Germline BRCA Mutations Denote a Clinicopathologic Subset of Prostate Cancer

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Abstract

Purpose: Increased prostate cancer risk has been reported for BRCA mutation carriers, but BRCA-associated clinicopathologic features have not been clearly defined.

Experimental Design: We determined BRCA mutation prevalence in 832 Ashkenazi Jewish men diagnosed with localized prostate cancer between 1988 and 2007 and 454 Ashkenazi Jewish controls and compared clinical outcome measures among 26 BRCA mutation carriers and 806 noncarriers. Kruskal-Wallis tests were used to compare age of diagnosis and Gleason score, and logistic regression models were used to determine associations between carrier status, prostate cancer risk, and Gleason score.

Results: BRCA2 mutations were associated with a 3-fold risk of prostate cancer [odds ratio, 3.18; 95% confidence interval (95% CI), 1.52-6.66; \( P = 0.002 \)] and presented with more poorly differentiated (Gleason score \( \geq 7 \)) tumors (85% versus 57%; \( P = 0.0002 \)) compared with non–BRCA-associated prostate cancer. BRCA1 mutations conferred no increased risk. After 7,254 person-years of follow-up, and adjusting for clinical stage, prostate-specific antigen, Gleason score, and treatment, BRCA2 and BRCA1 mutation carriers had a higher risk of recurrence [HR (95% CI), 2.41 (1.23-4.75) and 4.32 (1.31-13.62), respectively] and prostate cancer–specific death [HR (95% CI), 5.48 (2.03-14.79) and 5.16 (1.09-24.53), respectively] than noncarriers.

Conclusions: BRCA2 mutation carriers had an increased risk of prostate cancer and a higher histologic grade, and BRCA1 or BRCA2 mutations were associated with a more aggressive clinical course. These results may have implications for tailoring clinical management of this subset of hereditary prostate cancer.

Clin Cancer Res; 16(7); OF1-7. ©2010 AACR.

Genome-wide association studies have identified common susceptibility loci in more than a dozen independent chromosomal regions associated with an increased risk for prostate cancer (1), but candidate genes at these loci have yet to be functionally implicated. Although present in only a small proportion of prostate cancer cases overall, mutations of the BRCA2 and BRCA1 genes are commonly observed in families with multiple cases of breast cancer.

Whether detected in affected families or in the general population, BRCA mutations cause an increased risk for breast and ovarian cancer in women, and breast and prostate cancer in men (2–8).

Histologic differentiation is an established surrogate for survival in prostate cancer, and Gleason scoring is the most widely used grading system (9, 10). Clinical management of this malignancy depends on assessment of clinical features, age of the patient, as well as histopathology of the tumor. There remains a critical need for prognostic markers to tailor therapeutic strategies, which may range from “watch and wait” to surgery or radiation therapy (11). BRCA mutations may constitute one such prognostic marker; however, few studies have investigated the tumor characteristics of BRCA-associated prostate cancer. A more aggressive phenotype has been suggested by four analyses of BRCA-associated prostate cancer (12–15), but the largest study found no difference in histopathology between carriers and noncarriers of BRCA mutations (16). Furthermore, loss of heterozygosity has been identified in prostate tumors of BRCA2 carriers and has been associated with higher Gleason score (17). Prostate cancer–specific mortality is a more robust end point, and an association...
between BRCA2 mutation and earlier death due to prostate cancer has been reported for patients with advanced disease (12). Here, we confirm a more aggressive histology associated with BRCA2-associated prostate cancer and, for the first time, show the independent prognostic significance of this genetic marker in early-stage prostate cancer, taking into account known prognostic factors for the disease, including prostate-specific antigen (PSA) and clinical features.

### Materials and Methods

DNA was extracted from blood samples of 894 prostate cancer cases treated at the Memorial Sloan-Kettering Cancer Center between June 1988 and December 2007. DNA samples were also acquired from 454 noncancer controls who provided informed consent as part of a prospective study of healthy people conducted from 2000 to 2002 in New York City (18). Both cases and controls identified themselves as being of Ashkenazi Jewish background. The inclusion of only Ashkenazi Jewish men enabled targeted genotyping for founder mutations, and all blood samples were genotyped for the two major Ashkenazi BRCA founder mutations BRCA1*185delAG and BRCA2*6174delT. The third founder mutation BRCA1*5382insC was not genotyped. The Taqman (fluorogenic 5′ nuclease) assay was used for single-nucleotide polymorphism genotyping. The primers and probes were obtained from Applied Biosystems. PCR was conducted with both primers and probes added in ABI 9700 thermocycler, and the endpoint results were scored using the ABI 7900HT Sequence Detection System (version 2.3). In each 384-well plate, one reference sample and one negative control were included for quality control. Cases’ medical records and pathology reports were collected as part of an institutional prostate cancer research database using standardized questionnaires and chart abstraction forms, created and maintained by the prostate cancer disease management team at the Memorial Sloan-Kettering Cancer Center. Analysis for this study was based on data on clinical stage, Gleason score (from needle biopsy), PSA levels, and age at diagnosis of the primary prostate tumor as well as dates of biochemical recurrences, development of castrate metastasis, death due to prostate cancer, and overall survival. Biochemical recurrence refers to the detection of rising PSA after local therapy, and castrate metastasis refers to time to progression of disease following initiation of antiandrogen therapy. Biochemical recurrence was defined as PSA of ≥0.2 ng/mL after radical prostatectomy and a value of "nadir + 2" after other therapy (19, 20). Castrate metastasis was defined as progression of disease despite castrate levels of testosterone. Data were collected on 894 genotyped cases, but only patients with localized disease at presentation were included in the analysis of clinical outcome; 62 cases presented with metastatic prostate cancer and were excluded for the survival analysis. In accordance with an Institutional Research Board–approved protocol, patient identifiers were removed at time of genetic analysis. Therefore, 832 prostate cancer cases and 454 controls were included in subsequent analyses.

Gleason scores of the prostate tumors were categorized into <7 and ≥7 subgroups. This cutoff was chosen based on clinical experience and prior literature suggesting that clinical outcome for Gleason score 7 prostate cancer is more similar to that for Gleason score 8 to 10 than for Gleason score <7 disease (21). Among cases, Kruskal-Wallis tests were used to compare distribution of age at diagnosis and Gleason score by carrier status. Logistic regression models, adjusted for age and clinical stage, were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between carrier status and prostate cancer risk, and between carrier status and Gleason score (case only model). Unconditional logistic regression was used as controls and cases were not matched. Time at risk was calculated from the date of diagnosis of prostate cancer to the date of death or date of last contact. As a secondary analysis, time at risk intervals were calculated from date of blood draw for genetic testing (left truncation). The Kaplan-Meier method stratified by genotype was used to generate survival curves (22). Hazard ratios (HR) and 95% CI for mortality, biochemical recurrence, and castrate metastases associated with mutation status were estimated using Cox proportional hazard models (23), adjusting for age, clinical stage, Gleason score, PSA levels of primary tumor, and treatment type. We checked for violations of the proportional hazards assumption for all variables by visual inspection of the log (−log) plots and analytically using Schoenfeld residuals (24). All statistical analyses were conducted using Stata 10.0 (StataCorp LP).

### Results

The median age for controls was 42 years (interquartile range, 42-57), whereas the median age for cases was 68
years (interquartile range, 62-73). Prostate cancer cases were more likely to carry a BRCA2 mutation than controls (2.4% versus 0.7%; \(P = 0.002\)). Men who carried a BRCA2 mutation had a 3.18 times higher risk of prostate cancer than noncarriers (OR, 3.18; 95% CI, 1.52-6.66; Table 1). The frequency of BRCA1 mutation was similar for cases and controls (\(P = 0.34\)); 3.1% of prostate cancer cases in this series carried either a BRCA1 or a BRCA2 mutation.

Among the total of 832 cases eligible for analysis of clinical outcome with a median follow-up in excess of 8 years, the age of diagnosis was slightly greater (median age, 68.2 years) for 806 patients with no BRCA mutations compared with 20 cases with BRCA2 mutations (median age, 62.0 years), although this difference was not statistically significant (\(P = 0.1\)). After adjusting for Gleason score and stage, there was no difference in age at presentation between BRCA2 mutation carriers and noncarriers (HR, 1.23; 95% CI, 0.76-2.00; \(P = 0.41\)) nor between BRCA1 mutation carriers and noncarriers (HR, 0.67; 95% CI, 0.28-1.61; \(P = 0.37\)). Mutation carriers' dates of diagnoses were spread across the duration of the study, and carriers do not represent a more contemporary cohort that could have received higher Gleason scoring. Poorly differentiated prostate cancers (Gleason score 7-10; Fig. 1) were found in 57% of noncarrier cases and in 85% of BRCA2 mutation-associated cases (\(P = 0.0002\)), but there were no differences between BRCA1 mutation carriers and noncarriers (\(P = 0.71\)). Adjusting for age and stage, BRCA2 mutation carriers were more than twice as likely to have a Gleason score 7 to 10 (HR, 2.63; 95% CI, 1.23-5.6; \(P = 0.01\)) than noncarriers, but the distribution of Gleason scores did not differ for BRCA1 mutation carriers and noncarriers (HR, 0.53; 95% CI, 0.09-3.29; \(P = 0.50\); Table 2). Younger patients were more likely to have a Gleason score 7 to 10 compared with lower scores (HR, 0.76; 95% CI, 0.65-0.89; \(P = 0.001\)). Distribution by type of treatment received is shown in Table 2; half of BRCA2 mutation carriers were treated by radical prostatectomy compared with 30% of BRCA wild-type cases.

After 7,254 person-years of follow-up for the entire cohort, the following outcomes occurred: 369 biochemical recurrences, 158 castrate metastases, and 184 deaths, of which 98 were due specifically to prostate cancer (Table 3; Fig. 2). Compared with noncarriers, prostate cancer patients who carried mutations in BRCA1/2, were at higher risk of recurrence and death (Fig. 2). Results of a Cox proportional hazards model (Table 3) analysis taking into account age, clinical stage, Gleason score, PSA, and treatment showed that both BRCA1 and BRCA2 mutation carriers had an increased risk of developing biochemical recurrence (HR, 4.32; 95% CI, 1.31-13.62; \(P = 0.016\) and HR, 2.41; 95% CI, 1.23-4.75; \(P = 0.011\), respectively). BRCA2 mutation carriers had a greater risk of castrate metastases (HR, 3.01; 95% CI, 1.26-7.14; \(P = 0.013\)) compared with noncarriers. This translated into a greater risk of death due to prostate cancer (HR, 5.16; 95% CI, 1.09-24.53; \(P = 0.039\) and HR, 5.48; 95% CI, 2.03-14.79; \(P = 0.001\)) for BRCA1 and BRCA2 carriers, respectively.

The median time from diagnosis to blood collection for genotyping in this cohort was 4.6 years. When we left truncated time at risk, HR estimates were in a similar direction and magnitude, and the HR for risk of death due to prostate cancer in BRCA2 mutation carriers was 11.21 (95% CI, 3.6-34.53; other data not shown).

A separate analysis was made comparing time from biochemical recurrence to castrate metastasis. There were 369 men with biochemical recurrence, and 158 of those had castrate metastasis. There was a trend toward a higher frequency of biochemical recurrence progressing to castrate metastasis in BRCA2 carriers than noncarriers (HR, 2.01; 95% CI, 0.85-4.79). There was no difference in the frequency of castrate metastasis after biochemical recurrence in BRCA1 carriers compared with controls (HR, 1.08; 95% CI, 0.15-7.85).

### Table 1. Frequency of BRCA1/2 mutation carrier status in prostate cases and controls

<table>
<thead>
<tr>
<th>Case, (n (%))</th>
<th>Control, (n (%))</th>
<th>Age-adjusted OR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier</td>
<td>806 (96.9)</td>
<td>447 (98.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>BRCA1 carrier</td>
<td>6 (0.7)</td>
<td>4 (0.9)</td>
<td>0.38 (0.05-2.75)</td>
</tr>
<tr>
<td>BRCA2 carrier</td>
<td>20 (2.4)</td>
<td>3 (0.7)</td>
<td>3.18 (1.52-6.66)</td>
</tr>
</tbody>
</table>

![Figure 1. Example of a poorly differentiated (Gleason 4 + 5 = 9) prostate adenocarcinoma in a 76-yr-old carrier of a BRCA2 mutation.](image)
Discussion

Although early studies of smaller subsets of patients were inconclusive (7, 25–28), recent studies have associated BRCA1 and BRCA2 mutations with a hereditary predisposition to prostate cancer, noting up to a 33% cumulative risk by age 80 (3, 4, 16). It has previously been suggested that BRCA mutation confers a greater risk of early-onset prostate cancer (<65 years; ref. 29), although Giusti et al. (16) reported no difference in mean age of presentation between

### Table 2. Features of prostate cancer cases

<table>
<thead>
<tr>
<th></th>
<th>BRCA wild-type</th>
<th>BRCA1 mutant</th>
<th>BRCA2 mutant</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n (%)</td>
<td>806 (96.9)</td>
<td>6 (0.7)</td>
<td>20 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Median age (range)</td>
<td>68.2</td>
<td>67.1</td>
<td>62.0</td>
<td></td>
</tr>
<tr>
<td>Gleason score &lt;7 (%)</td>
<td>324 (40.2)</td>
<td>3 (50)</td>
<td>17 (85)</td>
<td>0.057</td>
</tr>
<tr>
<td>Gleason score ≥7 (%)</td>
<td>437 (54.2)</td>
<td>3 (50)</td>
<td>1 (5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Median PSA (range)</td>
<td>7 (2-10)</td>
<td>6.5 (5-8)</td>
<td>7 (6-9)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Treatment

- RP: 244 (30.3)
- XRT: 276 (34.2)
- XRT with hormones: 217 (26.9)
- Hormone therapy alone: 34 (4.2)
- Chemotherapy alone: 1 (0.1)
- Watchful waiting: 34 (4.2)

Abbreviations: RP, radical prostatectomy; XRT, radiation therapy; NA, not available.

### Table 3. HRs and 95% CIs for the associations between BRCA1/2 mutation status and recurrence or mortality among 832 prostate cancer cases

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. events</th>
<th>Start of follow-up at date of diagnosis</th>
<th>Median survival time (y)</th>
<th>Total person-years</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation</td>
<td>354</td>
<td>8.7</td>
<td>4,560.3</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>4</td>
<td>2.3</td>
<td>19.6</td>
<td>4.32 (1.31-13.62)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>11</td>
<td>2.6</td>
<td>72.4</td>
<td>2.41 (1.23-4.75)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Castrate metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation</td>
<td>149</td>
<td>17.2</td>
<td>6,669.0</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>2*</td>
<td>10.5</td>
<td>49.9</td>
<td>2.15 (0.28-16.31)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>7</td>
<td>10.5</td>
<td>139.9</td>
<td>3.01 (1.26-7.14)</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Death due to prostate cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation</td>
<td>90</td>
<td>22.0</td>
<td>7,036.2</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>3</td>
<td>13.0</td>
<td>54.0</td>
<td>5.16 (1.09-24.63)</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>5</td>
<td>13.8</td>
<td>161.1</td>
<td>5.48 (2.03-14.79)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Death due to any cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation</td>
<td>132</td>
<td>19.1</td>
<td>7,036.2</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>3</td>
<td>13.0</td>
<td>54.0</td>
<td>2.35 (0.53-10.37)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>8†</td>
<td>12.5</td>
<td>161.1</td>
<td>5.26 (2.29-12.08)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: HRs were adjusted for age, clinical stage, PSA levels, Gleason score at biopsy, and treatment (radical prostatectomy, radiation therapy alone, radiation therapy with hormone therapy, hormone therapy, chemotherapy, and watchful waiting).

*Date of biochemical recurrence could not be confirmed in one additional BRCA mutation carrier.

†The three additional cancer-related deaths in BRCA2 carriers were due to papillary thyroid cancer, angioimmunoblastic lymphoma, and non–small cell lung cancer.
men with and without BRCA mutations; such mutations were found in only 0.78% of 290 men diagnosed with prostate cancer at <55 years of age (30). Our study, one of the largest to date, again shows no significant difference in age of presentation between BRCA mutation carriers and noncarriers.

The proportion of high-grade prostate cancer in our population was significantly higher in the subset with inherited BRCA2 mutations compared with other subsets analyzed. The findings were striking, with 17 of 20 (85%) of BRCA2 mutation carriers showing Gleason ≥7 disease, representing a group with an aggressive phenotype and confirming this recently reported association (15). However, the proportion of cases with high-grade prostate cancer was higher than expected for both cases and controls. Although the Prostate Cancer Prevention Trial included only patients with a PSA of ≤4 ng/mL, only 14.9% of cases had Gleason ≥7 disease (31) compared with 53% in controls in a large study in Iceland (12) and 57% of our population. It is probable that differences in these populations could be due to differences in PSA or stage. Cases referred for care at a specialty center, for example, may be weighted toward more aggressive disease. The 57% of cases in this series with Gleason score ≥7 is comparable with the annual proportion (in 2007) of 59% of all cases biopsied at our institution and the 50% of cases biopsied outside the institution whose pathology showed Gleason score ≥7. It is also possible that the higher baseline Gleason scores in some series are population (e.g., Ashkenazi and Icelandic) specific. Racial variation in both Gleason score at presentation and clinical outcome has been reported (32, 33). However, in two prospective studies of >800,000 men, prostate cancer death rates were significantly lower among Jewish men than non-Jewish men (34), suggesting that the clinicopathologic associations observed here may result from genetic factors in a subset of cases.

When results were stratified by gene, BRCA2 mutations were associated with more poorly differentiated disease, but BRCA1 mutations were not. We found no differences in Gleason scores between BRCA1 mutation carriers and noncarriers, although we genotyped for only one of two BRCA1 founder mutations and may have been underpowered to observe such differences. The “threshold” Gleason score ≥7 was chosen based a priori on previous literature and on clinical experience. Reanalysis of the data using an alternative definition of Gleason score ≥8 revealed essentially the same correlation, with a HR of >3 (95% CI 1.38-7.53) for BRCA2 mutation carriers. The association between BRCA mutation and aggressive histology has now been repeatedly reported but remains unexplained. Recent data suggest that double-strand DNA breaks, acting through the androgen receptor, produce the TMPRSS2-ERG gene fusion that is found in 50% of prostate cancer (35, 36). The TMPRSS2-ERG gene fusion has been associated with aggressive disease, and it is possible that, in the absence of BRCA, accumulating double-stranded breaks facilitate this translocation.

BRCA mutations were not only associated with a more aggressive histology but also independently predicted increased risk of disease progression through the prostate cancer clinical states model (37). A Cox proportional hazards model incorporating the clinical predictors included in commonly used prostate cancer nomograms (Gleason score, PSA at diagnosis, and stage; ref. 38) and treatment
type showed a significance of BRCA mutation status that was independent of these known prognostic factors; there was an increased risk of biochemical recurrence and the development of castrate metastases for BRCA carriers compared with noncarriers. As expected, the more advanced disease in BRCA mutation carriers was associated with worse overall and disease-specific survival. In a previous report suggesting an inferior survival for BRCA-associated prostate cancer (12), 16 of 29 (55%) cases with the Icelandic founder mutation (BRCA2 999del5) had metastatic prostate cancer at presentation, whereas all men in our study had localized disease. In the prior study, the 13 cases with localized disease had a greater risk of dying from prostate cancer compared with noncarriers, a finding that is supported by our larger study. A recent consortium of prostate cancer patients in BRCA1- and BRCA2-linked families noted an inferior survival of BRCA2 compared with BRCA1-associated prostate cancer cases; however, direct genotyping of all cases was not done, there was no available BRCA wild-type comparison group, and no information was available on pathology or clinical features of the disease (14). In contrast to that series, we observed an association with aggressive disease in both BRCA1 and BRCA2 mutation carriers (14). Although the size of our BRCA1 cohort was small, carriers had more aggressive disease with earlier biochemical recurrence and more prostate-specific deaths compared with noncarriers despite similar Gleason scores, suggesting that the effect of BRCA1 mutation on clinical outcome may be independent of aggressive histology.

The current series of BRCA-genotyped prostate cancer cases is among the largest to date, but there is the general concern that combining incident and prevalent cases could have introduced a survival bias in our results. Recent studies of genetic risk factors have noted that inclusion of prevalent cases did not result in a bias of the HR estimates with or without left truncation of the data, as was observed in our study (39, 40). In addition, a survival bias due to a higher HR in the years following diagnosis would tend to obscure adverse prognostic markers (a bias toward the null) and would lead to an underestimation of the adverse prognostic effect of BRCA mutations in the current study. Another limitation of this study is the use of a non-concurrent, albeit more recent, cohort of controls, which may not have had the same opportunity for being diagnosed with prostate cancer due to secular trends. However, the prevalence of subclinical prostate cancer in a younger control group would have resulted in a bias toward the null in the OR analysis and would not have affected the prognostic findings that are based on a case-case analysis.

If it is confirmed that BRCA mutations confer a more aggressive clinical course for men with localized prostate cancer, tailored interventions may be warranted. However, due to the small number of mutation carriers in this study, the strong effect reported must be viewed as hypothesis generating and requires confirmation in a larger cohort. The additional finding that the interval to castrate metastases after biochemical relapse seems shorter in BRCA2 mutation carriers may be an appropriate factor to include in the consideration of antiandrogens in this genetically defined subset. Recent therapeutic strategies, such as small molecules inhibiting poly(ADP-ribose) polymerase (PARP), may biologically target a spectrum of BRCA-deficient tumors, with evidence of response in hereditary breast, ovarian, and prostate cancers (41). Given the estimated 0.0069 BRCA2 mutation frequency in the population and the relative risk for prostate cancer of 3.18 observed here, this translates to ~1.5% of the 180,000 prostate cancer cases in the United States attributable to BRCA2 mutations or 2,790 cases each year that could benefit from treatments tailored to BRCA2 status. PARP inhibitors may improve outcome for patients with advanced BRCA-associated prostate cancer, but due to the aggressive nature of this disease, investigation of PARP inhibitors in the neoadjuvant setting may also be warranted.

Further large-scale studies will be needed to determine if the findings shown here, in a genetic isolate (Ashkenazi Jews), can be generalized to the population at large. The types of protein-truncating mutations of BRCA studied here are representative of BRCA mutations in the general population, and the clinical findings about risk and outcome of BRCA-associated malignancies in Ashkenazim have been applied to other populations (3, 42). This is further supported by concordant findings in an Icelandic population with advanced BRCA2-associated prostate cancer (12). Nonetheless, due to the small number of BRCA carriers in this study, large consortia will be needed to confirm the associations with histology and clinical outcome reported here. Pending such studies, recommendations for screening for and treatment of BRCA-associated prostate cancer should be individualized based on established clinical factors and prognostic markers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Dr. Hans Lilja (Department of Clinical Laboratories) for helpful conversations. H.I. Scher thanks the Memorial Sloan-Kettering Cancer Center Prostate Cancer Specialized Program of Research Excellence program supported by the National Cancer Institute and the Prostate Cancer Foundation. DNA from control subjects was provided as part of the New York Cancer Study of the Academic Medicine Development Company (AMDec) of New York City.

Grant Support

Breast Cancer Research Foundation (K. Offit), W. James and Jane K. Truettner Foundation, Carmel Cancer Research Fund, Lymphoma Foundation, and Robert and Kate Niehaus Research Foundation. D.J. Gallagher has been funded by a scholarship from the Irish Society of Medical Oncology. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 10/27/2009; revised 12/23/2009; accepted 01/23/2010; published OnlineFirst 03/09/2010.
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Clin Cancer Res Published OnlineFirst March 9, 2010.

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doi:10.1158/1078-0432.CCR-09-2871

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