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ORIGINAL RESEARCH

Association of estrogen receptor α PvuII and XbaI polymorphisms with prostate cancer susceptibility and risk stratification: a meta-analysis from case-control studies

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Background: Studies on the association between two single nucleotide polymorphisms (SNPs) in estrogen receptor α (ERα), PvuII (rs2234693 T>C) and XbaI (rs9340799 A>G), and the prostate cancer risk are inconsistent. Therefore, we performed a meta-analysis to derive a more accurate estimation of this relationship.

Methods: A literature search of PubMed, Embase, Web of Science databases until October 1, 2016, was conducted. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of this association.

Results: Eighteen case-control studies, with a total of 3,317 prostate cancer patients and 8,324 controls, were included. Results showed that both PvuII and XbaI polymorphisms were significantly associated with a higher prostate cancer risk in overall populations. To derive a more accurate estimation, subgroup analysis stratified by ethnicity revealed that this relationship existed only in Caucasians, but not in Asians. Furthermore, PvuII polymorphism was significantly associated with high Gleason grade (Gleason score ≥7) cancers.

Conclusion: The current meta-analysis demonstrates that ERα PvuII and XbaI polymorphisms are associated with a higher prostate cancer risk in Caucasians, but not in Asians, and PvuII polymorphism is significantly associated with high Gleason grade tumors, indicating the probability of inherited susceptibility to prostate cancer arising from different genomic ERα SNPs, which may help us understand the pathogenesis of prostate cancer in Caucasians.

Keywords: estrogen receptor α, PvuII, XbaI, prostate cancer, meta-analysis

Introduction

Prostate cancer is the most common malignancy in men and a major cause of cancer-related deaths.[1] Since prostate-specific antigen (PSA)-based screening regime for prostate cancer remains controversial because of the high rate of overdiagnosis and overtreatment, a validated biomarker to complement PSA for screening and prognostic biomarkers with clinical utility remain an unmet need.[2]

In addition to androgens, estrogens also affect prostatic growth and carcinogenesis.[3] The cellular effects of estrogens are mediated by two estrogen receptors (ERs), ERα and ERβ. The human ERα encoding gene locates on chromosome 6q25.1 and consists of eight exons and seven introns.[4] Previous studies showed that the expression of ERα is gradually increased from prostate intraepithelial neoplasia, locally invasive cancers to metastatic lesions at both mRNA and protein levels.[5] Furthermore, in vivo studies

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using ERα knockout mice revealed that ERα is an important determinant of prostatic carcinogenesis.[3]

Although several single nucleotide polymorphisms (SNPs) have been identified in the ERα gene, only a few have been extensively studied in prostate cancer. Furthermore, substantial controversial conclusions have been drawn by these studies. To address these issues, we chose two common polymorphisms in the ERα gene, PvuII (rs2234693 T>C) and XbaI (rs9340799 A>G), and conducted a meta-analysis on case-control studies between prostate cancer patients and prostate cancer-free controls. The aim of this study was to investigate the potential role of ERα PvuII and XbaI polymorphisms in the prostate cancer risk stratification.

Methods

The current meta-analysis was designed and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Table S1).[6]

Literature search

Relevant papers published before October 1, 2016, were identified through a literature search in PubMed, Embase, and Cochrane databases using the following strategy: [("gene mutation" OR "polymorphism") OR ("SNP") OR ("genetic variants")] AND [("prostate carcinoma") OR ("prostate neoplasms") OR ("prostate cancer")] AND [("estrogen receptor") OR ("estradiol receptor") OR ("ER") OR ("ESR")]. References from eligible articles were also manually searched to identify other potential publications.

Study eligibility

Studies were eligible for inclusion if, 1) studies focused on the association between ERα PvuII and *Xba*I polymorphisms and the prostate cancer risk; 2) they were case-control clinical studies on human subjects; 3) all diagnoses with prostate cancer were confirmed by pathological or histological examinations and controls were confirmed to be cancer free; 4) sufficient data were provided to estimate crude odds ratios (ORs) with 95% confidence intervals (CIs).

Two authors independently completed the screening process according to the Cochrane Collaboration guidelines.[7] The methodological quality of each retrieved study was assessed using the Strengthening the Reporting of Genetic Association Studies (STREGA) quality score system.[8] Forty-nine assessment items related to the quality appraisal were used in this score system with scores ranging from 0 to 49. Scores of 0–25, 26–37, and 38–49 were defined as low, moderate, and high quality, respectively (Table S2).

Data extraction

Detailed data from each publication were independently extracted by two authors using a standardized data extraction sheet and were checked by a third author (Table S3). The following information was extracted from each article: first author, year of publication, SNP ID and alternate name, ethnicity, country, language, study design, number of subjects, source of cases and controls, detecting sample, genotype method, allele and genotype frequencies, minor allele frequency (MAF), and evidence of Hardy–Weinberg equilibrium (HWE) in controls. Clinical parameters of prostate cancer patients were also collected, including tumor stage, serum PSA level at prostate cancer diagnosis, age at prostate cancer diagnosis, and smoking status. Risk of bias in each individual study was also evaluated.

Statistical analysis

The association strength between both polymorphisms and the prostate cancer risk was measured by ORs with 95% CIs under five genetic models: allele model, dominant model, recessive model, homozygous model, and heterozygous model. The statistical significance of the pooled OR was examined by the *Z* test. Heterogeneity between studies was estimated using the I^2 test. $I^2<50\%$ indicated that heterogeneity among studies was acceptable, and the fixed effects model (the Mantel–Haenszel method) was used. Otherwise, the random effects model (DerSimonian Laird method) was used. Subgroup analyses through ethnicity, country, source of cases and controls, genotype method, and whether HWE was in control or not were also conducted. We also stratified prostate cancer patients according to selected clinical parameters. HWE was evaluated by the χ^2 test in controls. Sensitivity analysis was performed by omitting each study in order to assess the stability of pooled results. Begger's funnel plots and Egger's linear regression test were used to evaluate publication bias. If significant publication bias existed, the trim and fill method was used to adjust pooled estimates.[9] All tests were two sided, and $P<0.05$ was considered statistically significant. Data analysis was performed using the STATA software (version 12.0; Stata Corp, College Station, TX, USA).

Results

Characteristics of included studies

According to the inclusion criteria, 18 case-control studies were included in the current meta-analysis.[10–27] The flow chart presenting the selection process is shown in Figure 1. A total of 3,317 prostate cancer patients and 8,324 controls were included in the synthesis. Years of publications ranged from

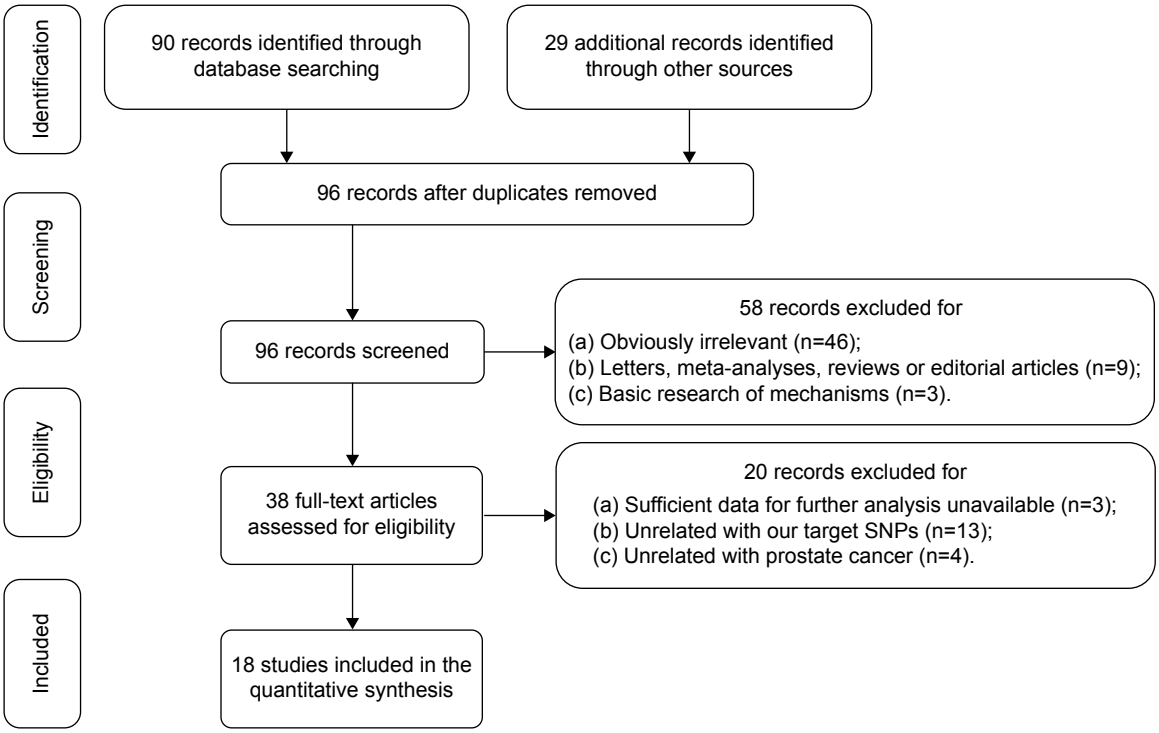


Figure 1 Flow of information through different phases of the present meta-analysis.
Abbreviation: SNP, single nucleotide polymorphisms.

2001 to 2015. Genotype frequencies among controls were consistent with the HWE test, except for three studies.[11,24,26] STREGA scores ranged from 29 to 36, which suggested that all of these studies were qualified to the quantitative synthesis. The characteristics and methodological quality of the included studies are summarized in Tables 1 and S4.

ERα PvuII (rs2234693 T>C) polymorphism and the prostate cancer risk

Eighteen studies, comprising 3,317 cases and 8,324 controls, were involved in the synthesis. The results showed that PvuII polymorphism was related to an increased prostate cancer risk in overall populations under four genetic models (allele model OR: 1.16, 95% CI: 1.04–1.29, $P<0.01$; dominant model OR: 1.24, 95% CI: 1.06–1.47, $P=0.01$; recessive model OR: 1.16, 95% CI: 1.04–1.30, $P<0.01$; homozygous model OR: 1.37, 95% CI: 1.09–1.72, $P<0.01$; Tables 2 and S5). To derive a more accurate estimation, subgroup analyses stratified by ethnicity were conducted. The results indicated that PvuII polymorphism was significantly correlated with a higher prostate cancer risk in Caucasians (allele model OR: 1.12, 95% CI: 1.03–1.21, $P<0.01$; dominant model OR: 1.19, 95% CI: 1.05–1.35, $P<0.01$; recessive model OR: 1.13, 95% CI: 1.03–1.29, $P=0.04$; homozygous model OR: 1.25, 95% CI: 1.06–1.46, $P=0.01$; Tables 2 and S5), but not in Asians. Furthermore, when grouped according to Gleason grades, PvuII polymorphism was found to be significantly correlated with high Gleason grade cancers (Gleason score ≥7) under the allele model (OR: 1.90, 95% CI: 1.44–2.50, $P<0.01$, Table 3).

Sensitivity analysis suggested that individual studies did not affect pooled ORs (Figure S1). Begger's funnel plot and Egger's linear regression test did not show any statistical evidence of publication bias (Figure 2A). In addition, we excluded one study that deviated significantly from HWE, as the results showed that this non-HWE study had no effect on pooled ORs (Table 2).

ERα XbaI (rs9340799 A>G) polymorphism and the prostate cancer risk

The correlation between XbaI polymorphism and the prostate cancer risk was investigated in 13 studies with 1,946 cases and 2,744 controls. The results showed that XbaI polymorphism had a positive association with the risk of prostate cancer in overall populations under four genetic models (allele model OR: 1.23, 95% CI: 1.06–1.43, $P<0.01$; dominant model OR: 1.38, 95% CI: 1.11–1.72, $P<0.01$; recessive model OR: 1.24, 95% CI: 1.03–1.49,

Table 1 Characteristics and methodological quality of included studies

Study	Ethnicity	Country	SOC	Sample	Genotyping method	Participants		HWE	STREGA score
						Case	Control		
PvuII (rs2234693 T>C) (n=18)									
Modugno et al,[10] 2001	Caucasian	America	PB	Blood	PCR	81	233	Y	30
Suzuki et al,[11] 2003	Asian	Japan	PB	Blood	PCR	101	114	Y	31
Tanaka et al,[12] 2003	Asian	Japan	PB	Tissue	PCR	115	200	Y	29
Fukatsu et al,[13] 2004	Asian	Japan	Mixed	Tissue	PCR	116	238	Y	31
Hernández et al,[14] 2006	Mixed	NA	Mixed	Blood	TaqMan	598	1,098	Y	31
Low et al,[15] 2006	Caucasian	Britain	NA	Urine	TaqMan	75	158	Y	32
Berndt et al,[16] 2007	Caucasian	NA	PB	Blood	TaqMan	470	603	Y	31
Kjaergaard et al,[17] 2007	Caucasian	Denmark	HB	NA	PCR	116	4,005	Y	36
Onsory et al,[18] 2008	Asian	India	HB	Tissue	PCR	100	100	Y	32
Sobti et al,[19] 2008	Asian	India	HB	Blood	PCR	157	170	Y	31
Gupta et al,[20] 2010	Asian	India	HB	Blood	PCR	157	170	Y	31
Balistreri et al,[21] 2011	Caucasian	Sicily	NA	Tissue	TaqMan	50	47	Y	32
Sissung et al,[22] 2011	Caucasian	America	PB	Blood	PCR	128	126	Y	32
Szendroi et al,[23] 2011	Caucasian	Hungary	PB	Blood	PCR	194	103	Y	31
Safarinejad et al,[24] 2012	Asian	Iran	NA	Blood	PCR	162	324	Y	32
Jurecekova et al,[25] 2013	Caucasian	Slovakia	PB	Blood	PCR	311	256	Y	33
Pazarbasi et al,[26] 2013	Asian	Turkey	PB	Blood	PCR	34	27	N	32
Lu et al,[27] 2015	Asian	Japan	PB	Blood	PCR	352	352	Y	30
XbaI (rs9340799 A>G) (n=11)									
Modugno et al,[10] 2001	Caucasian	America	PB	Blood	PCR	82	237	Y	30
Suzuki et al,[11] 2003	Asian	Japan	PB	Blood	PCR	101	114	N	31
Fukatsu et al,[13] 2004	Asian	Japan	Mixed	Tissue	PCR	117	242	Y	31
Hernández et al,[14] 2006	Mixed	NA	Mixed	Blood	TaqMan	598	1,098	Y	31
Gupta et al,[20] 2010	Asian	India	HB	Blood	PCR	157	170	Y	31
Balistreri et al,[21] 2011	Caucasian	Sicily	NA	Tissue	TaqMan	50	47	Y	32
Sissung et al,[22] 2011	Caucasian	America	PB	Blood	PCR	129	127	Y	32
Szendroi et al,[23] 2011	Caucasian	Hungary	PB	Blood	PCR	205	101	Y	31
Safarinejad et al,[24] 2012	Asian	Iran	NA	Blood	PCR	162	324	N	32
Jurecekova et al,[25] 2013	Caucasian	Slovak	PB	Blood	PCR	311	256	Y	33
Pazarbasi et al,[26] 2013	Asian	Turkish	PB	Blood	PCR	34	28	Y	32

Notes: The study also used blood as testing sample. All cases came from hospital-based populations.
Abbreviations: SOC, source of controls; HWE, Hardy–Weinberg equilibrium (Y, HWE in controls; N, HWE out of controls); STREGA, Strengthening the Reporting of Genetic Association Studies; PB, population-based; PCR, polymerase chain reaction; NA, nonapplicable; HB, hospital-based.

P=0.03; homozygous model OR: 1.44, 95% CI: 1.17–1.76, *P*<0.01; Tables 4 and S6). Similarly, we performed a subgroup analyses based on ethnicity to derive a more accurate estimate, and the results showed that XbaI polymorphism was significantly correlated with an increased risk of prostate cancer in Caucasians (allele model OR: 1.31, 95% CI: 1.07–1.61, *P*<0.01; dominant model OR: 1.43, 95% CI: 1.07–1.92, *P*=0.01; recessive model OR: 1.36, 95% CI: 1.09–1.69, *P*<0.01; homozygous model OR: 1.48, 95% CI: 1.17–1.88, *P*<0.01; Tables 4 and S6), but not in Asians.

Sensitivity analysis suggested that individual studies did not affect pooled ORs (Figure S2). Begger's funnel plot and Egger's linear regression test did not show any statistical evidence of publication bias (Figure 2B). Moreover, we excluded two studies that deviated significantly from the HWE test, and the results showed that these two non-HWE studies had no effect on pooled ORs (Table 4).

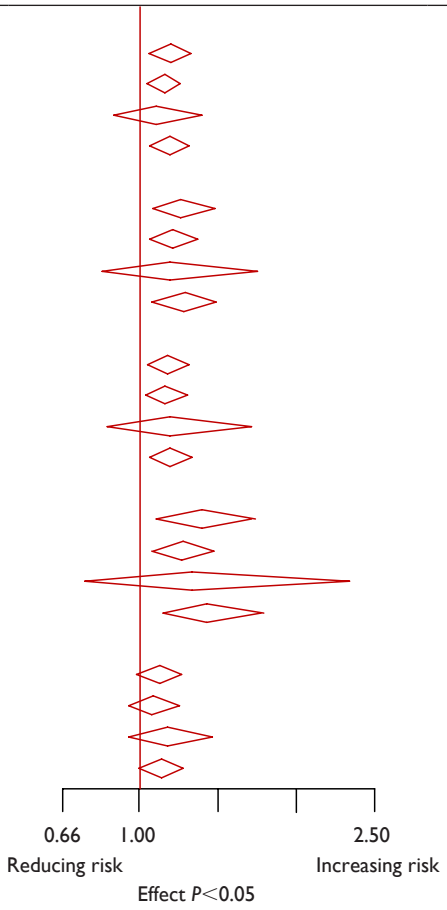
Discussion

The role of PSA as a biomarker in prostate cancer remains unsatisfactory, leading to considerable overdiagnoses and overtreatment. This study on novel biomarkers in prostate cancer represents a long-standing hotspot in biomedical research.[28] Since ERα is an important determinant of prostatic carcinogenesis,[3] various studies have focused on SNPs in the ERα gene to determine their possible associations with the prostate cancer susceptibility. In the current study, we chose two common SNPs in the ERα gene, PvuII (rs2234693 T>C) and XbaI (rs9340799 A>G), and conducted a meta-analysis to evaluate their associations with prostate cancer susceptibility.

To our knowledge, the present work represents the largest meta-analysis performed to estimate the association of ERα SNPs with the risk of prostate cancer. The results showed that both PvuII and XbaI polymorphisms were correlated with an increased risk of prostate cancer in Caucasians, but not in Asians, and this disparity might be attributable to discrepancies in racial backgrounds and geography.[14,29] Furthermore, there was a significant positive correlation of PvuII polymorphism and high Gleason grade cancers (Gleason score ≥7), which indicated its potential role in prostate cancer malignant transformation.

Table 2 Meta-analysis findings on the association between ERα PvuII (rs2234693 T>C) polymorphism and prostate cancer risk

Subgroup (size)	I^2	OR (95% CI)	*P*-value
Allele model (C vs T)			
Overall (n=20)	57.1%	1.16 (1.04–1.29)	<0.01
Caucasian (n=11)	37.8%	1.12 (1.03–1.21)	<0.01
Asian (n=8)	74.6%	1.09 (0.85–1.39)	0.50
HWE in controls (n=19)	56.7%	1.17 (1.05–1.30)	<0.01
Dominant model (TC + CC vs TT)			
Overall (n=20)	55.2%	1.24 (1.06–1.46)	0.01
Caucasian (n=11)	38.0%	1.19 (1.05–1.35)	<0.01
Asian (n=8)	73.3%	1.17 (0.79–1.73)	0.42
HWE in controls (n=19)	57.1%	1.25 (1.06–1.48)	<0.01
Recessive model (CC vs TT + TC)			
Overall (n=20)	38.1%	1.16 (1.04–1.30)	<0.01
Caucasian (n=11)	4.4%	1.13 (1.03–1.29)	0.04
Asian (n=8)	62.5%	1.17 (0.81–1.70)	0.13
HWE in controls (n=19)	33.1%	1.18 (1.05–1.31)	<0.01
Homozygous model (CC vs TT)			
Overall (n=20)	58.6%	1.37 (1.09–1.72)	<0.01
Caucasian (n=11)	29.5%	1.25 (1.06–1.46)	0.01
Asian (n=8)	77.2%	1.31 (0.73–2.33)	0.35
HWE in controls (n=19)	58.2%	1.41 (1.12–1.77)	<0.01
Heterozygous model (CC vs TC)			
Overall (n=20)	14.7%	1.11 (0.99–1.25)	0.07
Caucasian (n=11)	0.0%	1.07 (0.93–1.23)	0.29
Asian (n=8)	44.4%	1.16 (0.93–1.45)	0.17
HWE in controls (n=19)	3.5%	1.12 (1.00–1.26)	0.05

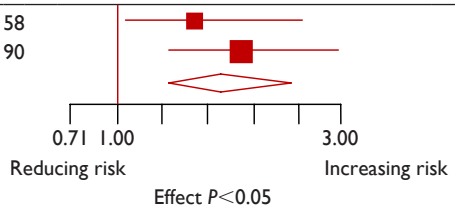


Notes: If I^2<50%, the fixed effects model was used. Otherwise, the random effects model was used.
Abbreviations: ERα, estrogen receptor α; OR, crude odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium.

Both PvuII and XbaI polymorphisms lie in intron 1 of the ERα gene, which is part of the A/B domain, the trans-activating factor 1. This domain is an important site for stimulating transcription from certain estrogen-responsive promoters.[25] Among the possible explanations as to how these intronic polymorphisms affected prostate cancer risk are that, 1) both polymorphisms may be in linkage disequilibrium with other unknown variants in the gene, which may affect the gene expression or function;[24,25,30] 2) the alteration of another unidentified gene was adjacent to the ERα gene;[30] and 3) intronic changes may have an impact on the expression of receptors by influencing the

Table 3 Subgroup analysis by Gleason score of the association between ERα *Pvu*II (rs2234693 T>C) polymorphism and prostate cancer risk under the allele model (T vs C)

Study (n=2)	Ethnicity	Gleason score				OR (95% CI)	Weight (%)
		≥7		<7			
		C	T	C	T		
Safarinejad et al,[24] 2012	Asian	150	58	90	58	1.67 (1.06–2.60)	41.09
Jurecekova et al,[25] 2013	Caucasian	299	133	98	90	2.07 (1.45–2.93)	58.91
Overall (I^2=0.0%)						**1.90 (1.44–2.50)**	**100**



Note: I^2<50%, the fixed effects model was used.
Abbreviations: ERα, estrogen receptor α; OR, crude odds ratio; CI, confidence interval.

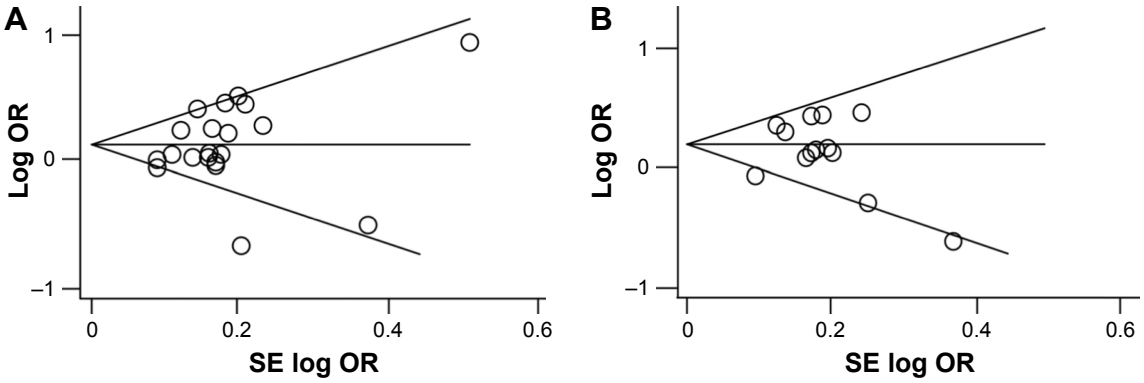
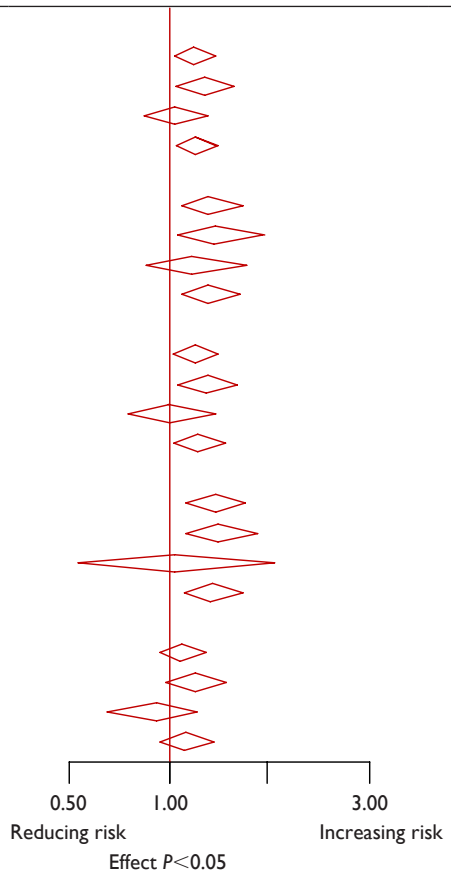


Figure 2 Begg's funnel plot for the publication bias test of the meta-analysis.
Notes: Each point represents a separate study for the indicated association. Horizontal line represents size of effect. (**A**) ERα PvuII polymorphism (t=1.07, P=0.30) and (**B**) ERα XbaI polymorphism (t=0.66, P=0.52).
Abbreviations: ERα, estrogen receptor α; OR, crude odds ratio; SE, standard error.

transcription through alternative splicing of the mRNA transcript.[24] Although the susceptibility of Caucasians to prostate cancer is known to be much higher than that of Asians, the underlying mechanism remains unknown.[28] Our findings demonstrated the different roles of two ERα SNPs in prostate cancer risk estimation between Caucasians and Asians, indicating the probability of inherited susceptibility to prostate cancer arising from different genomic ERα SNPs, which may help elucidate the pathogenesis of prostate cancer.

Table 4 Meta-analysis findings on the association between ERα *XbaI* (rs9340799 A>G) polymorphism and prostate cancer risk

Subgroup (size)	I^2	OR (95% CI)	*P*-value
Allele model (G vs A)			
Overall (n=13)	56.5%	1.23 (1.06–1.43)	<0.01
Caucasian (n=7)	64.5%	1.31 (1.07–1.61)	<0.01
Asian (n=5)	54.5%	1.05 (0.80–1.37)	0.70
HWE in controls (n=11)	56.6%	1.25 (1.06–1.47)	<0.01
Dominant model (AG + GG vs AA)			
Overall (n=13)	59.2%	1.38 (1.11–1.72)	<0.01
Caucasian (n=7)	65.5%	1.43 (1.07–1.92)	0.01
Asian (n=5)	58.1%	1.21 (0.82–1.79)	0.31
HWE in controls (n=11)	53.1%	1.37 (1.11–1.70)	<0.01
Recessive model (GG vs AA + AG)			
Overall (n=13)	6.0%	1.24 (1.03–1.49)	0.03
Caucasian (n=7)	0.0%	1.36 (1.09–1.69)	<0.01
Asian (n=5)	26.1%	1.00 (0.71–1.42)	0.79
HWE in controls (n=11)	10.5%	1.27 (1.04–1.55)	0.01
Homozygous model (GG vs AA)			
Overall (n=13)	43.5%	1.44 (1.17–1.76)	<0.01
Caucasian (n=7)	45.1%	1.48 (1.17–1.88)	<0.01
Asian (n=5)	59.6%	1.05 (0.52–2.09)	0.21
HWE in controls (n=11)	38.0%	1.40 (1.13–1.74)	<0.01
Heterozygous model (GG vs AG)			
Overall (n=13)	0.0%	1.11 (0.92–1.35)	0.25
Caucasian (n=7)	0.0%	1.24 (0.98–1.57)	0.06
Asian (n=5)	0.0%	0.90 (0.62–1.29)	0.57
HWE in controls (n=11)	0.0%	1.15 (0.92–1.42)	0.20



Notes: If I^2<50%, the fixed effects model was used. Otherwise, the random effects model was used.
Abbreviations: ERα, estrogen receptor α; OR, crude odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium.

Several limitations in this meta-analysis should be noted when interpreting our findings. First, the statistical power was still limited in the stratified analysis. Second, heterogeneity between studies was observed, although subgroup analyses were conducted to minimize the perturbation. Third, only published studies in English were included. Published studies in other languages, ongoing studies, and unpublished data were not obtained. Given these limitations, our conclusions should be interpreted cautiously.

Conclusion

In summary, the current meta-analysis demonstrates the different roles of ERα PvuII and XbaI polymorphisms in prostate cancer risk stratification between Caucasians and Asians, indicating the probability of inherited susceptibility to prostate cancer arising from different genomic ERα SNPs, a finding that may help elucidate the pathogenesis of prostate cancer in Caucasians.

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Author contributions

Yining Zhao, Xi Zheng, and Xiang Zhang conceived and designed the experiment; Yining Zhao performed the experiment; Lijie Zhang and Hua Jiang screened the studies; Lijie Zhang, Qiang Hu, and Xi Zheng extracted the data; Yining Zhao, Xi Zheng, and Shennan Shi performed the data analysis; and Yining Zhao and Xiang Zhang wrote the paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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