The Role of the BRCA2 Gene in Susceptibility to Prostate Cancer Revisited

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Abstract

Prostate cancer is a genetically complex disease with multiple predisposing factors affecting presentation, progression, and outcome. Epidemiologic studies have long shown an aggregation of breast and prostate cancer in some families. More recently, studies have reported an apparent excess of prostate cancer cases among BRCA2 mutation–carrying families. Additionally, population-based screens of early-onset prostate cancer patients have suggested that the prevalence of deleterious BRCA2 mutations in this group is 1% to 2%, imparting a significantly increased risk of the disease compared with non-carrier cases. However, studies of high-risk prostate cancer families suggest that BRCA2 plays at most a minimal role in these individuals, highlighting the potential genetic heterogeneity of the disease. In this commentary, we review the current literature and hypotheses surrounding the relationship between BRCA2 mutations and susceptibility to prostate cancer and speculate on the potential for involvement of additional genes. (Cancer Epidemiol Biomarkers Prev 2008;17(8):1843–8)

Introduction

Prostate cancer is the most commonly diagnosed solid tumor among men in the United States, with about 186,320 men expected to be diagnosed in 2008, and 28,660 expected to die (1). Prostate cancer is a genetically complex disease with multiple predisposing factors affecting presentation, progression, and outcome (2–7). About 10% of prostate cancers are assumed to be hereditary, although the number increases dramatically for younger men (8). Several approaches have been used in an effort to identify genes that contribute to disease-related variables, including age at diagnosis, stage and tumor grade at diagnosis, metastasis, response to therapy, and prostate cancer–related mortality. Complicating the issue are several factors, including shifting screening criteria, potential differences between sporadic and so-called “hereditary” forms of the disease, locus heterogeneity, and rapid changes in treatment choice. Currently, most men will die with rather than of their disease, highlighting the genetic and epidemiologic complexity of this disease.

As early as 1974, epidemiologic studies showed an aggregation of breast and prostate cancer in some families (9–13). More recently, studies have reported an apparent excess of prostate cancer cases among BRCA2 mutation carriers (14). With estimates that BRCA2 carriers may experience a 23-fold increased relative risk (RR) for developing prostate cancer by the age of 56 years (15), it is timely to review the current state of the literature and comment on the public health importance of germ-line BRCA2 mutations in susceptibility to prostate cancer. Of equal importance is an effort to learn as much as possible about as yet undiscovered genes causing susceptibility to hormonal cancers.

Finding Prostate Cancer Genetics

Considerations in this commentary are made against the backdrop of many published genome-wide scans for prostate cancer susceptibility genes using high-risk prostate cancer families (5, 16–24) and, more recently, whole-genome association studies (25–31) that have generally relied on meta-analyses of existing collections of affected cases and unaffected controls. Both types of studies have been aimed at identifying loci that contribute to prostate cancer susceptibility, morbidity, and mortality.

High-risk prostate cancer families have traditionally been described as those that fell into one of three criteria: (a) three or more first-degree relatives affected with prostate cancer; (b) prostate cancer in three or more generations; or (c) an early age of prostate cancer diagnosis among at least two first-degree relatives, usually siblings (8). Since 1993, at least two dozen linkage scans for prostate cancer loci have been completed, often with conflicting results (2, 3, 5, 6). Exceptions have included multiple studies confirming loci at chromosomes 8q24 (26–29, 31–36), 22q12 (19, 24, 37–41), and 17q24 (28–30, 38, 42, 43).

A Role for BRCA2 and Prostate Cancer Susceptibility

In addition to looking for “new” prostate cancer loci, considerable research has also focused on determining
whether the known breast cancer susceptibility genes \textit{BRCA1} and \textit{BRCA2} confer risk of prostate cancer. In women, germ-line mutations in \textit{BRCA1} and \textit{BRCA2} increase a carrier’s risk of breast, ovary, fallopian tube, and peritoneal cancer. Additionally, families harboring these mutations show clustering of cancer in men. The contribution of \textit{BRCA1} and \textit{BRCA2} mutations to male cancers has been studied extensively, with greater evidence mounting for the role of \textit{BRCA2} than of \textit{BRCA1} (reviewed by Liede et al. 44). Here, we focus on the risk of prostate cancer in \textit{BRCA2} mutation carriers.

In 2003, Edwards and colleagues showed that mutations in \textit{BRCA2} accounted for a measurable level, ~2%, of early-onset prostate cancer in the United Kingdom (15). The groundwork for this study came from studies of (a) families with clustering of cancer cases and (b) large families harboring known \textit{BRCA2} mutations, particularly those derived from isolated populations.

Several studies of cancer clusters within families have reported the co-occurrence of breast, ovarian, endometrial, and prostate cancers, suggesting that a single gene or a limited number of genes is responsible for these hormonal cancers (9, 10, 13, 45-48). For example, in 1992, an Icelandic study looked at 947 families in which a female proband had breast cancer and found that blood relatives of the probands had an increased risk of prostate, ovarian, and endometrial cancer compared with spouses of the probands. In particular, the risk of prostate cancer was significantly increased for all relatives of women with breast cancer, with the highest risk observed in first-degree relatives [RR, 1.4; 95% confidence interval (95% CI), 1.1-1.9; ref. 10]. In addition, a large prospective cohort of nearly 31,000 Iowa women reported the co-occurrence of breast, prostate, and ovarian cancer family histories significantly more often than expected by chance (13).

Following the mapping and cloning of \textit{BRCA2} by Wooster et al. in 1995 (49), families known to harbor \textit{BRCA2} mutations could be studied to obtain a clearer picture of cancer risk. In a large series of 173 European and North American families with \textit{BRCA2} mutations, the Breast Cancer Linkage Consortium reported an excess not only of prostate cancer (RR, 4.65; 95% CI, 3.48-6.22) but also pancreatic, gallbladder and bile duct, and stomach cancers, as well as malignant melanoma (14). The RR of prostate cancer among male carriers diagnosed before age 65 years increased considerably (RR, 7.3; 95% CI, 4.7-11.5). This observation was supported by another study of 139 Dutch \textit{BRCA2} families (50). The cumulative risk of developing prostate cancer before 80 years of age has been estimated by the Breast Cancer Linkage Consortium to be 20% (95% CI, 15-24%; ref. 14). In these families, 97 distinct \textit{BRCA2} mutations were observed, including two founder mutations identified in the Icelandic and Ashkenazi Jewish populations (999del5 and 6174delT, respectively). \textit{BRCA2} mutations occurring in the central region of the \textit{BRCA2} gene, known as the ovarian cancer cluster region, have been hypothesized to confer a lower risk of prostate cancer, although the association reached only borderline significance in an analysis by the Breast Cancer Linkage Consortium of 164 families with known \textit{BRCA2} mutations (RR, 0.52; 95% CI, 0.24-1.00; ref. 51). Additional studies of mutations in the ovarian cancer cluster region and prostate cancer risk have generated inconsistent results (50, 52-55).

The association between \textit{BRCA2} and increased prostate cancer risk has been supported by additional studies of families segregating \textit{BRCA2} mutations, including families in Sweden (48, 56), Finland (57), the Netherlands (50), Iceland (58), and Chile (59). The findings of the Breast Cancer Linkage Consortium and of additional studies focused specifically on founder mutations (discussed further in the next section) provide strong evidence of increased prostate cancer risk in \textit{BRCA2} mutation carriers, particularly early-onset disease.

To determine the contribution of \textit{BRCA2} mutations to early-onset prostate cancer, Edwards et al. screened the complete \textit{BRCA2} coding sequence for germ-line mutations in 263 men diagnosed with cancer who were ≤55 years at diagnosis. Men were not selected based on family history. Protein-truncating mutations were found in six men (2.3%; 95% CI, 0.8-5.0). The RR of developing prostate cancer by age 56 years from a deleterious germ-line \textit{BRCA2} mutation was estimated to be 23-fold (15). Interestingly, four of the patients in this study who carried mutations did not have a family history of breast or ovarian cancer. However, given the early age at diagnosis of the prostate cases, it may be that the women in the family who carried the mutation had not aged sufficiently to get breast cancer. Little information was given about the families and it is not known how many women were at risk. One additional explanation is that in this genetic context (i.e., these mutations in the genetic background given), the mutations were weakly penetrant for breast cancer. A great deal more work would need to be done to address this speculation.

\textbf{Studies of Special Populations}

Two particular founder \textit{BRCA2} mutations have been studied extensively: the 999del5 mutation in Icelandic families and the 6174delT mutation in Ashkenazi Jews. In an initial study of Icelandic breast cancer families, the 999del5 mutation was found in 21 of 21 \textit{BRCA2} families investigated, indicating a strong founder effect (60, 61). The resulting frameshift mutation causes an early termination of translation at codon 273, leading to a severely truncated protein and concomitant loss of function. First-degree relatives of carriers of this mutation have been found to have an increased risk of prostate cancer (RR, 4.79; 95% CI, 3.27-6.32; refs. 58, 62). In 1996, Johannesdottir et al. (63) tested unsselected prostate cases diagnosed at ≤65 years of age for the 999del5 mutation to estimate its prevalence in prostate cancer patients. They found that 2.7% of patients carried the mutation, a prevalence level similar to that later reported by Edwards and colleagues for all protein-truncating mutations.

In Ashkenazi Jews, a 6174delT \textit{BRCA2} mutation has been implicated in breast cancer and thus studied extensively for its putative association with prostate cancer. The carrier frequency of the 6174delT mutation in the general Jewish population is estimated to be approximately 1% (64, 65). In 1997, Struwing et al. recruited more than 5,000 American-Ashkenazi Jewish volunteers from the Washington, District of Columbia, area and used a kin-cohort approach to estimate the risk of prostate cancer in individuals with any of the three so-called “\textit{BRCA} Jewish mutations”: 185delAG and 5382insC in
BRCA1 and 6174delT in BRCA2. The cumulative risk of prostate cancer by age 70 years was estimated to be 16% (95% CI, 6.28) for BRCA2 carriers compared with 3.8% for noncarriers (95% CI, 3.3-4.4; ref. 66).

The results from subsequent studies of Ashkenazi Jewish men and the BRCA2 6174delT mutation have been mixed (67-72), with several studies, particularly Ashkenazi PC family studies, reporting negative findings. Many of those studies, however, were underpowered. For instance, Wilkens et al. (67) examined germ-line DNA from both affected and unaffected men from 18 PC families of Ashkenazi Jewish descent for the same three BRCA1 and BRCA2 mutations described above. In the 47 individuals screened, they found only one man with a BRCA2 mutation and this person was unaffected at the time of analysis. A larger population-based study of 979 Ashkenazi men in Israel diagnosed with prostate cancer found a non-significant 2-fold increase (95% CI, 0.16-5.72) in the occurrence of the 6174delT mutation in these individuals, compared with age-matched Ashkenazi controls (71). The authors found no evidence of a distinctive histopathology among tumors from men bearing the mutation. A second large population-based study conducted by the Memorial Sloan-Kettering Cancer Center in New York screened 251 Ashkenazi Jewish prostate cancer cases for the 6174delT mutation and compared mutation incidence with that in 1,472 male Ashkenazi controls. The authors reported that cases were significantly more likely than controls to harbor the mutation (odds ratio, 4.8; 95% CI, 1.9-12.2; ref. 72).

### Subsequent Studies of Prostate Cancer and BRCA2

The role of BRCA2 mutations in high-risk prostate cancer families has been investigated by several groups, including our own. We examined 266 subjects from 194 high-risk prostate cancer families participating in the PROGRESS study (73). PROGRESS is a large family-based study aimed at finding genes that contribute to susceptibility and progression of hereditary forms of prostate cancer (16, 37, 74). Study subjects for BRCA2 analysis were selected from the PROGRESS families based on Jewish ancestry, a family history of breast or ovarian cancer, pancreatic cancer family history, or early age at diagnosis (<60 years). No disease-associated, protein-truncating mutations were found, although a number of variants of unknown significance were noted. This study, the largest of its kind, suggested that known BRCA2 mutations play a small role, if any, in disease among high-risk prostate cancer families.

To address the significance of BRCA2 mutations in a population-based setting, we screened the coding regions and intron-exon boundaries of 290 population-based patients from King County, Washington, who were <55 years at age of diagnosis (75). Men were selected from a larger well-characterized, population-based, case-control study of nearly 1,500 cases and controls (76). Only two protein-truncating BRCA2 mutations were identified, yielding a mutation prevalence of 0.78% (95% CI, 0.09-2.81) and a RR of 7.8 (95% CI, 1.8-9.4) for early-onset prostate cancer in White men (75). We estimate that <1% of early-onset prostate cancers in the general U.S. Caucasian population can be attributed to these rare disease-associated BRCA2 mutations, which is less than half that reported by Edwards et al. (15).

To assess whether BRCA2 mutations contribute to prostate cancer prognosis, Tryggyvadottir et al. (77) examined 596 unselected Icelandic prostate cancer patients, comparing prognostic measures among the 30 BRCA2 6174delT mutation patients with noncarrier cases, matched for year of diagnosis and birth. Compared with noncarrier cases, the mutation carrier cases had a significantly lower mean age of diagnosis (69 versus 74 years), more advanced tumor stage at diagnosis (stage III or IV, 79% versus 39%), higher grade (grades G3-G4, 84% versus 53%), and shorter mean survival time (2.1 years; 95% CI, 1.4-3.6 years versus 12.4 years; 95% CI, 9.9-19.7 years). Supportive results were reported by Mitra et al. (78), who found that BRCA2 mutation carriers in the U.K. population had significantly higher Gleason scores compared with noncarrier cases (P = 0.016). The latter study, which included 16 BRCA2 mutation carriers, was not able to detect a significant difference in perineural or lymphovascular invasion.

### A New Gene?

In one very interesting study of Swedish individuals, published in 2003, standardized incidence ratios (SIR) and cumulative cancer incidences were evaluated for relatives of a population-based set of early-onset breast cancer index cases (<41 years) who had known BRCA mutation status (n = 203; ref. 79). The investigators found that first-degree relatives of mutation-negative cases had an increased incidence of breast (SIR, 2.3; 95% CI, 1.6-3.4), prostate (SIR, 1.7; 95% CI, 1.0-2.8), and cervical cancers (SIR, 3.3; 95% CI, 1.1-7.6) as well as nonmelanoma skin cancer (SIR, 2.8; 95% CI, 1.0-6.1). The risks of breast cancer, prostate cancer, and nonmelanoma skin cancer were further increased in first-degree relatives of breast cancer cases <36 years at diagnosis. Whereas the authors argue that this indicates a possible association between these cancers and early-onset breast cancer (79), two other possible scenarios exist. It is likely that some mutations were missed using the denaturing high-performance liquid chromatography screening method. Although this method is considered very robust (80) for finding missense changes and indels, it does not readily detect large genomic rearrangements, the frequency of which is population dependent and can easily reach over 10% (81). An alternative hypothesis is that a second BRCA2-like gene exists that increases the risk of hormonal cancers such as breast, ovary, and prostate. The latter hypothesis is interesting and worthy of additional consideration. It is entirely plausible that additional multihormonal cancer genes exist, but that locus heterogeneity, shifting diagnosis criteria, and an inability to distinguish genetic versus sporadic cases have contributed to our inability to find such genes.

One hypothesis recently suggested by Erkko and colleagues (82) in Nature was that a mutation in the PALB2 gene is important in Finnish cancer families. They showed that BRCA2 interacted with PALB2 in a way that was critical for the BRCA2 protein to carry out its DNA damage response functions as well as tumor suppressor activities. In addition, the 1592delT mutation was present at significantly elevated levels in familial breast cancer
cases compared with ancestry-matched controls (82). The findings were particularly exciting because the examination of unselected breast cancer cases showed a 4-fold enrichment of the mutation in cases compared with controls, and one multigenerational prostate cancer family segregated the same protein-truncating mutation, suggesting that this gene was important for both breast and prostate cancer susceptibility (82). At this point, the situation is unresolved. A recent report showed no evidence for deleterious variants within the \textit{PALB2} gene when 95 probands from high-risk prostate cancer families were examined, suggesting that \textit{PALB2} is unlikely to be important in hereditary prostate cancer (83). The work, however, is tantalizing and hints that a \textit{BRCA1/PC} gene remains to be found.

**Summary**

The field of prostate cancer genetics has enjoyed enormous forward momentum in the last few years. Loci have finally been identified with confidence, and positional cloning efforts are well under way at several places in the genome. Both linkage-based studies combining data from many families, as well as whole-genome association studies that largely took advantage of existing case-control cohorts, have been responsible for reproducible identification of prostate cancer loci on several chromosomes. Just as important, however, has been the long-term follow-up of cases and controls from existing data sets and an awareness of changing trends in diagnosis and treatment. Although there is no doubt that recently published whole-genome association studies and meta-analyses involving large number of families have finally broken the logjam of poorly reproduced reports that the prostate cancer genetics community faced for so many years, critical eyes and a high level of scrutiny are still called for. Buried within existing family-based and cohort studies remain hints about what type of genes remain to be found.

The \textit{BRCA2} story is a promise unfulfilled. However, it assures us that other hormonal cancer genes remain to be found. Vigilant attention to the data sets so carefully assembled over the last decades combined with collaborative analyses between groups is sure to reveal the new loci only hinted at by recent studies. The coming months promise to be an exciting time for prostate cancer gene hunters as we await further breakthroughs. Let us be sure to bring all our resources to the table, as that will assure us the best chance of finally unraveling the genetics of these intriguing and important public health diseases.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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