Prostate cancer genetic testing: NCCN familial high-risk assessment: breast/ovarian

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The National Comprehensive Cancer Network (NCCN) clinical practice guidelines have become the most recognized standard for clinical policy in cancer care. The Genetic Breast and Ovarian Guideline was introduced in 1999 with an emphasis on BRCA1/2. Based on evidence linking prostate cancer to the BRCA genes, prostate cancer was added to the guideline as a criterion for risk assessment in 2013. The current criteria include aggressive/metastatic disease and family history of BRCA-related cancers.

Key Words: prostate cancer, *BRCA* genes, genetic testing, risk management

The National Comprehensive Cancer Network (NCCN) is an alliance of cancer centers devoted to patient care, research and education. The overall mission of NCCN is to improve and facilitate quality, effective, efficient and accessible cancer care on a global scale.[1] The alliance is made up of 28 leading academic cancer centers in the United States which develop and communicate scientific, evaluative information to better inform the decision-making process between patients and physicians. The NCCN clinical practice guidelines have become the most recognized standard for clinical policy in cancer care. Each of the 59 guideline panels, comprised of 28-35 experts representing each member institution, meet on a regular basis to update the guidelines based on the best and most current evidence.

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The genetic/familial risk assessment

Breast and Ovarian Guideline was first introduced in 1999 with an emphasis on the *BRCA1/2* genes. Over the years the scope has broadened to include other genes and other cancers shown to be related to hereditary breast/ovarian syndrome. Based on evidence linking both aggressive prostate cancer and a family history of BRCA-related cancers to the *BRCA* genes, it was first added to the guideline as a criterion for risk assessment in 2013. NCCN relies on the growing body of evidence which is helping to further characterize the features of prostate cancer which indicate a heritable component. While earlier studies failed to find an association between the three founder mutations in the Ashkenazi population with prostate cancer, a large case-control study found a significantly increased risk of prostate cancer in carriers of the *BRCA2* founder mutation, but not in carriers of the two *BRCA1* founder mutations.[2] A subsequent case-control study found both an increased risk of prostate cancer in Ashkenazi prostate cancer

patients who carried a *BRCA2* mutation, and a higher risk of poorly differentiated histology, recurrence and prostate cancer-specific death.[3] A retrospective analysis of clinical outcomes of non-AJ prostate patients with germline *BRCA* mutations in the UK found that poorly differentiated cancer, advanced stage, nodal involvement and metastatic disease were all more common in carriers than non-carriers. In this population, median overall survival was significantly decreased in *BRCA2* carriers compared to non-carriers.[4]

A multicenter study evaluated the frequency of mutations in a series of 20 DNA-repair genes, including the *BRCA* genes, in men unselected for family history who had metastatic prostate cancer. At least one presumed pathogenic germline mutation involved in DNA-repair was found in 11.8% of men. Of these, 44% of mutations were in the *BRCA2* gene. The odds ratio of finding a DNA-repair gene among men with metastatic prostate cancer was 5.3 compared to a control group of men with localized low-to-intermediate-risk tumors. Metastatic disease in this study was a better predictor of a DNA-repair mutation than was a family history of prostate cancer.[5] Mutation status of *BRCA1/2* and *ATM* was a significant predictor of lethal disease in a case-case study which compared men who died from prostate cancer to those with low-risk localized disease. The association of lethality and mutation status was observed in Caucasian, African American and Chinese men.[6] A predominant finding in all of these studies is the much greater association of *BRCA2* with prostate cancer compared to *BRCA1*. The current guideline includes prostate cancer with a Gleason score of ≥ 7 in the context of a family history of other *BRCA*- related cancers, or metastatic prostate cancer as indications for genetic testing. The current guideline also recognizes the potential benefit of testing of men with prostate cancer for targeted therapeutic options.

There is less evidence to guide screening recommendations for men with hereditary prostate cancer. The IMPACT screening network is following a cohort of men with *BRCA1/2* mutations and a control group of true negative *BRCA1/2* men to determine the optimal screening protocol for men with germline *BRCA* mutations. Using a PSA threshold of 3.0 ng/mL for considering prostate biopsy, their first screening round found a positive predictive value of 48% among *BRCA2* carriers, which is double that seem in population screening studies.[7] This cohort will continue to be followed to provide further data on the value of regular screening in BRCA men. The current NCCN guideline recommends prostate cancer screening for *BRCA2* carriers, and a consideration of prostate cancer screening for *BRCA1* carriers. It directs readers to the Guidelines for Prostate Cancer Early Detection.

Cancer genetics is a constantly evolving field and NCCN will continue to update its guidelines as more evidence becomes available. Some of the pressing questions are: what other genes are associated with prostate cancer, and what is their prevalence and penetrance: what additional therapeutic options may become available based on mutation carrier status; what is the optimal threshold for PSA level in screening mutation carriers; and what is the role of MRI scanning in detecting early stage prostate cancer.

Disclosures

Dr Mary B. Daly has no disclosures. □

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