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Journal of Urology and Research

Mini Review

Genetics in Prostate Cancer: Current Understanding of Germ Line Mutations and Future Implications

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Submitted: 14 December 2016

Accepted: 20 February 2017

Published: 22 February 2017

ISSN: 2379-951X

Keywords
- Germ line prostate cancer
- Prostate cancer
- Genetic screening

Abstract

Germ line associated prostate cancers are a rare entity, but have powerful implications in terms of screening and targeted treatment options. Here, we assess the genetics of germ line prostate cancer, as well as specific genes associated with prostate cancer. We also discuss potential screening tests that can be used in practice. We discuss future aims and implications for research associated with germ line prostate cancer.

ABBREVIATIONS

PCa: Prostate Cancer; APC: Adenomatous Polyposis Coli Gene; BRCA: Breast Cancer Susceptibility Gene

INTRODUCTION

Prostate cancer represents the most frequently diagnosed non-cutaneous cancer and second-most common cause of cancer-related mortality among American males [1]. Localized prostate cancer has a high response rate to therapy, while 5-year survival rates of metastatic cancer remain less than 25% [2]. Therefore, an accurate screening tool which can discover prostate cancer early could be the cornerstone for improving survival. Since its approval in 1994, DRE with PSA screening has been the major screening mechanism in urologic practice but PSA screening has been controversial, however, due to its low sensitivity and specificity [3,4]. Though evident PSA screening has reduced prostate mortality, many men have undergone unnecessarily risky treatment for clinically insignificant disease [5]. Research efforts in the past 5 years have greatly increased our knowledge about the role of genetics in prostate cancer. Hereditary germ line cancers specifically have been demonstrated to provide a pathway for more clinically effective and actionable screening [6]. These patients make up a significant portion of all prostate cancer and tend to have more severe disease [7]. The purpose of this paper is to inform primary care physicians and urologists on germ line prostate cancer and the screening tools available.

Hereditable mutations and their impact on prostate cancer

Twin-association studies have estimated inheritance plays a role in more than 40% of all prostate cancers [8]. More than 100 single nucleotide polymorphisms (SNPs) have been identified in the risk of developing PCa, however no single SNP has been found to produce a significant risk alone. As such, currently identifying SNPs in individuals or populations has no apparent clinical effectiveness [9]. Regarding somatic mutations, they are found only in the tumor tissue and confer no risk to other family members as they are not heritable. Conversely, germ line mutations are a set of hereditary aberrations in cancer-regulatory genes, of which every cell in the body contains the same inherited mutation and is stable but can predict the risk for future cancers [10]. They can be defined by the activation of cancer-promoting genes (oncogenes) such as *RET*, or defects in tumor-suppressing genes like *BRCA1/2* and *APC*. Inheritance of the defective gene accounts for the "first hit" in the two hit hypothesis and thus increases the risk of cancer development via a sporadic "second hit" [11]. Germ line cancers comprise about 15% of prostate cancer, with *BRCA1/2* and *HOXB13* mutations involved as the most common susceptible genetic loci [12,13].

Specifically, multiple studies have confirmed *BRCA2* mutations confer several-fold higher risk of early-onset high grade (Gleason ≥ 7) PCa and mortality on average, as well as higher probability of nodal involvement and distant metastases [7,12,14,15]. Further

evidence has implicated *BRCA* mutations as an independent negative prognostic indicator after prostatectomy and radiation [16]. Additionally, newer research suggests approximately 11.8% of men with metastatic prostate cancer exhibit germ line mutations in DNA-repair mechanisms (*BRCA1/2*), much higher than the 1.5% of men exhibiting similar mutations in primary localized prostate cancer [17].

Systemic targeted therapies such as a Poly-ADP ribose polymerase (PARP) inhibitor (Olaparib) may be an effective management for *BRCA* patients with advanced metastatic castration resistant PCa (mCRPC). Others have demonstrated successful treatment utilizing cytotoxic platinum analogs in cases without neuroendocrine differentiation [7,18]. Two-small scale studies indicate a germ line BRCA mutation, however, may not prevent positive response to taxane-based therapy as there was no statistical response difference between carriers and non-carriers [19]. Given the recent data, it may be useful in to obtain genetic testing in metastatic prostate cancer patients due to the high incidence of carriers, aggressive disease course, and clinically actionable treatment strategies. In an ongoing, large scale study to define the screening indicators for BRCA positive individuals more effectively (IMPACT), preliminary results suggest utilizing a screening PSA in known *BRCA2* carriers starting at 40 years old as this has been demonstrated to potentially reduce mortality. This study recommends a PSA value over 3ng/ml warrants a prostate biopsy, as positive predictive value at this level was twice that described by wide-scale studies (ERSPC) in the normal population [6].

The *HOX* genes are important in the embryologic formation of the lobes of the prostate gland, seminal vesicles, and epididymis [20]. Several studies have identified an association with a **HOXB13** [G84E] mutation and prostate cancer risk [13,21]. This mutation has an estimated 5-fold lifetime risk of developing prostate cancer, and up to 8 times increased risk in those younger than 55 or with a family history [21]. This mutation is present in ~5 % of with family history of prostate cancer and in patients predominantly of European descent (although there has also been an association in Chinese men). Importantly, the carrier rate is rare (0.1-0.2%) and thus the usefulness for screening in general urologic practice is limited [22]. The Engrailed genes (EN1 and EN2), members of the *HOX* family, are secreted into the urine by PCa cells but not by normal prostate tissue [23]. Urine *EN2* has acceptable specificity for PCa detection (sensitivity 66%, specificity 88.2%) and thus may be utilized as part of a screening protocol in the future [24]. More extensive research is being conducted on *HOX*'s relation to prostate cancers.

Several other genes involved in cellular function have been implicated in heritable prostate cancer. For example, DNA repair genes such as PALB2, MLH1, MSH2, and PMS2 have recently been identified as possible DNA repair genes implicated in heritable prostate cancer [25]. The PTEN tumor suppressor gene is involved with the PI3K/AKT signaling pathway, which influences several key cellular functions such as cell growth, proliferation, and migration. PTEN mutations do occur in both a sporadic and heritable fashion, and have been implicated in multiple cancers, including prostate [26].

Giri et al., have published one of the most comprehensive reviews outlining the risk associated with various gene mutations in prostate cancer. The authors suggest that while BRCA and HOXB13 mutations are consistently demonstrated to be involved with increase prostate cancer risk, they account for only a small amount of the inherited predisposition to prostate cancer. Checkpoint inhibitor gene mutations, mismatch repair genes (such as those implicated in Lynch syndrome), as well as approximately 100 new gene loci found on recent genome-wide association studies contribute to an increased risk of familial prostate cancer as well (Table 1) [27].

Genetic screening

A family history consisting of first or second degree relatives with breast, ovarian, pancreatic, or prostate cancers, as well as known familial *BRCA* mutations, may necessitate formal genetic testing. The more profound the family history (i.e. the greater number of relatives, degree of relation, age at onset), the greater correlation to an individual's relative risk as a genetic carrier of potential genes associated with PCa [28]. Using breast cancer as a parallel, it is important to note that a significant percentage of *BRCA*-mutated breast cancer patients had limited family history of the disease. As such, an unimpressive family history in prostate cancer may not necessarily suggest a normal *BRCA* gene, which may have clinically relevant implications [29].These factors must be accounted for in evaluating the need for formal testing.

Formal genetic testing is available through a number of services and accessible for most clinicians in the US. Screening tests evaluate the DNA sequence of select genes to evaluate for mutations predictive of hereditary cancer susceptibility [30]. Pathogenic mutations, as opposed to deleterious mutations, are more clinically relevant. Any given test may yield Variants of Unknown Significance (VUS), which are point changes in the gene which may or may not have increased cancer risks [31]. As more data and testing becomes available, different VUS can be classified as benign or pathogenic. There are multiple genetic testing panels available (Table 2) which can evaluate for the presence of *BRCA* and other mutations available from companies such as Ambry Genetics (www.ambrygen.com), including: BRCA Plus (6 genes), BRCA Plus Expanded (8 genes), Prostate Next (14 genes), Cancer Next (32 genes) and Cancer Next Expanded (67 genes). Generally, panels describing more genes have increased VUS rates, and limited consensus for moderate penetrant genes, but allow more comprehensive analysis and can more effectively determine causative gene mutations. Turnaround time ranges from 7-14 days (BRCA Plus) to 2-3 weeks for some panels [32]. Over 90% of those insured are covered (including Medicare/Medicaid) and 4 out of 5 patients pay $100 or less for testing with cash prices being around $999 for uninsured patients. Importantly, the genetic testing mentioned previously can evaluate whether an individual will develop cancer; moreover, it is useful in patients who have already developed cancer to examine a potential germ line mutation as the cause of the cancer [30]. Subsequently, other family members can be tested for targeted management and prevention. Communication with the family before, during, and after the testing period is critical. There may be barriers to cost, time for result turnaround, and accuracy, all of which can evoke uneasiness and anxiety. Family members may also not want to be screened or experience a variety of emotions during the process

Table 1: Characteristics of Genes Involved in Germline Prostate Cancer.

Mutated Gene(s)	Risk of Prostate Cancer**	Carrier Frequency	Associated Cancers Besides Prostate Cancer
BRCA1	1.07-3.81		Breast, Ovarian, Pancreatic, Melanoma
BRCA2*	3.18-8.6	1.3-3.2%	Same as BRCA1
Mismatch Repair Genes (i.e. such as those implicated in Lynch syndrome)	1.99-3.67		Colon, Uterus, Ovaries, Upper Tract Urothelial cancers, Stomach, Small Bowel, Biliary tract, Brain
HoxB13*	2.80-8.47	0.66-6.25%	
Chek 2 check point inhibitor	2.0-2.7		

Adopted from: *Giri and Beebe-Dimmer. Familial Prostate Cancer. Seminars in Oncology, 2016-10-01, Volume 43, Issues 5, pg 560-565.* (Reference 27; includes primary sources for data cited).
*BRCA2/HoxB13: most consistently demonstrated mutations in prostate cancer
**Combination of odds ratios, relative risks, hazard rations, or standardized incidence ratios.

Table 2: Various Genetic Tests.

Test	Number of Genes Analyzed	Manufacturer	Use in:	Turnaround time for blood sample
BRCA Plus	6	Ambry Genetics	Consider in patients with prostate cancer, who have a strong family history of breast and/or ovarian cancer	7-14 days
BRCA Plus Expanded	8	Ambry Genetics	Same as BRCA Plus	14-21 days
Prostate Next	14	Ambry Genetics	Patient with personal history of prostate cancer, and strong family history of breast, ovarian, pancreatic, or prostate cancer.	14-21 days
Cancer Next	32	Ambry Genetics	Patient with family history of hereditary cancers, but do not fit a particular hereditary syndrome	14-21 days
Cancer Next Expanded	67	Ambry Genetics	Patient with family history of hereditary cancers, but do not fit a particular hereditary syndrome	14-21 days

[33]. Clinicians can be advocates for their patients by screening at high quality locations with dual methodologies (array and Next-Gene Sequencing), confirm the findings, and have access to comprehensive interpretation. Speaking with the lab directly and asking questions when appropriate can help clarify the next directions for care.

DISCUSSION AND CONCLUSION

Heritable germ line cancers represent about 15% of prostate cancers in the US with the most commonly implicated genes *BRCA2*. Germ line associated cancers are an independent negative prognostic indicator and have more aggressive disease type and metastasis incidence, especially *BRCA2* mutations. Preliminary results from the IMPACT study suggest annual screening in *BRCA2*-mutated individuals above the age of 40, with PSA value ≥ 3 mg/dl warranting biopsy. Those with mCRPC should be screened for *BRCA2* and may respond to PARP inhibitors (Olaparib) or platinum-based therapy. Early studies suggest urine *EN2* related to *HOX* may have higher sensitivity and specificity than PSA, with further research currently underway. Positive family history consisting of prostate, breast, ovarian and pancreatic cancers should prompt discussion and evaluation for formal genetic testing, although positive family history is not an absolute to carry mutated alleles. Genetic testing panels evaluating *BRCA1/2* are available to community physicians; larger panels are more accurate and comprehensive but have higher VUS rate. Cost, turnaround time, and patient-centered care should help guide screening decisions.

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Cite this article

Catarinicchia SP, Clinkenbeard A, Crawford DE (2017) Genetics in Prostate Cancer: Current Understanding of Germ Line Mutations and Future Implications. J Urol Res 4(1): 1078.