RE: *BRCA1* and *BRCA2* Gene Mutations and Colorectal Cancer Risk: Systematic Review and Meta-analysis

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To the Editors:

Identifying cancer risks in BRCA1/2 carriers is important for counseling patients on appropriate strategies for cancer risk management. It was therefore with great interest that we read the recent JNCI article by Mok Oh and colleagues [1]. This meta-analysis of 14 studies examining colorectal (CRC) cancer risk in BRCA1/2 carriers concluded that BRCA1 mutation carriers had increased CRC risk (OR 1.49, CI 1.19-1.85) whereas BRCA2 mutation carriers did not (OR 1.09, CI 0.75-1.58). While we appreciate this effort to address the important topic of CRC risk in BRCA1/2 carriers, we have some concerns regarding the conclusions drawn and their applicability to the BRCA1/2 community.

First, it is important to highlight that the significance of the observed CRC risk disappeared when subgroup analysis was performed to include confirmed BRCA1/2 carriers, rather than including family members with unknown mutation status. The risk in confirmed mutation carriers provides the most accurate BRCA1/2 dataset with which to calculate CRC risk, giving this subgroup analysis particular relevance. Second, there are many factors known to increase CRC risk that are unable to be accounted for in this analysis and which may skew the risk assessment. For example, given the abundance of Ashkenazi Jewish (AJ) individuals in the analyzed studies, the presence of the moderate-risk CRC gene APC*I1307K, present in ~7% of AJ individuals [2], may influence CRC risk.

Third, only one study analyzed in the BRCA1 meta-analysis had a calculated OR that was significant [3], and it was this study that had the largest weight in the meta-analysis. To our knowledge this study by Brohet and colleagues is a dissertation that has not yet been published in a peer-reviewed journal; thus it is not clear that it merits inclusion in a meta-analysis. Additionally, the risk data selected from the Brohet study was for colon cancer risk only (RR 2.51, 2.02-3.07), whereas we believe the more appropriate data to use from this study is the more inclusive CRC risk (RR 1.29, 1.05-1.57), which was substantially lower with inclusion of
rectal cancers. Fourth, even if the data from the study is taken “as is”, the clinical significance of an OR for CRC risk of 1.49 and the medical management of at-risk individuals is unclear. This OR is lower than having a first degree relative with CRC [4], and also lower than the risk estimates for other moderate penetrance CRC genes, such as CHEK2 and APC*I1307K, where risk management also remains uncertain [5].

Although the possibility of a small increase in CRC risk in BRCA1/2 mutation carriers cannot be completely ruled out (including at younger ages), based on the available data we favor basing CRC screening in BRCA1/2 carriers on family history, as family history likely remains the most important predictor of CRC risk in this cohort. In conclusion, BRCA1/2 carriers have significantly elevated cancer risks that require aggressive surveillance and management, however we believe at this time the data on CRC risk is not strong enough to advocate for enhanced CRC screening in BRCA1/2 individuals.

References:


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Disclosures:

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First, it is important to highlight that the statistical significance of the observed CRC risk disappeared when subgroup analysis was performed to include confirmed \textit{BRCA1/2} carriers, rather than including family members with unknown mutation status. The risk in confirmed mutation carriers provides the most accurate \textit{BRCA1/2} dataset with which to calculate CRC risk, giving this subgroup analysis particular relevance. Second, there are many factors known to increase CRC risk that are unable to be accounted for in this analysis and which may skew the risk assessment. For example, given the abundance of Ashkenazi Jewish individuals in the analyzed studies, the presence of the moderate-risk CRC gene \textit{APC}^{*}I1307K, present in \text{~7\% of Ashkenazi Jewish individuals} [2], may influence CRC risk.

Third, only one study analyzed in the \textit{BRCA1} meta-analysis had a calculated OR that was statistically significant (Reference 27 from [1]), and it was this study that had the largest weight in the meta-analysis. To our knowledge this study by Brohet and colleagues is a dissertation that has not yet been published in a peer-reviewed journal (Reference 27 from [1]); thus it is not clear that it merits inclusion in a meta-analysis. Additionally, the risk data selected from the Brohet study was for colon cancer risk only (RR 2.51, 2.02-3.07), whereas we believe the more appropriate data to use from this study is the more inclusive CRC risk (RR 1.29, 1.05-1.57), which was substantially lower with inclusion of rectal cancers. Fourth, even if the data
from the study is taken “as is”, the clinical significance of an OR for CRC risk of 1.49 and the medical management of at-risk individuals is unclear. This OR is lower than having a first degree relative with CRC [3], and also lower than the risk estimates for other moderate penetrance CRC genes, such as CHEK2 and APC*1307K, where risk management also remains uncertain [4].

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