British Journal of Cancer (2007) 97, 826–831

www.bjcancer.com

Rare germline mutations in the *BRCA2* gene are associated with early-onset prostate cancer

I Agalliu[1], E Karlins[2], EM Kwon[2], LM Iwasaki[1], A Diamond[2,3], EA Ostrander[2] and JL Stanford[*,1,4]

[1]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, WA 98109, USA; [2]Cancer Genetics Branch, National Human Genome Research Institute, National Institutes of Health, 50 South Drive, MSC 8000, Building 50, Bethesda, MD 20892, USA; [3]Edinburgh Molecular Genetics Service, Molecular Medicine Centre, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK; [4]Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Mail Box 357236, Seattle, WA 98195, USA

Studies of families who segregate *BRCA2* mutations have found that men who carry disease-associated mutations have an increased risk of prostate cancer, particularly early-onset disease. A study of sporadic prostate cancer in the UK reported a prevalence of 2.3% for protein-truncating *BRCA2* mutations among patients diagnosed at ages ⩽55 years, highlighting the potential importance of this gene in prostate cancer susceptibility. To examine the role of protein-truncating *BRCA2* mutations in relation to early-onset prostate cancer in a US population, 290 population-based patients from King County, Washington, diagnosed at ages <55 years were screened for germline *BRCA2* mutations. The coding regions, intron–exon boundaries, and potential regulatory elements of the *BRCA2* gene were sequenced. Two distinct protein-truncating *BRCA2* mutations were identified in exon 11 in two patients. Both cases were Caucasian, yielding a mutation prevalence of 0.78% (95% confidence interval (95%CI) 0.09–2.81%) and a relative risk (RR) of 7.8 (95%CI 1.8–9.4) for early-onset prostate cancer in white men carrying a protein-truncating *BRCA2* mutation. Results suggest that protein-truncating *BRCA2* mutations confer an elevated RR of early-onset prostate cancer. However, we estimate that <1% of early-onset prostate cancers in the general US Caucasian population can be attributed to these rare disease-associated *BRCA2* mutations.

British Journal of Cancer (2007) **97,** 826–831. doi:10.1038/sj.bjc.6603929 www.bjcancer.com
Published online 14 August 2007

Keywords: *BRCA2* gene; protein-truncating *BRCA2* mutations; prostate cancer; early-onset disease

Genetics and Genomics

Studies of families segregating *BRCA2* mutations (BCLC, 1999; Johannsson *et al*, 1999; Eerola *et al*, 2001; Tulinius *et al*, 2002; Bermejo and Hemminki, 2004; van Asperen *et al*, 2005), kin-cohort studies of cancer incidence among relatives of population-based breast or ovarian cancer cases (Loman *et al*, 2003; Risch *et al*, 2006), as well as studies of populations who harbour founder *BRCA2* mutations (Sigurdsson *et al*, 1997; Struewing *et al*, 1997, Kirchhoff *et al*, 2004) suggest that men who carry a disease-associated *BRCA2* allele have an increased relative risk (RR) of prostate cancer (two- to five-fold elevation). Two of the family studies in which data were stratified on age at diagnosis of prostate cancer reported that the RR was even higher (seven- to eight-fold increase) in men diagnosed before age 65 years (BCLC, 1999; van Asperen *et al*, 2005). These findings suggest that protein-truncating *BRCA2* mutations may play a role in prostate cancer susceptibility. However, the majority of studies that have investigated the role of *BRCA2* mutations in hereditary prostate cancer (HPC) families, which usually include men diagnosed with prostate cancer at younger ages, have reported no disease-associated mutations (Wilkens *et al*, 1999; Gayther *et al*, 2000; Sinclair *et al*, 2000; Agalliu *et al*, 2007).

To date, only one study has assessed the contribution of *BRCA2* mutations in early-onset sporadic prostate cancer (Edwards *et al*, 2003). In a case series of 263 men in the UK diagnosed with prostate cancer at younger ages (⩽55 years), and who were not selected on the basis of either breast or prostate cancer family history, the prevalence of protein-truncating *BRCA2* mutations was 2.3% (95% confidence interval (95%CI) 0.8–5.0%) (Edwards *et al*, 2003). The estimated RR of prostate cancer was 23.0 (95%CI 9.0–57.0) among protein-truncating *BRCA2* mutation carriers in that study. The main goal of the current study was to determine the frequency of germline protein-truncating *BRCA2* mutations in early-onset prostate cancer patients in a US population.

MATERIALS AND METHODS

Study population

Case patients ($n = 290$) included in this analysis are Caucasian and African American men diagnosed with histologically confirmed adenocarcinoma of the prostate before age 55 years and who participated in one of two population-based case–control studies

*Correspondence: Dr JL Stanford, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B874, Seattle, WA 98109, USA;
E-mail: jstanfor@fhcrc.org
Received 3 May 2007; revised 16 July 2007; accepted 16 July 2007; published online 14 August 2007

of prostate cancer conducted in King County, Washington. Case patients in the first study ($n=168$) were diagnosed from January 1, 1993 to December 31, 1996 (Stanford *et al*, 1999), and those in the second study ($n=128$) were diagnosed from January 1, 2002 to December 31, 2005. Incident cases in both studies were identified through the population-based Seattle-Puget Sound SEER cancer registry, which also provided information on Gleason score, tumour stage, and serum prostate-specific antigen (PSA) level at diagnosis. Case patients completed a structured in-person interview that collected information about demographic and lifestyle characteristics, medical history, prostate cancer screening history, and family history of prostate cancer and other cancers. After the interview, patients were asked to provide a blood sample.

A total of 429 eligible prostate cancer case patients aged <55 years were identified during the ascertainment periods. Of eligible patients, 381 (89%) were interviewed and 301 (79%) provided a blood sample. A total of 290 case patients with adequate amounts of DNA were sequenced for *BRCA2* mutations. The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center and the National Human Genome Research Institute, and written informed consent was obtained from all study participants.

BRCA2 gene sequencing

Genomic DNA was purified from peripheral blood lymphocytes using a standard proteinase K digestion and alkaline lysis followed by phenol–chloroform extraction (Sambrook *et al*, 1989). All coding and non-coding regions of the *BRCA2* gene were screened for mutations using 47 primer pairs described previously (Malone *et al*, 2000, 2006; Agalliu *et al*, 2007). Exons 5 and 6 were amplified in a single fragment and longer exons were amplified using multiple PCR reactions. There were five amplicons for exon 10 (10A–10E), 16 for exon 11 (11A–11P), and two for each of the following exons: 14 (14A and 14B), 18 (18A and 18B), and 27 (27A and 27B). PCR reactions were performed in a 10 μl volume containing 5 ng of genomic DNA, 1 mM dNTPs, 1.5 mM, or 2.5 mM $MgCl_2$, 1 μM of both the forward and reverse primers, and 0.25 U Amplitaq DNA polymerase (Applied Biosystems, Foster City, CA, USA).

PCR products were treated using the ExoSAP-IT method (USB Corporation, Cleveland, OH, USA). DNA-sequencing reactions were carried out using BigDye® Terminator v3.1 Cycle Sequencing Kits (Applied Biosystems, Foster City, CA, USA) and sequence data were obtained on both forward and reverse PCR primers using the ABI 3730xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Contigs were assembled using PhredPhrap/Consed (Gordon *et al*, 1998). Variants were detected using Polyphred (Nickerson *et al*, 1997) and MutationSurveyor (http://www.softgenetics.com/mutation Surveyor.html) by two independent researchers. All variants were unanimously confirmed.

Statistical analyses

The 95% CI for the prevalence of protein-truncating *BRCA2* mutations among prostate cancer patients was computed using a Poisson-distributed events-table under the assumption that these mutations are rare and follow a Poisson distribution. The prevalence of germline protein-truncating *BRCA2* mutations in the general population was taken from a recently published study of US women aged 35–64 years (Malone *et al*, 2006), and was used to estimate the RR of prostate cancer in men aged <55 years associated with carrying a *BRCA2* mutation.

A χ^2 test was used to evaluate whether the distribution of genotypes for single nucleotide polymorphisms (SNPs) in the *BRCA2* gene differed by race (Caucasians *vs* African Americans), family history of prostate cancer (yes *vs* no) or clinical characteristics such as Gleason score (2–6 or $7=3+4$ *vs* $7=4+3$ or 8–10), stage of cancer (localised *vs* regional or distant) or a composite measure of disease aggressiveness. The definition of more aggressive prostate cancer included a Gleason score of $7=4+3$ or 8–10 or regional or distant stage or serum PSA $\geqslant 20\,\mathrm{ng\,ml^{-1}}$ at prostate cancer diagnosis; men with a Gleason score of 2–6 or $7=3+4$ and local stage tumours and a serum diagnostic PSA level $<20\,\mathrm{ng\,ml^{-1}}$ at diagnosis were classified as having less aggressive cancer. SAS version 9.1 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

RESULTS

Table 1 shows characteristics of the 290 population-based prostate cancer patients screened for *BRCA2* mutations; 11% were African-American and 2% were Jewish. The proportion of patients that reported either a first- or second-degree family history of prostate, breast, or ovarian cancer was 37, 16, and 3%, respectively. Five percent reported a family history of prostate, breast, and/or ovarian cancers; 3% reported first-degree relatives with either prostate or breast cancers. Most of the patients (79%) reported that they had received at least one PSA test and/or digital rectal examination (DRE) in the 5-year period before diagnosis. The majority of the patients had localised tumours (73%), Gleason scores of 2–6 (59%), and 36% of them were classified as having tumours with more aggressive clinical features at diagnosis.

Two distinct protein-truncating *BRCA2* mutations were identified, yielding an overall prevalence of 0.69% (95%CI 0.08–2.49%). Table 2 shows characteristics of the two prostate cancer patients with protein-truncating *BRCA2* mutations. One of these mutations was a 5-bp deletion (4625_4629delACATT) and the other was a 2-bp deletion (4074_4075delGT), both located in exon 11. Both cases with protein-truncating *BRCA2* mutations were Caucasian, one reported a first-degree relative with prostate cancer, but neither reported a family history of breast or ovarian cancer, and both were diagnosed with Gleason score 7 tumours. As the protein-truncating *BRCA2* mutations were detected in Caucasians only, the prevalence of such mutations in whites is 0.78% (95%CI 0.09–2.81%). Recently, Malone *et al* (2006) reported a weighted prevalence of protein-truncating *BRCA2* mutations of 0.1% (95%CI 0.0–0.3%) among US population-based Caucasian control women aged 35–64 years. Assuming that the prevalence of disease-associated *BRCA2* mutations among Caucasian men in the general population is similar to the prevalence of such mutations reported for US Caucasian women, the estimated RR of prostate cancer in white men <55 years of age associated with carrying a protein-truncating *BRCA2* mutation is 7.78 (95%CI 1.80–9.37).

In addition to the two protein-truncating mutations, 84 sequence variants were detected in the *BRCA2*-coding exons, intron–exon boundaries, and putative regulatory regions that were sequenced. One SNP was in the 5′ UTR region, 19 (22.6%) were intronic SNPs, and 40 (47.6%) non-synonomous and 24 (28.6%) synonomous SNPs were in coding exons. Most of these 84 SNPs were rare; only 11 (13.1%) had a minor allele frequency of 3% or greater, and of these, only four resulted in an amino-acid change (Table 3). There were two SNPs that differed ($P<0.05$) between Caucasian and African-American patients; both the C allele of SNP 1341A>C located in exon 10 and the T allele of the intronic SNP (IVS17-14) were more common in white than African American patients (26.7 *vs* 7.6% and 48.8 *vs* 34.8%, respectively). The distribution of genotypes for the SNPs having a minor allele frequency of $\geqslant 3\%$ did not vary substantially according to family history of prostate cancer or clinical features of the disease (data not shown). One exception was that the frequency of the T allele for the SNP 5971C>T located in exon 11 was higher in patients with more aggressive disease in comparison to cases with less aggressive clinical features, 5.2 *vs* 1.9%, respectively ($P=0.02$).

Table 1 Characteristics of 290 population-based prostate cancer patients aged <55 years at diagnosis screened for *BRCA2* mutations

	1993–1996 ($n=162$)		2002–2005 ($n=128$)		Total case patients ($n=290$)	
Ascertainment period	**N**	**%**	**N**	**%**	**N**	**%**
Age at diagnosis (years)						
35–49	39	24.1	58	45.3	97	33.4
50–54	123	75.9	70	54.7	193	66.6
Race						
Caucasian	154	95.1	103	80.5	257	88.6
African-American	8	4.9	25	19.5	33	11.4
Jewish						
No	159	98.1	126	98.4	285	98.3
Yes	3	1.9	2	1.6	5	1.7
Family history of prostate cancer						
None	111	68.5	71	55.5	182	62.8
First-degree	33	20.4	40	31.3	73	25.2
Second-degree only	18	11.1	17	13.3	35	12.1
Family history of breast cancer						
None	134	82.7	109	85.2	243	83.8
First-degree	22	13.6	15	11.7	37	12.8
Second-degree only	6	3.7	4	3.1	10	3.4
Family history of ovarian cancer						
None	157	96.9	123	96.1	280	96.6
First-degree	2	1.2	3	2.3	5	1.7
Second-degree only	3	1.9	2	1.6	5	1.7
Prostate cancer screening[a]						
None	32	19.8	28	21.9	60	20.7
DRE only	46	28.4	25	19.5	71	24.5
PSA and DRE	84	51.9	75	58.6	159	54.8
Gleason score						
2–4	19	11.7	—	—	19	6.6
5–6	82	50.6	69	53.9	151	52.1
7 (3+4)	39	24.1	40	31.3	79	27.2
7 (4+3)	9	5.6	11	8.6	20	6.9
8–10	10	6.2	6	4.7	16	5.5
Missing	3	1.9	2	1.6	5	1.7
Stage of cancer						
Localised	114	70.4	97	75.8	211	72.8
Regional	40	24.7	29	22.7	69	23.8
Distant	8	4.9	2	1.6	10	3.4
PSA at diagnosis (ng/ml)[b]						
0–3.9	26	16.1	29	22.7	55	19.0
4.0–9.9	77	47.6	63	49.2	140	48.3
10.0–19.9	21	12.9	15	11.7	36	12.4
⩾20	19	11.7	11	8.6	30	10.3
Missing	19	11.7	10	7.8	29	10.0

[a]One or more prostate-specific antigen (PSA) test or digital rectal exam (DRE) in the 5-year period before diagnosis date. [b]Serum prostate-specific antigen (PSA) level at diagnosis.

DISCUSSION

In this population-based study of 290 patients diagnosed with prostate cancer before age 55 years, there were two patients with germline protein-truncating *BRCA2* mutations, yielding an overall prevalence of 0.69% (95%CI 0.08–2.49%). One of the cases with a *BRCA2* mutation reported a first-degree relative with prostate cancer, but neither reported a family history of breast or ovarian cancer. As both disease-associated *BRCA2* mutation carriers were Caucasian, the prevalence of such mutations in whites is 0.78% (95%CI 0.09–2.81%); the estimated RR of prostate cancer is 7.8 (95%CI 1.8–9.4) in Caucasian *BRCA2* mutation carriers. Although this represents a substantially elevated RR of earlier-onset prostate cancer associated with carrying a germline protein-truncating *BRCA2* mutation, such mutations are very rare (~0.1%) in the general US population (Malone *et al*, 2006). The estimated cumulative risk (i.e. penetrance) of prostate cancer to age 55 years in Caucasian men due to carrying a disease-associated *BRCA2* mutation is about 1.1%, and the population attributable risk of prostate cancer in this same group is 0.7%.

In a hospital-based series ($n=263$) of prostate cancer patients with early ages at diagnosis (⩽55 years) in the UK, Edwards *et al* (2003) reported a prevalence of germline protein-truncating *BRCA2* mutations of 2.3% (95%CI 0.8–5.0%). The estimated RR

of developing prostate cancer by age 56 years from a deleterious germline *BRCA2* mutation was 23.0 (95%CI 9.0–57.0). To compute this RR estimate, Edwards *et al* (2003) used the average of the estimated prevalence (i.e., 0.12 and 0.07%) of germline disease-associated *BRCA2* mutations in the general UK population, which was indirectly estimated from two prior studies of breast cancer in the UK (Peto *et al*, 1999; Antoniou *et al*, 2002). Interestingly, of the six prostate cancer patients carrying disease-associated *BRCA2* mutations, 50% were diagnosed before age 50 and most had no family history of prostate cancer (five out of six) or breast cancer (four out of six) (Edwards *et al*, 2003).

Although the overall finding is consistent with our results, a lower prevalence of disease-associated *BRCA2* mutations was observed in our population-based patient series. This difference may be due to different study designs and populations. Edwards *et al* (2003) utilised prostate cancer patients recruited through three different sources: Cancer Research UK/British Prostate Group, UK Familial Prostate Cancer Study, and the British Association of Urological Section of Oncology, and 90% of them had clinically detected prostate cancer. By contrast, our patients were ascertained from a population-based SEER registry. Most of these men had received a PSA and/or DRE test within the 5-year period before diagnosis, and 27% of the cases reported one or more clinical signs or symptoms at the time of diagnosis.

Studies of families with breast and/or ovarian cancer who harbour disease-associated *BRCA2* mutations have reported that male family members who carry such mutations have an increased RR of prostate cancer (BCLC, 1999; Johannsson *et al*, 1999; Eerola *et al*, 2001; Tulinius *et al*, 2002; Bermejo and Hemminki, 2004; van Asperen *et al*, 2005). In the Breast Cancer Linkage Consortium cohort of 173 breast and/or ovarian cancer families, a RR of 4.7 (95%CI 3.5–6.2) was reported for prostate cancer among *BRCA2*

Table 2 Characteristics of prostate cancer patients with germline protein-truncating *BRCA2* mutations

	Case A	Case B
BRCA2 mutation		
Exon location	11	11
Nucleotide change	4625_4629delACATT	4074_4075delGT
Protein effect	STOP 1467	STOP 1284
Characteristics		
Age at diagnosis (years)	51	47
Race	Caucasian	Caucasian
Family history of		
Prostate cancer	Yes (first-degree)	No
Breast cancer	No	No
Ovarian cancer	No	No
Clinical characteristics		
Gleason score	7 (3+4)	7 (4+3)
Stage of cancer	Localised	Localised
PSA at diagnosis (ng/ml)	Missing	6.3

Table 3 SNPs with a ⩾3% minor allele frequency in the *BRCA2* gene among 290 prostate cancer patients, by race

Exon	Nucleotide position	Nucleotide change	Amino-acid change	Genotype	Total $N=290$	%	Caucasian $N=257$	%	African American $N=33$	%	*P*-value[a]
SNP in the 5′ UTR region											
	202	G>A	5′ UTR	GG	160	55.2	139	54.1	21	63.6	0.51
				AG	100	34.5	90	35.0	10	30.3	
				AA	30	10.3	28	10.9	2	6.1	
Non-synonomous SNPs											
10	1092	A>C	N289H	AA	269	92.8	240	93.4	29	87.9	0.25
				AC[b]	21	7.2	17	6.6	4	12.1	
10	1341	A>C	N372H	AA	170	58.6	142	55.3	28	84.8	0.004
				AC	98	33.8	93	36.2	5	15.2	
				CC	22	7.6	22	8.6	—	—	
11	3198	A>G	N991D	AA	268	92.4	240	93.4	28	84.8	0.08
				AG[b]	22	7.6	17	6.6	5	15.2	
11	5971	C>T	T1915M	CC	272	93.8	243	94.6	29	87.9	0.13
				CT[b]	18	6.2	14	5.4	4	12.1	
Synonomous or intronic SNPs											
10	1592	A>G	S455S	AA	269	92.8	240	93.4	29	87.9	0.25
				AG[b]	21	7.2	17	6.6	4	12.1	
11	2456	T>C	H743H	TT	269	92.8	240	93.4	29	87.9	0.25
				CT[b]	21	7.2	17	6.6	4	12.1	
11	3623	A>G	K1132K	AA	134	46.2	121	47.1	13	39.4	0.68
				AG	121	41.7	105	40.9	16	48.5	
				GG	35	12.1	31	12.1	4	12.1	
11	4034	T>C	V1269V[c]	TT	195	67.2	171	66.5	24	72.7	0.72
				CT	77	26.6	69	26.8	8	24.2	
				CC	16	5.5	15	5.8	1	3.0	
14	7469	A>G	S2414S	AA	170	58.6	155	60.3	15	45.5	0.23
				AG	104	35.9	89	34.6	15	45.5	
				GG	16	5.5	13	5.1	3	9.1	
17	IVS17-14	T>C	intronic	CC	86	29.7	70	27.2	16	48.5	0.04
				CT	134	46.2	123	47.9	11	33.3	
				TT	70	24.1	64	24.9	6	18.2	

[a]χ^2 *P*-value comparing the distribution of genotypes between Caucasian and African-American prostate cancer cases. [b]No homozygous variants were detected. [c]Two Caucasian men had missing data for this SNP and thus percentages do not add up to 100%.

protein-truncating mutation carriers (BCLC, 1999). In that study, the RR was higher in men diagnosed at ages <65 years (RR = 7.3, 95%CI 4.7–11.5). A Finnish study (Eerola *et al*, 2001) of 107 breast or ovarian cancer families reported a five-fold increase in the RR of prostate cancer among men carrying protein-truncating *BRCA2* mutations (RR = 4.9, 95%CI 1.8–11.0). Similar findings were reported by Tulinius *et al* (2002) in an analysis of 995 breast cancer pedigrees from Iceland. In that study, first-degree male relatives of breast cancer patients carrying protein-truncating *BRCA2* mutations had a RR of 4.8 (95%CI 3.3–6.3) for prostate cancer (Tulinius *et al*, 2002). Finally, van Asperen *et al* (2005) in a analysis of 139 *BRCA2* families from the Netherlands reported an RR of 2.5 (95%CI 1.6–3.8) for prostate cancer among *BRCA2* protein-truncating mutation carriers. When the analysis was stratified by the age at diagnosis, the RR of prostate cancer was 8.0 (95%CI 4.1–14.0) among protein-truncating *BRCA2* mutation carriers diagnosed at ages <65 years.

In contrast to the above studies and the current analysis, most studies of HPC families investigating the contribution of protein-truncating *BRCA2* mutations to prostate cancer susceptibility have reported null results (Wilkens *et al*, 1999; Gayther *et al*, 2000; Sinclair *et al*, 2000; Agalliu *et al*, 2007). Only one study conducted in the UK of 38 affected individuals from HPC families with two to five affected men per family reported a prevalence of 5.3% for protein-truncating *BRCA2* mutations (Gayther *et al*, 2000). In that study, the two men with protein-truncating *BRCA2* mutations were diagnosed with prostate cancer at ages ⩽56 years, and both had a brother with prostate cancer. There is still uncertainty as to why *BRCA2* families, ascertained on the basis of members with breast and/or ovarian cancer, have a higher RR of prostate cancer in men carrying protein-truncating *BRCA2* mutation (BCLC, 1999; Johannsson *et al*, 1999; Eerola *et al*, 2001; Tulinius *et al*, 2002; Bermejo and Hemminki, 2004; van Asperen *et al*, 2005). By comparison, when HPC families that include members with a history of breast or ovarian cancer are screened for *BRCA2* mutations, no excess of protein-truncating *BRCA2* mutations is found (Agalliu *et al*, 2007).

A more complete understanding of the role of the *BRCA2* gene in relationship with prostate cancer susceptibility may provide insight on prostate carcinogenesis. For example, the encoded BRCA2 protein is involved in DNA repair, transcription, and cell cycle control (Davies *et al*, 2001; Venkitaraman, 2002; Powell *et al*, 2003; Yoshida and Miki, 2004). BRCA2 interacts directly with RAD51, which is an essential protein for error-free double-strand DNA break repair by homologous recombination (Sharan *et al*, 1997; Wong *et al*, 1997; Xia *et al*, 2001; Pellegrini *et al*, 2002; Venkitaraman, 2002; Jackson, 2002; Powell *et al*, 2003). *BRCA2* regulates both the intracellular localisation and DNA-binding ability of RAD51, and therefore loss of this control following BRCA2 inactivation may be a key event leading to genomic instability and carcinogenesis (Davies *et al*, 2001; Jackson, 2002; Yoshida and Miki, 2004). Whether prostate tissue is particularly susceptible to *BRCA2* loss is not clear. The fact that protein-truncating mutations in the *BRCA2* gene predispose to breast and ovarian cancers suggests that the hormonal nature of these cancers may be important. In relation to the prostate, a study found that BRCA2 functions as a co-activator for the androgen receptor (AR) in conjunction with histone acetyltransferase (Shin and Verma, 2003). This finding suggests a novel mechanism by which BRCA2 protein may exert its tumour suppressor function, by altering AR signalling.

Our study has strengths and limitations that should be considered when interpreting the results. The current study is population-based; patients were not selected on the basis of family history of prostate, breast, or ovarian cancer, which offers a less-biased assessment of the role of *BRCA2* protein-truncating mutations in men from the general population. In addition, this is one of the largest such studies completed to date. A limitation of this study is that no screening for large genomic deletions in the *BRCA2* gene was performed, as this method requires a relatively large amount of DNA per patient. It has been estimated that large genomic deletions account for an additional 10–15% of reported disease-associated *BRCA2* mutations (Szabo and King, 1997). Thus, the prevalence of protein-truncating *BRCA2* mutations might have been underestimated in this study. In addition, owing to the high cost of genetic sequencing and the rarity of germline *BRCA2* protein-truncating mutations in the general population, it was not feasible to screen the large number of control men that would be required for direct case–control comparisons. Therefore, we used the previously reported prevalence of *BRCA2* mutations in Caucasian control women from the general US population (Malone *et al*, 2006) to estimate the RR. There is no reason to believe that the prevalence of *BRCA2* mutations in the general population would be substantially different between men and women, as the gene is located on chromosome 13. Malone *et al* (2006) reported a prevalence of 0.1% for germline *BRCA2* protein-truncating mutations among US Caucasian control women. This prevalence is similar to the estimates of 0.12 and 0.07% for *BRCA2* protein-truncating mutations in the general UK population (Peto *et al*, 1999; Antoniou *et al*, 2002). By contrast, a recent population-based study of ovarian cancer in Ontario, Canada, estimated a higher carrier frequency of protein-truncating *BRCA2* mutations of 0.69% (95%CI 0.43%–1.10%) in the general population (Risch *et al*, 2006). However, the Canadian estimate was based on data from ovarian cancer patients. In addition, the ovarian cancer patient population was enriched with subjects, such as Ashkenazi Jews, known to have a higher prevalence of *BRCA2* disease-associated founder mutations (Risch *et al*, 2006).

In conclusion, the results of this study indicate that germline protein-truncating mutations in the *BRCA2* gene confer an elevated RR (almost eight-fold) of developing early-onset prostate cancer in Caucasian men. However, the population attributable risk of prostate cancer in US Caucasians under age 55 due to carrying one of these rare germline protein-truncating *BRCA2* mutation is estimated to be <1%. Given the relatively high cost of *BRCA2* mutation screening and the rarity of these high-risk *BRCA2* protein-truncating mutations in the general population, screening for these mutations in the general population would not be cost effective and is not currently recommended.

ACKNOWLEDGEMENTS

We thank Dr KE Malone for providing data from the CARE study. We thank all the men who participated in this study for their time, effort, and cooperation. This work was supported by Grants RO1-CA56678 and RO1-CA092579, and Contract NO1-CN-05230 from the National Cancer Institute. Additional support was provided by the Fred Hutchinson Cancer Research Center, and the Intramural Program of the National Human Genome Research Institute.

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