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Association of estrogen receptor-beta (ESR2) polymorphism and cancer risk: a meta-analysis

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Summary

Estrogen signal medicated by estrogen receptor (ER), which is involved in various diseases related to steroid hormone, such as cancer. A number of association studies have focused on ESR2 polymorphisms to investigate the relationship with cancer risk. However, the results are inconsistent and inconclusive. To examine this controversy, 33 studies were enrolled for the pooled analysis for three polymorphisms (rs3020450, rs4986938, and rs1256049) in cancer risk using odds ratios (ORs) with 95% confidence intervals (CIs). Regarding rs4986938, A allele was associated with decreased breast cancer. Ethnicity subgroup analysis observed a decreased risk in both Asian and Caucasian descendent. Regarding rs1256049, cancer type subgroup analysis revealed a significant association with increased prostate and endometrial cancer risk. rs3020450 was not associated with cancer risk in any model. Further studies for clarifying the roles of ESR2 polymorphisms in cancer risk seem of vital importance.

Key words: ESR2; Polymorphism; Cancer risk; Meta-analysis.

Introduction

Cancer is one of the most serious medical problems threatening human life and ranks as the leading cause of death. As is well known, many factors that contribute to cancer occurrence have been reported, such as lifestyle, tobacco, alcohol addiction, environment, and so on [1]. Moreover, recent studies indicated that estrogen was associated with an increased risk of multiple types of cancer, especially breast and prostate cancer and may represent a leading preventable cause of death [2, 3]. Estrogen is mediated by the estrogen receptor (ESR), which interacts with other cell-signaling pathways to influence cell behavior. There are two major ESR subtypes: ESR1 and ESR2, which are encoded by two separate genes located on chromosome 6q25.1 and chromosome 14q23.1, respectively [4, 5]. Since ESR2 was identified in 1996 [6], there has been mounting evidence that the genetic variants in ESR2 gene have an influence on body weight [7], Alzheimer's disease, [8], anorexia nervosa [9], and so on, whereas the specific functions of ESR2 in carcinogenesis are not yet known. Currently, related studies have drawn close attention to ESR2 polymorphisms (rs3020450, rs4986938, and rs1256049) which were thought to be associated with the risk of various cancers, such as breast and prostate cancer, uterine fibroids, and other cancers; however, the results were generally inconclusive and inconsistent. The inconsistencies in previous studies might be due to small sample sizes, different research populations, and random errors. Therefore, the present authors performed a comprehensive meta-analysis to derive a more precise estimation of the correlation between these three polymorphisms and the cancer risks.

Materials and Methods

Identification and selection of eligible studies

The following bibliographic databases were searched by using the combined words ''ESR2/ERβ/ER-beta/estrogen receptor beta'', ''cancer'' or ''carcinoma'', ''genetic variation'' or ''polymorphism''. A comprehensive systematic bibliographic search was applied through the medical databases PubMed, CNKI, and WanFang for all publications up to June 2014. The criteria for acceptance of the studies were as follows: (1) studies evaluated ESR2 (rs3020450, rs4986938, and rs1256049) gene polymorphisms and available cancer risk; (2) case-control studies; (3) the numbers of the genotype or allele were reported in the article or could be obtained from authors or other source; (4) available genotype frequency. Moreover, the studies were eliminated as follows: (1) case-only studies, case reports, editorials, and review articles (including meta-analyses); (2) studies without raw data available; (3) duplicated studies.

Data extraction

Two authors (Wenkai Xia and Weidong Mao) independently extracted all the data based on the inclusion criteria listed above. All disagreements regarding eligibility were resolved by discussion with a third author (Qiwen Deng). Any study with incorrect or inconsistent data was excluded. The following variables were extracted from each study if available: first author's last name and the year of publication, country of subjects, cancer type, genotyping method and ethnicity of the population, matching numbers

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Table 1. — *Characteristics of studies included in the meta-analysis.*

Year	Cancer	Country	Ethnicity	Source of control	Genotyping method	Polymorphism sites	Cases	Controls
2009	Uterine fibroids	Germany	Caucasian	HB	PCR-ARMS	rs3020450	101	102
2010	Uterine fibroids	China	Asian	HB	TaqMan	rs4986938, rs1256049	92	193
2010	TGCT	Italy	Caucasian	HB	TaqMan	rs1256049	234	218
2009	PC	France	Caucasian	HB	Taqman	rs4986938, rs1256049	382	381
2010	PC	Japanese	Asian	HB	Taqman	rs1256049	180	177
2007	PC	[1]Mix	[2]Mix	HB	Taqman	rs3020450, rs4986938, rs1256049	8323	9412
2009	PC	USA	Caucasian	PB	TaqMan	rs4986938	219	370
2012	PC	Iran	Asian	PB	PCR-RFLP	rs4986938,rs1256049	162	324
2005	PC	China	Asian	HB	TaqMan	rs1256049	40	86
2004	PC	Japan	Asian	HB	TaqMan	rs1256049	136	236
2014	OC	Germany	Caucasian	HB	PCR-ARMS	rs3020450	184	182
2009	OC	USA	Mix	PB	TaqMan	rs3020450	147	251
2009	OC	USA	Caucasian	PB	TaqMan	rs3020450	72	146
2009	OC	USA	Asian	PB	TaqMan	rs3020450	94	172
2010	LC	USA	Caucasian	PB	Taqman	rs3020450, rs4986938, rs1256049	1021	826
2011	Melanoma	Italy	Caucasian	HB	TaqMan	rs4986938	112	195
2012	LC	Singapore	Asian	PB	TaqMan	rs4986938, rs1256049	702	1578
2009	HCC	China	Asian	HB	TaqMan	rs4986938, rs1256049	100	100
2012	GBC	India	Asian	HB	PCR-LDR	rs1256049	410	220
2009	EC	Australia	Caucasian	HB	TaqMan	rs4986938, rs1256049	191	291
2004	EC	USA	Caucasian	PB	Taqman	rs1256049	220	661
2013	EC	Germany	Caucasian	HB	PCR-ARMS	rs3020450	135	135
2013	EC	China	Asian	HB	TaqMan	rs4986938, rs1256049	60	60
2011	CRC	Germany	Caucasian	HB	PCR-ARMS	rs4986938	676	669
2010	BTC	China	Asian	PB	TaqMan	rs4986938, rs1256049	411	786
2009	BC	Germany	Caucasian	HB	PCR-ARMS	rs3020450	318	318
2006	BC	USA	Caucasian	PB	TaqMan	rs4986939	88	1272
2007	BC	[1]Mix	Caucasian	PB	Taqman	rs3020450, rs4986938, rs1256049	5789	7761
2005	BC	Sweden	Caucasian	HB	PCR-RFLP	rs4986938, rs1256049	723	480
2003	BC	China	Asian	PB	PCR-RFLP	rs1256049	1113	1209
2009	BC	Sweden	Caucasian	PB	Sequencing	rs3020450	538	1073
2009	BC	Japan	Asian	PB	PCR-LDR	rs4986938, rs1256049	388	388
2009	BC	Japan	Mix	PB	PCR-LDR	rs4986938, rs1256049	458	458
2003	BC	Sweden	Caucasian	HB	PCR-RFLP	rs4986938, rs1256049	219	238
2009	BC	India	Asian	HB	PCR-RFLP	rs4986938	248	249
2009	BC	Gernany	Caucasian	PB	TaqMan	rs4986938, rs1256049	3919	7421

[1] Mixed United States and Europe, [2] Mixed population including Caucasian, Asian, and African.
TGCT: testicular germ cell tumor; OC: ovarian cancer; BTC: biliary tract cancer; BC: breast cancer; CRC: colorectal cancer; EC: endometrial cancer; HCC: hepatocellular cancer; PC: prostate cancer; LC: lung cancer; GBC: gallbladder carcinoma; PB: population based; HB: hospital based; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR: polymerase chain reaction-ligation detection reaction; PCR-ARMS: polymerase chain reaction-amplification refractory mutation system.

of genotyped cases and controls, and polymorphism site (Table 1). If difference and discrepancies were existed after data collection, discussion was carried out to reach a consensus.

Statistical analysis

Odds ratio (OR) with its 95% confidence intervals (CI) was calculated to assess the overall association of ESR2 rs3020450, rs4986938, and rs1256049 polymorphisms with cancer risk. The pooled ORs were calculated for the risks of carriage of the mutant allele on cancers compared with the wide-type homozygote, followed by evaluating the risk in the recessive model and dominant model. Stratified analysis was also performed according to cancer type (endometrial, prostate, breast, and other cancer groups which combined the cancer types containing less than two individual studies), source of control and genotyping method. Chi-square test based Q-statistic test was used to evaluate heterogeneity across the studies [10], and was considered significant if $p_{\text{heterogeneity}} < 0.05$. Both fixed-effects (the Mantel-Haenszel method) and random effects (the DerSimonian and Laird method) models were used to pool the results [10]. A fixed-effect model was employed when no heterogeneity existed. Otherwise, the random-effect model was employed to pool the results. Publication bias was applied by funnel plots and the Egger's linear regression test. For the controls of each study, the genotype frequencies of the three polymorphisms of ESR2 were assessed for Hardy-Weinberg equilibrium using a web-based program. All statistical tests were performed with STATA version 11.0.

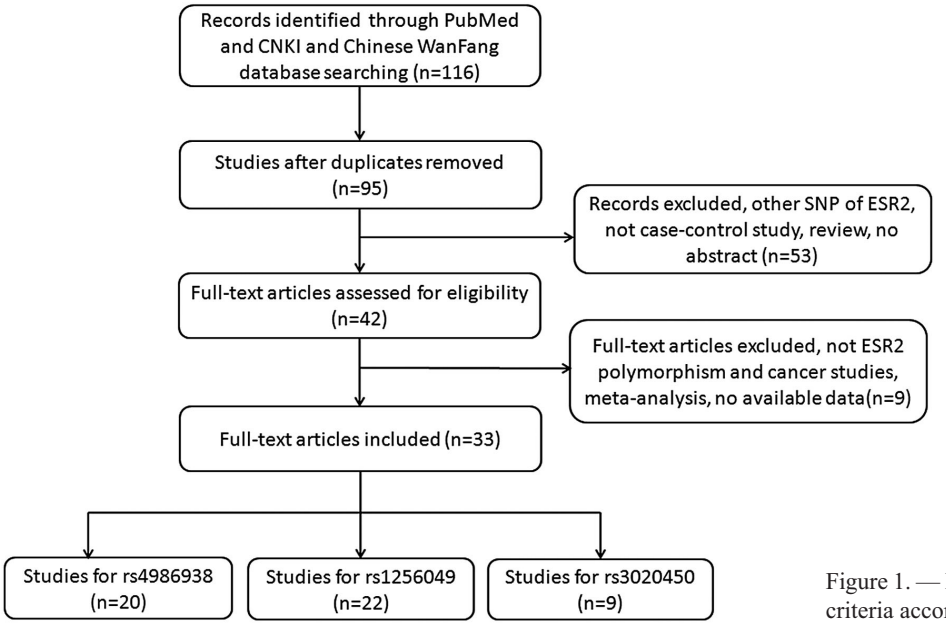

Figure 1. — Flow chart of studies identified with criteria according to inclusion and exclusion.

Results

Characteristics of studies

This study enrolled 33 eligible papers [2, 12-41] (Figure 1) according to the inclusion criteria. For ESR2 rs3020450 polymorphism, nine studies including 14,369 cases and 17,661 controls were classified into ovarian cancer (two studies), breast cancer (three studies), and the others, which were categorized into "other cancers". Meanwhile, there were nine studies of Caucasian descendent, two mixed descendent, and one Asian descendent. For ESR2 rs4986938 polymorphism, 20 studies provided available data, 22,833 cases and 30,319 controls included which were classified into prostate cancer (four studies), lung cancer (two studies), endometrial cancer (two studies), breast cancer (seven studies), and others (five studies) which were categorized into "other cancers". Meanwhile, these studies with data of studies of 12 Caucasian descendent, eight of Asian descendent, and two mixed descendent were collected for the pooled analysis. For ESR2 rs1256049 polymorphism, 22 studies including 22,722 cases and 28,952 controls consisted of Caucasian descendent (12 studies), Asian descendent (13 studies), and mixed descendent provided available data, which related to prostate cancer (six studies), lung cancer (two studies), breast cancer (six studies), and other cancers. Furthermore, the controls of most studies were population-based and the main genotyping method was PCR-RFLP (Table 1).

Main results

For ESR2 rs4986938 polymorphism, subgroup analysis revealed a low decreased risk for breast cancer in heterozygote comparison (AG *vs.* GG: OR = 0.94, 95% CI: 0.90-1.0, $p_{heterogeneity} = 0.62$) and dominant model comparison (AA + AG *vs.* GG: OR = 0.94, 95% CI: 0.90−0.99, $p_{heterogeneity} = 0.285$) (Table 2 and Figure 2). In a stratified analysis by ethnicity, a decreased risk was observed for Asian descendent (AA *vs.* GG: OR = 0.56, 95% CI: 0.39−0.82, $p_{heterogeneity} = 0.096$; AA *vs.* AG + GG: OR = 0.76, 95% CI: 0.63−0.92, $p_{heterogeneity} = 0.065$). Moreover, a decreased risk was observed for Caucasian descendent (AA + AG *vs.* GG: OR = 0.96, 95% CI: 0.92−1.00, $p_{heterogeneity} = 0.562$). In addition, cancer type subgroup analysis revealed A allele was associated with decreased breast cancer (OR = 0.96, 95% CI: 0.93−1.00, $p_{heterogeneity} = 0.088$).

For ESR2 rs1256049 polymorphism, cancer type's subgroup analysis revealed a significant association in the comparison of homozygote model (AA *vs.* GG: OR = 3.5, 95% CI: 1.27-9.64, $p_{heterogeneity} = 0.842$), heterozygote model (AG *vs.* GG: OR = 1.53, 95% CI: 1.03−2.25, $p_{heterogeneity} = 0.305$), and dominant model (AA + AG vs GG: OR = 1.60, 95% CI: 1.09−2.35, $p_{heterogeneity} = 0.205$) in endometrial cancer. Similarly, an increased risk was observed for the comparison of homozygote model (AA *vs.* GG: OR = 1.40, 95% CI: 1.16−4.49, $p_{heterogeneity} = 0.411$) with recessive model (AA *vs.* AG + GG: OR = 1.50, 95% CI: 1.10−2.04, $p_{heterogeneity} = 0.654$) in prostate cancer (Table 3 and Figure 3). In a stratified analysis by ethnicity, there was no association between ESR2 rs1256049 and cancer risk.

For overall analysis, results of pooled analysis revealed no significant associations between the genotypes of ESR2 rs3020450 polymorphism and cancer risk in all genetic models (shown in Table 4).

Table 2. — *Stratified analyses of ESR2 rs4986938 polymorphism and cancer risk.*

Variables	Cases/controls	A/A *vs.* G/G		A/G *vs.* G/G		A/A *vs.* (G/G+G/A)		(A/A+G/A) *vs.* G/G	
		OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]
Total	22833 / 30319	0.96 (0.9-1.01)	0.109	0.98 (0.94-1.02)	0.178	0.97 (0.92-1.02)	0.245	0.98 (0.94-1.01)	0.07
Cancer type									
LC	1565 / 1790	0.96 (0.73-1.26)	0.476	1.04 (0.88-1.23)	0.357	0.97 (0.76-1.24)	0.446	1.03 (0.88-1.20)	0.427
PC	8801 / 10233	0.96 (0.74-1.23)[c]	0.026	1.03 (0.97-1.1)	0.305	0.96 (0.75-1.24)[c]	0.019	1.03 (0.97-1.09)	0.323
BC	10837 / 16021	0.94 (0.87-1.02)	0.161	**0.94 (0.90-1.00)**[b]	0.62	0.96 (0.89-1.03)	0.271	**0.94 (0.90-0.99)**[b]	0.285
EC	248 / 346	0.79 (0.46-1.36)	0.444	0.83 (0.57-1.22)	0.639	0.91 (0.58-1.43)	0.444	0.82 (0.57-1.17)	0.506
other	1382 / 1929	0.96 (0.74-1.25)	0.248	0.92 (0.76-1.11)	0.054	0.98 (0.82-1.18)	0.545	0.9 (0.61-1.33)	0.025[c]
Ethnicity									
Asian	1996 / 3050	**0.56 (0.39-0.82)**[b]	0.096	1.01 (0.86-1.19)	0.079	**0.76 (0.63-0.92)**[b]	0.065	0.93 (0.70-1.22)[c]	0.031
Caucasian	18331 / 24521	0.96 (0.90-1.02)	0.752	0.96 (0.92-1.01)	0.616	0.98 (0.92-1.03)	0.931	**0.96 (0.92-1.00)**[b]	0.562
Mixed	2506 / 2748	1.16 (0.93-1.45)	0.471	1.10 (0.98-1.24)	0.917	1.12 (0.90-1.39)	0.459	1.11(0.99-1.24)	0.755

LC: lung cancer, PC: prostate cancer, BC: breast cancer, EC: endometrial cancer. [a] *p* value of Q test for heterogeneity test; [b] Statistically significant results; [c] Random-effect model was applied when *p* value for heterogeneity < 0.05, otherwise, fixed-effect model was applied.

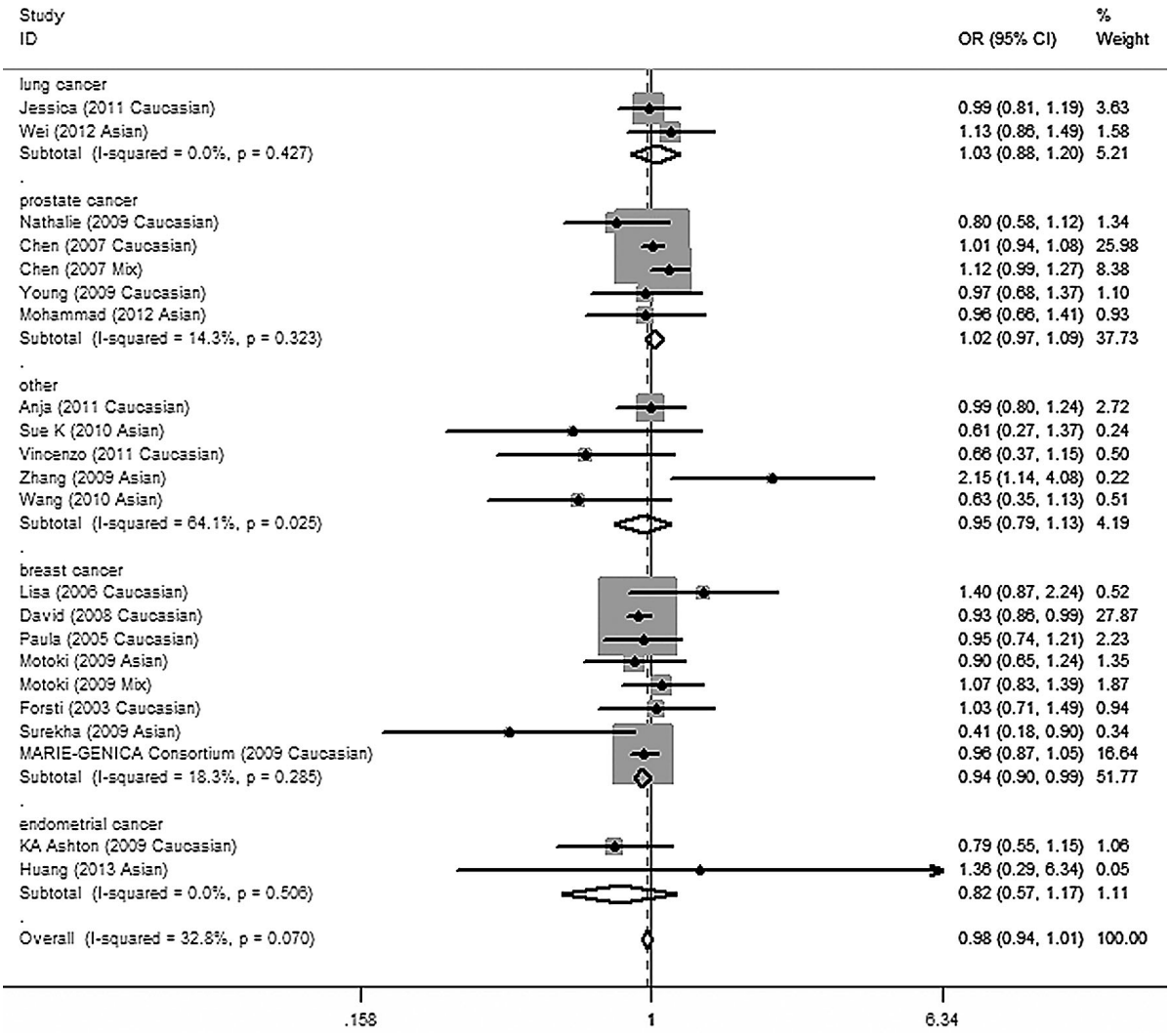

Figure 2. — Forest plots of effect estimates for cases and controls of 22 individual studies for rs4986938 stratified by cancer type (AA + GA *vs.* GG). For each study, the estimate of OR and its CI is plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.

Table 3. — *Stratified analyses of the ESR2 rs1256049 polymorphism and cancer risk.*

Variables	Cases/controls	A/A *vs.* G/G		A/G *vs.* G/G		A/A *vs.* (G/G+G/A)		(A/A+G/A) *vs.* G/G	
		OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]
Total	22673 / 28909	1.07 (0.75-1.54)[c]	0	0.93 (0.82-1.06)[c]	0	1.12 (0.84-1.48)[c]	0	0.94 (0.82-1.08)[c]	0
Cancer type									
lung cancer	1563 / 1779	1.13 (0.82-1.56)	–	1.01 (0.80-1.27)	–	1.13 (0.84-1.51)	–	1.01 (0.84-1.23)	0.606
prostate cancer	7796 / 8927	**1.40 (1.02-1.91)**[b]	0.411	0.91 (0.73-1.14)[c]	0.011	**1.50 (1.10-2.04)**[b]	0.654	0.98 (0.82-1.18)[c]	0.048
breast cancer	11652 / 15726	0.47 (0.19-1.13)[c]	0	0.91 (0.73-1.14)[c]	0	0.57 (0.26-1.23)[c]	0	0.83 (0.62-1.12)[c]	0
endometrial cancer	471 / 1010	**3.50 (1.27-9.64)**[b]	0.842	**1.53 (1.03-2.25)**[b]	0.305	1.72 (0.85-3.68)	0.549	**1.60 (1.09-2.35)**[b]	0.205
other	1240 / 1510	0.84 (0.27-2.60)[c]	0.001	0.72 (0.48-1.09)[c]	0.045	0.95 (0.42-2.16)[c]	0.01	0.72 (0.45-1.15)[c]	0.01
Ethnicity									
Asian	4085 / 5191	1.15 (0.88-1.51)[c]	0.008	0.89 (0.76-1.04)[c]	0.042	1.09 (0.96-1.24)	0.089	0.94 (0.81-1.09)[c]	0.022
Caucasian	17401 / 22337	0.23 (0.02-2.39)[c]	0	0.93 (0.72-1.19)[c]	0	0.34 (0.04-2.93)[c]	0	0.86 (0.65-1.15)[c]	0
Mixed	458 / 458	1.10 (0.72-1.69)	–	1.07 (0.81-1.40)	–	1.87 (0.53-6.65)	–	1.03 (0.79-1.33)	–
Africa	778 / 966	1.87 (0.53-6.65)	–	1.00 (0.77-1.31)	–	1.07 (0.71-1.61)	–	1.07 (0.83-1.08)	–

LC: lung cancer, PC: prostate cancer, BC: breast cancer, EC: endometrial cancer; [a] *p* value of Q test for heterogeneity test; [b] Statistically significant results; [c] Random-effect model was applied when *p* value for heterogeneity < 0.05; otherwise, fixed-effect model was applied.

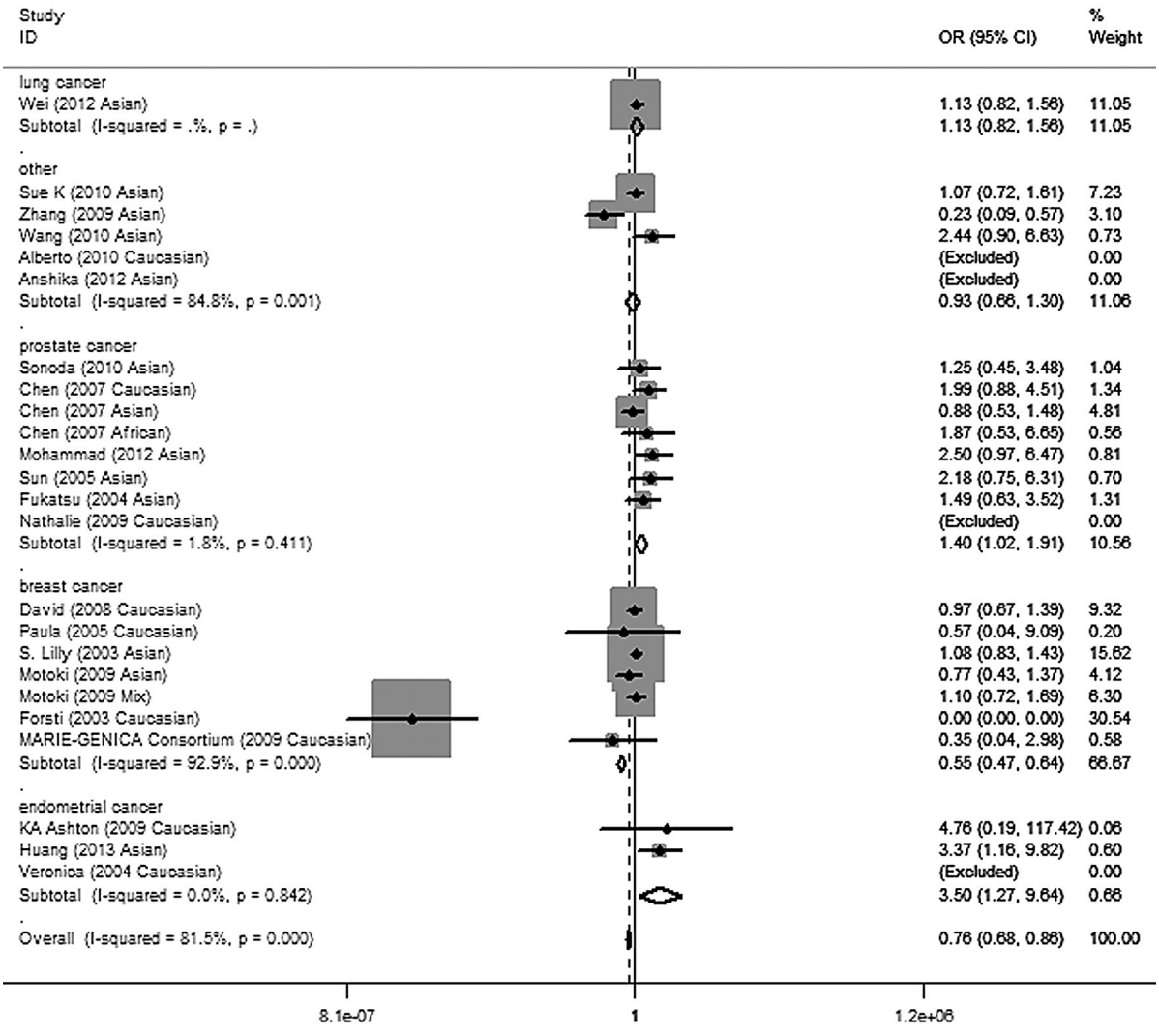

Figure 3. Forest plots of effect estimates for cases and controls of 25 individual studies for rs4986938 stratified by cancer type (AA *vs.* GG). For each study, the estimate of OR and its CI is plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.

Table 4. — *Stratified analyses of the ESR2 rs3020450 polymorphism and cancer risk.*

Variables	Cases/controls	A/A *vs.* G/G		A/G *vs.* G/G		A/A *vs.* (G/G+G/A)		(A/A+G/A) *vs.* G/G	
		OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]	OR (95% CI)	*p* [a]
Total	16417 / 19956	0.98 (0.92-1.06)	0.557	1.01 (0.97-1.05)	0.57	0.98 (0.91-1.05)	0.465	1.00 (0.96-1.05)	0.696
Cancer type									
OC	497 / 751	1.12 (0.72-1.73)	0.148	0.89 (0.59-1.36)[c]	0.046	1.07 (0.70-1.63)	0.102	0.94 (0.74-1.19)	0.085
BC	6481 / 8918	0.94 (0.84-1.05)	0.491	1.00 (0.94-1.07)	0.962	0.94 (0.84-1.04)	0.507	0.99 (0.93-1.05)	0.824
PC	8182 / 9224	1.00 (0.90-1.11)	0.818	1.03 (0.97-1.10)	0.612	0.99 (0.90-1.09)	0.929	1.02 (0.96-1.09)	0.614
other cancer	1257 / 1063	1.11 (0.84-1.47)	0.654	0.96 (0.81-1.15)	0.975	1.13 (0.87-1.47)	0.58	0.99 (0.84-1.17)	0.995
Ethnicity									
Asian	94 / 172	2.78 (0.87-8.86)	–	0.66 (0.38-1.22)	–	3.11 (0.99-9.79)	–	0.85 (0.50-1.47)	–
Caucasian	14128 / 17238	0.98 (0.91-1.06)	0.835	1.01 (0.96-1.06)	0.8	0.97 (0.91-1.05)	0.749	1.00 (0.96-1.05)	0.892
Mixed	2195 / 2546	0.99 (0.81-1.21)	0.126	1.03 (0.91-1.12)	0.077	0.97 (0.80-1.18)	0.186	0.87 (0.55-1.37)[c]	0.04

OC: ovarian cancer, PC: prostate cancer, BC: breast cancer; [a] *p* value of Q test for heterogeneity test; [b] Statistically significant results;
[c] Random-effect model was applied when *p* value for heterogeneity < 0.05, otherwise, fixed-effect model was applied.

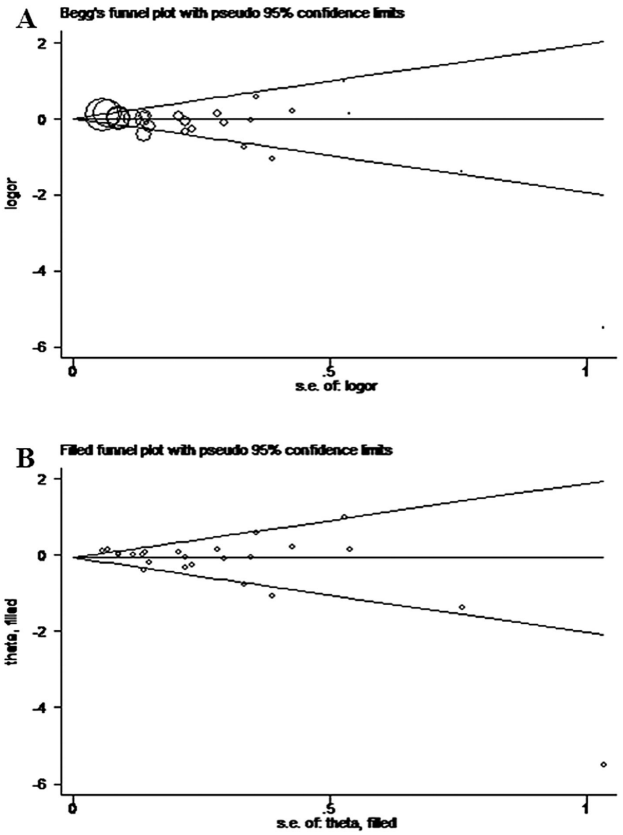

Figure 4. — Begg's funnel plot of Egger's test for publication bias tests for heterozygote comparison in ESR2 rs1256049. Each *circle* represents as an independent study for the indicated association. Log [OR], natural logarithm of OR. *Horizontal lines* mean effect size. A: Begg's funnel plot of publication bias test. B: Begg's funnel plot of publication bias test after trim-and-fill method.

Test of heterogeneity

For overall studies of ESR2 rs1256049 polymorphism, a significant heterogeneity was apparent among homozygous comparison (AA vs GG: $p_{\text{heterogeneity}}$ =0.000), heterozygote comparison (AG *vs.* GG: $p_{\text{heterogeneity}}$ =0.000), recessive comparison (AA *vs.* AG + GG: $P_{\text{heterogeneity}}$ =0.000), dominant model (AA + AG *vs.* GG: $P_{\text{heterogeneity}}$ =0.000)

There was no apparent heterogeneity for overall studies of ESR2 rs4986938 and ESR2 rs3020450.

Table 5. — *Egger's test for three polymorphisms of ESR2.*

Polymorphism	Egger's test	Homozygous	Heterozygous	Recessive	Dominant
rs3020450	*t*	0.96	-0.74	1.01	-0.37
	p	0.358	0.476	0.337	0.719
rs4986938	*t*	-0.66	-0.37	-0.27	-0.044
	p	0.52	0.715	0.788	0.665
rs1256049	*t*	-0.55	-2.62	-0.23	-2.09
	p	0.59	**0.016**	0.824	0.058

Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the stability of these results and to find the source of the heterogeneity by sequential removal of individual eligible study. The results of sensitivity analysis were obtained after sequentially excluding each case-control study, indicating the stability of the results.

Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plot indicated obvious asymmetry in ESR2 rs1256049 heterozygous model comparison and dominant model comparison (Figure 4A). Thus, Egger's test was used to provided statistical evidence of funnel plot asymmetry (t = -2.62, p = 0.016) (shown in Table 5), which suggested the existence of publication bias in the meta-analysis. To adjust this bias, a trim-and-fill method mentioned by Duval and Tweedie [42] was utilized (Figure 4B). As a result, the conclusion with or without the trim-and-fill method did not change, indicating that the present results were statistically robust. While the shapes of the funnel plots did not reveal any evidence of obvious asym-

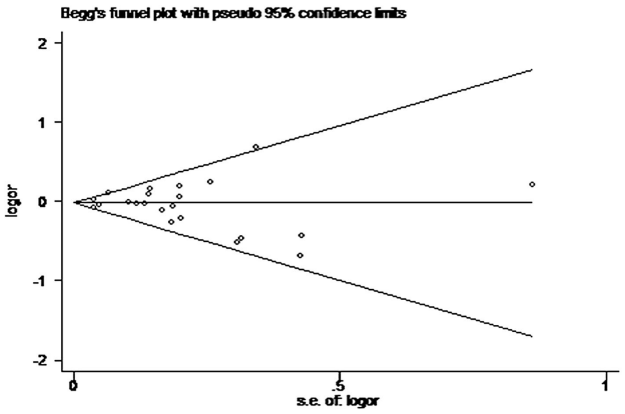

Figure 5. — Begg's funnel plot of the Egger's test of allele comparison for publication bias for AG versus GG in ESR2 rs4986938 polymorphism.

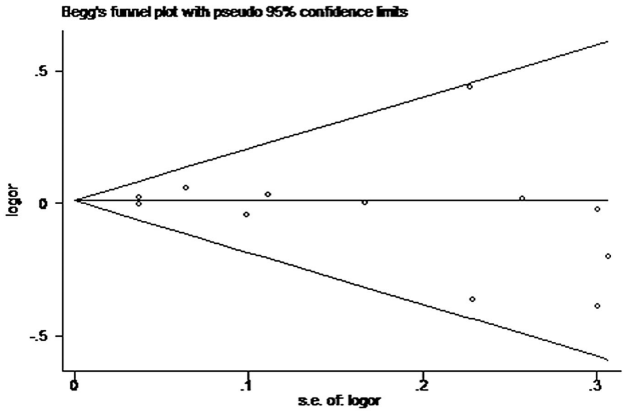

Figure 6. — Begg's funnel plot of the Egger's test of allele comparison for publication bias for AG versus GG in ESR2 rs3020450 polymorphism.

metry in all genetic models of ESR2 rs3020450 and ESR2 rs4986938 polymorphisms (Figures 5, 6). In addition, all models of ESR2 rs3020450 and ESR2 rs4986938 did not show any evidence of publication bias ($p > 0.05$) (Table 5).

Discussion

Thirty-three studies were identified according to the acceptance and exclusion criteria to investigate the relationship between the genetic variants in the ESR2 gene and cancer risk. There was a correlation between estrogens and cancer risks. Estrogen metabolism was related to vitamin D, insulin sensitivity, and fat metabolism as well as inflammation development which closely linked with cancer occurrence [43]. Estrogens have significant direct and/or indirect effects on development and progression of cancer, in which ESR2 was a key factor [44, 45]. To date, it is known that the genetic polymorphisms in ESR2 gene locate on chromosome14 and can change the stability of the transcript [5, 26, 46]. It was not difficult to observe that this evidence supported the present results regarding the association between ESR2 rs4986938, rs1256049 and rs3020450, and cancer occurrence.

As for the ESR2 rs4986938 polymorphism, subgroup study revealed that there was only a single comparison model (GA + AA *vs.* GG) in Caucasian descendent showed the significant association with cancer risk. Meanwhile, significant associations were found in Asian descendent for the comparison of AA *vs*. GG and AA *vs.* GA + GG, which suggested ethnic differences did not influence the cancer risk. Significant results of different genetic models, however, were observed in two descendent, which suggested that relatively limited study number and small sample size contributed to the results. Cancer type subgroup analysis revealed that ESR2 rs4986938 polymorphism was a protective factor in breast cancer. Recently, several studies have revealed that ESR2 rs4986938 polymorphism was associated with cancer risk [16, 26, 28, 31]. However, some studies did not demonstrate a significant association between rs4986938 and cancer risk [2, 13, 27, 29]. Inconsistent results might be caused by phytoestrogen intake and BMI in different descendent which might be critical for genetic effect. In addition, the approach to select participants and study design should also be taken into account.

As for the ESR2 rs1256049 polymorphism, cancer type subgroup analysis revealed that there existed a correlation between ESR2 rs1256049 polymorphism and the risk of prostate cancer under homozygous (AA *vs.* GG) model, it showed the same pattern of results as that under recessive model (AA *vs.* AG + GG). Meanwhile, a significant association was also observed between ESR2 rs1256049 and endometrial cancer. In the subgroup analysis by ethnicity, no significant association was associated with cancer risk in any genetic model. However, the results might be caused by relatively limited study number, only two studies of rs1256049 in subgroup analysis specific to Caucasians [2, 27]. For the ESR2 rs1256049 polymorphism, due to many conflicted results [20, 27, 35, 38], further well-designed, unbiased, large case-control studies need to be performed to confirm these results.

As for the ESR2 rs3020450 polymorphism, no significant associations were found in all comparisons. In similarly, three studies did not show a significant association by comparison ESR2 rs3020450 with ovarian cancer. In addition, no significant association was found among uterine fibroids, prostate, lung, and breast cancer [2, 15, 18, 37]. Therefore, more related studies need to further clarify the relationship between ESR2 rs3020450 polymorphism and cancer risk.

Some potential limitations of this meta-analysis should be acknowledged. First, all the eligible studies the authors searched were from the database in English and Chinese, articles with potentially high-quality data that were pub-

lished in other languages were not included in this paper because of potential medical translation inaccuracies. Second, though most controls were selected from healthy populations, there was no uniform definition of controls. Finally, some potentially suspected factors such as age, sex, living habits, menstrual history, and environmental factors were not considered so that the authors' unadjusted estimates still need further validation. However, the present meta-analysis had some advantages. First, in order to increase the statistical power of the meta-analysis significantly, the authors extracted data from as many different studies as possible. Second, all case-control studies included in this research met the authors' selection criteria well.

In conclusion, the present study demonstrated the relationship between three polymorphisms of ESR2 and cancer risk. The result indicated that rs4986938 was associated with a decreased risk of breast cancer in Caucasians and Asians, and rs1256049 polymorphism was significantly associated with prostate cancer and endometrial cancer, while rs3020450 showed no obvious associations with cancer. However, further studies based on more comprehensive and large, stratified population to facilitate evaluation the association between ESR2 and cancer risk are warranted.

References

[1] Pharoah P.D., Dunning A.M., Ponder B.A., Easton D.F.: "Association studies for finding cancer-susceptibility genetic variants". *Nat. Rev. Cancer,* 2004, *4*, 850.

[2] Chen Y.C., Kraft P., Bretsky P., Bretsky P., Hunter D.J., Albanes D., *et al.*: "Sequence variants of estrogen receptor beta and risk of prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium". *Cancer Epidemiol. Biomarkers Prev.,* 2007, *16*, 1973.

[3] Yager J.D., Davidson N.E.: "Estrogen carcinogenesis in breast cancer". *N. Engl. J. Med.,* 2006, *354*, 270.

[4] Menasce L.P., White G.R., Harrison C.J., Boyle J.M.: "Localization of the estrogen receptor locus (ESR) to chromosome 6q25.1 by FISH and a simple post-FISH banding technique". *Genomics,*1993, *17*, 263.

[5] Enmark E., Pelto-Huikko M., Grandien K., Laqercrantz S., Laqercrantz J., Fried G., *et al.*: "Human estrogen receptor beta-gene structure, chromosomal localization, and expression pattern". *J. Clin. Endocrinol. Metab.,* 1997, *82*, 4258.

[6] Mosselman S., Polman J., Dijkema R.: "ER beta: identification and characterization of a novel human estrogen receptor". *FEBS Lett.,* 1996, *392*, 49.

[7] Goulart A.C., Zee R.Y., Rexrode K.M.: "Association of estrogen receptor 2 gene polymorphisms with obesity in women (obesity and estrogen receptor 2 gene)". *Maturitas,* 2009, *62*, 179.

[8] Pirskanen M., Hiltunen M., Mannermaa A., Helisalmi S., Lehtovirta M., Hänninen T., Soininen H.: "Estrogen receptor beta gene variants are associated with increased risk of Alzheimer's disease in women". *Eur. J. Hum. Genet.,* 2005, *13*, 1000.

[9] Eastwood H., Brown K.M., Markovic D., Pieri L.F.: "Variation in the ESR1 and ESR2 genes and genetic susceptibility to anorexia nervosa". *Mol. psychiatry,* 2002, *7*, 86.

[10] Handoll H.H.: "Systematic reviews on rehabilitation interventions". *Arch. Phys. Med. Rehabil.,* 2006, *87*, 875.

[11] Midgette A.S., Wong J.B., Beshansky J.R., Porath A., Fleming C., Pauker S.G.: "Cost-effectiveness of streptokinase for acute myocardial infarction: a combined meta-analysis and decision analysis of the effects of infarct location and of likelihood of infarction". *Med. Decis. Making,* 1994, *14*, 108.

[12] MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk: "Polymorphisms in genes of the steroid receptor superfamily modify postmenopausal breast cancer risk associated with menopausal hormone therapy". *Int. J. Cancer,* 2010, *126*, 2935.

[13] Ashton K.A., Proietto A., Otton G., Symonds I., McEvoy M., Attia J., *et al.*: "Estrogen receptor polymorphisms and the risk of endometrial cancer". *BJOG,* 2009, *116*, 1053.

[14] Chae Y.K., Huang H.Y., Strickland P., Hoffman S.C., Helzlsouer K: "Genetic polymorphisms of estrogen receptors alpha and beta and the risk of developing prostate cancer". *PloS One,* 2009, *4*, e6523.

[15] Breast and Prostate Cancer Cohort Consortium, Cox D.G., Bretsky P., Kraft P., Pharoah P., Albanes D., *et al.*: "Haplotypes of the estrogen receptor beta gene and breast cancer risk". *Int. J. Cancer,* 2008, *122*, 387.

[16] de Giorgi V., Sestini S., Gori A., Mazzotta C., Grazzini M., Rossari S., et al.: "Polymorphisms of estrogen receptors: risk factors for invasive melanoma - a prospective study". *Oncology,* 2011, *80*, 232.

[17] Ferlin A., Ganz F., Pengo M., Selice R., Frigo A.C., Foresta C: "Association of testicular germ cell tumor with polymorphisms in estrogen receptor and steroid metabolism genes". *Endocr. Relat. Cancer,* 2010, *17*, 17.

[18] Fischer C., Juhasz-Boess I., Lattrich C., Ortmann O., Treeck O: "Estrogen receptor beta gene polymorphisms and susceptibility to uterine fibroids". *Gynecol. Endocrinol.,* 2010, *26*, 4.

[19] Forsti A., Zhao C., Israelsson E., Dahlman-Wright K., Gustafsson J.A., Hemminki K: "Polymorphisms in the estrogen receptor beta gene and risk of breast cancer: no association". *Breast Cancer Res. Treat.,* 2003, *79*, 409.

[20] Fukatsu T., Hirokawa Y., Araki T., Hioki T., Murata T., Suzuki H., *et al.*: "Genetic polymorphisms of hormone-related genes and prostate cancer risk in the Japanese population". *Anticancer Res.,* 2004, *24*, 2431.

[21] Gallicchio L., Berndt S.I., McSorley M.A., Newschaffer C.J., Thuita L.W., Argani P., *et al.*: "Polymorphisms in estrogen-metabolizing and estrogen receptor genes and the risk of developing breast cancer among a cohort of women with benign breast disease". *BMC Cancer,* 2006, *6*, 173.

[22] Iwasaki M., Hamada G.S., Nishimoto I.N., Netto M.M., Motola J. Jr., Laginha F.M., *et al.*: "Isoflavone, polymorphisms in estrogen receptor genes and breast cancer risk in case-control studies in Japanese, Japanese Brazilians and non-Japanese Brazilians". *Cancer Sci.,* 2009, *100*, 927.

[23] Lattrich C., Haring J., Schuler S., Skrzypczak M., Ortmann O., Treeck O.: "Polymorphisms in the promoter region of estrogen receptor beta gene in endometrial cancer". *Arch. Gynecol. Obstet.,* 2014, *289*, 631.

[24] Lim W.Y., Chen Y., Chuah K.L., Eng P., Leong S.S., Lim E., et al.: "Female reproductive factors, gene polymorphisms in the estrogen metabolism pathway, and risk of lung cancer in Chinese women". *Am. J. Epidemiol.,* 2012, *175*, 492.

[25] Lurie G., Wilkens L.R., Thompson P.J., McDuffie K.E., Carney M.E., Terada K.Y., *et al.*: "Genetic polymorphisms in the estrogen receptor beta (ESR2) gene and the risk of epithelial ovarian carcinoma". *Cancer Causes Control,* 2009, *20*, 47.

[26] Maguire P., Margolin S., Skoglund J., Sun X.F., Gustafsson J.A., Børresen-Dale A.L., *et al.*: "Estrogen receptor beta (ESR2) polymorphisms in familial and sporadic breast cancer". *Breast Cancer Res. Treat.,* 2005, *94*, 145.

[27] Nicolaiew N., Cancel-Tassin G., Azzouzi A.R., Grand B.L., Mangin P., Cormier L., *et al.*: "Association between estrogen and androgen receptor genes and prostate cancer risk". *Eur. J. Endocrinol.,* 2009, *160*, 101.

[28] Park S.K., Andreotti G., Rashid A., Chen J., Rosenberg P.S., Yu K., *et al.*: "Polymorphisms of estrogen receptors and risk of biliary tract cancers and gallstones: a population-based study in Shanghai, China". *Carcinogenesis,* 2010, *31*, 842.

[29] Paulus J.K., Zhou W., Kraft P., Johnson B.E., Lin X., Christiani D.C.: "Haplotypes of estrogen receptor-beta and risk of non-small cell lung cancer in women". *Lung Cancer,* 2011, *71*, 258.
[30] Rudolph A., Sainz J., Hein R., Hoffmeister M., Frank B., Försti A., *et al.*: "Modification of menopausal hormone therapy-associated colorectal cancer risk by polymorphisms in sex steroid signaling, metabolism and transport related genes". *Endocr. Relat. Cancer,* 2011, *18*, 371.
[31] Safarinejad M.R., Safarinejad S., Shafiei N.: "Estrogen receptors alpha (rs2234693 and rs9340799), and beta (rs4986938 and rs1256049) genes polymorphism in prostate cancer: evidence for association with risk and histopathological tumor characteristics in Iranian men". *Mol Carcinog.,* 2012, *51*, E104.
[32] Schuler S., Lattrich C., Skrzypczak M., Fehm T., Ortmann O., Treeck O.: "Polymorphisms in the promoter region of ESR2 gene and susceptibility to ovarian cancer". *Gene,* 2014, *546*, 283.
[33] Setiawan V.W., Hankinson S.E., Colditz G.A., Hunter D.J., De Vivo I.: "Estrogen receptor beta (ESR2) polymorphisms and endometrial cancer (United States)". *Cancer Causes Control,* 2004, *15*, 627.
[34] Sonestedt E., Ivarsson M.I., Harlid S., Ericson U., Gullberg B., Carlson J., *et al.*: "The protective association of high plasma enterolactone with breast cancer is reasonably robust in women with polymorphisms in the estrogen receptor alpha and beta genes". *J. Nutr.,* 2009, *139*, 993.
[35] Sonoda T., Suzuki H., Mori M., Tsukamoto T., Yokomizo A., Naito S., *et al.*: "Polymorphisms in estrogen related genes may modify the protective effect of isoflavones against prostate cancer risk in Japanese men". *Eur. J. Cancer Prev.,* 2010, *19*, 131.
[36] Srivastava A., Sharma K.L., Srivastava N., Misra S., Mittal B.: "Significant role of estrogen and progesterone receptor sequence variants in gallbladder cancer predisposition: a multi-analytical strategy". *PloS One,* 2012, *7*, e40162.
[37] Treeck O., Elemenler E., Kriener C., Horn F., Sprinqwald A., Hartmann A., Ortmann O.: "Polymorphisms in the promoter region of ESR2 gene and breast cancer susceptibility". *J. Steroid. Biochem. Mol. Biol.,* 2009, *114*, 207.
[38] Duval S., Tweedie R.: "Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis". *Biometrics,* 2000, *56*, 455.
[38]Sun Y.H., Yang B., Wang X.H., Xu C.L., Gao X.F., Gao X., Wang L.H.: "Association between single-nucleotide polymorphisms in estrogen receptor beta gene and risk of prostate cancer". *Chin. J. Surg.,* 2005, *43*, 948.
[39]Wang J.Y., Zhang H.Z., Guan Y.Q., Xie F.: "Relationship of Estrogen Receptor βGene Polymorphisms with Leiomyoma of the Uterus in Han Population". *J. of Cap. Med. Univer.*, 2010, *31*, 660.
[40] Huang H.L., Zhao Q.Z., Xie J.S., Fang X.Y.: "Correlation between estrogen receptor gene polymorphism and estrogen receptor expression in endometrial cancer". *Mater. Child Heal Care of China*, 2013, *28*, 2772.
[41] Zhang W., Shi D., Du C.Y., Luo F.: "Association between RsaI and AluI polymorphism in the estrogen receptor beta gene and primary hepatocellular carcinoma". *Chin. J. Hepatol.*, 2009, *17*, 99.
[43] Ribeiro J.R., Freiman R.N.: "Estrogen signaling crosstalk: Implications for endocrine resistance in ovarian cancer". *J. Steroid Biochem. Mol. Biol.,* 2014, *143*, 160.
[44] Dey P., Jonsson P., Hartman J., Williams C., Strom A., Gustafsson J.A.: "Estrogen receptors beta1 and beta2 have opposing roles in regulating proliferation and bone metastasis genes in the prostate cancer cell line PC3". *Mol. Endocrinol.,* 2012, *26*, 1991.
[45] Ellem S.J., Risbridger G.P.: "The dual, opposing roles of estrogen in the prostate". *Ann. N. Y. Acad. Sci.,* 2009, *1155*, 174.
[46] Herrington D.M., Howard T.D., Brosnihan K.B., McDonnell D.P., Li X., Hawkins G.A., *et al.*: "Common estrogen receptor polymorphism augments effects of hormone replacement therapy on E-selectin but not C-reactive protein". *Circulation,* 2002, *105*, 1879.

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