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Original Article

Association of glutathione S-transferase T1, M1 and P1 polymorphisms in the breast cancer risk: a meta-analysis in Asian population

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Abstract: Background: Published data regarding the associations between glutathione S-transferase (*GST*) T1, M1 and P1 polymorphisms and breast cancer risk are inconclusive. The aim of this study is to comprehensively evaluate the genetic risk of *GST* genes for breast cancer. Materials and Methods: A systematic literature search was carried out in Pubmed, Medline (Ovid), Embase, CBM, CNKI, Weipu, and Wanfang database, covering all publications (last search was performed on May 20, 2015). Statistical analysis was performed using Revman 5.2 and STATA 12.0 softwares. Results: A total of 12,035 cases and 13,911 controls in 34 case-control studies were included in this meta-analysis. The results suggested that the *GSTM1* and *GSTP1* polymorphisms can obviously increase the risk of breast cancer in Asian population (odds ratio (OR) = 1.18, 95% confidence interval (CI) = 1.04-1.33, *P* = 0.008 and OR = 1.23, 95% CI = 1.07-1.41, *P* = 0.003, respectively), especially in East Asian (OR = 1.14, 95% CI = 1.01-1.27, *P* = 0.03 and OR = 1.15, 95% CI = 1.03-1.28, *P* = 0.01, respectively) and hospital-based case-control study (HCC) group (OR = 1.32, 95% CI = 1.11-1.56, *P* = 0.001 and OR = 1.38, 95% CI = 1.03-1.84, *P* = 0.03, respectively), while the association between *GSTT1* null genotype and breast cancer risk is not significant (OR = 1.08, 95% CI = 0.93-1.25, *P* = 0.3). Conclusions: This meta-analysis indicated that the *GSTM1* and *GSTP1* polymorphisms might significantly contribute to breast cancer susceptibility in Asian population, especially in East Asian, while the *GSTT1* polymorphism might not be associated with breast cancer.

Keywords: *GSTT1*, *GSTM1*, *GSTP1*, polymorphism, breast cancer, susceptibility, meta-analysis

Introduction

Breast cancer was reported to be the most frequently diagnosed cancer and one of the leading causes of cancer-related death in females worldwide, which has become a major public health challenge [1, 2]. Some studies suggested that Asian women were highly susceptible to breast cancer, and it was reported that the number of women with incident breast cancer in Asia was estimated at 651,000 in 2012, comprising 38.8% of all cases globally, followed by Europe (27.7% of all cases) and North America (15.3% of all cases) [3, 4]. Now, the mechanism of breast cancer is still not fully understood. It has been suggested that susceptibility genes combining with environmental factors may be important in the development of breast cancer [5, 6].

In recent years, several common genes have been identified as potential breast cancer susceptibility genes. An important one is glutathione S-transferase (GST), which plays a key role in the detoxification of a broad range of toxic and potentially carcinogenic compounds [7]. In humans, five common classes of GST enzymes have been identified (GST classes α, μ, π, ω and θ) and each class is encoded by a separate gene or gene family (respectively are *GSTA*, *GSTM*, *GSTP*, *GSTO* and *GSTT* genes). Allelic variants for each of these genes may result in less effective or absent enzymatic detoxification and thus increase susceptibility to cancer, although the exact biochemical processes are not yet fully understood. Among these genes, the deletion mutations in *GSTT1* and *GSTM1* and the amino acid transition (A313G→Ile105Val) in *GSTP1* to breast cancer risk have

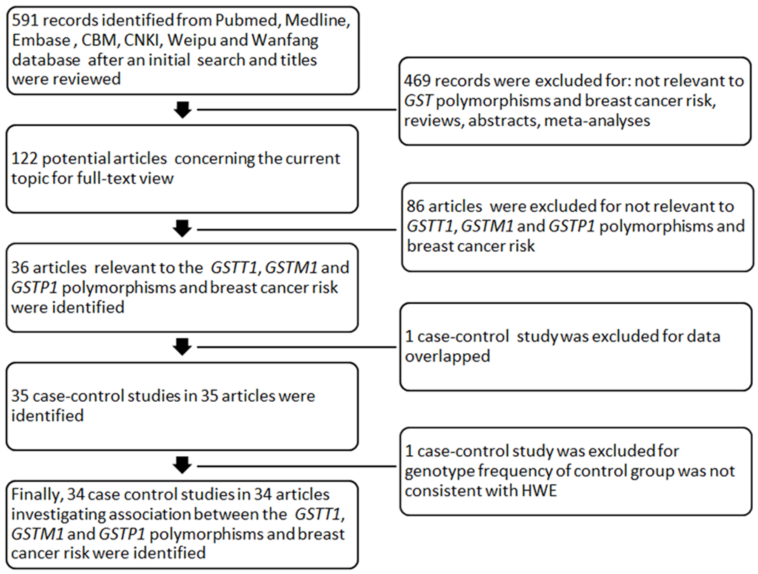


Figure 1. Flow diagram of included/excluded studies in this meta-analysis.

been a research focus in scientific community and have drawn increasing attention. Despite the fact that lots of the epidemiologic investigations studying the association of these three polymorphisms with breast cancer risk were conducted in the past decades, the available evidences are still weak at present, due to the possible small effect of each individual polymorphism on breast cancer risk and the relatively small sample size in each of published studies. Therefore, we performed the present meta-analysis aimed at utilizing the acquirable data of *GST* polymorphisms with breast cancer risk in Asian population to derive a more precise estimation of these associations and evaluating the trends in occurrence of breast cancer in this population.

Materials and methods

Selection of studies

A comprehensive literature search was carried out in Pubmed, Medline (Ovid), Embase, Chinese biomedical database (CBM), China national knowledge infrastructure (CNKI), Weipu and Wanfang database to identify studies involving association between the *GSTT1*, *GSTM1* and *GSTP1* polymorphisms and breast cancer risk in Asian population (last search was updated on May 20, 2015). The search terms were used as follows: (glutathione S-transferase T1) OR (glutathione S-transferase M1) OR (glutathione S-transferase P1) OR (*GSTT1*) OR (*GSTM1*) OR (*GSTP1*) in combination with (polymorphism) OR (variant) OR (mutation), (breast cancer) OR (breast carcinoma) OR (breast neoplasm) AND (Asia) OR (Asian). The search results were limited to English and Chinese languages. Studies included in our meta-analysis met the following inclusion criteria: (1) evaluation of the glutathione S-transferase T1, M1 and P1 polymorphisms and breast cancer risk in Asian population, (2) the design had to be a case-control design published in a journal, (3) genotype distributions in both cases and controls were available for estimating an odds ratio with 95% confidence interval (CI) and *P* value, and (4) genotype distributions in control group should be consistent with Hardy-Weinberg equilibrium (HWE). Studies were excluded if one of the following existed: (1) no controls, (2) genotype frequencies or numbers not reported, and (3) abstracts, reviews. For duplications or overlapping publications, the studies with larger number of cases and controls or been published latest were included.

Data extraction

Two independent reviewers (QXZ and JQT) collected the data and reached a consensus on all items. In case of disagreement, a third author (FZ) would assess these articles. A standardized data form was used and included: first author's name, year of publication, original country, subregion of Asia, case age, study design, total number of cases and controls and genotyping method.

Quality assessment

We evaluated the methodological quality of the included studies according to the Newcastle-Ottawa Scale (NOS) criteria [8]. The NOS criteria is scored based on three aspects: (1) subject selection, 0~4; (2) comparability of subject, 0~2; and (3) clinical outcome, 0~3. Total NOS scores range from 0 to 9, with scores ≥ 7 indicating good quality.

Statistical analysis

Odds ratios (OR) with 95% CI were used to assess the strength of association between the glutathione S-transferase T1, M1 and P1 polymorphisms and breast cancer risk in Asian population. We first examined *GSTT1* and *GSTM1* genotypes using (Null *vs* Present) model. Then, the relationship between the *GSTP1* polymorphism and susceptibility to breast cancer was estimated with the dominant (GG+AG *vs* AA) and allelic (G *vs* A) models. The pooled OR was calculated by a fixed-effect model or a random-effect model according to the heterogeneity. Heterogeneity was checked by a χ^2-based Q statistic and $P < 0.10$ was considered statistically significant. A P-value $\geq$ 0.10 for the Q-test indicated the lack of heterogeneity among the studies, and so the summary OR estimate of each study was calculated by the fixed-effect model [9]. Otherwise, the random-effect model was used [10]. The statistical significance of OR was analyzed by Z test, and $P < 0.05$ was considered statistically significant. To evaluate the subregion-specific, menopausal status-specific and study design-specific effects, we performed stratification analyses on subregion, menopausal status and study design. For the subgroup analysis by subregion, the study populations were stratified into four groups: East Asia, Southeast Asia, South Asia and West Asia. And for stratification analysis by menopausal status, the available study populations were stratified into two groups: premenopausal and postmenopausal. In addition, subjects were categorized into different classifications according to study design: population-based case-control study (PCC) and hospital-based case-control study (HCC). Sensitivity analysis was also performed by sequentially excluding individual study to check the robustness of the result [11]. The possible publication bias was examined visually in a Begg's funnel plot and the degree of asymmetry was tested by Egger's test ($P < 0.05$ was considered representative of statistically significant publication bias). HWE was tested by Pearson's x^2 test [12]. Statistical analysis was performed using Revman 5.2 and Stata 12.0 softwares.

Results

Study inclusion and characteristics

As shown in **Figure 1**, the initial search identified 591 results from the selected electronic databases. After reading the titles and abstracts, 122 potential articles were included for full-text view. After reading full texts, 86 studies were excluded for being irrelevant to the glutathione S-transferase T1, M1 and P1 polymorphisms and breast cancer risk. Therefore, 36 full-text articles remained for data extraction. 1 article was excluded for repeating or overlapping [13]. In addition, the control group genotype for *GSTP1* in 1 case-control study was not consistent with HWE and this study was excluded [14]. Finally, a total of 34 case-control studies published in 34 articles which met our inclusion criteria were identified, including 12,035 cases and 13,911 controls. The characteristics and methodological quality of each case-control study were listed in **Table 1**. *GST* genotypes and allele distributions for each case-control study are shown in **Table 2**. *GST* genotypes distributions for each case-control study in subgroup by menopausal status are shown in **Table 3**. There was 1 case-control study of *GSTT1* polymorphism [15], 3 of *GSTM1* polymorphism [16-18], 6 of *GSTP1* polymorphism [19-24], 10 of *GSTT1* and *GSTM1* polymorphisms [25-34], 2 of *GSTM1* and *GSTP1* polymorphisms [35, 36], 12 of *GSTT1*, *GSTM1* and *GSTP1* polymorphisms [37-48]. All the included 34 eligible reports were written in English or Chinese.

Quantitative data synthesis

GSTT1 polymorphism with breast cancer risk: In this meta-analysis, we found that *GSTT1* polymorphism was not associated with breast cancer risk in Asian population (OR = 1.08, 95% CI = 0.93-1.25, P = 0.30) (**Figure 2A**). However, in the subgroup analyses, this meta-analysis indicated that null/present polymorphism of *GSTT1* significantly increased breast cancer risk in East Asian (OR = 1.20, 95% CI = 1.00-1.45, P = 0.05), premenopausal (OR = 1.45, 95% CI = 1.10-1.93, P = 0.009) and HCC (OR = 1.30, 95% CI = 1.07-1.59, P = 0.009) groups. Interestingly, *GSTT1* polymorphism may have a lowered risk for breast cancer in Southeast Asian (OR = 0.73, 95% CI = 0.58-0.90, P = 0.004) (**Figure 3A**). The detailed data were listed in **Table 4**.

GSTM1 polymorphism with breast cancer risk: Using the random-effect model, significantly elevated breast cancer risk was associated with the *GSTM1* null/present polymorphism

Table 1. Baseline characteristics and methodological quality of all included studies in the meta-analysis

First author	Year	Country	Subregion	Case age (year)	Study design	Sample size (Cases/Controls)	Genotyping method	NOS score
Ceschi et al.	2005	Singapore	Southeast Asia	55.6 ± 7.4†	PCC	257/668	TaqMan & PCR	7
Chacko et al.	2005	India	South Asia	49 ± 10.3†	HCC	112/112	multiplex-PCR	6
Chang et al.	2006	China	East Asia	NM	HCC	189/420	PCR	7
Cheng et al.	2005	China	East Asia	NM	PCC	465/736	multiplex-PCR	7
Egan et al.	2004	China	East Asia	47	PCC	1143/1221	multiplex-PCR & RFLP-PCR	8
Gago-Dominguez et al.	2004	Singapore	Southeast Asia	NM	PCC	180/466	TaqMan	7
Ge et al.	2013	China	East Asia	54.3	HCC	920/783	TaqMan	7
Geng et al.	2010	China	East Asia	46.8	HCC	50/15	PCR	5
Hashemi et al.	2012	Iran	West Asia	47.9 ± 13.3†	HCC	134/152	multiplex-PCR & PCR	7
Kadouri et al.	2008	Israel	West Asia	NM	HCC	211/109	PCR	6
Kaushal et al.	2010	India	South Asia	45.5 ± 12.86†	PCC	117/174	RFLP-PCR	7
Khabaz et al.	2014	Jordan	West Asia	44.66	PCC	100/48	RFLP-PCR	5
Khabaz et al.	2015	Saudi Arabia	West Asia	54.6	HCC	86/35	PCR	5
Kim et al.	2004	Korea	East Asia	NM	HCC	171/171	RFLP-PCR	6
Lee et al.	2008	China	East Asia	49.6 ± 8.3†	PCC	3026/3037	RFLP-PCR & TaqMan	8
Li et al.	2008	China	East Asia	46.7 ± 8.75†	HCC	78/78	multiplex-PCR	8
Luo et al.	2012	China	East Asia	52.8 ± 8.8†	PCC	353/701	PCR	7
Ma et al.	2007	China	East Asia	46 ± 9†	HCC	105/100	PCR	7
Masoudi et al.	2010	Iran	West Asia	45.9	HCC	181/181	PCR	7
Nosheen et al.	2011	Pakistan	South Asia	48	PCC	150/150	PCR	7
Park et al.	2000	Korea	East Asia	NM	HCC	188/181	PCR	7
Park et al.	2004	Korea	East Asia	47.9 ± 11.2†	HCC	200/289	multiplex-PCR	7
Pongtheerat et al.	2009	Thailand	Southeast Asia	NM	HCC	43/56	mutiplex-PCR & PCR	5
Rajkumar et al.	2008	India	South Asia	46	PCC	250/500	PCR	7
Sakoda et al.	2008	China	East Asia	45	PCC	615/878	multiplex-PCR & PCR	8
Samson et al.	2007	India	South Asia	46	PCC	250/500	TaqMan & PCR	7
Saxena et al.	2009	India	South Asia	NM	HCC	406/403	multiplex-PCR & RFLP-PCR	7
Sohail et al.	2013	Pakistan	South Asia	NM	HCC	100/102	multiplex-PCR & PCR	7
Syamala et al.	2008	India	South Asia	NM	HCC	347/250	multiplex-PCR & RFLP-PCR	6
Wang et al.	2002	China	East Asia	49	PCC	42/108	PCR	5
Wu et al.	2002	China	East Asia	46.7 ± 10.2†	HCC	60/60	PCR	7
Wu et al.	2006	China	East Asia	49.11	HCC	262/225	PCR	7
Yu et al.	2009	China	East Asia	47.6 ± 10.6†	HCC	1017/903	RFLP-PCR	7
Zgheib et al.	2013	Lebanon	West Asia	48.9 ± 11.6†	HCC	227/99	PCR	7

HCC: hospital-based case-control study; PCC: population-based case-control study; NM: not mentioned; PCR: polymerase chain reaction; RFLP-PCR: polymerase chain reaction-restriction fragment length polymorphism; NOS: Newcastle-Ottawa Scale; †Mean ± SD.

when all 27 studies were pooled into the current study (OR = 1.18, 95% CI = 1.04-1.33, *P* = 0.008) (**Figure 2B**). In the subgroup analysis by subregion, obviously increased risk was found in East Asian (OR = 1.14, 95% CI = 1.01-1.27, *P* = 0.03), but no significant associations were found in other subregions. When stratified by menopausal status, statistically significantly increased risk was detected in premenopausal group (OR = 1.51, 95% CI = 1.23-1.86, *P* < 0.0001) but not in postmenopausal group (OR = 1.29, 95% CI = 0.96-1.73, *P* = 0.09). In the subgroup analysis by study design, the data suggested that *GSTM1* was significantly associated with breast cancer risk in HCC group (OR = 1.32, 95% CI = 1.11-1.56, *P* = 0.001) (**Figure 3B**). The detailed data were listed in **Table 4**.

GSTP1 polymorphism with breast cancer risk: Analysis using available data of *GSTP1* genotypes revealed statistical noteworthy association in Asian population (GG+AG *vs* AA: OR = 1.23, 95% CI = 1.07-1.41, *P* = 0.003; G *vs* A: OR = 1.30, 95% CI = 1.12-1.51, *P* = 0.0006) (**Figure 2C**, **2D**). Furthermore, the *GSTP1* A/G polymorphism might play an effective role in the risk of breast cancer in East Asian (GG+AG *vs* AA: OR = 1.15, 95% CI = 1.03-1.28, *P* = 0.01 and G *vs* A:

Table 2. Distribution of *GST* genotypes and allele among breast cancers and controls

Author	*GSTT1*				*GSTM1*				*GSTP1*										HWE[a] for control *P*
	Cases (n)		Controls (n)		Cases (n)		Controls (n)		Cases (n)			Controls (n)			Cases (n)		Controls (n)		
	Null	Present	Null	Present	Null	Present	Null	Present	GG	AG	AA	GG	AG	AA	G	A	G	A	
Ceschi et al.	87	169	282	385	119	137	298	369	9	87	161	27	199	442	105	409	253	1083	0.4429
Chang et al.	111	78	210	210	107	82	227	193	NA	66*	123	NA	133*	288	—	—	—	—	
Egan et al.	557	579	596	614	628	497	683	523	53	363	723	31	371	809	469	1809	433	1989	0.1315
Gago-Dominguez et al.	66	114	204	262	82	98	218	248	NA	65*	115	NA	162*	304	—	—	—	—	
Hashemi et al.	18	116	12	140	86	48	71	81	26	72	36	3	52	97	124	144	58	246	0.1833
Kadouri et al.	53	158	24	84	105	106	63	46	16	74	121	3	29	76	106	316	35	181	0.9073
Kaushal et al.	33	84	69	105	23	94	52	122	7	48	62	4	62	108	62	172	70	278	0.1515
Pongtheer at et al.	18	25	25	28	14	26	24	32	NA	13*	30	NA	21*	32	—	—	—	—	
Saxena et al.	96	310	88	315	215	191	134	269	66	193	147	32	171	200	325	487	235	571	0.5860
Sohail et al.	27	73	32	70	43	57	45	57	90	10	0	67	28	7	190	10	162	42	0.1050
Syamala et al.	56	291	23	227	119	228	63	187	21	140	186	16	109	125	182	512	141	359	0.2254
Zgheib et al.	43	183	20	78	111	115	47	51	NA	110*	117	NA	49*	49	—	—	—	—	
Sakoda et al.	—	—	—	—	321	294	428	450	20	215	378	30	277	569	255	971	337	1415	0.6000
Samson et al.	—	—	—	—	65	185	110	390	29	103	118	51	219	230	161	339	321	679	0.9150
Chacko et al.	29	83	10	102	40	72	28	84	—	—	—	—	—	—	—	—	—	—	
Cheng et al.	223	238	336	400	234	231	362	371	—	—	—	—	—	—	—	—	—	—	
li et al.	35	43	44	34	31	47	37	41	—	—	—	—	—	—	—	—	—	—	
Luo et al.	186	167	364	337	207	146	414	286	—	—	—	—	—	—	—	—	—	—	
Ma et al.	49	56	22	78	52	53	25	75	—	—	—	—	—	—	—	—	—	—	
Masoudi et al.	47	134	45	136	111	70	91	90	—	—	—	—	—	—	—	—	—	—	
Nosheen et al.	13	137	28	122	3	147	12	138	—	—	—	—	—	—	—	—	—	—	
Park et al. -2000	94	94	76	105	110	78	95	86	—	—	—	—	—	—	—	—	—	—	
Park et al. -2004	101	99	121	168	116	84	152	137	—	—	—	—	—	—	—	—	—	—	
Wu et al. -2002	27	33	26	34	34	26	25	35	—	—	—	—	—	—	—	—	—	—	
Rajkumar et al.	44	206	84	416	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Wang et al.	—	—	—	—	24	18	52	56	—	—	—	—	—	—	—	—	—	—	
Wu et al. -2006	—	—	—	—	123	139	103	122	—	—	—	—	—	—	—	—	—	—	
Yu et al.	—	—	—	—	622	395	510	393	—	—	—	—	—	—	—	—	—	—	
Ge et al.	—	—	—	—	—	—	—	—	55	325	540	34	230	519	435	1405	298	1268	0.1903
Geng et al.	—	—	—	—	—	—	—	—	NA	12*	38	NA	1*	14	—	—	—	—	
Khabaz et al. -2014	—	—	—	—	—	—	—	—	2	40	58	2	18	28	44	156	22	74	0.6704
Khabaz et al. -2015	—	—	—	—	—	—	—	—	1	45	40	2	14	19	47	125	18	52	0.7809
Kim et al.	—	—	—	—	—	—	—	—	5	44	122	6	52	113	54	288	64	278	0.9953
Lee et al.	—	—	—	—	—	—	—	—	123	953	1950	85	949	2003	1199	4853	1119	4955	0.2910

[a]HWE: Hardy-Weinberg equilibrium for controls of GSTP1 gene; NA: not available; *Numbers of GG+AG.

Table 3. Distribution of *GST* genotypes among breast cancers and controls in subgroup by menopausal status

Author	Premenopausal						Postmenopausal					
	Cases (n)			Controls (n)			Cases (n)			Controls (n)		
	Null	Present		Null	Present		Null	Present		Null	Present	
GSTT1												
Chacko et al.	9	45		3	51		6	52		7	51	
Hashemi et al.	9	54		8	111		9	62		4	29	
Park et al. -2000	57	57		42	55		37	37		32	48	
Park et al. -2004	61	59		75	92		40	40		46	76	
Saxena et al.	34	146		24	150		62	164		64	165	
GSTM1												
Chacko et al.	9	45		3	51		6	52		7	51	
Hashemi et al.	9	54		8	111		9	62		4	29	
Park et al. -2000	57	57		42	55		37	37		32	48	
Park et al. -2004	61	59		75	92		40	40		46	76	
Saxena et al.	34	146		24	150		62	164		64	165	
Chacko et al.	9	45		3	51		6	52		7	51	
Hashemi et al.	9	54		8	111		9	62		4	29	
GSTM1												
	GG	AG	AA	GG	AG	AA	GG	AG	AA	GG	AG	AA
Kim et al.	2	32	67	4	27	70	3	12	55	2	25	43
Lee et al.	86	579	1161	48	553	1096	37	374	789	37	396	907
Sakoda et al.	11	100	181	18	156	353	9	115	197	12	121	216
Saxena et al.	18	92	70	14	106	51	48	101	77	18	65	149

OR = 1.14, 95% CI = 1.04-1.26, *P* = 0.006), HCC (GG+AG *vs* AA: OR = 1.38, 95% CI = 1.03-1.84, *P* = 0.03 and G *vs* A: OR = 1.58, 95% CI = 1.14-2.19, *P* = 0.006) and PCC (GG+AG *vs* AA: OR = 1.10, 95% CI = 1.02-1.19, *P* = 0.01 and G *vs* A: OR = 1.11, 95% CI = 1.04-1.19, *P* = 0.001) groups. In the subgroup analysis by menopausal status, no associations were detected in premenopausal or postmenopausal groups not only under dominant model (GG+AG *vs* AA: OR = 1.23, 95% CI = 0.85-1.77, *P* = 0.27 and OR = 1.55, 95% CI = 0.84-2.84, *P* = 0.16, respectively) but also under allelic model (G *vs* A: OR = 1.26, 95% CI = 0.92-1.72, *P* = 0.15 and OR = 1.46, 95% CI = 0.88-2.44, *P* = 0.14, respectively) (**Figure 3C**, **3D**). The detailed data were listed in **Table 4**.

Sensitivity analysis

The one-way sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. After sequentially excluding each case-control study, the corresponding pooled ORs were not materially altered (**Figure 4**), confirming that our meta-analysis was statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. As shown in **Figure 5**, the shapes of the funnel plots did not show obvious asymmetry. In addition, the results of Egger's test also revealed the absence of publication bias in the *GSTT1* (*P* = 0.493 for Null *vs* Present model), *GSTM1* (*P* = 0.836 for Null *vs* Present model) and *GSTP1* (*P* = 0.204 for dominant model GG+AG *vs* AA and *P* = 0.170 for allelic model G *vs* A) polymorphisms.

Discussion

The glutathione S-transferase (GST) family is an important phase II isoenzyme which can implicate in the inactivation of procarcinogens and detoxify environmental carcinogens and

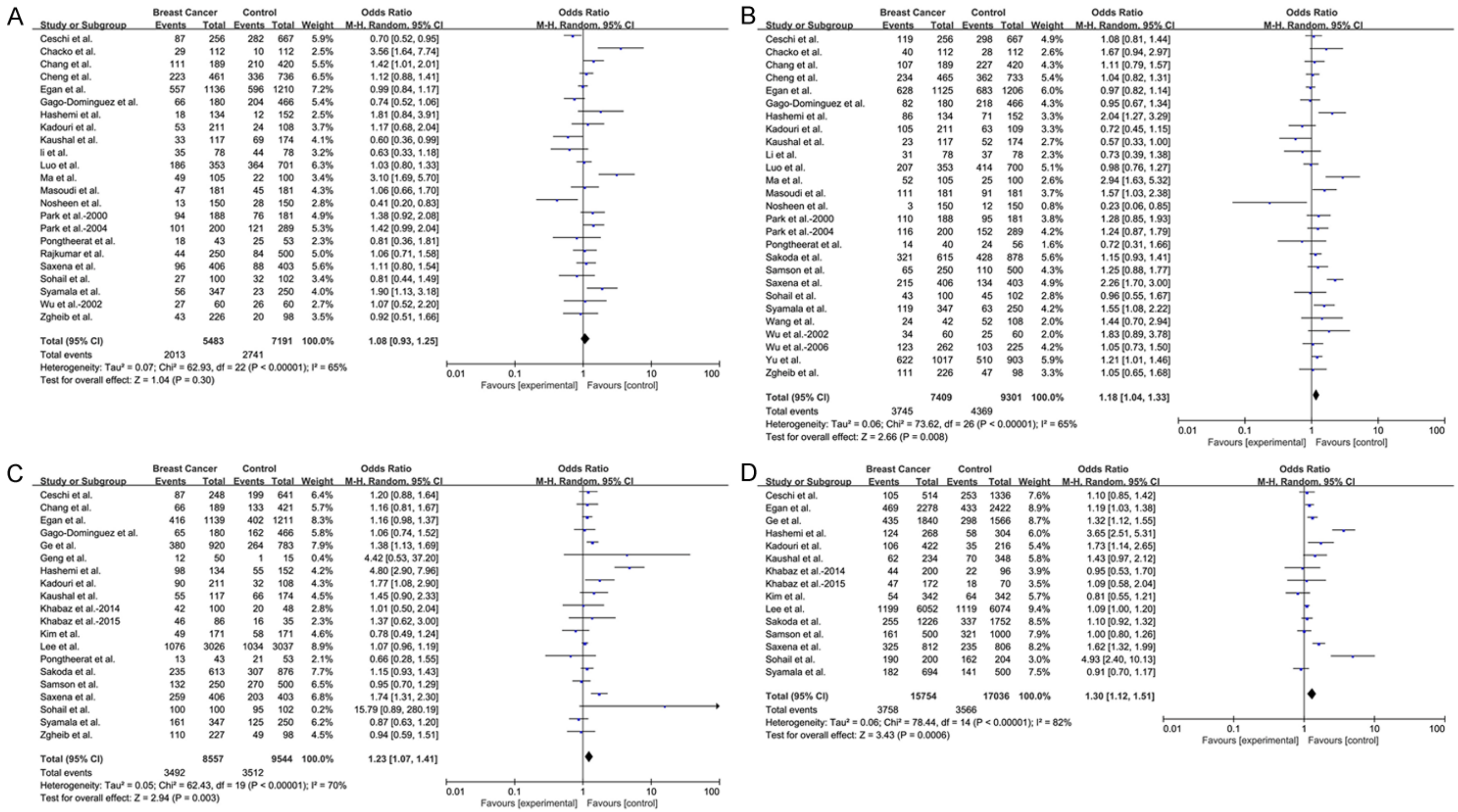


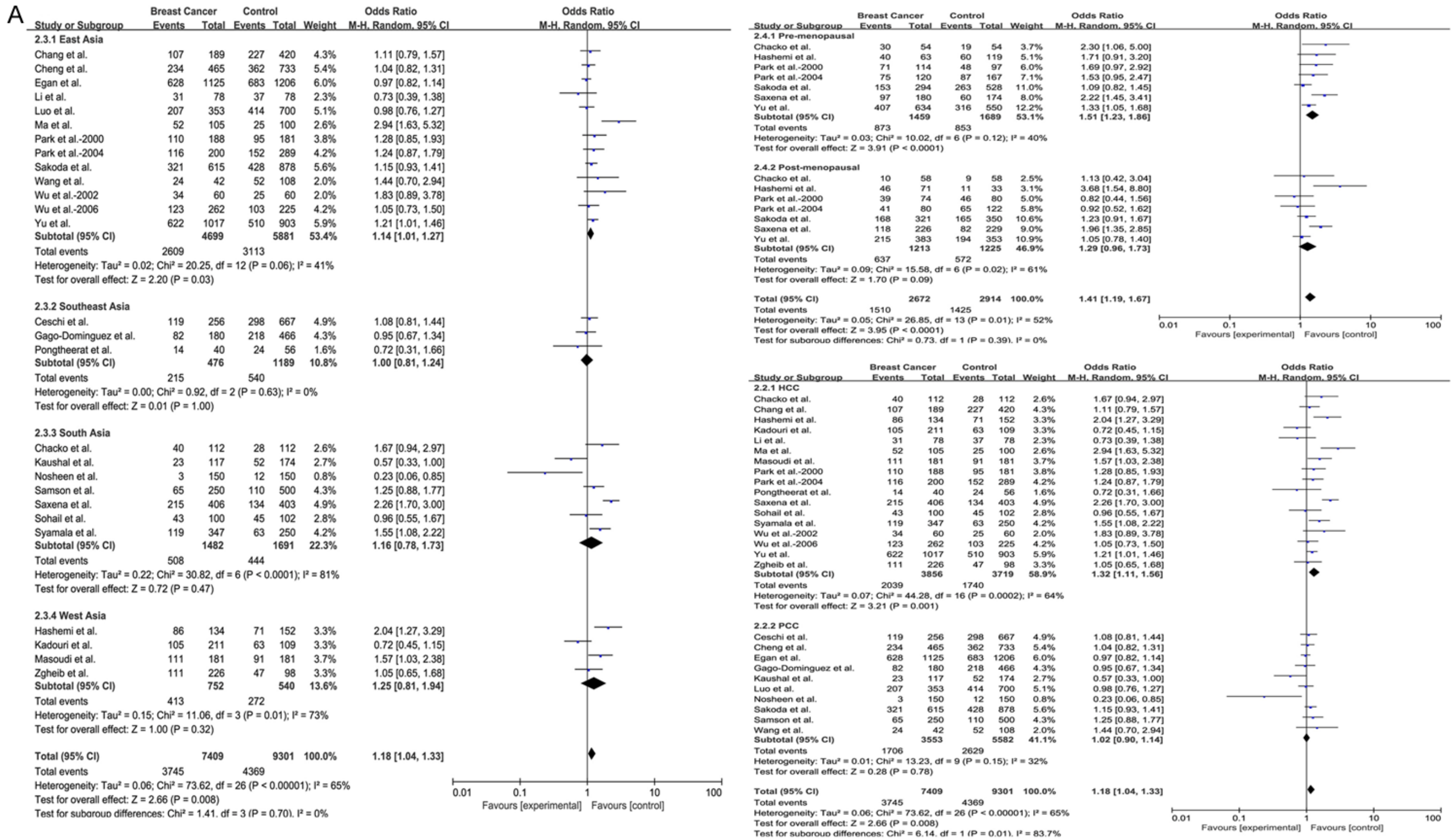
Figure 2. Forest plots for the association between *GST* polymorphisms and breast cancer risk. *Boxes* represent the ORs of individual studies, and *diamonds* represent the overall OR. *Horizontal lines* represent the 95% CI. A. *GSTT1* polymorphism. B. *GSTM1* polymorphism. C. *GSTP1* polymorphism under dominant model (GG+AG *vs* AA). D. *GSTP1* polymorphism under allelic model (G *vs* A).

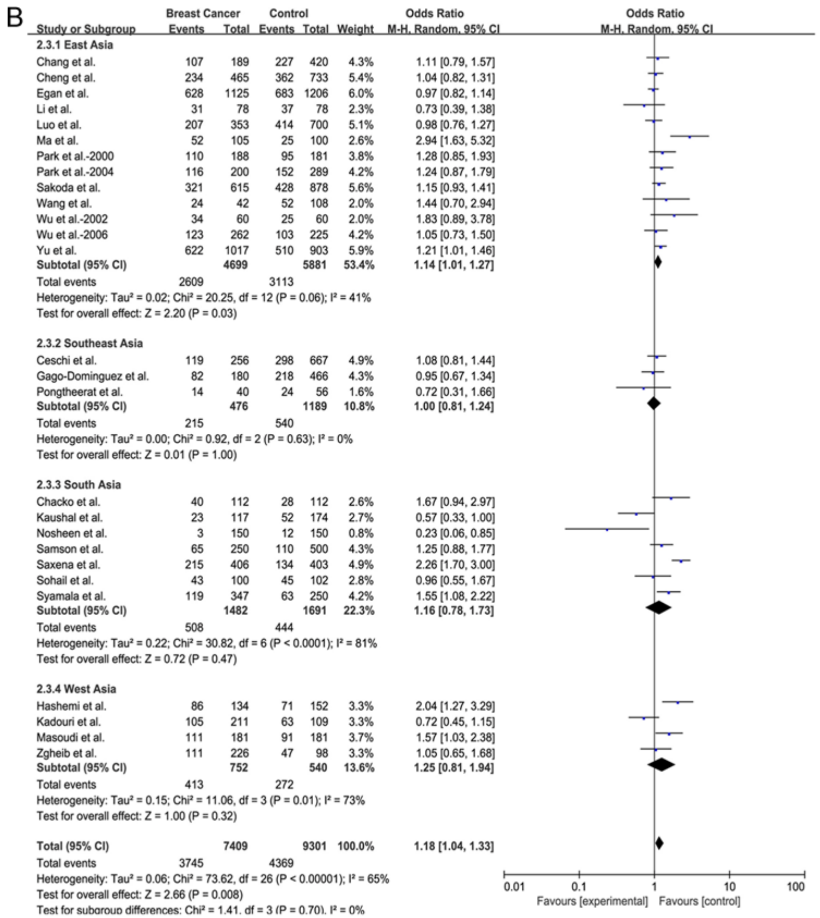
toxins [7, 49]. Given the important roles of GST in breast cancer etiology makes it possible that genetic variations of the *GST* genes may affect the susceptibility to the development of breast cancer. At present, some studies found that some mutant sites of the *GSTT1*, *GSTM1* and *GSTP1* might play roles in the multifunctional physiological processes in breast cancer. However, results on the associations of these polymorphisms with breast cancer risk have been controversial since the first investigation was reported. In our study, we evaluated whether the *GSTT1* and *GSTM1* null/present and *GSTP1* A/G polymorphisms could become valuable indicators to predict the risk of breast cancer, and tried to derive a more stable conclusion using meta-analysis method.

To the best of our knowledge, the present study is the first meta-analysis of the literature performed to explore the association between *GST* polymorphisms and breast cancer risk in Asian population. This analysis of pooled individual data revealed no noteworthy associations between *GSTT1* null genotype and breast cancer risk in Asian population, while significantly increased risks for *GSTM1* null and *GSTP1* GG/AG genotypes were observed in breast cancer.

With regard to the subregion, we concluded that *GSTT1*, *GSTM1* and *GSTP1* polymorphisms conferred significant increase in the risk of breast cancer in East Asian, and we also detected a 44% increase in the risk of breast cancer under allelic model in South Asian for *GSTP1*. In contrast to these findings, however, there was a suggestion that the carriers of *GSTT1* null genotype had a 27% lowered risk of breast cancer in Southeast Asian. In addition, our results indicated the lack of association between the all three polymorphisms and breast cancer risk in West Asian. These results could be due to the fact that almost half of the studies were about East Asian people (weighted more than 40% in all comparisons for the all three polymorphisms), therefore the analyses on Southeast Asian and West Asian might be insufficient. And there was another explanation that the geographically diverse populations might contribute to the possible presence of heterogeneity between the studies and affect the results of genetic association studies. By analyzing the subgroup by menopausal status, our results indicated that *GSTT1* and *GSTM1* polymorphisms were obviously associated with premenopausal breast cancer, while no evidence of positive estimates was observed in both premenopausal and postmenopausal groups for *GSTP1*. Possible explanation to these different results may be that the *GST* genes are, almost in part, under the control of sex hormones which may have association with the risk of breast cancer and the premenopausal women have a higher level of sex hormones than the postmenopausal women, which may cause a high susceptibility to breast cancer in premenopausal women [50]. There are also other explanations. For example, our case patients were slightly younger and, therefore, the proportion of premenopausal women in cases may be higher than that in controls. In addition, there might be more premenopausal women in case patients of our studies exposed to cigarette smoking and alcohol which contain a wide variety of potentially carcinogenic compounds. These two factors would cause a bias toward a false positive finding. Unluckily, no adequate data were available for stratified analyses by smoking status, drinking status, age and hormone levels. Data from future indepth research regarding the gene-environment interactions and the role of hormone levels in the development of premenopausal breast cancer among Asian women may further interpret this issue. When summarizing the results of stratification analysis by study design, the HCC group was more strongly associated with the risk of breast cancer in *GSTT1*, *GSTM1* and *GSTP1* polymorphisms compared with PCC group. This reason may be that the hospital-based studies have some biases because such controls may be just the representative of a sample of ill-defined reference population, and may not represent the general population very well.

Heterogeneity is one of the potential problems when elucidating the results of the present meta-analysis. Although we minimized the likelihood by performing a careful search for published studies, using the explicit criteria for study inclusion, performing data extraction and data analysis strictly, the significant between-study heterogeneity still existed not only in null/present model for *GSTT1* and *GSTM1*, but also in both dominant and allelic models for *GSTP1*. After subgroup analyses by subregion, menopausal status and study design, the heterogeneity was effectively removed in Southeast


A
Study or Subgroup | Breast Cancer Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI
Odds Ratio M-H, Random, 95% CI
2.3.1 East Asia
Chang et al. 107 189 227 420 4.3% 1.11 [0.79, 1.57]
Cheng et al. 234 465 362 733 5.4% 1.04 [0.82, 1.31]
Egan et al. 628 1125 683 1206 6.0% 0.97 [0.82, 1.14]
Li et al. 31 78 37 78 2.3% 0.73 [0.39, 1.38]
Luo et al. 207 353 414 700 5.1% 0.98 [0.76, 1.27]
Ma et al. 52 105 25 100 2.6% 2.94 [1.63, 5.32]
Park et al.-2000 110 188 95 181 3.8% 1.28 [0.85, 1.93]
Park et al.-2004 116 200 152 289 4.2% 1.24 [0.87, 1.79]
Sakoda et al. 321 615 428 878 5.6% 1.15 [0.93, 1.41]
Wang et al. 24 42 52 108 2.0% 1.44 [0.70, 2.94]
Wu et al.-2002 34 60 25 60 2.0% 1.83 [0.89, 3.78]
Wu et al.-2006 123 262 103 225 4.2% 1.05 [0.73, 1.50]
Yu et al. 622 1017 510 903 5.9% 1.21 [1.01, 1.46]
Subtotal (95% CI) 4699 5881 53.4% 1.14 [1.01, 1.27]
Total events 2609 3113
Heterogeneity: Tau² = 0.02; Chi² = 20.25, df = 12 (P = 0.06); I² = 41%
Test for overall effect: Z = 2.20 (P = 0.03)
2.3.2 Southeast Asia
Ceschi et al. 119 256 298 667 4.9% 1.08 [0.81, 1.44]
Gago-Dominguez et al. 82 180 218 466 4.3% 0.95 [0.67, 1.34]
Pongtheerat et al. 14 40 24 56 1.6% 0.72 [0.31, 1.66]
Subtotal (95% CI) 476 1189 10.8% 1.00 [0.81, 1.24]
Total events 215 540
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)
2.3.3 South Asia
Chacko et al. 40 112 28 112 2.6% 1.67 [0.94, 2.97]
Kaushal et al. 23 117 52 174 2.7% 0.57 [0.33, 1.00]
Nosheen et al. 3 150 12 150 0.8% 0.23 [0.06, 0.85]
Samson et al. 65 250 110 500 4.3% 1.25 [0.88, 1.77]
Saxena et al. 215 406 134 403 4.9% 2.26 [1.70, 3.00]
Sohail et al. 43 100 45 102 2.8% 0.96 [0.55, 1.67]
Syamala et al. 119 347 63 250 4.2% 1.55 [1.08, 2.22]
Subtotal (95% CI) 1482 1691 22.3% 1.16 [0.78, 1.73]
Total events 508 444
Heterogeneity: Tau² = 0.22; Chi² = 30.82, df = 6 (P < 0.0001); I² = 81%
Test for overall effect: Z = 0.72 (P = 0.47)
2.3.4 West Asia
Hashemi et al. 86 134 71 152 3.3% 2.04 [1.27, 3.29]
Kadouri et al. 105 211 63 109 3.3% 0.72 [0.45, 1.15]
Masoudi et al. 111 181 91 181 3.7% 1.57 [1.03, 2.38]
Zgheib et al. 111 226 47 98 3.3% 1.05 [0.65, 1.68]
Subtotal (95% CI) 752 540 13.6% 1.25 [0.81, 1.94]
Total events 413 272
Heterogeneity: Tau² = 0.15; Chi² = 11.06, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 1.00 (P = 0.32)
Total (95% CI) 7409 9301 100.0% 1.18 [1.04, 1.33]
Total events 3745 4369
Heterogeneity: Tau² = 0.06; Chi² = 73.62, df = 26 (P < 0.00001); I² = 65%
Test for overall effect: Z = 2.66 (P = 0.008)
Test for subgroup differences: Chi² = 1.41, df = 3 (P = 0.70), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
Study or Subgroup | Breast Cancer Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI
Odds Ratio M-H, Random, 95% CI
2.4.1 Pre-menopausal
Chacko et al. 30 54 19 54 3.7% 2.30 [1.06, 5.00]
Hashemi et al. 40 63 60 119 5.1% 1.71 [0.91, 3.20]
Park et al.-2000 71 114 48 97 6.0% 1.69 [0.97, 2.92]
Park et al.-2004 75 120 87 167 7.1% 1.53 [0.95, 2.47]
Sakoda et al. 153 294 263 528 11.0% 1.09 [0.82, 1.45]
Saxena et al. 97 180 60 174 8.0% 2.22 [1.45, 3.41]
Yu et al. 407 634 316 550 12.2% 1.33 [1.05, 1.68]
Subtotal (95% CI) 1459 1689 53.1% 1.51 [1.23, 1.86]
Total events 873 853
Heterogeneity: Tau² = 0.03; Chi² = 10.02, df = 6 (P = 0.12); I² = 40%
Test for overall effect: Z = 3.91 (P < 0.0001)
2.4.2 Post-menopausal
Chacko et al. 10 58 9 58 2.5% 1.13 [0.42, 3.04]
Hashemi et al. 46 71 11 33 3.1% 3.68 [1.54, 8.80]
Park et al.-2000 39 74 46 80 5.0% 0.82 [0.44, 1.56]
Park et al.-2004 41 80 65 122 5.8% 0.92 [0.52, 1.62]
Sakoda et al. 168 321 165 350 10.6% 1.23 [0.91, 1.67]
Saxena et al. 118 226 82 229 9.0% 1.96 [1.35, 2.85]
Yu et al. 215 383 194 353 10.9% 1.05 [0.78, 1.40]
Subtotal (95% CI) 1213 1225 46.9% 1.29 [0.96, 1.73]
Total events 637 572
Heterogeneity: Tau² = 0.09; Chi² = 15.58, df = 6 (P = 0.02); I² = 61%
Test for overall effect: Z = 1.70 (P = 0.09)
Total (95% CI) 2672 2914 100.0% 1.41 [1.19, 1.67]
Total events 1510 1425
Heterogeneity: Tau² = 0.05; Chi² = 26.85, df = 13 (P = 0.01); I² = 52%
Test for overall effect: Z = 3.95 (P < 0.0001)
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
Study or Subgroup | Breast Cancer Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI
Odds Ratio M-H, Random, 95% CI
2.2.1 HCC
Chacko et al. 40 112 28 112 2.6% 1.67 [0.94, 2.97]
Chang et al. 107 189 227 420 4.3% 1.11 [0.79, 1.57]
Hashemi et al. 86 134 71 152 3.3% 2.04 [1.27, 3.29]
Kadouri et al. 105 211 63 109 3.3% 0.72 [0.45, 1.15]
Li et al. 31 78 37 78 2.3% 0.73 [0.39, 1.38]
Ma et al. 52 105 25 100 2.6% 2.94 [1.63, 5.32]
Masoudi et al. 111 181 91 181 3.7% 1.57 [1.03, 2.38]
Park et al.-2000 110 188 95 181 3.8% 1.28 [0.85, 1.93]
Park et al.-2004 116 200 152 289 4.2% 1.24 [0.87, 1.79]
Pongtheerat et al. 14 40 24 56 1.6% 0.72 [0.31, 1.66]
Saxena et al. 215 406 134 403 4.9% 2.26 [1.70, 3.00]
Sohail et al. 43 100 45 102 2.8% 0.96 [0.55, 1.67]
Syamala et al. 119 347 63 250 4.2% 1.55 [1.08, 2.22]
Wu et al.-2002 34 60 25 60 2.0% 1.83 [0.89, 3.78]
Wu et al.-2006 123 262 103 225 4.2% 1.05 [0.73, 1.50]
Yu et al. 622 1017 510 903 5.9% 1.21 [1.01, 1.46]
Zgheib et al. 111 226 47 98 3.3% 1.05 [0.65, 1.68]
Subtotal (95% CI) 3856 3719 58.9% 1.32 [1.11, 1.56]
Total events 2039 1740
Heterogeneity: Tau² = 0.07; Chi² = 44.28, df = 16 (P = 0.0002); I² = 64%
Test for overall effect: Z = 3.21 (P = 0.001)
2.2.2 PCC
Ceschi et al. 119 256 298 667 4.9% 1.08 [0.81, 1.44]
Cheng et al. 234 465 362 733 5.4% 1.04 [0.82, 1.31]
Egan et al. 628 1125 683 1206 6.0% 0.97 [0.82, 1.14]
Gago-Dominguez et al. 82 180 218 466 4.3% 0.95 [0.67, 1.34]
Kaushal et al. 23 117 52 174 2.7% 0.57 [0.33, 1.00]
Luo et al. 207 353 414 700 5.1% 0.98 [0.76, 1.27]
Nosheen et al. 3 150 12 150 0.8% 0.23 [0.06, 0.85]
Sakoda et al. 321 615 428 878 5.6% 1.15 [0.93, 1.41]
Samson et al. 65 250 110 500 4.3% 1.25 [0.88, 1.77]
Wang et al. 24 42 52 108 2.0% 1.44 [0.70, 2.94]
Subtotal (95% CI) 3553 5582 41.1% 1.02 [0.90, 1.14]
Total events 1706 2629
Heterogeneity: Tau² = 0.01; Chi² = 13.23, df = 9 (P = 0.15); I² = 32%
Test for overall effect: Z = 0.28 (P = 0.78)
Total (95% CI) 7409 9301 100.0% 1.18 [1.04, 1.33]
Total events 3745 4369
Heterogeneity: Tau² = 0.06; Chi² = 73.62, df = 26 (P < 0.00001); I² = 65%
Test for overall effect: Z = 2.66 (P = 0.008)
Test for subgroup differences: Chi² = 6.14, df = 1 (P = 0.01), I² = 83.7%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]


B
Study or Subgroup | Breast Cancer Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI
Odds Ratio M-H, Random, 95% CI
2.3.1 East Asia
Chang et al. 107 189 227 420 4.3% 1.11 [0.79, 1.57]
Cheng et al. 234 465 362 733 5.4% 1.04 [0.82, 1.31]
Egan et al. 628 1125 683 1206 6.0% 0.97 [0.82, 1.14]
Li et al. 31 78 37 78 2.3% 0.73 [0.39, 1.38]
Luo et al. 207 353 414 700 5.1% 0.98 [0.76, 1.27]
Ma et al. 52 105 25 100 2.6% 2.94 [1.63, 5.32]
Park et al.-2000 110 188 95 181 3.8% 1.28 [0.85, 1.93]
Park et al.-2004 116 200 152 289 4.2% 1.24 [0.87, 1.79]
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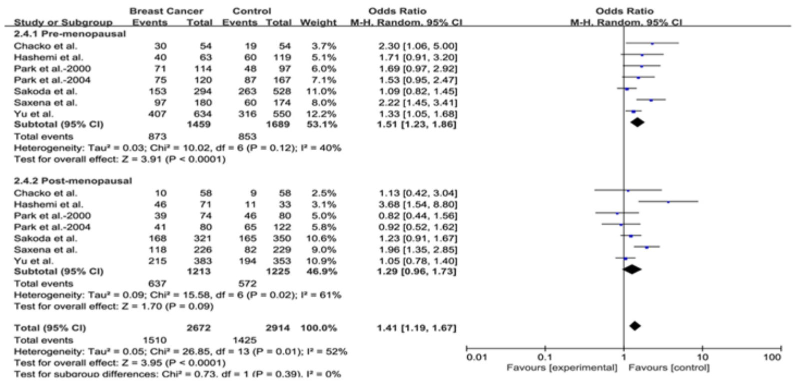
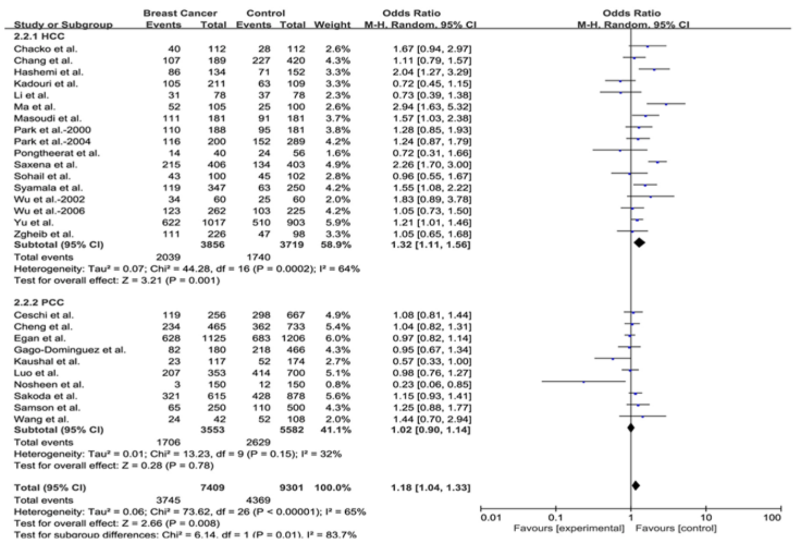
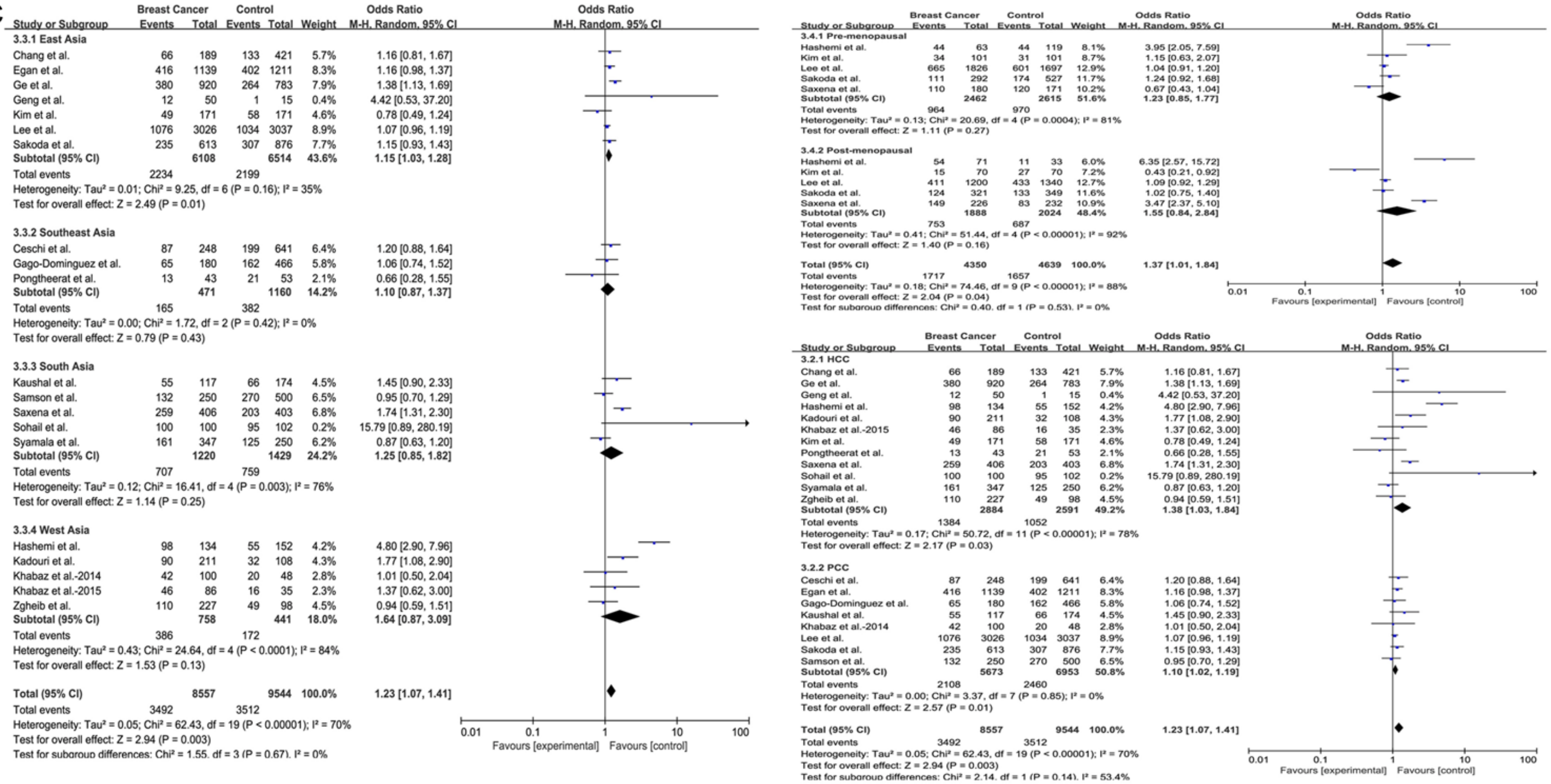
Wang et al. 24 42 52 108 2.0% 1.44 [0.70, 2.94]
Wu et al.-2002 34 60 25 60 2.0% 1.83 [0.89, 3.78]
Wu et al.-2006 123 262 103 225 4.2% 1.05 [0.73, 1.50]
Yu et al. 622 1017 510 903 5.9% 1.21 [1.01, 1.46]
Subtotal (95% CI) 4699 5881 53.4% 1.14 [1.01, 1.27]
Total events 2609 3113
Heterogeneity: Tau² = 0.02; Chi² = 20.25, df = 12 (P = 0.06); I² = 41%
Test for overall effect: Z = 2.20 (P = 0.03)
2.3.2 Southeast Asia
Ceschi et al. 119 256 298 667 4.9% 1.08 [0.81, 1.44]
Gago-Dominguez et al. 82 180 218 466 4.3% 0.95 [0.67, 1.34]
Pongtheerat et al. 14 40 24 56 1.6% 0.72 [0.31, 1.66]
Subtotal (95% CI) 476 1189 10.8% 1.00 [0.81, 1.24]
Total events 215 540
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)
2.3.3 South Asia
Chacko et al. 40 112 28 112 2.6% 1.67 [0.94, 2.97]
Kaushal et al. 23 117 52 174 2.7% 0.57 [0.33, 1.00]
Nosheen et al. 3 150 12 150 0.8% 0.23 [0.06, 0.85]
Samson et al. 65 250 110 500 4.3% 1.25 [0.88, 1.77]
Saxena et al. 215 406 134 403 4.9% 2.26 [1.70, 3.00]
Sohail et al. 43 100 45 102 2.8% 0.96 [0.55, 1.67]
Syamala et al. 119 347 63 250 4.2% 1.55 [1.08, 2.22]
Subtotal (95% CI) 1482 1691 22.3% 1.16 [0.78, 1.73]
Total events 508 444
Heterogeneity: Tau² = 0.22; Chi² = 30.82, df = 6 (P < 0.0001); I² = 81%
Test for overall effect: Z = 0.72 (P = 0.47)
2.3.4 West Asia
Hashemi et al. 86 134 71 152 3.3% 2.04 [1.27, 3.29]
Kadouri et al. 105 211 63 109 3.3% 0.72 [0.45, 1.15]
Masoudi et al. 111 181 91 181 3.7% 1.57 [1.03, 2.38]
Zgheib et al. 111 226 47 98 3.3% 1.05 [0.65, 1.68]
Subtotal (95% CI) 752 540 13.6% 1.25 [0.81, 1.94]
Total events 413 272
Heterogeneity: Tau² = 0.15; Chi² = 11.06, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 1.00 (P = 0.32)
Total (95% CI) 7409 9301 100.0% 1.18 [1.04, 1.33]
Total events 3745 4369
Heterogeneity: Tau² = 0.06; Chi² = 73.62, df = 26 (P < 0.00001); I² = 65%
Test for overall effect: Z = 2.66 (P = 0.008)
Test for subgroup differences: Chi² = 1.41, df = 3 (P = 0.70), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]


Study or Subgroup | Breast Cancer Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI
Odds Ratio M-H, Random, 95% CI
2.4.1 Pre-menopausal
Chacko et al. 30 54 19 54 3.7% 2.30 [1.06, 5.00]
Hashemi et al. 40 63 60 119 5.1% 1.71 [0.91, 3.20]
Park et al.-2000 71 114 48 97 6.0% 1.69 [0.97, 2.92]
Park et al.-2004 75 120 87 167 7.1% 1.53 [0.95, 2.47]
Sakoda et al. 153 294 263 528 11.0% 1.09 [0.82, 1.45]
Saxena et al. 97 180 60 174 8.0% 2.22 [1.45, 3.41]
Yu et al. 407 634 316 550 12.2% 1.33 [1.05, 1.68]
Subtotal (95% CI) 1459 1689 53.1% 1.51 [1.23, 1.86]
Total events 873 853
Heterogeneity: Tau² = 0.03; Chi² = 10.02, df = 6 (P = 0.12); I² = 40%
Test for overall effect: Z = 3.91 (P < 0.0001)
2.4.2 Post-menopausal
Chacko et al. 10 58 9 58 2.5% 1.13 [0.42, 3.04]
Hashemi et al. 46 71 11 33 3.1% 3.68 [1.54, 8.80]
Park et al.-2000 39 74 46 80 5.0% 0.82 [0.44, 1.56]
Park et al.-2004 41 80 65 122 5.8% 0.92 [0.52, 1.62]
Sakoda et al. 168 321 165 350 10.6% 1.23 [0.91, 1.67]
Saxena et al. 118 226 82 229 9.0% 1.96 [1.35, 2.85]
Yu et al. 215 383 194 353 10.9% 1.05 [0.78, 1.40]
Subtotal (95% CI) 1213 1225 46.9% 1.29 [0.96, 1.73]
Total events 637 572
Heterogeneity: Tau² = 0.09; Chi² = 15.58, df = 6 (P = 0.02); I² = 61%
Test for overall effect: Z = 1.70 (P = 0.09)
Total (95% CI) 2672 2914 100.0% 1.41 [1.19, 1.67]
Total events 1510 1425
Heterogeneity: Tau² = 0.05; Chi² = 26.85, df = 13 (P = 0.01); I² = 52%
Test for overall effect: Z = 3.95 (P < 0.0001)
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]


Study or Subgroup | Breast Cancer Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI
Odds Ratio M-H, Random, 95% CI
2.2.1 HCC
Chacko et al. 40 112 28 112 2.6% 1.67 [0.94, 2.97]
Chang et al. 107 189 227 420 4.3% 1.11 [0.79, 1.57]
Hashemi et al. 86 134 71 152 3.3% 2.04 [1.27, 3.29]
Kadouri et al. 105 211 63 109 3.3% 0.72 [0.45, 1.15]
Li et al. 31 78 37 78 2.3% 0.73 [0.39, 1.38]
Ma et al. 52 105 25 100 2.6% 2.94 [1.63, 5.32]
Masoudi et al. 111 181 91 181 3.7% 1.57 [1.03, 2.38]
Park et al.-2000 110 188 95 181 3.8% 1.28 [0.85, 1.93]
Park et al.-2004 116 200 152 289 4.2% 1.24 [0.87, 1.79]
Pongtheerat et al. 14 40 24 56 1.6% 0.72 [0.31, 1.66]
Saxena et al. 215 406 134 403 4.9% 2.26 [1.70, 3.00]
Sohail et al. 43 100 45 102 2.8% 0.96 [0.55, 1.67]
Syamala et al. 119 347 63 250 4.2% 1.55 [1.08, 2.22]
Wu et al.-2002 34 60 25 60 2.0% 1.83 [0.89, 3.78]
Wu et al.-2006 123 262 103 225 4.2% 1.05 [0.73, 1.50]
Yu et al. 622 1017 510 903 5.9% 1.21 [1.01, 1.46]
Zgheib et al. 111 226 47 98 3.3% 1.05 [0.65, 1.68]
Subtotal (95% CI) 3856 3719 58.9% 1.32 [1.11, 1.56]
Total events 2039 1740
Heterogeneity: Tau² = 0.07; Chi² = 44.28, df = 16 (P = 0.0002); I² = 64%
Test for overall effect: Z = 3.21 (P = 0.001)
2.2.2 PCC
Ceschi et al. 119 256 298 667 4.9% 1.08 [0.81, 1.44]
Cheng et al. 234 465 362 733 5.4% 1.04 [0.82, 1.31]
Egan et al. 628 1125 683 1206 6.0% 0.97 [0.82, 1.14]
Gago-Dominguez et al. 82 180 218 466 4.3% 0.95 [0.67, 1.34]
Kaushal et al. 23 117 52 174 2.7% 0.57 [0.33, 1.00]
Luo et al. 207 353 414 700 5.1% 0.98 [0.76, 1.27]
Nosheen et al. 3 150 12 150 0.8% 0.23 [0.06, 0.85]
Sakoda et al. 321 615 428 878 5.6% 1.15 [0.93, 1.41]
Samson et al. 65 250 110 500 4.3% 1.25 [0.88, 1.77]
Wang et al. 24 42 52 108 2.0% 1.44 [0.70, 2.94]
Subtotal (95% CI) 3553 5582 41.1% 1.02 [0.90, 1.14]
Total events 1706 2629
Heterogeneity: Tau² = 0.01; Chi² = 13.23, df = 9 (P = 0.15); I² = 32%
Test for overall effect: Z = 0.28 (P = 0.78)
Total (95% CI) 7409 9301 100.0% 1.18 [1.04, 1.33]
Total events 3745 4369
Heterogeneity: Tau² = 0.06; Chi² = 73.62, df = 26 (P < 0.00001); I² = 65%
Test for overall effect: Z = 2.66 (P = 0.008)
Test for subgroup differences: Chi² = 6.14, df = 1 (P = 0.01), I² = 83.7%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

C


Breast Cancer Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
3.3.1 East Asia
Chang et al. 66 189 133 421 5.7% 1.16 [0.81, 1.67]
Egan et al. 416 1139 402 1211 8.3% 1.16 [0.98, 1.37]
Ge et al. 380 920 264 783 7.9% 1.38 [1.13, 1.69]
Geng et al. 12 50 1 15 0.4% 4.42 [0.53, 37.20]
Kim et al. 49 171 58 171 4.6% 0.78 [0.49, 1.24]
Lee et al. 1076 3026 1034 3037 8.9% 1.07 [0.96, 1.19]
Sakoda et al. 235 613 307 876 7.7% 1.15 [0.93, 1.43]
Subtotal (95% CI) 6108 6514 43.6% 1.15 [1.03, 1.28]
Total events 2234 2199
Heterogeneity: Tau² = 0.01; Chi² = 9.25, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 2.49 (P = 0.01)
3.3.2 Southeast Asia
Ceschi et al. 87 248 199 641 6.4% 1.20 [0.88, 1.64]
Gago-Dominguez et al. 65 180 162 466 5.8% 1.06 [0.74, 1.52]
Pongtheerat et al. 13 43 21 53 2.1% 0.66 [0.28, 1.55]
Subtotal (95% CI) 471 1160 14.2% 1.10 [0.87, 1.37]
Total events 165 382
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)
3.3.3 South Asia
Kaushal et al. 55 117 66 174 4.5% 1.45 [0.90, 2.33]
Samson et al. 132 250 270 500 6.5% 0.95 [0.70, 1.29]
Saxena et al. 259 406 203 403 6.8% 1.74 [1.31, 2.30]
Sohail et al. 100 100 95 102 0.2% 15.79 [0.89, 280.19]
Syamala et al. 161 347 125 250 6.2% 0.87 [0.63, 1.20]
Subtotal (95% CI) 1220 1429 24.2% 1.25 [0.85, 1.82]
Total events 707 759
Heterogeneity: Tau² = 0.12; Chi² = 16.41, df = 4 (P = 0.003); I² = 76%
Test for overall effect: Z = 1.14 (P = 0.25)
3.3.4 West Asia
Hashemi et al. 98 134 55 152 4.2% 4.80 [2.90, 7.96]
Kadouri et al. 90 211 32 108 4.3% 1.77 [1.08, 2.90]
Khabaz et al.-2014 42 100 20 48 2.8% 1.01 [0.50, 2.04]
Khabaz et al.-2015 46 86 16 35 2.3% 1.37 [0.62, 3.00]
Zgheib et al. 110 227 49 98 4.5% 0.94 [0.59, 1.51]
Subtotal (95% CI) 758 441 18.0% 1.64 [0.87, 3.09]
Total events 386 172
Heterogeneity: Tau² = 0.43; Chi² = 24.64, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 1.53 (P = 0.13)
Total (95% CI) 8557 9544 100.0% 1.23 [1.07, 1.41]
Total events 3492 3512
Heterogeneity: Tau² = 0.05; Chi² = 62.43, df = 19 (P < 0.00001); I² = 70%
Test for overall effect: Z = 2.94 (P = 0.003)
Test for subgroup differences: Chi² = 1.55, df = 3 (P = 0.67), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
Breast Cancer Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
3.4.1 Pre-menopausal
Hashemi et al. 44 63 44 119 8.1% 3.95 [2.05, 7.59]
Kim et al. 34 101 31 101 8.7% 1.15 [0.63, 2.07]
Lee et al. 665 1826 601 1697 12.9% 1.04 [0.91, 1.20]
Sakoda et al. 111 292 174 527 11.7% 1.24 [0.92, 1.68]
Saxena et al. 110 180 120 171 10.2% 0.67 [0.43, 1.04]
Subtotal (95% CI) 2462 2615 51.6% 1.23 [0.85, 1.77]
Total events 964 970
Heterogeneity: Tau² = 0.13; Chi² = 20.69, df = 4 (P = 0.0004); I² = 81%
Test for overall effect: Z = 1.11 (P = 0.27)
3.4.2 Post-menopausal
Hashemi et al. 54 71 11 33 6.0% 6.35 [2.57, 15.72]
Kim et al. 15 70 27 70 7.2% 0.43 [0.21, 0.92]
Lee et al. 411 1200 433 1340 12.7% 1.09 [0.92, 1.29]
Sakoda et al. 124 321 133 349 11.6% 1.02 [0.75, 1.40]
Saxena et al. 149 226 83 232 10.9% 3.47 [2.37, 5.10]
Subtotal (95% CI) 1888 2024 48.4% 1.55 [0.84, 2.84]
Total events 753 687
Heterogeneity: Tau² = 0.41; Chi² = 51.44, df = 4 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.40 (P = 0.16)
Total (95% CI) 4350 4639 100.0% 1.37 [1.01, 1.84]
Total events 1717 1657
Heterogeneity: Tau² = 0.18; Chi² = 74.46, df = 9 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.04 (P = 0.04)
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
Breast Cancer Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
3.2.1 HCC
Chang et al. 66 189 133 421 5.7% 1.16 [0.81, 1.67]
Ge et al. 380 920 264 783 7.9% 1.38 [1.13, 1.69]
Geng et al. 12 50 1 15 0.4% 4.42 [0.53, 37.20]
Hashemi et al. 98 134 55 152 4.2% 4.80 [2.90, 7.96]
Kadouri et al. 90 211 32 108 4.3% 1.77 [1.08, 2.90]
Khabaz et al.-2015 46 86 16 35 2.3% 1.37 [0.62, 3.00]
Kim et al. 49 171 58 171 4.6% 0.78 [0.49, 1.24]
Pongtheerat et al. 13 43 21 53 2.1% 0.66 [0.28, 1.55]
Saxena et al. 259 406 203 403 6.8% 1.74 [1.31, 2.30]
Sohail et al. 100 100 95 102 0.2% 15.79 [0.89, 280.19]
Syamala et al. 161 347 125 250 6.2% 0.87 [0.63, 1.20]
Zgheib et al. 110 227 49 98 4.5% 0.94 [0.59, 1.51]
Subtotal (95% CI) 2884 2591 49.2% 1.38 [1.03, 1.84]
Total events 1384 1052
Heterogeneity: Tau² = 0.17; Chi² = 50.72, df = 11 (P < 0.00001); I² = 78%
Test for overall effect: Z = 2.17 (P = 0.03)
3.2.2 PCC
Ceschi et al. 87 248 199 641 6.4% 1.20 [0.88, 1.64]
Egan et al. 416 1139 402 1211 8.3% 1.16 [0.98, 1.37]
Gago-Dominguez et al. 65 180 162 466 5.8% 1.06 [0.74, 1.52]
Kaushal et al. 55 117 66 174 4.5% 1.45 [0.90, 2.33]
Khabaz et al.-2014 42 100 20 48 2.8% 1.01 [0.50, 2.04]
Lee et al. 1076 3026 1034 3037 8.9% 1.07 [0.96, 1.19]
Sakoda et al. 235 613 307 876 7.7% 1.15 [0.93, 1.43]
Samson et al. 132 250 270 500 6.5% 0.95 [0.70, 1.29]
Subtotal (95% CI) 5673 6953 50.8% 1.10 [1.02, 1.19]
Total events 2108 2460
Heterogeneity: Tau² = 0.00; Chi² = 3.37, df = 7 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)
Total (95% CI) 8557 9544 100.0% 1.23 [1.07, 1.41]
Total events 3492 3512
Heterogeneity: Tau² = 0.05; Chi² = 62.43, df = 19 (P < 0.00001); I² = 70%
Test for overall effect: Z = 2.94 (P = 0.003)
Test for subgroup differences: Chi² = 2.14, df = 1 (P = 0.14), I² = 53.4%
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

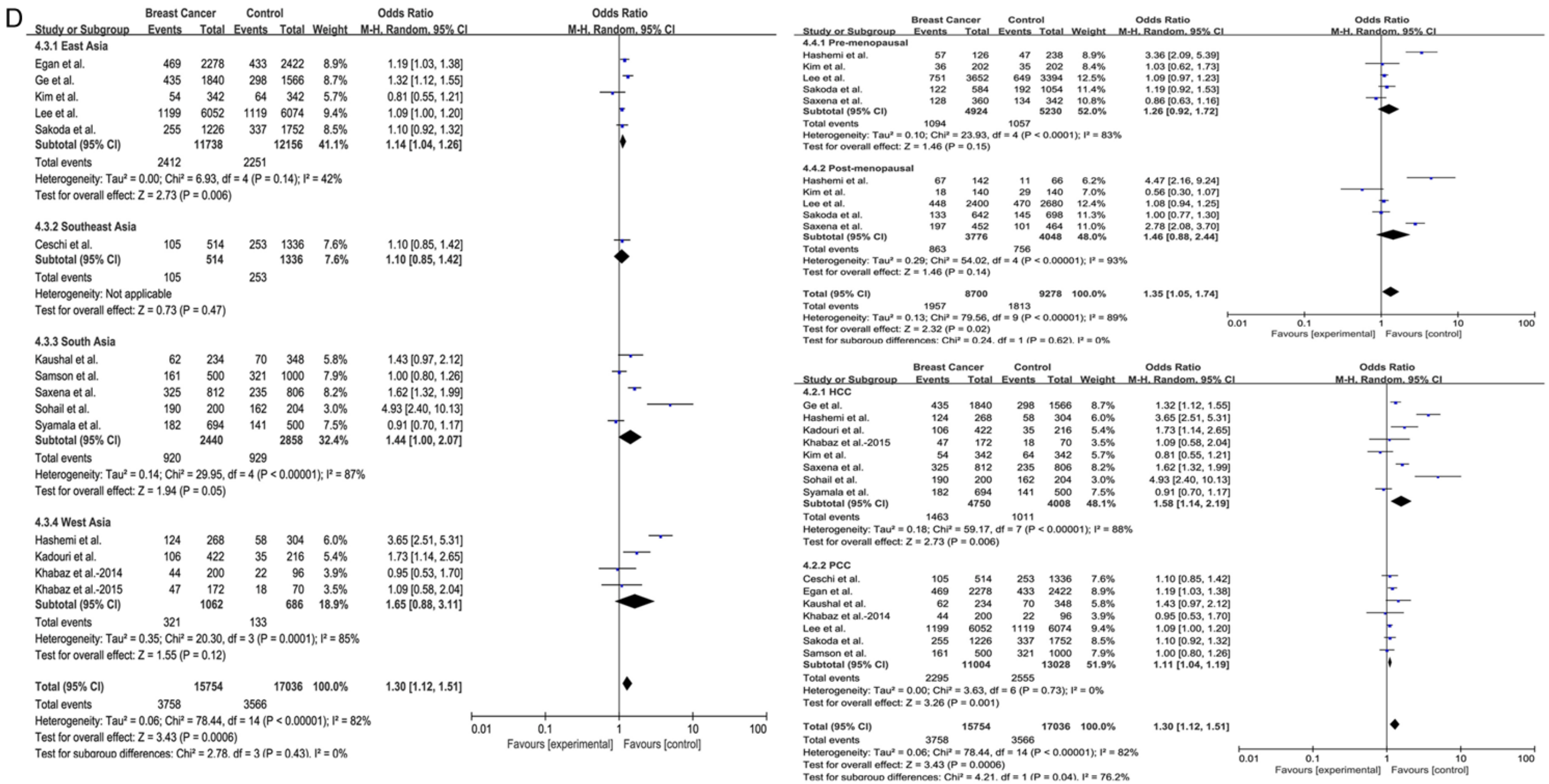


Figure 3. Subgroup analyses for the association between *GST* polymorphisms and breast cancer risk. *Boxes* represent the OR of individual studies, and *diamonds* represent the overall OR. *Horizontal lines* represent the 95% CI. A. *GSTT1* polymorphism. B. *GSTM1* polymorphism. C. *GSTP1* polymorphism under dominant model (GG+AG *vs* AA). D. *GSTP1* polymorphism under allelic model (G *vs* A).

Table 4. Meta-analysis of the *GST* polymorphisms on breast cancer risk in Asian population

Description (No. of studies)	Subgroup (No. of studies)	Sample size		Analysis model	Test of association☆		*P* value for Egger's test	Test for heterogeneity	
		Cases	Controls		OR (95% CI)	P		*P*	I^2 %
GSTT1 (Null vs Present)									
Total [23]		5483	7191	R	1.08 [0.93, 1.25]	0.3000	0.493	<0.00001	65
Subregion [23]	East Asia [9]	2770	3775	R	1.20 [1.00, 1.45]	0.0500		0.0070	62
	Southeast Asia [3]	479	1186	R	0.73 [0.58, 0.90]	0.0040		0.9400	0
	South Asia [7]	1482	1691	R	1.05 [0.70, 1.59]	0.8000		0.0001	78
	West Asia [4]	752	539	R	1.13 [0.85, 1.51]	0.3900		0.5700	0
Menopausal status [5]	Premenopausal [5]	531	611	F	1.45 [1.10, 1.93]	0.0090		0.6000	0
	Postmenopausal [5]	509	522	F	1.19 [0.90, 1.58]	0.2100		0.5500	0
Study design [23]	HCC [15]	2580	2587	R	1.30 [1.07, 1.59]	0.0090		0.0080	53
	PCC [8]	2903	4604	R	0.87 [0.73, 1.03]	0.1100		0.0200	59
GSTM1 (Null vs Present)									
Total [27]		7409	9301	R	1.18 [1.04, 1.33]	0.0080	0.836	<0.00001	65
Subregion (27)	East Asia [13]	4699	5881	R	1.14 [1.01, 1.27]	0.0300		0.0600	41
	Southeast Asia [3]	476	1189	R	1.00 [0.81, 1.24]	1.0000		0.6300	0
	South Asia [7]	1482	1691	R	1.16 [0.78, 1.73]	0.4700		<0.0001	81
	West Asia [4]	752	540	R	1.25 [0.81, 1.94]	0.3200		0.0100	73
Menopausal status [7]	Premenopausal [7]	1459	1689	R	1.51 [1.23, 1.86]	<0.0001		0.1200	40
	Postmenopausal [7]	1213	1225	R	1.29 [0.96, 1.73]	0.0900		0.0200	61
Study design [27]	HCC [17]	3856	3719	R	1.32 [1.11, 1.56]	0.0010		0.0002	64
	PCC [10]	3553	5582	R	1.02 [0.90, 1.14]	0.7800		0.1500	32
GSTP1 (GG+AG vs AA)									
Total [20]		8557	9544	R	1.23 [1.07, 1.41]	0.0030	0.204	<0.00001	70
Subregion [20]	East Asia [7]	6108	6514	R	1.15 [1.03, 1.28]	0.0100		0.1600	35
	Southeast Asia [3]	471	1160	R	1.10 [0.87, 1.37]	0.4300		0.4200	0
	South Asia [5]	1220	1429	R	1.25 [0.85, 1.82]	0.2500		0.0030	76
	West Asia [5]	758	441	R	1.64 [0.87, 3.09]	0.1300		<0.0001	84
Menopausal status [5]	Premenopausal [5]	2462	2615	R	1.23 [0.85, 1.77]	0.2700		0.0004	81
	Postmenopausal [5]	1888	2024	R	1.55 [0.84, 2.84]	0.1600		<0.00001	92
Study design [20]	HCC [12]	2884	2591	R	1.38 [1.03, 1.84]	0.0300		<0.00001	78
	PCC [8]	5673	6953	R	1.10 [1.02, 1.19]	0.0100		0.8500	0
GSTP1 (G vs A)									
Total [15]		15754	17036	R	1.30 [1.12, 1.51]	0.0006	0.170	<0.00001	82
Subregion [15]	East Asia [5]	11738	12156	R	1.14 [1.04, 1.26]	0.0060		0.1400	42
	Southeast Asia [1]	514	1336	R	1.10 [0.85, 1.42]	0.4700		–	–
	South Asia [5]	2440	2858	R	1.44 [1.00, 2.07]	0.0500		<0.00001	87
	West Asia [4]	1062	686	R	1.65 [0.88, 3.11]	0.1200		0.0001	85
Menopausal status [15]	Premenopausal [5]	4924	5230	R	1.26 [0.92, 1.72]	0.1500		<0.0001	83
	Postmenopausal [5]	3776	4048	R	1.46 [0.88, 2.44]	0.1400		<0.00001	93
Study design [15]	HCC [8]	4750	4008	R	1.58 [1.14, 2.19]	0.0060		<0.00001	88
	PCC [7]	11004	13028	R	1.11 [1.04, 1.19]	0.0010		0.7300	0

vs: versus; OR: odds ratio; CI: confidence interval; F: fixed-effect mode; R: random-effect model; HCC: hospital-based case-control study; PCC: population-based case-control study; ☆The data of positive results are represented in bold type.

Asian group or decreased in East Asian and PCC groups for all 3 polymorphisms. The presence of heterogeneity can result from genetic heterogeneity between the samples that were drawn from geographically diverse populations. Another important factor contributing to heterogeneity was that homogeneity in either the case or control groups was uncertain. Although most of the controls were selected from healthy populations, some studies had selected controls among friends or family of breast cancer patients or patients with other diseases. In addition, we attempted to determine if the heterogeneity might also be explained by other variables such as stages of breast cancer, smoking status, older age at first birth, and environmental factors included in the different studies, but are unable to provide a reliable

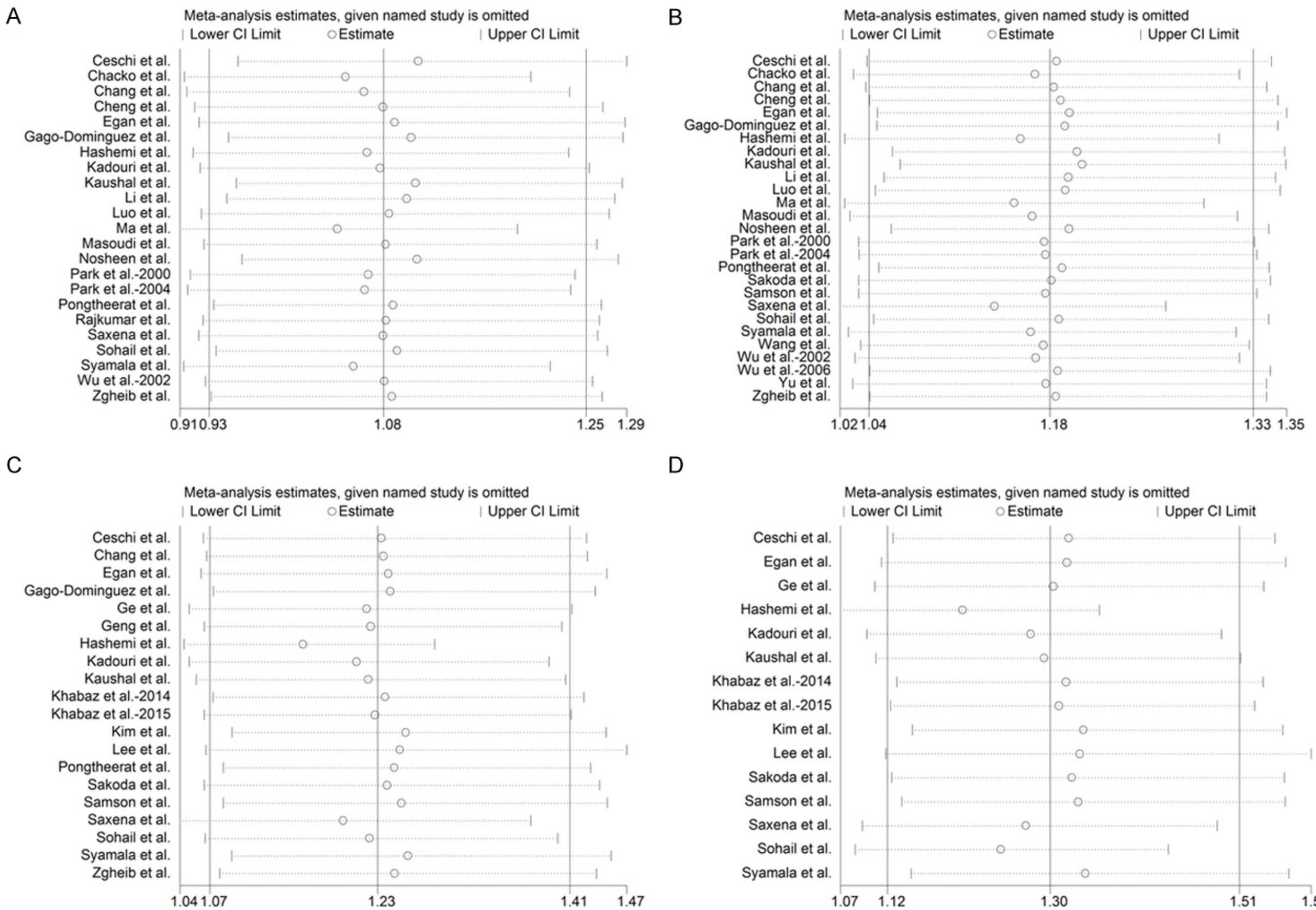


Figure 4. Sensitivity analysis of the summary odds ratio coefficients on the relationships between *GST* polymorphisms and breast cancer risk. Results were computed by omitting each study in turn. The two ends of the *dotted lines* represent the 95% CI. A. *GSTT1* polymorphism. B. *GSTM1* polymorphism. C. *GSTP1* polymorphism under dominant model (GG+AG *vs* AA), D *GSTP1* polymorphism under allelic model (G *vs* A).

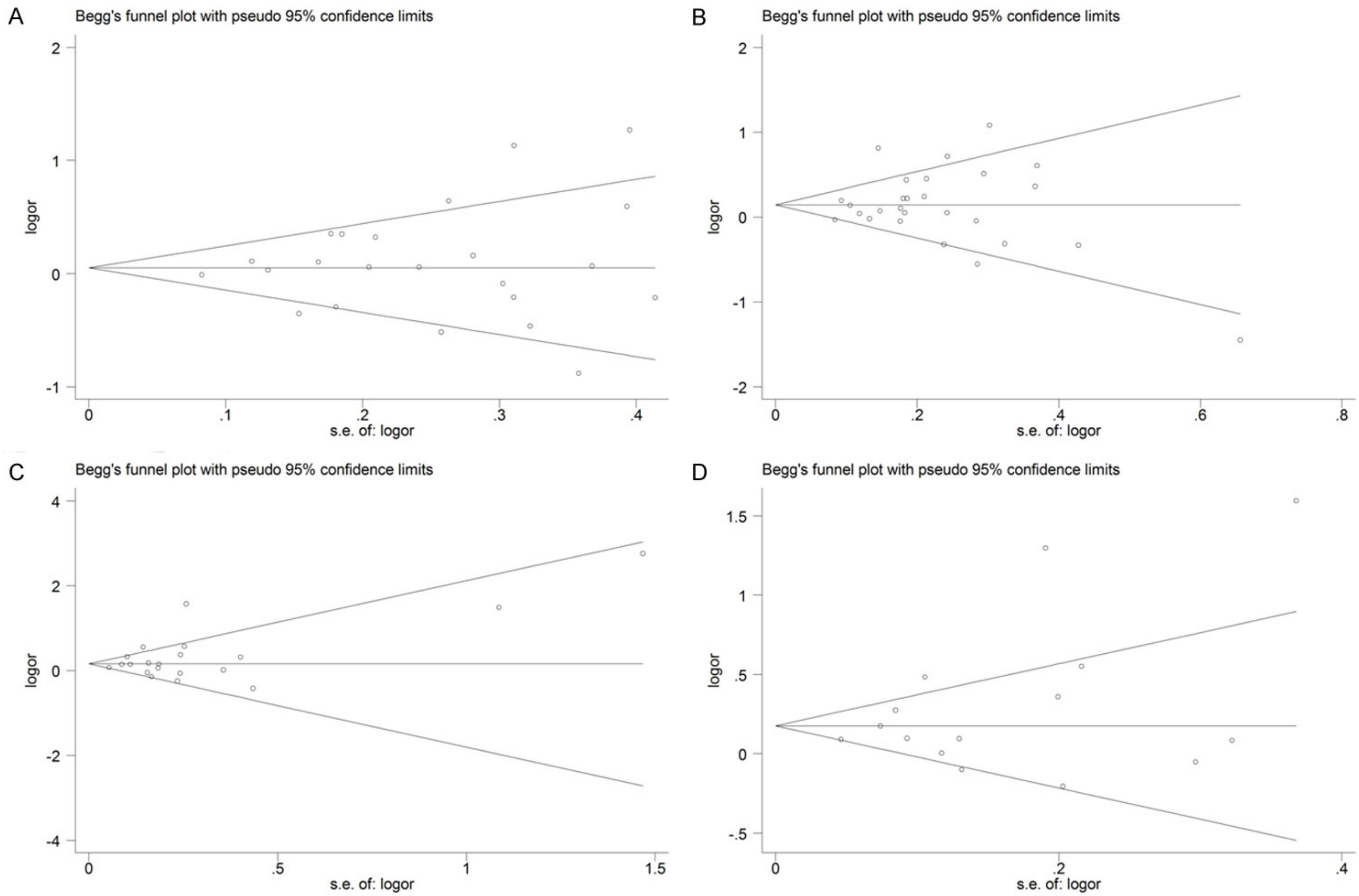


Figure 5. Begg's funnel plot for publication bias in selection of studies on *GST* polymorphisms. A. *GSTT1* polymorphism. B. *GSTM1* polymorphism. C. *GSTP1* polymorphism under dominant model (GG+AG *vs* AA). D. *GSTP1* polymorphism under allelic model (G *vs* A).

answer to this question because of insufficient information for these variables.

Several limitations of this meta-analysis should be acknowledged when explaining our results. Firstly, in our meta-analysis, as only certain published studies written in English or Chinese were included, which indicates that some potential published studies in other languages or unpublished studies could be missed, publication bias is very likely to occur in *GSTT1*, *GSTM1* and *GSTP1* polymorphisms, although it was not shown in the statistical test. Secondly, the overall outcomes were based on individual unadjusted ORs, while a more precise estimation should be conducted adjusted by confounding factors such as smoking status, age and environmental factors if individual data were available. Thirdly, the results should be cautiously interpreted because participants of some studies draw from different populations were not uniformly defined, which could cause some biases and might distort the results. And the last, in the subgroup analyses, the number of Southeast and West Asian population were relatively small, not having enough statistical power to explore the real association. Therefore, more subjects of different subregions would be required to accurately clarify whether subregion has a biological influence on the susceptibility of breast cancer.

Conclusions

The present meta-analysis revealed that the *GSTM1* and *GSTP1* polymorphisms can obviously increase the risk of breast cancer in Asian population, especially in East Asian and HCC groups, while the association between *GSTT1* null genotype and breast cancer risk is not significant. Thus, our results may have important practical significance for further medical research concerning breast cancer and personalized therapy for breast cancer patients. To further assess gene-to-gene and gene-to-environment combined effects on *GST* polymorphisms and breast cancer, future large-scale studies in Asian population with different environmental backgrounds are urgently needed.

Disclosure of conflict of interest

None.

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