RESEARCH ARTICLE

The influence of ESR1 rs9340799 and ESR2 rs1256049 polymorphisms on prostate cancer risk

Chenying Fu · Wen-Qi Dong · Ani Wang · Guozhen Qiu

Abstract Estrogen receptor 1 (ESR1) and estrogen receptor 2 (ESR2) may play a role in the development of prostate cancer. Many studies focused on ESR1 rs9340799 and ESR2 rs1256049 polymorphisms to explore associations with prostate cancer risk. These studies showed inconsistent and conflicting results. The aim of this meta-analysis was to investigate the pooled association of ESR1 rs9340799 and ESR2 rs1256049 polymorphisms with prostate cancer risk. A systematic literature search was conducted to identify related studies (up to February 2014) in several online databases including PubMed, Google Scholar, CNKI and Wanfang online libraries. A total of 16 eligible articles were enrolled in this updated meta-analysis. The result suggested that ESR1 rs9340799 polymorphism was significantly associated with prostate cancer in overall populations (GG+GA vs. AA: $P=0.002$; G vs. A: $P=0.004$), Caucasians (GG+GA vs. AA: $P=0.008$; G vs. A: $P=0.016$) and Africans (GG+GA vs. AA: $P=0.005$; G vs. A: $P=0.006$), but not in Asians (GG+GA vs. AA: $P=0.462$; G vs. A: $P=0.665$). The result also showed that there was a significant association between ESR2 rs1256049 polymorphism and prostate cancer in Caucasians (AA+AG vs. GG: $P=0.016$; A vs. G: $P=0.005$), but no association in overall populations (AA+AG vs. GG: $P=0.826$; A vs. G: $P=0.478$), Asians (AA+AG vs. GG: $P=0.177$; A vs. G: $P=0.703$) and Africans (AA+AG vs. GG: $P=0.847$; A vs. G: $P=0.707$). The cumulative meta-analysis and sensitivity analysis showed the results were robust. In conclusion, this meta-analysis indicated that ESR1 rs9340799 polymorphism was associated with prostate cancer risk in overall populations, Caucasians and Africans, while ESR2 rs1256049 polymorphism was associated with prostate cancer risk in Caucasians. However, the biological mechanisms need to be further investigated.

Keywords ESR · rs9340799 · rs1256049 · Polymorphism · Prostate cancer · Meta-analysis

Introduction

Prostate cancer, one of the most common medical problems in males, accounted for 10 % of cancer-related male deaths [1]. Like other complex diseases, prostate cancer is caused by many factors [2]. Hormonal factors are also considered to play a fundamental role in the pathogenesis of prostate cancer [3]. Estrogen as a kind of sex steroid hormone has been implicated in the stimulation of aberrant prostate growth, development and progression of prostate cancer [4, 5]. The direct effects of estrogens are mediated by estrogen receptor (ESR), which interacts with other cell-signaling pathways to influence cell behavior. There are two major ESR subtypes: ESR1 and ESR2, and their encoded genes are respectively located on chromosome 6q25.1 and chromosome 14q23.1 [6, 7]. There have been evidences to suggest that the genetic polymorphisms in ESR1 and ESR2 genes can cause transcription change or affect the stability of the transcript [8, 9], which may have an influence on the risk of prostate cancer. Several single nucleotide polymorphisms (SNPs) have been identified in ESR1 and ESR2 genes, but two common SNPs have showed significant effects on the expression and function of the receptor: one is ESR1 rs9340799 at intron 1 which is also

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known as –351A>G variant or *Xba*I A/G [8]; the other is ESR2 rs1256049 at exon 5 which is also known as 1082G>A variant or *Rsa*I G/A [9].

Lots of studies have been conducted in the last few years to evaluate the rs9340799 polymorphism on ESR1 and rs1256049 polymorphism on ESR2 and their association with prostate cancer. However, the results were inconsistent. A few studies initially discovered a significant association of ESR1 rs9340799 and ESR2 rs1256049 polymorphism with prostate cancer risk [10–17], but these results have not been replicated [18–25]. The meta-analysis on ESR1 rs9340799 polymorphism was first reported by Ding et al. [26] and then updated by Wang et al. [27]. However, it has been noticed that results of these two reports were inconsistent, due to different eligible studies they included. In addition, Gu et al. [28] recently performed a meta-analysis and concluded that ESR1 rs9340799 polymorphism increased the risk of prostate cancer only in Africans, but the appropriate genetic model was not chosen in this study. On the other hand, there was a lack of meta-analysis concerning the association between ESR2 rs1256049 polymorphism and prostate cancer risk.

In order to assess the influence of ESR1 rs9340799 and ESR2 rs1256049 polymorphisms on prostate cancer risk, a meta-analysis including 16 eligible articles was performed under the most appropriate genetic model and cumulative meta-analysis and sensitivity analysis were conducted to ensure the pooled results were robust.

Materials and methods

Search strategy and inclusion criteria

To identify all the published studies based on the association between ESR1 rs9340799 and ESR2 rs1256049 polymorphisms and the risk of prostate cancer, we performed a systematic literature search in PubMed, Google Scholar, CNKI and Wanfang online libraries (up to February 2014) using the terms "single nucleotide polymorphism or SNP or variants" and "Prostate cancer or carcinoma" and "ESR or ESR1 or ESR2 or estrogen receptor alpha or estrogen receptor beta." We also conducted a manual search of references identified in the retrieved articles to find other relevant studies.

We defined strict criteria for inclusion of studies: (a) studies evaluated ESR1 rs9340799 and ESR2 rs1256049 gene polymorphisms and prostate cancer risk; (b) the design of studies must be clinical case-control; (c) the numbers of the genotype or allele were reported in the article or could be obtained from authors or other source; (d) the study with the largest sample size or with the latest data was selected if overlapped publications existed. Accordingly, studies were excluded if any of the following conditions applied: (a) abstracts, reviews, conference reports; (b) insufficient data referring to genotype.

Data extraction

Two authors independently extracted all the data based on the inclusion criteria listed above. Any disagreement was subsequently resolved by discussing with a third author. The following data were extracted from each article: name of first author, year of publication, ethnicity of the population, sample size, genotype and allele distributions in prostate cancer cases and healthy controls.

Assessment of study quality

We assessed methodological quality according to the approach by Hu et al. [29] and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (www.cochrane.org). Three independent authors (C. Fu, W.Q. Dong and A. Wang) assessed the methodological quality of included studies, and disagreement was resolved by consensus and discussion.

Statistical analysis

Data management and analysis were performed using Stata (version 10.1, Stata Corp., College Station, TX, USA). Since included studies were retrospective and case-control studies, the association between ESR1 rs9340799, ESR2 rs1256049 polymorphism and risk of prostate cancer was measured by the odds ratio (OR) with 95 % confidence intervals (CI), which was according to methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions. The statistical significance of the summary OR was determined with the Z-test, a P value less than 0.05 was considered statistically significant. OR_1, OR_2 and OR_3 were calculated for the genotype: (1) GG vs. AA (OR_1), GA vs. AA (OR_2), and GG vs. GA (OR_3) for the ESR1 rs9340799 polymorphism; (2) AA vs. GG (OR_1), AG vs. GG (OR_2), and AA vs. AG (OR_3) for the ESR2 rs1256049 polymorphism. These pairwise differences were used to determine the most appropriate genetic model [30]: (a) If OR_1=OR_3≠1 (P_1<0.05 and P_3<0.05), and OR_2=1 (P_2>0.05), a recessive model is suggested. (b) If OR_1=OR_2≠1 (P_1<0.05 and P_2<0.05), and OR_3=1 (P_3>0.05), a dominant model is suggested. (c) If OR_2=1/OR_3≠1 and OR_1=1, an over dominant model is suggested. (d) If OR_1>OR_2>1 and OR_1>OR_3>1 (or OR_1<OR_2<1 and OR_1<OR_3<1), a codominant model is suggested. The Cochran's Q test and I^2 test were used to evaluate potential heterogeneity between studies [31, 32]. A P value less than 0.05 and values of I^2 more than 50 % were considered statistically significant. If there was a significant heterogeneity across the included studies, the random effect model was used [33]. To explore the source of the heterogeneity and evaluate the ethnic-specific effects, subgroup analyses were performed by ethnicity. To access the stability of pooled results,
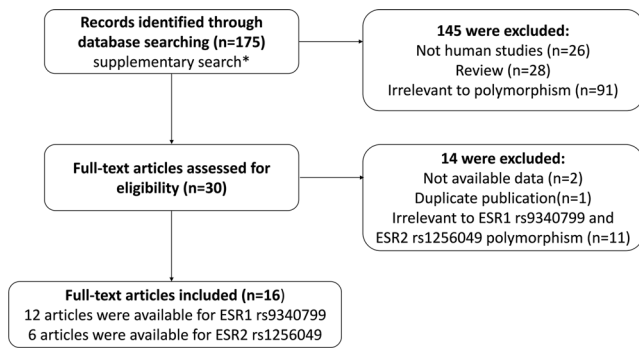
Fig. 1 The flow chart of literature search and study selection (*Supplementary search includes reference lists and corresponding authors)

sensitivity analyses were performed by removing one study each time. Cumulative meta-analysis was initially performed by date of publications to evaluate the trend of pooled results as studies accumulated over time [34]. Begg's test [35] was applied to evaluate the evidence for publication bias, a P value less than 0.05 was considered statistically significant. If publication bias existed, the Duval and Tweedie nonparametric "trim and fill" method was used to adjust for it [36]. Hardy–Weinberg equilibrium (HWE) was evaluated by using chi-square test in case and control groups for each study [37]. P values less than 0.05 was considered significant departure from HWE.

Table 1 Main characteristics of all eligible studies

Study	Distribution of genotypes						Frequency of alleles				HWE[a] tests		Sample size	Ethnicity
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	P value[b]	P value[c]	Case/ Control	
ESR1 rs9340799	GG		GA		AA		G		A					
Modugno 2001	10	28	38	93	34	116	58	106	149	325	1.000	0.175	82/237	Caucasian
Suzuki 2003	5	9	24	30	72	75	34	48	168	180	0.152	0.147	101/114	Asian
Fukatsa 2004	6	11	37	68	74	163	49	90	185	394	0.583	0.286	117/242	Asian
Hernandez(a) 2006	13	31	51	119	56	153	77	181	163	425	0.834	0.274	120/303	Caucasian
Hernandez(b) 2006	58	72	191	281	182	229	307	425	555	739	0.528	0.371	431/582	Caucasian
Hernandez(c) 2006	5	19	25	77	17	117	35	115	59	311	0.532	0.226	47/213	African
Cunningham 2007	121	71	417	227	380	189	659	369	1,177	605	0.720	0.847	918/487	Caucasian
Beuten(a) 2009	9	13	36	78	37	118	54	104	110	314	1.000	1.000	82/209	African
Beuten(b) 2009	20	59	84	88	91	224	124	206	266	536	0.924	1.000	195/371	Caucasian
Beuten(c) 2009	74	115	277	393	258	335	425	623	793	1,063	1.000	1.000	609/843	Caucasian
Gupta 2010	11	11	75	72	71	87	97	94	217	246	0.190	0.565	157/170	Asian
Sissung 2010	18	8	69	61	42	58	105	77	153	177	0.275	0.146	129/127	Caucasian
Balistreri 2011	3	1	13	4	34	42	19	6	81	88	0.347	0.156	50/47	Caucasian
Szendroi 2011	59	18	111	54	35	29	229	90	181	112	0.202	0.545	205/101	Caucasian
Safarinejad 2012	34	56	108	187	20	81	176	299	148	349	0.007	0.005	162/324	Caucasian
Jurecekova 2013	56	32	145	105	110	119	257	169	365	343	0.485	0.259	311/256	Caucasian
ESR2 rs1256049	AA		AG		GG		A		G					
Fukatsu 2004	11	12	43	91	82	133	65	115	207	357	0.154	0.596	136/236	Asian
Sun 2005	9	11	16	35	15	40	34	57	46	115	0.330	0.468	40/86	Asian
Chen(a) 2007	6	4	115	143	657	819	127	151	1429	1781	0.632	0.507	778/966	African
Chen(b) 2007	33	32	166	212	259	222	232	276	684	656	0.387	0.059	458/466	Asian
Chen(c) 2007	16	9	488	471	5442	6,096	520	489	11,372	12,663	0.160	1.000	5,946/6,576	Caucasian
Nicolaiew 2009	0	0	8	7	88	89	8	7	184	185	1.000	1.000	96/96	Caucasian
Sonoda 2010	9	7	75	77	96	93	93	91	267	263	0.329	0.078	180/177	Asian
Safarinejad 2012	10	8	2	16	150	300	22	32	302	616	0.162	0.364	162/324	Caucasian

[a] Hardy–Weinberg equilibrium

[b] For case

[c] For control

Results

Characteristics of included studies

The flow chart in Fig. 1 summarized the literature review process. A total of 16 eligible articles met the inclusion criteria and were included in this meta-analysis [10–25]. Specifically, 16 studies were selected from 12 articles [10–16, 18–22] on ESR1 rs9340799 polymorphism and eight studies were selected from six

articles [14, 17, 20, 23–25] on ESR2 rs1256049 polymorphism. The criteria that covered the representativeness of cases and controls, the ascertainment of cases and controls, genotyping examination, and association assessment, indicated the methodological quality of included studies was generally good. Main characteristics of the eligible studies were showed in Table 1. Studies on ESR1 rs9340799 enrolled 3,716 cases and 4,626 controls, including 11 Caucasian studies, three Asian studies and two African studies. Comparatively, studies

Table 2 Meta-analysis of the association between ESR1 rs9340799, ESR2 rs1256049 polymorphism and prostate cancer risk

| Comparisons	Studies no.	Ethnics	OR (95 % CI)	P value[a]	I^2 (%)[b]	P value[b]	P value[c]
ESR1 rs9340799							
GG vs. AA	16	All	1.31 (1.03, 1.68)	0.029	53.3 %	0.006	0.065
Codominant model	11	Caucasian	1.33 (0.99, 1.78)	0.057	64.4 %	0.002	0.079
	3	Asian	1.00 (0.56, 1.79)	0.994	0.0 %	0.547	0.296
	2	African	2.04 (1.00, 4.14)	0.050	0.0 %	0.788	1.000
GG+GA vs. AA	16	All	1.34 (1.11, 1.60)	0.002	68.8 %	0.000	0.032
Dominant model	11	Caucasian	1.36 (1.09, 1.71)	0.008	75.7 %	0.000	0.020
	3	Asian	1.11 (0.84, 1.47)	0.462	0.0 %	0.376	0.296
	2	African	1.78 (1.19, 2.66)	0.005	0.0 %	0.464	1.000
GG vs. GA+AA	16	All	1.11 (0.93, 1.31)	0.254	24.9 %	0.173	0.282
Recessive model	11	Caucasian	1.11 (0.90, 1.37)	0.320	42.7 %	0.065	0.213
	3	Asian	0.95 (0.54, 1.68)	0.862	0.0 %	0.665	1.000
	2	African	1.55 (0.79, 3.06)	0.203	0.0 %	0.543	1.000
G vs. A	16	All	1.20 (1.06, 1.35)	0.004	63.4 %	0.000	0.115
Allele model	11	Caucasian	1.20 (1.03, 1.38)	0.016	70.4 %	0.000	0.109
	3	Asian	1.06 (0.83, 1.35)	0.665	14.5 %	0.310	0.296
	2	African	1.53 (1.13, 2.07)	0.006	0.0 %	0.800	1.000
ESR2 rs1256049							
AA vs. GG	7	All	1.41 (1.02, 1.94)	0.035	1.8 %	0.411	0.764
Codominant model	2	Caucasian	2.19 (1.18, 4.08)	0.013	0.0 %	0.722	0.855
	4	Asian	1.15 (0.79, 1.68)	0.468	0.0 %	0.432	0.308
	1	African	1.87 (0.53, 6.65)	0.334	No data	No data	No data
AA+AG vs. GG	8	All	0.98 (0.82, 1.18)	0.826	50.7 %	0.048	0.569
Dominant model	3	Caucasian	1.17 (1.03, 1.33)	0.016	0.0 %	0.910	1.000
	4	Asian	0.85 (0.66, 1.08)	0.177	28.7 %	0.240	0.308
	1	African	1.03 (0.79, 1.33)	0.847	No data	No data	No data
AA vs. AG+GG	7	All	1.50 (1.11, 2.04)	0.009	0.0 %	0.654	1.000
Recessive model	2	Caucasian	2.22 (1.19, 4.12)	0.012	0.0 %	0.664	1.000
	4	Asian	1.29 (0.89, 1.86)	0.180	0.0 %	0.642	0.734
	1	African	1.87 (0.53, 6.65)	0.334	No data	No data	No data
A vs. G	8	All	1.05 (0.91, 1.22)	0.478	44.4 %	0.083	0.902
Allele model	3	Caucasian	1.19 (1.06, 1.35)	0.005	0.0 %	0.844	1.000
	4	Asian	0.96 (0.78, 1.19)	0.703	39.9 %	0.173	0.308
	1	African	1.05 (0.82, 1.34)	0.707	No data	No data	No data

[a] Z-test

[b] Heterogeneity test

[c] Begg's test

on ESR2 rs1256049 enrolled 7,796 cases and 8,927 controls, including three Caucasian studies, four Asian studies and one African study. All identified studies showed no deviation from HWE (P>0.05) except for one study [14]. The results of the meta-analysis are summarized in Table 2.

Association between ESR1 rs9340799 polymorphism and risk of prostate cancer

The estimated OR$_1$, OR$_2$ and OR$_3$ of ESR1 rs9340799 polymorphism for overall populations were 1.31 (95 % CI 1.03–1.68, P=0.029), 1.35 (95 % CI 1.11–1.63, P=0.002), 1.00

Fig. 2 Summary odds ratio (*OR*) for the association between ESR1 rs9340799 polymorphism and prostate cancer risk (*upper panel*, based on GG+GA vs. AA; *lower panel*, based on G vs. A). A random-effects model was used for all analyses. *Horizontal lines* represent 95 % confidence intervals (*CIs*). *Boxes* represent the OR in each study, with the size of each box is proportional to the weight of each study. *Diamonds* represent summary effects with corresponding 95 % CIs
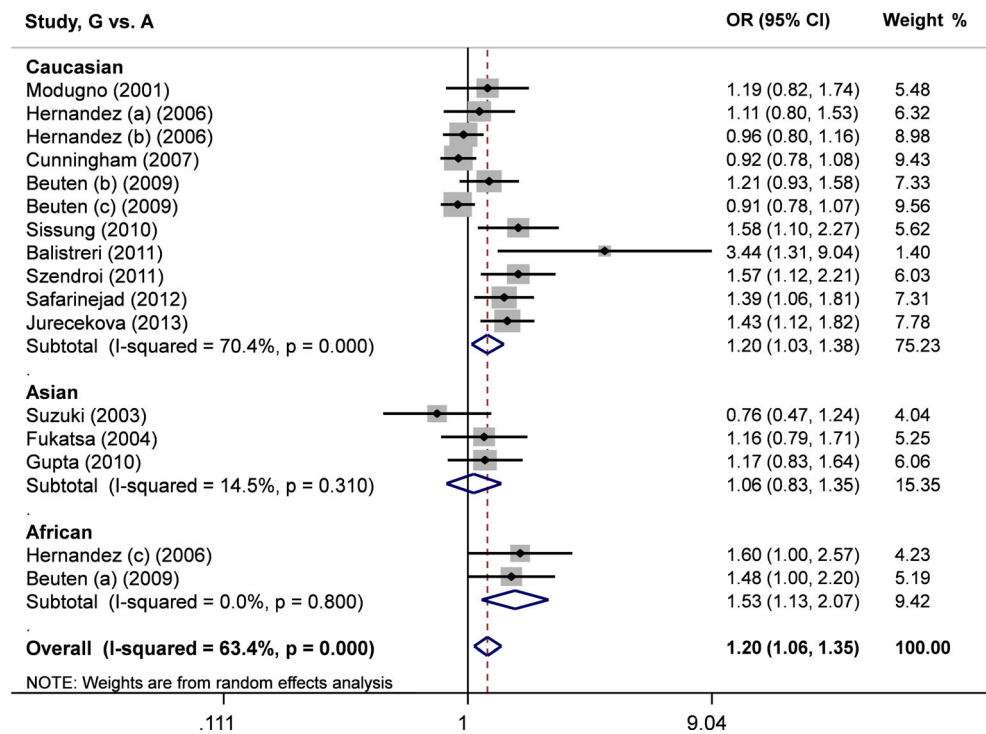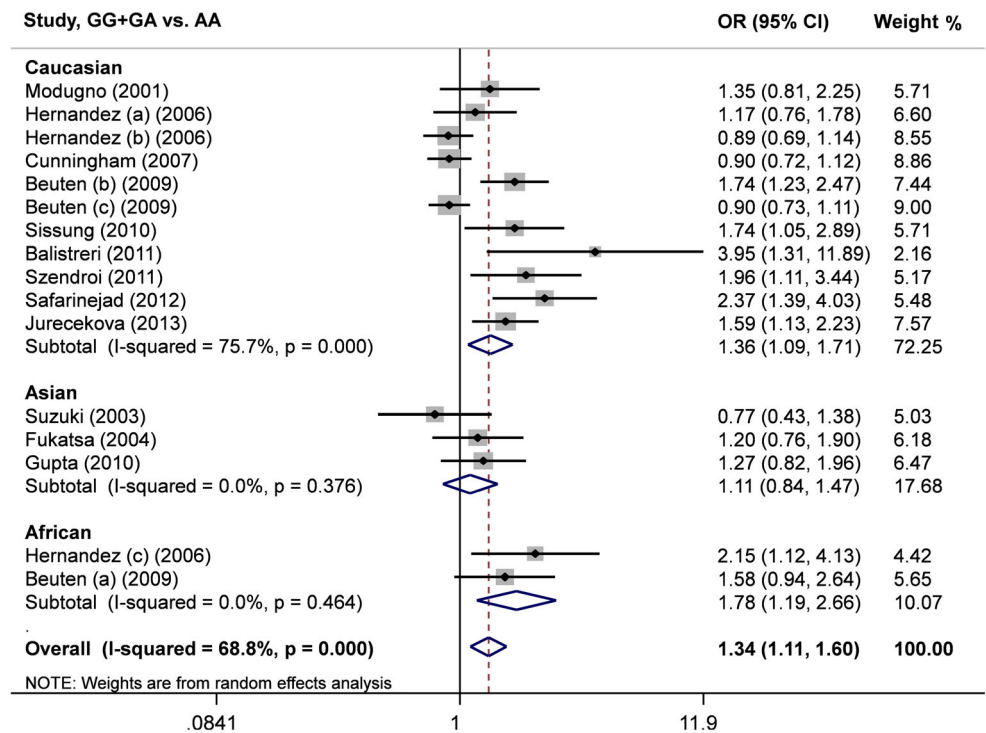
Fig. 3 Funnel plots with and without "trim and fill" method: **a** (without trim and fill) and **b** (with trim and fill) for the association of ESR1 rs9340799 polymorphism with prostate cancer risk in Caucasians. *Circles* represent individual studies
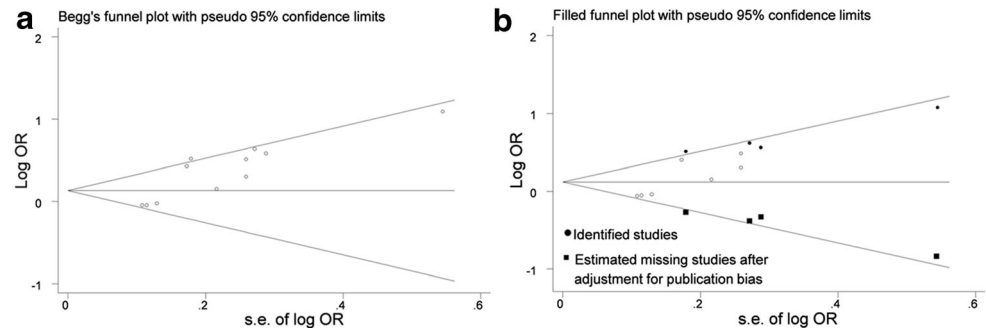
(95 % CI 0.83–1.19, *P*=0.963), respectively. These estimates suggested a dominant model (GG+GA vs. AA) was the best fit. The pooled meta-analysis result showed an increased risk of prostate cancer among G carriers (GG and GA) as compared with AA (OR=1.34, 95 % CI: 1.11–1.60, *P*=0.002) (Fig. 2). However, publication bias might exist from Begg's test (*P*=0.032; Table 2). This might be caused by overall populations with high OR estimates. Subgroup analysis was further performed by Ethnicity (Fig. 2). Unexpectedly, the risk of prostate cancer was significantly higher among G carriers in Caucasians (OR=1.36, 95 % CI 1.09–1.71, *P*=0.008) and Africans (OR=1.78, 95 % CI 1.19–2.66, *P*=0.005) but not in Asians (OR=1.11, 95 % CI 0.84–1.47, *P*=0.462). With regard to the subgroup of Caucasians, Begg's test suggested the possibility of publication bias (*P*=0.020; Table 2) and visual inspection of the funnel plot revealed asymmetry (Fig. 3a). We took an adjustment for the likely effect of bias using "trim and fill" method, which imputes four hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry. The imputed studies gave a symmetrical funnel plot (Fig. 3b) and showed a pooled OR of 1.29 (95 % CI 1.04–2.48, *P*=0.015), which was only a slight change from our estimate of 1.36.

The association between ESR1 rs9340799 polymorphism and risk of prostate cancer was also reported under allele model (G vs. A). It showed the same pattern of results as that under dominant model (Fig. 2), which suggested a significant
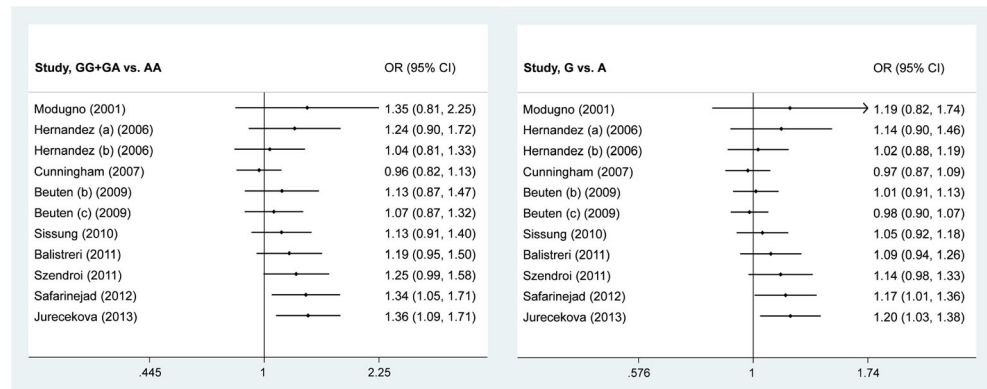
association between allele G and prostate cancer risk in overall populations (OR=1.20, 95 % CI 1.06–1.35, *P*=0.004), Caucasians (OR=1.20, 95 % CI 1.03–1.38, *P*=0.016), Africans (OR=1.53, 95 % CI 1.13–2.07, *P*=0.006), and a null association in Asians (OR=1.06, 95 % CI 0.83–1.35, *P*=0.665). No publication bias was indicated here (Table 2).

In the cumulative meta-analysis for Caucasians, the evidence was observed to support a significant association of ESR1 rs9340799 polymorphism with prostate cancer risk under the dominant and allele model (Fig. 4). As shown in Fig. 5, sensitivity analysis did not influence the results, which were stable and statistically robust.

Association between ESR2 rs1256049 polymorphism and risk of prostate cancer

The estimated OR_1, OR_2 and OR_3 of ESR2 rs1256049 polymorphism for overall populations were 1.41 (95 % CI 1.02–1.91, *P*=0.035), 1.29 (95 % CI 1.13–1.54, *P*=0.018), 1.37 (95 % CI 0.91–2.02, *P*=0.414), respectively. These estimates also suggested a dominant model (AA+AG vs. GG) was the best fit. As shown in Fig. 6, no significant association was detected between A carriers (AA and AG) and the risk of prostate cancer in overall populations (OR=0.98, 95 % CI 0.82–1.18, *P*=0.826). However, in the stratified analysis by ethnicity, a statistically significant association was found in Caucasians (OR=1.17, 95 % CI 1.03–1.33, *P*=0.016) but was

Fig. 4 Cumulative meta-analysis of association between ESR1 rs9340799 polymorphism and prostate cancer risk in Caucasians (*left panel*, based on GG+GA vs. AA; *right panel*, based on G vs. A)

Fig. 5 Sensitivity analysis of association between ESR1 rs9340799 polymorphism and prostate cancer risk in Caucasians (*left panel*, based on GG+GA vs. AA; *right panel*, based on G vs. A)
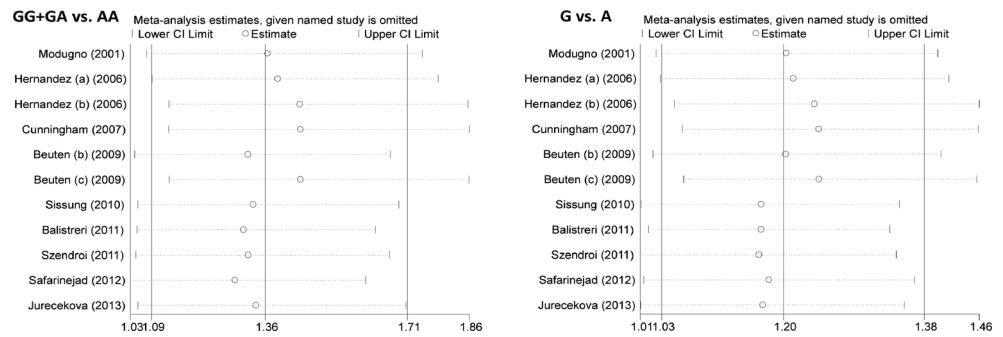
not observed in Asians (OR=0.85, 95 % CI 0.66–1.08, *P*=0.177) and Africans (OR=1.03, 95 % CI 0.79–1.33, *P*=0.847).

Similar results were observed under allele model (A vs. G) (Fig. 6), which revealed that allele A was a risk factor for prostate cancer in Caucasians (OR=1.19, 95 % CI 1.06–1.35, *P*=0.005), and there was no association between allele A and prostate cancer risk in overall populations (OR=1.05, 95 % CI 0.91–1.22, *P*=0.478), Asians (OR=0.96, 95 % CI 0.78–1.19, *P*=0.703) and Africans (OR=1.05, 95 % CI 0.82–1.34, *P*=0.707).

There was no evidence of publication bias in dominant and allele model according to the results of Begg's test (Table 2).

Discussion

Estrogens have significant direct and indirect effects on aberrant prostate growth, development and progression of prostate cancer, in which ESR1 and ESR2 are two key factors [4, 5]. ESR1 as an oncogenic factor promotes cell proliferation and survival, whereas ESR2 is a protective factor that is anti-carcinogenic and proapoptotic [38, 39]. It is known that the genetic polymorphisms in ESR1 and ESR2 genes can cause transcription change or affect the stability of the transcript [8, 9]. Thus, polymorphisms of ESR1 gene located on chromosome 6 [6] and ESR2 gene located on chromosome 14 [7] may be a risk factor for prostate cancer.

In recent years, there were several ESR1 and ESR2 gene polymorphisms that had been identified as candidates for prostate cancer research. Moreover, ESR1 rs9340799 and ESR2 rs1256049 polymorphisms had been extensively studied. Since the first study [18] reported the association between ESR1 rs9340799 polymorphism and prostate cancer in 2001, many subsequent studies have showed inconsistent results [10–16, 19–21]. There were three meta-analysis studies attempting to get conclusive results on the association of ESR1 rs9340799 polymorphism with prostate cancer risk [26–28], but they failed. Obviously, the combined results remained conflicting, which might be caused by that different

number of eligible studies were enrolled and the most appropriate genetic model was not used to evaluate the association between ESR1 rs9340799 polymorphism and prostate cancer. In fact, the results can be misleading when an inappropriate model was assumed [40]. For the ESR2 rs1256049 polymorphism, there were also many studies reporting inconsistent results [14, 17, 20, 23–25], but no meta-analysis had been performed to analyze the combined results.

Therefore, it was essential for us to perform a refined meta-analysis choosing the most appropriate genetic model and including all relevant studies. In this study, a total of 16 studies pertained to ESR1 rs9340799 polymorphism, which enrolled 3,716 cases and 4,626 controls, and eight studies involved ESR2 rs1256049 polymorphism, which enrolled 7,796 cases and 8,927 controls. We used a "model free" approach to show the most appropriate genetic model. For ESR1 rs9340799 polymorphism, a dominant model (GG+GA vs. AA) was suggested. The results showed that G carriers (GG and GA) had increased prostate cancer risk compared with AA. In the subgroup analysis by ethnicity, the significant association was observed in Caucasians and Africans, but not in Asians. It is possible that different genetic backgrounds may account for these differences. However, there was still significant heterogeneity in Caucasians that might influence the results. We then conducted the cumulative meta-analysis and sensitivity analysis which suggested high stability and reliability of our results. When the association between ESR1 rs9340799 polymorphism and risk of prostate cancer was reported under allele model (G vs. A), it showed the same pattern of results as that under dominant model. For ESR2 rs1256049 polymorphism, a dominant model (AA+AG vs. GG) was also suggested. There was no significant association between A carriers (AA and AG) and prostate cancer risk. When stratified analysis was performed by ethnicity, significant association was found in Caucasians, but not in Asians and Africans. Similar results were observed under an allele model (A vs. G). The implications of ESR1 rs9340799 and ESR2 rs1256049 polymorphisms have not been elucidated. The ESR1 rs9340799 polymorphism is located at intron 1, which is an enhancer region. This intronic polymorphism may

Fig. 6 Summary odds ratio (*OR*) for the association between ESR2 rs1256049 polymorphism and prostate cancer risk (*upper panel*, based on AA+AG vs. GG; *lower panel*, based on A vs. G). A random-effects model was used for all analyses. *Horizontal lines* represent 95 % confidence intervals (*CIs*). *Boxes* represent the OR in each study, with the size of each box is proportional to the weight of each study. *Diamonds* represent summary effects with corresponding 95 % CIs
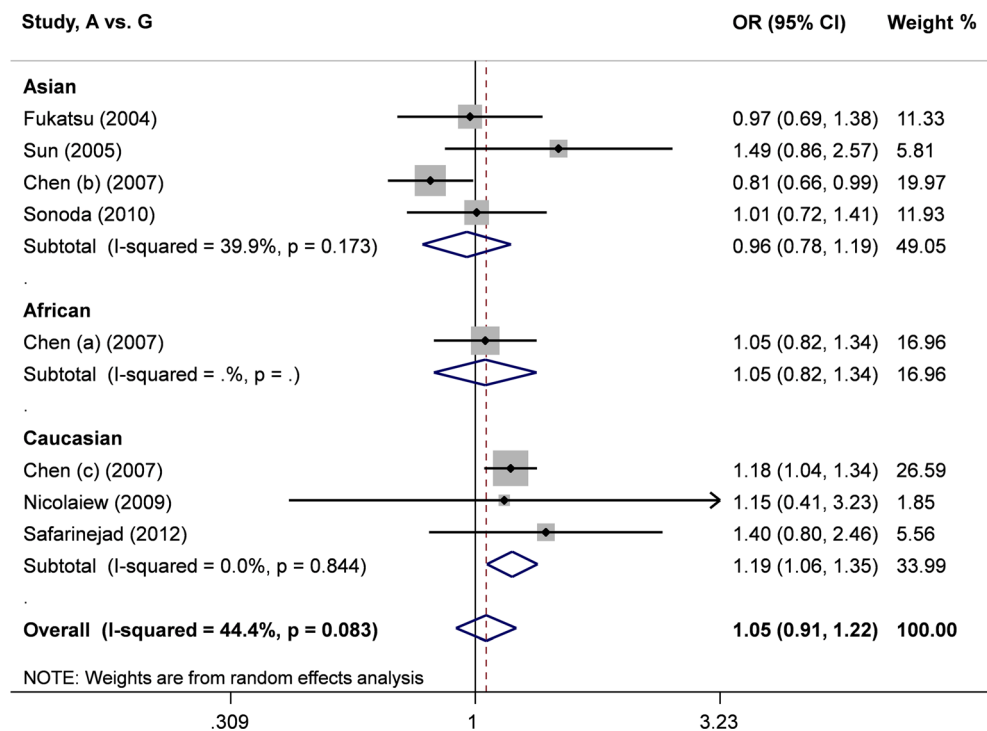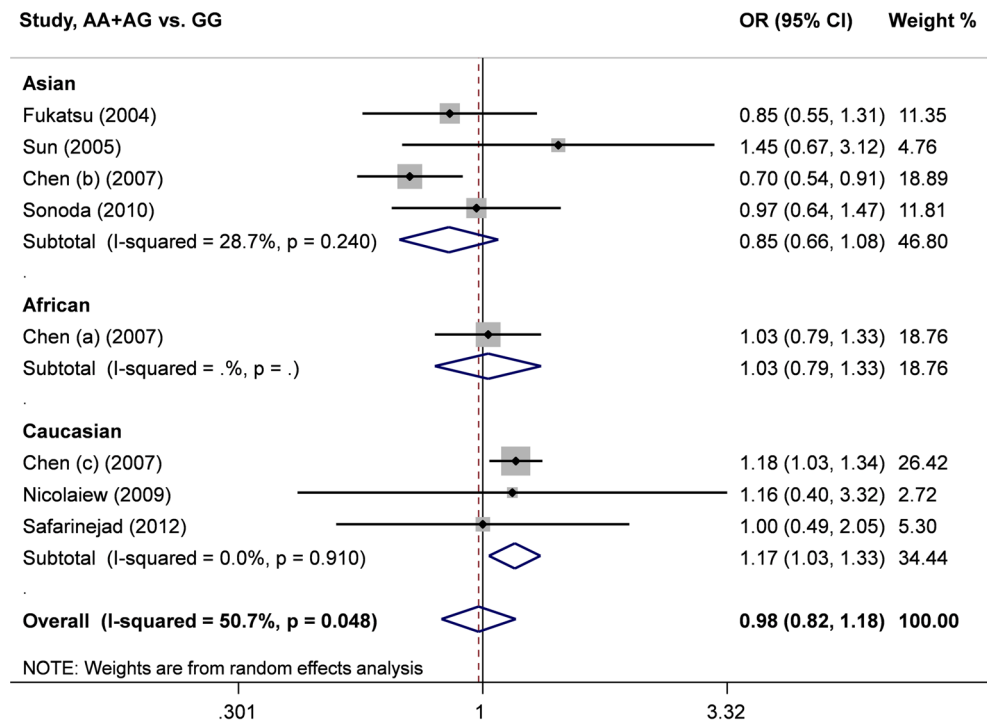
modify the splicing of messenger RNA (mRNA) transcripts, resulting in significant changes in gene function [8, 41]. The ESR2 rs1256049 polymorphism is a silent mutation in codon 328 and the G to A mutation does not change amino acid in the protein. However, this polymorphism may have a direct effect on modifying the secondary structure of the

mRNA and leading to changes in mRNA stability and translation [9, 42].

Some potential limitations of this meta-analysis should be considered. First, selection bias might have played a role because the genotype distribution among cases and controls of one study deviated from HWE. Second, the number of case

and control in Asians and Africans was not sufficiently large. Third, we searched articles from the database in English and Chinese, so articles with potentially high-quality data that were published in other languages were not included because of potential medical translation inaccuracies. Nonetheless, our meta-analysis had some advantages. First, it showed pooled results under the most appropriate genetic model, and cumulative meta-analysis and sensitivity analysis were conducted to validate the robustness of pooled results. Second, although possible publication bias was suggested between ESR1 rs9340799 polymorphism and prostate cancer risk, adjustment for the likely effect of bias using "trim and fill" method only showed a slight change, indicating that the conclusion should be unbiased.

Conclusions

In conclusion, the present study demonstrates that ESR1 rs9340799 polymorphism was significantly associated with prostate cancer in overall populations, Caucasians and Africans, while ESR2 rs1256049 polymorphism was significantly associated with prostate cancer only in Caucasians. Given that Prostate cancer is a multifactorial disease, future studies should be expected to explore the possible functional role of ESR1 rs9340799 and ESR2 rs1256049 polymorphisms in prostate cancer.

Conflicts of interest None

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