SYSTEMATIC REVIEW

Association of ESRα Gene Pvu II T>C, XbaI A>G and BtgI G>A Polymorphisms with Knee Osteoarthritis Susceptibility: A Systematic Review and Meta-Analysis Based on 22 Case-Control Studies

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Abstract

Background: Many studies have reported the association of estrogen receptor α gene (ESRα) ESRα PvuII T>C, XbaI A>G and BtgI G>A polymorphisms with Knee osteoarthritis (KOA) risk, but the results remained controversial. In order to drive a more precise estimation, the present systematic review and meta-analysis was performed to investigate the association between ESRα polymorphisms and KOA susceptibility.

Methods: Eligible articles were identified by search of databases including PubMed, ISI Web of Knowledge and Google scholar up to March 1, 2017. Data were extracted by two independent authors and pooled odds ratio (OR) with 95% confidence interval (CI) was calculated.

Results: A total of 22 case-control studies in eleven publications with 6,575 KOA cases and 7,459 controls were included in the meta-analysis. By pooling all the studies, either ESRα PvuII T>C and XbaI A>G polymorphisms was not associated with KOA risk in the overall population. However, ESRα BtgI G>A was significantly associated with KOA risk under all five genetic models. In the subgroup analysis by ethnicity, a significant association was observed between ESRα PvuII T>C polymorphism and KOA risk in Asians under heterozygote model. In addition, significant association was found between ESRα XbaI A>G polymorphism and KOA in Caucasians under allelic, homozygote, dominant and recessive models.

Conclusion: The present meta-analysis suggests that ESRα BtgI G>A rather than ESRα PvuII T>C and XbaI A>G polymorphisms is associated with an increased KOA risk in overall population. Moreover, we have found that ESRα PvuII T>C and XbaI A>G polymorphisms associated with KOA susceptibility by ethnicity backgrounds.

Keywords: Estrogen receptor gene, Knee, Osteoarthritis, Polymorphism

Introduction

Osteoarthritis (OA) is a degenerative joint condition that affects roughly 80% of the population over 65 years of age (1). As of 2004, OA was the cause for moderate to severe disability in as many as 43.4 million people worldwide (2). The financial burden associated with posttraumatic OA was projected at $3.06 billion annually in 2006 (3). Knee Osteoarthritis (KOA) is the most prevalent type of arthritis. KOA is expected to be

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the fourth leading cause of disability in 2020 (4, 5). The KOA-related symptoms have a major impact on subject's social and physical wellbeing (5). KOA normally occurs as a result of aging; however, genetics, muscle weakness around joints, malpositioning, obesity, and altered mechanical loading conditions such as repeated motions and trauma can all increase the risk of OA development (4, 6).

Rapid progress has been made in recent years to identify the locus that affect KOA risk, such as vitamin D receptor (VDR) gene, insulin-like growth factor I (IGF-I) gene, collagen type I alpha 1(COL1A1) gene and estrogen receptor α (ESRα) gene, etc. (6). Previous studies have suggested that ER-α plays an important role in the pathological process of KOA (7). Human ESRα, a member of the nuclear receptor superfamily of ligand-activated transcription factors, is one of the key mediators of hormonal response in estrogen-sensitive tissues (8, 9). The estrogen- ESRα complex is primarily responsible for regulating cellular signal pathways in vivo, as well as bone mass in skeletal systems (10). After binding to estrogen, ESRα acts as a transcriptional factor that regulates gene expression and function by interacting with the regulatory regions of target genes (11).

ESRα gene polymorphisms have been among the most intensively studied polymorphisms in genetic regulation of KOA, but, with contradictory results (11-22). This disparity can be attributed to small sample sizes, low statistical power, and/or clinical heterogeneity. In view of the uncertain association between ESRα polymorphisms and KOA risk, we sought to obtain more precise information by conducting a systematic review and meta-analysis including all the evidence produced to the date.

Materials and Methods

Literature Search Strategy

To identify the case–control studies investigating the association between ESRα PvuII T>C, XbaI A>G and BtgI G>A polymorphisms and KOA risk, we conducted a search in PubMed, Google scholar, Web of Science, and SID databases using the following keywords: ''osteoarthritis'', "knee osteoarthritis", "KOA", ''estrogen receptor alpha'', ''ESRα'', "PvuII T>C", "XbaI A>G", "BtgI G>A", ''rs2234693'', ''rs9340799'', ''rs2228480'', "polymorphism", "mutation", "variant", "gene", "genotype", "SNP", and "allele". The last updated search was performed on March 1, 2017. Language restriction was set to English, Chinese and Persian. Additionally, the reference list of each retrieved article was thoroughly reviewed for more original papers.

Inclusion and Exclusion Criteria

The studies were further filtered to fit in the inclusion criteria that: a) full-text published studies; b) case-control or cohort studies; c) assessment of the association between ESRα PvuII T>C, XbaI A>G and BtgI G>A polymorphisms and KOA risk; d) having available genotype frequencies in both cases and controls for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies without usable data or reviews were all excluded. For more than two studies with overlapping data, the study with the most subjects or newest published data was selected; and e) written in English or Persian. The exclusion criteria were as follows: a) abstract only, short communications or case reports, letter to editor, and reviews; b) studies on other ESRα polymorphisms; c) studies with only case subjects (no healthy controls); d) studies without detailed genotype frequencies, which were unable to be calculated OR; e) studies on other osteoarthritis types; and f) duplicate data publications from the same study.

Data Extraction

Necessary information was carefully extracted from all eligible publications by two independent authors. The following data were extracted for each study: the first author's surname, year of publication, ethnicity of the subjects, number of KOA patients and controls, genotype distribution in cases and controls, minor allele frequencies (MAFs) in control subjects, and Hardy-Weinberg equilibrium test in control subjects. In case of evaluation conflicts, the two authors carried out discussions until a consensus was reached, otherwise, a 3rd author was consulted to resolve the dispute and a final decision was made through votes.

Quality Assessment

Two independent authors assessed the study quality using the Newcastle-Ottawa quality Scale which is a star rating system. The studies were qualified based on 3 broad perspectives: selection, comparability, and exposure (case-control studies) or outcome (cohort studies). Studies scoring five or more stars were considered as moderate to high quality (23).

Statistical Analysis

The strength of association between ESRα polymorphisms and KOA was assessed by using odds ratio (OR) and 95% confidence interval (CI). The significance of the pooled OR was determined with the Z-test. The meta-analysis was performed on the association between ESRα PvuII T>C polymorphism and KOA under the allele model (C vs. T), the heterozygote model (CC vs.TT), the homozygote model (CT vs. TT), the dominant model (CC+CT vs. TT), and the recessive model (CC vs. CT+TT). For ESRα XbaI A>G polymorphism and KOA under the allele model (G vs. A), the heterozygote model (GA vs. AA), the homozygote model (GG vs. AA), the dominant model (GG+GA vs. AA), and the recessive model (GG vs. GA+AA). For ESRα BtgI G>A polymorphism and KOA under the allele model (A vs. G), the heterozygote model (AG vs. GG), the homozygote model (AA vs. GG), the dominant model (AA+AG vs. GG), and the recessive model (AA vs. GA + GG). Heterogeneity was assessed by both the Q statistic as well as I^2 statistics (24, 25). The heterogeneity was considered significant if either the Q statistic had a $P<0.10$. An I^2 value of 0% represents no heterogeneity, while values of 25%, 50%, 75%, or more represent low, moderate, high, and extreme heterogeneity, respectively. When inter-study heterogeneity existed, a random-effects model

weighted by the DerSimonian–Laird method was used to calculate pooled OR (26). Otherwise, a fixed-effects model weighted by the Mantel–Haenszel method would be applied (27). Chi-Square test was used to determine the frequency distribution of genotypes in control group of each study, which were in accordance with HWE. A *P>0.05* signified a departure from HWE. Subgroup analyses were performed by ethnicity and HWE status. The one-way sensitivity analyses were used to assess the stability of the results, namely, a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set to the pooled OR. Additionally, sensitivity analysis was performed to evaluate the stability of the results by removing the studies not in HWE. Visual inspection of Begg's funnel plot symmetry was performed to assess the potential publication bias. Egger's test was also conducted to analyze the publication bias statistically (*P<0.05* was considered as statistically significant) (28, 29). In the presence of a bias, the Duval and Tweedie non-parametric ''trim and fill'' methods were used to adjust for it (30). All the statistical analyses were performed by comprehensive meta-analysis (CMA) V2.0 software (Biostat, USA). All tests were two-sided, and a *P<0.05* was considered statistically significant.

Results

Characteristics of Studies

Based on our search strategy, the primary screening produced 26 potentially relevant articles. Fifteen articles were excluded because they clearly did not meet the inclusion criteria or overlapping references. Finally, a total of 22 case-control studies in eleven 11 publications were included in the meta-analysis involving 6,575 KOA cases and 7,459 controls (11-22). The main characteristics of studies included in the current meta-analysis are presented in Table 1; among them, nine studies were identified for the ESRαPvuII

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

First author	Country (Ethnicity)	Case/ Control	Cases					Control					MAFs	HWE
			Genotypes			Alleles		Genotypes			Alleles			
Pvu II T>C			**CC**	**TC**	**TT**	**C**	**T**	**CC**	**TC**	**TT**	**C**	**T**		
Bergink 2003 (12)	Netherlands (Caucasian)	1483/687	434	737	312	1605	1361	225	333	129	783	591	0.430	0.767
Jin 2004 (13)	Korea (Asian)	151/397	61	68	22	190	112	152	183	62	487	307	0.386	0.575
Xue 2004 (14)	China (Asian)	55/176	17	23	15	57	53	57	87	32	201	151	0.429	0.905
Tian 2009 (15)	China (Asian)	38/40	16	15	7	47	29	15	16	9	46	34	0.425	0.250
Yang 2009 (16)	China (Asian)	41/40	14	17	10	45	37	12	23	5	47	33	0.412	0.238
Riancho a 2010 (17)	UK (Caucasian)	445/862	77	245	123	399	491	167	442	253	776	948	0.549	0.292
Riancho b 2010 (17)	Spain (Caucasian)	272/802	53	140	79	246	298	179	394	229	752	852	0.531	0.699
Riancho c 2010 (17)	Spain (Caucasian)	254/473	46	143	65	235	273	80	217	176	377	569	0.601	0.349
Borgonio-Cuadra 2012 (18)	Mexico (Mixed)	115/117	52	49	14	153	77	51	50	16	152	82	0.350	0.507
Dai 2014 (19)	China (Asian)	469/514	167	217	85	551	387	198	242	74	638	390	0.379	0.996
Liu 2014 (20)	China (Asian)	98/196	30	41	27	101	95	63	97	36	223	169	0.431	0.900
XbaI A>G			**AA**	**GA**	**GG**	**A**	**G**	**AA**	**GA**	**GG**	**A**	**G**		
Bergink (2003) (12)	Netherlands (Caucasian)	1483/687	643	682	158	1968	998	372	263	52	1007	367	0.267	0.560
Jin 2004 (14)	Korea (Asian)	151/397	98	49	4	245	57	256	126	15	638	156	0.196	0.917
Xue 2004 (14)	China (Asian)	55/176	21	24	10	66	44	40	82	54	162	190	0.539	0.408
Tian 2009 (15)	China (Asian)	38/40	18	16	4	52	24	6	21	13	33	47	0.587	0.598
Yang 2009 (16)	China (Asian)	41/40	28	11	2	67	15	24	13	3	61	19	0.237	0.516
Borgonio-Cuadra 2012 (18)	Mexico (Mixed)	115/117	70	41	4	181	49	62	47	8	171	63	0.269	0.821
Dai 2014 (19)	China (Asian)	469/514	288	152	29	728	210	348	155	19	851	193	0.184	0.736
Liu 2014 (20)	China (Asian)	98/196	36	43	19	115	81	49	92	55	190	202	0.515	0.398
BtgI G>A			**GG**	**AG**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**		
Jin 2004 (13)	Korea (Asian)	151/397	84	57	10	225	77	257	122	18	636	158	0.199	0.472
Jiao 2007 (21)	China (Asian)	76/118	5	56	15	66	86	16	97	5	129	107	0.453	<0.001
Tawonsawatruk 2009 (22)	Thailand (Asian)	104/104	62	37	5	131	17	63	37	4	163	45	0.216	0.615

Table 2. Quality assessment conducted according to the Newcastle-Ottawa Scale for all the included studies

First author	Quality indicators		
	Selection	Comparability	Exposure
Bergink 2003	***	*	**
Jin 2004	***	*	***
Xue 2004	***	*	***
Tian 2009	**	*	**
Yang 2009	***	*	**
Riancho a 2010	***	*	**
Riancho b 2010	***	*	**
Riancho c 2010	***	*	***
Borgonio-Cuadra 2012	**	*	***
Dai 2014	***	*	**
Liu 2014	****	*	**
Jiao 2007	**	*	**
Tawonsawatruk 2009	***	*	**

T>C polymorphism, including a total of 3,421 cases and 4,304 controls, for the ESRαXbaI A>G polymorphism, eight studies involved a total of 2,450 cases and 2,167 controls and for the ESRαBtgI G>A polymorphism three studies were identified covering a total of 333 cases and 619 controls (11-22). All selected studies were evaluated by Newcastle-Ottawa Scale and met the high quality [Table 2]. The studies were carried out in Netherlands, China, Korea, Spain, Mexico, and Thailand. The genotype frequencies in the control group of one study on ESRαBtgI G>A polymorphism was not in agreement with HWE (*P<0.05*).

Quantitative Synthesis

ESRα PvuII T>C Polymorphism

Table 3 shows the summary ORs for the ESRα PvuII T>C polymorphism and KOA risk. The pooled results based on all included studies did not show any significant association between the ESRα PvuII T>C polymorphism and KOA risk under the allele model (C vs. T: OR = 0.958, 95% CI = 0.894-1.025, *P = 212*, Figure 1A), the heterozygote model (CT vs. TT: OR = 0.971, 95% CI = 0.791-1.193, *P = 0.78*), homozygote model (CC vs. TT, OR = 0.888, 95% CI = 0.772-1.021, *P = 0.096*), the dominant model (CC+CT vs. TT: OR = 0.868, 95% CI = 0.664-1.135, *P = 0.300*), and the recessive model (CC vs. CT+TT: OR = 0.905, 95% CI = 0.813-1.008, *P = 0.070*) [Table 3]. In the subgroup analyses, there was a significant association between ESRα PvuII T>C polymorphism and KOA risk under the heterozygote model (CT vs. TT: OR = 0.750, 95% CI = 0.586-0.960, *P = 0.022*) in the Asians, but not in Caucasian and mixed populations.

ESRα XbaI A>G Polymorphism

Table 4 shows the summary ORs for the ESRα XbaI A>G with KOA risk. Overall, this meta-analysis of included studies suggested that there was no significant association between ESRα XbaI A>G polymorphism and KOA risk under allele model (G vs. A: OR = 1.225, 95% CI = 0.896-1.675, *P = 0.203*), the heterozygote model (GA vs. AA: OR = 1.033, 95% CI = 0.537-1.986, *P = 0.922*), the homozygote model (GG vs. AA: OR = 1.572, 95% CI = 0.812-3.041, *P = 0.179*), the dominant model (GA+GG vs. AA: OR = 1.24, 95% CI = 0.719-2.167,*p = 0.431*, Figure 1B) and the recessive model (GG vs. GA+AA: OR = 1.252, 95% CI = 0.871-1.801, *P = 0.225*). In the subgroup analyses, there was a significant association between ESRα XbaI A>G with the KOA risk under allele model (G vs. A: OR = 0.719, 95% CI = 0.624-0.828, *P <0.001*), the homozygote model (GG vs. AA: OR = 0.569, 95% CI = 0.406-0.798, *P = 0.001*), the dominant model (GA+GG vs. AA: OR = 687, 95% CI = 0.495-0.953, *P = 0.024*) and the recessive model (GG vs. GA+AA: OR = 0.648, 95% CI = 0.540-0.777, *P <0.001*) in the Caucasians, but not in Asian and mixed populations.

ESRα BtgI G>A Polymorphism

Table 5 summarizes the ORs for the ESRα BtgI G>A polymorphism with the KOA risk. Overall, this meta-analysis of included studies suggested that there was significant association between ESRα BtgI G>A polymorphism and KOA risk under the allele model (A vs. G: OR = 0.639, 95% CI = 0.515-0.793, *P <0.001*), the heterozygote model (AG vs. GG: OR = 0.526, 95% CI = 0.291-0.953, *P = 0.034*), the homozygote model (AA vs. GG: OR = 0.448, 95% CI = 0.240-0.838, *P = 0.012*), the dominant model (AA+AG vs. GG: OR = 0.469, 95% CI = 0.264-0.833, *P = 0.010*), and the recessive model (AA vs. GA + GG: OR = 0.729, 95% CI = 0.540-0.986, *P = 0.040*, Figure 1C). Moreover, a significant association was

Table 3. The meta-analysis of ESRα Pvu II T>C polymorphism and KOA risk

Subgroup	Study Number	Genetic Model	Type of Model	Heterogeneity		Odds ratio			Publication Bias		
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall											
	11	C vs. T	Fixed	24.38	0.211	0.958	0.894-1.025	-1.247	0.212	0.350	0.678
	11	CT vs. TT	Random	53.75	0.017	0.971	0.791-1.193	-0.279	0.780	0.533	0.323
	11	CC vs.TT	Fixed	10.23	0.347	0.888	0.772-1.021	-1.665	0.096	0.640	0.722
	11	CC+CT vs. TT	Random	74.93	<0.001	0.868	0.664-1.135	-1.036	0.300	0.533	0.292
	11	CC vs. CT+TT	Fixed	0.00	0.942	0.905	0.813-1.008	-1.812	0.070	0.436	0.073
By Ethnicity											
Caucasian											
	4	C vs. T	Random	65.99	0.032	1.003	0.865-1.163	0.039	0.969	0.308	0.204
	4	CT vs. TT	Random	68.68	0.023	1.155	0.890-1.499	1.082	0.279	0.308	0.203
	4	CC vs.TT	Fixed	52.37	0.098	0.925	0.780-1.098	-0.888	0.374	0.308	0.190
	4	CC+CT vs. TT	Random	73.23	0.011	1.103	0.844-1.442	0.720	0.472	0.308	0.192
	4	CC vs. CT+TT	Fixed	0.00	0.739	0.878	0.765-1.008	-1.841	0.066	0.308	0.338
Asian											
	6	C vs. T	Fixed	0.00	0.687	0.905	0.797-1.026	-1.557	0.120	0.452	0.769
	6	CT vs. TT	Fixed	0.00	0.467	0.750	0.586-0.960	-2.289	0.022	0.452	0.585
	6	CC vs.TT	Fixed	0.00	0.646	0.788	0.610-1.018	-1.826	0.068	1.000	0.859
	6	CC+CT vs. TT	Random	73.90	0.002	0.602	0.349-1.038	0.068	0.068	0.452	0.509
	6	CC vs. CT+TT	Fixed	0.00	0.827	0.935	0.779-1.122	-0.724	0.469	0.707	0.445
Mixed											
	1	C vs. T	Ref.	0.00	1.000	1.072	0.730-1.573	0.355	0.723	NA	NA
	1	CT vs. TT	Ref.	0.00	1.000	1.120	0.494-2.539	0.271	0.786	NA	NA
	1	CC vs.TT	Ref.	0.00	1.000	1.165	0.516-2.632	0.368	0.713	NA	NA
	1	CC+CT vs. TT	Ref.	0.00	1.000	1.143	0.530-2.465	0.341	0.733	NA	NA
	1	CC vs. CT+TT	Ref.	0.00	1.000	1.068	0.636-1.793	0.249	0.803	NA	NA

observed when stratified by HWE status only under the allele model (A vs. G: OR = 0.640, 95% CI = 0.496-0.825, *P = 0.001*).

Sensitivity Analyses

Sensitivity analyses were performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. However, the results suggested that no individual study significantly affected the pooled OR, thus suggesting that the results of this meta-analysis are stable (data not shown). Additionally, sensitivity analysis was performed by excluding HWE-violating studies for ESRα BtgI G>A polymorphism and the corresponding pooled ORs were materially altered, indicating that the results are statistically affected by HWE status [Table 5].

Publication bias

Begg's funnel plot and Egger's test were performed to access the small study effects of the literatures. The funnel plot revealed no obvious publication bias for ESRα PvuII T>C and BtgI G>A polymorphisms, and this was confirmed by Begg's test and Egger's test [Figure 2A]. However, the shapes of the funnel plots revealed obvious asymmetry for ESRα XbaI A>G in the allele model [Figure 2B], homozygote model and recessive model [Figure 2C], suggesting that there were obvious publication biases in these two genetic models. Moreover, the results of Egger's regression test also provided sufficient evidence for publication bias (allele model: $P_{Begg's}$ = 0.035, $P_{Egger's}$ = 0.003; the homozygote model: $P_{Begg's}$ = 0.265, $P_{Egger's}$ = 0.023; and the recessive model: $P_{Begg's}$ = 0.009, $P_{Egger's}$ <0.001). However, adjusting the models by the trim and fill method was

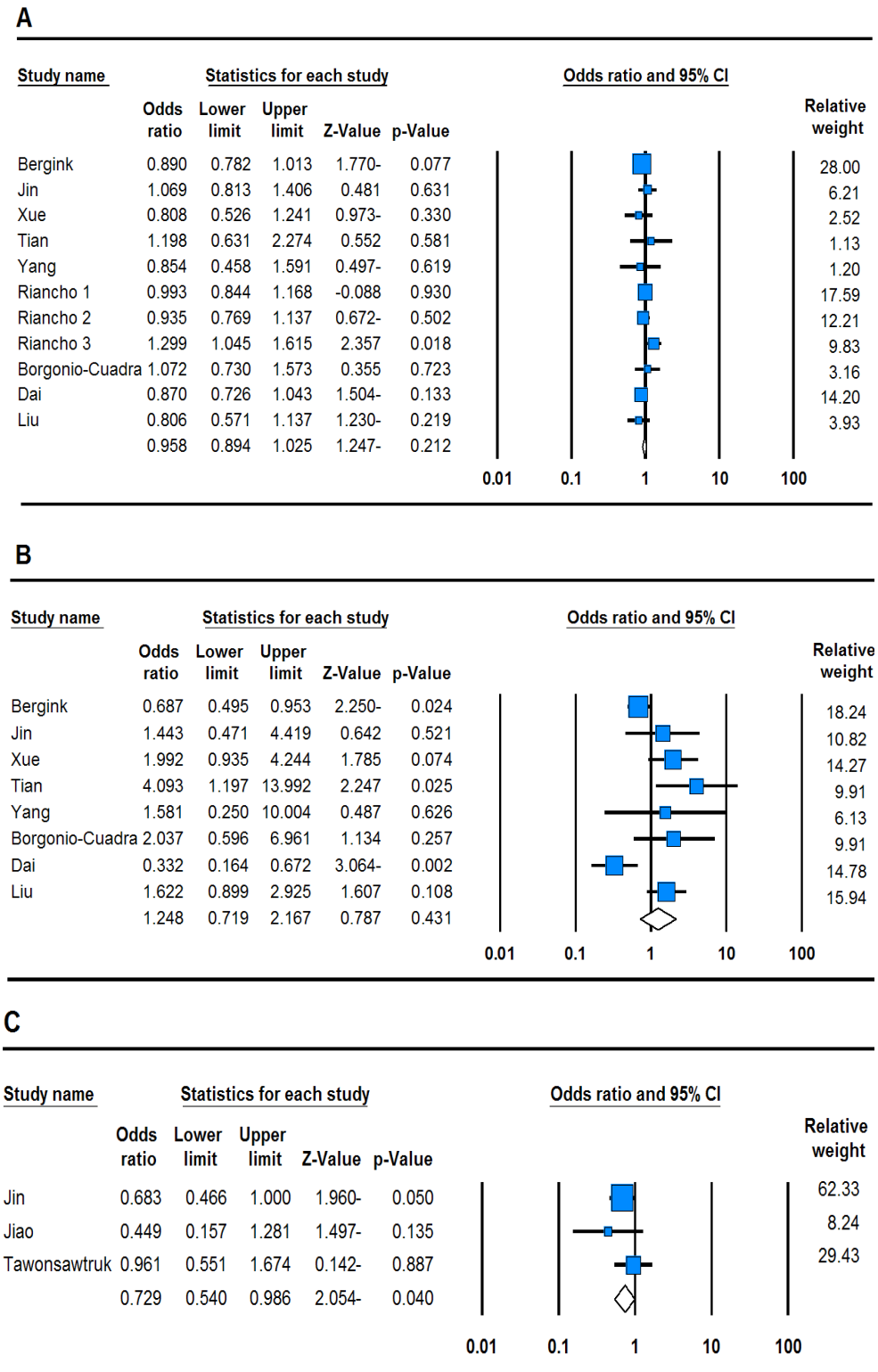

Figure 1. Forest plots describing the association of ESRα polymorphisms and KOA risk. A: PvuII T>C (allele model: C vs. T), B: XbaI A>G (dominant model: GG+GA vs. AA), C: BtgI G>A (recessive model: AA vs. GA+GG).

Table 4. The meta-analysis of ESRα XbaI A>G polymorphism and KOA risk

Subgroup	Study Number	Genetic Model	Type of Model	Heterogeneity		Odds ratio			Publication Bias		
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
XbaI A>G											
Overall											
	8	G vs. A	Random	86.08	<0.001	1.225	0.896-1.675	1.272	0.203	0.035	0.003
	8	GA vs. AA	Random	81.90	<0.001	1.033	0.537-1.986	0.097	0.922	0.901	0.366
	8	GG vs. AA	Random	80.80	<0.001	1.572	0.812-3.041	1.343	0.179	0.265	0.023
	8	GG+GA vs. AA	Random	73.93	<0.001	1.248	0.719-2.167	0.787	0.431	0.536	0.148
	8	GG vs. GA+AA	Random	82.50	<0.001	1.252	0.871-1.801	1.213	0.225	0.009	<0.001
Caucasian											
	1	G vs. A	Ref.	0.00	1.000	0.719	0.624-0.828	-4.569	<0.001	NA	NA
	1	GA vs. AA	Ref.	0.00	1.000	0.853	0.605-1.204	-0.903	0.367	NA	NA
	1	GG vs. AA	Ref.	0.00	1.000	0.569	0.406-0.798	-3.268	0.001	NA	NA
	1	GG+GA vs. AA	Ref.	0.00	1.000	0.687	0.495-0.953	-2.250	0.024	NA	NA
	1	GG vs. GA+AA	Ref.	0.00	1.000	0.648	0.540-0.777	-4.673	<0.001	NA	NA
Asian											
	6	G vs. A	Random	84.00	<0.001	1.364	0.909-2.048	1.500	0.134	0.132	0.045
	6	GA vs. AA	Random	86.23	<0.001	1.042	0.388-2.798	0.082	0.934	0.707	0.228
	6	GG vs. AA	Random	75.71	0.001	1.895	0.857-4.189	1.578	0.114	0.452	0.241
	6	GG+GA vs. AA	Random	74.31	0.002	1.380	0.659-2.891	0.853	0.394	1.000	0.600
	6	GG vs. GA+AA	Random	77.89	<0.001	1.461	0.920-2.321	1.608	0.108	0.060	0.012
Mixed											
	1	G vs. A	Ref.	0.00	1.000	1.361	0.887-2.088	1.412	0.158	NA	NA
	1	GA vs. AA	Ref.	0.00	1.000	1.745	0.489-6.220	0.858	0.391	NA	NA
	1	GG vs. AA	Ref.	0.00	1.000	2.258	0.648-7.865	1.279	0.201	NA	NA
	1	GG+GA vs. AA	Ref.	0.00	1.000	2.037	0.596-6.961	1.134	0.257	NA	NA
	1	GG vs. GA+AA	Ref.	0.00	1.000	1.380	0.819-2.325	1.210	0.226	NA	NA

not materially altered.

Discussion

Despite the fact that ESRα gene is one of the most studied genes in OA, to the best of our knowledge this is the most comprehensive meta-analysis that focused on the association between ESRα PvuII T>C, XbaI A>G and BtgI G>A polymorphisms and susceptibility of KOA (31). In the present study, neither ESRα PvuII T>C and XbaI A>G polymorphisms had a statistically significant association with the risk of KOA in the overall population. Moreover, we have found a significant association between the ESRα PvuII T>C polymorphism and KOA in Asians under the heterozygote model, but not in Caucasian and mixed populations, and that the ESRα XbaI A>G polymorphism was significantly associated with KOA in Caucasian, but not Asian mixed populations. In a more recent meta-analysis by Ren et al. they have suggested that ERα PvuII polymorphism was not associated with OA in either population. However, they have observed that the ERα XbaI polymorphism associated with OA in Europeans but not Asians. In addition, we have found that ESRα BtgI G>A polymorphism significantly associated with KOA risk under all five genetic models.

Compared with the previous meta-analyses, in this meta-analysis we have focused only on association between ESRα gene polymorphisms and risk of KOA (32-36). Our meta-analysis results were different from a previous meta-analysis, which revealed no significant association between BtgI G>A polymorphism and risk of KOA risk. Several reasons may explain this difference (36-38). It seems the inclusion and exclusion criteria were different. However, Ma et al. suggested that XbaI A>G

Table 5. The meta-analysis of ESRα BtgI G>A polymorphism and KOA risk

Polymorphism	Study Number	Genetic Model	Type of Model	Heterogeneity		Odds ratio			Publication Bias	
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
BtgI G>A											
	3	A vs. G	Fixed	32.61	0.227	0.639	0.515-0.793	-4.064	<0.001	0.296	0.294
	3	AG vs. GG	Fixed	59.94	0.082	0.526	0.291-0.953	-2.117	0.034	1.000	0.865
	3	AA vs. GG	Fixed	60.89	0.078	0.448	0.240-0.838	-2.513	0.012	0.296	0.651
	3	AA+AG vs. GG	Fixed	55.50	0.106	0.469	0.264-0.833	-2.583	0.010	1.000	0.894
	3	AA vs. GA+GG	Fixed	0.00	0.390	0.729	0.540-0.986	-2.054	0.040	1.000	0.790
By HWE											
	2	A vs. G	Fixed	66.30	0.085	0.640	0.496-0.825	-3.444	0.001	NA	NA
	2	AG vs. GG	Fixed	0.00	0.952	0.830	0.406-1.698	-0.510	0.610	NA	NA
	2	AA vs. GG	Fixed	0.00	0.719	0.635	0.316-1.275	-1.277	0.202	NA	NA
	2	AA+AG vs. GG	Fixed	0.00	0.833	0.700	0.352-1.388	-1.022	0.307	NA	NA
	2	AA vs. GA+GG	Fixed	0.00	0.321	0.762	0.556-1.043	-1.695	0.090	NA	NA

and BtgI G>A rather than Pvu II T>C polymorphisms are associated with OA risk (37). In another meta-analysis, Yin et al. found a significant associations between the XbaI A>G polymorphism and the OA risk in Europeans and Asians (34). Ren et al, suggested that there may be a significant association between the ERα XbaI polymorphism and OA by ethnicity (33).

The preset meta-analysis results are consistent with the study performed by Ge et al, who failed to detect any association between the ESRα PvuII polymorphism and fracture risk in postmenopausal women (39). However Sun et al., in a different meta-analysis, reported that ESRα PvuII polymorphism may be the risk factor for different cancers such as hepatocellular carcinoma, prostate cancer and gallbladder cancer (40). Luo et al. reported that ESRα PvuII and XbaI polymorphisms were significantly associated with precocious puberty susceptibility (41). In another meta-analysis, He et al. observed that ESRα PvuII polymorphism was significantly associated with risk of premature ovarian failure, while ESRα XbaI polymorphism was not associated with the condition risk (42). Therefore, these findings indicate that the ESRα polymorphisms exert different effect on various conditions. So, it is necessary to get a better understanding of ESRα polymorphisms on KOA susceptibility, especially when inclusive and controversial findings still exist.

Between-study heterogeneity is a common problem in meta-analysis for genetic association studies (43). In the current meta-analysis, we have used fixed-effects or random-effects models based on heterogeneity results. A significant heterogeneity was seen in association of ESRα polymorphisms for ESRα XbaI A>G under all genetic models and ESRα Pvu II T>C polymorphism under two heterozygote and dominant models with KOA risk. A number of characteristics that vary among studies could be the sources of heterogeneity between-study such as ethnicity, gender, sample selection, source of controls, age, sample size, environmental exposures etc. (43-45). As so, we used meta-regression and sensitivity analysis by ethnicity, which aim to reduce heterogeneity; however, the results indicated that ethnicity was not the source of heterogeneity in the study.

Publication bias is a known threat to the validity of meta-analysis, which occurs when studies with statistically significant or clinically favorable results are more likely to be published than studies with non-significant or unfavorable results. Consistent with the results of Yin et al., there were obvious publication biases in the XbaI A>G under the allele and recessive genetic models in this study. However, adjusting the models by the trim and fill method was not materially altered.

We conducted the largest and most comprehensive quantitative meta-analysis of the relationship between ESRα PvuII T>C, XbaI A>G and BtgI G>A polymorphisms and susceptibility of KOA. However, the results of the present meta-analysis should also be interpreted within the context of its limitations. The number of studies and the number of subjects in the studies included in the current meta-analysis were small or medium and had insufficient statistical power to detect the association. Therefore, more studies with larger sample size and providing more detailed information are needed. Secondly, the subjects in this meta-analysis were from mostly Asian descent populations; hence, our results are only applicable to this ethnic population. Therefore, more studies containing the full range of possible ethnic differences are required to avoid selection bias.

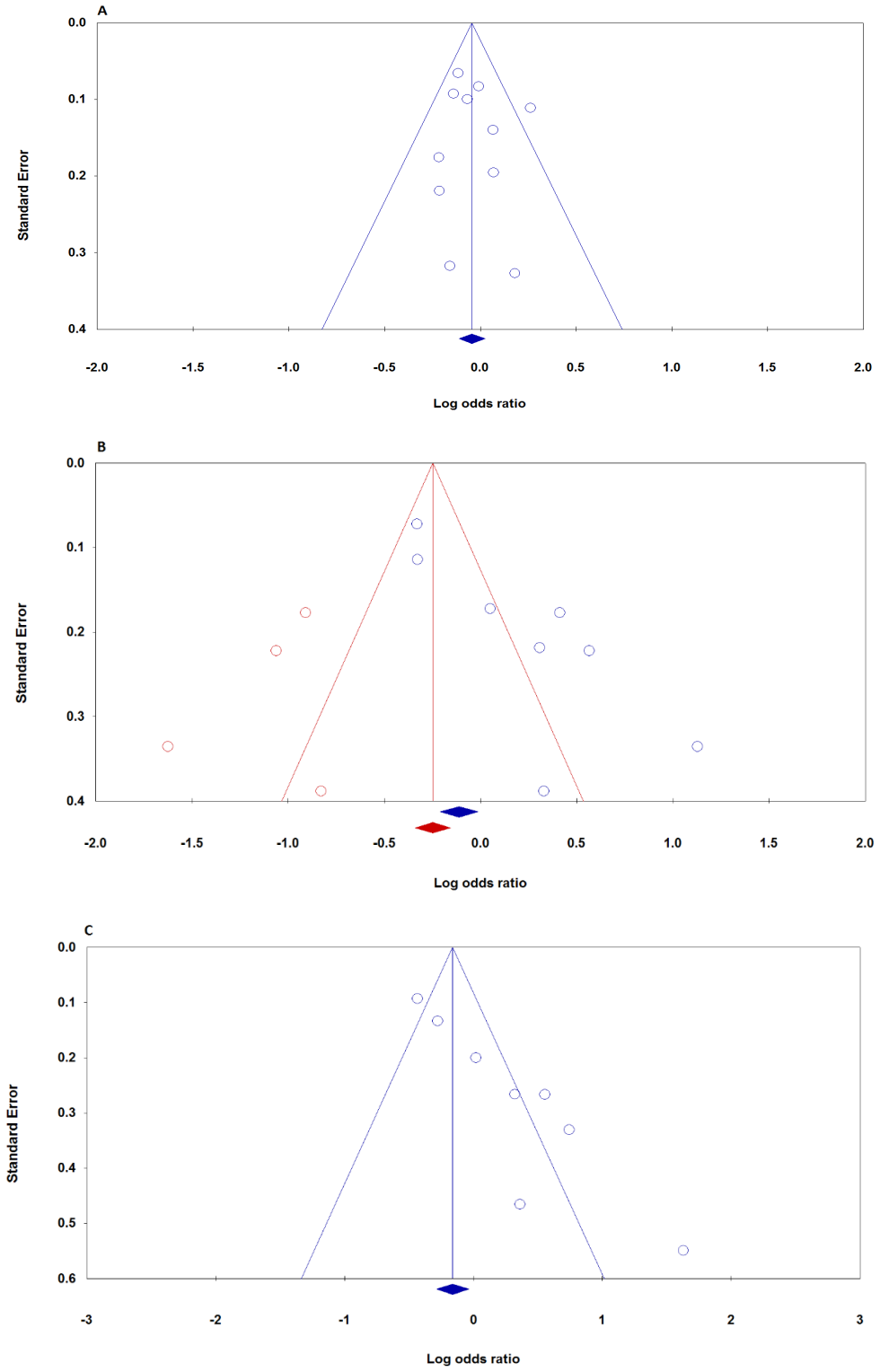

Figure 2. Begg's funnel plots of the ESRα polymorphisms and KOA risk for publication bias test. A: Pvu II T>C (allele model: C vs. T), B: XbaI A>G (allele model: G vs. A, with trim and fill test), C: XbaI A>G (recessive model: GG vs. GA+AA).

Also, due to limited individual data, we did not conduct a more precise analysis on other covariates such as age, gender, and environmental factors. Moreover, in this meta-analysis publication bias existed for some genetic models. Only full-text articles published in English were included in this meta-analysis, missing some eligible studies which were unpublished or reported in other languages. This may bias the present results. Therefore, the results should be interpreted with caution. Finally, several genes were identified to significantly mutate in KOA. The possible gene–gene and gene–environment interactions may play central roles in the KOA susceptibility and need further confirmation in future studies.

In conclusion, our meta-analysis suggested that ESRα BtgI G>A rather than ESRα PvuII T>C and XbaI A>G polymorphisms is associated with an increased KOA risk in overall population. However, we have found that ESRα PvuII T>C and XbaI A>G polymorphisms are associated with KOA susceptibility by ethnicity backgrounds. Moreover, due to the limited sample size, more large-scale and multi-racial association studies are required to further clarify the genetic association between various ESRα polymorphisms and risk of KOA.

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