Prostate cancer screening characteristics in men with BRCA1/2 mutations attending a high-risk prevention clinic

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Abstract

Introduction: The prostate-specific antigen (PSA) era and resultant early detection of prostate cancer has presented clinicians with the challenge of distinguishing indolent from aggressive tumours. Mutations in the BRCA1/2 genes have been associated with prostate cancer risk and prognosis. We describe the prostate cancer screening characteristics of BRCA1/2 mutation carriers, who may be classified as genetically-defined high risk, as compared to another high-risk cohort of men with a family history of prostate cancer to evaluate the utility of a targeted screening approach for these men.
Methods: We reviewed patient demographics, clinical screening characteristics, pathological features, and treatment outcomes between a group of BRCA1 or BRCA2 mutation carriers and age-matched men with a family history of prostate cancer followed at our institutional Prostate Cancer Prevention Clinic from 1995 to 2012.
Results: Screening characteristics were similar between the mutation carriers (n = 53) and the family history group (n = 53). Some cancers would be missed in both groups by using a PSA cut-off of >4 ug/L. While cancer detection was higher in the family history group (21% vs. 15%), the mutation carrier group was more likely to have intermediate- or high-risk disease (88% vs. 36%). BRCA2 mutation carriers were more likely to have aggressive disease, biological recurrence, and distant metastasis.
Conclusions: In our cohort, regular screening appears justified for detecting prostate cancer in BRCA1 and BRCA2 carriers and other high-risk populations. Lowering PSA cut-offs and defining monitoring of PSA velocity as part of the screening protocol may be useful. BRCA2 is associated with more aggressive disease, while the outcome for BRCA1 mutation carriers requires further study. Large multinational studies will be important to define screening techniques for this unique high-risk population.

Introduction

More than 25 000 men are diagnosed with prostate cancer each year in Canada, with more than 4000 men dying of the disease each year.[1] The widespread use of prostate-specific antigen (PSA) testing in prostate cancer has defined the last 20 years as the "PSA era" and was largely fueled by the eponymous biomarker's success in detecting prostate cancer. The D'Amico risk (low, intermediate and high) stratification system accurately predicts prostate cancer specific mortality (PCSM) across various treatment modalities and provides a useful treatment guide.[2] However, a significant proportion of prostate cancer patients remain over-treated when diagnosed by PSA screening with low-risk cancers.

The recent European Randomized Screening Study of Prostate Cancer (ERSPC) found that 48 prostate cancer patients needed to be treated for every cause-specific death avoided.[3] PSA screening continues to be controversial[4] and testing is no longer recommended by the US Preventive Services Task Force due to similar mortality rates in screened and unscreened populations.[5] The often indolent nature of low-risk prostate cancer and the overtreatment of these patients confound the appropriate use of PSA as increased detection of indolent cancers may not lead to decreased mortality in most cases. With PSA tests detecting both indolent and life-threatening cancers, clinicians must re-evaluate screening protocols to identify only those men who will benefit from treatment, distinguishing the cancers that can be managed with surveillance.[6] The discovery of new and complementary prognostication markers therefore remains clinically important.

Excluding advanced age and black ancestry, the strongest risk factor for prostate cancer is a family history of the disease, as the risk of prostate cancer in first-degree relatives is

twice that of the general population.[7] Genome-wide association studies show that combining susceptibility loci could explain up to a third of familial risk for prostate cancer.[8] Special cases of genetically defined high risk are men who carry mutations in the BRCA1 and BRCA2 genes. BRCA2 carriers have an 8- to 9-fold increased risk for prostate cancer and these cancers occur at a younger age (e.g., under 65).[9] Male BRCA1 carriers have a 2- to 5-fold increased chance of prostate cancer.[10] It has been argued that targeted screening of these men could be warranted based on recent evidence that men with BRCA2 mutations who develop prostate cancer have an aggressive course of the disease.[11] Indeed, Castro and colleagues analyzed the clinicpathological characteristics of prostate cancers in BRCA1 and BRCA2 carriers and found carriers more frequently had high Gleason scores (8 or above), T3/4 stage, nodal involvement, metastases at diagnosis, and found that cause specific survival was shorter compared to non-carriers.[12] Other similar studies corroborate these findings.[13-16]

Until recently, reports on the screening outcomes of male BRCA1/2 carriers have been scarce and often limited to specific founder mutations studied in a select population. In 2005, our centre evaluated the utility of targeted screening for detecting prostate cancer in BRCA1/2 carriers.[17] This preliminary evaluation was limited by having only a small cohort of 19 carriers. Bancroft and colleagues reported in 2014 on the outcome of the first year of screening for over 1500 mutation carriers. Their preliminary results supported the use of targeted PSA screening as it yielded a high proportion of aggressive disease. This study used a PSA cut-off of >3 ug/L and did not have long-term follow-up data on patient outcomes.[18]

In this study, we reevaluated the utility of targeted prostate cancer screening for high-risk patients. To do this, we compared the screening and clinicopathological characteristics between men with a BRCA1 or BRCA2 mutation and men with a family history of prostate cancer followed for an average of 4 years.

Methods

A retrospective chart review was performed for patients followed at the Prostate Cancer Prevention Clinic (PCPC), which is part of the Genitourinary Clinic at the University Health Network, Toronto, Ontario. The PCPC provides screening and treatment to men at an increased risk for prostate cancer due to their Caribbean ancestry, family history of prostate cancer, or BRCA1 or BRCA2 mutation carrier status. Screening includes annual PSA and digital rectal exam (DRE). Transrectal ultrasound (TRUS) guided biopsy is offered in patients with a PSA greater than 4 ug/L, an abnormal DRE, or if warranted by assessment of PSA velocity.

After identifying all known BRCA1 and BRCA2 mutation carriers (known as the Mutation Carrier group) who had begun screening after age 40, we identified an age-matched one-to-one comparison group. This comparison group (known as the Family History group) contained men with a positive family history of prostate cancer (defined as at least 1 first-degree relative with prostate cancer) who had been followed at the PCPC. Men of Caribbean ancestry were excluded, as this was predicted to confer an additional risk component. Chart review included obtaining demographic features (age at first visit, cancer diagnosis, family history of prostate cancer, BRCA1 or BRCA2 mutation status), clinicopathologic screening characteristics (PSA, DRE, biopsy, cancer detection, Gleason score), and treatment and outcome information for men diagnosed with prostate cancer.

Results

Demographics

In total, 53 men were identified for the Mutation Carrier group. This included 29 (55%) with BRCA1 mutations (representing 25 families) and 23 (43%) with BRCA2 mutations (representing 21 families). For 1 individual the type of BRCA mutation was not available. This individual was included in the analyses between the Mutation Carrier group and Family History group, but was omitted from the comparisons between BRCA1 and BRCA2 patients.

We tallied the age at first visit, screening period, personal diagnosis of cancer, and family history of cancer for the 2 groups (Table 1). The average age at presentation was similar between the Family History and Mutation Carrier groups (50.7 and 52.7 years, respectively, $p = 0.26$), but the average screening period was significantly longer in the Family History group (7 vs. 4.8 years, $p = 0.01$). The propor-

Table 1. Demographic description of family history and mutation carrier groups

	Family history (n = 53)		Mutation carriers (n = 53)	
	n	Percent	n	Percent
Mean age at first visit (years)	50.7	-	52.7	-
Screening period (years)*	7	-	4.8	-
Any diagnosis of cancer	15	28%	20	38%
Prostate cancer	11	21%	8	15%
≥2 Primary tumours	2	4%	6	11%
Family history of prostate cancer	53	100%	10	19%
≥1 First-degree relative	53	100%	7	7.5%
Second-degree relative only	-	-	3	6%

*$p = 0.01$

tion of men with any cancer diagnosis or multiple primaries was slightly higher in the Mutation Carrier group ($p = 0.41$, $p = 0.27$, respectively). However, the proportion of men with prostate cancer, specifically, was slightly higher in the Family History group ($p = 0.61$). Ten mutation carriers (19%) had a family history of prostate cancer.

Screening characteristics

We noted the outcomes of PSA screening, DRE, and biopsy (Table 2). Most men in the Family History and the Mutation Carrier groups had normal screening values during the course of their follow-up, as assessed by PSA and DRE (58% and 62%, respectively, $p = 0.84$).

The proportion of men with elevated PSA, abnormal DRE, rising PSA, and biopsy were similar between the 2 groups. Cancer detection after biopsy because of PSA >4 ug/L was slightly higher in the Mutation Carrier group (66% vs. 55%) and lower after biopsy for abnormal DRE (25% vs. 66%), but was the same between the 2 groups for rising PSA.

Overall, the cancer detection rate was higher in the Family History group (21%) compared to the Mutation Carrier group (15%). However, when the detection rate was calculated for the BRCA1 group and the BRCA2 group separately, the highest overall detection rate occurred in men with BRCA2 mutations (26%) and the lowest overall detection rate was in BRCA1 mutation carriers (7%) ($p = 0.11$).

Clinicopathological features in men with prostate cancer

In the men diagnosed with prostate cancer, the age of diagnosis and mean PSA was slightly lower in the Family History group (57.8 years; mean PSA 4.86) compared to the Mutation Carrier group (59.1 years; mean PSA 6.5). The age of diagnosis in BRCA2 mutation carriers (58.1 years) was lower than in BRCA1 mutation carriers (62 years). On average, the Mutation Carrier group had longer term follow-up data (5.4 years) than the Family History group (3.7 years) (Table 3).

Mutation carriers were more than twice as likely to have intermediate- or high-risk disease (88%) as compared to the Family History group (36%). However, this result was not statistically significant ($p = 0.17$). In the Mutation Carrier group, most had BRCA2 mutations (86%), with only 1 BRCA1 mutation carrier with intermediate-risk disease (14%).

The proportion of men undergoing active surveillance (AS) or radical prostatectomy (RP) was similar between groups (Table 3). However, there was a significant difference ($p = 0.04$) between groups in terms of additional treatments, with the mutation carriers regularly requiring androgen deprivation therapy (ADT) and in a few cases chemotherapy and/or salvage radiation therapy (Table 3). Of note, all of these participants were BRCA2 mutation carriers and additional treatments were not required in any BRCA1 mutation carriers with prostate cancer. One patient in the Family History group underwent adjuvant radiation therapy because of a positive margin after RP.

Fifty percent of mutation carriers (all BRCA2 carriers) had biological recurrence or distant metastasis, which was significantly higher than patients in the Family History group ($p = 0.02$). No BRCA1 or family history patients had documented recurrence or progression of disease.

Table 4 describes patient-specific clinicopathological characteristics and treatment outcomes in the mutation carriers diagnosed with prostate cancer. Patient 6 was initially diagnosed with intermediate-risk disease (Gleason 6,

Table 2. Comparison of screening characteristics between the Family History and Mutation Carrier groups

	Family history (n = 53)		All BRCA1/2 (n = 53[A])		BRCA1 only (n = 29)		BRCA2 only (n = 23[A])	
	n	Percent	n	Percent	n	Percent	n	Percent
Normal PSA and DRE	31	58%	32A	62%	19	66%	13A	59%
PSA >4 ug/L	13	24.5%	11A	22%	6	21%	5	23%
Biopsy	11	85%	6	54%	2	33%	4	80%
Cancer	6	55%	4	66%	1	50%	3	75%
PIN	2	18%	1	17%	-	-	-	-
PSA rising+/3-4 ug/L	6	11%	4A	8%	2	7%	2A	9%
Biopsy	2+, 1*	50%	2*	50%	1	50%	1	50%
Cancer	3	100%	2	100%	1	100%	1	100%
Abnormal DRE	3	6%	4A	8%	2	7%	2A	9%
Biopsy	3	100%	4	100%	2	100%	2	100%
Cancer	2	66%	1	25%	-	-	1	50%
PIN	1	33%	-	-	-	-	-	-
Total biopsies	16	30%	16	30%	7	24%	9	39%
Cancer detection	11	21%	8A	15%	2	7%	6A	26%

PSA: prostate-specific antigen; DRE: digital rectal exam; PIN: prostate intraepithelial neoplasia. +PSA level was rising, but below 3 ug/L. *PSA level was rising and fell between 3-4 ug/L. [A]Details on screening characteristics in one man diagnosed with prostate cancer were not available – in the All BRCA1/2 column group (n = 52) and in the BRCA2 only (n = 22).

Table 3. Comparison of clinicopathological features, treatments, and outcomes between the Family History and the Mutation Carrier groups

	Family history (n = 11)	All mutation carriers (n = 8)	BRCA1 only (n = 2)	BRCA2 only (n = 6)
Mean age at diagnosis	57.8	59.1	62	58.1
Mean PSA at diagnosis	4.86	6.5	5.05	5.9
Follow-up post-diagnosis (years)	3.7	5.4	8	4.6
Clinical stage*				
T1c	4 (36%)	1 (14%)	1	0
T2	7 (64%)	4 (57%)	1	3
T3	-	2 (29%)	-	2
Gleason score				
6	7 (64%)	2 (25%)	2 (100%)	-
7	4 (36%)	3 (37%)	-	3 (50%)
8	-	1 (13%)	-	1 (17%)
9	-	2 (25%)		2 (33%)
Treatment				
AS	3 (27%)	2** (25%)	1 (50%)	1**
IMRT	-	1 (12%)	-	1
RP	8 (73%)	6** (75%)	1 (50%)	6**
Adjuvant RT	1 (9%)	-	-	-
ADT	-	5 (62%)	-	5 (p = 0.04)
Salvage RT	-	1 (12%)	-	1
Chemotherapy	-	1 (12%)	-	2
Outcome				
NEP or NED	11 (100%)	4 (0%)	2	2
Recurrence or Mets	-	4 (50%)	-	4 (p = 0.02)

PSA: prostate-specific antigen; AS: active surveillance; IMRT: intensity-modulated radiation therapy; RP: radical prostatectomy; RT: radiation therapy; ADT: androgen deprivation therapy; NED: no evidence of disease; NEP: no evidence of progression, Recurrence: biological recurrence; Mets: metastatic Disease;*Clinical staging information was not available for one mutation carrier (n = 7) **One patient began with AS, but later proceeded to RP.

PSA 11.51) and was on AS for 6 years. After an abnormal magnetic resonance imaging, he was re-biopsied and found to have high-risk disease (Gleason 8 [4+4]). He underwent an RP which showed perineural invasion and extraprostatic extension involving 90% of the prostate. Patient 4 and 6 showed biological recurrence at their first PSA post-RP. Patient 7 had hormone refractory prostate cancer 2 years after diagnosis and died 5 years after his cancer diagnosis. Patient 8 had extraprostatic disease and positive margins. He died 4 years after his diagnosis from a cardiovascular event unrelated to his prostate cancer.

Discussion

Despite the utility of PSA testing in diagnosis and risk classification, its limitations as a biomarker are beginning to be realized.[2] The ERSPC, which reported on 182 000 men, estimated the rate of over-diagnosis as high as 50%,[19] and

Table 4. BRCA1/2 carriers diagnosed with prostate cancer: Clinicopathological characteristics, treatment, and outcome

	Specific mutation	PSA at diagnosis	Clinical stage	Age at diagnosis	Diagnosis	Treatment	Pathological grade	Outcome
BRCA1								
Patient 1	c.185delAG	6.55	cT1c	58	GS6 (3+3)	AS	-	NEP
Patient 2	c.5382insC	3.55	cT2c	66	GS6 (3+3)	RP	GS6 (3+3)	NED
BRCA2								
Patient 3	c.6137C>A	4.6	cT2a	65	GS9 (4+5)	IMRT, ADT	-	NED
Patient 4	c.6174delT	9.79	cT2c	48	GS7 (4+3)	RP, ADT	GS7 (4+3)	Recurrence
Patient 5	n/a	4	cT2a	62	GS7 (3+4)	RP	GS7 (3+4)	NED
Patient 6	c.6174delT	11.51	cT1c, cT3a	59	GS6 (3+3)	AS, RP, ADT	GS8 (4+4)	Recurrence
Patient 7	n/a	n/a	n/a	49	GS7 (3+4)	RP, ADT, RT, Chemotherapy	n/a	Mets, Deceased
Patient 8	c.7757G>A	5.5	cT3b	66	GS9 (4+5)	RP, ADT	n/a	Mets, Deceased

PSA: prostate-specific antigen; AS: active surveillance; IMRT: intensity-modulated radiation therapy; RP: radical prostatectomy; RT: radiation therapy; ADT: androgen deprivation therapy; NED: no evidence of disease; NEP: no evidence of progression, Recurrence: biological recurrence; Mets: metastatic Disease.

the Prostate Cancer Intervention versus Observation Trial (PIVOT) found that in PSA-screened detected men, RP did not reduce prostate cancer mortality.[20] BRCA1 and BRCA2 mutations increase the risk of developing prostate cancer and BRCA2 carriers appear to have a worse prognosis.[11-16,21-24]

This study sought to understand the screening characteristics, cancer detection, and treatment outcomes for mutation carriers as compared to men with a family history of prostate cancer to understand the most appropriate screening and treatment regimens for these high-risk patients.

Family history vs. mutation carriers

Screening characteristics between these 2 high-risk populations were similar. However, contrary to the findings of our previous study,[17] a PSA cut-off of >4 ug/L would have been ineffective in triggering the workup necessary for diagnosing several cancers in both groups. Instead, a rising PSA prompted biopsy which led to a diagnosis of prostate cancer in both groups. Adopting screening criteria used in the IMPACT study by Bancroft and colleagues[18] of >3.0 ug/L would have identified the cancers in the BRCA1/2 population. However, without incorporating consideration of PSA velocity, two cancers in the Family History group would have still been missed. This suggests that a lower cut-off combined with monitoring changes in PSA velocity are both important components of a screening program for high-risk cohorts.

In this study, 15% of carriers were diagnosed with prostate cancer, which is consistent with prostate cancer detection in our previous study (10.5%),[17] and higher than that reported in the general population (8.2%).[19] Cancer detection was slightly lower in the Mutation Carrier group with an older age at diagnosis (59.1 years) compared to the Family History group (21%, 57.8 years). However, these ages are still lower than the median age of diagnosis in Canada (between 65 and 69).[25] This result is comparable to the mean age from our previous study (61.5).[17] Other studies report no difference in age at presentation between carriers and controls,[12,15,26,27] although there is evidence that BRCA1/2 mutations have a more significant impact on cancer risk in younger carriers compared to older carriers.[23,28] This may be explained if BRCA1/2 mutations reduced the onset age of prostate cancer, thus increasing the risk of younger men.

The Mutation Carrier group showed higher mean PSA levels at diagnosis (6.5 vs. 4.86 ug/L) and a much higher rate of intermediate- or high-risk disease (88% vs. 36%). The higher rate of intermediate- or high-risk disease in BRCA1 and BRCA2 mutation carriers is consistent with findings from the IMPACT study, in which 66% of mutation carriers had intermediate- or high-risk disease.[18] Moreover, disease recurrence and metastasis were significantly increased (50% vs. 0%). Therefore, while cancer was not more frequent in the Mutation Carrier group it did appear to be more aggressive, which is consistent with previous studies.[12-16,18]

BRCA1 vs BRCA2

When comparing screening characteristics and outcomes using a PSA cut-off of >4 ug/L in the BRCA1 and the BRCA2 mutation carriers separately, the rate of biopsy was much lower in the BRCA1 group (33%) compared to the BRCA2 group (80%). Cancer detection in those who had biopsy because of PSA >4 ug/L was high in both groups (BRCA1 50% vs. BRCA2 75%). Although we did not gather the reasons why biopsy was not completed in this study, it may be useful to investigate this further. If this is a result of a more conservative approach for BRCA1 mutation carriers specifically, this may lead to missed cancer diagnoses.

Within the BRCA1 population, only 7% of men were diagnosed with cancer, as compared to 26% in the BRCA2 group. Only 1 BRCA1 mutation carrier had intermediate-risk disease in contrast to 6 BRCA2 mutation carriers with intermediate- or high-risk disease. This finding suggests that BRCA1 mutation carriers may have a lower chance of developing cancer and that they generally have less aggressive disease. However, our small sample size prevents such conclusions. Our results are contrary to the findings of Bancroft and colleagues,[18] in which 61% of BRCA1 mutation carriers had intermediate- or high-risk cancers. Therefore, further study is needed to determine whether BRCA1 mutation status warrants more aggressive management even in low-risk patients.

BRCA2 mutation carriers had a younger age at diagnosis than BRCA1 mutation carriers – a finding demonstrated in a study by Bancroft and colleagues.[18] Also similar to other reports,[12-16] our BRCA2 mutation carriers had a higher rate of aggressive and non-curable disease than in the BRCA1 mutation carrier and Family History groups.

A number of limitations must be acknowledged with regards to this study. Our small number of prostate cancer events may not be representative of the entirety of the men with BRCA1/2 mutations who develop prostate cancer. Also, given that most patients were BRCA-screened and referred either due to a previous non-prostate primary, or a very strong family history of cancer, we acknowledge a degree of selection bias. Finally, the retrospective nature of this study has limited our follow-up data based on completeness of medical records.

Conclusion

In our experience, rates of prostate cancer in BRCA1/2 mutation carriers are higher than in the general population, and comparable to previously published studies. A targeted screening approach (PSA and DRE) in this population

appears justified. However, consideration should be given to lowering the PSA cut-off and ensuring that monitoring PSA velocity is part of the screening protocol. While establishing a consensus on the most appropriate screening and management of BRCA1 mutation requires further study, this report is consistent with previous studies showing BRCA2 mutation carrier status is associated with aggressive disease.

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References

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. *Canadian Cancer Statistics 2012*. Toronto, ON: Canadian Cancer Society; 2012.
2. D'Amico AV, Whittington R, Malkowicz S, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-74. http://dx.doi.org/10.1001/jama.280.11.969
3. Roobol MJ, Kerkhof M, Schröder FH, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol* 2009;56:584-91. http://dx.doi.org/10.1016/j.eururo.2009.07.018
4. Mitka M. PSA screening debated. *JAMA* 2010;303:1358.
5. Moyer VA, US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;157:120-34. http://dx.doi.org/10.7326/0003-4819-157-2-201207170-00459
6. Klotz L. Active Surveillance for prostate cancer: Patient selection and management. *Curr Oncol* 2010;17:S11-7. http://dx.doi.org/10.3747/co.v17i0.713
7. Kiciński M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: A meta-analysis. *PLoS One* 2011;6:e27130. http://dx.doi.org/10.1371/journal.pone.0027130
8. Eeles RA, Olama AA, Benlloch S, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet* 2013;45:385-91. http://dx.doi.org/10.1038/ng.2560
9. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J *Natl Cancer Inst* 1999;91:1310-6. http://dx.doi.org/10.1093/jnci/91.15.1310
10. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. *Br J Cancer* 2012;106:1697-701. http://dx.doi.org/10.1038/bjc.2012.146
11. Castro E, Goh CL, Eeles RA. Prostate cancer screening in BRCA and Lynch syndrome mutation carriers. *Am Soc Clin Oncol Educ Book* 2013;2013:50-5. http://dx.doi.org/10.1200/EdBook_AM.2013.33.e50
12. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013;31:1748-57. http://dx.doi.org/10.1200/JCO.2012.43.1882
13. Mitra A, Fischer C, Foster CS, et al. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. *Br J Cancer* 2008;98:502-7. http://dx.doi.org/10.1038/sj.bjc.6604132
14. Edwards SM, Evans DGR, Hope Q, et al. Prostate cancer in BRCA2 germline mutation carriers is associated with poorer prognosis. *Br J Cancer* 2010;103:918-24. http://dx.doi.org/10.1038/sj.bjc.6605822
15. Thorne H, Willems AJ, Niedermayr E, et al. Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. *Cancer Prev Res* 2011;4:1002-10. http://dx.doi.org/10.1158/1940-6207.CAPR-10-0397
16. Tryggvadóttir L, Vidarsdóttir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. *J Natl Cancer Inst* 2007;99:929-35.
17. Horsburgh S, Matthew A, Bristow R, et al. Male BRCA1 and BRCA2 mutation carriers: A pilot study investigating medical characteristics of patients participating in a prostate cancer prevention clinic. *Prostate* 2005;65:124-9. http://dx.doi.org/10.1002/pros.20278
18. Bancroft EF, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: Results from the initial screening round of the IMPACT study. *Eur Urol* 2014;66:489-99. http://dx.doi.org/10.1016/j.eururo.2014.01.003
19. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-8. http://dx.doi.org/10.1056/NEJMoa0810084
20. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203-13. http://dx.doi.org/10.1056/NEJMoa1113162
21. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: A review of the literature. *J Clin Oncol* 2004;22:735-42. http://dx.doi.org/10.1200/JCO.2004.05.055
22. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997;336:1401-8. http://dx.doi.org/10.1056/NEJM199705153362001
23. Thompson D, Easton DF; Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. *J Natl Cancer Inst* 2002;94:1358-65. http://dx.doi.org/10.1093/jnci/94.18.1358
24. Raaijmakers R, Kirkels WJ, Roobol MJ. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology* 2002;60:826-30. http://dx.doi.org/10.1016/S0090-4295(02)01958-1
25. Canadian Cancer Society's Advisory. Committee on Cancer Statistics. *Canadian Cancer Statistics 2013*. Toronto, ON: Canadian Cancer Society; 2013. http://www.cancer.ca/en/cancer-information/cancer-101/canadian-cancer-statistics-publication/?region=sk. Accessed November 4, 2014.
26. Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. *Clin Cancer Res* 2010;16:2115-21. http://dx.doi.org/10.1158/1078-0432.CCR-09-2871
27. Giusti RM, Rutter JL, Duray PH, et al. A twofold increase in BRCA mutation related prostate cancer among Ashkenazi Israelis is not associated with distinctive histopathology. *J Med Genet* 2003;40:787-92. http://dx.doi.org/10.1136/jmg.40.10.787
28. Hubert A, Peretz T, Manor O, et al. The Jewish Ashkenazi founder mutations in the BRCA1/BRCA2 genes are not found at an increased frequency in Ashkenazi patients with prostate cancer. *Am J Hum Genet* 1999;65:921-4. http://dx.doi.org/10.1086/302525

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