Research Article

Cancer Prevention Research

Decreased Prostate Cancer-Specific Survival of Men with *BRCA2* Mutations from Multiple Breast Cancer Families

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Abstract

The role of a germ-line *BRCA2* mutation in the development of prostate cancer is established, but the clinical presentation linked to outcome for this group of men has not been well described.

A total of 148 men from 1,423 families were ascertained from the kConFab consortium. Each participant met the following criteria: (i) a verified case of prostate cancer; (ii) confirmed as either a carrier or noncarrier of a family-specific *BRCA* pathogenic mutation; (iii) comprehensive clinical and treatment data were available. Clinical data were linked to treatment received and overall survival was analyzed by Kaplan–Meier.

Prostate cancer in men from breast cancer-prone families has a high risk of disease progression, irrespective of mutation status. *BRCA2* mutation carriers have an increased risk of death and prostate cancer-related death [HR (95% CI) 4.5 (2.12–9.52), $P = 8.9 \times 10^{-5}$] by comparison with noncarriers. Serum PSA readings taken prior to diagnosis in 90% of all men, age adjusted, were above clinical significance. Following D'Amico risk stratification, 77.5% of *BRCA2* mutation carriers and 58.7% of noncarriers had high-risk disease. *BRCA2* mutation status was also an independent prognostic indicator of overall survival. Furthermore, there was a poor overall survival outcome for both the *BRCA2* mutation carriers and noncarriers given curative-intent treatment.

All men in breast cancer-prone families are at risk of developing aggressive prostate cancer. This information is significant and should be included in discussions with genetic counselors and medical professionals when discussing prostate cancer treatment options for men in these families, irrespective of mutation status. *Cancer Prev Res; 4(7); 1002–10. ©2011 AACR.*

Introduction

Prostate cancer is the most common noncutaneous malignancy in Western men and the second most common cause of male cancer-specific death (1). Although it is accepted that the majority of men diagnosed with prostate cancer will not die of this disease, efforts are continuing to identify the groups of men at risk of clinically significant prostate cancer. Between 1990 and 2007 (1), the proportion of men diagnosed with disease at high risk of progression, using a restrictive definition, was approximately 16.9%. Given that high-risk prostate cancer is associated with significant social and financial cost (2), it is important to focus on this proportion of men in the population to maximize their chances of overall survival.

The *BRCA1* and *BRCA2* genes are tumor suppressor genes associated with an increased risk of cancer development including breast, ovarian, and prostate cancer (3). Early studies estimated the relative risk for developing prostate cancer in men from *BRCA2* mutation carrier families as being 2.9 to 4.8 (3–5), with some subgroups (men <65 years) having a relative risk as high as 7.3 (3). Later studies, estimated that men with a pathogenic *BRCA2* mutation are at 3.5-fold (95% CI: 1.8–12) increased risk of developing prostate cancer (6). Furthermore, prostate cancers arising in *BRCA2* mutation carriers display an aggressive tumor phenotype (6–7) and present as more poorly differentiated tumors when compared with noncarrier prostate cancer controls (8).

Although a specific role for *BRCA1* and *BRCA2* in the development of prostate cancer has not yet been elucidated, a recently described mouse model employing *Cre-LoxP*–mediated recombination was used to conditionally delete the *BRCA2* gene from adult mouse prostate epithelia. The study demonstrated the development of

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hyperplasia at 10 to 14 and 15 to 20 months, and focal low grade PIN at the 15 to 20 months time point within the prostate epithelium. This mouse model further supports the role of *BRCA2* in prostate tumorigenesis and provides an opportunity for further testing of new therapeutics and cellular interactions to be analyzed and mapped (9).

In terms of screening strategies for early detection of cancer within this subset of men, the uptake of PSA-based case selection modalities, treatment and optional clinical management is neither well defined nor implemented in the same way as it is for women at increased risk of breast and/or ovarian cancer. However, studies examining the impact of men at risk of prostate cancer and the associated recruitment and retention into early detection programs have shown that these programs are becoming more prevalent (10–11).

The clinical impact of *BRCA1* or *BRCA2* mutations on prostate cancer survival was initially reported in men with prostate cancer from families with a *BRCA* mutation but who were not necessarily carriers of the family-specific mutation (12). More recently, a cohort of Ashkenazi Jewish men who were carriers of a *BRCA1* or *BRCA2* founder mutation were compared with men with prostate cancer who did not harbor a founder variant (8). In that cohort, the *BRCA1* and *BRCA2* mutation carriers were shown to display a poor clinical outcome with a higher risk of recurrence [HR (95% CI): 4.32 (1.31–13.62) and 2.41 (1.23–4.75), respectively] and a decrease in prostate cancer-related survival [HR (95% CI): 5.16 (1.09–24.53) and 5.48 (2.03–14.79), respectively; ref. 8]. In late 2010, Edwards and colleagues compared a group of *BRCA2* carriers with early onset prostate cancer ($\leq$55 years) to a control group of prostate cancer patients (13). The results indicated that the median overall survival of early onset *BRCA2* mutation carriers was shorter than the control group (overall survival of 4.8 years compared with 8.5 years; ref. 13). Furthermore, this study confirmed our previously published data that loss of heterozygosity is observed in the tumor tissue of the majority of *BRCA2* carriers (6). While this study demonstrates that a *BRCA2* mutation is an independent factor in overall survival, it does so in a group of men unselected for family history.

Our study, the largest reported to date, examines the impact of a variety of *BRCA2* mutations (26 unique mutations)—not simply founder mutations—on prostate cancer-specific survival in a group of men ascertained from families at high-risk of breast/ovarian cancer. Therefore, the purpose of this study was to evaluate the impact of a confirmed pathogenic *BRCA2* mutation on prostate cancer-specific survival linked to cancer treatment in a setting of multicase breast cancer family history.

Methods

Study population and procedures

Men diagnosed with prostate cancer were identified from 1,423 families recruited into the Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab), the Australian and New Zealand consortium for families at high risk of breast cancer (14). For inclusion in this consortium, families must have a strong family history of multicase breast and/or ovarian cancer, or be known to be segregating a germline mutation in a breast cancer predisposition gene; including *BRCA1* and *BRCA2* (see www.kconfab.org for full recruitment criteria).

In our study, male family members were eligible for inclusion if: (i) they had a verified diagnosis of prostate cancer, (ii) complete diagnostic and treatment notes were available, and (iii) their individual *BRCA* mutation status was known.

From the multigenerational kConFab cohort, the final group of participants selected for this study consisted of 148 men from 130 families. Each of these cases had a verified diagnosis of prostate cancer via a clinical pathology report, plus a complete set of medical and treatment reports (including PSA test reports, radiology/CT scans, surgical notes, radiotherapy, and chemotherapy schedules) enabling analysis of overall survival linked to treatment. Unfortunately, an additional 102 participants were excluded from this study as complete treatment notes were not available.

Ethics and access to medical records

Ethics approval was obtained from the IRB at the Peter MacCallum Cancer Centre. Informed consent at study entry to kConFab permitted access to medical/treatment reports, blood collection, and archived tumor tissue. For deceased participants, proxy consent was obtained from the next of kin. Where applicable, cause of death was verified from a death certificate, doctor's notes or hospital medical records. Treatment and medical notes were accessed through physicians, hospitals, medical diagnostic laboratories, and state cancer registries.

Pathology and cancer treatment

Central pathology review was undertaken for 130 of the 148 tumor cases (either biopsies and/or radical prostatectomy surgical specimens) by an uropathologist (D. Cloustan), blinded to mutation status and clinical details. Data were extracted from the original diagnostic pathology reports for the remaining 18 specimens that were not available for review, though it is not known if an uropathologist reported all cases as surgery was performed in various cities and regional/remote sites. Staging evaluation was standardized according to the UICC TNM classification of malignant tumors (15).

D'Amico risk algorithm (16) was used to stratify participants into low, intermediate, and high-risk disease of prognosis and death.

Participants were categorized into 2 treatment groups for statistical analyses. Curative-intent treatment was defined as radical prostatectomy and/or radiotherapy (including brachytherapy). Noncurative treatment was defined as hormone manipulation, chemotherapy, and expectant management.

Serum PSA readings at diagnosis, defined as the value obtained within 4-weeks of prostate cancer diagnosis, were obtained for 110 participants (74.3%). PSA testing, defined as 2 or more PSA readings 12 months prior to diagnosis, was carried out for 31% of participants.

Mutation detection

Individual *BRCA2* mutation status was confirmed using (i) PCR and Sanger sequencing for point mutations and micro insertion/deletion mutations; or (ii) multiplex ligation-dependent probe amplification for large genomic rearrangements (MRC-Holland; ref. 17). Testing was carried out on DNA derived from blood or unstained sections of formalin-fixed paraffin-embedded tissue, using the QIAamp mini blood kit or DNeasy Blood & Tissue kit (Qiagen) and the Wu protocol (18). Obligate mutation carriers were confirmed by pedigree review.

Families tested for *BRCA* mutations were categorized as *BRCA1* or *BRCA2* mutation carriers or *BRCAX*. A *BRCAX* family is defined as a family where genetic screening for both *BRCA1* and *BRCA2* mutations and large genomic rearrangements has been carried out in the youngest cancer affected (usually breast cancer) family member, but where no pathogenic germline mutation has been identified. Participants with unclassified variants were included in the *BRCAX* group. *BRCA1* mutation carriers were excluded from the study due to the small sample size ($n = 11$), leaving a final cohort for survival analysis of 137 men.

With regards to prostate cancer family history within first and second degree relatives, only 15 families had multiple verified cases of prostate cancer: 11 *BRCA2* families having 2 to 3 cases, and 4 *BRCAX* families with 2 cases.

The 2 groups for survival analysis were: (1) Carriers: men who carried a pathogenic family-specific *BRCA2* mutation, and (2) Noncarriers: men who tested negative for their family-specific *BRCA1* or *BRCA2* mutation or who were from a *BRCAX* family.

Statistical analysis

Student's *t* test was used to evaluate differences between participant groups. Overall survival, prostate cancer-related survival and treatment outcomes were analyzed using the Kaplan–Meier method (19). Cause of death was verified by doctors' notes and/or a death certificate for every participant. Mutation status, age, log PSA at diagnosis, and Gleason score were analyzed in a univariate manner to identify factors associated with prognosis. The categorical predictor (*BRCA2* mutation status) was tested for significance using a log-rank test, whereas other continuous covariates were tested for significance with a likelihood ratio test within a Cox proportional hazards model (20). The significant factors were then combined in a multivariate Cox model to test for independent prognostic power. Due to the absence of PSA and/or Gleason scores, 22 participants (8 *BRCA2* mutation carriers and 14 noncarriers) were excluded from both univariate and multivariate analyses. Fisher's exact test was used to compare specific features between *BRCA2* mutation carriers and noncarriers, including prostate cancer-specific survival, D'Amico high-risk stratification, Gleason score, T stage, and treatment options in D'Amico high-risk participants. These analyses included participants with metastatic disease at diagnosis.

Results

In total, 137 kConFab participants with prostate cancer were evaluable for this study (median age at diagnosis 66.2 years, range 33–87). The *BRCA2* mutations were varied and unique, and not clustered into a single region of the gene (24 frameshift, nonsense, missense mutations and 2 large genomic rearrangements). All participants nominated Anglo-Saxon ethnicity on their epidemiological questionnaire except one who indicated Asian ancestry.

As there was no statistical significance between *BRCA1* family-specific mutation-negative ($n = 9$), *BRCA2* family-specific mutation-negative ($n = 16$) and *BRCAX* participants in terms of age of diagnosis, age of death/prostate cancer-specific death, or duration to death (data not shown), they were combined as a single control group ($n = 97$) for the purpose of overall survival and treatment analyses. Furthermore, comparison of the *BRCA2* mutation-positive group with those who did not carry their family-specific *BRCA2* mutation ($n = 16$) did not show any significant difference in median age at diagnosis (data not shown).

BRCA2 mutation carriers were diagnosed at 64.9 years compared with 66.8 years for the noncarriers (Table 1). In this mutation positive group ($n = 40$), 23 participants died with a median overall survival of 3.5 years. Of the 23 deaths, only 2 were unrelated to prostate cancer, compared with 17/29 in the noncarrier group ($P = 0.01$).

In addition, 65.8% (25/38) of *BRCA2* mutation positive tumors had Gleason scores 8 or greater, and a large proportion were $\geq$ stage pT3 disease at presentation (17/38, 44.7%) confirmed radiologically or with a pathology report. The *BRCA2* mutation carriers presented with higher grade (Gleason score >7) and larger, more locally advanced ($\geq$pT3) disease than the noncarriers ($P = 8.59 \times 10^{-4}$ and $P = 0.04$, respectively; Table 1). This led to the *BRCA2* mutation carriers having a greater proportion of D'Amico stratified high-risk disease compared with the noncarriers (77.5% and 58.7%, $P = 0.05$; data not shown).

Fisher's *t* test of additional variables such as age at diagnosis and age at overall death of *BRCA2* carriers versus noncarriers were performed (data not shown). Comparisons of the mean of age at prostate cancer-specific death (72 vs. 72.9 years, respectively, $P = 0.79$), duration to death (4.4 vs. 5.6 years, respectively, $P = 0.28$), and duration to prostate cancer-specific death (4.5 vs. 4.9 years, respectively, $P = 0.73$) indicated that there was no statistical difference between these 2 groups.

When comparing the carriers and noncarriers, *BRCA2* mutation status was shown to be a significant prognostic predictor of both overall survival [HR (95% CI): 3.12

Table 1. Participant demographic within the *BRCA2* mutation carriers and the noncarrier group

	***BRCA2* mutation carriers**	**Noncarriers**	***P***
No. of patients (no. of families)	40 (34)	97[a] (89)[b]	N/A
Gleason score, %			
≤6	2 (5.3)	19 (19.6)	8.59×10^{-4}[d]
7	11 (28.9)	46 (49.4)	
≥8	25 (65.8)	32 (33.0)	
Unknown	2	0	N/A
T stage[c], %			
≤pT2	21 (55.2)	70 (75.3)	0.04[e]
pT3–T4	15 (39.5)	21 (22.6)	
Tx	2 (5.3)	2 (2.1)	N/A
Unknown	2	4	
Participants with metastatic disease at (N1M1) diagnosis[f]	7	4	N/A
PSA (Pre-Dx)[g]			
No pre-Dx, *n* (%)	11 (27.5)	21 (21.6)	N/A
<4 ng/mL	1 (2.5)	10 (10.3)	
Mean ± SD (range), ng/mL	0.4	2.3 ± 1.0 (0.72–3.8)	
4–10 ng/mL,	10 (25)	37 (38.1)	
Mean ± SD (range), ng/mL	5.6 ± 1.7 (4.0–9.4)	7.2 ± 1.5 (4.3–10)	
10–100 ng/mL	14 (35)	27 (27.9)	
Mean ± SD (range), ng/mL	24.9 ± 15.3 (10.5–56.5)	21.6 ± 15.7 (10.9–81.3)	
101+ ng/mL	4 (10.0)	2 (2.1)	
Mean ± SD (range), ng/mL	1289 ± 1709 (111–3750)	103–195 (149.0 ± 65.1)	
Median/mean age at diagnosis (range)	64.9/65.9 (43–84)	66.8/65.7 (33–87)	0.92[h]

NOTE: Age given in years; duration to death (including PCRD) given in years.
All percentages calculated excluding unknown values.
[a]Participants negative for a family mutation (9 *BRCA1* and 16 *BRCA2*) were placed into the noncarrier group.
[b]There are 3 families that include 2 participants each with 1 participant positive for the family mutation and 1 participant negative for the family mutation.
[c]Highest T stage used where clinical and pathology T stage differs; Participants with metastatic disease at diagnosis not included in percentages.
[d]Fisher's exact test comparing proportion of Gleason score 7 or less with Gleason score less than 7 between *BRCA2* mutation carriers and the noncarrier group.
[e]Fisher's exact test comparing proportion of T stage ≤T2 with T3/T4 between *BRCA2* mutation carriers and the noncarrier group.
[f]Number of participants with metastatic disease at diagnosis have been included in T-stage values.
[g]PSA numbers given are numbers of participants; No pre-Dx PSA includes cases where no PSA data were available at all.
[h]Student's *t* test comparing ages between *BRCA2* mutation carriers and the noncarrier group.
Abbreviation: Dx, diagnosis.

(1.64–6.14), $P = 3.0 \times 10^{-4}$] and prostate cancer-specific survival [HR (95% CI): 4.97 (2.19–11.25), $P = 2.4 \times 10^{-5}$] on univariate analysis (Table 2). Similarly, Gleason score was also predictive of overall survival [HR (95% CI): 1.53 (1.14–2.04), $P = 4.6 \times 10^{-3}$] and prostate cancer-specific survival [HR (95% CI): 2.12 (1.48–3.03), $P = 1.96 \times 10^{-5}$], whereas age at diagnosis was not (Table 2). Serum PSA at diagnosis was also a statistically significant factor for both overall survival [HR (95% CI): 1.84 (1.48–2.28), $P = 1.29 \times 10^{-7}$] and prostate cancer-specific survival [HR (95% CI): 1.83 (1.41–2.37), $P = 1.5 \times 10^{-5}$], although only moderately (Table 2).

While the majority of *BRCA2* mutation carriers with a serum PSA of more than 4 ng/mL at diagnosis (a commonly used value to trigger investigation in asymptomatic screening programs) fell into the D'Amico high-risk category, the only 2 men with a low PSA reading (0.4 and 4.0 ng/mL) were still stratified as high-risk due to their Gleason score and/or T staging. These men were diagnosed at 43 years (in 2001) and 65 years (in 2003), and both had stage T3 disease with Gleason scores of 10 and 7, respectively. Similarly, 2 of the 3 participants within the noncarrier group with PSA readings 4 ng/mL or less at diagnosis (3.2 and 3.1 ng/mL, respectively) were stratified

Table 2. Factors evaluated for overall survival and prostate cancer-specific survival for the *BRCA2* mutation carrier group ($n = 40$) compared with the noncarrier group ($n = 97$)

	All deaths		PCRD	
Factors	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**
Mutation status	3.0×10^{-4}	3.12 (1.64–6.14)	2.4×10^{-5}	4.97 (2.19–11.25)
Age at diagnosis	0.26	NS	0.95	NS
Log PSA	1.29×10^{-7}	1.84 (1.48–2.28)	1.5×10^{-5}	1.83 (1.41–2.37)
Gleason score >7	4.6×10^{-3}	1.53 (1.14–2.04)	1.96×10^{-5}	2.12 (1.48–3.03)

NS, not significant; PCRD, prostate cancer-related death.

as D'Amico high-risk due to advanced disease on subsequent staging. The PSA reading for the remaining 43-year-old participant fell below the 2 ng/mL age-specific threshold of total serum PSA for biopsy in men diagnosed between age 40 and 49 (21). An additional D'Amico high-risk noncarrier had a PSA of 3.8 ng/mL at diagnosis but as he was diagnosed at 47 years, his PSA value exceeds the age-specific threshold of total serum PSA for biopsy in men diagnosed between age 40 and 49 (21).

Using Cox regression and Kaplan–Meier analysis over a 15-year period (Fig. 1), the age-adjusted HR for the total cohort of *BRCA2* mutation carriers versus noncarriers was 2.87 (95% CI: 1.63–5.03, $P = 2.50 \times 10^{-4}$). Considering prostate cancer-specific survival, the age-adjusted Cox HR of 3.79 was significant (95% CI: 1.95–7.35, $P < 5.0 \times 10^{-4}$; Fig. 1A and B, solid line).

When participants with metastatic disease at diagnosis were removed from both the *BRCA2* mutation carrier and noncarrier groups, poor survival was still observed between the 2 groups, with an age-adjusted HR (95% CI) for overall survival of 2.90 (1.56–5.41, $P = 8.0 \times 10^{-4}$) and HR (95% CI) of 4.50 (2.12–9.52, $P = 8.9 \times 10^{-5}$) for prostate cancer-specific survival (Fig. 1A and B, broken line).

Participants were categorized into curative-intent and noncurative treatment groups based on the treatment received (Table 3). When participants were stratified for D'Amico high-risk only and the participants with metastatic disease at diagnosis were excluded, 79.2% of both *BRCA2* mutation carriers and noncarriers received curative-intent treatment (Table 4). Survival analysis between both treatment groups in the *BRCA2* mutation carrier group compared with the noncarrier group indicated no significant difference (data not shown).

Discussion

This is the largest retrospective study to date of confirmed *BRCA2* mutation carriers with prostate cancer in a predominantly unscreened cohort, detailing clinical features, primary treatment and survival outcomes. Further to our previous findings that men with a pathogenic *BRCA2* mutation have a 3.5 times greater risk of developing prostate cancer than the general population (6), this study indicates that *BRCA2* mutation carriers also have 4.5 times decreased risk of prostate cancer-specific survival when compared with the noncarrier group. Although the ideal control group would have been the noncarriers of the family-specific *BRCA2* mutation alone, the overall numbers within this group ($n = 16$) were too small for adequate statistical analyses.

As supported by recent reports (8, 22), this study did not identify a significant difference in age at diagnosis, age at death/prostate cancer-specific death, nor duration to death/prostate cancer-specific death between *BRCA2* mutation carriers and noncarriers. However, our study shows a reduced age at prostate cancer diagnosis in breast cancer prone families (64.9 years and 66.8 years) compared with the general population (median presentation 75 years, range 40–96 years; ref. 23).

The majority of men in our cohort were diagnosed with poor prognosis prostate cancer based on D'Amico stratification, irrespective of mutation status, and most of the participants in both groups had clinically significant PSA scores (>4 ng/mL) at diagnosis (93.1% and 86.8%, respectively). With regards to prostate cancer management, treatment with curative-intent is often offered to men with high grade prostate cancer as these tumors exhibit an aggressive natural history. In this study, no significant difference was observed in the duration of prostate cancer-specific survival between the *BRCA2* mutation carriers and noncarriers for those treated with curative intent (Table 4). However, the short duration to prostate cancer-specific death for both groups, irrespective of treatment, was an important finding (3.5 and 3.3 years, respectively, Table 1). When stratified for D'Amico high-risk only (Table 4), there was no statistical difference between survival of *BRCA2* carriers treated with curative or noncurative intent, with both groups surviving less than 6 years post treatment. However, those in the noncarrier group had a significantly reduced survival outcome when treated with noncurative intent than those who were treated via either surgery or radiotherapy (1.92 years compared with 7.17 years, respectively). This suggests

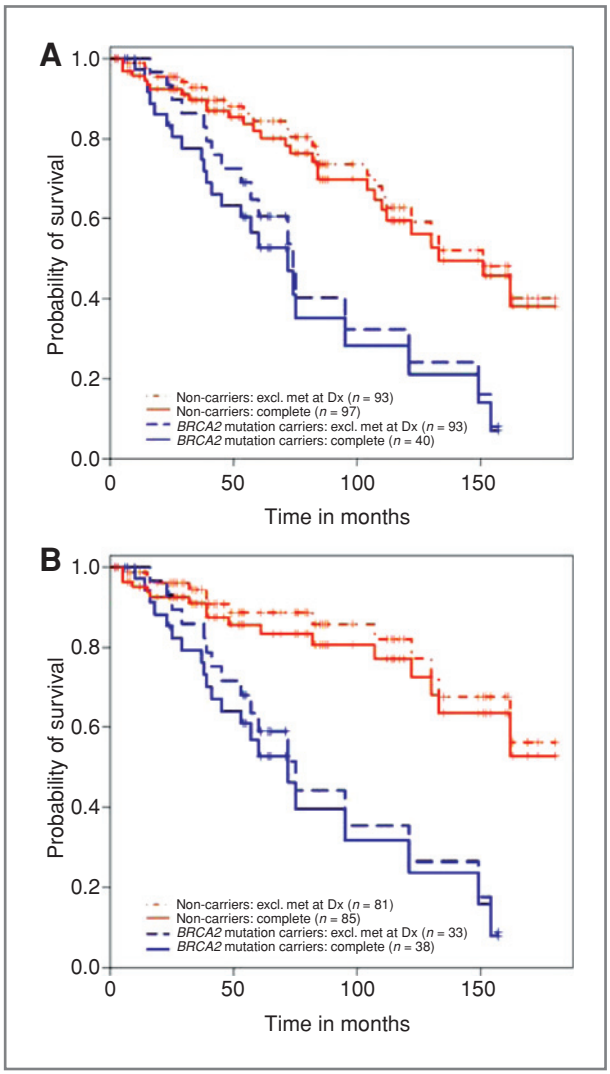

Figure 1. Fifteen years of Kaplan–Meier overall survival analysis of *BRCA2* mutation carrier group versus the noncarrier group. The solid blue and red line is the total number of participants in the *BRCA2* mutation carrier and noncarrier groups. The broken blue and red lines represent these groups with participant who had metastatic disease at diagnosis excluded. A, overall deaths. Age-adjusted COX HR (95% CI): 2.87 (1.63 5.03), $P = 2.5 \times 10^{-4}$ (solid line). Age-adjusted COX HR (95% CI): 2. 90 (1.56–5.41), $P = 8.0 \times 10^{-4}$ (broken line). B, prostate cancer-related deaths. Age-adjusted COX HR (95% CI): 3.79 (1.95–7.35), $P < 5.0 \times 10^{-4}$ (solid line). Age-adjusted COX HR (95% CI): 4.50 (2.12–9.52), $P = 8.9 \times 10^{-5}$ (broken line).

that with regards to noncarriers within a high-risk breast cancer setting, individuals diagnosed with aggressive prostate cancer would be better served by more aggressive treatment methods.

The median duration of overall survival in our *BRCA2* mutation carriers is consistent with reports of poor prostate cancer survival arising in association with the Icelandic *BRCA2* 999del5 founder mutation (24). This Icelandic cohort displayed a median survival of 2.1 years (95% CI: 1.4–3.6 years), a lower mean age of diagnosis, plus

Table 3. Participant treatment statistics defined by treatment received for *BRCA2* mutation carrier and noncarrier groups

	***BRCA2* mutation carrier**	**Noncarrier**
	n = 36	*n = 90*
Curative, %	69.4	75.5
Surgery	14 (38.8)	38 (42.2)
Radiotherapy	11 (30.6)	28 (31.1)
Brachytherapy	0	2 (2.2)
Noncurative, %	30.6	24.5
Hormones	10 (27.8)	16 (17.8)
Chemotherapy	0	1 (1.1)
Expectant management	1 (2.8)	5 (5.6)
Unknown	4	7

advanced prostate cancer with higher tumor grade than their *BRCA2* wild-type counterparts (24). We have demonstrated that the presence of a *BRCA2* mutation is associated with overall survival [HR (95% CI): 3.12 (1.64–6.14), $P = 3.0 \times 10^{-4}$] and prostate cancer-specific survival [HR (95% CI): 4.97 (2.19–11.25), $P = 2.4 \times 10^{-5}$] and the presence of the *BRCA2* mutation is an independent prognostic indicator of survival.

It is not known why prostate cancer survival is different in men with a *BRCA2* mutation, but it is likely to involve a number of factors including the method of cancer detection, tumor biology, genetic profile and the occurrence of other malignancies. The method of cancer detection is an important consideration as the advent of serum PSA screening, especially in the United States and Europe (25–26), has substantially increased annual prostate cancer incidence with a downward stage migration at diagnosis. Improved prostate cancer-specific survival in the general population could be explained, in part, by diagnosis of proportionally less clinically significant prostate cancer. In our study, however, PSA testing prediagnosis was employed by only 31% of participants, yet the majority of participants were stratified with D'Amico high-risk disease implying a more aggressive disease than is usually observed in the general population (23). Although routine PSA screening is not currently recommended in Australia (27), the results presented here suggest that in this group of men, PSA-based case selection may have clinical utility. The current IMPACT study is examining the utility of PSA-based case selection in *BRCA* mutation carriers to identify prostate cancer in presymptomatic patients (28). In year 1, 3.3% prostate cancers were detected by PSA screening (28). As The IMPACT study also offers a prostate biopsy to all men at study exit, it may be able to provide important insights into the prevalence of prostate cancer in this cohort as well as an indication of an appropriate PSA threshold for biopsy. To date, the positive predictive value of biopsy at a threshold of 3.0 ng/mL or more is 45.5% (28).

Table 4. D'Amico high-risk participants categorized according to the received treatment method (curative-intent versus noncurative treatment), excluding participants with metastatic disease at diagnosis

	BRCA2 Mutation carrier			Noncarrier group		
		PCRD			PCRD	
Treatment method	All patients ($N = 24$)	Age at Dx[a] (range)	Survival[b] (number of deaths)	All patients ($N = 48$)	Age at Dx[a] (range)	Survival[b] (number of deaths)
Curative, *n* %	19 (79.2)	68 (44–77)	5.57 ± 3.50 (9)	38 (79.2)	73 (64–76)	7.17 ± 4.28 (5)
Noncurative, *n* %	5 (20.8)	64 (57–66) $P = 0.15$[c]	3.54 ± 1.04 (3)	10 (20.8) $P = 0.05$[c]	83 (65–85)	1.92 ± 1.12 (3)

NOTE: The mean duration from diagnosis to treatment for all groups was within 10 months (data not shown).
[a]Age, y = median age at diagnosis (Dx).
[b]Survival is in years (mean ± standard deviation).
[c]Student's *t* test comparing curative-intent treatment with noncurative treatment in *BRCA2* mutation carrier and noncarrier groups.

With regards to alternatives to current treatment options for this group of men, clinical trials are imperative. We await the results of current PARP inhibitor studies in advanced *BRCA1* and *BRCA2* associated cancers (29–32) with interest. These targeted therapies have shown great promise in breast and ovarian cancer (29–30, 32) and may also prove effective in *BRCA*-associated prostate cancer. A recently described prostate cancer *BRCA2*-deficient mouse model (9) will also provide an invaluable tool for *in vivo* testing of targeted therapies such as PARPi and provide a mechanism for tracking and defining the *BRCA2* tumorigenesis pathway.

The observed reduced overall survival in our cohort may be explained by inherent differences in tumor biology, given that our results are consistent with other reports of a more aggressive prostate cancer phenotype in *BRCA2* mutation carriers (6–8), with 65.8% in our cohort displaying tumors with a Gleason score 8 or more; and 44.8% having high T stage (≥pT3) at diagnosis. Although a precise biological basis for this aggressive phenotype of *BRCA2*-associated prostate cancers is still to be determined, it has been suggested that downregulation of *BRCA2* expression via introduction of siRNAs in prostate cancer cells may promote cancer cell migration and invasion, possibly by upregulation of matrix metalloproteinase-9 (33–34).

The main focus of our study was the nature of *BRCA2*-associated prostate cancer, however, it is important to highlight that the noncarrier group in our study also had a strikingly poor prostate cancer-specific survival (41.4%) compared with the general population [95.3% at 75 years (35)], and an earlier age of cancer onset [66.8 years, range 33–87 vs. 75 years, range 40–96 years (23)]. That the average age of diagnosis in carriers and noncarriers is similar, suggests that in families with a strong history of breast cancer, even the family member who does not carry the deleterious *BRCA* family-specific mutation, may have an inherited an underlying genetic instability that increases their risk of cancer. In support of this, a recent study by Dite and colleagues (36) indicated that first degree relatives of women diagnosed with breast cancer at a young age (≤35 years) had an increased risk of developing a variety of cancers, irrespective of mutation status. The authors suggest that there are underlying familial factors in these families, such as variants in other genes, that predispose individuals to cancer (36). This work supports our findings in that the families within our study, irrespective of mutation status, have a strong family history of breast cancer (38.5% diagnosed under the age of 35) and ovarian cancers, plus additional occurrences of prostate cancer. The poor survival in the noncarriers observed in our study is a new finding and different to what has been reported in Edwards and colleagues (13). The survival difference observed between these 2 studies can possibly be explained by participant ascertainment. Our noncarriers were ascertained from high-risk breast cancer families, whereas the Edwards study ascertained men from cancer prostate cancer clinic. Expansion and analysis of noncarriers of other familial and population-based cohorts will help determine the overall risk status within this group.

It is worth noting that although the multivariate analysis indicates a correlation between high-risk disease and variables such as Gleeson score and PSA, it does not provide any new or additionally prognostic information in this setting; though the presence of the *BRCA2* mutation does appear to be an independent prognostic indicator of survival. With this in mind, we are continuing the recruitment of male participants to perform large-scale prospective studies to improve the statistical analyses of these different variables, including mutation status and Gleason score.

The poor overall survival and high-risk tumor characteristics of prostate cancer arising in the setting of *BRCA2* mutation carriers and noncarriers seen in this study have implications for the clinical management of these

men. These findings strongly support the contribution of additional, as yet unknown, genetic factors to prostate cancer etiology and prognosis in breast cancer–prone families (37–38). Furthermore, these findings indicate that genetic testing of presymptomatic men within such families may have clinical utility. Subsequent discussions about prostate cancer screening with an experienced urologist is also encouraged to inform both *BRCA2* mutation carriers and noncarriers alike that due to their underlying genetic changes they are at an increased risk of developing clinically significant prostate cancer that is difficult to manage and has a poor clinical outcome. Whilst there is uncertainty surrounding the optimal management and treatment of *BRCA2*-associated prostate cancer, knowledge of the poor overall survival outcome in this unique cohort provides a good starting point for discussion with treating specialists.

Our study suggests that existing familial breast cancer cohorts may be a fertile cohort to test the relevance of genetic variants identified by genome wide association studies and/or to search for novel genetic variants associated with prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed

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