# 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* polymorphisms and *GSTP1* polymorphisms 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  $\alpha$ ,  $\mu$ ,  $\pi$ ,  $\omega$  and  $\theta$ ) 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 $\rightarrow$ 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 (Cl) 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,  $0 \sim 4$ ; (2) comparability of subject,  $0 \sim 2$ ; and (3) clinical outcome,  $0 \sim 3$ . Total NOS scores range from 0 to 9, with scores  $\geq 7$  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  $\chi^2$ -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 designspecific 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<sup>2</sup> 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 casecontrol 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 casecontrol study in subgroup by menopausal status are shown in Table 3. There was 1 casecontrol 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 =  $0.93 \cdot 1.25$ , P = 0.30) (Figure 2A). However, in the subgroup analyses, this metaanalysis 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

First author	Year	Country	Subregion	Case age	Study	Sample size	Genotyping method	NOS
	Tear	obuildy	Gubicgion	(year)	design	(Cases/Controls)		score
Ceschi et al.	2005	Singapore	Southeast Asia	$55.6 \pm 7.4^{+}$	PCC	257/668	TaqMan & PCR	7
Chacko et al.	2005	India	South Asia	$49 \pm 10.3^{+}$	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 <sup>†</sup>	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 <sup>+</sup>	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	$49.6 \pm 8.3^{\dagger}$	PCC	3026/3037	RFLP-PCR & TaqMan	8
Li et al.	2008	China	East Asia	46.7 ± 8.75 <sup>†</sup>	HCC	78/78	multiplex-PCR	8
Luo et al.	2012	China	East Asia	$52.8 \pm 8.8^{+}$	PCC	353/701	PCR	7
Ma et al.	2007	China	East Asia	$46 \pm 9^{+}$	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 <sup>†</sup>	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 <sup>†</sup>	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 <sup>+</sup>	HCC	1017/903	RFLP-PCR	7
Zgheib et al.	2013	Lebanon	West Asia	$48.9 \pm 11.6^{\dagger}$	HCC	227/99	PCR	7

Table 1. Baseline characteristics and me	ethodological quality o	of all included studies	s in the meta-analy-
sis			

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 associ-

ated 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:

		GS	TT1			GST	TM1						(	GSTP1					
Author	Ca	ses (n)	Con	trols (n)	Ca	ses (n)	Con	trols (n)		Cases	(n)	С	ontrols	s (n)	Case	es (n)	Contr	ols (n)	HWE <sup>a</sup> for
	Null	Present	Null	Present	Null	Present	Null	Present	GG	AG	AA	GG	AG	AA	G	Α	G	Α	control P
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 al2000	94	94	76	105	110	78	95	86	_	_	_	_	_	_	_	_	_	_	
Park et al2004	101	99	121	168	116	84	152	137	_	_	_	_	_	_	_	_	_	_	
Wu et al2002	27	33	26	34	34	26	25	35	_	_	_	_	_	_	_	_	_	_	
Rajkumar et al.	44	206	84	416	_	_	_	_	_	_	_	_	_	_	_	_	_	_	
Wang et al.	_	_	_	_	24	18	52	56	_	_	_	_	_	_	_	_	_	_	
Wu et al2006	_	_	_	_	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 al2014	_	_	_	_	_	_	_	_	2	40	58	2	18	28	44	156	22	74	0.6704
Khabaz et al2015	_	_	_	_	_	_	_	_	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

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

<sup>a</sup>HWE: Hardy-Weinberg equilibrium for controls of GSTP1 gene; NA: not available; \*Numbers of GG+AG.

			Premer	nopaus	al			F	ostmer	nopaus	al	
Author		Cases (	(n)	(	Controls	(n)	(	Cases (I	า)	C	ontrols	(n)
	Null	Pre	esent	Null	Pre	esent	Null	Pre	sent	Null	Pres	sent
GSTT1												
Chacko et al.	9	4	45	3	ļ	51	6	5	2	7	5	51
Hashemi et al.	9	į	54	8	1	.11	9	6	2	4	2	9
Park et al2000	57	į	57	42	Ę	55	37	Э	57	32	4	-8
Park et al2004	61	į	59	75	9	92	40	4	0	46	7	6
Saxena et al.	34	1	46	24	1	.50	62	10	64	64	16	65
GSTM1												
Chacko et al.	9	4	45	3	į	51	6	5	2	7	5	51
Hashemi et al.	9	į	54	8	1	.11	9	6	2	4	2	9
Park et al2000	57	!	57	42	Ę	55	37	Э	57	32	4	.8
Park et al2004	61	Į	59	75	ę	92	40	4	0	46	7	6
Saxena et al.	34	1	46	24		.50	62	10	64	64	16	65
Chacko et al.	9	4	45	3 51		51	6	5	2	7	5	51
Hashemi et al.	9	Į	54	8	1	.11	9	6	2	4	2	9
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

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

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 metaanalysis 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

Δ		Breast Ca	ancer	Control			Odds Ratio	Odds Ratio	R		Breast Ca	ancer	Control		Odds Ratio	Odds Ra	atio
~	Study or Subgroup	Events	Total	Events T	otal We	eight N	I-H. Random, 95% Cl	M-H. Random, 95% Cl		Study or Subgroup	Events	Total	Events Tot	al Weight	M-H. Random, 95%	M-H. Random	n. 95% CI
	Ceschi et al.	87	256	282	667	5.9%	0.70 [0.52, 0.95]			Ceschi et al.	119	256	298 66	7 4.9%	1.08 [0.81, 1.44	· +	
	Chacko et al.	29	112	10	112	2.5%	3.56 [1.64, 7.74]			Chacko et al.	40	112	28 1	2 2.6%	1.67 [0.94, 2.97		-
	Chang et al.	111	189	210	420	5.5%	1.42 [1.01, 2.01]			Chang et al.	107	189	227 43	0 4.3%	1.11 [0.79, 1.57	- T	
	Cheng et al.	223	461	336	736	6.5%	1.12 [0.88, 1.41]	T		Cheng et al.	234	465	362 73	3 5.4%	1.04 [0.82, 1.31	! T	
	Egan et al.	557	1136	596 1	210	7.2% E 4%	0.99 [0.84, 1.17]	-		Egan et al.	628	1125	683 120	6 6.0%	0.97 [0.82, 1.14		
	Gago-Dominguez et al.	10	124	204	400 162	0.4%	1 91 (0 94 2 01)			Gago-Dominguez et al.	82	180	218 40	6 4.3%	0.95 [0.67, 1.34	-	
	Kadouri et al.	53	211	24	102 1	3 7%	1 17 [0.68, 2.04]			Hashemi et al.	86	134	/1 10	2 3.3%	2.04 [1.27, 3.25		
	Kaushal et al	33	117	69	174	4 1%	0.60 (0.36, 0.99)			Kadouri et al.	105	211	63 10	19 3.376	0.72 [0.45, 1.10		
	li et al.	35	78	44	78	3.2%	0.63 [0.33, 1.18]			Lietal	31	78	37 3	18 2.3%	0.73 [0.39, 1.36		
	Luo et al.	186	353	364	701	6.3%	1.03 [0.80, 1.33]	+		Luo et al.	207	353	414 70	0 5.1%	0.98 [0.76, 1.27	i +	
	Ma et al.	49	105	22	100	3.4%	3.10 [1.69, 5.70]			Ma et al.	52	105	25 10	0 2.6%	2.94 [1.63, 5.32		
	Masoudi et al.	47	181	45	181	4.3%	1.06 [0.66, 1.70]			Masoudi et al.	111	181	91 18	1 3.7%	1.57 [1.03, 2.38	i ⊢	-
	Nosheen et al.	13	150	28	150 3	2.8%	0.41 [0.20, 0.83]			Nosheen et al.	3	150	12 1	0 0.8%	0.23 [0.06, 0.85	·	
	Park et al2000	94	188	76	181	4.9%	1.38 [0.92, 2.08]			Park et al2000	110	188	95 18	1 3.8%	1.28 [0.85, 1.93	i +•	_
	Park et al2004	101	200	121	289	5.3%	1.42 [0.99, 2.04]			Park et al2004	116	200	152 20	9 4.2%	1.24 [0.87, 1.79	i +-	-
	Pongtheerat et al.	18	43	25	53 :	2.3%	0.81 [0.36, 1.81]			Pongtheerat et al.	14	40	24 5	6 1.6%	0.72 [0.31, 1.66	·	-
	Rajkumar et al.	44	250	84	500	5.0%	1.06 [0.71, 1.58]			Sakoda et al.	321	615	428 8	8 5.6%	1.15 [0.93, 1.41	1 T	
	Saxena et al.	96	406	88	403	5.6%	1.11 [0.80, 1.54]			Samson et al.	65	250	110 50	0 4.3%	1.25 [0.88, 1.77	1 1	_
	Sonali et al.	21	247	32	260	3.4%	1 00 (1 12 2 19)			Saxena et al.	215	406	134 40	3 4.9%	2.26 [1.70, 3.00		-
	Wu et al -2002	27	60	25	60	2.7%	1.07 [0.52, 2.20]			Sohail et al.	43	100	45 10	2 2.8%	0.96 [0.55, 1.67		-
	Zoheib et al.	43	226	20	98	3.5%	0.92 [0.51, 1.66]			Syamala et al.	119	347	63 25	0 4.2%	1.55 [1.08, 2.22		
							0.02 (0.01) 1.00)			Wang et al.	24	42	52 10	8 2.0%	1.44 [0.70, 2.94		
	Total (95% CI)		5483	7	191 10	0.0%	1.08 [0.93, 1.25]	+		Wu et al2002	122	262	102 2	0 2.0%	1.83 [0.89, 3.78	-	
	Total events	2013		2741						Yu et al2000	622	1017	510 0	3 5 0%	1 21 [1 01 1 46		
	Heterogeneity: Tau <sup>2</sup> = 0.0	07; Chi <sup>2</sup> = 63	2.93, df =	22 (P < 0.0	00001);	I <sup>2</sup> = 65%		01 1 10 100		Zobeih et al	111	226	47 (	8 3.3%	1 05 10 65 1 65	i —	-
	Test for overall effect: Z =	= 1.04 (P = 0	0.30)				0.01	Favours [experimental] Favours [control]		agricio ot or.		LLU		0.076	1.00 [0.00, 1.00	' I	
								rareau (experimental) rareau (eeneed)		Total (95% CI)		7409	930	1 100.0%	1.18 [1.04, 1.33	•	
										Total events	3745		4369				
										Heterogeneity: Tau <sup>2</sup> = 0.	.06; Chi <sup>2</sup> = 73	3.62, df =	26 (P < 0.00	001); l <sup>2</sup> = 65	%		10 100
										Test for overall effect: Z	= 2.66 (P = 0	0.008)				0.01 0.1 1 Eavours [experimental] E	10 100
																ravous (experimental)	avous [control]
$\mathbf{c}$		Breast Ca	ancer	Control			Odds Ratio	Odds Ratio		1	Breast Cance	er C	ontrol		Odds Ratio	Odds Rati	io
U.	Study or Subgroup	Events	Total	Events T	otal We	eight N	I-H. Random, 95% CI	M-H. Random, 95% Cl		Study or Subgroup	Events T	otal Eve	nts Total	Weight M	I-H. Random, 95% CI	M-H. Random.	95% CI
	Ceschi et al.	87	248	199	641 (	6.4%	1.20 [0.88, 1.64]	+-		Ceschi et al.	105	514 2	253 1336	7.6%	1.10 [0.85, 1.42]	+	
	Chang et al.	66	189	133	421	5.7%	1.16 [0.81, 1.67]	+		Egan et al.	469 2	278	133 2422	8.9%	1.19 [1.03, 1.38]	-	
	Egan et al.	416	1139	402 1	211 4	8.3%	1.16 [0.98, 1.37]	-		Ge et al.	435 1	840 2	298 1566	8.7%	1.32 [1.12, 1.55]	-	
	Gago-Dominguez et al.	65	180	162	466	5.8%	1.06 [0.74, 1.52]	<b>T</b>		Hashemi et al.	124	268	58 304	6.0%	3.65 [2.51, 5.31]		
	Ge et al.	380	920	264	783	7.9%	1.38 [1.13, 1.69]	-		Kadouri et al.	106	422	35 216	5.4%	1.73 [1.14, 2.65]		
	Geng et al.	12	50	1	15 0	0.4%	4.42 [0.53, 37.20]			Kaushal et al.	62	234	70 348	5.8%	1.43 [0.97, 2.12]		-
	Hashemi et al.	98	134	55	152 4	4.2%	4.80 [2.90, 7.96]			Khabaz et al2014	44	200	22 96	3.9%	0.95 [0.53, 1.70]		_
	Kadouri et al.	90	117	32	174	4.3%	1.77 [1.06, 2.90]	L		Knabaz et al2015 Kim et al	4/ 5/	342	18 70	5.7%	1.09 [0.58, 2.04]		
	Khabaz et al -2014	42	100	20	48	2.8%	1.01 [0.50, 2.04]			Leo et al	1100 6	052 1	119 6074	9.4%	1.09 [1.00, 1.20]	Ļ.	
	Khabaz et al2015	46	86	16	35	2.3%	1.37 [0.62, 3.00]			Sakoda et al.	255 1	226 3	337 1752	8.5%	1.10 [0.92, 1.32]	+	
	Kim et al.	49	171	58	171	4.6%	0.78 [0.49, 1.24]			Samson et al.	161	500 3	321 1000	7.9%	1.00 [0.80, 1.26]	+	
	Lee et al.	1076	3026	1034 3	037 4	8.9%	1.07 [0.96, 1.19]	+		Saxena et al.	325	812 2	235 806	8.2%	1.62 [1.32, 1.99]	-	-
	Pongtheerat et al.	13	43	21	53 3	2.1%	0.66 [0.28, 1.55]			Sohail et al.	190	200	162 204	3.0%	4.93 [2.40, 10.13]	I	
	Sakoda et al.	235	613	307	876	7.7%	1.15 [0.93, 1.43]	-		Syamala et al.	182	694	141 500	7.5%	0.91 [0.70, 1.17]	-+	
	Samson et al.	132	250	270	500	6.5%	0.95 [0.70, 1.29]	T					1844				
	Saxena et al.	259	406	203	403	6.8%	1.74 [1.31, 2.30]			Total (95% CI)	15	754	17036	100.0%	1.30 [1.12, 1.51]	▼	
	Sohail ét al.	100	100	95	102 0	0.2%	15.79 [0.89, 280.19]			Total events	3758	3	566				
	Syamala et al.	161	347	125	250 0	0.2%	0.87 [0.63, 1.20]			Heterogeneity: Tau <sup>2</sup> = 0.	Ub; Chi <sup>2</sup> = 78	5.44, df = 1	14 (P < 0.000	U1); I <sup>2</sup> = 829	• (	.01 0.1 1	10 100
	Zgnelo et al.	110	221	49	30 .	4.3%	0.84 [0.89, 1.51]			rest for overall effect: Z	= 3.43 (P = 0	.0006)				Favours (experimental) Fav	ours (control)
	Total (95% CI)		8557	9	544 10	0.0%	1.23 [1.07, 1.41]	♦									
	Total events	3492		3512				·									
	Heterogeneity: Tau <sup>2</sup> = 0.0	05; Chi <sup>2</sup> = 62	2.43, df =	19 (P < 0.0	00001); I	l² = 70%	<u> </u>										
	Test for overall effect: Z =	2.94 (P = 0	0.003)				0.01	U.1 1 10 100 Eavours (experimental) Eavours (control)									
								ravours texperimental ravours (control)									

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% Cl. 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 betweenstudy 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

Δ	Breast Ca	ncer	Contro	bl		Odds Ratio	Odds Ratio		Breast Can	cer	Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total 1	Neight M	-H. Random, 95% CI	M-H. Random, 95% CI	Study or Subgroup	Events	Total E	vents To	tal Weig	ght M-I	H. Random, 95% CI	M-H. Random, 95% Cl
2.3.1 East Asia								2.4.1 Pre-menopausal							
Chang at al	107	190	227	420	4 20/	1 11 10 70 1 571	<u> </u>	Chacko et al.	30	54	19	54 3.	7%	2.30 [1.06, 5.00]	
Chang et al.	107	109	221	420	4.3%	1.11[0.79, 1.57]		Hashemi et al.	40	63	60 1	19 5.	1%	1.71 [0.91, 3.20]	
Cheng et al.	234	465	362	733	5.4%	1.04 [0.82, 1.31]	T	Park et al2000	71	114	48	97 6. 67 7	1%	1.69 [0.97, 2.92]	
Egan et al.	628	1125	683	1206	6.0%	0.97 [0.82, 1.14]	T	Sakoda et al.	153	294	263 5	28 11.	0%	1.09 [0.82, 1.45]	+
Li et al.	31	78	37	78	2.3%	0.73 [0.39, 1.38]		Saxena et al.	97	180	60 1	74 8.	0%	2.22 [1.45, 3.41]	
Luo et al.	207	353	414	700	5.1%	0.98 [0.76, 1.27]	+	Yu et al.	407	634	316 5	50 12.	2%	1.33 [1.05, 1.68]	-
Ma at al	52	105	25	100	2.6%	2 04 [1 63 5 32]		Subtotal (95% CI)		1459	16	89 53.	1%	1.51 [1.23, 1.86]	•
Dedicated 2000	110	100	25	100	2.0%	2.04 [1.00, 0.02]		Total events	873 03: Ch2 = 1	0.02.46	853 - 6 (B - 0	12)-12 -	109/		
Park et al2000	110	100	95	101	3.0%	1.26 [0.65, 1.95]		Test for overall effect: Z	= 3.91 (P <	0.002, 01	= 0 (P = 0.	12), 1 1	40 70		
Park et al2004	116	200	152	289	4.2%	1.24 [0.87, 1.79]			0.0.1	,					
Sakoda et al.	321	615	428	878	5.6%	1.15 [0.93, 1.41]		2.4.2 Post-menopausal							
Wang et al.	24	42	52	108	2.0%	1.44 [0.70, 2.94]		Chacko et al.	10	58	9	58 2.	5%	1.13 [0.42, 3.04]	
Wu et al2002	34	60	25	60	2.0%	1.83 [0.89, 3.78]		Park et al -2000	46	71	11	33 3.	1%	3.68 [1.54, 8.80]	
Wu et al 2006	123	262	103	225	4.2%	1 05 (0 73 1 50)	+	Park et al2004	41	80	65 1	22 5.	8%	0.92 [0.52, 1.62]	
Yu et al	622	1017	510	002	5.0%	1 21 [1 01 1 46]	-	Sakoda et al.	168	321	165 3	50 10.	6%	1.23 [0.91, 1.67]	-
Subtotal (05% CI)	022	4600	510	5004	5.5%	1.21 [1.01, 1.40]	•	Saxena et al.	118	226	82 2	29 9.	0%	1.96 [1.35, 2.85]	
Subtotal (95% CI)		4099		3001	33.476	1.14[1.01, 1.27]	ľ	Yu et al. Subtetal (95% CI)	215	383	194 3	53 10.1	9% 0%	1.05 [0.78, 1.40]	T_
Total events	2609		3113					Total events	637	1213	572	20 40.	976	1.29 [0.90, 1.73]	•
Heterogeneity: Tau <sup>2</sup> = 0.0	02; Chi² = 20	.25, df =	12 (P = (	0.06); l²	= 41%			Heterogeneity: Tau <sup>2</sup> = 0.	.09; Chi <sup>2</sup> = 1	5.58, df	= 6 (P = 0.	02); I <sup>2</sup> = (	61%		
Test for overall effect: Z =	= 2.20 (P = 0	.03)						Test for overall effect: Z	= 1.70 (P =	0.09)					
2.3.2 Southeast Asia								Total (95% CI)	1510	2672	1426	14 100.	0%	1.41 [1.19, 1.67]	•
Coschi at al	110	256	208	667	4 9%	1 08 0 81 1 441	+	Heterogeneity: Tau <sup>2</sup> = 0.	.05: Chi <sup>2</sup> = 2	6.85. df	= 13 (P = )	0.01): I <sup>2</sup> =	52%		<u>t</u>
Gago Dominguez et al	92	190	219	466	4.3%	0.05 [0.67, 1.34]	-	Test for overall effect: Z	= 3.95 (P <	0.0001)				0.01	0.1 1 10 100 Favours [experimental] Favours [control]
Gago-Dominguez et al.	02	100	210	400	4.376	0.35 [0.07, 1.34]		Test for subaroup differe	ences: Chi <sup>2</sup> =	0.73. d	f = 1 (P = 0)	0.39). I <sup>2</sup> =	0%		r arours (experimental) r arours (eentrol)
Pongtneerat et al.	14	40	24	50	1.6%	0.72 [0.31, 1.66]									
Subtotal (95% CI)		4/6		1189	10.8%	1.00 [0.81, 1.24]	Ť		Breast C	ancer	Contro	ol		Odds Ratio	Odds Ratio
Total events	215		540					Study or Subgroup	Events	Total	Events	Total W	/eight	M-H. Random, 95% CI	M-H. Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 0.9	92, df = 2	(P = 0.6	i3); l² = (	0%			2.2.1 HCC	40	112	20	112	2 6%	1 67 10 04 2 071	
Test for overall effect: Z =	= 0.01 (P = 1	.00)						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]	
2.3.3 South Asia								Kadouri et al.	105	211	63	109	3.3%	0.72 [0.45, 1.15]	
Chacko et al	40	112	28	112	2.6%	1 67 (0 94 2 97)		Li et al.	31	78	37	78	2.3%	0.73 [0.39, 1.38]	
Kaushal at al	22	117	52	174	2.0%	0.57 [0.33, 1.00]		Masoudi et al	111	105	20	181	2.0%	2.94 [1.03, 5.32]	
Nausiai et al.	23	450	40	450	2.770	0.07 [0.00, 1.00]		Park et al2000	110	188	95	181	3.8%	1.28 [0.85, 1.93]	
Nosneen et al.	3	150	12	150	0.8%	0.23 [0.06, 0.85]		Park et al2004	116	200	152	289	4.2%	1.24 [0.87, 1.79]	
Samson et al.	65	250	110	500	4.3%	1.25 [0.88, 1.77]	·	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]		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]	
Syamala et al.	119	347	63	250	4.2%	1.55 [1.08, 2.22]		Wu et al2002	34	60	25	60	2.0%	1.83 [0.89, 3.78]	
Subtotal (95% CI)		1482		1691	22.3%	1.16 [0.78, 1.73]	◆	Wu et al2006	123	262	103	225	4.2%	1.05 [0.73, 1.50]	-
Total events	508		444					Yu et al.	622	1017	510	903	5.9%	1.21 [1.01, 1.46]	
Heterogeneity: Tau? = 0.2	22. Chi2 = 30	82 df =	6/P<0	0001)-1	2 = 81%			Zgheib et al. Subtotal (95% CI)	111	3856	4/	3719	3.3%	1.05 [0.65, 1.68]	•
Test for overall effect: 7	- 0 72 /P - 0	47)	0 (0 . 0.		0170			Total events	2039		1740				
rescior overall effect. 2	- 0.72 (F = 0	.47)						Heterogeneity: Tau <sup>2</sup> = 0.	.07; Chi <sup>2</sup> = 4	4.28, df	= 16 (P =	0.0002); I	$^{2} = 64\%$		
2.2.4 West Asia								Test for overall effect: Z	= 3.21 (P =	0.001)					
2.3.4 West Asia			-					2.2.2 PCC							
Hashemi et al.	86	134	71	152	3.3%	2.04 [1.27, 3.29]		Ceschi et al.	119	256	298	667	4.9%	1.08 [0.81, 1.44]	+
Kadouri et al.	105	211	63	109	3.3%	0.72 [0.45, 1.15]		Cheng et al.	234	465	362	733	5.4%	1.04 [0.82, 1.31]	+
Masoudi et al.	111	181	91	181	3.7%	1.57 [1.03, 2.38]	-	Egan et al.	628	1125	683	1206	6.0%	0.97 [0.82, 1.14]	Ť
Zgheib et al.	111	226	47	98	3.3%	1.05 [0.65, 1.68]	-	Gago-Dominguez et al.	82	180	218	466	4.3%	0.95 [0.67, 1.34]	
Subtotal (95% CI)		752		540	13.6%	1.25 [0.81, 1.94]	◆	Luo et al.	207	353	414	700	5.1%	0.98 [0.76, 1.27]	+
Total events	413		272					Nosheen et al.	3	150	12	150	0.8%	0.23 [0.06, 0.85]	
Heterogeneity: Tau <sup>2</sup> = 0.1	15: Chi2 = 11	06 df =	3 (P = 0	01)  2 =	73%			Sakoda et al.	321	615	428	878	5.6%	1.15 [0.93, 1.41]	-
Test for everall effect: 7	- 1 00 /P = 0	22)	0 (i - 0.	01),1 -	1070			Samson et al.	65	250	110	500	4.3%	1.25 [0.88, 1.77]	
Test for overall effect. 2.	= 1.00 (F = 0	.32)						Subtotal (95% CI)	24	3553	52	5582	2.0%	1.44 [0.70, 2.94]	•
								Total events	1706	0000	2629	ODOL .	41.170	1.02 [0.00, 1.14]	I
T-1-1 (059/ CI)		7400		0204	100 00/	4 40 74 04 4 000									
Total (95% CI)		7409		9301	100.0%	1.18 [1.04, 1.33]	•	Heterogeneity: Tau <sup>2</sup> = 0.	.01; Chi <sup>2</sup> = 1	3.23, df	= 9 (P = 0	15); I <sup>2</sup> = (	32%		
Total (95% CI) Total events	3745	7409	4369	9301	100.0%	1.18 [1.04, 1.33]		Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z	.01; Chi <sup>2</sup> = 1 = 0.28 (P =	3.23, df 0.78)	= 9 (P = 0	.15); l² = ;	32%		
Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.0	3745 06; Chi² = 73	7409 .62, df =	4369 26 (P < 0	9301 0.00001	100.0% ); l² = 65%	1.18 [1.04, 1.33]		Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z	.01; Chi <sup>2</sup> = 1 = 0.28 (P =	3.23, df 0.78) 7400	= 9 (P = 0	.15); l <sup>2</sup> = ;	32%	1 18 [1 04 1 22]	•
Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =	3745 06; Chi² = 73 = 2.66 (P = 0	7409 .62, df = .008)	4369 26 (P < 0	9301 0.00001	100.0% ); I² = 65%	1.18 [1.04, 1.33]	0.01 0.1 1 10 100	Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z Total (95% CI) Total events	.01; Chi <sup>2</sup> = 1 = 0.28 (P = 3745	3.23, df 0.78) 7409	= 9 (P = 0. 4369	.15); I <sup>2</sup> = ; 9301 10	32% 00.0%	1.18 [1.04, 1.33]	•
Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z = Test for subaroup differe	3745 06; Chi <sup>2</sup> = 73 = 2.66 (P = 0 nces: Chi <sup>2</sup> =	7409 .62, df = .008) 1.41. df =	4369 26 (P < ( = 3 (P = (	9301 0.00001 0.70). I <sup>2</sup>	100.0% ); I² = 65% = 0%	1.18 [1.04, 1.33]	0.01 0.1 1 10 100 Favours [experimental] Favours [control]	Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.	.01; Chi <sup>2</sup> = 1 = 0.28 (P = 3745 .06; Chi <sup>2</sup> = 7	3.23, df 0.78) 7409 3.62, df	= 9 (P = 0 4369 = 26 (P < 1	.15); I <sup>2</sup> = ; 9301 1( 0.00001);	32% 00.0% ; l² = 65%	1.18 [1.04, 1.33]	• • • • • • • • • • • • • • • • • • •
Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z = Test for subarouo differen	3745 06; Chi² = 73 = 2.66 (P = 0 nces: Chi² =	7409 .62, df = .008) 1.41. df =	4369 26 (P < 0 = 3 (P = 0	9301 0.00001 0.70). I <sup>2</sup>	100.0% ); I² = 65% = 0%	1.18 [1.04, 1.33]	0.01 0.1 1 10 100 Favours [experimental] Favours [control]	Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z	.01; Chi <sup>2</sup> = 1 = 0.28 (P = 3745 .06; Chi <sup>2</sup> = 7 = 2.66 (P =	3.23, df 0.78) 7409 3.62, df 0.008)	4369 = 26 (P < 0	.15); I <sup>2</sup> = ; 9301 1( 0.00001);	32% 00.0% ; I² = 65%	1.18 [1.04, 1.33]	.01 0.1 10 10 Favours [experimental] Favours [control]

## The GST polymorphisms and breast cancer risk in Asian population: a meta-analysis

R	Breast Ca	ncer	Contro	ol		Odds Ratio	Odds Ratio		Breast Can	cer	Contro			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	Study or Subgroup	Events	Total E	Events 1	otal W	eight M-	H. Random, 95% CI	M-H, Random, 95% Cl
2.3.1 East Asia								2.4.1 Pre-menopausal					0.74		
Chang et al.	107	189	227	420	4.3%	1.11 [0.79, 1.57]	+	Chacko et al. Hashemi et al.	30	54 63	19	54 119	3.7% 5.1%	2.30 [1.06, 5.00]	
Cheng et al.	234	465	362	733	5.4%	1.04 [0.82, 1.31]	+	Park et al2000	71	114	48	97	6.0%	1.69 [0.97, 2.92]	
Egan et al.	628	1125	683	1206	6.0%	0.97 [0.82, 1.14]	+	Park et al2004	75	120	87	167	7.1%	1.53 [0.95, 2.47]	
Li et al.	31	78	37	78	2.3%	0.73 [0.39, 1.38]		Saxena et al.	153	294	263	528 1 174	1.0%	1.09 [0.82, 1.45]	
Luo et al.	207	353	414	700	5.1%	0.98 [0.76, 1.27]	+	Yu et al.	407	634	316	550 1	2.2%	1.33 [1.05, 1.68]	-
Maetal	52	105	25	100	2.6%	2 94 [1 63 5 32]		Subtotal (95% CI)		1459	1	689 5	53.1%	1.51 [1.23, 1.86]	
Park et al -2000	110	188	95	181	3.8%	1 28 [0 85 1 93]		Heterogeneity: Tau <sup>2</sup> = 0.1	073 03: Chi <sup>2</sup> = 1	0.02. df	= 6 (P =	0.12): 12	= 40%		
Park et al -2004	116	200	152	289	4.2%	1.24 [0.87, 1.79]		Test for overall effect: Z	= 3.91 (P <	0.0001)					
Sakoda et al	321	615	428	878	5.6%	1 15 [0 93 1 41]	-	2.4.2 Post-monopoural							
Wang et al.	24	42	420	108	2.0%	1 44 [0 70 2 94]		Chacko et al.	10	58	9	58	2.5%	1.13 [0.42, 3.04]	
Wu at al. 2002	24	60	25	60	2.0%	1 93 [0 90 3 79]	<u> </u>	Hashemi et al.	46	71	11	33	3.1%	3.68 [1.54, 8.80]	
We at al. 2002	100	262	102	225	4 20%	1.05 [0.09, 5.70]	+	Park et al2000	39	74	46	80	5.0%	0.82 [0.44, 1.56]	
Wu et al2006	123	202	103	225	4.276	1.05 [0.73, 1.50]	<b>_</b>	Sakoda et al.	168	321	165	350 1	0.6%	1.23 [0.91, 1.67]	
Tu et al. Subtotal (95%, CI)	022	4699	510	5903	53.4%	1.21 [1.01, 1.40]	•	Saxena et al.	118	226	82	229	9.0%	1.96 [1.35, 2.85]	
Tatal averate	0000	4033	0440	3001	33.470	1.14[1.01, 1.27]	ľ	Yu et al. Subtotal (95% CI)	215	383	194	353 1	0.9%	1.05 [0.78, 1.40]	<b>—</b>
I otal events	2609		3113					Total events	637	12.10	572		0.070	1.20 [0.00, 1.10]	·
Heterogeneity: Tau <sup>4</sup> = 0.0	J2; Chi* = 20	.25, df =	12 (P =	0.06); 1*	= 41%			Heterogeneity: Tau <sup>2</sup> = 0.	09; Chi <sup>2</sup> = 1	5.58, df	= 6 (P =	0.02); I <sup>z</sup>	= 61%		
Test for overall effect: Z =	= 2.20 (P = 0	0.03)						Test for overall effect: Z	= 1.70 (P =	0.09)					
								Total (95% CI)		2672	2	914 10	0.0%	1.41 [1.19, 1.67]	◆
2.3.2 Southeast Asia								Total events	1510		1425				
Ceschi et al.	119	256	298	667	4.9%	1.08 [0.81, 1.44]		Heterogeneity: Tau <sup>e</sup> = 0. Test for overall effect: Z	05; Chi <sup>2</sup> = 2 = 3.95 (P <	0.0001)	= 13 (P =	= 0.01); P	* = 52%	ć	.01 0.1 1 10 100
Gago-Dominguez et al.	82	180	218	466	4.3%	0.95 [0.67, 1.34]		Test for subaroup differe	nces: Chi <sup>2</sup>	= 0.73. d	if = 1 (P =	0.39). P	<sup>2</sup> = 0%		Favours [experimental] Favours [control]
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]	Ť		Breast C	ancer	Cont	trol		Odds Ratio	Odds Ratio
Total events	215		540					Study or Subgroup	Events	Tota	Events	Total	Weight	M-H. Random. 95% C	I M-H. Random. 95% Cl
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 0.9	92, df = 2	2 (P = 0.6	53); I <sup>2</sup> =	0%			Z.Z.1 HCC Chacko et al	40	112	28	112	2.6%	1 67 10 94 2 97	. <u> </u>
Test for overall effect: Z =	= 0.01 (P = 1	.00)						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]	
2.3.3 South Asia								Kadouri et al.	105	211	63	109	3.3%	0.72 [0.45, 1.15]	
Chacko et al.	40	112	28	112	2.6%	1.67 [0.94, 2.97]		Ma et al.	52	105	25	100	2.6%	2.94 [1.63, 5.32]	
Kaushal et al.	23	117	52	174	2.7%	0.57 [0.33, 1.00]		Masoudi et al.	111	181	91	181	3.7%	1.57 [1.03, 2.38]	
Nosheen et al.	3	150	12	150	0.8%	0.23 [0.06, 0.85]		Park et al2000 Park et al2004	110	188	95	181	3.8%	1.28 [0.85, 1.93]	
Samson et al.	65	250	110	500	4.3%	1.25 [0.88, 1.77]		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]	· · · · · · · · · · · · · · · · · · ·	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]		Sohail et al. Svamala et al	43	100	45	250	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 al2002	34	60	25	60	2.0%	1.83 [0.89, 3.78]	
Subtotal (95% CI)		1482		1691	22.3%	1.16 [0.78, 1.73]	◆	Wu et al2006	123	262	103	225	4.2%	1.05 [0.73, 1.50]	t t
Total events	508		444					Yu et al. Zobeib et al.	622	1017	510	903	5.9%	1.21 [1.01, 1.46]	
Heterogeneity: Tau <sup>2</sup> = 0.2	22; Chi <sup>2</sup> = 30	.82, df =	6 (P < 0	.0001); I	l² = 81%			Subtotal (95% CI)		3856		3719	58.9%	1.32 [1.11, 1.56]	
Test for overall effect: Z =	= 0.72 (P = 0	.47)						Total events	2039		1740				
								Heterogeneity: Tau <sup>e</sup> = 0. Test for overall effect: Z	= 3 21 (P =	4.28, df	= 16 (P =	= 0.0002;	); I* = 64%		
2.3.4 West Asia															
Hashemi et al.	86	134	71	152	3.3%	2.04 [1.27, 3.29]		2.2.2 PCC	110	266	200	667	4.0%	1 09 10 91 1 44	
Kadouri et al.	105	211	63	109	3.3%	0.72 [0.45, 1.15]		Cheng et al.	234	465	362	733	5.4%	1.04 [0.82, 1.31]	. +
Masoudi et al.	111	181	91	181	3.7%	1.57 [1.03, 2.38]		Egan et al.	628	1125	683	1206	6.0%	0.97 [0.82, 1.14]	+
Zgheib et al.	111	226	47	98	3.3%	1.05 [0.65, 1.68]	-	Gago-Dominguez et al.	82	180	218	466	4.3%	0.95 [0.67, 1.34]	
Subtotal (95% CI)		752		540	13.6%	1.25 [0.81, 1.94]	◆	Luo et al.	207	353	414	700	5.1%	0.98 [0.76, 1.27]	+
Total events	413		272					Nosheen et al.	3	150	12	150	0.8%	0.23 [0.06, 0.85]	
Heterogeneity: Tau <sup>2</sup> = 0.1	15; Chi <sup>2</sup> = 11	.06, df =	3 (P = 0	.01); l <sup>2</sup> =	= 73%			Sakoda et al.	321	615	428	878	5.6%	1.15 [0.93, 1.41]	
Test for overall effect: Z =	= 1.00 (P = 0	.32)		,.				Wang et al.	24	250 42	52	108	2.0%	1.25 [0.88, 1.77]	
		,						Subtotal (95% CI)		3553		5582	41.1%	1.02 [0.90, 1.14]	• •
Total (95% CI)		7409		9301	100.0%	1.18 [1.04, 1.33]	•	Total events	1706	0.00	2629		- 00%		
Total events	3745		4369					Test for overall effect: Z	= 0.28 (P =	0.78)	= 9 (P =	0.15); l <sup>2</sup>	= 32%		
Heterogeneity: Tau <sup>2</sup> = 0.0	06: Chi <sup>2</sup> = 73	.62. df =	26 (P <	0.00001	):   <sup>2</sup> = 65%	6 F									
Test for overall effect: Z =	= 2.66 (P = 0	008)			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		0.01 0.1 1 10 100	Total (95% CI)		7409	1000	9301	100.0%	1.18 [1.04, 1.33]	•
Test for subgroup differen	nces: Chi <sup>2</sup> =	1.41. df	= 3 (P = )	0.70). 12	= 0%		Favours [experimental] Favours [control]	Heterogeneity: Tau <sup>2</sup> = 0	3745 .06: Chi <sup>2</sup> = 7	3.62. df	4369 = 26 (P +	< 0.0000	1): l <sup>2</sup> = 65%	6	
			2 (		0.00			Test for overall effect: Z	= 2.66 (P =	0.008)	20 (2			-	0.01 0.1 1 10 100 Eavours [experimental] Eavours [control <sup>1</sup>
								Test for subaroup differe	nces: Chi <sup>2</sup> :	= 6.14. c	f = 1 (P =	= 0.01). I	² = 83.7%		· access faybaungungi · axona fearingi

$\sim$		Breast Ca	ncer	Contro	d		Odds Ratio	Odds Ratio									
	Study or Subgroup	Events	Total E	vents	Total W	eight	M-H, Random, 95% CI	M-H. Random, 95% CI	Study or Subgroup Ex	vents To	er C otal Eve	control ents To	tal Wei	aht M-H	Odds Ratio I. Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl	
	3.3.1 East Asia								3.4.1 Pre-menopausal								
	Chang et al.	66	189	133	421	5.7%	1.16 (0.81, 1.67)		Hashemi et al. Kim et al	44	63 101	44 1	19 8. 01 8	1%	3.95 [2.05, 7.59]		
	Egan et al.	416	1139	402	1211	8.3%	1.16 (0.98, 1.37)	-	Lee et al.	665 18	826	601 16	97 12	9%	1.04 [0.91, 1.20]	+	
	Ge et al.	380	920	264	783	7.9%	1.38 [1.13, 1.69]	-	Sakoda et al.	111 2	292	174 5	27 11.	7%	1.24 [0.92, 1.68]		
	Geng et al.	12	50	1	15	0.4%	4.42 [0.53, 37,20]		Subtotal (95% CI)	24	462	26	15 51	.6%	1.23 [0.85, 1.77]	◆	
	Kim et al.	49	171	58	171	4.6%	0.78 [0.49, 1.24]		Total events	964		970					
	Lee et al.	1076	3026	1034	3037	8.9%	1.07 [0.96, 1.19]	-	Heterogeneity: Tau <sup>2</sup> = 0.13 Test for overall effect: Z = 1	3; Chi <sup>2</sup> = 20. 1.11 (P = 0.	.69, df = -	4 (P = 0.)	0004); I <sup>2</sup>	= 81%			
	Sakoda et al	235	613	307	876	7.7%	1 15 [0 93, 1 43]				,						
	Subtotal (95% CI)	200	6108		6514 4	13.6%	1.15 [1.03, 1.28]	•	3.4.2 Post-menopausal				~ ~	~	6 05 ID 57 45 701		
	Total events	2234		2100				*	Kim et al.	15	70	27	70 7.	2%	0.43 [0.21, 0.92]		
	Heterogeneity: Tau <sup>2</sup> = 0.01	1. Chi² = 9.2	25  df = 6	(P = 0.1)	6): $I^2 = 3!$	5%			Lee et al.	411 12	200	433 13	40 12	7%	1.09 [0.92, 1.29]	<u>+</u>	
	Test for overall effect: 7 =	2 49 (P = 0	01)	(i = 0.11	0), 1 = 00				Sakoda et al. Saxena et al.	124 3	321 226	133 3	49 11. 32 10.	6% 9%	1.02 [0.75, 1.40]		
	reactor overall encor. L -	E.40 (i - 0	.01)						Subtotal (95% CI)	18	388	203	24 48	4%	1.55 [0.84, 2.84]	-	
	3.3.2 Southeast Asia								Total events	753	44 44 -	687	000011	R = 0.2%			
	Coschi et al	97	249	100	641	6 49/	1 20 (0 99, 1 64)		Test for overall effect: Z =	1.40 (P = 0.	.16)	4 (1- < 0.)	00001),	1- = 92.76			
	Coso Dominguoz et el	65	190	160	466	E 00/	1.20 [0.00, 1.04]	_									
	Gago-Dominguez et al.	12	42	102	400	0.0%	0.66 (0.29, 1.52)		Total (95% CI)	43	350 1	657	39 100.	.0%	1.37 [1.01, 1.84]	-	
	Subtotal (95% CI)	13	40	21	1160 4	2.170	1 10 [0 87 1 37]	•	Heterogeneity: Tau <sup>2</sup> = 0.18	8; Chi <sup>2</sup> = 74.	.46, df =	9 (P < 0.	00001);	l² = 88%	L.	01 01 1 10	100
	Total events	105	4/1	202	1100	14.2.70	1.10 [0.07, 1.07]	ľ	Test for overall effect: Z = :	2.04 (P = 0.	.04) 0.40 df =	1 (P = 0	52) IZ -	0%	0.	Favours [experimental] Favours [control]	100
	Heteregeneiter Teu? = 0.00	100 Chi2 = 1.7	70 df = 0	30Z	2)- 12 - 00	×			Test for adoutous difference	Gua. Gril - (	0.40. 01 -			0.18			
	Test for overall effect: 7 =	0 70 /P = 0	(2, 0) = 2	(P = 0.4)	2), 1- = 0	70				Breast Ca	incer	Contr	ol		Odds Ratio	Odds Ratio	
	rest for overall effect. Z =	0.79 (P = 0	.43)						Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95%	M-H. Random. 95% Cl	
	3.3.3 South Asia								3.2.1 HCC								
	Kaushal et al.	55	117	66	174	4.5%	1.45 (0.90, 2.33)		Chang et al. Ge et al.	380	189	133	421	5.7%	1.16 [0.81, 1.67	-	
	Samson et al.	132	250	270	500	6.5%	0.95 (0.70, 1.29)	+	Geng et al.	12	50	1	15	0.4%	4.42 [0.53, 37.20	·	
	Savena et al	259	406	203	403	6.8%	1 74 [1 31 2 30]	-	Hashemi et al.	98	134	55	152	4.2%	4.80 [2.90, 7.96		
	Sobail et al	100	100	95	102	0.2%	15 79 (0 89, 280, 19)	<u>↓</u>	Kadouri et al.	90	211	32	108	4.3%	1.77 [1.08, 2.90		
	Syamala et al	161	347	125	250	6.2%	0.87 [0.63, 1.20]	-	Kinabaz et al2015 Kim et al.	40	171	16	171	2.3%	0.78 [0.62, 3.00	-+	
	Subtotal (95% CI)	101	1220	120	1429 3	24.2%	1.25 [0.85, 1.82]	•	Pongtheerat et al.	13	43	21	53	2.1%	0.66 [0.28, 1.55	·	
	Total events	707	1220	750	1420 1		the [otoo, then]	-	Saxena et al.	259	406	203	403	6.8%	1.74 [1.31, 2.30		
	Hotorogonoity: Tou? = 0.1'	- Chi2 - 16	41 df - /	109	002\- 12 -	76%			Sohail et al.	100	100	95	102	0.2%	15.79 [0.89, 280.19		,
	Test for everall effect: 7 =	1 14 /D = 0	.41, UI = 4	+ (F = 0.1	003), 1	10%			Zoheib et al.	101	227	49	250	4.5%	0.87 [0.63, 1.20		
	rest for overall effect. Z =	1.14 (P = 0	.23)						Subtotal (95% CI)		2884		2591	49.2%	1.38 [1.03, 1.84	◆	
	3 3 A West Asia								Total events	1384		1052					
	Hachomi of al	08	124	55	152	4 2%	4 90 12 00 7 061		Heterogeneity: Tau <sup>2</sup> = 0.17 Test for overall effect: Z =	7; Chi <sup>2</sup> = 50 2 17 ( $P = 0$	0.72, df =	11 (P <	0.00001	); l² = 78%			
	Kadouri et al.	00	211	22	102	4.2.70	4.00 [2.00, 7.00]		reactor overall endot. 2 -	2.17 (1 0							
	Kauburi et al. Khabaz et al. 2014	42	100	20	100	9.3%	1.01 [0.50, 2.90]		3.2.2 PCC								
	Khabaz et al. 2015	42	90	16	25	2.0%	1.07 [0.00, 2.04]		Ceschi et al.	87	248	199	641	6.4%	1.20 [0.88, 1.64	T.	
	Zaholh of al	110	227	40	00	2.370 A E9/	0.04 (0.60, 1.61)		Egan et al. Gago-Dominguez et al.	410	180	402	466	5.8%	1.16 [0.96, 1.37		
	Subtotal (95% CI)	110	759	49	441 -	4.5%	1 64 [0.55, 1.51]	•	Kaushal et al.	55	117	66	174	4.5%	1.45 [0.90, 2.33	i +	
	Total events	200	100	170		10.070	1.04 [0.07, 0.00]	-	Khabaz et al2014	42	100	20	48	2.8%	1.01 [0.50, 2.04		
	Hotorogonoity: Tou? = 0.42	300 Chi2 = 24	64 46 -	1/2	00041-12	- 0.40/			Lee et al. Sakada at al	1076	3026	1034	3037	8.9%	1.07 [0.96, 1.19	Ļ.	
	Teet for everall effects 7 =	1 52 /D = 0	.04, 01 - 4	* (P < 0.1	0001), 1-	- 0470			Samson et al.	132	250	270	500	6.5%	0.95 [0.70, 1.29		
	rest for overall effect: Z =	1.55 (P = 0	.13)						Subtotal (95% CI)		5673		6953	50.8%	1.10 [1.02, 1.19	•	
	Total (95% CI)		9557		0544 44	0.0%	1 23 [1 07 1 44]	•	Total events	2108		2460					
	Total (95% CI)	0.400	000/	0540	9044 10	10.0%	1.23 [1.07, 1.41]	•	Heterogeneity: Tau <sup>2</sup> = 0.00 Test for guerall effect: 7 =	$O; Chi^2 = 3.3$	37, df = 7	7 (P = 0.8	B5); I <sup>2</sup> = 1	0%			
	I otal events	3492	10 -16	3512	00000	12 - 700	, L		reactor overall endot: Z =	a.or (r = 0							
	meterogeneity: rau <sup>2</sup> = 0.05	; Chi* = 62	.43, df = '	19 (P < 0	.00001);	r- = 70%	° 0.0	11 0.1 1 10 100	Total (95% CI)		8557		9544	100.0%	1.23 [1.07, 1.41	•	
	rest for overall effect: Z =	2.94 (P = 0	.003)					Favours [experimental] Favours [control]	Total events	3492		3512					
	lest for subaroup difference	ces: Chi <sup>2</sup> =	1.55. df =	3 (P = 0	1.67). I <sup>2</sup> =	0%			Heterogeneity: Tau <sup>2</sup> = 0.05 Test for overall effect: 7 =	2 04 (P = 0)	2.43, df =	19 (P <	0.00001	); i <sup>z</sup> = 70%	•	0.01 0.1 1 10	100
									i cos foi overall elidet: Z =	(r = 0						Favours [experimental] Favours [control]	

### The GST polymorphisms and breast cancer risk in Asian population: a meta-analysis

П		Breast Ca	ancer	Contr	ol		Odds Ratio	Odds Ratio	Breast Cancer Control Odds Ratio Odds Ratio
U_!	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	_Study or Subgroup Events Total Veight M-H, Random, 95% Cl M-H, Random, 95% Cl
4	4.3.1 East Asia								4.4.1 Pre-menopausal
1	Egan et al.	469	2278	433	2422	8.9%	1.19 [1.03, 1.38]	+	Hashemi et al. 57 126 47 238 8.9% 3.36[2.09, 5.39]
	Ge et al.	435	1840	298	1566	8.7%	1.32 [1.12, 1.55]	-	Lee et al. 751 3652 649 3394 12.5% 1.09 [0.97, 1.23]
	Cim et al	54	342	64	342	5 7%	0.81 [0.55, 1.21]	-	Sakoda et al. 122 584 192 1054 11.4% 1.19 [0.92, 1.53]
	on et al.	1100	6052	1110	6074	0.49/	1 00 [1 00 1 20]		Saxona et al. 128 360 134 342 10.8% 0.86 [0.63, 1.16]
	Lee et al.	055	10052	227	4750	9.470	1.09 [1.00, 1.20]	L_	Total events 1094 1057
	Sakoua et al.	200	14720	331	1732	0.076	1.10 [0.92, 1.32]	•	Heterogeneity: Tau <sup>2</sup> = 0,10; Chi <sup>2</sup> = 23,93, df = 4 (P < 0.0001); l <sup>2</sup> = 83%
	Subtotal (95% CI)		11/30	0054	12150	41.170	1.14 [1.04, 1.20]	ľ	Test for overall effect: Z = 1.46 (P = 0.15)
	l otal events	2412		2251					4.4.2 Post-menopausal
1	Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup> =	= 6.93, df	= 4 (P =	0.14); I²	= 42%			Hashemi et al. 67 142 11 66 6.2% 4.47 [2.16, 9.24]
1	Test for overall effect: Z	2 = 2.73 (P	= 0.006)						Nimetal. 18 140 29 140 7.0% 0.56 [0.30,1.07]
									Sakoda et al. 133 642 145 698 11.3% 1.00 [0.77, 1.30]
4	4.3.2 Southeast Asia								Saxena et al. 197 452 101 464 11.0% 2.78[2.08, 3.70]
(	Ceschi et al.	105	514	253	1336	7.6%	1.10 [0.85, 1.42]	T	Total events 863 756
:	Subtotal (95% CI)		514		1336	7.6%	1.10 [0.85, 1.42]	•	Heterogeneity: Tau <sup>2</sup> = 0.29; Chi <sup>2</sup> = 54.02, df = 4 (P < 0.00001); l <sup>2</sup> = 93%
1	Total events	105		253					Test for overall effect: Z = 1.46 (P = 0.14)
1	Heterogeneity: Not appl	licable							Total (95% Cl) 8700 9278 100.0% 1.35 [1.05, 1.74]
1	Test for overall effect: Z	z = 0.73 (P	= 0.47)						Total events 1957 1813
			,						Heterogeneity: Tau* = 0.13; Chi* = 79.56, df = 9 (P < 0.00001); I* = 89% Text for overall effect 2 = 23 2(P = 0.02) 0.01 0.1 1 10 100
	4.3.3 South Asia								Test for subaroup differences: Chi <sup>2</sup> = 0.24, df = 1 (P = 0.62), l <sup>2</sup> = 0% Favours [experimental] Favours [control]
	Kaushal et al.	62	234	70	348	5.8%	1.43 [0.97, 2.12]		
	Samson et al.	161	500	321	1000	7.9%	1.00 [0.80, 1.26]	+	Breast Cancer Control Odds Ratio Odds Ratio
	Savena et al	325	812	235	806	8 2%	1 62 [1 32 1 99]	-	3tudy of subgroup Events Total Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
	Cohoil et al	100	200	162	204	2.0%	4 02 [2 40 10 12]		Ge et al. 435 1840 298 1566 8.7% 1.32 (1.12, 1.55)
			200	102	204	3.070	4.55 [2.40, 10.15]		
	Summala et al.	192	604	141	500	7 59/	0.01 [0.70 1.17]	-	Hashemi et al. 124 268 58 304 6.0% 3.65 [2.51, 5.31]
	Syamala et al. Syamala et al.	182	694	141	500	7.5%	0.91 [0.70, 1.17]	-	Hashemi et al. 124 268 58 304 6.0% 3.65 [2.51, 5.31] Kadouri et al. 106 422 35 216 5.4% 1.73 [1.14, 2.65]
	Syamala et al. Syamala et al. Subtotal (95% CI)	182	694 2440	141	500 2858	7.5% 32.4%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07]	<b>•</b>	Hashemi et al. 124 288 58 304 6.0% 3.65 [251, 5.31]
1	Sonali et al. Syamala et al. Subtotal (95% CI) Total events	182 920	694 2440	141 929	500 2858	7.5% 32.4%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07]		Hashemi et al.         124         268         56         304         6.0%         3.65 [2.51, 5.31]           Kadouri et al.         106         422         35         216         5.4%         1.73 [1.14, 2.65]           Khabaz et al2015         47         172         18         70         3.5%         1.09 [0.58, 2.04]           Kim et al.         54         342         6.7%         0.81 [0.55, 1.21]
1	Soriali et al. Syamala et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0	182 920 0.14; Chi <sup>2</sup> :	694 2440 = 29.95, d	141 929 f = 4 (P <	500 2858	7.5% 32.4% 1); I² = 87%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07]		Hashemi et al.         124         208         59         304         6.0%         3.65 [2.51, 5.31]           Kadouri et al.         106         422         35         216         5.4%         1.73 [1.14, 2.65]           Khabaz et al.2015         47         172         18         70         3.5%         1.09 [0.58, 2.04]           Kim et al.         54         342         64         342         5.7%         0.81 [0.55, 1.21]           Saxona et al.         325         812         235         806         8.2%         1.62 [1.32, 1.99]           Sohali et al.         190         200         162         204         30.7%         4.93 [2.40, 10.13]
	Soriali et al. Syamala et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	182 920 ).14; Chi² : 2 = 1.94 (P	694 2440 = 29.95, d = 0.05)	141 929 f = 4 (P <	500 2858	7.5% 32.4% 1); I² = 87%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07]		Hashemi et al.         124         208         58         304         6.0%         3.65 [2:51, 5:31]           Kadouri et al.         106         422         35         216         5.4%         1.73 [1:41, 2:65]           Knabaz et al2015         47         172         18         70         3.5%         1.09 [0.58, 2:04]           Kim et al.         105         422         325         816         3.2%         1.09 [0.58, 2:04]           Saxona et al.         325         812         235         806         8.2%         1.62 [1:32, 1:99]           Sohall et al.         190         200         162         204         3.0%         4.93 [2:0, 0.103]           Symmath et al.         182         604         141         500         7.5%         0.81 [0.70, 1.17]
	Soriali et al. Syamala et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	182 920 ).14; Chi² = 2 = 1.94 (P	694 2440 = 29.95, d	141 929 If = 4 (P <	500 2858	7.5% 32.4% 1); I² = 87%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07]		Hashemi et al.         124         288         58         304         6.0%         3.65 [2.51, 5.31]           Kadouri et al.         106         422         325         216         5.4%         1.73 [1.41, 2.65]           Kinabaz et al2015         47         172         18         70         3.5%         1.09 [0.58, 2.04]           Saxon et al.         54         342         64         342         5.7%         0.81 [0.55, 1.21]           Saxon et al.         325         812         235         806         8.2%         1.62 [1.32, 1.99]           Saxon et al.         102         203         3.5%         4.83 [2.40, 16.13]
	Sorial et al. Syamala et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: 2 4.3.4 West Asia	182 920 ).14; Chi <sup>2</sup> = 2 = 1.94 (P	694 2440 = 29.95, d	141 929 f = 4 (P <	500 2858	7.5% 32.4% 1); l <sup>2</sup> = 87%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07]		Hashemi et al.         124         208         58         30.4         6.0%         3.65 [2.51, 5.31]           Kadouri et al.         106         422         35         216         5.4%         1.73 [1.14, 2.65]           Khabaz et al2015         47         172         18         70         3.5%         1.09 [0.58, 2.04]           Kim et al.         54         342         64         342         5.7%         0.81 [0.55, 1.21]           Saxona et al.         325         812         235         806         8.2%         1.62 [1.32, 1.99]           Sobhail et al.         190         200         162         204         3.0%         4.91 [2.40, 10.13]           Syamala et al.         182         694         141         500         7.5%         0.91 [0.70, 1.17]           Subtotal (95% Cl)         4750         4068         48.1%         1.58 [1.14, 2.19]         4.1%           Heterogeneity: Tau <sup>2</sup> = 0.18; Chi <sup>2</sup> = 59.17, cf. = 7 (P < 0.00001); P = 88%
	Sorial et al. Syamala et al. Subtotal (95% CI) Fotal events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2 4.3.4 West Asia Hashemi et al.	182 920 0.14; Chi <sup>2</sup> = 2 = 1.94 (P 124	694 2440 = 29.95, d = 0.05) 268	141 929 If = 4 (P <	500 2858 0.0000 304	7.5% 32.4% 1); l <sup>2</sup> = 87% 6.0%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31]		Hashemi et al.       124       288       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       35       216       5.4%       1.731 [1.41, 2.65]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Kim et al.       54       342       64       342       5.7%       0.81 [0.55, 1.21]         Saxona et al.       325       812       235       806       8.2%       1.62 [1.32, 1.99]         Sohall et al.       190       200       162       204       3.0%       4.93 [2.40, 10.13]         Syamala et al.       182       604       141       500       7.5%       0.81 [0.70, 1.17]         Subtotal (95% C)       4750       4008       48.1%       1.58 [1.14, 2.19]         Total events       1463       1011       1608       48.1%       1.58 [1.14, 2.19]         Total ovents       1.463       1011       188%       1011       1.58 [1.14, 2.19]
	Sonali et al. Syamala et al. Subtotal (95% CI) Fotal events Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: Z 4.3.4 West Asia Hashemi et al. Kadouri et al.	130 182 920 0.14; Chi <sup>2</sup> = 2 = 1.94 (P 124 106	694 2440 = 29.95, d = 0.05) 268 422	141 929 If = 4 (P <	500 2858 0.0000 304 216	7.5% 32.4% 1); I <sup>2</sup> = 87% 6.0% 5.4%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31] 1.73 [1.14, 2.65]		Hashemi et al.       124       288       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       35       216       5.4%       1.73 [1.14, 2.65]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Kinabaz et al.       54       342       57%       0.51 [0.55, 1.21]
	sonai et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 4.3.4 West Asia Hashemi et al. Khabaz et al2014	130 182 920 0.14; Chi <sup>2</sup> = 2 = 1.94 (P 124 106 44	694 2440 = 29.95, d = 0.05) 268 422 200	141 929 if = 4 (P < 58 35 22	500 2858 < 0.0000 304 216 96	7.5% 32.4% 1); l <sup>2</sup> = 87% 6.0% 5.4% 3.9%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70]		Hashemi et al.       124       208       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       35       216       5.4%       1.73 [1.14, 2.65]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Kim et al.       54       342       64       342       5.7%       0.81 [0.55, 1.21]         Saxena et al.       325       812       235       806       8.2%       1.82 [1.32, 1.99]         Solutiotal (95% C)       4750       4008       48.1%       0.51 [0.70, 1.17]         Subtotal (95% C)       4750       4008       48.1%       1.58 [1.14, 2.19]         Total avents       1463       1011         Heterogeneity: Tau <sup>2</sup> = 0.18; Chi <sup>2</sup> = 59.17; df = 7 (f < 0 < 0.00001); P = 88%
	sonal et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z 4.3.4 West Asia Hashemi et al. Kadouri et al. Khabaz et al2014 Khabaz et al2015	130 182 920 0.14; Chi <sup>2</sup> = 2 = 1.94 (P 124 106 44 44	694 2440 = 29.95, d = 0.05) 268 422 200 172	141 929 f = 4 (P < 58 35 22 18	500 2858 < 0.0000 304 216 96 70	7.5% 32.4% 1); l <sup>2</sup> = 87% 6.0% 5.4% 3.9% 3.5%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31] 1.73 [1.44, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04]		Hashemi et al.       124       288       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       35       216       5.4%       1.73 [1.41, 2.65]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Saxon et al.       325       812       235       806       8.2%       1.62 [1.32, 1.99]         Saxon et al.       325       812       235       806       8.2%       1.62 [1.32, 1.99]         Saxon et al.       162       204       307       0.5% (4.01, 0.13)       1.10 [0.5% (21)
	Sorial et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2 4.3.4 West Asia Hashemi et al. Kadouri et al. Khabaz et al2014 Khabaz et al2014 Subtotal (95% CI)	130 182 920 0.14; Chi <sup>2</sup> = 1.94 (P 124 106 44 47	294 2440 = 29.95, d = 0.05) 268 422 200 172 1062	141 929 If = 4 (P < 58 35 22 18	500 2858 <0.0000 304 216 96 70 686	7.5% 32.4% 1);   <sup>2</sup> = 87% 6.0% 5.4% 3.9% 3.5% 18.9%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04] 1.65 [0.88, 3.11]		Hashemi et al.       124       288       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       35       216       5.4%       1.73 [1.14, 2.65]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Saxona et al.       325       812       235       806       8.2%       1.62 [1.32, 1.99]         Saxona et al.       190       200       162       204       3.0%       4.91 [2.40, 10.13]         Syamala et al.       190       200       162       204       3.0%       4.91 [2.40, 10.13]         Subtotal (05% CI)       4750       408       48.1%       0.51 [1.74, 2.19]       4.08         Heterogeneity: Tau* = 0.18; Ch* = 59.17; df = 7.0 (P < 0.00001); P = 88%
	Sorial et al. Symhola et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z 4.3.4 West Asia Hashemi et al. Kabaz et al2014 Khabaz et al2015 Subtotal (95% CI) Total events	130 182 920 0.14; Chi <sup>2</sup> = 1.94 (P 124 106 44 47 321	694 2440 = 29.95, d = 0.05) 268 422 200 172 1062	141 929 f = 4 (P < 58 35 22 18 133	500 2858 <0.0000 304 216 96 70 686	7.5% 32.4% 1); l² = 87% 6.0% 5.4% 3.9% 3.5% 18.9%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.66 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04] 1.65 [0.88, 3.11]		Hashemi et al.       124       208       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       35       216       5.4%       1.73 [1.14, 2.65]         Kim et al.       106       422       32       216       5.4%       1.73 [1.14, 2.65]         Kim et al.       105       424       342       5.7%       0.81 [0.55, 1.21]         Saxena et al.       325       812       235       806       8.2%       1.82 [1.32, 1.99]         Sobali et al.       190       204       307       4.53 [2.40, 10.13]       3.5%         Symanale et al.       182       694       141       500       7.5%       0.91 [0.70, 1.17]         Subtotal (95% C)       4750       4008       48.1%       1.58 [1.14, 2.19]       4.64         Heterogeneity: Tau" = 0.16; C.16" = 50.17, df = 7 (P < 0.00001); P = 88%
	Sonail et al. Sysmala et al. Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: 2 4.3.4 West Asia Hashemi et al. Gadouri et al. Gadouri et al. Chabaz et al2014 Khabaz et al2015 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0	130 182 920 0.14; Chi <sup>2</sup> : = 1.94 (P 124 106 44 47 321 0.35; Chi <sup>2</sup> :	694 2440 = 29.95, d = 0.05) 268 422 200 172 1062 = 20.30, d	141 929 f = 4 (P < 58 35 22 18 133 f = 3 (P =	500 2858 0.0000 304 216 96 70 686 = 0.0001	7.5% 32.4% 1); l <sup>2</sup> = 87% 6.0% 5.4% 3.9% 3.5% 18.9% ; l <sup>2</sup> = 85%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 3.66 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04] 1.65 [0.88, 3.11]		Hashemi et al.       124       288       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       32       52 16       5.4%       1.73 [1.41, 2.65]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Kinabaz et al2015       47       172       18       70       3.5%       1.09 [0.58, 2.04]         Saxena et al.       325       812       235       806       8.2%       1.62 [1.32, 1.99]         Soutotal (65% CI)       4750       4008       4.41%       0.51 [1.71, 7]       1011         Heterogeneity: Tau* = 0.16; Ch* = 50.17; df = 7.04       1001       1.48 [1.14, 2.19]       4.22 PCC         Geschi et al.       105       514       253       1336       7.6%       1.10 [0.85, 1.42]         Egan et al.       105       514       253       1336       7.6%       1.10 [0.85, 1.42]         Knubata et al.       105       514       253       1336       7.6%       1.10 [0.85, 1.42]         Egan et al.       469       2278       4.38       5.6%       1.10 [0.85, 1.37]       4.312         Knubata et al.       219       0.39%       0.56 (5.53, 1.
	sonan et al. Syamala et al. Subtotal (95% CI) Total events feterogeneity: Tau <sup>2</sup> = C feterogeneity: Tau <sup>2</sup> = C 4.3.4 West Asia tashemi et al. Khabaz et al2015 Khabaz et al2014 Khabaz et al2014 Khabaz et al2014 Subtotal (95% CI) Total events feterogeneity: Tau <sup>2</sup> = C feterogeneity: Tau <sup>2</sup> = C	130 182 920 0.14; Chi <sup>2</sup> = 1.94 (P 124 106 44 47 321 0.35; Chi <sup>2</sup> = 1.55 (P	694 2440 = 29.95, d = 0.05) 268 422 200 172 1062 = 20.30, d = 0.12)	141 929 If = 4 (P < 58 35 22 18 133 If = 3 (P =	500 2858 0.0000 304 216 96 70 686 = 0.0001	7.5% 32.4% 1); l <sup>2</sup> = 87% 6.0% 5.4% 3.9% 3.5% 18.9% ; l <sup>2</sup> = 85%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04] 1.65 [0.88, 3.11]		Hashemi et al.       124       288       58       304       6.0%       3.65 [2.51, 5.31]         Kadouri et al.       106       422       35       216       5.4%       1.73 [1.41, 2.65]         Kim et al.       104       422       325       216       5.4%       1.73 [1.41, 2.65]         Sobali et al.       194       342       64       342       5.7%       0.81 [0.55, 1.21]         Sownan et al.       122       235       806       8.2%       1.62 [1.32, 1.99]         Sobali et al.       190       200       162       204       3.0%       4.93 [2.40, 10.13]         Symmale et al.       182       694       141       500       7.5%       0.91 [0.70, 1.17]         Total avents       1463       1011       Heterogeneity. Tau" = 0.18; Chi" = 59.17; df = 7 (f < 0.00001); i" = 88%
	sonan et al. Syamala et al. Subtotal (95% CI) Total events Heierogeneity: Tau <sup>2</sup> = C Heierogeneity: Tau <sup>2</sup> = C 4.3.4 West Asia Hashemi et al. Kabaz et al2014 Khabaz et al2014 Subtotal (95% CI) Total events Heierogeneity: Tau <sup>2</sup> = C fest for overall effect. 2	130 182 920 0.14; Chi <sup>2</sup> = 1.94 (P 124 106 44 47 321 0.35; Chi <sup>2</sup> = 1.55 (P	694 2440 = 29.95, d = 0.05) 268 422 200 172 1062 = 20.30, d = 0.12)	141 929 If = 4 (P < 58 35 22 18 133 If = 3 (P =	500 2858 304 216 96 70 686 = 0.0001	7.5% 32.4% 1); I <sup>2</sup> = 87% 6.0% 5.4% 3.9% 3.5% 18.9% ; I <sup>2</sup> = 85%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04] 1.65 [0.88, 3.11]		Hashemi et al. 124 288 58 304 6.0% 3.65 [2.51, 5.31] Kadouri et al. 106 422 35 216 5.4% 1.73 [1.41, 2.65] Kinabaz et al2015 47 172 18 70 3.5% 1.09 [0.55, 1.21] Somail et al. 194 342 64 342 5.7% 0.51 [0.55, 1.21] Somail et al. 192 200 182 204 307.4 4.51 [2.40, 10.13] Sobal (95% Cf) 14 150 200 182 204 307.4 4.51 [2.40, 10.13] Subbal (95% Cf) 14 150 200 182 204 307.4 4.51 [2.40, 10.13] Heterogeneity: Tau <sup>2</sup> = 0.18; Ch <sup>2</sup> = 59.17, df = 7 (P < 0.00001); P = 88% Test for overall effect: Z = 2.73 (P = 0.006) 4.22 PCC Ceschi et al. 105 514 253 1336 7.0% 1.10 [0.85, 1.42] Egan et al. 469 2278 438 5.8% 1.13 [0.37, 12] Knubaz et al. 2015 44 200 22 96 3.9% 0.055 [0.53, 1.70] Lee et al. 2014 44 200 22 96 3.9% 0.056 [0.53, 1.70] Lee et al. 2014 44 200 22 96 3.9% 0.056 [0.53, 1.70] Lee et al. 2014 44 200 22 36 3.9% 0.056 [0.53, 1.70] Lee et al. 2014 44 200 22 96 3.9% 0.056 [0.53, 1.70] Lee et al. 2014 44 200 22 96 3.9% 0.056 [0.53, 1.70] Sakoda et al. 225 [1226 337 1752 8.5% 1.10 [0.02, 1.32] Samon et al. 205 (1226 193 1752 8.5% 1.10 [0.02, 1.22] Samon et al. 205 1226 337 1752 8.5% 1.10 [0.02, 1.22] Samon et al. 205 1226 337 1752 8.5% 1.10 [0.02, 1.22] Samon et al. 205 1226 337 1752 8.5% 1.10 [0.02, 1.22] Samon et al. 205 1226 337 1752 8.5% 1.10 [0.02, 1.22] Samon et al. 205 1226 337 1752 8.5% 1.10 [0.02, 1.22] Samon et al. 205 1226 337 1752 8.5% 1.10 [0.02, 1.22] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.10 [0.02, 1.28] Samon et al. 205 126 337 1752 8.5% 1.5% 1.10 [0.02,
	sonain et al. Syamala et al. Subtotal (95% CI) Total events Test for overall effect: 2 4.3.4 West Asia tashemi et al. Knabaz et al2015 Knabaz et al2014 Khabaz et al2015 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C Total (95% CI)	182 920 0.14; Chi <sup>2</sup> = 1.94 (P 124 106 44 47 321 0.35; Chi <sup>2</sup> = 2 = 1.55 (P	694 2440 = 29.95, d = 0.05) 268 422 200 172 1062 = 20.30, d = 0.12) 15754	141 929 f = 4 (P < 58 35 22 18 133 f = 3 (P =	500 2858 < 0.00000 304 216 96 70 686 = 0.0001	7.5% 32.4% 1); I <sup>2</sup> = 87% 6.0% 5.4% 3.9% 3.5% 18.9% ; I <sup>2</sup> = 85%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 3.65 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04] 1.65 [0.88, 3.11] 1.30 [1.12, 1.51]		Hashemi et al. 124 288 58 304 6.0% 3.65 [2.51, 5.31] Kadouri et al. 106 422 35 216 5.4% 1.73 [1.44, 2.65] Kin at al. 2015 47 172 18 70 3.5% 1.09 [0.55, 1.21] Saxona et al. 325 812 235 806 8.2% 1.62 [1.32, 1.99] Sobali et al. 190 200 182 204 3.0% 4.39 [2.40, 10.13] Symala et al. 182 694 141 500 7.5% 0.91 [0.70, 1.17] Total events 1463 1011 Heterogeneity: Tau" = 0.18; Chi" = 50.17, df = 7.10 $\times$ 0.09 [1.07, 1.17] Ceschi et al. 105 514 253 1336 7.6% 1.10 [0.85, 1.42] Ceschi et al. 105 514 253 1336 7.6% 1.10 [0.85, 1.42] Ceschi et al. 105 514 253 1336 7.6% 1.10 [0.85, 1.42] Ceschi et al. 105 514 253 1336 7.6% 0.59 [1.07, 1.17] Kausthai et al. 469 2278 433 2422 8.9% 1.19 [1.03, 1.38] Kausthai et al. 469 2278 433 2422 8.9% 0.59 [1.07, 1.21] Kausthai et al. 469 277 3 433 2422 8.5% 0.59 [1.07, 1.21] Kausthai et al. 469 277 3 433 2422 8.5% 0.59 [1.07, 1.21] Kausthai et al. 105 514 253 1336 7.6% 0.59 [1.00, 1.28] Sakoda et al. 105 514 253 1336 7.6% 0.59 [1.00, 1.20] Sakoda et al. 105 514 253 1336 7.6% 0.59 [1.00, 1.20] Sakoda et al. 105 514 253 1336 7.6% 0.59 [1.00, 1.20] Sakoda et al. 105 514 253 1336 7.6% 0.59 [1.00, 1.20] Sakoda et al. 105 514 253 1336 7.6% 0.59 [1.00, 1.20] Sakoda et al. 105 514 253 1336 7.6% 0.59 [1.00, 1.20] Sakoda et al. 129 6.002 111 6.002 1.32] Samon et al. 161 500 321 11000 7.9% 1.00 [0.80, 1.26] Sakoda et al. 2205 2265 2555 Heterogeneity $Tau" = 0.16; 0.205 126 0.50;$
	yonan et al. Syamala et al. Subtotal (95% CI) Total events telerogeneity: Tau <sup>2</sup> = ( Fest for overall effect: Z 4.3.4 West Asia tashemi et al. Kadouri et al. Kabazet et al-2015 Subtotal (95% CI) Total (95% CI) Total (95% CI) Total (95% CI)	182 920 0.14; Chi <sup>2</sup> = 1.94 (P 124 106 44 47 321 0.35; Chi <sup>2</sup> = 1.55 (P 3758	694 2440 = 29.95, d = 0.05) 268 422 200 172 1062 = 20.30, d = 0.12) 15754	141 929 f = 4 (P < 58 35 22 18 133 f = 3 (P = 3566	500 2858 0.00000 304 216 96 70 686 0.00001 17036	7.5% 32.4% I); I <sup>2</sup> = 87% 6.0% 5.4% 3.9% 3.5% 18.9% I; I <sup>2</sup> = 85%	0.91 [0.70, 1.17] 1.44 [1.00, 2.07] 6 3.65 [2.51, 5.31] 1.73 [1.14, 2.65] 0.95 [0.53, 1.70] 1.09 [0.58, 2.04] 1.65 [0.88, 3.11] 1.30 [1.12, 1.51]		Hashemi et al. 124 288 58 304 6.0% 3.65 [2.51, 5.31] Kadouri et al. 106 422 35 216 5.4% 1.73 [1.41, 2.65] Kin at al. 2015 47 172 18 70 3.5% 1.09 [0.55, 1.21] Saxena et al. 325 812 235 806 8.2% 1.52 [1.32, 1.99] Sohal et al. 190 200 162 204 3.0% 4.93 [2.40, 10.13] Syamala et al. 182 694 141 500 7.5% 0.91 [0.70, 1.17] Subtotal (65% C) 4750 4008 44.1% 1.58 [1.14, 2.19] Heterogeneity: Tau <sup>2</sup> = 0.18; Chi <sup>2</sup> = 50.17; df = 7 (P < 0.00001); l <sup>2</sup> = 88% Test for overall effect: $Z = 2.73$ (P = 0.006) <b>4.2. PC</b> Ceschi et al. 105 514 253 1336 7.6% 1.10 [0.85, 1.42] Egan et al. 469 2278 433 2422 8.9% 1.19 [1.03, 1.38] Kaushal et al. 62 234 70 348 5.5% 1.43 [0.97, 2.12] Khabaz et al2014 44 200 22 96 3.9% 0.95 [0.53, 1.70] Lee et al. 119 6052 111 6074 9.4% 1.09 [1.00, 1.20] Sakoda et al. 255 1226 337 1752 8.5% 1.10 [0.89, 1.42] Samson et al. 165 01 11004 13028 51.9% 1.11 [1.00, 1.02] Sakoda et al. 255 2255 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.6, df = 6 (P = 0.73); P = 0% Test for overall effect: $Z = 2.00; Chi2 = 3.6, df = 6 (P = 0.73); P = 0% Test for overall effect: Z = 2.00; Chi2 = 3.6, df = 6 (P = 0.73); P = 0% Test for overall effect: Z = 2.00; Chi2 = 3.6, df = 6 (P = 0.73); P = 0%$
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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% Cl. 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).

Description	Subgroup	Sam	ple size	Analysis	Test of associa	ation☆	P value for	Test for hete	erogeneity
(No. of studies)	(No. of studies)	Cases	Controls	model	OR (95% CI)	Р	Egger's test	Р	I <sup>2</sup> %
GSTT1 (Null vs Present)					i				
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

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

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

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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% Cl. 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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