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ARTICLE

Prostate Cancer Progression and Survival in BRCA2 Mutation Carriers

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Background Mutations in the BRCA2 gene are associated with an increased risk of prostate cancer, but it is not known whether they are associated with progression of the disease. We compared prostate cancer–specific survival, disease stage, and tumor grade between prostate cancer patients carrying the Icelandic BRCA2 999del5 founder mutation and noncarriers.

Methods Using population-based registries, we identified all 596 prostate cancer patients who were diagnosed in Iceland during 1955 through 2004 among 29 603 male relatives of unselected breast cancer probands. BRCA2 mutation status could be determined for 527 patients (88.4%). Stage and grade were abstracted from original records, blindly with respect to mutation status, for a subgroup of 89 patients that included all mutation carriers and, for each carrier, two control patients without the BRCA2 999del5 mutation who were matched to the carrier on years of diagnosis and birth. Hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer–specific survival were estimated using multivariable regression models. All statistical tests were two-sided.

Results The mutation was carried by 30 patients (5.7%). Compared with noncarriers, BRCA2 999del5 mutation carriers had a lower mean age at diagnosis (69.0 years versus 74.0 years; $P = .002$), more advanced tumor stage (stages 3 or 4, 79.3% versus 38.6%; $P<.001$), higher tumor grade (grades G3–4, 84.0% versus 52.7%, $P = .007$), and shorter median survival time (2.1 years, 95% CI = 1.4 to 3.6 years, versus 12.4 years, 95% CI = 9.9 to 19.7 years). Carrying the BRCA2 999del5 mutation was also associated with an increased risk of dying from prostate cancer (adjusting for year of diagnosis and birth, HR = 3.42, 95% CI = 2.12 to 5.51); the association remained after adjustment for stage and grade (HR = 2.35, 95% CI = 1.08 to 5.11). The prognosis of BRCA2 999del5 mutation carriers was not associated with period of diagnosis or with relatedness to breast cancer probands.

Conclusions The Icelandic BRCA2 999del5 founder mutation was strongly associated with rapidly progressing lethal prostate cancer.

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Cancer of the prostate ranks second highest among cancers in males worldwide, with a more than fivefold higher incidence in developed countries than in developing countries (1). The incidence of prostate cancer in North America is approximately twice that in Northern Europe (1). This wide international variation in incidence can be explained at least partly by the high and constantly growing diagnostic activity in most Western countries, which leads to increasing numbers of tumors of uncertain clinical significance, with a highly favorable prognosis (2,3). In Iceland, the age-standardized incidence of prostate cancer has increased nearly sixfold since 1955 and is currently 91.4 per 100 000 (for the period 2001–2005) (4). The incidence is similar to that in Norway, Sweden, and Finland (5). Five-year relative survival of prostate cancer patients has steadily improved in Iceland since 1955, being 80% for males diagnosed from 1991 to 2000 (4,6).

The increasing proportion of prostate cancers with a very favorable prognosis supports the need for new methods to predict outcome because the factors currently used, TNM (tumor–node–metastasis) stage, tumor grade, and preoperative serum prostate-specific antigen level, often fail to provide reliable individual prediction. It remains an important challenge to determine which men are at risk of developing lethal prostate cancer (7).

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See "Notes" following "References."

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CONTEXT AND CAVEATS

Prior knowledge

An association exists between BRCA2 gene mutations and risk for prostate cancer, but associations with disease progression are unknown.

Study design

Icelandic population–based study of Icelandic BRCA2 999del5 founder mutation status and prostate cancer–specific survival among relatives of breast cancer patients with prostate cancer.

Contribution

Carrying the Icelandic BRCA2 999del5 founder mutation was associated with younger diagnosis, higher grade and stage of disease, and higher rate of mortality from prostate cancer compared with carrying only the wild-type gene.

Implications

The Icelandic BRCA2 999del5 founder mutation is associated with an aggressive and lethal form of prostate cancer.

Limitations

The study was of a single protein-truncating BRCA2 mutation in a specific population, and thus, the data may not reflect a general association between BRCA2 mutations and aggressive prostate cancer.

Mutations in the tumor suppressor gene BRCA2 are among the few genetic markers known to be associated with increased risk of prostate cancer (8–15). Germline mutations in both the BRCA1 and BRCA2 genes are associated with increased risk of breast cancer and also, to a lesser extent, other cancers, such as ovarian and prostate cancers (16–18). In the Icelandic population, only one mutation has been detected in each of the BRCA genes—a rare BRCA1 mutation that is found in approximately 0.4% of breast cancer patients and a much more frequent BRCA2 999del5 mutation in exon 9 that is present in 6%–7% of breast cancer patients and in 0.6% of unselected population control subjects (19–22; Eyfjord JE: unpublished data). The BRCA2 mutation results in an early truncation of translation; thus, no detectable mutant protein is expressed (23). This mutation appears to completely explain (11) the previously observed (24,25) increased risk of prostate cancer in relatives of Icelandic breast cancer patients.

Although the association between BRCA2 mutations and prostate cancer risk is well documented, little is currently known about the potential association between BRCA2 mutations and the progression of prostate cancer after diagnosis. However, an earlier Icelandic study (8) and two small studies from Israel (26) and Sweden (27) have indicated that BRCA mutations might be associated with aggressive disease, but all these studies lacked statistical power for comparisons or for survival analyses. The aim of this study was to use the population-based Icelandic resources to compare for the first time, to our knowledge, disease stage and tumor grade in prostate cancer patients with and without a BRCA2 mutation. We sought prostate cancer patients among relatives of breast cancer probands to attain an increased prevalence of the 999del5 BRCA2 mutation.

Subjects and Methods

Study Population

The population-based Icelandic Cancer Registry was the source of information on prostate cancer patients. The first year of registration for all cancers was 1955, but the registry also has information on all breast cancer patients who were diagnosed in Iceland from 1911 to 1954 (28,29). The Breast Cancer Family Collection of the Icelandic Cancer Registry includes 994 population-based, unselected breast cancer probands and their first-, second-, and third-degree relatives—a total of 28 806 female relatives and 29 603 male relatives (30,31). The study group was identified by cross-referencing all prostate cancer patients who were listed in the cancer registry with male relatives of the breast cancer probands. Before the linkage was performed, personal identifiers in both databases were replaced with unique study identifiers. The record linkage identified 596 males who had been diagnosed with prostate cancer from January 1, 1955, through December 31, 2004, among the relatives of the breast cancer probands, excluding males who were first diagnosed at autopsy.

Paraffin-embedded tissue samples were sought from all pathology departments in the country for the 453 patients who were deceased at the time of study. Of these patients, tissue samples could be retrieved for 407 (90%). Of the 143 individuals who were still alive at the time of the study, 120 (84%) gave written informed consent and provided blood samples for research on prostate cancer either as part of the Icelandic Cancer Project (32) or to the Icelandic Cancer Society. Thus, genetic analysis could be performed on 527 (88%) of the 596 identified prostate cancer patients. Tissue and blood samples were precoded before genetic analysis, and approval was obtained for this study from the Data Protection Authorities and the National Bioethics Committee of Iceland.

Genetic Analysis

DNA was extracted from blood by conventional methods and from formalin-fixed tumor tissue embedded in paraffin, as previously described (8,33). BRCA2 (GenBank accession code NM_000059) exon 9 fragments were amplified from the DNA by polymerase chain reaction using the following conditions: single denaturing step of 2 min at 94 °C; 40 cycles of 30 s at 94 °C, 30 s at 54 °C, and 45 s at 72 °C; and a final elongation step of 5 min at 72 °C. The primers used for the polymerase chain reaction were 5′-AAAGTCTGAAGAAAAATGATAGATTTA-3′ and 5′-AAAACCTGTAGTTCAACTAAACAG-3′. Amplified fragments were then separated on 7.5% polyacrylamide gels and stained with ethidium bromide to detect the Icelandic BRCA2 founder mutation, 999del5 (19,34). This mutation was identified by the presence of an extra band as compared with the pattern in carriers of only the wild-type allele.

Tumor Stage and Grade

Information was obtained on tumor stage and grade for all 30 patients carrying the BRCA2 mutation and for 59 control patients. Two control patients carrying the wild-type gene were individually matched to 29 of the mutation carriers on year of diagnosis (within 4 years) and year of birth (within 7 years); for one mutation carrier, only one matched control patient could be identified. The

stage of tumors in this subgroup of 89 patients was obtained from the patients' medical records. TNM staging was performed according to standard guidelines (35), and all uncertainties in stage were reviewed by an experienced urologist (E. Jonsson). Tumor grade, according to the Gleason grading system (36,37), was abstracted from pathology reports whenever possible. For 14 out of 25 (56.0%) and 31 out of 55 (56.4%) mutation carriers and noncarriers, respectively, most of whom were diagnosed before year 1991, Gleason grade was determined by one of the authors (J. G. Jonasson) by histologic review of slides because it had not been determined earlier. Patients were grouped according to their tumor stage and grade (35). Tumor stage and histologic grade were determined blindly with respect to the mutation status of the patient.

Statistical Analysis

For the univariate analysis of prostate cancer–specific survival, we used the Kaplan–Meier method (38) with log-rank tests to compare groups. Patients who died of causes other than prostate cancer were censored at the date of death. Multivariable relative hazards were estimated using the Cox proportional hazards model. In these analyses, the endpoint was death from prostate cancer as registered on death certificates and end of follow-up was December 31, 2004. Proportionality was verified by testing the null hypothesis of nonzero slope (39). Of the 527 prostate cancer patients in the study, 138 were first-degree relatives of each other, constituting 62 clusters of interrelated individuals; thus, type II error due to a potentially reduced effective sample size was possible. To check whether statistically significant associations were due to this potentially reduced sample size, we also estimated the relative hazard of dying from prostate cancer when only one randomly selected relative from each cluster of related patients was included. To investigate possible changes over time in the relationship between survival and mutation status, we did a separate analysis by dividing the period at year 1985, which was the median year of diagnosis for mutation carriers. Mean age at diagnosis was compared between mutation carriers and noncarriers using the *t* test statistic. The score test for trend was used to determine trends in proportions. Stage and grade were compared using Wilcoxon matched-pairs signed rank test. The chi-square test was used for comparing proportions. All statistical tests were two-sided; *P* values less than .05 were considered to be statistically significant. The analyses were performed using STATA statistical software Stata 8.2 for Windows.

Results

Characteristics of BRCA2 Mutation 999del5 Carriers and Noncarriers

The BRCA2 999del5 mutation was carried by 30 of the 527 patients (5.7%) (Table 1). Mutation carriers were 5 years younger than noncarriers at diagnosis (69.0 years versus 74.0 years; $P = .002$). The 527 prostate cancer patients in the study group had the following relatedness to the breast cancer probands: 148 were first-degree relatives, 191 were second-degree relatives, and 188 were third-degree relatives. Mutation carriers accounted for 11.5%, 4.7%, and 2.1% of these first-, second-, and third-degree relatives, respectively ($P_{trend}<.001$). Of the 527 prostate cancer patients in the study group, 389 (74%) were not first-degree relatives of each other. Of the remaining 138 patients, 104 had one relative in the study group, 24 had two relatives, four had three relatives, and six had five relatives. Thus, 62 clusters of related prostate cancer patients were present: 52 clusters with two relatives, eight clusters with three relatives, one cluster with four relatives, and one cluster with six relatives.

Table 1. Characteristics of prostate cancer patients in the study of progression of prostate cancer in carriers of the mutation BRCA2 999del5, according to mutation status*

Characteristic	BRCA2 mut (n = 30)	BRCA2 wt (n = 497)
Year of diagnosis, mean (range)	1982 (1960–1999)	1988 (1955–2004)
Year of birth, mean (range)	1913 (1885–1935)	1914 (1877–1952)
Age at diagnosis, y, mean (range)	69.0 (48–84)	74.0 (50–93)
Prevalence of mutation among relatives, %		
First-degree (n = 148)	11.5	–
Second-degree (n = 191)	4.7	–
Third-degree (n = 188)	2.1	–

* mut = carriers of the BRCA2 999del5 mutation; wt = noncarriers; – = not applicable.

Survival Without Adjustment for Stage and Grade

At 5 and 10 years after diagnosis, 79% and 90% of mutation carriers had died from prostate cancer, compared with 29% and 45% of noncarriers, respectively (Fig. 1). The median survival time for mutation carriers was 2.1 years (95% confidence interval [CI] = 1.4 to 3.6 years), whereas it was 12.4 years (95% CI = 9.9 to 19.7 years) for patients who did not carry the mutation. Carrying the mutation was strongly associated with reduced survival from prostate cancer both in unadjusted analyses (hazard ratio [HR] = 3.64, 95% CI = 2.29 to 5.78) and after adjustment for year of birth and year of diagnosis (HR = 3.42, 95% CI = 2.12 to 5.51).

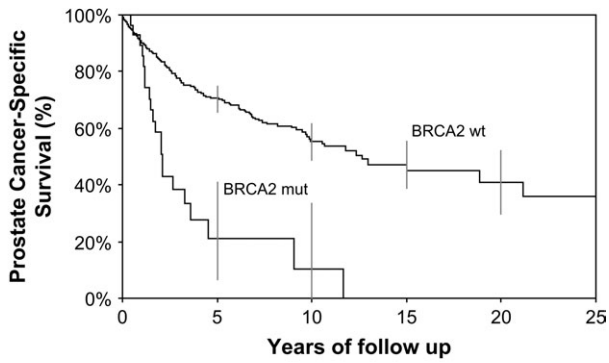
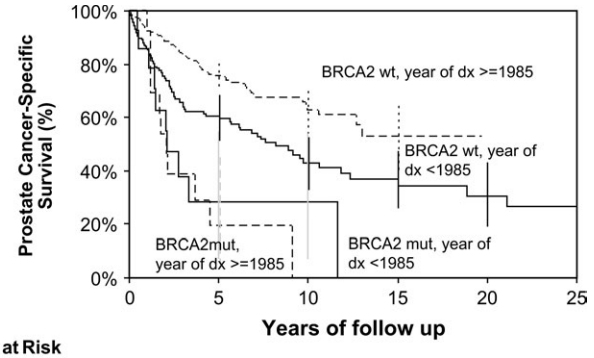


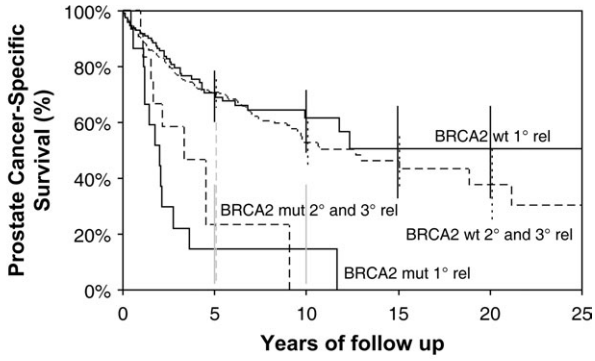
Fig. 1. Kaplan–Meier analysis of prostate cancer–specific survival (%) by BRCA2 999del5 mutation status. The proportion surviving was 21%, 10%, and 0% at 5, 10, and 15 years, respectively, among mutation carriers (BRCA2 mut) and 71%, 55%, 47%, and 41% at 5, 10, 15, and 20 years, respectively, among noncarriers (BRCA2 wt) ($P<.001$, two-sided log-rank test). **Vertical lines** indicate 95% confidence intervals.



Number at Risk

BRCA2 wt dx <1985	166	66	26	15	8	3
BRCA2 wt dx>=1985	331	137	39	7		
BRCA2 mut dx <1985	15	1	1			
BRCA2 mut dx>=1985	15	2				

Fig. 2. Kaplan–Meier analysis of survival of prostate cancer–specific survival (%) by BRCA2 999del5 mutation status and period of diagnosis. Patients who were diagnosed before 1985 (year of dx < 1985) were compared with patients who were diagnosed in 1985 and later (year of dx ≥ 1985). Among mutation carriers (BRCA2 mut), the proportion surviving was 28% and 28% at 5 and 10 years, respectively, among patients who were diagnosed before 1985 and 19% and 0% at 5 and 10 years, respectively, among patients who were diagnosed in 1985 or later ($P = .745$, two-sided log-rank test). For noncarriers (BRCA2 wt), at 5, 10, 15, and 20 years, the proportion surviving was 60%, 43%, 37%, and 30%, respectively, among patients who were diagnosed before 1985 and 76%, 63%, 53%, and 53% among patients who were diagnosed in 1985 or later ($P<.001$, two-sided log-rank test). **Vertical lines** indicate 95% confidence intervals.



Number at Risk

BRCA2 wt 1° rel	131	53	22	6	3	2
BRCA2 wt 2° and 3° rel	366	150	43	16	5	1
BRCA2 mut 1° rel	17	2	1			
BRCA2 mut 2° and 3° rel	13	1				

Fig. 3. Kaplan–Meier analysis of prostate cancer–specific survival (%) by BRCA2 999del5 mutation status and relatedness to breast cancer probands. First-degree relatives (1° rel) were compared with second- and third-degree relatives (2° and 3° rel). Among mutation carriers (BRCA2 mut), the proportion surviving was 15%, 15%, and 0% at 5, 10, and 15 years, respectively, among first-degree relatives and 23% and 0% at 5 and 10 years, respectively, among second- and third-degree relatives ($P = .277$, two-sided log-rank test). For noncarriers (BRCA2 wt), at 5, 10, 15, and 20 years, the proportion surviving was 70%, 61%, 50%, and 50%, respectively, among first-degree relatives and 71%, 53%, 46%, and 38% among second- and third-degree relatives ($P = .376$, two-sided log-rank test). **Vertical lines** indicate 95% confidence intervals.

Because 138 of the 527 prostate cancer patients in the study group were first-degree relatives of each other, there might be a risk of a type II error because of a potentially reduced effective sample size. Thus, we also estimated the relative hazard of dying from prostate cancer when only one randomly selected relative from each of the 62 clusters of related patients was included. This exclusion resulted in a study group of 451 patients, among whom the hazard ratio for mutation carriers of dying from prostate cancer was 3.41 (95% CI = 1.90 to 6.13) after adjustment for year of birth and year of diagnosis. Thus, the potentially reduced sample size had no effect on the results.

The patients in this study were diagnosed for a nearly 50-year period, from 1955 through 2004. To study whether the relationship between survival and mutation status had changed with time, we divided the period at year 1985, which was the median year of diagnosis for mutation carriers. The survival rate in 15 mutation carriers diagnosed in 1985 or later was virtually identical to that in the 15 mutation carriers who were diagnosed before 1985 (HR = 1.16, 95% CI = 0.48 to 2.82), whereas the survival rate had improved statistically significantly for noncarriers between the two periods (Fig. 2). The hazard ratio for prostate cancer–specific survival when comparing the latter period with the earlier period was 0.52 (95% CI = 0.38 to 0.72) when only noncarriers were included in the analysis.

We also investigated the association between relatedness to the breast cancer probands and prostate cancer–specific survival (Fig. 3). No differences in survival rates were observed between prostate cancer patients who were first-degree relatives of breast cancer patients and those who were second- and third-degree relatives, either among patients carrying the BRCA2 mutation or among patients not carrying the mutation. The multivariable hazard ratios (adjusting for year of diagnosis and year of birth) when comparing prostate cancer–specific survival in first-degree relatives with that in second- and third-degree relatives did not deviate from unity (for mutation carriers, HR = 0.62, 95% CI = 0.25 to 1.55; for noncarriers, HR = 1.18, 95% CI = 0.82 to 1.70).

Tumor Stage and Grade

From the study group of 527 patients, 30 patients carrying the BRCA2 mutation and 59 matched patients not carrying the mutation formed the subgroup for which information on tumor stage and grade was sought. Information on TNM stage could be obtained for 29 (97%) of the mutation carriers and 57 (97%) of the matched patients not carrying the mutation. Information on Gleason grade could be obtained for 25 (83%) and 55 (93%) of the carriers and noncarriers, respectively. A majority (55.2%) of mutation carriers had metastatic disease at diagnosis, as compared with 24.6% of noncarriers (Table 2). Furthermore, 79.3% of the mutation carriers were diagnosed at advanced stages (stages 3 or 4), as compared with 38.6% of the patients not carrying the mutation ($P<.001$). Among mutation carriers, 84.0% had tumors of grade groups G3–4 at diagnosis, as compared with 52.7% of the noncarriers ($P = .007$). None of the mutation carriers had tumors that belonged to the lowest grade group (G1), whereas 18.2% of the noncarriers did. The mutation carriers and noncarriers had statistically significantly different stage ($P = .006$) and grade ($P = .006$).

When the analyses were restricted to the 24 mutation carriers and 53 noncarriers among whom information on both stage and grade could be obtained, there was still a strong association between increased risk of dying from prostate cancer and carrying the mutation (mutation carriers versus noncarriers, unadjusted HR = 3.60,

Table 2. Distribution of TNM stage and Gleason grade (groups) for prostate cancer patients carrying the mutation and matched control patients, in the study of progression of prostate cancer in carriers of the mutation BRCA2 999del5*

Tumor stage and grade	BRCA2 mut, %	BRCA2 wt, %
Stage	n = 29	n = 57
1 (T1a, NX/0, MX/0, G1)	3.5	8.8
2 (T1a, NX/0, MX/0, G2/3–4; T1b/1c/1/2, NX/0, MX/0, any G)	17.2	52.6
3 (T3, NX/0, MX/0, any G)	24.1	14.0
4 (T4, NX/0, MX/0; any T, N1, and/or M1; any G)	55.2	24.6
Grade	n = 25	n = 55
1 (well differentiated, Gleason score 2–4)	0	18.2
2 (moderately differentiated, Gleason score 5–6)	16.0	29.1
3–4 (poorly differentiated/ undifferentiated, Gleason score 7–10)	84.0	52.7

* TNM = tumor–node–metastasis (36); mut = carriers of the BRCA2 999del5 mutation; wt = noncarriers; G = Gleason grade (37,38).

95% CI = 1.77 to 7.29). The similarity between this hazard ratio and that from the unadjusted analysis of the whole study group indicates that the subgroup was representative of the whole study group. After adjusting for year of birth, year of diagnosis, and tumor stage and grade, the risk of dying from prostate cancer continued to be higher among mutation carriers than carriers of the wild-type gene (HR = 2.35, 95% CI = 1.08 to 5.11).

Discussion

Using population-based data, we found that a truncating BRCA2 mutation in prostate cancer patients was strongly associated with the development of lethal disease. The especially rapid progression of the disease in mutation carriers was underlined by the fact that the advanced stage and grade at diagnosis were not sufficient to explain their poorer survival. The risk of dying from the disease was still double that of noncarriers after the effects of stage and grade had been taken into account. Thus, our present results are, to our knowledge, the first to give a strong indication that in addition to an increased risk of prostate cancer in BRCA2 mutation carriers, the course of the disease in affected mutation carriers will be rapid and the disease will be aggressive.

In this study, we sought prostate cancer patients among relatives of breast cancer probands to attain an increased prevalence of the BRCA2 mutation, in accordance with a previous Icelandic study (11). In agreement with that study, we found a positive association between prevalence of the mutation and relatedness (P_{trend}<.001). It was possible that poorer survival of mutation carriers might only apply for close relatives of breast cancer patients, i.e., if it were due to an interaction of the BRCA2 mutation with some unknown genetic or environmental factors prevailing in breast cancer patients and their relatives. Therefore, survival analysis was repeated, and first-degree relatives were analyzed separately. However, no apparent difference in survival between first-degree relatives and second- and third-degree relatives was detected, either for patients who carried the BRCA2 mutation or for noncarriers. Thus, it is unlikely that the results can be explained by some unknown effect present in close relatives of breast cancer patients.

Another potential study limitation relates to the fact that 26% of the patients were interrelated. Having a closely related population could lead to a reduced effective sample size and a risk of a type II error. Therefore, we also estimated the adjusted relative hazard of dying associated with the mutation in analyses that included only one randomly selected individual from each cluster of related prostate cancer patients. Because doing so did not change the results, we conclude that 26% of the study group members being closely related did not explain the observed statistically significant associations.

The patients in the study were diagnosed with prostate cancer from 1955 through 2004. Because both treatment and diagnostic activity have changed substantially during that time, we divided the period at the median year of diagnosis for the mutation carriers (1985) to determine whether the relationship between survival and mutation status had also changed with time. Prostate cancer–specific survival rates for mutation carriers did not differ between the two periods, whereas for patients with the wild-type BRCA2 gene, the risk of dying from prostate cancer in the latter period was only half of that in the earlier period. This difference indicates that, among mutation carriers, the course of the disease has been unaffected by changes in treatment and diagnostic activity that occurred with time, contrary to what was seen among noncarriers.

The study has several strengths. First, the definition of the study group was based on two population-based registries, the Icelandic Cancer Registry and the Breast Cancer Family Collection of the Cancer Registry. Thus, there was no risk of the recall bias that may happen when the information on cancer or familiality is obtained directly from the patients. Neither was there a selection of high-risk families into this study because the selection of breast cancer families was population based. Furthermore, the presence of a single common BRCA2 founder mutation and only one very rare BRCA1 mutation in the population facilitated the search for BRCA2 mutation carriers. Finally, risk of misclassification or bias in the assignment of TNM stage and Gleason grade was minimized by careful review of medical records, pathology reports, and histology slides (to the same extent for mutation carriers and noncarriers) when necessary. TNM stage and Gleason grade were assigned blindly with respect to mutation status.

The results call for improved understanding of the role of alterations in BRCA2-related pathways in the progression of prostate cancer. The BRCA2 protein interacts with the DNA repair and recombination protein RAD51 and is involved in repair of double-strand breaks and maintenance of genomic stability (40). Consequently, BRCA2 deficiency leads to complex chromosomal changes both in murine cells and in human breast tumors (33,41,42). Absence of BRCA2 has also been shown to lead to centrosome amplification and abnormal cell division, which might point to a potential mechanism whereby loss of BRCA2 within subclones could drive the loss of genes that regulate cell cycle and could thus enable proliferation and tumorigenesis (42,43). Our findings raise the possibility that prostate cells in BRCA2 mutation carriers may be particularly sensitive to such changes.

Cancer risk in carriers of BRCA2 mutations differs according to the location of the mutations within the gene. A higher risk of ovarian cancer and a lower risk of breast and prostate cancers appear to be associated with mutations located within the so-called ovarian cancer cluster region (OCCR), when compared with mutations located outside the OCCR (12,15,44–46). The Icelandic founder mutation 999del5 is an early truncation mutation that is located outside the OCCR. Therefore, the relative risk of prostate cancer associated with this mutation is possibly best approximated by the recently reported population relative risk of 3.5 for prostate cancer in carriers of BRCA2 mutations located outside the OCCR (46).

The proportion of prostate cancer that can be attributed to BRCA2 mutations, i.e., the population attributable risk percent, differs between populations. In Iceland, the estimated population attributable risk is 1.5%, assuming a relative risk of 3.5 (46) and given that 0.6% of the population carry the mutation (21). In this study, the prevalence of the BRCA2 999del5 mutation was 2.1% among third-degree relatives, which could serve as the upper limit for the prevalence among unselected Icelandic prostate cancer patients. Thus, it seems likely that the prevalence of the mutation is between 1% and 2% among prostate cancer patients in Iceland.

The extent to which the present results of an aggressive behavior of prostate cancer associated with the BRCA2 mutation 999del5 can be extrapolated to populations with mutations at other locations in the BRCA2 gene is an important question. The general answer to that question can only be provided by studies in populations among which other mutations are common. However, our results are likely to apply to all populations of carriers of BRCA2 mutations that lead to complete inactivation of the BRCA2 gene because the Icelandic founder mutation leads to a premature truncation of protein translation and no mutant protein is detected (23).

In this study, we identified a group of patients with unusually fast-progressing prostate cancer. This finding has obvious relevance for carriers of BRCA2 mutations. Furthermore, examination of gene expression or methylation patterns in tumors from BRCA2 mutation carriers using different types of microarray technology might identify pathways that are associated with fast progression that could also be important to a larger group of prostate cancer patients. Interestingly, both allelic loss at the BRCA2 locus (47) and deletions on chromosome 13, where the BRCA2 gene is located (48), have been associated with poor survival of prostate cancer patients. Furthermore, those deletions are among the most common deletions in advanced prostate cancer (48). These results suggest that BRCA2-related pathways might be involved in tumor progression in a larger group of prostate cancer patients than in BRCA2 mutation carriers alone.

To conclude, the Icelandic BRCA2 999del5 mutation is strongly associated with a highly aggressive form of prostate cancer. This finding suggests the need for prostate cancer surveillance of carriers of early truncating BRCA2 mutations. Also, it is of great importance to study whether these results can be confirmed for carriers of mutations at other locations within the BRCA2 gene. Finally, the results indicate that in the search for new methods to predict prostate cancer progression, it may be fruitful to look for gene or protein expression patterns in prostate cancers resembling the patterns seen in BRCA2 mutation carriers.

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