BRCA Mutations and Risk of Prostate Cancer in Ashkenazi Jews

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Abstract

Purpose: The Breast Cancer Linkage Consortium and other family-based ascertainment studies have suggested that male carriers of BRCA mutations are at increased risk of prostate cancer. Several series looking at the frequency of BRCA mutations in unselected patients with prostate cancer have not confirmed this finding. To clarify this issue, we conducted a large case-control study.

Experimental Design: Blood specimens from 251 unselected Ashkenazi men with prostate cancer were screened for the presence of one of the three common Ashkenazi founder mutations in BRCA1 and BRCA2. The incidence of founder mutations was compared with the incidence of founder mutations in 1472 male Ashkenazi volunteers without prostate cancer using logistic regression analysis after adjusting for age.

Results: Thirteen (5.2%) cases had a deleterious mutation in BRCA1 or BRCA2 compared with 28 (1.9%) controls. After adjusting for age, the presence of a BRCA1 or BRCA2 mutation was associated with the development of prostate cancer (odds ratio, 3.41; 95% confidence interval, 1.64–7.06; P = 0.001). When results were stratified by gene, BRCA2 mutation carriers demonstrated an increased risk of prostate cancer (odds ratio, 4.78; 95% confidence interval, 1.87–12.25; P = 0.001), whereas the risk in BRCA1 mutation carriers was not significantly increased.

Conclusions: BRCA2 mutations are more likely to be found in unselected individuals with prostate cancer than age-matched controls. These results support the hypothesis that deleterious mutations in BRCA2 are associated with an increased risk of prostate cancer.

Introduction

Early reports from the Breast Cancer Linkage Consortium and other family-based ascertainment studies suggested that families with deleterious mutations in BRCA1 and BRCA2 had an increased number of prostate cancers compared with families without known inherited predisposition (1–5). Biological support for this association was provided by Gao et al. (6), who demonstrated loss of heterozygosity at the BRCA1 locus in hereditary prostate cancer cases. In an attempt to confirm these findings, several groups have looked at the incidence of deleterious BRCA1 and BRCA2 mutations in unselected series of patients with prostate cancer (7–11). The majority of these series have been performed in Ashkenazi populations because of the high frequency of three founder mutations in BRCA1 and BRCA2 in this group. Most series of unselected patients have concluded that deleterious BRCA mutations contribute little, if anything, to the incidence of prostate cancer in the Ashkenazi population. In the only series of unselected patients suggesting a weak association of BRCA mutations with prostate cancer risk, the effect was limited to BRCA1 mutation carriers (11). However, this finding was not confirmed in two recent family-based ascertainment studies limited to BRCA1 mutation carriers (12, 13). To better elucidate the impact of deleterious BRCA1 and BRCA2 mutations on prostate cancer risk, we conducted a large case-control study comparing the incidence of deleterious BRCA1 and BRCA2 founder mutations in unselected Ashkenazi prostate cancer patients and compared this with the frequency of BRCA1 and BRCA2 founder mutations in a well-characterized control population.

Patients and Methods

DNA was extracted from lymphocytes of blood specimens from 251 individuals of Ashkenazi Jewish ancestry diagnosed with adenocarcinoma of the prostate who received care at the outpatient urology clinic at Memorial Sloan-Kettering Cancer Center from April 2000 to September 2002. The samples were unselected for age or family history. Clinical and pathological records were reviewed to confirm the diagnosis of prostate cancer in all subjects. Once pathological diagnosis of prostate cancer was confirmed, the age of diagnosis was recorded, and all other identifying links were destroyed. The study design and anonymization method were approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board.

DNA from case samples was analyzed for the three common Ashkenazi founder mutations in BRCA1 and BRCA2 (185delAG and 5182insC in BRCA1 and 6174delT in BRCA2) as described previously (14). Briefly, DNA was purified using the QiaAmp Blood DNA midi kit (Qiagen, Valencia, CA). DNA specimens were then analyzed for the presence of the Ashkenazi founder mutations using the following oligonucleotide primers flanking the mutation loci: BRCA1, 185delAG forward (5′-
The model (16). For stratified analyses, after adjusting for age by treating it as an additional covariate in cases with a control group that included 1472 Ashkenazi Jewish men, we estimated the odds ratio for prostate cancer in cases compared with controls using a logistic regression model, with the comparison of test digest with digests of PCR analyses of BRCA1 (538insC), and HIP (ACRES) for restriction enzymes TaqI (185delAG), DdeI (538insC), and BsrXI [6174delT (15)]. Carriers were recognized by the comparison of test digest with digests of PCR analyses of previously verified BRCA1/2 carriers.

We then compared the incidence of founder mutations in cases with a control group that included 1472 Ashkenazi Jewish male volunteers without prostate cancer identified as part of the Washington Ashkenazi Jewish Study who had previously undergone genotyping for the three Ashkenazi founder mutations (3). The authors of this study kindly provided the primary data files after excluding cases with a prior diagnosis of prostate cancer. The odds ratio for prostate cancer in cases compared with controls was estimated using a logistic regression model, after adjusting for age by treating it as an additional covariate in the model (16). For stratified analyses, χ² tests of association and Fisher’s exact tests were conducted. Exact confidence intervals were computed for odds ratios. SAS version 8.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

Genotyping revealed that 13 of 251 cases (5%) were carriers of either a BRCA1 or BRCA2 mutation. Among the 13 carriers, 4 carriers had BRCA1 185delAG (1.6%), 1 carrier had BRCA1 5382insC (0.4%), and 8 carriers had BRCA2 6174delT (3.1%). Of the 1472 controls, 28 (1.9%) had either a BRCA1 or BRCA2 mutation: 9 (0.6%) had BRCA1 185delAG mutation; 3 (0.2%) had BRCA1 5382insC mutation; and 16 (1%) had a BRCA2 6174delT mutation.

Logistic regression analysis demonstrated that, after adjusting for age, the presence of an Ashkenazi founder mutation in BRCA1 or BRCA2 had a significant association with prostate cancer risk (odds ratio, 3.41; 95% confidence interval, 1.64–7.06; P = 0.001). In the multivariate model, age was also a significant predictor of prostate cancer risk (P < 0.001).

Table 1 Frequency of BRCA1 and BRCA2 mutations in cases and controls

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Cases (n = 251)</th>
<th>Controls (n = 1472)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Mean age of mutation carriers (range) (yrs)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>5 (2.0%)</td>
<td>68.4 (65–71)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>8 (3.2%)</td>
<td>64.0 (48–78)</td>
</tr>
<tr>
<td>BRCA1 or BRCA2</td>
<td>13 (5.2%)</td>
<td>65.7</td>
</tr>
</tbody>
</table>

* CI, confidence interval.

In the Ashkenazi Jewish population, the three founder mutations in BRCA1 and BRCA2 account for the vast majority of inherited breast and ovarian cancer families (17, 18). Despite evidence from several groups (2, 4) that prostate cancer was overrepresented in hereditary breast cancer families linked to BRCA2 (Table 2), no series of unselected Ashkenazi Jewish men with prostate cancer prior to the current series has been able to confirm this association (Table 3). For BRCA1-linked kindreds, the prior family-based series have shown either a higher (1), lower (12), or average (13) risk of prostate cancer (Table 2). In unselected series examining the impact of BRCA1 mutations on prostate cancer risk, four series did not demonstrate an association (7–10), and one population-based series observed a modest elevation in prostate cancer risk (95% confidence interval, 1.05–6.04; Ref. 11; Table 3). In contrast to these results, our study showed a significantly increased risk of prostate cancer in BRCA2 but not BRCA1 mutation carriers.

Several studies have suggested that BRCA2 mutations are predominately associated with an increased rate of early-onset prostate cancer (13, 19, 20). When our results were stratified by age, we were able to confirm that presence of a BRCA2 mutation was associated with a significantly increased risk for prostate after the age of 60 years (odds ratio, 3.71; 95% confidence interval, 1.05–6.04; Ref. 11; Table 3). In contrast to these results, our study showed a significantly increased risk of prostate cancer in BRCA2 but not BRCA1 mutation carriers.

Whereas our finding of increased BRCA2-associated risk for prostate cancer is consistent with predictions based on family-based ascertainment, one of the reasons that our results may differ from prior unselected series is that these studies were not powered to discern different risks in BRCA1 versus BRCA2 mutation carriers. Four of these series were limited to fewer than 200 cases. In one large series from Israel, the frequency of BRCA2 mutations in prostate cancer cases (1.5%) was less than half the 3.1% frequency seen in our series. This difference may be due to the inclusion of only incident cases in the Israeli series, whereas we included both incident and prevalent cases. It is possible that a survival bias in our series resulted from a BRCA2 mutation-associated survival advantage for patients with pros-
tate cancer, leading to an over representation of the 6174delT allele in our largely prevalent cohort. Such an effect, as has been observed in BRCA-associated ovarian cancer (21–23), requires confirmation through prospective studies.

Another possible bias in our series could have occurred because the Washington Ashkenazi study was not population based but rather was composed of volunteers somewhat enriched for familial cancer history. If the frequency of founder mutations in unaffected individuals in the Washington Ashkenazi Study was different than the population frequency in Ashkenazi individuals in the greater New York area, this could have resulted in an over- or underestimation of the impact of BRCA mutations on prostate cancer risk. We believe this is unlikely because the founder mutation frequency seen in the Washington Ashkenazi Study is consistent with other large series of Ashkenazi individuals from both the greater New York area and other regions of the United States (24, 25).

Different methodologies were used for genotyping cases and controls. This theoretically could have introduced a bias in favor of a significant finding if the genotyping method for cases was more sensitive than the method used for controls. We believe this is unlikely, however, because the restriction site analysis used to genotype the cases and the allele-specific oligonucleotide assay used to genotype the controls have both been

Table 2  Association of prostate cancer with BRCA1 or BRCA2 mutations: family-based ascertainment

<table>
<thead>
<tr>
<th>Genes/Study</th>
<th>Ascertainment</th>
<th>Analysis method</th>
<th>Relative risk</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>33 families with evidence of linkage to BRCA1</td>
<td>Prostate cancer incidence compared with population-specific rates</td>
<td>3.33</td>
<td>1.78–6.20</td>
</tr>
<tr>
<td>Brose et al., 2002 (12)</td>
<td>147 families with a BRCA1 mutation seen in a risk evaluation clinic</td>
<td>Prostate cancer incidence compared with population-specific rates</td>
<td>0.39</td>
<td>0.09–0.68</td>
</tr>
<tr>
<td>Thompson et al., 2002 (13)</td>
<td>699 families with a documented BRCA1 mutation</td>
<td>Prostate cancer incidence compared with population-specific rates</td>
<td>1.07</td>
<td>0.75–1.54</td>
</tr>
<tr>
<td>BRCA2</td>
<td>173 families selected for linkage analysis with a demonstrated BRCA2 mutation</td>
<td>Prostate cancer incidence compared with population-specific rates</td>
<td>4.65</td>
<td>3.48–6.22</td>
</tr>
<tr>
<td>Sigurdsson et al., 1997 (4)</td>
<td>16 families in which a woman with breast cancer was demonstrated to have the Icelandic founder mutation 999del5 in BRCA2</td>
<td>Prostate cancer incidence in first-degree relatives of case patients compared with population-specific incidence</td>
<td>4.6</td>
<td>1.9–8.8</td>
</tr>
<tr>
<td>BRCA1 and BRCA2</td>
<td>48 Ashkenazi Jewish breast cancer patients with a founder mutation in BRCA1 or BRCA2</td>
<td>Prostate cancer incidence in 1st degree relatives compared with incidence in 1st degree relatives of healthy controls</td>
<td>3.36</td>
<td>1.49–7.56</td>
</tr>
</tbody>
</table>

*a* BCLC, Breast Cancer Linkage Consortium.

Table 3  Incidence of founder BRCA1 or BRCA2 mutations in unselected series of Jewish patients with prostate cancer

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Comparison group</th>
<th>Frequency of BRCA mutations in cases</th>
<th>Association of BRCA mutation and prostate cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lehrer et al., 1998 (7)</td>
<td>60</td>
<td>268 Ashkenazi Jewish women with sporadic breast cancer</td>
<td>0 (0%) BRCA1 0 (0%) BRCA2</td>
<td>No</td>
</tr>
<tr>
<td>Nastjuk et al., 1999 (8)*</td>
<td>83</td>
<td>Reported population incidence</td>
<td>1 (1.2%) BRCA1 2 (2.4%) BRCA2</td>
<td>No</td>
</tr>
<tr>
<td>Hubert et al., 1999 (9)*</td>
<td>87</td>
<td>87 Ashkenazi Jewish men without prostate cancer</td>
<td>2 (2.3%) BRCA1 1 (1.1%) BRCA2</td>
<td>No</td>
</tr>
<tr>
<td>Vazina et al., 2000 (10)</td>
<td>174</td>
<td>Reported population incidence</td>
<td>4 (2.3%) BRCA1 1 (0.6%) BRCA2</td>
<td>No</td>
</tr>
<tr>
<td>Giusti et al., 2003 (11)</td>
<td>940</td>
<td>472 Ashkenazi Jewish men without prostate cancer</td>
<td>16 (1.7%) BRCA1 14 (1.5%) BRCA2</td>
<td>BRCA1- No  BRCA2- No</td>
</tr>
</tbody>
</table>

*a* Analysis limited to 185delAG mutation in BRCA1 and 6174delT mutation in BRCA2.

*b* When control population was combined with 872 controls from the United States, presence of the 185delAG mutation in BRCA1 was associated with an increased risk of prostate cancer. (odds ratio, 2.52; 95% confidence interval, 1.05–6.04).
shown in other studies to have a sensitivity for detecting the Ashkenazi founder mutations comparable with that of sequencing (22, 26, 27).

These results provide evidence that deleterious mutations in BRCA2 are associated with an increased risk of prostate cancer. Current recommendations for male carriers of BRCA mutations include prostate cancer screening with digital rectal examination and serum prostate-specific antigen level annually beginning at age 50 years (28). Whereas there was no significantly increased risk for early-onset prostate cancer in this series, this finding requires confirmation in a larger cohort. Additional family-based studies may also help clarify the relative penetrance of BRCA2 mutations for prostate cancer. Additionally, because a substantial proportion of familial prostate cancer is not linked to mutations in BRCA1 and BRCA2, the search for other major prostate cancer predisposition genes will remain a high priority.

Acknowledgments

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References

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