Int J Clin Exp Med 2014;7(12):5031-5040
www.ijcem.com /ISSN:1940-5901/IJCEM0003899

Original Article

Current evidence on the relationship between rs1256049 polymorphism in estrogen receptor-β gene and cancer risk

Zhi-Jun Dai[1,2], Bao-Feng Wang[1*], Yun-Feng Ma[3*], Hua-Feng Kang[1], Yan Diao[1], Yang Zhao[1], Shuai Lin[1], Ye Lv[1], Meng Wang[1], Xi-Jing Wang[1]

[1]Department of Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, China; [2]Center for Translational Medicine, Frontier Institute of Science and Technology, Xi'an Jiaotong University, Xi'an 710049, China; [3]Department of Immunology and Pathogenic Biology, School of Medicine, Xi'an Jiaotong University, Xi'an 710061, China. [*]Equal contributors.

Received November 16, 2014; Accepted November 17, 2014; Epub December 15, 2014; Published December 30, 2014

Abstract: Previous studies have suggested that estrogen receptor-β (ESR2) rs1256049 polymorphism is associated with the susceptibility of cancer. However, the results are inconsistent. We performed a meta-analysis to evaluate the association between the rs1256049 polymorphism and cancer risk. PubMed, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure (CNKI), were searched for eligible studies. The odds ratios (ORs) with 95% confidence interval (CI) were used to assess the strength of association. 22 studies including 22,994 cases and 30,514 controls were identified. There was no significant association between rs1256049 and cancer risk in the overall population. Stratified analysis by ethnicity revealed that the rs1256049 polymorphism was associated with cancer risk in Caucasians (A vs. G: OR = 1.09, 95% CI = 1.01-1.16; GA vs. GG: OR = 1.10, 95% CI = 1.02-1.18; AA+GA vs. GG: OR = 1.09, 95% CI = 1.02-1.17), but not in Asians. Further subgroup analysis by cancer type indicated that the rs1256049 polymorphism may contribute to prostate cancer risk (AA vs. GG: OR = 1.41, 95% CI = 1.02-1.96; AA vs. GG+GA: OR = 1.52, 95% CI = 1.10-2.10), whereas negative results were obtained for breast cancer in any genetic model. This meta-analysis suggested that the ESR2 rs1256049 polymorphism is a candidate gene polymorphism for cancer susceptibility in Caucasians, especially in prostate cancer.

Keywords: ESR2, cancer risk, polymorphism, meta-analysis

Introduction

Estrogen and its receptors (ERs) influence many biological processes in physiology and pathology in men and women [1]. The classical actions of estrogen are mainly mediated via the two ERs, ER-α and ER-β [1]. ER genes are highly expressed and involved in the progression of many cancers, such as breast cancer [2], prostate cancer [3], endometrial cancer [4], esophageal cancer [5], and lung cancer [6], etc.

ER-α and ER-β are transcribed from two genes (ESR1 and ESR2 respectively) that are located on different chromosomes [1]. ESR2 is located on chromosome 14q23.1 [7]. Single nucleotide polymorphisms (SNPs) are the most frequent sequence variations in the human genome. There have been evidences to suggest that the genetic polymorphisms in ESR2 gene can cause transcription change or affect the stability of the transcript [8]. Many studies have been conducted in recent years to evaluate the association between ESR2 polymorphisms and cancer risk. However, the results are inconsistent.

Wu et al. reported that ESR2 rs1256049 polymorphism was associated with reduced risk of colorectal cancer (OR = 0.7, 95% = 0.5-1.0) [9]. In a largest sample study, the Breast and Prostate Cancer Cohort Consortium (BPC3), results indicated that the AA/GA carriers had an increased risk in breast cancer (OR = 1.11, 95% CI = 1.00-1.24) [10]. An additional study by Maguire et al. reported that rs1256049 might decrease breast cancer risk in Swedens [8].

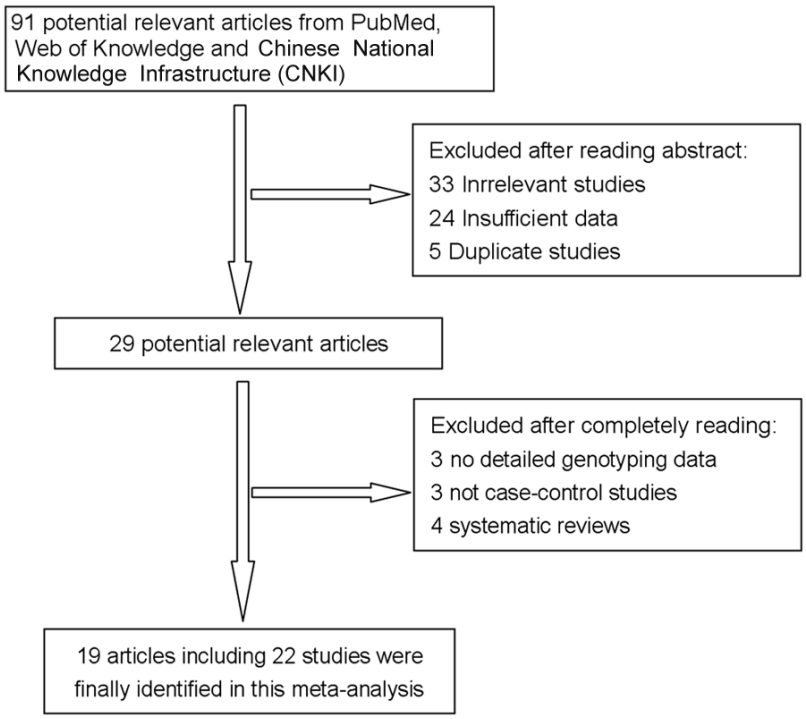

Figure 1. The flow chart of study selection process.

However, there was no significant association between rs1256049 and cancer risk in some other studies [11-14].

It is important to summarize inconclusive results from different studies to provide evidence on the association of one polymorphism with cancer risk [15]. To clarify the effect of the ESR2 rs1256049 polymorphism on cancer risk, we performed this meta-analysis on all eligible case-control studies to estimate the overall cancer risk of the rs1256049 polymorphism. Furthermore, we conducted the subgroup analysis by ethnicity and cancer type.

Materials and methods

Literature searching strategy

A comprehensive search strategy was conducted from Pubmed, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure (CNKI) using terms "cancer/carcinoma/tumor/neoplasm", "estrogen receptor beta/ESR2/ER-β" and "polymorphism/genotype/variation/SNP". The last search was updated on June 30, 2014. Furthermore, reference cited in the retrieved articles were also reviewed by a manual search to identify additional potential studies.

Selection criteria

The following criteria were used to select studies for further meta-analysis: (1) case-control study design; (2) investigation of the association between ESR2 rs1256049 polymorphism and cancer risk; (3) provision of detailed genotyping data; (4) Cancer cases diagnosed and confirmed by histopathology. Accordingly, case-only studies, reviews, duplicated publications or studies without sufficient genotyping data were excluded.

Data extraction and Quality score assessment

Articles were performed independently by two reviewers and data with discrepancies in identification were discussed by all authors. The following information was collected: first author, year of publication, country, ethnicity, source of control, genotyping method, cancer type, numble of cases and controls, genotype distribution in cases and controls. Different ethnicity descents were categorized as Caucasian, Asian, African, and "mixed". All the case and control groups were well controlled. The non-cancer controls no present evidence of any malignant disease. The quality of eligible studies was evaluated independently by two authors according to the scale of Thakkinstian et al. [16]. Scores ranged from 0 (lowest) to 10 (highest). Articles with scores ≤6 were considered "low-quality" studies, whereas those with scores >6 were considered "high-quality" studies.

Statistical analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the associations between ESR2 rs1256049 polymorphism and cancer risk. The significance of the pooled OR was determined by the Z test. Statistical heterogeneity among studies was assessed with the Q and I^2 statistics. The Q test and I^2 were claimed to test the variation which was

Table 1. Characteristics of the eligible studies

Study	Year	Country	Ethnicity	Cancer type	Genotyping medthod	Control Source	case/control	Quality score	HWE (*P*)
Wu [9]	2012	China	Asian	CRC	Taqman	HB	390/445	H	>0.05
Lim [11]	2012	Singapore	Asian	LC	Taqman	HB	559/988	H	>0.05
Srivastava [12]	2012	India	Asian	GBC	PCR-RFLP	HB	410/450	H	>0.05
Safarinejad [13]	2012	Iran	Asian	PC	PCR-RFLP	HB	162/324	L	>0.05
Paulus [14]	2011	USA	Caucasian	LC	TaqMan	PB	1021/826	H	>0.05
Park [17]	2010	China	Asian	BTC	TaqMan	HB	411/1681	H	>0.05
MARIE-GENICA [18]	2010	Germany	Caucasian	BC	MassARRAY	PB	3149/5489	H	>0.05
Sonoda [19]	2010	Japan	Asian	PC	TaqMan	HB	180/176	L	>0.05
Ashton [20]	2009	Australia	Caucasian	EC	PCR–RFLP	PB	191/291	L	NA
Iwasaki 1 [21]	2009	Brazil	Asian	BC	TaqMan	HB	467/467	H	>0.05
Iwasaki 2 [21]	2009	Brazil	Caucasian	BC	TaqMan	HB	379/379	H	>0.05
Nicolaiew [22]	2009	France	Caucasian	PC	DHPLC	HB	219/248	L	>0.05
BPC3 [10]	2008	USA	Caucasian	BC	TaqMan	PB	5789/7761	H	>0.05
Chen 1 [23]	2007	USA	African	PC	TaqMan	PB	778/966	H	>0.05
Chen 2 [23]	2007	USA	Asian	PC	TaqMan	PB	458/466	H	>0.05
Chen 3 [23]	2007	USA and Europe	Caucasian	PC	TaqMan	PB	5946/6576	H	>0.05
Maguire [8]	2005	Sweden	Caucasian	BC	Pyrosequencing	PB	723/480	H	>0.05
Sun [24]	2005	China	Asian	PC	Pyrosequencing	HB	40/86	L	NA
Setiawan [25]	2004	USA	Caucasian	EC	TaqMan	HB	222/666	H	>0.05
Fukatsu [26]	2004	Japan	Asian	PC	PCR	HB	147/266	L	NA
Forsti [27]	2003	Finland	Caucasian	BC	PCR–RFLP	HB	219/248	L	>0.05
Zheng [28]	2003	China	Asian	BC	MassARRAY	PB	1134/1235	H	>0.05

BC: breast cancer; EC: endometrial cancer; CRC: colorectal cancer; LC: lung cancer; GBC: gallbladder cancer; PC: prostate cancer; BTC: biliary tract cancers; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; DHPLC: denaturing high-performance liquid chromatography; HWE: Hardy-Weinberg equilibrium; PB: population based; HB: hospital-based; H: high-quality; L: low-quality; NA: not available.

due to heterogeneity or by random error. When *P* value of heterogeneity tests was no more than 0.1 ($P \leq 0.1$), we used random effects model. When *P* value of heterogeneity test was more than 0.1 ($P \geq 0.1$), we used fixed effects model. Sensitivity analysis was also tested by removing one study at a time to calculate the overall homogeneity and effect size. Publication bias were evaluated by the funnel plot and further assessed by the method of Egger's linear regression test. All statistical analyses were carried out with the review manager version 5.2 (Revman; The Cochrane Collaboration, Oxford, UK). All *P* values in the meta-analysis were two-sided, and *P* value less than 0.05 were considered significant.

Results

Characteristics of Studies

As show in **Figure 1**, 22 studies from 19 literatures were identified according to the eligible criteria, containing 22,994 cases and 30,514 controls [8-14, 17-28]. The main characteristics of these included studies were listed in **Table 1**. Among these studies, 21 were published in English and 1 was in Chinese. There were 10 studies conducted in Caucasians, 11 in Asians and 1 in Africans. All studies were case-control studies, including 7 breast cancer studies, 8 prostate cancer studies, 2 lung cancer studies, 2 endometrial cancer studies, one colorectal cancer study, one gallbladder cancer study, and one biliary tract cancers study. All cancers were confirmed by histology or pathology. Moreover, controls were mainly matched on age, of which 9 were population-based and 13 were hospital-based.

Meta-analysis results

The frequency of the A allele varied widely across the eligible studies, ranging from 0.04 to 0.66 (**Table 2**). The average frequency of the A allele in overall population, Caucasian population and Asian population were 0.10, 0.05, and 0.31, respectively. There was significant difference between Asians and Caucasians ($P<0.05$).

The main results of this meta-analysis were listed in **Table 3**. Overall, no significant association between rs1256049 and cancer risk was

Table 2. ESR2 rs1256049 polymorphism Genotype Distribution and Allele Frequency in Cases and Controls

Study	Genotype (N)								Allele frequency (N)				MAF
	Case				Control				Case		Control		
	total	GG	GA	AA	total	GG	GA	AA	G	A	G	A	
Wu 2012	383	168	215		441	167	274		-	-	-	-	-
Lim 2012	542	206	251	85	953	371	447	135	663	421	1189	717	0.39
Srivastava 2012	410	385	25	0	450	418	32	0	795	25	868	32	0.03
Safarinejad 2012	162	150	2	10	324	300	16	8	302	22	616	32	0.07
Paulus 2011	1021	972	49		826	783	43		-	-	-	-	
Park 2010	404	44	186	174	1660	210	737	713	274	534	1157	2163	0.66
MARIE-GENICA 2010	3146	2921	224	1	5480	5086	389	5	6066	226	10561	399	0.04
Sonoda 2010	180	96	84		176	93	83		-	-	-	-	-
Ashton 2009	191	172	18	1	289	273	16	0	362	20	562	16	0.05
Iwasaki 1 2009	467	250	187	30	467	230	208	29	687	247	668	266	0.26
Iwasaki 2 2009	379	342	36	1	379	345	32	2	720	38	722	36	0.05
Nicolaiew 2009	96	88	8	0	96	89	7	0	184	8	185	7	0.04
BPC3 2008	5647	4987	610	50	7555	6751	734	70	10584	710	14236	874	0.06
Chen 1 2007	778	657	115	6	966	819	143	4	1429	127	1781	151	0.08
Chen 2 2007	458	259	166	33	466	222	212	32	684	232	656	276	0.25
Chen 3 2007	5946	5442	488	16	6576	6096	471	9	11372	520	12663	489	0.04
Maguire 2005	681	628	52	1	398	356	41	1	1308	54	753	43	0.04
Sun 2005	40	15	16	9	86	40	35	11	46	34	115	57	0.42
Setiawan 2004	220	201	19		661	611	50		-	-	-	-	-
Fukatsu 2004	136	82	43	11	236	133	91	12	213	65	357	115	0.23
Forsti 2003	219	189	30	0	248	198	39	1	408	30	435	41	0.07
Zheng 2003	1113	480	506	127	1209	537	541	131	1466	760	1615	803	0.34

MAF: minor allele frequencies.

found under all genetic models (A vs. G: OR = 1.03, 95% CI = 0.99-1.08; AA vs. GG: OR = 1.12, 95% CI = 0.97-1.29; GA vs. GG: OR = 1.03, 95% CI = 0.97-1.09; GA+AA vs. GG: OR = 1.03, 95% CI = 0.98-1.09; AA vs. GG+GA: OR = 1.09, 95% CI = 0.96-1.23).

There were ten articles including 17,858 cases and 22,964 controls based on Caucasians used to evaluate the relationship between the rs1256049 polymorphism with cancer susceptibility. In the stratified analysis by ethnicity, as shown in **Table 3** and **Figure 2**, significantly increased cancer risk was found among Caucasians based on the allele contrast genetic model (OR = 1.09, 95% CI = 1.01-1.16, *P* = 0.02), heterozygote genetic model (OR = 1.10, 95% CI = 1.02-1.18, *P* = 0.01), and the dominant genetic model (OR = 1.09, 95% CI = 1.02-1.17, *P* = 0.02). However, no significant association was found among Asians in any genetic model (**Table 3**).

Seven studies containing 11,652 cases and 15,736 controls were used to evaluate the relationship between ESR2 rs1256049 polymorphism and breast cancer risk. In the stratified analysis by cancer type, as shown in **Table 3** and **Figure 3**, rs1256049 has no association with breast cancer risk in any genetic model (AA vs. GG: OR = 1.00, 95% CI = 0.82-1.22; GA vs. GG: OR = 1.04, 95% CI = 0.96-1.12; dominant model: OR = 1.03, 95% CI = 0.98-1.09 and recessive model: OR = 1.00, 95% CI = 0.83-1.21).

The association of the rs1256049 polymorphism and prostate cancer risk was investigated in eight studies including 7,796 cases and 8,926 controls. We found that the increased prostate cancer risk associated with the rs1256049 polymorphism in two genetic models (AA vs. GG: OR = 1.41, 95% CI = 1.02-1.96, *P* = 0.04 and the recessive model: OR = 1.52, 95% CI = 1.10-2.10, *P* = 0.01) (**Table 3** and **Figure 3**).

Table 3. Meta-analysis results

Comparisons	OR	95% CI	*P* value	Heterogeneity		Effects model
				I^2	*P* value	
A vs G	1.03	0.99-1.08	0.18	51%	0.006	Random
Caucasian	1.09	1.01-1.16	0.02	39%	0.12	Fixed
Asian	0.98	0.89-1.05	0.50	56%	0.02	Random
Breast cancer	1.02	0.96-1.09	0.48	17%	0.30	Fixed
Prostate cancer	1.05	0.96-1.15	0.30	74%	0.0007	Random
AA vs GG	1.12	0.97-1.29	0.11	0%	0.67	Fixed
Caucasian	1.04	0.76-1.43	0.80	0%	0.50	Fixed
Asian	1.13	0.97-1.32	0.12	0%	0.55	Fixed
Breast cancer	1.00	0.82-1.22	0.98	0%	0.91	Fixed
Prostate cancer	1.41	1.02-1.96	0.04	17%	0.30	Fixed
GA vs GG	1.03	0.97-1.09	0.27	44%	0.03	Random
Caucasian	1.10	1.02-1.18	0.01	18%	0.29	Fixed
Asian	0.93	0.84-1.02	0.14	46%	0.06	Random
Breast cancer	1.04	0.96-1.12	0.36	29%	0.21	Fixed
Prostate cancer	1.01	0.91-1.12	0.80	67%	0.006	Random
GA+AA vs GG	1.03	0.98-1.09	0.29	31%	0.08	Random
Caucasian	1.09	1.02-1.17	0.02	15%	0.31	Fixed
Asian	0.94	0.86-1.03	0.18	26%	0.20	Fixed
Breast cancer	1.03	0.96-1.11	0.40	25%	0.23	Fixed
Prostate cancer	1.04	0.95-1.15	0.40	51%	0.05	Random
AA vs GG+GA	1.09	0.96-1.23	0.17	0%	0.66	Fixed
Caucasian	1.03	0.75-1.41	0.86	0%	0.51	Fixed
Asian	1.09	0.96-1.24	0.19	0%	0.51	Fixed
Breast cancer	1.00	0.83-1.21	0.99	0%	0.92	Fixed
Prostate cancer	1.52	1.10-2.10	0.01	0%	0.54	Fixed

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias. As shown in **Figure 4**, the shape of funnel plots did not reveal any obvious asymmetry in all genotypes in overall population, and the results of Egger's test revealed no publication bias (*P*>0.05).

Discussion

Many studies have investigated the predictive and prognostic role of ER-β and thus observed a survival benefit and an enhanced response to tamoxifen treatment in women with high ER-β expression [29, 30]. In estrogen-sensitive malignancies, ER-β usually is a tumor suppressor [1]. The measurement of ER-β activity in sera could potentially serve as a prognostic marker to predict lung cancer survival, and selective blockage of ER-β signaling may have a role in lung cancer therapy [6]. Studies on the ESR2 gene in prostate cancer patients have found the SNPs of ESR may be linked with higher risk for being diagnosed to have advanced stage disease [31].

A previous meta-analysis by Yu et al. [32] reported no association between rs1256049 polymorphism and breast cancer risk. However, this meta-analysis was only involved breast cancer, and only 8 studies with 11,652 cases and 15,726 controls for rs1256049 in Yu's study [32]. The present meta-analysis, including 22,994 cases and 30,514 controls from 22 case-control studies, was conducted to evaluate the association between the rs1256049 polymorphism and cancer risk. Our study is the first meta-analysis for rs1256049 in the overall cancer risk and the largest one to date. We found no significant association between ESR2 rs1256049 G>A variant and cancer risk in overall population.

In the subgroup meta-analysis by ethnicity, compared with G allele, a significantly increased cancer risk is associated with A allele in Caucasians. Furthermore, compared with GG genotype, an increased cancer risk is associated with AA/GA genotype. However, no significant association was found in any genetic model among Asians. We cannot determine the effect on Africans because there were only one study based on America African.

When stratified analysis was performed by cancer type, we found no significant association between rs1256049 and breast cancer risk in any genetic model. Our findings were consistent with the previous meta-analysis [32]. However, rs1256049 polymorphism was significantly associated with the increased risk of prostate cancer (homozygote comparison: OR = 1.41, 95% CI = 1.02-1.96 and the recessive model: OR = 1.52, 95% CI = 1.10-2.10). There were only a few studies in the other cancers such as lung cancer, endometrial cancer, and

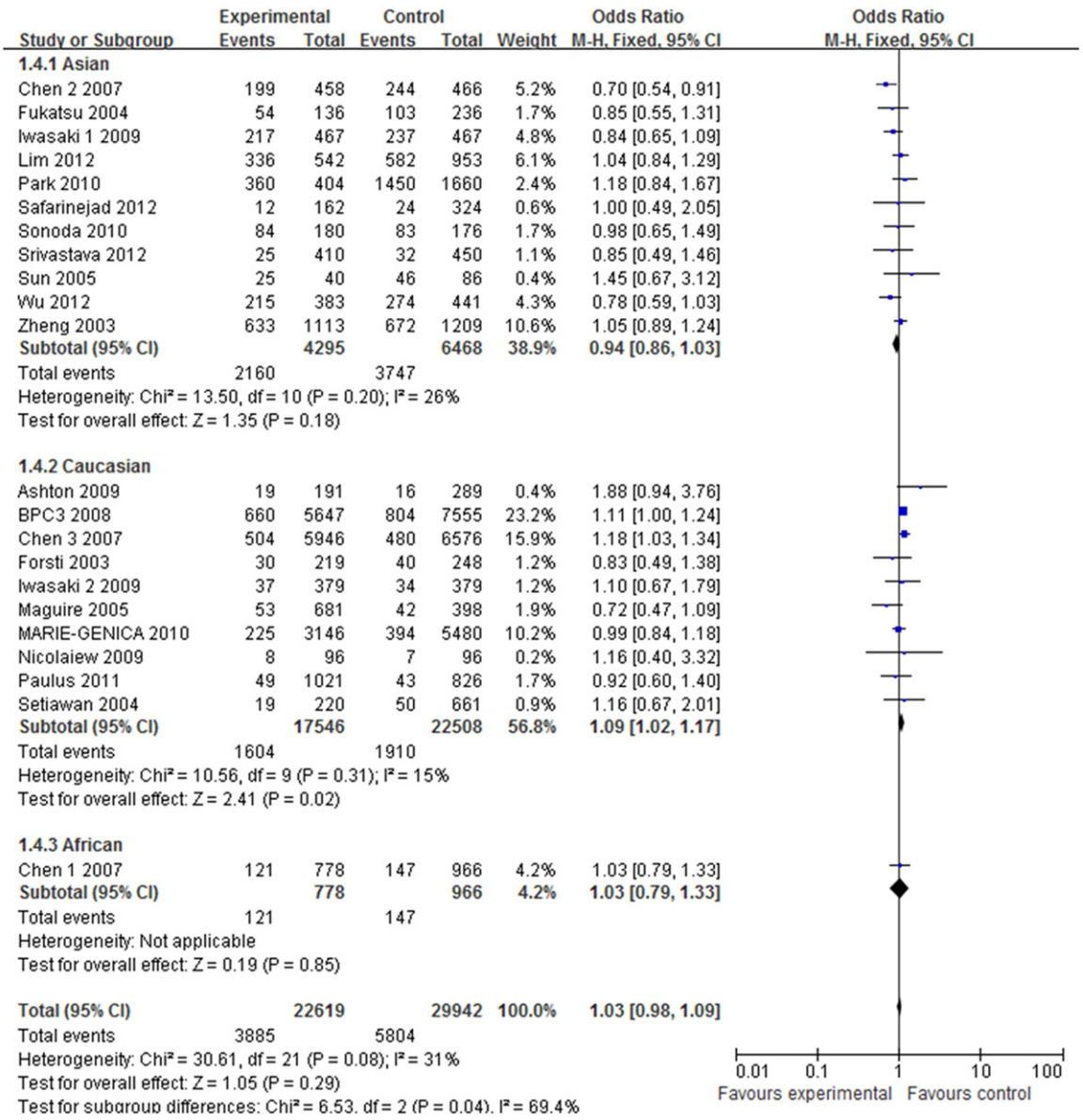

Figure 2. Subgroup analysis by ethnicity of ORs with a fixed-effects model for association between ESR2 rs1256049 polymorphism and cancer risk (AA+GA vs GG). CI, confidence interval; OR, odds ratio; M-H, Mantel-haenszel.

colorectal cancer. Further subgroup analyses were not performed because of limited data for this polymorphism.

In interpreting the results, some limitations of this meta-analysis should be noted. Firstly, though most controls were selected mainly from healthy populations, some had benign disease [12, 17], which might lead to misclassification bias because those controls have potential risks of developing cancer. Secondly, this meta-analysis was based on pooled data and no individual data was available; thus, we could not assess the risk of cancer according to stratification of age, environment factors, and other risk factors of cancer. Thirdly, only published studies were included in this meta-analysis. Finally, in the stratified analysis by cancer type, we only analyzed breast cancer and prostate cancer. Relatively limited study number made it impossible to perform subgroup analysis for other cancers. Moreover, further large scale multicenter studies with more detailed individual data, with different environmental background are warranted to further validated gene-gene and gene-environment interactions on ESR2 rs1256049 polymorphism and cancer risk.

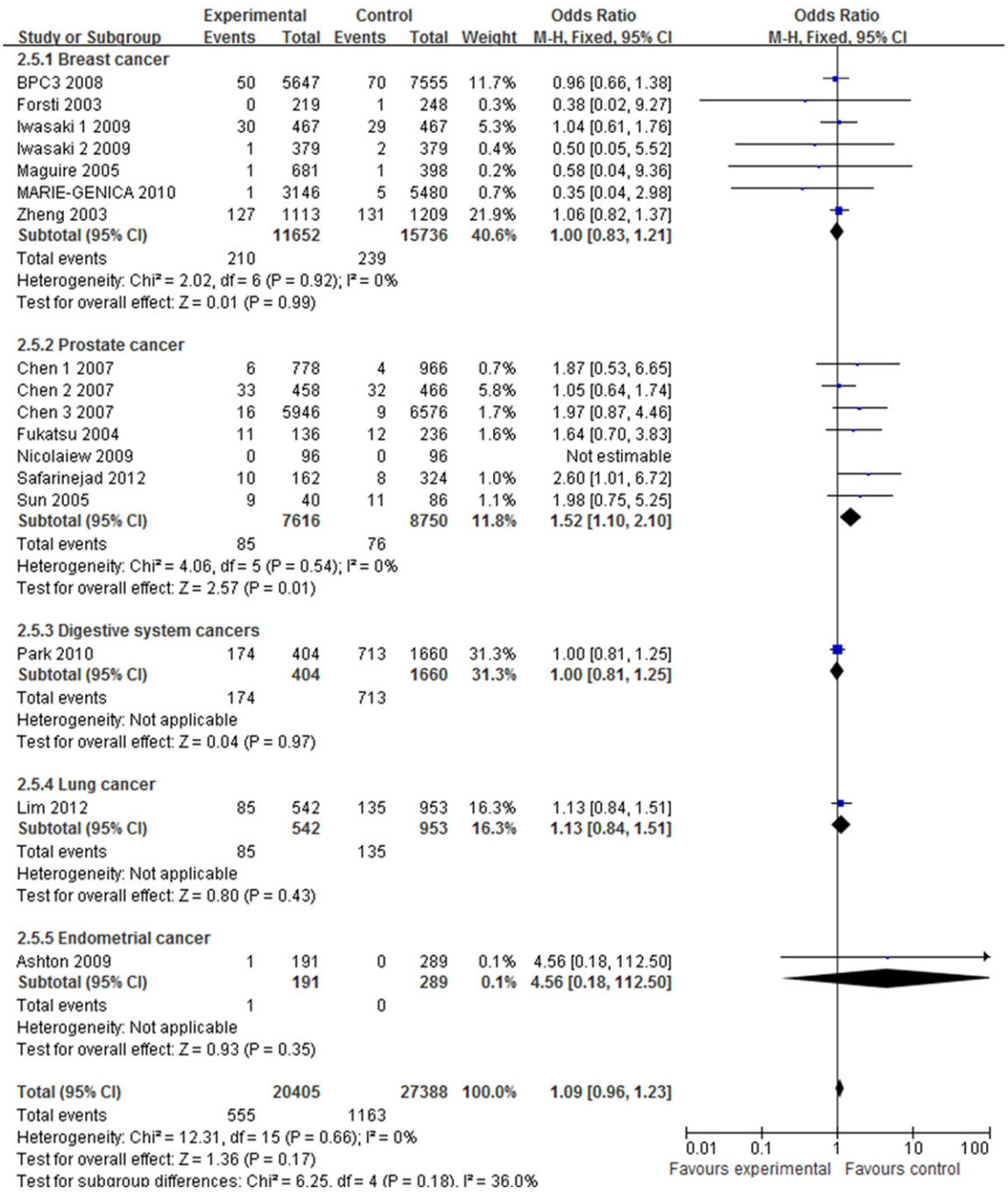

Figure 3. Subgroup analysis by cancer type of ORs with a fixed-effects model for association between ESR2 rs1256049 polymorphism and cancer risk (AA vs GG+GA). CI, confidence interval; OR, odds ratio; M-h, Mantel-haenszel.

Conclusion

In summary, our present meta-analysis provides evidence for the association of ESR2 rs1256049 polymorphism with cancer risk. ESR2 rs1256049 polymorphism plays a possible promoting effect in cancer in Caucasians, especially in prostate cancer. Further studies based on different ethnicities and various cancer types are warranted to verify our findings.

Acknowledgements

We acknowledge the Grants from the National Natural Science Foundation of China, No. 81471670, 81472822; the International

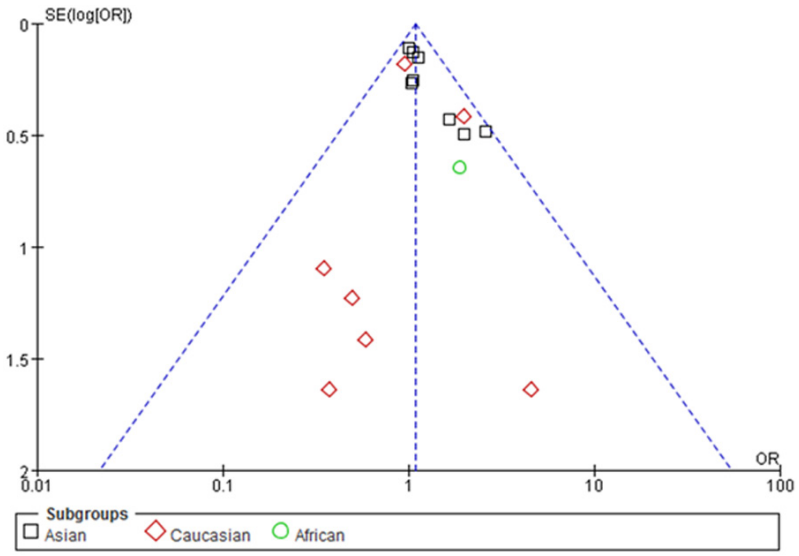

Figure 4. Funnel plot assessing evidence of publication bias from 22 studies (AA+GA vs. GG).

Cooperative Project of Shaanxi province, China, No. 2013KW-32-01; the Fundamental Research Funds for the Central Universities, China and Specialized Research Fund of the Second Affiliated Hospital of Xi'an Jiaotong University, China, No.RC (GG) 201203.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhi-Jun Dai, Department of Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, China. Tel: 86-29-8767-9226; Fax: 86-29-8767-9282; E-mail: dzj0911@126.com

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