Systematic Review and Meta-Analysis

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ESR2 polymorphisms on prostate cancer risk

A systematic review and meta-analysis

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Abstract

Background: This meta-analysis was performed to address the association of 2 *ESR2* gene polymorphisms (rs1256049 and rs4986938) with susceptibility to cancer.

Methods: An extensive literature search for eligible candidate gene studies published before May 10, 2022, was conducted in PubMed, Medline, and Web of Science. The search strategy was as follows: (ESR2 OR ERβ OR ER beta OR estrogen receptor beta) AND (polymorphism OR mutation OR variation OR SNP OR genotype) AND (PCa OR PC OR prostate cancer). Potential sources of heterogeneity were sought out via trial sequential analysis, subgroup, and sensitivity analysis.

Results: Overall, a total of 10 articles involving 18,064 cases and 19,556 controls for 2 polymorphisms of the *ESR2* gene were enrolled. In the stratified analysis of rs1256049, we found that Caucasians might be correlated with an increased risk of prostate cancer (PCa), while less susceptibility was found in Asians. We observed that rs4986938 was not associated with PCa risk.

Conclusion: *ESR2* rs1256049 polymorphism is associated with a higher risk of PCa in the Caucasian population and a lower risk of PCa in the Asian population.

Abbreviations: CI = confidence interval, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, PCa = prostate cancer, TSA = trial sequential analysis.

Keywords: ESR2, estrogen receptor beta, meta-analysis, prostate cancer, SNP

1. Introduction

Prostate cancer (PCa) is the second most common tumor in males and the most common cancer-related male death cause.[1] According to the latest EUA clinical guidelines, the correlation between family history and ethnic background and the incidence rate of PCa indicates the genetic susceptibility of PCa. Genome-wide association studies have identified over 100 common susceptibility sites associated with (invasive) PCa risk.[2] It is estimated that up to 10% of cancer events are attributed to gene modification insertion.[3] PCa is known to be an androgen-dependent cancer.[4] Androgens play a fundamental role in the occurrence and development of PCa. In addition, the incidence of PCa increases significantly with age. However, there are many studies demonstrating that both total and bioavailable serum testosterone levels decline significantly with age.[5] Compared with testosterone, circulating estradiol declines less with age, resulting in an increased ratio of estradiol to testosterone.[6] Estrogen plays a pivotal role in the development and progression of PCa.[7,8] Estrogen exerts its biological effects through the estrogen receptor (ESR) mediated interaction. ESR mainly includes 2 isoforms, ESR1 and ESR2. Numerous studies have shown that genetic polymorphisms of the *ESR2* gene can affect ESR2 expression, which might affect cancer risk.[9,10]

The ESR2 gene is located on chromosome 14q23.1. The polymorphisms in the coding regions of *ESR2* may affect gene expression or transcriptional stability.[11] Christoforou et al reported that the loss of ESR2 expression may be a risk factor for PCa.[12] Several single nucleotide polymorphisms have been identified in the *ESR2* genes. The most widely studied polymorphisms in the *ESR2* gene are rs1256049 and rs4986938. *ESR2* rs1256049 is a synonymous variant located within the ligand binding domain at exon 5, which is also known as 1082G > A variant or RsaI G/A. *ESR2* rs4986938 represents a G > A transition in the 3'-untranslated region of exon 8 = which is also known as 1730G > A or AluI G/A. Numerous studies have investigated the association between *ESR2* rs1256049 = rs4986938 and PCas. Fu et al reported that *ESR2* rs1256049 was significantly associated with PCa in Caucasians.[13] Li et al found no

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significant association of *ESR2* rs4986938 with PCa risk.[14] However, the results of these reports were inconsistent. Recently, many studies have investigated the association between *ESR2* polymorphisms and the risk of PCa. Therefore, it is necessary to perform a meta-analysis to assess the influence of *ESR2* rs1256049, rs4986938 polymorphisms, and PCa susceptibility.

2. Methods

2.1. Literature search

Eligible publications were identified by searching PubMed, Medline, and Web of Science on the association between *ESR2* polymorphisms and the risk of PCa (up to May 10, 2022) with the following search terms (ESR2 OR ERβ OR ER beta OR estrogen receptor beta) AND (polymorphism OR mutation OR variation OR SNP OR genotype) AND (PCa OR PC OR prostate cancer). The language of enrolled studies was restricted to English. Two polymorphisms (rs1256049 and rs4986938) were enrolled for further investigation.

2.2. Inclusion criteria and exclusion criteria

Articles enrolled in our meta-analysis met the following inclusion criteria: case-control studies that evaluated the association between *ERS2* polymorphisms and PCa risk; publications focusing on population genetic polymorphisms; articles with sufficient genotype data to assess odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). The major exclusion criteria were: case-only studies, case reports, or reviews; studies without raw data for the *ESR2* genotype; combined with other influencing factors.

2.3. Data extraction

Two investigators (X.C. and Z.Y.) independently extracted the data according to the selection criteria listed above, and consensus for any controversy was achieved. The data from the eligible articles comprise the first author's name, year of publication, ethnicity, source of control, and number of cases and controls in *ESR2* genotypes. Ethnicity was categorized as "Mix," "African," "Caucasian" and "Asian."

2.4. Statistical analysis

We estimated the risk between the *ESR2* polymorphisms and PCa using summary ORs and the corresponding 95% CIs in allelic (B vs A), dominant (AB + BB vs AA), and recessive (BB vs AB + AA) models (A: wild allele; B: mutated allele). We assessed the heterogeneity between studies using the Cochrane *Q*-statistic test, and the inconsistency was quantified with the I^2 statistic. The pooled OR of studies with heterogeneity when $I^2 > 50\%$ or $P_Q \leq .1$ was calculated by the random effect model; otherwise, the fixed effects model was applied. Hardy–Weinberg equilibrium (HWE) was estimated by the asymptotic test, and deviation was considered when $P < .05$. Subgroup meta-analyses were performed by ethnicity, genotyping, source of control, and HWE. Sensitivity analysis was conducted to assess the stability of the results by omitting 1 study each time to exclude studies. The potential publication bias of the eligible studies was evaluated by Begg and Egger regression test quantitatively. Trial sequential analysis (TSA) was performed to minimize random errors and strengthen the robustness of our conclusions.[15] The data were analyzed using the Stata 14.0 software (version 14.0; State Corporation, College Station, TX). A 2-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Main characteristics of the enrolled studies

The study selection processes are presented in Figure 1. For polymorphisms of the *ESR2* gene (rs1256049 and rs4986938), a total of 10 articles (including 12 case-control studies) with 18,064 cases and 19,556 controls met the inclusion criteria.[16–25] Controls of 9 studies were population-based controls, and 10 studies were hospital-based controls. A total of 13 studies were compliant with HWE, and 6 studies were incompliant with HWE. Table 1 shows the characteristics of all the eligible studies and genotype frequency distributions of the 2 *ESR2* polymorphisms included in our meta-analysis. Newcastle–Ottawa scale was used to evaluate the quality of the enrolled studies, as shown in Table 2.

3.2. Quantitative synthesis

1.3.2. rs1256049. The pooled results based on 11 included studies (including 9:390 cases and 10:1058 controls) indicated that no significant association between rs1256049 polymorphism and PCa risk was found. However, in the stratification analysis by ethnicity, we observed that the Caucasian group was significantly related to an increased PCa risk in the allele contrast model (B vs A: OR = 1.15, 95% CI = 1.02–1.29, $P = .018$) and dominant model (AB + BB vs AA: OR = 1.14, 95% CI = 1.01–1.28, $P = .032$). However, the Asian group was significantly related to a reduced risk of cancer in the dominant model (AB + BB vs AA: OR = 0.80, 95% CI = 0.68–0.94, $P = .006$) (Table 3 and Fig. 2).

2.3.2. rs4986938. The pooled results based on 8 included studies (including 8:674 cases and 9:498 controls) indicated that rs4986938 was not significantly related to PCa risk in allelic contrast (B vs A: OR = .99, 95% CI = 0.89–1.10, $P = .826$) = dominant model (AB + BB vs AA: OR = 0.99, 95% CI = 0.78–1.26, $P = .945$) = and recessive model (BB vs AB + AA: OR = 0.99, 95% CI = 0.75–1.30, $P = .948$). Then = in the stratification analysis by ethnicity = genotyping = source of control and HWE = no significant association between rs4986938 polymorphism and PCa risk was discovered (Table 4 and Fig. 3).

3.3. Sensitivity analysis and publication bias

Sensitivity analysis was performed to evaluate the influence of each separate case-control study. The results showed that there was no material alteration in corresponding pooled ORs for rs1256049 and rs4986938 (Supplementary Figure S1, Supplemental Digital Content, http://links.lww.com/MD/J94). In addition, Begg test and Egger regression test were performed to evaluate the publication bias (Supplementary Table S1, Supplemental Digital Content, http://links.lww.com/MD/J95). No evidence of publication bias was identified (Supplementary Figure S2, Supplemental Digital Content, http://links.lww.com/MD/J96).

3.4. TSA

To evaluate random errors, we performed TSA. This analysis showed that the cumulative *z*-curve didn't cross the trial sequential monitoring boundary and the required information size, suggesting that more evidence is needed to verify the conclusions (Fig. 4).

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist is reported in Supplementary Table S2, Supplemental Digital Content, http://links.lww.com/MD/J97.

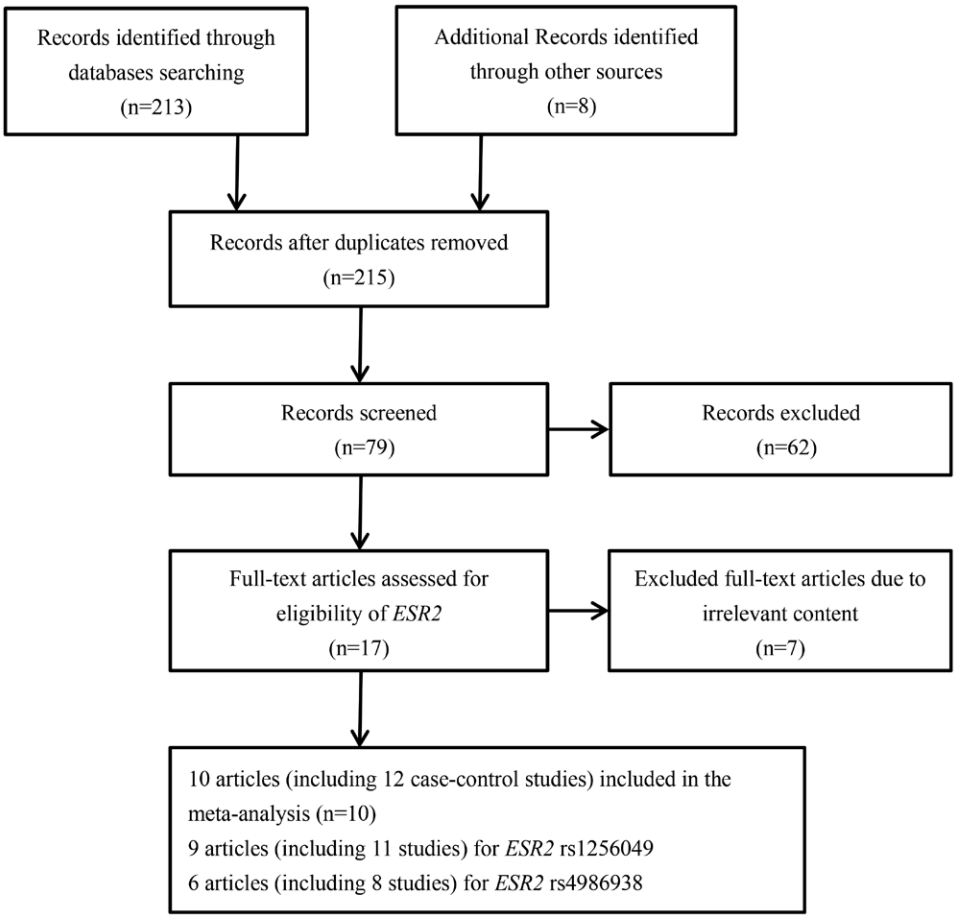

Figure 1. Flowchart of studies selection process for *ESR2* gene polymorphisms.

4. Discussion

PCa is a heterogeneous disease as evidenced by numerous factors contributing to its variable clinical progression.[26] Numerous studies have demonstrated that genetic mutations are a significant factor in the development of PCa, with BRCA genes being tumor suppressors involved in DNA repair, especially in the homologous recombination repair process of double-strand breaks. In a recent study by Nicolosi et al, the incidence of BRCA2 mutations in 620 PCa patients was 24.3%, and the incidence of BRCA lineage mutations was 6.4%.[27] Felice et al also indicated in their research that BRCA germline mutations have significant implications for the prognosis and treatment of PCa patients.[28]

PCa is hormone-dependent, and estrogen plays an important role in its pathological progression. Numerous studies reported that ERβ (encoded by ESR2) plays a protective role in PCa.[29–31] However, some studies have also suggested a negative role for ERβ in PCa progression.[32,33] These opposite results may be partly explained by the existence of different isomers of ERβ. ERβ1 is a tumor suppressor and is downregulated during PCa progression. ERβ2, on the other hand, promotes proliferation and is upregulated in PCa progression.[34] In recent years, liquid biopsy has become increasingly attractive and diagnostically valuable for the early detection of PCa, compared to transrectal prostatic biopsy. Some blood biomarkers can be used as indicators for diagnosis, prediction, and prognosis. Given that the detection of nucleotide polymorphism of ERβ in the blood can be used as a candidate biomarker for clinical diagnosis of PCa.[35]

In recent years, *ESR2* rs1256049 and rs4986938 polymorphisms have been extensively studied. The majority of published studies have investigated the association of *ESR2* rs1256049 and rs4986938 polymorphisms with PCa risk. Fu et al conducted a meta-analysis to assess the association between *ESR2* rs1256049 and PCa risk, revealing a higher risk of PCa only in Caucasians.[13] A meta-analysis performed by Li et al showed no significant association between *ESR2* rs4986938 polymorphism and PCa risk.[14] However, the combined results remained conflicting. Recently, more studies about this topic have been published. Therefore, it was necessary for us to perform a refined meta-analysis to accurately determine the association between *ESR2* rs1256049 and rs4986938 and PCa susceptibility.

In this study, a total of 10 articles including 12 case-control studies were enrolled to validate the association between the 2 *ESR2* gene polymorphisms (rs1256049 and rs4986938) and PCa risk. We assessed the association of *ESR2* rs1256049 and rs4986938 polymorphisms with PCa under 3 common models (allelic contrast, dominant model, and recessive model), however, no significant association was uncovered.

In subgroup meta-analysis stratified by ethnicity and HWE, we identified that rs1256049 was positively associated with PCa risk under allele contrast and dominant model. Interestingly, under the dominant model, rs1256049 was inversely associated with the risk of PCa in Asians and HWE disequilibrium subgroups. Fu et al reported that rs1256049 polymorphism was associated with PCa risk in Caucasians.[13] We included more studies and we discovered that rs1256049 polymorphism was inversely related to PCa risk in Asians. However, in the subgroup meta-analysis stratified by HWE, rs1256049 was also inversely associated with the risk of PCa in the HWE disequilibrium subgroup. To some extent, there might be some correlation between them. Therefore, we performed TSA to evaluate the sample size,

Table 1

Characteristics of eligible case-control studies included in the meta-analysis.

						Case			Control			
SNP	First author	Year	Ethnicity	Source of Control	Cancer Type	AA	AB	BB	AA	AB	BB	HWE
rs1256049	Chen-African	2007	African	PB	PCa	657	115	6	819	143	4	Y
	Chen-Caucasian	2007	Caucasian	PB	PCa	5442	488	16	6096	471	9	Y
	Chen-Asian	2007	Asian	PB	PCa	259	166	33	222	212	32	N
	Fukatsu	2004	Asian	HB	PCa	82	43	11	133	91	12	Y
	Jurecekova	2021	Caucasian	HB	PCa	460	47	3	166	18	0	Y
	Lu	2015	Asian	HB	PCa	185	142	25	167	146	39	Y
	Nicolaiew	2009	Caucasian	HB	PCa	88	8	0	89	7	0	Y
	Robles-Fernandez	2017	Caucasian	HB	PCa	139	17	0	141	14	0	Y
	Safarinejad	2012	Asian	PB	PCa	150	2	10	300	16	8	N
	Sonoda	2010	Asian	HB	PCa	96	75	9	93	77	7	Y
	Tang	2018	Caucasian	HB	PCa	576	40	0	485	41	0	Y
rs4986938	Chae	2009	Mix	PB	PCa	81	105	33	134	185	51	Y
	Chen-African	2007	African	PB	PCa	408	300	65	538	360	63	Y
	Chen-Caucasian	2007	Caucasian	PB	PCa	2274	2739	904	2481	3039	1031	N
	Chen-Asian	2007	Asian	PB	PCa	315	131	13	346	122	3	N
	Jurecekova	2021	Caucasian	HB	PCa	228	229	49	88	77	19	Y
	Lu	2015	Asian	HB	PCa	280	67	5	254	90	8	Y
	Nicolaiew	2009	Caucasian	HB	PCa	138	100	48	122	116	47	N
	Safarinejad	2012	Asian	PB	PCa	81	76	5	159	124	41	N

HB = hospital-based, HWE = Hardy–Weinberg equilibrium, N = no, PB = population-based, PCa = prostate cancer, SNP = single nucleic polymorphism, Y = yes.

Table 2

Methodological quality of the enrolled studies according to the Newcastle–Ottawa scale.

SNP	First author	Adequacy definition	Representativeness of the cases	Control selection	Control definition	Comparability cases/controls	Exposure ascertainment	Same method ascertainment	Nonresponse rate
rs1256049	Chen-African	*	*	*	*	**	*	*	*
	Chen-Caucasian	*	*	*	*	**	*	*	*
	Chen-Asian	*	*	*	*	**	*	*	*
	Fukatsu	*	*	NA	*	**	*	*	*
	Jurecekova	*	*	NA	*	**	*	*	*
	Lu	*	*	NA	*	**	*	*	*
	Nicolaiew	*	*	NA	*	**	*	*	*
	Robles-Fernandez	*	*	NA	*	**	*	*	*
	Safarinejad	*	*	*	*	**	*	*	*
	Sonoda	*	*	NA	*	**	*	*	*
	Tang	*	*	NA	*	**	*	*	*
rs4986938	Chae	*	*	*	*	**	*	*	*
	Chen-African	*	*	*	*	**	*	*	*
	Chen-Caucasian	*	*	*	*	**	*	*	*
	Chen-Asian	*	*	*	*	**	*	*	*
	Jurecekova	*	*	NA	*	**	*	*	*
	Lu	*	*	NA	*	**	*	*	*
	Nicolaiew	*	*	NA	*	**	*	*	*
	Safarinejad	*	*	*	*	**	*	*	*

A study can be awarded a maximum of 1 star for each numbered item within the selection and exposure categories. A maximum of 2 stars can be given for comparability.
NA = not applicable, SNP = single nucleic polymorphism.

which indicated that more evidence is needed to confirm these results. Despite the small sample size, we believe that rs1256049 might promote PCa susceptibility in Caucasians and reduce PCa susceptibility in Asians.

For *ESR2* rs4986938, subgroup meta-analysis stratified by ethnicity, genotyping, source of control, and HWE showed no association with cancer susceptibility in various models. Due to the small number of included studies, there will inevitably be a large bias. More case-control studies are needed for further evaluation.

In this study, we conducted a systematic review and meta-analysis to assess the association of PCa risk and *ESR2* polymorphisms. We then used Newcastle–Ottawa Scale to evaluate the quality of the included studies. In order to eliminate heterogeneity, subgroup analysis was performed.

Table 3

Meta-analysis of rs1256049.

Variables	n	Allele contrast		Dominant model		Recessive model	
		P, OR (99% CI)	*P* (*Q* test), I^2	*P*, OR (99% CI)	*P* (Q test), I^2	*P*, OR (99% CI)	*P* (*Q* test), I^2
Total	11	.856, 0.99 (0.87, 1.12)	.072, 41.6%	.428, 0.94 (0.82, 1.09)	.078, 40.6%	.300, 1.15 (0.88, 1.15)	.112, 40.0%
Ethnicity							
African	1	.707, 1.05 (0.82, 1.34)	NA	.847, 1.03 (0.79, 1.33)	NA	.334, 1.87 (0.53, 6.65)	NA
Caucasian	5	**.018, 1.15 (1.02, 1.29)**	**.659, 0.0%**	**.032, 1.14 (1.01, 1.28)**	**.648, 0.0%**	.081, 2.01 (0.92, 4.43)	.870, 0.0%
Asian	5	.110, 0.89 (0.77, 1.03)	.297, 18.5%	**.006, 0.80 (0.68, 0.94)**	**.678, 0.0%**	.843, 1.03 (0.77, 1.39)	.068, 54.2%
Genotyping							
TaqMan	7	.635, 0.96 (0.82, 1.13)	.015, 61.8%	.491, 0.94 (0.78, 1.13)	.013, 62.8%	.953, 1.01 (0.75, 1.36)	.128, 44.1%
PCR	3	.581, 1.08 (0.83, 1.40)	.558, 0.0%	.597, 0.92 (0.68, 1.25)	.874, 0.0%	**.024, 2.04 (1.10, 3.77)**	**.770, 0.0%**
DHPLC	1	.792, 1.15 (0.41, 3.23)	NA	.788, 1.16 (0.40, 3.32)	NA	NA	NA
Source of control							
PB	4	.688, 1.05 (0.84, 1.30)	.013, 72.1%	.791, 0.96 (0.73, 1.27)	.006, 75.9%	.050, 1.45 (1.00, 2.10)	.297, 18.6%
HB	7	.195, 0.91 (0.79, 1.05)	.817, 0.0%	.191, 0.89 (0.75, 1.06)	.937, 0.0%	.556, 0.89 (0.60, 1.32)	.179, 38.9%
HWE							
Y	9	.721, 1.02 (0.91, 1.15)	.249, 21.8%	.330, 1.05 (0.95, 1.16)	.416, 2.2%	.633, 1.09 (0.77, 1.53)	.126, 41.9%
N	2	.992, 1.00 (0.59, 1.69)	.069, 69.8%	**.011, 0.73 (0.57, 0.93)**	**.359, 0.0%**	.279, 1.28 (0.82, 1.99)	.100, 63.1%

CI = confidence interval, HB = hospital-based, OR = odds ratio, PB = population-based, PCR = polymerase chain reaction, DHPLC = denaturing high-performance liquid chromatography, HWE = Hardy–Weinberg equilibrium, N = no, n = number, NA = not applicable, Y = yes.

P < .05 was considered statistically significant.

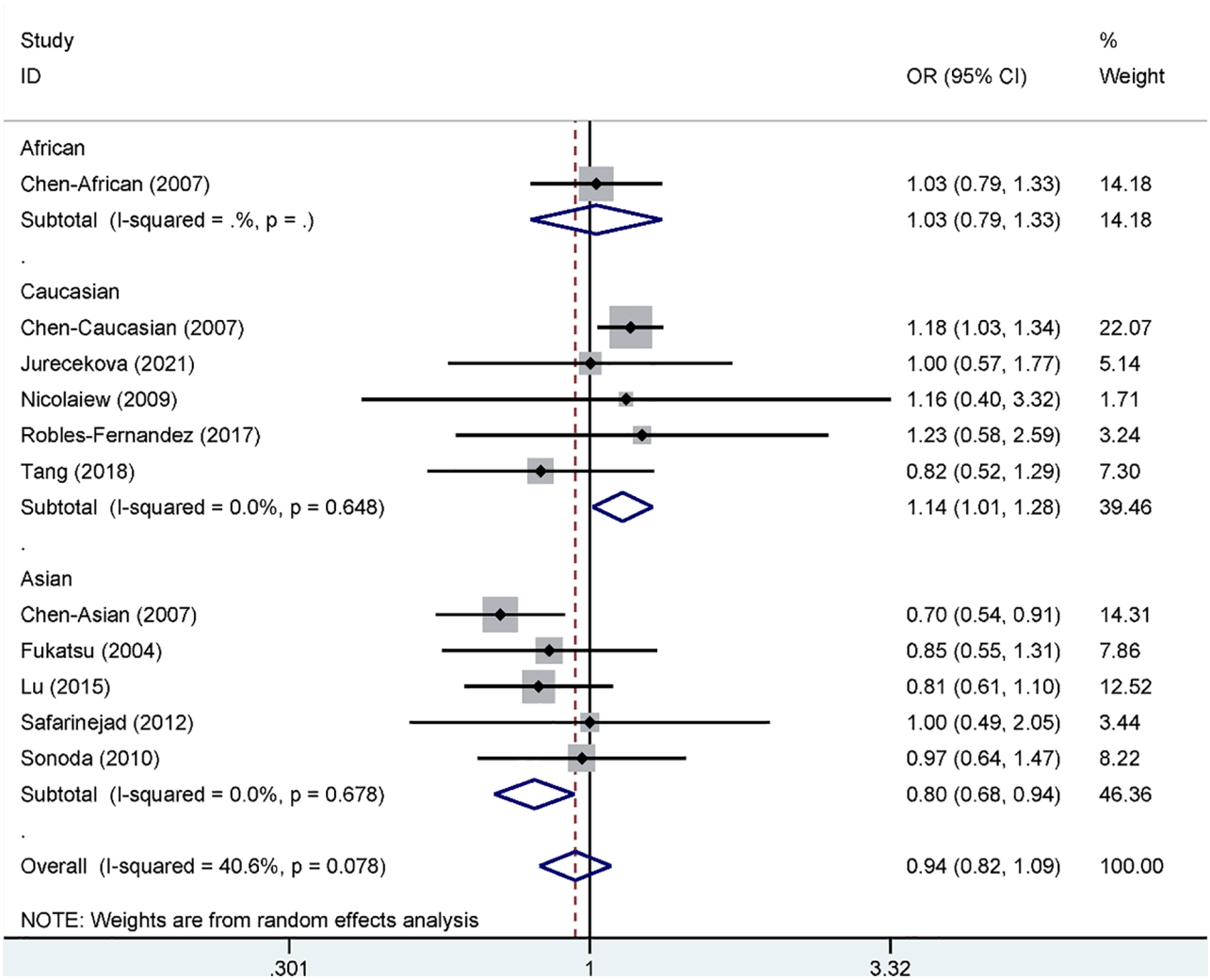

Figure 2. Forest plot of *ESR2* rs1256049 polymorphism and prostate cancer risk in dominant model stratified by ethnicity.

Sensitivity analysis was used to test the stability of the studies. TSA was conducted to evaluate the sample size. Egger and Begg tests were also used to evaluate publication bias. Despite our strict quality control, there are still some limitations. First, the small sample size of included studies limited the reliability. Second, we included studies published only in English, which

Table 4

Meta-analysis of rs4986938.

		Allele contrast		Dominant model		Recessive model	
Variables	**n**	***P*, OR (99% CI)**	***P* (*Q* test), I^2**	***P*, OR (99% CI)**	***P* (*Q* test), I^2**	***P*, OR (99% CI)**	***P* (*Q* test), I^2**
Total	8	.826, 0.99 (0.89, 1.10)	.020, 58.0%	.945, 0.99 (0.78, 1.26)	.055, 49.2%	.948, 0.99 (0.75, 1.30)	.009, 62.7%
Ethnicity							
Mix	1	.930, 1.01 (0.79, 1.29)	NA	.683, 0.90 (0.56, 1.47)	NA	.667, 1.11 (0.69, 1.78)	NA
African	1	.093, 1.14 (0.98, 1.32)	NA	.349, 0.84 (0.58, 1.22)	NA	.143, 1.31 (0.91, 1.88)	NA
Caucasian	3	.365, 0.98 (0.93, 1.03)	.661, 0.0%	.726, 1.02 (0.92, 1.12)	.800, 0.0%	.481, 0.97 (0.88, 1.06)	.962, 0.0%
Asian	3	.599, 0.90 (0.60, 1.34)	.003, 83.2%	.878, 1.13 (0.24, 5.27)	.004, 82.1%	.818, 0.82 (0.15, 4.48)	.001, 85.9%
Genotyping							
TaqMan	5	.745, 1.02 (0.89, 1.18)	.011, 69.5%	.519, 0.94 (0.76, 1.15)	.248, 26.1%	.412, 1.13 (0.84, 1.52)	.060, 55.8%
PCR	2	.538, 0.91 (0.68, 1.23)	.130, 56.5%	.281, 2.00 (0.57, 7.09)	.024, 80.3%	.312, 0.48 (0.11, 2.01)	.009, 85.4%
DHPLC	1	.363, 0.89 (0.70, 1.14)	NA	.616, 0.89 (0.56, 1.41)	NA	.925, 1.02 (0.66, 1.59)	NA
Source of control							
PB	5	.593, 1.03 (0.91, 1.17)	.030, 62.7%	.971, 0.99 (0.69, 1.44)	.010, 69.9%	.916, 1.02 (0.67, 1.56)	.001, 77.8%
HB	3	.256, 0.88 (0.71, 1.10)	.133, 50.5%	.952, 0.99 (0.70, 1.40)	.788, 0.0%	.747, 0.95 (0.68, 1.32)	.719, 0.0%
HWE							
Y	4	.883, 0.99 (0.82, 1.19)	.049, 61.7%	.532, 0.92 (0.71, 1.19)	.829, 0.0%	.346, 1.13 (0.88, 1.45)	.533, 0.0%
N	4	.798, 0.98 (0.83, 1.15)	.045, 62.7%	.852, 1.05 (0.61, 1.82)	.006, 75.7%	.777, 0.92 (0.51, 1.65)	.002, 80.3%

CI = confidence interval, DHPLC = denaturing high-performance liquid chromatography, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, PB = population-based, PCR = polymerase chain reaction, N = no, n = number, NA = not applicable, Y = yes.

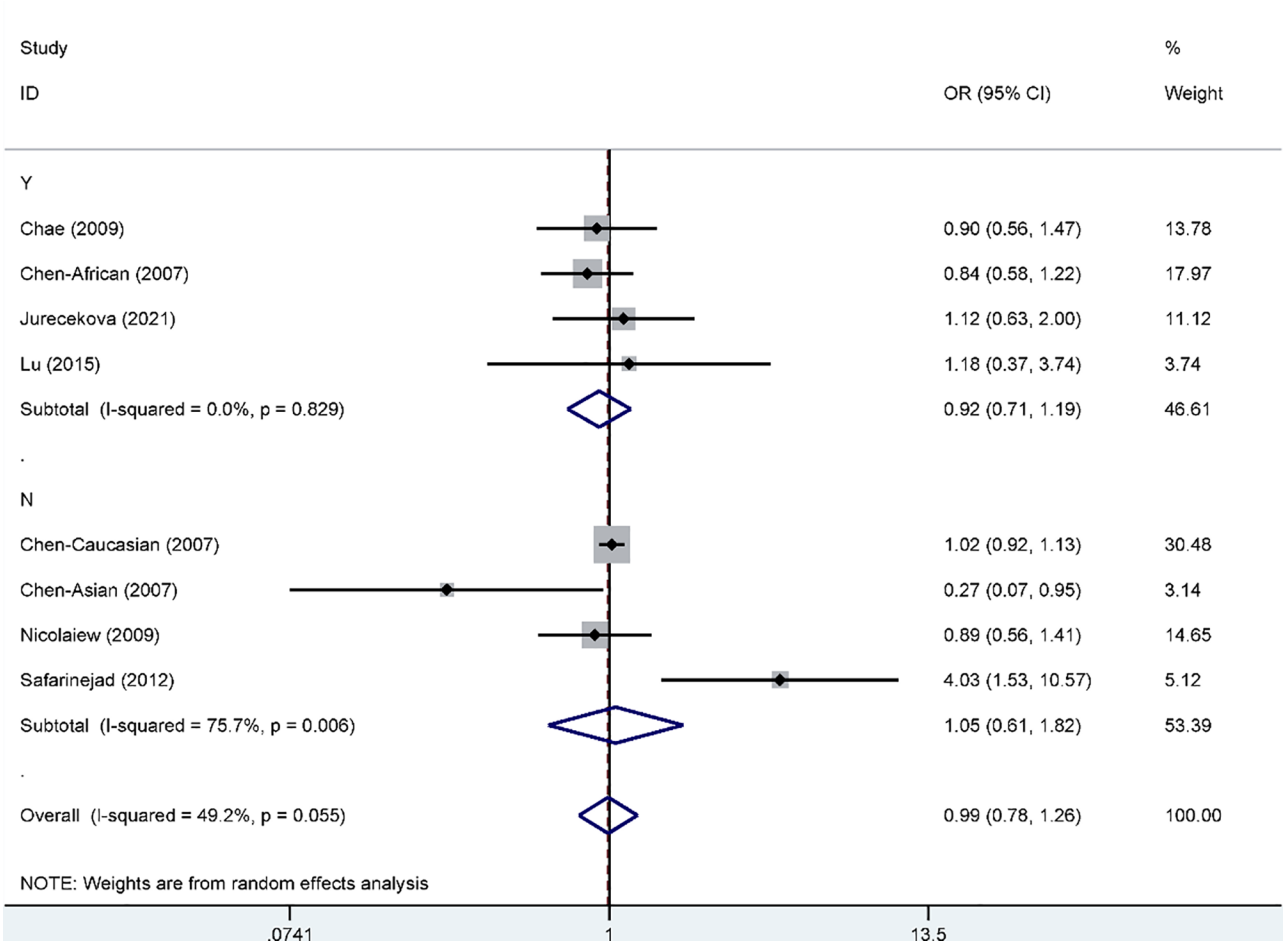

Figure 3. Forest plot of *ESR2* rs4986938 polymorphism and prostate cancer risk in dominant model stratified by HWE. HWE = Hardy–Weinberg equilibrium.

might be a reason for the small sample size. Third, we didn't assess the linkage disequilibrium. Fourth, we were unable to obtain enough data to assess the ERβ expression levels of *ESR2* rs1256049 and rs4986938. More large sample case-control studies are needed to investigate the functions of *ESR2* polymorphisms.

5. Conclusion

Our meta-analysis suggests that *ESR2* rs1256049 polymorphism is associated with a higher risk of PCa in the Caucasian population and a lower risk in the Asian population. Meanwhile, no significant association between *ESR2* rs4986938 polymorphism

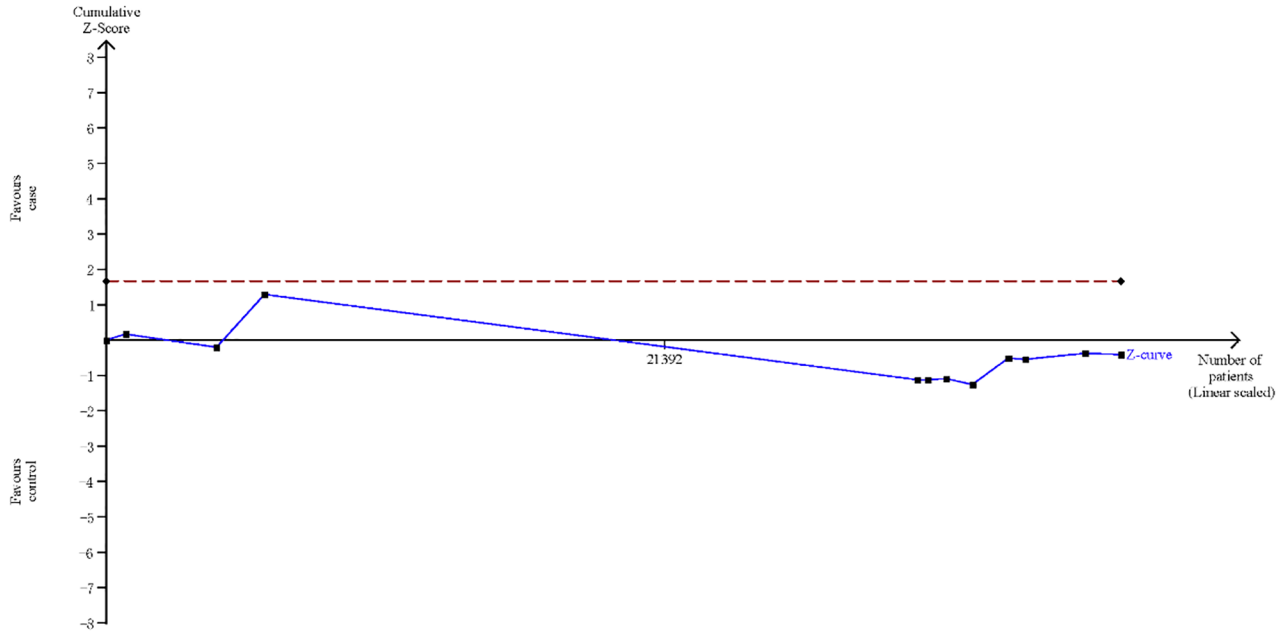

Figure 4. TSA for *ESR2* rs1256049 polymorphism under the allele contrast model. TSA = trial sequential analysis.

and PCa susceptibility was discovered. More case-control studies with larger sample sizes are needed to confirm these findings.

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Funding acquisition: Zhenwei Han.
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Software: Xueliang Chang, Hu Wang, Yaxuan Wang, Jingdong Li.
Visualization: Hu Wang, Jingdong Li.
Writing – original draft: Xueliang Chang.
Writing – review & editing: Zhan Yang.

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