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RESEARCH HIGHLIGHT

Is prostate cancer a Lynch syndrome cancer?

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The question of whether men with an inherited genetic condition called Lynch syndrome have an increased risk of developing prostate cancer has been controversial. It is important to answer this question, for understanding the role of DNA mismatch repair in carcinogenesis of prostate as well as for clinical implications for screening.

Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer,[1] is an autosomal dominantly inherited cancer susceptibility disorder caused by germline mutations in the DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2*. Carriers of MMR gene mutations have a substantial burden of increased risk for cancers of the colon, rectum, endometrium, stomach, ovary, ureter, renal pelvis, brain, small bowel and hepatobiliary tract which generally occur at younger ages than for the general population.[2] In a recent publication in the *Journal of Clinical Oncology*, Raymond *et al.*[3] reported that men carrying MMR gene mutations have a twofold increased risk of prostate cancer compared with the general population.

Worldwide, prostate cancer is the second most common cancer for men, after lung cancer, with approximately 913 000 new cases (14% of the total cancers) in 2008.[4] Men with a family history of prostate cancer are more likely to be diagnosed with prostate cancer than those without a family history,[5] suggesting the existence of hereditability. So far, only a few cancer predisposition genes have been known to be associated with an increased risk of prostate cancer, including *BRCA1*,[6] *BRCA2*[7,8] and *HOXB13*.[9,10] The question of whether prostate cancer is a Lynch syndrome cancer has been controversial.

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Lynch syndrome cancers typically exhibit MMR deficiency in terms of high DNA microsatellite instability and/or loss of MMR protein expression by immunohistochemistry.[2] Previous studies[11–15] reported that prostate cancers identified in the MMR gene mutation carriers showed MMR deficiency, suggesting that prostate cancers in Lynch syndrome may have been predisposed by defective DNA mismatch repair, but these molecular studies could not demonstrate empirical evidence of risk, i.e., whether prostate cancer is more likely to develop in MMR gene mutation carriers compared with non-carriers (or the general population).

Raymond *et al.*[3] investigated the risk of prostate cancer for men with Lynch syndrome using 4127 men from 198 families carrying germline mutations in MMR genes (74 *MLH1*, 101 *MSH2* and 23 *MSH6*) who were identified through cancer genetics clinics at the Dana-Farber Cancer Institute, Boston, MA, and the University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA. They reported that MMR gene mutation carriers were at a twofold increased risk of prostate cancer compared with the general population (hazard ratio (HR) 1.99, 95% confidence interval (CI) 1.31–3.03, $P=0.001$). They provided penetrance estimates of 17% (95% CI: 10%–24%) at age 70 years and 30% (95% CI: 17%–41%) at age 80 years.

Raymond *et al.*[3] used a modified segregation analysis conditioning on the *probands*' genotype and phenotype status to reduce ascertainment bias, but not on family members. Therefore, the cumulative and relative risks provided from this study will be useful only to estimate risk of prostate cancer for MMR gene mutation carriers from high-risk cancer genetics clinics or MMR gene mutation carriers with a relative affected with colorectal cancer or endometrial cancer, but not for MMR gene mutation carriers from the general population.

As it is very difficult to know the exact reason(s) influencing a person/family to be referred and/or attend a genetics clinic, the correction for ascertainment is usually conservative, i.e., by conditioning on the phenotype status of all family members to avoid overestimation of any particular cancer risk that may have, in part, contributed to referral or attendance,[16] and therefore could provide estimates which are generalizable to mutation carriers from the general population. The consequence of this method is that, if families are ascertained only because of colorectal and/or other cancers but not prostate cancer, the power to identify an increased risk for prostate cancer will be reduced. For example, Dowty *et al.*[17] conditioned on all family members and did not observe evidence for an increased risk of prostate cancer for MMR gene mutation carriers (HR: 0.79, 95% CI: 0.25–2.5 for *MLH1* mutation carriers; and HR: 1.0, 95% CI: 0.47–2.3 for *MSH2* mutation carriers).

Conducting retrospective studies using clinic-based families and conditioning on ascertainment are tricky especially when estimating risks for uncommon cancers in Lynch syndrome. Only a prospective study of mutation carriers with no prior diagnosis of cancer can escape these issues and provide unbiased estimates of cancer risks. To date, there has been only one prospective study of MMR gene mutation carriers who had no prior diagnosis of cancer.[18] In this study, there was no evidence of an increased risk of prostate cancer for MMR gene mutation carriers (standardized incidence ratio (SIR) 2.49, 95% CI: 0.51–7.27, $P=0.18$). The estimates from this study[18] and Raymond *et al.*[3] cannot be said to differ, given the high degree of overlap in the confidence intervals ($P=0.75$).

In an analysis of the Colon Cancer Family Registry, a statistically significantly increased risk of prostate cancer risk was observed for men with a prior diagnosis of colorectal cancer (SIR: 2.05, 95% CI: 1.23–3.01)[19] and,

when stratified by specific MMR gene mutations, the risk was more pronounced for *MSH2* mutation carriers (SIR: 3.62, 95% CI: 2.07–5.36). Raymond *et al.*[3] were not able to provide mutation-specific risks for prostate cancer due to the limited sample size, as the authors noted.

Further, estimates from Raymond *et al.*'s study[3] may not be applicable to Asian populations given that their study sample came from the Caucasian populations (however, this is not explicitly stated within the study).[3] Prostate cancer incidence varies significantly by country (the highest in Australia, New Zealand, Europe and North America, and the lowest in Asia),[4] and there is evidence that the risks for Lynch syndrome cancers differ between Asian and Caucasian populations.[20]

Given current data are inconclusive to provide prostate cancer risk for MMR gene mutation carriers at a general population level, we recommend prospective studies with a long follow-up of MMR gene mutation carriers who do not have any prior diagnosis of cancer to remove any potential ascertainment bias encountered by retrospective cohort studies. Large cohorts will be required to specify prostate cancer risks for specific MMR gene mutation carriers. Further studies would be subsequently required to investigate the role of prostate cancer screening for MMR gene mutation carriers to determine age of onset for screening, optimal method for screening and cost-effectiveness.

COMPETING FINANCIAL INTERESTS

I have no conflict of interest to declare with respect to this manuscript.

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