Germline testing in those at risk of prostate cancer

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Men with germline mutations in DNA repair genes are at an increased risk of prostate cancer. These germline mutations are commonly seen in conjunction with somatic DNA repair gene mutations in prostate tumors. This indicates that men with a personal or family history of prostate cancer—as well as other cancer syndromes arising from mutations in DNA repair genes—should be considered for genetic testing and counseling.

Key Words: prostate cancer, genetic testing, germline mutations

Recent data indicate that men with germline mutations in DNA repair genes are at an increased risk of prostate cancer. These germline mutations are commonly seen in conjunction with somatic DNA repair gene mutations in prostate tumors.[1,2] This indicates that men with a personal or family history of prostate cancer—as well as other cancer syndromes arising from mutations in DNA repair genes—should be considered for genetic testing and counseling.[3]

Germline mutations in a number of homologous DNA repair genes have been observed in men with prostate cancer, including (in approximate order of frequency observed in cases): *BRCA2*, *ATM*, *CHEK2*, *BRCA1*, *MUTYH*, *RAD51D*, *PALB2*, *ATR*, *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, or *FAM175A*.[4,5] Moreover, germline mutations in DNA repair genes occur at a higher rate in men with metastatic prostate cancer than in men with localized disease.[5] This finding is clinically noteworthy in that men with metastatic prostate cancer and DNA repair mutations respond well to poly-ADP ribose polymerase (PARP) inhibitors and platinum-based chemotherapy.[6,7]

A recent study of 3607 men with prostate cancer who were clinically referred for genetic testing found that 17% carried a tested germline mutation, with 11.5% in *BRCA2*, *CHEK2*, *ATM*, *BRCA1*, or *PALB2*.[4] However, in this population, Gleason scores and family history were not associated with variant detection, and a relatively large percentage of men carrying genetic mutations (> 30%) would not have been screened using the current NCCN guidelines.[4]

Germline *BRCA1* and *BRCA2* mutations (associated with hereditary breast and/or ovarian cancer syndrome) occur in approximately 0.2% to 0.3% of the

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general population, with higher rates seen in certain racial/ethnic groups.[8] These mutations have been associated with an increased risk for prostate cancer in numerous reports.[9-19] In particular, *BRCA2* mutations have been associated with a 2- to 6-fold increase in the risk for prostate cancer, whereas the association of *BRCA1* mutations and increased risks for prostate cancer are less consistent.[9-21] Furthermore, prostate cancer in men with germline *BRCA* mutations appears to occur earlier, has a more aggressive phenotype, and is associated with significantly reduced survival times than in non-carrier patients.[22-28] Among lethal prostate cancer cases, 60% of mutation carriers of *BRCA1/2* and *ATM* report a negative family history.[22]

Results from the first round of screening of the IMPACT study, which enrolled men aged 40 to 69 years with germline *BRCA1/2* mutations and a control group of men with wild-type *BRCA1/2* who are related to mutation carriers, were recently reported.[29] Whereas it was evident that there was no difference between carriers and controls in the rate of prostate cancer detection or the PPV of biopsy for detecting cancer in men with PSA > 3.0 ng/mL, a significant difference was seen in the PPV of biopsy for detecting intermediate/high-grade cancer in *BRCA2* carriers with PSA > 3.0 ng/mL (2.4% versus 0.7%; p = .04). Future rounds of screening in this trial may help inform the best strategy for screening in this high-risk population.

Men with Lynch syndrome (germline mutations in DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) have a 2- to 5.8-fold increase in risk for prostate cancer.[30-36] Age of onset and aggressiveness of prostate cancer in these individuals, however, do not generally appear to be different than in sporadic cases.[32,35] Carriers of the G84E mutation of the *HOXB13* gene also have a significantly higher risk for prostate cancer and are more likely to have early-onset familial disease.[37,38] *HOXB13* mutations are more frequent among families of Scandinavian heritage.

There is a significantly increased risk of a family history of first-degree relatives with non-prostate cancers among men with mutations in DNA repair genes.[5] This is especially meaningful for three reasons: 1) men with DNA repair mutations have been shown to be candidates for specific therapeutics; 2) the detection of mutations in DNA repair genes can inform personalized screening strategies; and 3) because the mutations are germline and implicated in various malignancies, they help to identify whole families that may be particularly susceptible to cancer.[39,40]

Commercial panels are now available to assess most of the main high-penetrance prostate cancer risk genes. Information regarding the status of high-risk germline mutations should be used as part of the discussion about prostate cancer screening; patients may not be aware of the increased risk for prostate cancer associated with such mutations.

Disclosures

Dr. Peter R. Carroll and Dr. John S. Witte have no disclosures.
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