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LETTER TO THE EDITOR

Prostate Cancer

Germline mutations in 5' to c.7914 of *BRCA2* significantly increase risk of prostate cancer

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Dear Editor,

Here, we report the association of mutations in the prostate cancer cluster region (PCCR; c.7914 to 3') and non-PCCR (5' to c.7914) in breast cancer susceptibility gene 2 (*BRCA2*) with prostate cancer (PCa) risk at the population level in Caucasian and Chinese cohorts.

Pathogenic mutations of *BRCA2* have been reported to significantly increase the risk of PCa and disease aggressiveness.[1–3] The overall risk of developing PCa by age 65 years is increased 2.5–8.6-fold for *BRCA2* carriers. *BRCA2*-mutant prostate tumors were associated with high-grade disease and progression to metastatic castration-resistant PCa, affecting treatment effectiveness.[4,5] Some recent studies suggested that pathogenic mutations in the PCCR of *BRCA2* were related to a higher PCa risk than mutations elsewhere in the gene, by 1.78–2.34-fold hazard ratio (HR).[6,7] Both studies evaluated the hypothesis of the PCCR in *BRCA2* carrier cohorts of Caucasians or nonrace-specific populations under either a prospective or retrospective design. However, whether PCCR mutations are associated with PCa risk at the population level is still unknown. In addition, the relationship between *BRCA2* regions and PCa has been poorly studied in the Chinese population.

We conducted the present study in two cohorts, the UK Biobank (UKB) prospective cohort and a Chinese PCa cohort. The study was approved by the North West Multi-centre Research Ethics Committee in Manchester, UK (IRAS project ID: 299116; approval No. 66813), and the Institutional Review Board of Shanghai Huashan Hospital in Shanghai, China (approval No. KY2011-009). Written informed consent was obtained from each participant. The UKB is a large-scale biomedical database containing genetic and phenotype information from a prospective cohort study.[8] We established a prospective cohort of 83 181 European who had not been diagnosed with PCa at recruitment and had not developed any other types of cancers during follow-up (last follow-up in January 2022). A PCa diagnosis was identified from national cancer registries and self-report records (International Classification of Diseases [ICD] 10: C61). PCa-related death (*i.e.*, lethal PCa) information was identified from death registries. The Chinese PCa cohort was a retrospective case-only cohort of 235 PCa patients who had undergone whole-exome sequencing (WES) of germline DNA samples within the ChinaPCa Consortium. Additional 91 blood samples were evaluated on a next-generation sequencing platform using a 556-gene panel at the discretion of the ordering clinicians in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China). East Asian WES data from the Genome Aggregation Database (gnomAD) were used for comparison with the Chinese PCa cohort. Mutation pathogenicity was defined based on the American College of Medical Genetics and Genomics criteria, and the location was based on the NM_000059.3 transcript. Categorical and continuous variables were compared between groups using the Chi-square test/Fisher's exact test and Student's *t*-test, respectively. A multivariate Cox proportional hazards regression model was fitted in the UKB cohort.

The clinical and demographic characteristics of the UKB cohort ($n = 83\,181$) and the Chinese PCa cohort ($n = 326$) are described in **Table 1**. A total of 4715 men in the UKB cohort developed PCa over a median follow-up of 12.5 years. Among them, 35 patients (0.7%) carried a *BRCA2* pathogenic or likely pathogenic (P/LP) mutation, while only 278 out of 78 466 non-PCa men (0.4%) carried a P/LP mutation in *BRCA2* (odds ratio [OR] = 2.10, 95% confidence interval [CI]: 1.48–2.99, $P < 0.001$; **Table 1**). Among the 35 cases of PCa in *BRCA2* P/LP carriers, 12 were lethal (OR = 11.55, 95% CI: 6.41–20.81, $P < 0.001$), and 32 involved mutations located outside the PCCR. The carrier rate of non-PCCR mutations was 0.7% in PCa patients, significantly higher than the rate in healthy men (0.3%; OR = 2.44, 95% CI: 1.63–3.55, $P < 0.001$). Compared to the carrier rate of PCCR mutations, it was still significantly elevated (OR = 4.85, 95% CI: 1.12–21.09, $P = 0.04$) after adjusting for age and family history. However, no significant difference in the carrier rate of PCCR mutations was observed between PCa patients (0.1%) and healthy individuals (0.1%; $P = 1.00$). Moreover, the risk of PCa in non-PCCR carriers was 12.7%, which was 2.43-fold higher (relative risk [RR], 95% CI: 1.68–3.52, $P < 0.001$; **Supplementary Table 1**) than that in noncarriers (5.6%). Insignificant risks of PCa were observed in PCCR carriers (4.8%) and noncarriers (5.6%; $P = 1.00$). Additional analyses suggested that mutations in exons 7, 9, and 11 were significantly associated with PCa (all $P < 0.05$; **Supplementary Table 2**). Survival analysis indicated a potential association between non-PCCR mutations and PCa-free survival since recruitment (HR = 2.87, 95% CI: 0.85–9.71, $P = 0.09$, log-rank $P = 0.08$). The result was significant after adjusting for age and family history (HR = 4.69, 95% CI: 1.12–19.61, $P = 0.03$).

In the Chinese PCa cohort, all 6 carriers harbored a deleterious non-PCCR mutation in *BRCA2* and had metastatic PCa (**Table 1**). The carrier rate of non-PCCR mutations was significantly higher in

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Table 1: Demographic characteristics of the study population, and the association between prostate cancer risk and *BRCA2* pathogenic mutations

Variable	*UKB*				*Chinese/gnomAD East Asian*			
	Case	*Control*	*OR (95% CI)*	*P*	*Chinese case*	*East Asian control*	*OR (95% CI)*	*P*
Participants (*n*)	4715	78 466	NA	NA	326	9197	NA	NA
Age at recruitment (year), median (IQR)	63.0 (59.0–66.0)	58.0 (50.0–63.0)	1.10 (1.10–1.11)	<0.001	70.0 (65.0–75.0)	NA	NA	NA
Positive family history, *n* (%)	575 (12.7)	6769 (10.3)	1.48 (1.35–1.62)	<0.001	4 (6.0)[a]	NA	NA	NA
Carrier rates of *BRCA2*, *n* (%)	35 (0.7)	278 (0.4)	2.10 (1.48–2.99)	<0.001	6 (1.8)	27 (0.3)	6.37 (2.13–15.88)	<0.001
5' to c.7914 mutations	32 (0.7)	219 (0.3)	2.44 (1.63–3.55)	<0.001	6 (1.8)	23 (0.3)	7.48 (2.47–19.05)	<0.001
c.7914 to 3' mutations	3 (0.1)	59 (0.1)	0.85 (0.17–2.60)	1.00	0 (0)	4 (<0.05)	0 (0–27.16)	0.71

[a]Family history information is available for 67 PCa cases. *BRCA2*: breast cancer susceptibility gene 2; PCa: prostate cancer; UKB: UK Biobank; gnomAD: Genome Aggregation Database; OR: odds ratio; CI: confidence interval; IQR: interquartile range; NA: not applicable

PCa (1.8%) than in the normal control population (from gnomAD East Asian, 0.3%; OR = 7.48, 95% CI: 2.47–19.05, $P < 0.001$). Very few PCCR mutation carriers were observed among both Chinese PCa patients (0) and gnomAD East Asian healthy controls (<0.05%; $P = 1.00$). Exon-based analyses were also performed in the Chinese cohort and showed that exon 5 ($P = 0.03$) and exon 11 ($P = 0.02$) might be associated with PCa (**Supplementary Table 2**).

Different from the recently published evidence based on the *BRCA2* carrier cohorts, our study demonstrated that Caucasian and Chinese men carrying 5' to c.7914 mutations of *BRCA2* (*i.e.*, non-PCCR) had a significantly elevated risk of PCa, but the carriers of c.7914 to 3' mutations (*i.e.*, PCCR) did not.[6,7] Previous studies suggested that *BRCA2* exon 11 was closely related to breast/ovarian cancer risk and disease aggressiveness.[9] Our results also showed a critical correlation between PCa risk and P/LP in exon 11 in both Caucasian and East Asian cohorts. In addition, a previous study from our group demonstrated that Chinese men with a positive family history of breast/ovarian cancer have a significantly increased risk of PCa.[10] Although there is a lack of mutation data for *BRCA1/2*, this indicates that PCa and breast/ovarian cancer might share a similar genetic background and carcinogenesis mechanism in the Chinese population. An important limitation of the current study was that the number of *BRCA2* carriers was limited in both cohorts, which makes it difficult to further evaluate whether the *BRCA2* region is associated with disease aggressiveness, mortality, or drug response. We believe that these topics should be investigated further in future studies. A high-resolution and broad genetic assessment at a population level is pivotal to cancer risk evaluation.

In conclusion, our results suggested that PCa risk is significantly increased in men carrying deleterious *BRCA2* mutations in the 5' to c.7914 region (*i.e.*, non-PCCR mutations). Additional research is expected to determine the implications of carrying specific deleterious *BRCA2* mutations.

Data availability

All data used in this research are publicly available to qualified researchers on application to the UK Biobank (www.ukbiobank.ac.uk) and the Genome Aggregation Database (http://gnomad.broadinstitute.org).

AUTHOR CONTRIBUTIONS

RN and YSW conceived, designed, and supervised the study. YSW, QD, RN, XLL, and ZJF participated in the data collection and interpretation. XHR and DH analyzed the data and drafted the manuscript. YSW, QD, and RN contributed to the critical revision of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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Supplementary Table 1: Prostate cancer risk by location of breast cancer susceptibility gene 2 pathogenic variants in UK Biobank prospective cohort

BRCA2 mutation carrier	*Carriers No. PCa (%)*	*Noncarriers (n=82 868) No. PCa (%)*	*RR (95% CI)*	*P*
All (*n*=313)	35 (11.2)	4680 (5.6)	2.10 (1.48–2.97)	<0.001
Non-PCCR (5' to c.7914, *n*=251)	32 (12.7)	4680 (5.6)	2.43 (1.68–3.52)	<0.001
PCCR (c.7914 to 3', *n*=62)	3 (4.8)	4680 (5.6)	0.85 (0.27–2.71)	1.00

PCCR: prostate cancer cluster region; No. PCa: number of prostate cancer patients; RR: relative risk; CI: confidence interval; *BRCA2*: breast cancer susceptibility gene 2

Supplementary Table 2: Association between prostate cancer risk and breast cancer susceptibility gene 2 mutations by exons

BRCA2 exon	*UKB*				*Chinese case/gnomAD East Asian control*			
	Case, n (%) (n=4715)	*Control, n (%) (n=78 466)*	*OR (95% CI)*	*P*	*Case, n (%) (n=326)*	*Control, n (%) (n=9197)*	*OR (95% CI)*	*P*
1	0	0	-	-	0	0	-	-
2	0	1 (0.0)	0 (0–Inf.)	1.00	0	2 (0.0)*	0 (0–54.34)	1.00
3	0	2 (0.0)	0 (0–31.98)	1.00	0	0	-	-
4	0	2 (0.0)	0 (0–31.98)	1.00	0	0	-	-
5	0	0	-	-	1 (0.1)	0	Inf. (0.92–Inf.)	0.03
6	0	1 (0.0)	0 (0–Inf.)	1.00	0	0	-	-
7	4 (0.1)	7 (0.0)	9.52 (2.04–37.45)	0.003	0	0	-	-
8	0	1 (0.0)	0 (0–Inf.)	1.00	0	0	-	-
9	3 (0.1)	6 (0.0)	8.33 (1.35–38.99)	0.01	0	1 (0.0)	0 (0–Inf.)	1.00
10	1 (0.0)*	13 (0.0)	1.28 (0.03–8.53)	0.56	1 (0.1)	2 (0.0)	14.15 (0.24–272.12)	0.10
11	22 (0.5)	161 (0.2)	2.28 (1.39–3.58)	0.001	3 (0.9)	13 (0.1)	6.56 (1.19–24.03)	0.02
12	0	0	-	-	0	0	-	-
13	0	6 (0.0)	0 (0–10.65)	1.00	0	0	-	-
14	0	9 (0.0)	0 (0–7.10)	1.00	1 (0.1)	1 (0.0)	28.30 (0.36–2221.20)	0.07
15	1	2 (0.0)	8.32 (0.14–159.88)	0.16	0	3 (0.0)	0 (0–36.22)	1.00
16	1 (0.0)	8 (0.0)	2.08 (0.05–15.52)	0.41	0	1 (0.0)	0 (0–Inf.)	1
17	0	4 (0.0)	0 (0–15.98)	1.00	0	0	-	-
18	1 (0.0)	15 (0.0)	1.11 (0.03–7.22)	0.61	0	0	-	-
19	0	2 (0.0)	0 (0–31.98)	1.00	0	0	-	-
20	1 (0.0)	4 (0.0)	4.16 (0.08–42.05)	0.25	0	0	-	-
21	0	0	-	-	0	0	-	-
22	0	4 (0.0)	0 (0–15.98)	1.00	0	0	-	-
23	0	6 (0.0)	0 (0–10.65)	1.00	0	0	-	-
24	0	3 (0.0)	0 (0–21.31)	1.00	0	0	-	-
25	1 (0.0)	20 (0.0)	0.83 (0.02–5.21)	1.00	0	0	-	-
26	0	0	-	-	0	0	-	-
27	0	1 (0.0)	0 (0–Inf.)	1.00	0	4 (0.0)	0 (0–27.16)	1.00

*Proportion < 0.05%. UKB: UK Biobank; gnomAD: Genome Aggregation Database; OR: odds ratio; CI: confidence interval; Inf.: infinity; *BRCA2*: breast cancer susceptibility gene 2