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Association of Genomic Domains in *BRCA1* and *BRCA2* with Prostate Cancer Risk and Aggressiveness

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ABSTRACT

Pathogenic sequence variants (PSV) in *BRCA1* or *BRCA2* (*BRCA1/2*) are associated with increased risk and severity of prostate cancer. We evaluated whether PSVs in *BRCA1/2* were associated with risk of overall prostate cancer or high grade (Gleason 8+) prostate cancer using an international sample of 65 *BRCA1* and 171 *BRCA2* male PSV carriers with prostate cancer, and 3,388 *BRCA1* and 2,880 *BRCA2* male PSV carriers without prostate cancer. PSVs in the 3′ region of *BRCA2* (c.7914+) were significantly associated with elevated risk of prostate cancer compared with reference bin c.1001-c.7913 [HR = 1.78; 95% confidence interval (CI), 1.25–2.52; $P = 0.001$], as well as elevated risk of Gleason 8+ prostate cancer (HR = 3.11; 95% CI, 1.63–5.95; $P = 0.001$). c.756-c.1000 was also associated with elevated prostate cancer risk (HR = 2.83; 95% CI, 1.71–4.68; $P = 0.00004$) and elevated risk of Gleason 8+ prostate cancer (HR = 4.95; 95% CI, 2.12–11.54; $P = 0.0002$). No genotype–phenotype associations were detected for PSVs in *BRCA1*. These results demonstrate that specific *BRCA2* PSVs may be associated with elevated risk of developing aggressive prostate cancer.

Significance: Aggressive prostate cancer risk in BRCA2 mutation carriers may vary according to the specific BRCA2 mutation inherited by the at-risk individual.

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Introduction

Inherited pathogenic sequence variants (PSV) in DNA repair pathway genes including *BRCA1* and *BRCA2 (BRCA1/2)* are associated with prostate cancer risk and severity (1–15). Carriers of *BRCA2* PSVs have been reported to have increased levels of serum prostate-specific antigen (PSA) at diagnosis, increased proportion of high Gleason (7+) tumors, less favorable tumor stage, increased rates of nodal and distant metastases, and increased rate of recurrence after treatment (2, 11–18). *BRCA2* PSVs confer lower overall survival and prostate cancer–specific survival (13–15). Ashkenazi Jewish carriers of *BRCA1* PSVs have been reported to have elevated rates of Gleason 7+ tumors, higher rates of recurrence, and a 5-fold increase in prostate cancer death (5, 19), although the association of *BRCA1* and prostate cancer has not been replicated in all studies (20). Distinct tumor PSV, methylation, and expression patterns have been identified in *BRCA2* compared with non-*BRCA2*–mutant prostate tumors. These data suggest that *BRCA2*-mutant tumors have features that are more similar to metastatic castrate-resistant disease than localized prostate cancer (21–23).

Specific genotype–phenotype correlations have been reported (24), including *BRCA1/2*-associated breast and ovarian cancers (25–27), *APC* PSVs, and severity of familial adenomatous polyposis (28, 29), and *RET* PSVs in multiple endocrine neoplasia type 2 (MEN2) and familial medullary thyroid carcinoma (30). There have been suggestions in the literature that similar patterns exist for *BRCA1* or *BRCA2* and prostate cancer. Liede and colleagues (31) reported that early-onset prostate cancer (age <65 years) was more frequent in men with *BRCA2* PSVs outside of the ovarian cancer cluster region. More recently, Nielsen and colleagues (32), using a sample of 37 prostate cancer cases, 19 of whom had *BRCA2* PSVs, identified a region in *BRCA2* at c.6373-c.6492 in which PSVs were associated with an increased risk of prostate cancer.

We analyzed a large international cohort of 3,453 *BRCA1* and 3,051 *BRCA2* PSV male carriers to evaluate the distribution of germline PSVs in men diagnosed with prostate cancer and men without prior prostate cancer diagnosis. We hypothesized that specific PSVs in *BRCA1* or *BRCA2* might influence development of prostate cancer and be associated with prostate cancer severity.

Materials and Methods

Study sample

The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) is an international collaboration of centers on 6 continents that has collected information about carriers of *BRCA1/2* PSVs (33). All carriers participated in clinical assessment and/or research studies at a participating institution after providing informed consent under protocols approved by local institutional review boards. Participants' ascertainment date was defined as the time of study interview (e.g., enrollment in a research study). Forty-eight centers and multicenter consortia (Supplementary Table S1) in 31 countries submitted deidentified data that met the CIMBA inclusion criteria as described previously. No races/ethnicities were excluded from this study. Self-reported race/ethnicity data were collected across the various centers using either fixed categories or open-ended questions.

We analyzed only male carriers with clearly pathogenic *BRCA1/2* PSVs that occurred 3′ of nucleotide position 1 (A of the ATC translation initiation codon in either *BRCA1* and *BRCA2*. This excluded 101 males who had a PSV occurring 5′ translation start site. Definitions of these PSVs are shown in Supplementary Table S2. PSVs were defined using CIMBA criteria as follows: (i) PSVs generating a premature termination codon, except those in exon 27 at or after codon 3310 of *BRCA2*; (ii) large in-frame deletions that spanned $\geq$1 exons; and (iii) deletions of transcription regulatory regions (promoter and/or first exon) expected to cause lack of mutant allele expression (33–35). We also included missense variants considered pathogenic as determined by using multifactorial likelihood approaches (35, 36). PSVs are described using the Human Genome Variation Society (HGVS) nomenclature (Supplementary Table S2).

Authors have obtained written informed consent.

PSV binning

To identify segments across the intronic and exonic regions of *BRCA1* and *BRCA2* associated with different prostate cancer risks, we created PSV bins by base pair location within each gene. These genomic sequence bins contained all PSVs regardless of category or function, except for large genomic rearrangements, which were

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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excluded from this analysis because they may span multiple bins. Bins were constructed in two ways. First, we used an algorithm in which each bin contained approximately equal numbers of participants (including all cases and controls) with bin length defined by distance in base pairs. Thus, bin length for common PSVs (e.g., the Icelandic founder PSV c.771_775del) were small compared with bins with a wider range of PSVs. We divided the number of PSVs across the span of *BRCA1* or *BRCA2* into deciles of PSVs observed in cases and noncases (i.e., "decile" bins). Second, we identified putative functional domains in *BRCA1* or *BRCA2* and created bins that captured these domains, as well as bins that contained no functional domain. These domains were determined by boundaries reported in the pfam database (37). The resulting bin boundaries are presented in Supplementary Table S3 and shown graphically in **Fig. 1** for *BRCA1* and **Fig. 2** for *BRCA2*. We chose to use these two binning methods based on our earlier published research (24) that indicated the inferences about mutation risk association differences were similar regardless of the binning approach used. After the initial evaluation across all bins (Supplementary Table S3), we further collapsed bins that were inferred to have homogeneous prostate cancer, either elevated above or not different from the reference bin.

PSV type and function

In addition to the binning analyses described above, we also considered whether the predicted type and function of heritable *BRCA1/2* PSVs in the CIMBA database were associated with prostate cancer. The definition of these PSV types and their functions are presented in Supplementary Table S2. PSVs were grouped by type and function as frameshift (FS), nonsense (NS), missense (MS), and splice site (SP; Supplementary Table S2). PSVs expected to generate stable or unstable, or no proteins were designated into previously reported classes 1, 2, or 3 (38–40). Missense PSVs in *BRCA1* were combined into one group that contained PSVs in the RING (41, 42) and BRCT domains (43–46). We compared PSVs predicted to produce nonsense-mediated decay (NMD) versus those that were not. PSVs predicted not to cause NMD were defined as those creating a stop codon within 50 nucleotides before or within the last exon (47). Premature termination codons comprised all PSVs leading to a truncated open-reading frame.

Statistical analysis

For the first set of analyses assessing all bins across the genes, a different reference group was defined for each combination of gene (*BRCA1* or *BRCA2*) and binning scheme (decile or functional). Reference bins were chosen based on analysis of each bin's association with prostate cancer compared with all other bins as a group and found to have the lowest hazard of prostate cancer for each gene. The reference bins used in each analysis are shown in **Table 1**. An exploration of other reference bins did not change the inferences of this analysis.

To estimate the relative hazards associated with each bin compared with the reference bin, we fitted Cox proportional hazards regression models separately in *BRCA1* and *BRCA2* PSV carriers. The primary outcomes of interest were diagnosis of prostate cancer (vs. no prostate cancer) or Gleason 8+ prostate cancer (vs. no prostate cancer) and Gleason $\leq$7 (vs. no prostate cancer). Time to event was computed from birth to age at prostate cancer diagnosis or age at ascertainment (which ever occurred first). No time or events were considered after time of ascertainment. All analyses were adjusted for confounding by race (African American vs. any other ethnicity) and birth cohort, defined as those born before or after median birth date of the total sample. We also adjusted all analyses by country of ascertainment. We computed the prostate cancer HR for each defined bin relative to the common reference bin. To account for intracluster dependence due to multiple individuals from the same family, a robust sandwich variance estimate was specified in Cox proportional hazards models (48).

Hypothesis tests were judged to be statistically significant based on two-sided tests with $P < 0.05$. All P values were corrected for multiple hypothesis testing within each table of results by controlling the false discovery rate (FDR) using the method of Benjamini and Hochberg (49). Analyses were conducted in STATA v14, SPSS, or R version 2.7.2 (R Foundation for Statistical Computing).

Results

A total of 3,453 male *BRCA1* and 3,051 male *BRCA2 PSV* carriers were eligible for analysis (see **Table 2**). The median prostate cancer diagnosis ages were 64 years in both *BRCA1* and *BRCA2* PSV carriers. Among *BRCA1/2* PSV carriers, 74% and 81%, respectively, self-reported their race as white.

BRCA1

As shown in **Table 1**, there were no statistically significant associations between PSVs in any *BRCA1* bin and elevated prostate cancer risk. There was also no association of *BRCA1* PSVs with Gleason 8+ disease with region.

BRCA2

In *BRCA2*, we identified a "prostate cancer cluster region" (PCCR) in which PSVs were associated with elevated prostate cancer risk. The risk estimates were obtained by considering all PSVs within the region of interest defined by the overlap of bins generated using the "decile" and functional binning methods described above. The PCCR included all PSVs 3′ of c.7914 and associated with HR = 1.78 [95% confidence interval (CI), 1.25–2.52; $P = 0.001$] when compared with PSVs in the reference bin c.1001-c.7913 (**Table 1**). In addition, we identified a region bounded by c.756 and c.1000 (Supplementary Table S3; **Fig. 2**) that was associated with elevated prostate cancer risk with HR = 2.83 (95% CI, 1.71–4.68; $P = 4 \times 10^{-5}$) compared with PSVs in the reference bin c.1001-c.7913. This region contains the c.771_775del Icelandic founder PSV, which is the dominant PSV in this bin ($n =$ 92 of 117 total PSVs in this bin). Comparison of the risk in carriers of c.771_775del to the risk in carriers of PSVs in c.1001-c.7913 gave HR = 3.34 (95% CI, 2.01–5.55; $P = 3 \times 10^{-6}$). Because of the small number of carriers of other PSVs in this bin ($N = 25$), it was not possible to estimate risk of prostate cancer for carriers of the other (non-c.771_775del) PSVs in this bin. Risk of prostate cancer among those without a PCCR PSV was not elevated except for carriers of PSVs in bin 6 (c.5910-c.6275; HR = 2.83; 95% CI, 1.21–6.58; $P =$ 0.016; **Table 2**). Both the PCCR and region c.756-c.1000 were contained almost entirely within the previously identified breast cancer cluster regions (BCCR; ref. 24). Collectively, regions in which PSVs were associated with a significantly increased risk of prostate cancer development contained the *BRCA2* helical plasma domain, the oligonucleotide/oligosaccharide-binding domain 1 (OB1), the Tower domain (OB2), and the N-terminal PALB2-binding site (**Fig. 2**). Highest risk was associated with PSVs affecting OB1 and OB2 (**Fig. 2**).

Risk of high-grade prostate cancer (Gleason 8+) was even more strongly associated with PSVs in the PCCR (HR = 3.11; 95% CI, 1.63–5.95; $P = 0.001$; **Table 1**). A similar association was also observed for PSVs in the region containing the Icelandic founder PSV, c.771_775_del (HR = 4.95; 95% CI, 2.12–11.54; $P = 2 \times 10^{-4}$), and

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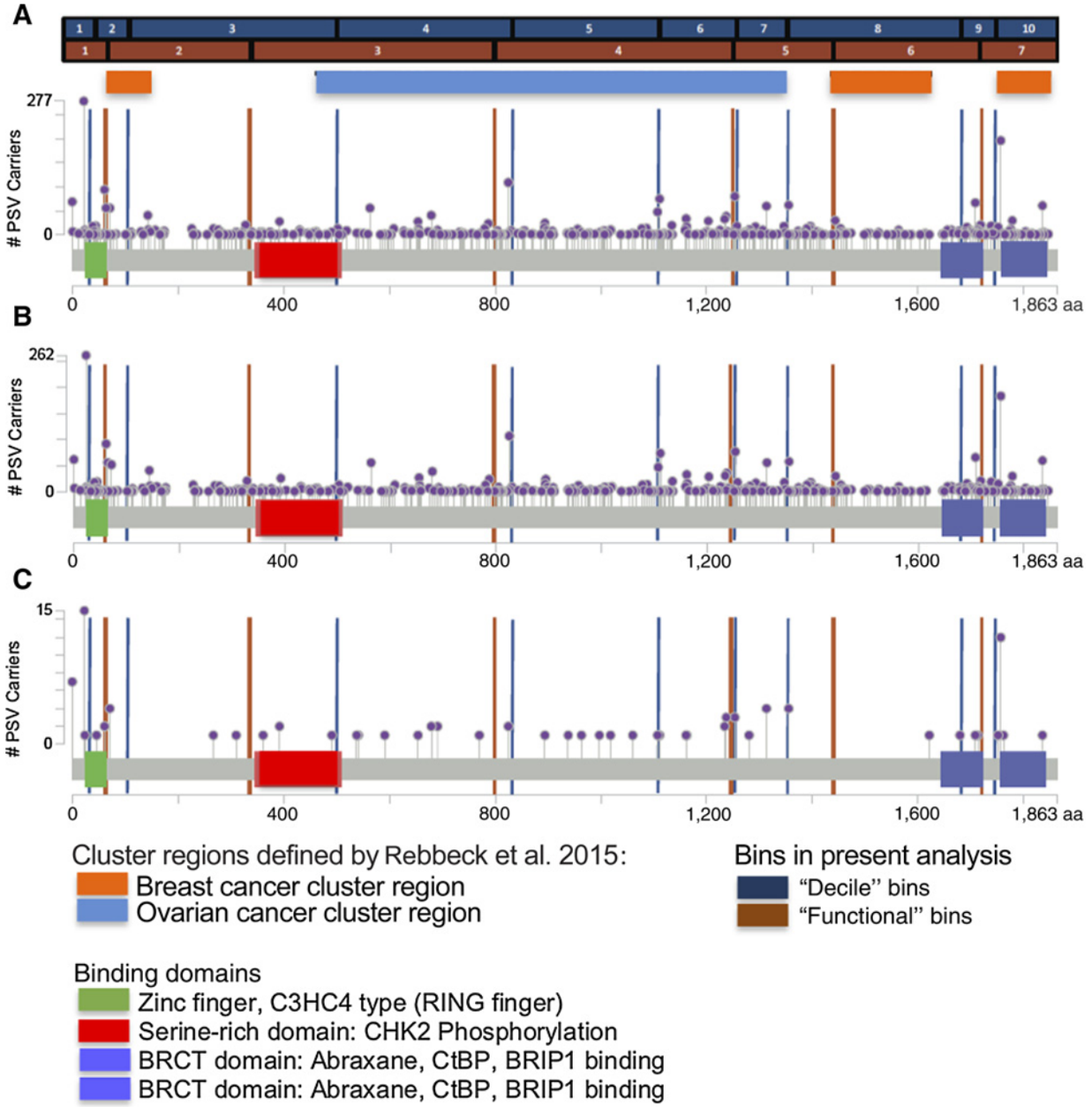

Figure 1.

BRCA1 PSV distribution. The *x*-axis displays the amino acid sequence of the *BRCA1* gene. The violet markers indicate the position of PSVs found in the *BRCA1* PSV carriers. The vertical position of the markers on the *y*-axis indicates the frequency of the PSV found in the cohort. In addition, the blue and tan bars with corresponding axis markers delineate the bins of the *BRCA1* PSVs that were created using the "decile" binning strategy and the "functional" binning strategy. Orange and light blue bars indicate the position of breast and ovarian cancer cluster regions, respectively, as identified in the CIMBA breast cancer cohort (Rebbeck et al.; ref. 24). Finally, known functional domains within the *BRCA1* gene are highlighted. **A,** Distribution of total *BRCA1* PSVs in carriers. **B,** Distribution of *BRCA1* PSVs in carriers who did not develop prostate cancer. **C,** Distribution of *BRCA1* PSVs in carriers who developed prostate cancer.

the c.771_775del PSV itself (HR = 5.66; 95% CI, 2.43–13.22; $P = 6 \times 10^{-5}$). Together, these regions were associated with increased Gleason 8+ prostate cancer risk (HR = 3.80; 95% CI, 2.10–6.89; $P = 1 \times 10^{-5}$). Risk of Gleason $\leq$ 7 prostate cancer was elevated for carriers of c.771_775del (HR = 3.29; 95% CI, 1.38–7.83; $P = 0.007$), but not elevated for those with PSVs in the PCCR (HR = 1.56; 95%CI, 0.88–2.78; $P = 0.130$; **Table 1**).

To ensure that the inferred effects were not due to the common Jewish founder PSV c.5946del that was included in the reference bin, we repeated calculations after excluding carriers these PSVs from the reference bin. After excluding these PSV carriers from the reference bin, the association with PSVs in the bin containing the c.771_775del and in the PCCR remained statistically significant (HR = 3.03; 95% CI, 1.83–5.04; $P = 2 \times 10^{-5}$ and HR = 1.89; 95%

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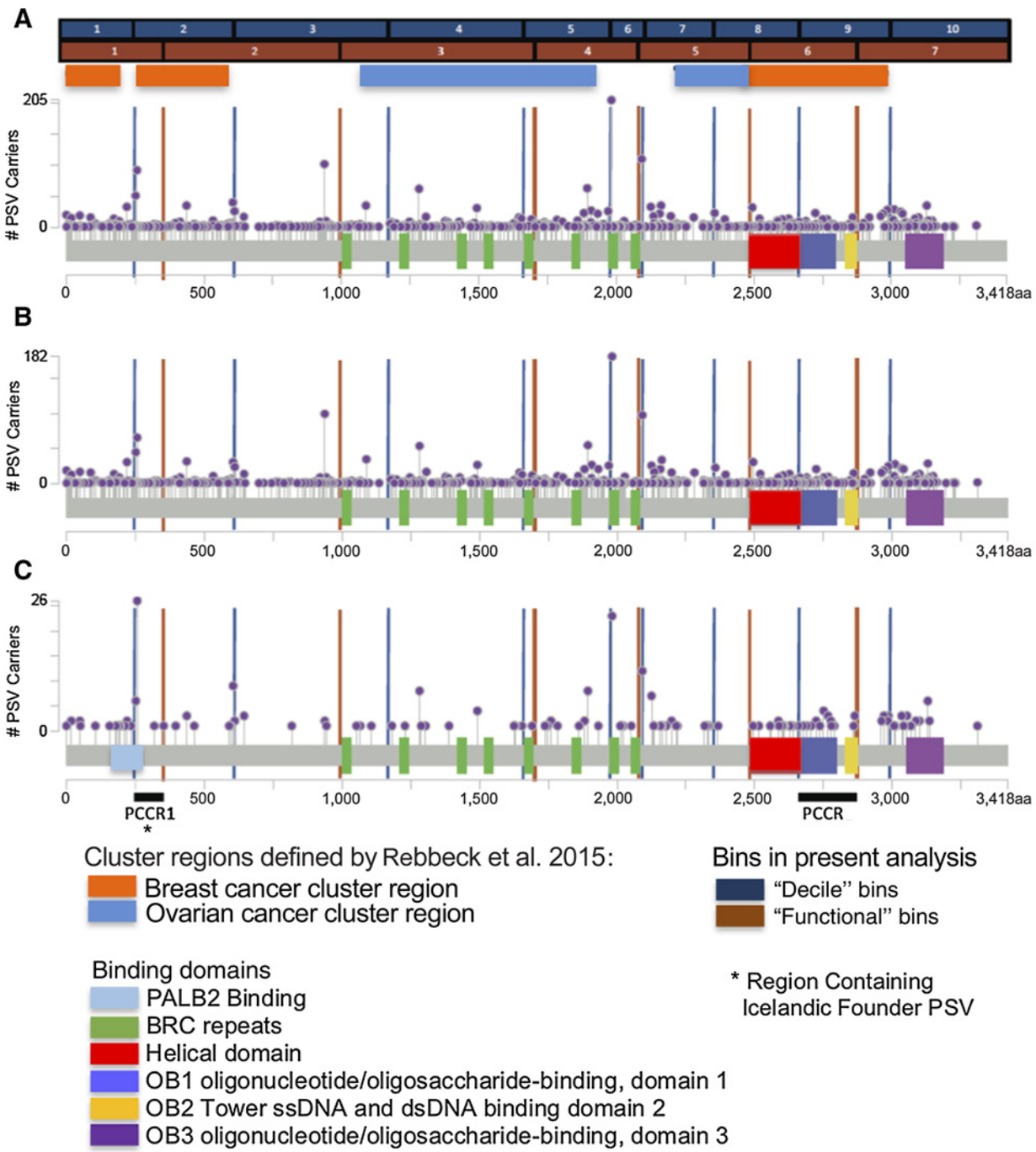

Figure 2.

BRCA2 PSV distribution. The *x*-axis displays the amino acid sequence of the *BRCA2* gene. The violet markers indicate the position of PSVs found in the *BRCA2* PSV carriers. The vertical position of the markers on the *y*-axis indicates the frequency of the PSV found in the cohort. In addition, the blue and tan bars with corresponding axis markers delineate the bins of the *BRCA2* PSVs that were created using the "decile" binning strategy and the "functional" binning strategy. Orange and light blue bars indicate the position of breast and ovarian cancer cluster regions, respectively, as identified in the CIMBA breast cancer cohort (Rebbeck et al.; ref. 24). Finally, known functional domains within the *BRCA2* gene are highlighted. **A,** Distribution of total *BRCA2* PSVs in carriers. **B,** Distribution of *BRCA2* PSVs in carriers who did not develop prostate cancer. **C,** Distribution of *BRCA2* PSVs in carriers who developed prostate cancer.

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Table 1. Association analyses of prostate cancer by bin for *BRCA1* and *BRCA2* PSVs.

Grouping	Bin	Nucleotide range	PC+	PC−	HR (95% CI)	*P*
BRCA1 – all prostate cancer						
BRCA1 Decile	1	≤c.81	11	339	1.06 (0.36–3.13)	0.917
	2	c.82-c.302	5	325	REF	
	3	c.303 – c.1504	4	331	0.82 (0.23–2.92)	0.761
	4	c.1505 – c.2475	8	431	1.09 (0.34–3.43)	0.888
	5	c.2476 – c.3319	3	274	0.33 (0.15–2.60)	0.526
	6	c.3320 – c.3710	5	308	1.32 (0.36–4.89)	0.677
	7	c.3711 – c.4065	9	318	1.96 (0.65–5.86)	0.230
	8	c.4066 – c.5030	1	333	0.16 (0.02–1.27)	0.084
	9	c.5031 – c.5266	13	425	1.68 (0.58–4.84)	0.339
	10	c.5267+	2	231	0.49 (0.10–2.49)	0.389
BRCA1 Functional	1	≤c.181	13	515	0.72 (0.34–1.53)	0.396
	2	c.182-c.1287	6	433	0.83 (0.32–2.20)	0.713
	3	c.1288-c.2475	9	478	0.93 (0.37–2.36)	0.887
	4	c.2476-c.3607	5	487	0.58 (0.19–1.75)	0.333
	5	c.3608-c.4183	12	462	1.19 (0.54–2.64)	0.671
	6	c.4184-c.5194	5	485	0.38 (0.12–1.25)	0.112
	7	c.5195+	11	455	REF	
BRCA2–All prostate cancer						
Grouping	**Bin**	**Nucleotide range**	**PC+**	**PC−**	**HR (95% CI)**	***P***
Decile	1	≤c.755	12	296	1.71 (0.66–4.46)	0.268
	2	c.756-c.1813	25	277	3.38 (1.24–9.19)	0.017
	3	c.1814-c.3530	6	293	REF	
	4	c.3531-c.4965	13	296	2.00 (0.69–5.76)	0.202
	5	c.4966-c.5909	13	307	2.14 (0.66–7.00)	0.207
	6	c.5910-c.6275	30	334	2.83 (1.21–6.58)	0.016
	7	c.6276-c.7007	12	214	2.69 (0.89–8.13)	0.079
	8	c.7008-c.7913	10	285	2.12 (0.60–7.42)	0.240
	9	c.7914-c.8953	26	281	3.32 (1.28–8.65)	0.014
	10	c.8954+	23	274	4.26 (1.60–11.37)	0.004
Functional	1	≤c.1000	27	398	1.39 (0.74–2.64)	0.307
	2	c.1001-c.3005	14	397	0.80 (0.39–1.63)	0.535
	3	c.3006-c.5172	16	408	REF	
	4	c.5173-c.6255	32	498	1.01 (0.53–1.93)	0.967
	5	c.6256-c.7436	24	400	1.44 (0.74–2.82)	0.286
	6	c.7437-c.8616	28	390	1.68 (0.91–3.13)	0.100
	7	c.8617+	29	366	1.64 (0.90–3.01)	0.106
Elevated vs. no elevated prostate cancer risk	1	≤c.755	12	296	0.73 (0.40–1.31)	0.288
	2[a]	c.756-c.1000	15	102	2.83 (1.71–4.68)	4×10^{-5}
	3	c.1001-c.7913	94	1,904	REF	
	PCCR	c.7914+	49	555	1.78 (1.25–2.52)	0.001
Elevated vs. no elevated prostate cancer risk	No Elevated PCa Risk	≤c.755, c.1001-c.7913	106	2,200	REF	
	Elevated PCa risk	c.756-c.1000, c.7914+	65	657	2.02 (1.48–2.77)	9×10^{-6}
BRCA2–Prostate cancer by Gleason grade						
Gleason 8+	**Bin**	**Nucleotide range**	**PC+**	**PC−**	**HR (95% CI)**	***P***
Bins with elevated risk	1	≤c.755	2	299	0.53 (0.12–2.32)	0.399
	2	c.756-c.1000	6	108	4.95 (2.12–11.54)	2×10^{-4}
	3	c.1001-c.7913	19	1,940	REF	
	PCCR	c.7914+	18	572	3.11 (1.63–5.95)	0.001
Bins with elevated risk	No elevated PCa risk	≤c.755, c.1001-c.7913	21	2,239	REF	
	Elevated PCa risk	c.756-c.1000, c.7914+	24	680	3.80 (2.10–6.89)	1×10^{-5}
Gleason <7						
Bins with elevated risk	1	≤c.755	3	298	0.47 (0.14–1.57)	0.221
	2[a]	c.756-c.1000	6	108	3.29 (1.38–7.83)	0.007
	3	c.1001-c.7913	36	1,923	REF	
	PCCR	c.7914+	17	573	1.56 (0.88–2.78)	0.130
Bins with elevated risk	No elevated PCa risk	≤c.755, c.1001-c.7913	39	2,221	REF	
	Elevated PCa risk	c.756-c.1000, c.7914+	23	681	1.89 (1.14–3.14)	0.014

Abbreviation: PCa, prostate cancer.

[a]Bin containing Icelandic Founder PSV c.771_775del.

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Table 2. Characteristics of study participants.

	Total		Carriers of PSV in *BRCA1* $N = 3,453$ (%)			Carriers of PSV in *BRCA2* $N = 3,051$ (%)	
Region	Asia		76 (2.2)			90 (2.9)	
	Australia		386 (11.2)			292 (9.6)	
	Europe		2,287 (66.2)			2,165 (71.0)	
	North America		662 (19.2)			497 (16.3)	
	South America		42 (1.2)			7 (0.2)	
Self-identified Race/ethnicity	Caucasian		2,557 (74.1)			2,455 (80.5)	
	African American		20 (0.6)			14 (0.5)	
	Asian		76 (2.2)			101 (3.3)	
	Hispanic		54 (1.6)			16 (0.5)	
	Jewish		124 (3.6)			94 (3.1)	
	Other		45 (1.3)			10 (0.3)	
	Unknown		575 (16.7)			358 (11.7)	
Ascertainment	Clinic-based		3,352 (97.1)			2,969 (97.3)	
	Population-based		101 (2.9)			82 (2.7)	
PCa	Yes		65 (1.9)			171 (5.5)	
	No		3,388 (98.1)			2,880 (94.4)	
Gleason Score	≤6		16 (24.6)			32 (18.7)	
	7		9 (13.8)			30 (17.5)	
	8		3 (4.6)			16 (3.1)	
	9		7 (10.8)			26 (15.2)	
	10		0 (0.0)			5 (2.9)	
	Missing		30 (46.2)			62 (36.2)	
M Stage	M0		18 (27.7)			33 (19.3)	
	M1		2 (3.1)			14 (8.2)	
	MX		8 (12.3)			28 (16.4)	
	Missing		37 (56.9)			96 (56.1)	
Other cancer diagnosis	Yes		332 (9.6)			657 (21.5)	
	No		3,121 (90.4)			2,389 (78.5)	
		N	Median	Range	N	Median	Range
Age at ascertainment, y		3,453	50	18–91	3,051	51	18–101
Time to PCa or censoring, y		3,453	50	18–91	3,051	54	18–101
Age at PCa diagnosis, y		65	64	30–85	171	64	29–87
Age at other cancer diagnosis, y		332	59	19–88	657	60	21–88

Abbreviation: PCa, prostate cancer.

CI, 1.34–2.66; $P = 3 \times 10^{-4}$, respectively). Similarly, we repeated the analysis including only self-identified Caucasians. In part, because of the small number of non-Caucasians in the study, the point estimates did not change to the second decimal place compared with the total sample that included non-Caucasians. Finally, we corrected for correlation due to the presence of multiple individuals in a family. With and without this correction, no change in the inferences was observed.

PSV type and function

In addition to seeking for regional variation in prostate cancer risk associated with PSVs across *BRCA1/2*, we also evaluated potential genotype–phenotype correlations by PSV type or function (**Table 3**). No PSV groups defined by type or function were significantly associated with prostate cancer for either *BRCA1* or *BRCA2*.

Discussion

Using a multinational data resource of approximately 6,500 men carrying a *BRCA1/2* PSV, we identified two regions in *BRCA2* (c.756-c 1000 and c.7914+) that were associated with increased risk of prostate cancer diagnosis and of Gleason 8+ prostate cancer. These data suggest that PSV-specific PCA risks exist for *BRCA2* PSV carriers. This observation is consistent with earlier studies reporting a PSV-specific increase in prostate cancer risk among *BRCA1/2* PSV carriers (31, 32). However, most studies that have made these observations have estimated the prevalence of *BRCA1/2* mutations in prostate cancer cases. Few studies have evaluated prostate cancer incidence in mutation *BRCA1/2* carriers. Nielsen and colleagues (32) reported an elevated prostate cancer relative risk in *BRCA2* mutation carriers whose mutations fell in c.6373-c.6492 with a relative risk of 3.7 for mutations within this region compared with mutations outside this region. This elevated relative risk was not observed in the larger current analysis, which included the carriers reported by Nielsen and colleagues. We also demonstrated a remarkable similarity between PSVs conferring increased prostate cancer risk and those associated with increased breast cancer risk in female *BRCA2* PSV carriers (24).

BRCA2 is among the few known clinically relevant loci, in which many deleterious variants cause a highly penetrant prostate cancer predisposition (50). Our work addressed the hypothesis that germline PSVs in *BRCA1/2* that influence development of overall prostate cancer and prostate cancer severity demonstrate nonrandom distribution by location and/or function of the gene. Because patients with prostate cancer with Gleason 8+ disease are far more likely than men with Gleason <8 prostate cancer to have unfavorable clinical outcome (2, 11–18), the observation that PCCR PSVs are associated

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Table 3. Association of PSV type or function with risk of prostate cancer.

			BRCA1 mutation carriers		*BRCA2* mutation carriers			
PSV type	**N**	**PCa**	**HR (95% CI)**	***P***	**N**	**PCa**	**HR (95% CI)**	***P***
Premature truncating codon	2,720	54 (2.0%)	1.04 (0.47–2.28)	0.931	2,699	151 (5.6%)	0.90 (0.40–2.04)	0.805
Nonsense-mediated decay	1,996	31 (1.6%)	0.65 (0.38–1.11)	0.117	2,692	150 (5.6%)	0.86 (0.41–1.82)	0.698
Class 1	2,489	48 (1.9%)	0.80 (0.44–1.47)	0.474	2,712	151 (5.6%)	0.81 (0.37–1.78)	0.596
Deletion	279	5 (1.8%)	0.79 (0.32–1.95)	0.606	57	5 (8.8)	1.25 (0.51–3.08)	0.469
Frameshift	1,845	43 (2.3%)	1.66 (0.99–2.77)	0.055	2,040	115 (5.6%)	1.01 (0.74–1.41)	0.910
Insertion	61	0	—[a]	—[a]	21	0	—[a]	—[a]
Missense	283	3 (1.1%)	0.66 (0.21–2.11)	0.488	60	4 (7%)	1.08 (0.37–3.17)	0.886
Nonsense	679	9 (1.3%)	0.68 (0.34–1.36)	0.271	591	32 (5.4%)	0.94 (0.64–1.39)	0.740
Splicing	306	5 (1.6%)	0.94 (0.39–2.30)	0.896	282	15 (5.3%)	1.00 (0.57–1.76)	0.994

Note: HRs represent the comparison of PSVs with a certain type or function designation vs. all other PSVs. HRs are adjusted for year of birth cohort, race, and country of ascertainment.
Abbreviation: PCa, prostate cancer.
[a]Could not be estimated.

with elevated Gleason score suggests that PCCR PSVs may be associated with poorer prognosis than other *BRCA2* PSVs. However, this needs to be investigated in future studies. We observe an elevated risk of both Gleason 8+ and Gleason $\leq$7 cancers, although the magnitude of association for Gleason 8+ is higher than that for Gleason $\leq$7. Thus, it is possible that the PCCR reported here is associated with prostate cancer in general, and not only with high-grade prostate cancer. This observation requires additional research to confirm. In addition, knowledge of the importance of DNA damage repair suggests that the mechanism of prostate carcinogenesis is broadly modified by *BRCA2*-related pathways (23). The IMPACT trial reported that PSA screening may be more informative in detecting prostate cancer in *BRCA2* PSV carriers compared with noncarriers (51). Additional research is needed to evaluate whether the PCCR PSVs reported here also influence the results of different management strategies.

In addition to its colocation with a previously identified breast cancer cluster region (24), PSVs in the PCCR (3′ of c.7914) are focused within two of the principal DNA-binding domains of the OB1 (i.e., oligonucleotide/oligosaccharide-binding domain 1; amino acids 2670–2796) and OB2 (i.e., Tower ssDNA and dsDNA binding domain 2; amino acids 2831–2872). However, the current dataset does not allow us to understand the mechanism that might explain why *BRCA2* PCCR PSVs are associated with elevated prostate cancer risks. Additional mechanistic research will be required to elucidate the biological basis for risk heterogeneity implied by the present results.

The most common PSV in the c.756-c.1000 region was the Icelandic and Finnish founder PSV, c.771_775del, which has long been known as a prostate cancer predisposition PSV (52–54) and is associated with a rapid progression to fatal prostate cancer (10). Thus, our results regarding the association of this founder PSV with prostate cancer severity are consistent with this prior report. We were not able to infer if c.756-c.1000 is a second PCCR region, or if the observed effect is due solely to c.771_775del. We returned to the original data from participants with this PSV to identify any potential bias in ascertainment that may have influenced this result. On the basis of original records from the Icelandic clinics from which these men were ascertained, no individual was ascertained based on genetic testing of prostate cancer. The carriers of this PSV were identified through family studies of breast cancer, mainly by screening unselected patients with breast cancer and then, if mutation positive, by screening their close relatives. There was no ascertainment preference for prostate cancer in Icelandic male carriers and there was no instance of a BRCA2 carrier identified by testing prostate cancer cases (Aðalgeir Arason; personal communication).

Our current results complement the growing body of knowledge that cancer-susceptible PSVs demonstrate clinically relevant genotype–phenotype relationships. PSV location within *APC* is associated with polyposis severity and prevalence of extracolonic features, such as desmoid fibromas (55). Similarly, genotype–phenotype relationships have been reported for (missense) PSVs in *RET* in multiple endocrine neoplasia type 2 (MEN2) and familial medullary thyroid carcinoma (30). These findings have shaped the Neuroendocrine Tumor Society consensus guidelines, which now suggest thyroidectomy before age 5 years for individuals with PSVs within these high-risk regions, providing insight into the structure and function of cancer susceptibility PSVs in these genes and guiding clinical risk assessment and management. Despite evidence of genotype–phenotype relationships at multiple loci, the characteristics and mechanistic influences on cancer risk are likely quite different for PVSs in *APC, RET, BRCA1/2,* and others.

In contrast to prior work that evaluated prevalence of PSVs in *BRCA1/2* in various prostate cancer case series, we have leveraged a large, international multicenter consortium study of *BRCA1/2* PSV carriers, irrespective of prostate cancer status. However, our analysis has some limitations. The CIMBA study uses a nonstandardized recruitment strategy from multiple referral centers. Thus, our data may not represent either the full spectrum of patients with prostate cancer or *BRCA1/2* PSV carriers in the general population. Similarly, we were not able to assess issues of survival bias in our data that may be related to cancer screening or treatment.

While this study identifies potentially interesting PSV-specific prostate cancer associations, there are limitations in the data and analysis that require future validation. We used two binning approaches to identify relevant regions of *BRCA1/2* that could have different risk or penetrance effects on prostate cancer based on our earlier research that undertook a similar analysis for breast and ovarian cancer (24). In that analysis, we determined that the combination of these two approaches were complementary and identified similar regions of interest. While this approach points toward genomic regions that may confer different prostate cancer risks, a full understanding of the causes of the effects we report will require experimental and mechanistic studies to further define the boundaries of the relevant domains and to understand the underlying mechanisms that lead to the observations reported here. In addition, the choice of the reference bin in our analysis will affect estimates of the HRs reported here. Thus,

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this report focuses on the identification of genomic regions that may confer elevated prostate cancer risks in *BRCA2* mutation carriers, and the HR estimates presented here should be interpreted with caution and not used for clinical risk estimation purposes.

Studies in female PSV carriers using a study design similar to that used here applied analytic corrections to account for the possibility that affected individuals (particularly those affected at younger ages) are more likely to be sampled than unaffected individuals. Unlike prior breast and ovarian cancer studies in *BRCA1/2* mutation carriers, this sample did not ascertain specific prostate cancer cases (e.g., those diagnosed at an early age). Our median age at diagnosis is 64 years, which is similar to that reported in other non-*BRCA1/2* populations. Our case sample is substantially older than prostate cancer cases ascertained for BRCA1/2 screening studies, which tend to have a large proportion of cases diagnosed before the age of 55 years (56). Thus, while there is limited evidence that ascertainment of cases conferred a major bias to the present results, future research is required to determine the extent of bias in our relative risk estimates arising from these issues.

Finally, pathology review of prostate tumors was neither centralized nor available for all cases. A relatively large proportion of Gleason score and tumor stage data were also missing from the present sample, because many cases were based on self-report only. Cases with missing tumor stage and grade were excluded from those analyses, so any differential reporting of tumor traits could have caused bias in those results.

This study indicates that personalized prostate cancer risk assessment may be a future option, as well as individualized clinical management based on the specific *BRCA2* PSV status. Additional research is required to fully understand the implication of carrying specific *BRCA2* PSVs. Further characterization of the relationship between these PSVs and various cancer outcomes might help direct the future use of DNA repair–directed treatments and radiotherapy in men carrying these PSVs.

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A. Borg has received speakers bureau honoraria from Roche and AstraZeneca (lecture honoraria). A.R. Bradbury has received other commercial research support and is a consultant/advisory board member for AstraZeneca and Merck. N. Ditsch has received speakers bureau honoraria from MSD, Roche, TEVA and has provided expert testimony as a mentor. D.M. Eccles has received speakers bureau honoraria from AstraZeneca and Pierre Fabre. R.A. Eeles has received speakers bureau honoraria from GU-ASCO meeting in San Francisco (January 2016; honorarium as speaker), from RMH FR meeting (November 2017; support from Janssen, honorarium as speaker; title: Genetics and Prostate Cancer), University of Chicago (invited talk May 2018; honorarium as speaker). D.G. Evans is a consultant/advisory member for AstraZeneca. G. Fountzilas has received speakers bureau honoraria from AstraZeneca. O.I. Olopade reports receiving other commercial research support from CancerIQ. M.A. Pujana has received other commercial research support from Roche Pharma. M.E. Robson has received other commercial research support from Invitae and Myriad and is a consultant/advisory board member for AstraZeneca, Merck, Pfizer, Daiichi Sankyo, McKesson. K.J. Ruddy has ownership interest (including patents) in Merck and Pfizer. L. Senter is a consultant/advisory board member for AstraZeneca and Clovis and has received speakers bureau honoraria from AstraZeneca. C.F. Singer is a consultant at Novartis, has received speakers bureau honoraria from Roche, Novartis, Amgen, and is a consultant/advisory board member for AstraZeneca. L. Varesco is on expert input forum at AstraZeneca–MSD. No potential conflicts of interest were disclosed by the other authors.

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Association of Genomic Domains in *BRCA1* and *BRCA2* with Prostate Cancer Risk and Aggressiveness

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