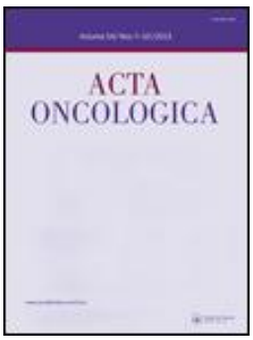

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Henriette Roed Nielsen, Janne Petersen, Christina Therkildsen, Anne-Bine Skytte & Mef Nilbert

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ORIGINAL ARTICLE

Increased risk of male cancer and identification of a potential prostate cancer cluster region in *BRCA2*

HENRIETTE ROED NIELSEN[1], JANNE PETERSEN[2,3], CHRISTINA THERKILDSEN[2], ANNE-BINE SKYTTE[4] & MEF NILBERT[2,5]

[1]*Department of Clinical Genetics, Vejle Hospital, Denmark,* [2]*HNPCC Register, Clinical Research Center, Copenhagen University Hospital, Hvidovre, Denmark,* [3]*Department of Biostatistics, University of Copenhagen, Denmark,* [4]*Department of Clinical Genetics, Aarhus University Hospital, Denmark and* [5]*Institute of Clinical Sciences, Division of Oncology and Pathology, Lund University, Lund, Sweden*

ABSTRACT

Background. The risk of cancer in men from *BRCA1* and *BRCA2* families is relevant to define to motivate genetic testing and optimize recommendations for surveillance.

Material and methods. We assessed the risk of cancer in male mutation carriers and their first-degree relatives in 290 *BRCA1* and *BRCA2* families with comparison to matched controls with the aim to motivate genetic testing and optimize recommendations for surveillance.

Results. Mutation carriers in *BRCA1* families were not at increased risk of cancer, whereas mutation carriers in *BRCA2* families were at increased risk of male breast cancer and prostate cancer with cumulative risks of 12.5% and 18.8%, respectively. Breast cancer developed at a mean age of 59 years, typically as ER/PR positive ductal carcinomas. Prostate cancer developed at a mean age of 68 years, with Gleason scores ≥ 8 in 40% of the tumors. The hazard ratio for *BRCA2*-associated prostate cancer was 3.7 ($p < 0.001$) in mutation carriers and 3.1 ($p = 0.001$) in first-degree relatives. Of the 37 prostate cancers, 19 were linked to four *BRCA2* mutations within a region defined by c.6373-c.6492. Individuals with mutations herein had a HR of 3.7 for prostate cancer compared to individuals with mutations outside of this region.

Conclusions. Male mutation carriers and first-degree relatives in *BRCA2* families are at an increased risk of breast cancer and prostate cancer with a potential prostate cancer cluster region within exon 11 of *BRCA2*.

Pathogenic mutations in the *BRCA1* and *BRCA2* genes are primarily linked to an increased risk of female cancers of the breast and the ovary, though a number of other tumor types have also been suggested to occur at increased incidences in these families, including male breast cancer, prostate cancer, pancreatic cancer and malignant melanoma [1–3]. Families with *BRCA1* or *BRCA2* gene mutations have been ascribed an increased risk of second primary cancers and males in these families have been reported to have a decreased life expectancy by 3.7 years [4,5]. Despite increased cancer risks, men in *BRCA1* and *BRCA2* families show a lower uptake on genetic testing. Primary motivational factors for genetic testing have in male family members have been found to relate to an increased risk of cancer in female relatives rather than to a personal risk of cancer [6].

Male breast cancer accounts for $<1\%$ of all breast cancer cases and for less than 1% of male cancer cases. Compared to females, men with breast cancer are diagnosed at a higher age, more often experience diagnostic delays and develop tumors characterized by ductal differentiation, lymph node involvement and hormone receptor-positivity [7,8]. Survival rates have been reported to be around 60% at five years and 40% at 10 years [7,8]. Male breast cancer most frequently affects *BRCA2* mutation

Correspondence: H. R. Nielsen, Department of Clinical Genetics, Odense University Hospital, Sdr. Boulevard 25, 5000 Odense C, Denmark. E-mail: henriette.roed.nielsen@rsyd.dk

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carriers with lifetime risks of 6–8% for *BRCA2* mutation carriers, whereas the increased risk in *BRCA1* mutation carriers is limited to risks around 1% [9–13]. Prostate cancer represents the most common tumor type in men in the western world and is the second leading cause of cancer-related death in men. Pathogenic mutations in *BRCA1* and *BRCA2* have been demonstrated in 0.5–2% of prostate cancer [14–16]. The relative risk of prostate cancer has been estimated to be 1.1–3.8 for *BRCA1* mutation carriers and 4.7–8.6 for *BRCA2* mutation carriers compared to the general population [2, 15–18]. The cumulative risks of prostate cancer have been estimated to be 3–9% for *BRCA1* mutation carriers and 19–34% for *BRCA2* mutation carriers [11,16,18]. Genotype–phenotype correlations have been suggested for ovarian cancer, with an ovarian cancer cluster region (OCCR) in exon 11 of *BRCA2* [11,19]. Limited data are available regarding genotypic effects related to development of prostate cancer though a higher risk has been suggested for individuals with mutations outside of an OCCR region defined by *BRCA2* c.2806-c.6401 [11].

Accurate risk estimates and recognition of genotypic effects are needed to optimize genetic counseling and recommendations for surveillance for men in *BRCA1* and *BRCA2* families. The limited knowledge on male cancer risk led us to assess these and study genotype–phenotype correlations in a cohort from western Denmark.

Patients and methods

Study cohorts and data collection

All individuals/families who had undergone genetic counseling between 1997 and 2011 at the three departments of clinical genetics in western Denmark (population 3 million) and had been found to carry disease-predisposing mutations in *BRCA1* or *BRCA2* were eligible for the study. Families diagnosed with concomitant cancer-predisposing mutations in other genes (e.g. MMR gene mutations) and individuals born after April 1994 were excluded. A three-generation pedigree with mutation carriers in at least two generations was required for inclusion. Family members were identified from the pedigrees and from the National Danish Civil Registration System, which contains data on date of birth, emigration and death. Data from mutation carriers, first-degree relatives and proven non-carriers were analyzed separately. A control population was defined from the National Danish Civil Registration System, with five population controls, matched on sex and year of birth, for mutation carriers as well as first-degree relatives. Controls were identified for all but six mutation carriers and 17 first-degree relatives, all of whom were born before 1920. Information on cancer diagnoses, excluding skin cancer other than malignant melanoma, was collected through ICD7 and ICD10 codes from the National Danish Cancer Register (available since 1943) and from the National Danish Pathology Register (available since 1997) until April 2014. Breast cancer and prostate cancer include cases with carcinoma in situ. The mean follow-up time was 49.2 years (56 years for proven *BRCA1*/*BRCA2* carriers, 46–50 years for first-degree relatives and 49–50 years for proven non-carriers). Genetic test results were collected between January 1997 and June 2013 from the respective molecular genetic laboratories. Information on date of birth, death and cancer diagnosis was based on pedigree information for family members who died before 1968. The study was reviewed and granted acceptance form the Danish Data Protection Agency. According to Danish regulations, registry studies are not subject to ethical review.

Statistical analyses

For each of the six groups, i.e. proven carriers, first-degree relatives of a proven (male or female) carrier and proven non-carriers in *BRCA1* and *BRCA2* families, respectively, we estimated the hazard ratio (HR) for cancer compared to the matched control population. We used a Proportional Hazard Ratio Model with death and other types of cancers as competing events. In all models, families were modeled with a cluster variable, where all controls were considered to be in their own family. We repeated the analyses for the four major outcomes, i.e. all cancers, breast cancer, prostate cancer and prostate cancer before age 65, after exclusion of male index individuals (to account for assessment bias) and after exclusion of men born before 1947 (to account for selection bias through inclusion only of men below age 50 at the time of introduction of genetic testing). Cumulative incidence plots were constructed with age as underlying time for *BRCA2* mutation carriers and first-degree relatives and were for mutation carriers calculated in relation to mutations inside/outside of the suggested prostate cancer cluster region (PCCR). Cancer diagnosis and death from any cause were modeled as competing events and members of the same family were modeled with a cluster variable to account for correlation. Genotype–phenotype correlations in the *BRCA2* gene were studied with the assumption that the risk of prostate cancer was equal along the *BRCA2* genetic sequence with estimates of the HR for prostate cancer development in relation to genetic region.

All data management, descriptive statistical analyses and Proportional Hazard models were made in SAS9.4. For the Proportional Hazard models we

used the phreg procedure with a robust sandwich covariance matrix estimate. Cumulative incidence plots were performed in R, version 3.03 with the *comp.risk* and *predict* functions from the *timereg* package. A p-value ≤ 0.05 was considered significant in all statistical analyses.

Results

Complete data were available from 290 families; 173 families with 49 different disease-predisposing mutations in *BRCA1* and 117 families with 49 mutations in *BRCA2*. In total, the study contains 1718 men aged ≥ 20 years; 447 proven or obligate mutation carries, 976 first-degree relatives and 295 non-mutation carriers. The distribution of birth cohorts were: birth prior to 1900, 1.3%; 1900–1919, 6.7%; 1920–1939, 14.5%; 1940–1959, 26.4%; 1960–1979, 32.9% and 1980–1994, 18.4%.

In the *BRCA1* families, 71 cancers developed in 51/265 mutation carriers and 97 cancers developed in 69/573 first-degree relatives (Supplementary Table I, available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1067714). The overall risk of cancer compared to the control population was not significantly increased in mutation carriers (HR 1.1, 95% CI 0.8–1.5, p = 0.62), but was significantly increased in first-degree relatives (HR 1.5, 95% CI 1.1–2.0, p = 0.01). Two male breast cancers were observed in mutation carriers at ages 38 and 56 years (HR 8.5, 95% CI 0.7–97.6, p = 0.09). Prostate cancer was diagnosed in eight mutation carriers at a mean age of 63 (57–70) years and in eight first-degree relatives at a mean age of 72 (55–81) years. The risk of prostate cancer was not significantly increased in mutation carriers (HR 1.0, 95% CI 0.4–2.6, p = 0.99) or first-degree relatives (HR 0.7, 95% CI 0.3–1.5, p = 0.32) compared to the controls though mutation carriers showed a trend for an increased risk of prostate cancer development before age 65 (HR 3.7, 95% CI 1.0–13.7, p = 0.05).

In the *BRCA2* families, 68 cancers developed in 54/182 mutation carriers and 73 cancers developed in 58/403 first-degree relatives (Supplementary Table I available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1067714). Increased risks for all cancers were identified in mutation carriers with a HR of 2.4 (95% CI 1.79–3.30, p < 0.001) and in first-degree relatives with a HR of 1.7 (95% CI 1.26–2.40, p = 0.001). The overall risk estimates were explained by increased risks for breast cancer and prostate cancer (data not shown). In total, 15 male breast cancers and 37 prostate cancers developed. Male breast cancer developed in 13 mutation carriers (including one patient with metachronous, bilateral breast cancer), in one first-degree relative and in none of the controls, which preclude an estimate of the HR. The cumulative incidence for male breast cancer at age 80 was 12.5% (95% CI 11.5–13.5%) (Figure 1). The male breast cancers developed at a mean age of 61 (37–84) years. Data on receptor status were available from nine tumors and showed estrogen positivity in eight, progesterone positivity in seven and HER2 positivity in two tumors. The tumors were predominantly ductal carcinomas with frequent areas of ductal carcinoma *in situ* (Table 1).

Prostate cancer developed in 17 mutation carriers and in 20 first-degree relative, which corresponds to a HR of 3.7 (95% CI 1.9–7.2, p < 0.001) in mutation carriers and a HR of 3.1 (95% CI 1.6–5.7, p = 0.001) in first-degree relatives compared to their matched controls. The HR for prostate cancer before age 65 was 5.5 (95% CI 1.6–18.7, p = 0.01) for mutation carriers. The cumulative incidence for prostate cancer at age 80 was 18.8% (95% CI 16.6–21.9) (Figure 1). The prostate cancers developed at a mean age of 67 (52–93) years (Table II). Gleason scores were available from 20 tumors and were five in two cases, six in three, seven in seven, eight in two, nine in five and 10 in one case. Hence Gleason scores ≥ 8 were found in 40% of the cases. Two individuals

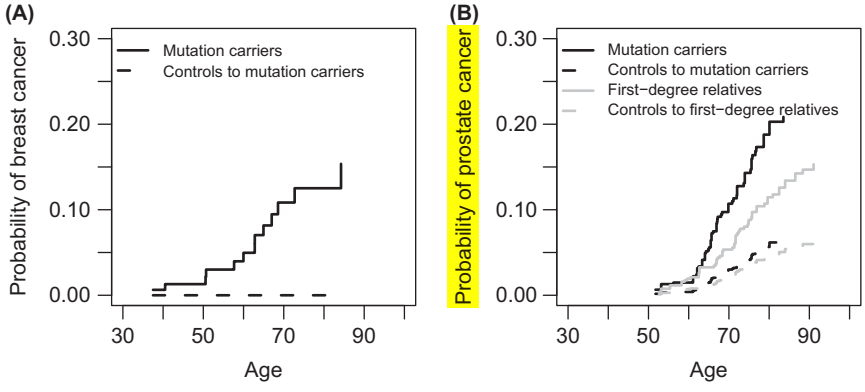

Figure 1. Cumulative risks of a) male breast cancer and b) prostate cancer in the *BRCA2* cohort.

developed primary breast cancers at ages 62 and 67, respectively, followed by prostate cancers at ages 85 and 86, respectively. Exclusion of the six male index cases (with male breast cancer) and individuals born after 1947, did not affect the results (data not shown). Neither in *BRCA1* nor in *BRCA2* did male family members who were proven non-carriers show any significantly increased risk of cancer.

Genotype–phenotype correlations in the *BRCA2* gene were analyzed in relation to male breast cancer and prostate cancer. The 15 male breast cancers were associated with 12 different *BRCA2* mutations, which were spread along the gene without any association to specific genetic regions (Figure 2). The 37 *BRCA2*-associated prostate cancers developed in 25 families with 13 distinct *BRCA2* mutations. Of these, four mutations, i.e. c.6373delA, c.6408_6414delAAATGGT, c.6486_6489delACAA and c.6490_6492del/insGACT were linked to 19/37 prostate cancers (Figure 2). Individuals who carried any of these four *BRCA2* mutations had a HR of 3.7 (95% CI 1.35–9.33) $p = 0.01$ for development of prostate cancer compared with mutations in other parts of *BRCA2*. When the HR for prostate cancer development in individuals with mutations within the PCCR was compared to controls, the HR was 9.7 (95% CI 4.0–23.7) $p \leq 0.001$. The cumulative incidence of prostate cancer at age 80 was 35.6% for individuals with mutations within the PCCR and 10.6% for individuals with mutations outside of the PCCR (Figure 3). When the OCCR region defined by Gayther et al., i.e. c.2807-c.6401, was applied to our data, the cumulative incidence for prostate cancer at age 80 was 29.4% for individuals with mutations in the OCCR and 8.2% for individuals with mutations outside of the OCCR. In the 13 families with mutations in the region c.3860-c.6244 prostate cancer developed in 1/11 mutation carriers and in the nine families with mutations between c.7008-1-c.7070, no prostate cancers were observed in six male mutation carries (Figure 2).

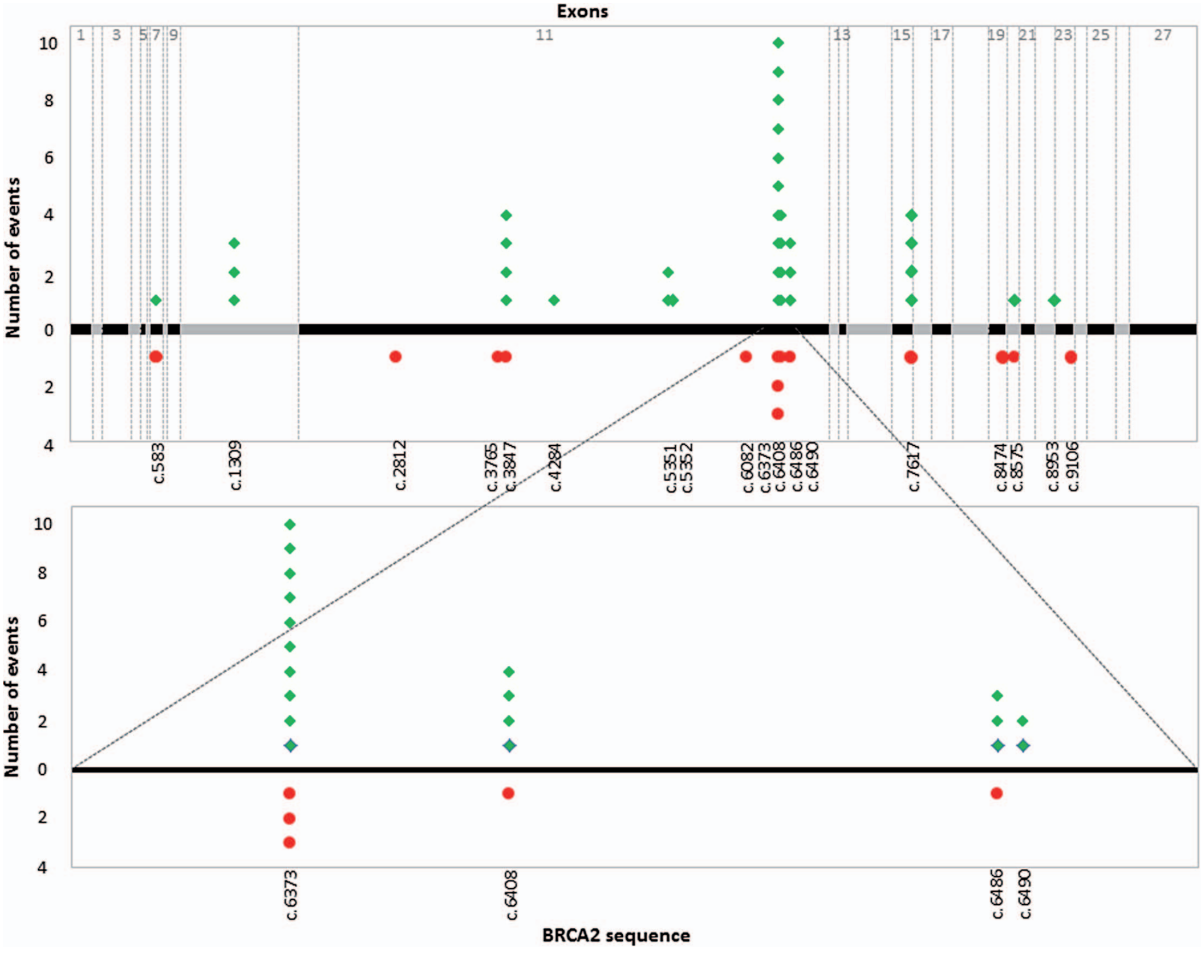

Figure 2. Summary plot of mutations in the *BRCA2* gene linked to development of male breast cancer (red) and prostate cancer (green). In total, 19 of the 37 prostate cancer cases are linked to four mutations in a suggested prostate cancer cluster region spanning c.6373-c.6492 within exon 11 of the *BRCA2* gene.

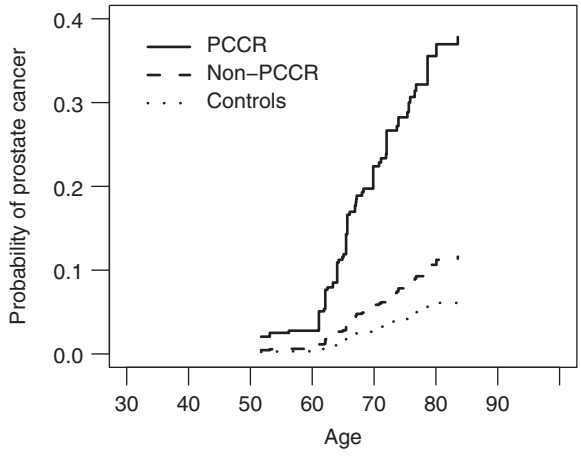

Figure 3. Cumulative incidence for prostate cancer in *BRCA2* mutation carriers in relation to mutations inside and outside of the suggested prostate cancer cluster region (PCCR) demonstrating cumulative incidences at age 80 of 35.6% and 10.6%, respectively.

Discussion

We demonstrate a limited risk of cancer for men in *BRCA1* families and a significantly increased risk of male breast cancer and prostate cancer for men in *BRCA2* families. Male breast cancer developed at a mean age of 61 years, which fits well with previous reports [20]. The breast tumors were typically estrogen and progesterone positive ductal carcinomas of histologic grades 2–3, often with areas of ductal carcinoma *in situ* (Table I) [20]. Cases with multifocal disease and bilateral tumors have been reported and were observed also in our cohort (Table I). The cumulative risk of male breast cancer in *BRCA2* mutation carriers was 12.5%, which is somewhat higher than previous reports of 6.9–8.6% risk at age 80 (Figure 1) [9,11,13]. Current risk estimates are sensitive to ascertainment bias as development of male breast cancer is a well recognized feature of hereditary breast cancer. Still, the risk of breast cancer demonstrated motivates awareness of this disease and prompt management of suspected cases in male *BRCA2* mutation carriers.

Mutation carriers as well as first-degree relatives in *BRCA2* families are at an increased risk of prostate cancer with HRs of 3.7 and 3.1, respectively, which supports previous observations [2,15,18,21–24]. The mean age at diagnosis of prostate cancer was 67 years. The risk of prostate cancer development before age 65 was significantly increased (HR 5.5), in line with previous reports with HRs of 5.5–8.6 for early-onset prostate cancer in *BRCA2* [10,15]. The cumulative risk of prostate cancer at age 80 was estimated to be 18.8% in mutation carriers and 12.5% in first-degree relatives (Figure 1). In our cohort, 8/20 (40%) prostate cancers had Gleason scores ≥ 8 suggestive of an aggressive prostate cancer phenotype (Table II). Prostate cancer associated with *BRCA1* and *BRCA2* mutations have been suggested to have higher Gleason scores, more frequent T3/T4 stages, nodal involvement and overall present with a worse prognosis [21–28]. Data on prevalent PSA testing in our cohort were not available and we cannot exclude that a smaller number of tumors were screening detected. As general recommendations for prostate cancer screening have not been enforced in Denmark and the majority of the cases were diagnosed in the years when widespread PSA testing was not prevalent, we consider the potential effect hereof as limited. Strategic surveillance for prostate cancer in male *BRCA1* and *BRCA2* mutation carriers has been suggested to identify high-risk tumors [29]. The high risk of prostate cancer and the early age at onset of the disease are important to recognize

Table I. Summary of clinical, pathologic and genetic data in male breast cancers linked to *BRCA2*.

Individual number	Carrier status	Mutation	Age at diagnosis	Tumor stage	Histology
122	Carrier	c.2812delGCAA	60	NA	Ductal cancer in situ
58	Carrier	c.3765delT	65	NA	Ductal cancer
9	Carrier	c.3847_3848delGT	69	T1N1	Ductal cancer
190	Carrier	c.583delT	84	T1N2	Ductal cancer
157	Carrier	c.6082_6086delGAAGA	63	T2N0	Ductal cancer
11	Carrier	c.6373delA	37	T1N1	Ductal cancer
137	Carrier	c.6373delA	41	T1N0	Ductal cancer
108	FDR	c.6373delA	82	T1N1	Ductal cancer
17	Carrier	c.6408_6414delAAATGTT	51	T1N2	Ductal cancer
85	Carrier	c.6486_6489delACAA	59	NA	Not specified
32	Carrier	c.7617 + 1 G>A	63	T2N2	Ductal cancer
186	Carrier	c.8474delC	51	NA	Comedo cancer
26	Carrier	c.8575delC	58	T2N0	Ductal cancer
162	Carrier	c.9106C>T	86	T2N1	Ductal cancer
162	Carrier	c.9106C>T	72	NA	Ductal cancer in situ

FDR, first-degree relative; NA, not available.

Table II. Summary of clinical and genetic data in prostate cancers linked to *BRCA2*.

Individual number	Carrier status	Mutation	Age at diagnosis
160	Carrier	c.3847_3848delGT	53
9a	Carrier	c.3847_3848delGT	74
9b	Carrier	c.3847_3848delGT	80
59	Carrier	c.5351delA	76
190	Carrier	c.583delT	84
101	Carrier	c.6373delA	52
98	Carrier	c.6373delA	70
113	Carrier	c.6373delA	64
27a	Carrier	c.6373delA	65
27b	Carrier	c.6373delA	61
101	Carrier	c.6373delA	62
27	Carrier	c.6373delA	72
11	Carrier	c.6373delA	66
17	Carrier	c.6408_6414delAAATGTT	79
85	Carrier	c.6486_6489delACAA	59
88	Carrier	c.6490_6492del/insGACT	63
2	Carrier	c.7617 + 1G>A	67
47a	FDR	c.1309_1312delAAAG	55
47b	FDR	c.1309_1312delAAAG	82
82	FDR	c.1309_1312delAAAG	55
160	FDR	c.3847_3848delGT	58
227	FDR	c.4284_4285insT	84
59	FDR	c.5351delA	72
223	FDR	c.5352delC	80
113	FDR	c.6373delA	87
137	FDR	c.6373delA	74
17a	FDR	c.6408_6414delAAATGTT	77
17b	FDR	c.6408_6414delAAATGTT	53
17c	FDR	c.6408_6414delAAATGTT	93
3143	FDR	c.6486_6489delACAA	59
205	FDR	c.6486_6489delACAA	53
88	FDR	c.6490_6492del/insGACT	67
132	FDR	c.7617 + 1G>A	68
163	FDR	c.7617 + 1G>A	63
143	FDR	c.7617 + 1G>A	76
6491	FDR	c.8575delC	77
86	FDR	c.8953 + 1G>T	63

FDR, first-degree relative.

during genetic counseling and the aggressive phenotype demonstrated is relevant to consider for treatment decisions in men affected by *BRCA2*-associated prostate cancer.

We identify a potential prostate cancer cluster region, PCCR, based on 19/37 prostate cancers clustering to a region defined by c.6373-c.6492 in exon 11 of *BRCA2*. The c.6373delA mutation was found in 14 families, among which 10 prostate cancer were diagnosed in six families. The c.6408_6414delAAATGGT mutation was identified in one family with four prostate cancers; the c.6486_6489delACAA mutation was seen in three families, each with one case of prostate cancer and one family with the c.6490_6492del/insGACT mutation contained two prostate cancers (Figure 2). Individuals with mutations in the suggested PCCR had a HR of 4.4 ($p = 0.01$) for prostate cancer development compared to individuals with *BRCA2* mutations outside of this region. Only occasional prostate cancer developed in families with mutations 5′or 3′of the PCCR, which supports observations of a significantly lower risk of prostate cancer for carriers of the Ashkenazi Jewish founder mutation, c.5946delT [30]. Data on genotype–phenotype correlations for prostate cancer in *BRCA2* are limited, though an increased risk has been described for individuals with mutations outside the OCCR region, i.e. *BRCA2* c.2806-6401 [11,30]. Our findings partly contradict these results, with an increased risk of prostate cancer linked to mutations herein, but these results may be explained by the 10 prostate cancers linked to the *BRCA2* c.6373del A mutation, which was not present in the former studies [17,30,31]. Estimates of genotype–phenotype effects are sensitive to cancer risk and penetrance and our observation needs validation in larger, prospective data sets to determine its clinical relevance.

In summary, our data, based on a western Danish *BRCA1* and *BRCA2* cohort and a control population, demonstrate significantly increased risks of breast cancer and prostate cancer in males from *BRCA2* families. Whereas breast cancer developed predominantly in mutation carriers, the risk of prostate cancer applied to mutation carriers and first-degree relatives. Half of the mutations linked to prostate cancer clustered in a region defined by c.6373-c.6492 in exon 11 of *BRCA2*, which lead us to suggest a potential PCCR herein.

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Supplementary material available online

Supplementary Table I online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1067714