DNA repair genes: contributions to prostate cancer predisposition and aggressiveness

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Germline pathogenic mutations in DNA repair genes have been linked to prostate cancer risk and aggressiveness. This observation was facilitated by tumor sequencing of men with advanced prostate cancer and has important implications for clinical management. In addition, cascade testing will identify at-risk individuals who should be assessed for cancer risk.

Key Words: prostatic neoplasms, cancer genetics, hereditary cancer syndrome

Introduction

Prostate cancer exhibits a high degree of heritability which is more significant than observed in other common cancers including breast, ovarian and colon cancer.[1] With the exception of the discovery of *HOXB13*,[2] however, it has been difficult to identify rare prostate cancer susceptibility genes using genetic linkage approaches. Since DNA repair genes play a key role in maintaining genomic integrity and are known to segregate with other heritable cancers, they are strong candidates for prostate cancer susceptibility. Recently, studies of men with metastatic prostate cancer have led to the recognition that germline mutations in DNA repair genes (*BRCA1/2*, *ATM*, etc.) may occur in ~10% of men with advanced prostate cancer.[3,4] Robinson et al[3] initially reported integrative tumor sequencing data from 150 men with castrate-resistant prostate cancer and identified DNA repair/recombination gene alterations in 23% of cases, with the majority harboring biallelic alterations. Notably, 13/150 (8.7%) of patients carried a pathogenic germline mutation in *BRCA1/2* or *ATM*. A larger multisite study of 692 men with metastatic prostate cancer found an even higher rate of germline mutations (11.8%) across 20 DNA repair genes.[5] Family history information was available for 88% of the patients in this study and, interestingly, men harboring a pathogenic germline mutation were more likely to have a first degree relative with a cancer other than prostate cancer (71%) than a first degree relative with prostate cancer (22%). These reports shed new light on the relationship of DNA repair mutation carrier status and prostate cancer risk which will be reviewed in this presentation.

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Hereditary breast and ovarian cancer (HBOC) families

Early studies of HBOC families demonstrated an increased risk of prostate cancer in male mutation carriers compared to non-mutation carriers. Deleterious germline mutations in both *BRCA1/2*, classically associated with HBOC, have been shown to increase the risk[6] and aggressiveness[7] of prostate cancer, with prostate cancer risk elevated more in HBOC families with *BRCA2* mutations than those with *BRCA1* mutations (data from the Breast Cancer Linkage Consortium).[8,9] These findings may have important prognostic and therapeutic implications for prostate cancer patients and men in HBOC families. However, it is important to note that studies of prostate cancer-only families have not found a significant number of *BRCA1/2* pathogenic mutations, indicating these mutations likely contribute to a small portion of hereditary prostate cancer.

Lynch syndrome families (LS)

In addition to colorectal cancer, there are a number of cancers that occur with increased frequency in individuals carrying a pathogenic germline mutation in an LS-associated mismatch repair (MMR) gene. These LS-associated cancers occur in the endometrium, ovary, stomach, small bowel and ureter, but data supporting an LS-prostate cancer correlation has been conflicting. In 2014, Raymond et al[10] reported an overall hazard

ratio for prostate cancer of 1.99 (95% CI, 1.34 to 4.59, p = 0.0038) across two large familial LS cancer registries, while an independent meta-analysis identified a risk elevation of 2.28-fold (95% CI, 2.32-6.67) for men with MMR mutations in LS families.[11] Interestingly, prostate cancer tumors sequenced from individuals with LS carry classic microsatellite instability signatures, an uncommon observation in prostate cancer.[12] In light of this new information, there is general consensus among experts that men harboring MMR mutations are at an increased risk for prostate cancer, but the magnitude of the risk elevation is not fully defined.

DNA repair genes and prostate cancer clinical attributes

Initial clinical reports with small cohort sizes suggested that prostate cancer patients harboring a *BRCA1/2* deleterious mutation may experience more aggressive forms of prostate cancer leading to poor clinical outcomes.[13,14] Castro et al[7] published a report comparing clinical presentations and outcomes of 18 *BRCA1* and 61 *BRCA2* carriers with prostate cancer compared to 1,940 noncarriers with prostate cancer. Men carrying a deleterious *BRCA1/2* mutation were more likely to have high grade (Gleason score > 8) and/or high stage (T3/T4 / N+ / M+) cancers, as well as experience shorter overall survival. Using a retrospective case: case study, Na et al[15] compared the frequency of *BRCA1/2* and *ATM* mutations between 313 men with lethal prostate cancer and 486 men with indolent prostate cancer from three distinct racial/ethnic groups. The overall mutation carrier rate was significantly elevated in the lethal prostate cancer cohort compared to the indolent prostate cancer cohort (6.07% versus 1.44%; p = 0.007). Additionally, *BRCA1/2* and *ATM* mutation carrier status was an independent predictor for prostate cancer-caused death in an adjusted model. Clinically, pathogenic DNA repair mutation carrier status has been shown to confer preferential response to platinum-containing regimens[16] and PARP inhibitors.[17]

Conclusions and future directions

In summary, pathogenic germline mutations in DNA repair genes, including *BRCA1/2* and *ATM*, increase the risk of prostate cancer development and clinically aggressive prostate cancer phenotypes. Identification of these mutations in prostate cancer patients has clinical and therapeutic implications, as patient outcomes improve with molecularly-informed treatment approaches. Among the many areas for future investigation, gaining a better understanding of optimal approaches for early stage prostate cancer detection in male pathogenic mutation carriers and pursuing further exploration of customized post-diagnosis treatment strategies are critical.

Disclosures

Julie Boyle has no disclosures.
Dr. Kathleen A. Cooney has ownership interest in a patent on *HOXB13* as a genetic marker of prostate cancer risk, owned by Johns Hopkins and University of Michigan. □

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