Clinical Commentary

Prostate Cancer Screening in a New Era of Genetics

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Abstract

Men who inherit pathogenic germline mutations in *BRCA2* and *BRCA1* are at increased risk of developing aggressive prostate cancer, and those with germline mutations in other DNA repair genes such as *ATM, CHEK2, and MSH2/MSH6* may also have increased risks. Although clinically important, there is lack of specific guidance regarding management strategies for men at increased risk owing to germline mutation status or family history of aggressive prostate cancer. We review prostate cancer genetic risk factors and the ongoing IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls) screening study. Pending results of IMPACT and unified guidelines, there are areas of uncertainty and need for further study. Ongoing and future research will be critical for optimizing prostate cancer screening approaches for men at the highest risk for aggressive prostate cancer. In the interim, we propose a practical approach to prostate cancer screening for men with a germline mutation in a known/suspected moderate to high-penetrance cancer predisposition gene (eg, *BRCA1/2*), and/or men with a first- or second-degree relative with metastatic prostate cancer (regardless of genetic testing): baseline prostate-specific antigen and digital rectal exam by experienced providers at age 40 years or 5 years earlier than age of diagnosis of the youngest first- or second-degree relative with metastatic prostate cancer, whichever is earlier. Then, based on age, digital rectal exam, and prostate-specific antigen, we suggest consideration of magnetic resonance imaging, biopsy, and/or continued monitoring.

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The past several years have delivered a succession of notable discoveries in prostate cancer involving DNA repair genes (DRGs) that have important implications for clinical care. These findings include somatic loss of DRG function in 20% of metastatic prostate cancers, high rates of therapeutic responses to PARP inhibitors and platinum chemotherapy in those tumors with homologous recombination DNA repair defects, and far higher than expected germline DRG mutations in men with metastatic prostate cancer.[1,2] In 2016, a dedicated study of nearly 700 men with metastatic prostate cancer found that 11.8% carried presumed pathogenic germline mutations in DRGs associated with cancer predisposition,[3] and subsequent studies have confirmed similarly high rates in metastatic compared with localized prostate cancer cases.[4-6] These changes point to new opportunities for precision oncology in prostate cancer, but also bring new conundrums. Germline genetic testing (ideally with genetic counseling support) to identify those men with advanced prostate cancer who harbor somatic homologous recombination DNA repair deficiency is already beginning to occur, as these individuals may benefit from PARP inhibitors and platinum chemotherapy. In contrast to guidelines for female carriers of *BRCA1/2* mutations at risk for breast and ovarian cancers, there is a lack of consensus for how to manage the male relatives including the brothers, sons, and nephews who undergo cascade testing and are found to carry the same mutation. How should we counsel and manage an unaffected man who carries a germline pathogenic *BRCA2* mutation? More challenging, what about a man with a pathogenic mutation in a newly implicated gene such as *ATM*, *CHEK2*, *or PALB2*, or a variant of uncertain significance (VUS)?

To begin to address these important issues, a brief review of prostate cancer genetic risk is warranted. Prostate cancer is one of the most heritable cancers, and family history of prostate cancer is a well-established risk factor.[7,8] An updated analysis of the Nordic Twin Studies estimates that up to 57% of prostate cancer risk may

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be accounted for by inherited factors.[4,9,10] These factors are comprised of 2 classes: (1) common variants (single nucleotide polymorphisms) identified through genome-wide association studies that individually carry a slightly increased risk, and (2) rare variants or mutations in genes that confer substantially higher risk if altered (eg, *BRCA1/2*). Genome-wide association studies have largely dominated prostate cancer research for the past few decades, with over 100 loci (eg, 8q24, 17p) implicated that may collectively account for up to one-third of familial risk of prostate cancer. However, these single nucleotide polymorphisms have not yet been incorporated into clinical practice, in part owing to relatively modest effects on risk (eg, less than 2-fold increases).[11,12]

On a population basis, relatively rare pathogenic germline mutations in tumor suppressor genes disrupt critical gene function and result in a significantly elevated risk of developing certain cancers. Pathogenic germline mutations in *BRCA2* and *BRCA1*, for example, have been studied in association with autosomal dominant hereditary breast and ovarian cancer predisposition syndrome. Studies have now shown that mutations in these genes also confer increased risks of developing prostate cancer, and more importantly, these cancers behave aggressively with higher rates of disease recurrence after primary treatment and increased mortality. Consequently, we recommend that men in families with relatives found to have a pathogenic *BRCA1* or *BRCA2* mutation also have germline testing. We strongly recommend consulting with a genetics professional when possible, especially when considering/planning cascade testing of family members (generally recommended once individuals are over the age of 18 years). This recommendation stems from potential patient and family confusion and stress around genetic testing results that may be delivered without appropriate pre- and post-test counseling. Many tests issue the following categories of result: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign, with "likely" used to mean a greater than 90% certainty of a variant being disease-causing or benign with specific criteria to evaluate supporting evidence.[13] Uncertain significance is ascribed when neither criteria for pathogenic/likely pathogenic or benign/likely benign are met. In the case of variants of uncertain significance, we recommend considering clinical risk factors, such as family history, to guide management.

Pathogenic germline mutations in *BRCA1* and *BRCA2* are estimated to confer 1.1- to 3.8-fold[4,14,15] and 4.7- to 8.6-fold increased risks of prostate cancer, respectively.[11,16,17] Moreover, a growing body of data indicates that men with prostate cancer who carry germline pathogenic *BRCA2* mutations have earlier onset disease and worse prostate cancer outcomes and survival.[5,18-20] The evidence for germline pathogenic *BRCA1* mutation carriers is less clear, though *BRCA1* mutations have been observed at a higher rate in the metastatic setting, suggesting a similar association. Thus, there is rationale for considering men who carry pathogenic and likely pathogenic mutations in high penetrance germline cancer predisposition genes as a group likely to be at particularly high risk for developing aggressive prostate cancer.

Currently there is a lack of consensus and specific direction in the prostate cancer screening and early detection guidelines in many of the professional societies, including the American Urological Association (2013),[21] National Comprehensive Cancer Network (2016),[22] and American Cancer Society (2016).[23] The current draft prostate cancer screening guidelines from the United States Preventative Service Task Force recommend that men with a family history of prostate cancer talk to their clinician about the potential benefits and harms of screening, with no additional specific guidance for *BRCA1/2* mutation carriers.[24] The National Comprehensive Cancer Network guidelines suggest inquiring about family history of *BRCA1/2* mutations, but stop short of further recommendations.[6,22] This is likely the result of guideline committees calling for evidence that is incomplete or pending with respect to prostate cancer screening in *BRCA1/2* mutation carriers.

The ongoing international IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls) study was designed to assess a targeted screening approach for mutation carriers and non-carriers as controls (clinicaltrials.gov; NCT00261456).[25] The initial screening round used a strategy of annual prostate-specific antigen (PSA) measurements followed by prostate biopsy for PSA $>$ 3.0 ng/mL. The positive predictive value for biopsy was higher in *BRCA2* mutation carriers compared with non-carriers (48% vs. 33%), and a significant difference was observed in detecting intermediate- or high-risk disease (68% vs. 43%) even within the first year of the study. Similarly, the positive predictive value for biopsy was higher in *BRCA1* mutation carriers compared with non-carriers (41% vs. 23%), although a significant difference in detecting intermediate- or high-risk disease were not observed within the first year. Longer follow-up and final results are eagerly anticipated, but even after completion, there will be unanswered questions.

In the case of known germline pathogenic *BRCA1/2* carriers for whom prostate cancer risk estimates are described, the biopsy threshold of PSA $>$ 3.0 ng/mL used in IMPACT can likely be further refined, even if it is demonstrated to be useful. For example, we will not learn from the IMPACT study if PSA $>$ 3.0 ng/mL is the optimal threshold to trigger biopsy. An alternative approach is to use a PSA threshold to recommend biopsy if the PSA exceeds the age-specific mean (which can be substantially lower than 4.0 ng/mL or the 3.0 ng/mL used for IMPACT). This approach may be complicated by lack of standard age-specific thresholds as well as by differences based on genetic background.[26-29] One series reported that lowering the cutpoint to $>$ 2.5 ng/mL may have a favorable detection rate with lower rates of eventual PSA progression.[30] In the Prostate Cancer Prevention Trial, high-grade prostate cancers were found in 12.5% of men with PSA $<$ 0.5 ng/mL.[31] This suggests that even a very low PSA threshold will miss some aggressive cancers and may justify considering a biopsy regardless of PSA if there is evidence of abnormality by another measure such as imaging or digital rectal exam (DRE).

The utility of early detection strategies for any cancer depends on a predictable natural history and disease course, typically on the order of years to decades. Colorectal cancer screening strategies are successful because adenocarcinomas typically arise from precancerous polyps on a temporal scale of many years, during which polyps can be detected and removed before or at least early in the disease course. By comparison, pancreatic cancer is much more challenging to detect early and effectively intervene upon owing to a relatively compressed temporal scale, conceivably on the order of months to years. It is tempting to take what we know about the increased aggressiveness of *BRCA1/2*-associated prostate cancer and conclude