MMR) variants and more than 50,000 follow-up years (26,131 for breast cancer). The data have been collected, through a prospective database, from the most important Lynch expert centers all over the world including the most important registries. The major aim of the study was to provide age and organ specific cancer risks according to gene and gender, to delineate the spectrum of the syndrome and to define proper management guidelines.

Breast cancer (BC) risk was comparable among the four MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), with a cumulative risk that shows only a marginal increase compared with the general population. More than 20% of BCs in *MLH1* and *MSH2* pathogenic variant carriers were diagnosed before 50 years of age, mostly between 40 and 50.

Whether BC is part of the LS spectrum is a question that has been debated for a long time, with studies providing evidence in different directions. Win et al. made a systematic review of the literature identifying 21 relevant studies,[2] but it was not possible to elaborate a meta-analysis from these data because most of the papers were not comparable. Thirteen of these did not observe an association between BC and LS, while 8 studies found an increased BC risk of 2 to 18 times more than the general population. Moreover, at that time, only 1 of 21 studies was prospective, with a standardized incidence ratio (SIR) of 3.95 (95% confidence interval [CI] = 1.59–8.13) for BC in LS female patients.[3]

Between 2013 and 2019, more studies have been published on this topic. Therefore, we planned to carry out a systematic review and meta-analysis of the literature up to 30 June 2019.

A total of nine independent cohort studies were summarized by our meta-analysis, including four prospective cohorts (Win et al.,[3] Engel et al.,[4] Pande et al.,[5] Win et al.,[6] Win et al.,[7] Harkness et al.,[8] Goldberg et al.,[9] Therkildsen et al.,[10] and Møller et al.[11]). Our selection criteria included only female carriers affected by LS or female relatives with a proven pathogenic variant.

We found a significant increased risk of BC in the presence of at least one MMR gene germline variant (summary SIR = 2.13; 95% CI = 1.66–2.74). Notably, the summary estimate was greater for *MSH2* gene (SIR = 2.27; 95% CI: 1.28–4.04). We applied random effects models to be conservative, even if no significant between-study heterogeneity was found (I^2 = 52% and 43% overall and for *MSH2* respectively).

Comparing the raw data published by Dominguez-Valentin et al. with the Finnish rate of breast cancer (per 100,000, age-standardized, reported by the Finnish Cancer Registry) we obtained a SIR of 1.37 (95% CI = 1.08–1.71). SIRs for single MMR genes were not significant. Only *MSH2* SIR showed borderline significance: SIR = 1.43 (95% CI = 0.97–2.03).

Discrepancies in results may be due to the different study designs and different inclusion criteria. The PLSD study used different criteria[12] enrolling only subjects without previous diagnosis of BC at baseline, thus leading to a lower cohort size and number of BC events compared with our meta-analysis.

Other reasons for the observed differences could be attributable to limits of meta-analyses; i.e., we could not include in our analysis seven studies because they did not report SIR nor raw data. However, in our meta-analysis we did not find any indication for publication bias. A further limit of a meta-analysis is related to possible overlapping between studies.

The article by Dominguez-Valentin et al. is a pooled analysis of individual patient data, which usually leads to more precise and reliable results. However, our meta-analysis includes more subjects (4898 female carriers), as well as twice as many BC events (177 versus 85). Of relevance, we identified a higher BC risk in LS compared with the one reported by Dominguez-Valentin et al., but these SIRs do not contradict each other, since CIs partially overlap.

Based on the results of Dominguez-Valentin et al., an intensive screening for breast cancer in LS does not seem to be advocated. However, this conclusion could derive from lower cohort size.

The European Society for Medical Oncology (ESMO) 2019 clinical practice guidelines for LS do not mention breast surveillance in LS.[13]

The National Comprehensive Cancer Network (NCCN) guidelines for LS reported that there have been suggestions of a higher risk for BC in the LS population, but data are not sufficient to support increased screening recommendations.[14]

On the whole, evidence from our meta-analysis could be not enough to recommend an intensive surveillance for BC in LS. However, we suggest that breast surveillance should not be

Submitted 28 October 2019; accepted: 19 November 2019
Published online: 5 December 2019

neglected and could be important for early detection. Thus, since in the study by Dominguez-Valentin et al., approximately 20% of breast cancers were diagnosed before 50 years of age, an anticipation of breast surveillance in LS female carriers might be considered, especially in *MSH2* carriers.

In conclusion, germline analysis of MMR genes in women with BC, with or without family history of colon and endometrial cancers, could be taken into account in case of wild-type *BRCA* testing. The diagnosis of LS in BC patients could be useful to identify individuals who need a personalized intensive surveillance.

DISCLOSURE

The authors declare no conflicts of interest.

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Advance online publication 5 December 2019. doi:10.1038/s41436-019-0716-6