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Original Article

The association between OGG1 Ser326Cys polymorphism and breast cancer risk: an updated meta-analysis of 20 case-control studies

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Abstract: Human 8-oxoguanine glycosylase 1 (hOGG1) plays an important role in the base excision repair (BER) pathway. Numerous epidemiological studies have explored the association between hOGG1 Ser326Cys polymorphism and breast cancer risk, but the results are inconsistent. We performed this meta-analysis to assess the association between Ser326Cys polymorphism and the risk of breast cancer, by critically reviewing 20 case-control studies including 9989 cases and 11759 controls. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects models to estimate the association strength. Our analysis suggested that Ser326Cys polymorphism was significant associated with an increased risk of breast cancer for recessive model (OR=1.10, 95% CI=1.01-1.19) in the whole population. In the subgroup analysis by ethnicity, a significant association was found among Asians (recessive model: OR=1.10, 95% CI=1.00-1.21; homozygote model: OR=1.15, 95% CI=1.01-1.31 and additive model: OR=1.07, 95% CI=1.01-1.14), but not Caucasians. When stratified by the source of controls, we observed a significantly increased risk of breast cancer in hospital-based studies (recessive model: OR=1.19, 95% CI=1.07-1.31; homozygote model: OR=1.16, 95% CI=1.01-1.32). Furthermore, we found a significant increased risk of breast cancer in hospital-based studies among both Asians (recessive model: OR=1.17, 95% CI=1.05-1.31; homozygote model: OR=1.19, 95% CI=1.02-1.39; additive model: OR=1.10, 95% CI=1.02-1.19) and Caucasians (recessive model: OR=1.25, 95% CI=1.01-1.56). This update meta-analysis suggests that OGG1 Ser326Cys polymorphism may be a risk factor of breast cancer. Nevertheless, large-scale, well-designed and population-based studies are needed to further evaluate gene-environment interaction on Ser326Cys polymorphism and breast cancer risk.

Keywords: OGG1, breast cancer, polymorphism, meta-analysis

Introduction

Breast cancer is one of the most common malignancies in females today, and its morbidity and mortality are still increasing [1]. Worldwide, breast cancer accounts for 22.9% of all cancers (excluding non-melanoma skin cancers) in females, with an estimated 1.38 million new cases and 458,000 deaths in 2008 [2]. Although the etiology of breast cancer is still not completely known, previous studies have shown that various factors have been associated with the increased risk of breast cancer, including family history of breast cancer, ionizing radiation (IR), reactive oxygen radicals, bulky DNA adducts, oxidized DNA bases, DNA strand breaks, heterocyclic aromatic amines, and alcohol [3-6]. However, only a portion of those who have been exposed to these risk factors will develop breast cancer, indicating that different genetic background may modify the individual's susceptibility to breast cancer.

DNA is continuously exposed to the assaults by numerous endogenous and exogenous mutagens or carcinogens, and the accumulation of unrepaired DNA damage may result in programmed cell death (apoptosis) or unregulated cell growth and cancer [7, 8]. Normally, efficient repair mechanisms prevent the harmful consequences of DNA damage [9]. It has suggested

that oxidative DNA damage induced by reactive oxygen species plays an important role in carcinogenesis, which is usually repaired through the base excision repair (BER) pathway. 8-Oxodeoxyguanosine, the most abundant lesion generated by oxidative stress can be excised by 8-oxoguanine DNA glycosylase/AP lyase, the key enzyme in BER pathway encoded by human 8-oxoguanine glycosylase 1 (hOGG1). hOGG1 located on chromosome 3p26, is highly polymorphic, and a number of single nucleotide polymorphisms (SNPs) have been identified, and a common functional polymorphism (Ser326Cys) on exon 7 (rs1052133; C/G) was extensively investigated for its association with the risks of several cancers, such as colorectal cancer, childhood acute lymphoblastic leukemia, nasopharyngeal carcinoma and lung cancer [10-12].

Although several epidemiological studies have reported the association between OGG1 Ser326Cys polymorphism and breast cancer risk, the results were contradictory [13-30]. Besides, two previous published meta-analyses reported the conflicting results regarding OGG1 Ser326Cys polymorphism and the susceptibility to breast cancer [31-33]. What's more, several new associated case-control studies of different population have since been published. In order to provide strong evidence of the effects of this polymorphism on breast cancer risk, we performed a meta-analysis with subgroup analysis based on all available studies to estimate the relationship between OGG1 Ser326Cys polymorphism and breast cancer risk.

Materials and methods

Search strategy

We managed to search the electronic literature by using PubMed and EMBASE databases for all relevant articles that evaluated the association between OGG1 Ser326Cys polymorphism and the risk of breast cancer up to June 28, 2015. The following terms were used in this search: ("human 8-oxoguanine DNA glycosylase" or hOGG1 or OGG1 or OGG) AND (polymorphism or variation or mutation) AND ("breast cancer" or "breast tumor" or "breast carcinoma" or "breast neoplasm"). The references cited in all studies were also reviewed to identify additional published articles, which was not indexed by the above databases.

Inclusion criteria

Studies which meet the following criteria were included in our meta-analysis: 1) a case-control study evaluating the OGG1 Ser326Cys polymorphism; 2) studies with full text articles; 3) containing enough data for estimating the odds ratios (OR) with the corresponding 95% confidence intervals (CI); 4) no overlapping data.

Exclusion criteria

Studies were excluded if they meet the following criteria: 1) studies without Ser326Cys frequency for the OGG1 polymorphism; 2) not design as a case-control study; 3) without sufficient data to estimate OR with 95% CI; 4) studies not in Hardy-Weinberg equilibrium (HWE).

Data extraction

Information was carefully extracted from all the eligible studies independently by three investigators according to the inclusion criteria listed above and reached a consensus on all of the eligibility items. For each study, the following data were collected: first author, publication year, country of origin, ethnicity, menopausal status, source of controls, genotyping method, numbers of cases and controls, genotype frequency of cases and controls, and the result of Hardy-Weinberg equilibrium test. Different racial descents were categorized as Caucasian and Asian.

Statistical analysis

A chi-square test was applied to detect whether the genotype distribution of the control population reported conformed to HWE ($P<0.05$ was considered significant). The strength of association between the hOGG1 Ser326Cys polymorphism and breast cancer risk was estimated by the combined OR corresponding to the 95% confidence interval (95% CI). The pooled ORs were performed for additive model (Cys allele versus Ser allele), codominant model (Cys/Cys versus Ser/Ser, Ser/Cys versus Ser/Ser), dominant model (Cys/Cys + Ser/Cys versus Ser/Ser), recessive model (Cys/Cys versus Ser/Cys + Ser/Ser) respectively. The significant of the pooled ORs were determined using Z test, and

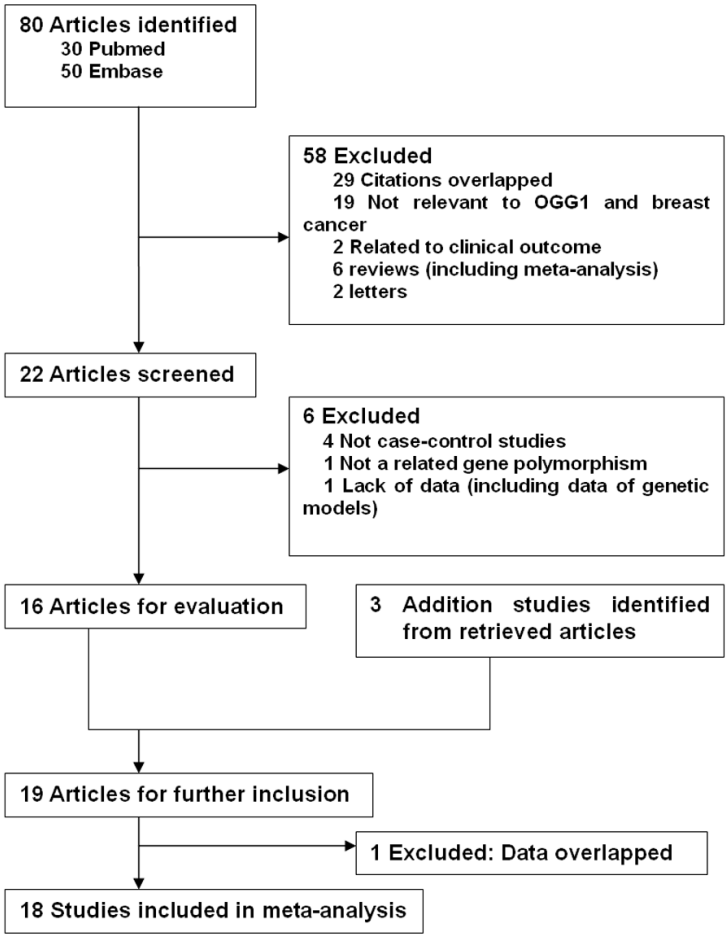

Figure 1. Flow of included studies.

a *P* value of less than 0.05 was considered significant. A chi-square-based *Q* test was used to test heterogeneity [34], and the proportion of the total variation due to heterogeneity was quantified by calculating I^2 statistics [35]. If the *P* value of the *Q* test was greater than 0.05 which indicates a lack of heterogeneity among studies, the Mantel-Haenszel method-based fixed-effects model was used to calculate the pooled OR [36]. Otherwise, the DerSimonian and Laird method-based random-effects model was applied [37]. Subgroup analyses were also performed by ethnicity, menopausal status and source of control. Moreover, sensitivity analysis was mainly performed by excluding a single study each time. Publication bias was evaluated with funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was further assessed by the method of Egger's linear regression test (*P*<0.05 was considered a significant publication bias) [38]. All of the statistical analyses were carried by STATA version 11.0 (Stata, College Station, TX, USA).

Result

Extraction process and study characteristics

According to our search criterion, 24 articles were found and 15 articles were eligible for the meta-analysis. In addition, 3 articles from other databases met the inclusion criteria. Finally, a total of 18 articles with a case-control design and available genotype frequency were included in our meta-analysis. Our initial search and the process of study selection were summarized in **Figure 1**. Two populations (Korean and Japanese) were included in the literature by Choi *et al*. [14], so we divided the relevant data into two separate studies. Because the literature by Rodrigues *et al*. [30] was carried out in two population groups, we also divided them into two separate studies. Although another two studies appeared to include small proportions of non-Caucasian subjects, the data for all subjects were used because we could not extract ethnicity specific data from the studies [20, 22]. Therefore, there were 11 studies of Caucasians and 9 studies of Asians. The study was by Vogel *et al*. [27] only provided the data of postmenopausal female, and it was still included in this meta-analysis. Among them, 8 studies (2 studies of Caucasians and 6 studies of Asians) provided the data of premenopausal females, and 9 studies (3 studies of Caucasians and 6 studies of Asians) of postmenopausal females. The main characteristics of these included studies and allele frequencies of OGG1 Ser326Cys polymorphism in case and control were shown in **Table 1**.

Meta-analysis results

The results of the meta-analysis of OGG1 Ser326Cys polymorphism were listed in **Table 2**. The combined result based on all studies

Table 1. Characteristics of studies included in the meta-analysis and their genotype distributions of OGG1 Ser326Cys polymorphisms

First author	Ethnicity	Year	Design	Sample size (case/control)		Case			Control			HWE	MAF
						AA	Aa	aa	AA	Aa	aa		
Choi	Asian	2003	HB	265	284	48	132	85	49	155	80	0.078	0.555
Choi	Asian	2003	HB	201	184	57	95	49	62	89	33	0.914	0.421
Vogel	Caucasian	2003	HB	425	434	256	147	22	245	169	20	0.175	0.241
Huang	Asian	2004	HB	136	232	25	63	48	38	106	88	0.525	0.608
Cai	Asian	2006	PB	1102	1167	186	534	382	214	537	416	0.080	0.587
Rossner	Caucasian	2006	PB	1041	1093	615	375	51	653	385	55	0.857	0.226
Zhang	Caucasian	2006	PB	1571	1244	967	532	72	760	424	60	0.930	0.219
Romanowicz-Makowska	Caucasian	2008	PB	100	106	32	34	34	20	52	34	0.988	0.566
Sangrajrang	Asian	2008	HB	506	424	112	232	162	104	217	103	0.627	0.499
Synowiec	Caucasian	2008	PB	41	48	10	19	12	4	23	21	0.507	0.677
Hsu	Asian	2009	HB	401	533	64	165	172	87	231	215	0.064	0.620
Loizidou	Caucasian	2009	PB	1108	1174	615	422	71	647	455	72	0.499	0.255
Sterpone	Caucasian	2010	HB	43	31	18	23	2	15	14	2	0.593	0.290
Roberts	Caucasian	2011	HB	1054	1887	634	366	54	1125	670	92	0.543	0.226
Xie	Asian	2012	HB	630	777	96	310	224	137	401	239	0.161	0.566
Kim	Asian	2013	HB	346	361	73	181	92	86	185	90	0.634	0.506
Smolarz	Caucasian	2013	HB	70	70	16	39	15	16	38	16	0.473	0.500
Luo	Asian	2014	HB	194	245	42	87	65	45	107	93	0.151	0.598
Rodrigues	Caucasian	2014	HB	347	665	319		28	631		34	0.870	0.213
Rodrigues	Caucasian	2014	HB	408	800	378		30	767		33	-	-

Abbreviations: HWE, Hardy-Weinberg equilibrium; HB, hospital-based; MAF, minor allele frequency; A, the major allele; a, the minor allele.

showed that OGG1 Ser326Cys polymorphism was significantly associated with an increased risk of breast cancer for recessive model (OR=1.10, 95% CI=1.01-1.19; **Figure 2**; **Table 2**). In terms of subgroup analyses by ethnicity, significantly increased risks were found among Asians for recessive model (OR=1.10, 95% CI=1.00-1.21; **Figure 2**; **Table 2**), homozygote model (OR=1.15, 95% CI=1.01-1.31; **Figure 2**; **Table 2**) and additive model (OR=1.07, 95% CI=1.01-1.14; **Figure 2**; **Table 2**), but not among Caucasians. As for the subgroup analyses by source of control, significantly increased risks were found in hospital-based studies (recessive model: OR=1.19, 95% CI=1.07-1.31; homozygote model: OR=1.16, 95% CI=1.01-1.32; **Figure 3**; **Table 2**), but not in population-based studies. However, we noticed a significant increased risk of breast cancer in hospital-based studies among both Asians (recessive model: OR=1.17, 95% CI=1.05-1.31; homozygote model: OR=1.19, 95% CI=1.02-1.39; additive model: OR=1.10, 95% CI=1.02-1.19; **Figure 3**; **Table 2**) and Caucasians (recessive model: OR=1.25, 95% CI=1.01-1.56; **Figure 3**; **Table 2**). Meanwhile, stratified analyses by menopausal status indicated that no significant association was found in both premenopausal and postmenopausal females for all genetic models. Additionally, further analyses stratified by menopausal status in different ethnicities revealed this polymorphism had no influence on the risk of breast cancer in either premenopausal or postmenopausal females of different ethnicities.

Test of heterogeneity and sensitivity analyses

The results of heterogeneity test indicated that there was no significant heterogeneity in overall comparisons (**Table 2**). Furthermore, influence analysis was performed to assess the influence of a single study on the pooled ORs by sequential omission of individual studies and no individual study significantly influenced the pooled ORs as a result, suggesting that the results of this meta-analysis are credible.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry. We present funnel plot for ORs of recessive model and additive model for OGG1 Ser326Cys poly-

Table 2. Results of meta-analysis for Ser326Cys polymorphisms and the risk of breast cancer

Genetic model		Recessive model			Dominant model			Homozygote			Heterozygote			Additive model		
Ser326Cys	n	Cys/Cys vs. Cys/Ser + Ser/Ser			Cys/Cys + Ser/Cys vs. Ser/Ser			Cys/Cys vs. Ser/Ser			Ser/Cys vs. Ser/Ser			Cys vs. Ser		
		OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)
Total	20 (9989/11759)	1.10 (1.01-1.19)	0.270	14.8	1.00 (0.94-1.07)	0.487	0.0	1.07 (0.97-1.19)	0.434	1.7	0.99 (0.93-1.06)	0.616	0.0	1.02 (0.98-1.07)	0.292	13.5
Ethnicity																
Asian	9 (3781/4207)	1.10 (1.00-1.21)	0.154	32.9	1.09 (0.97-1.22)	0.873	0.0	1.15 (1.01-1.31)	0.416	2.3	1.05 (0.93-1.19)	0.949	0.0	1.07 (1.01-1.14)	0.315	14.3
Caucasian	11 (6208/7552)	1.08 (0.94-1.25)	0.412	3.2	0.97 (0.90-1.04)	0.287	17.5	0.96 (0.81-1.13)	0.633	0.0	0.96 (0.89-1.04)	0.231	23.9	0.98 (0.92-1.04)	0.656	0.0
Menopausal status																
Premenopausal	8 (2553/2629)	1.12 (0.97-1.28)	0.054	49.4	1.03 (0.91-1.17)	0.599	0.0	1.11 (0.93-1.33)	0.121	38.7	1.01 (0.88-1.16)	0.907	0.0	1.05 (0.97-1.15)	0.074	45.9
Asian	6 (1651/1638)	1.21 (0.93-1.58)	0.033	58.8	1.08 (0.91-1.29)	0.459	0.0	1.18 (0.96-1.44)	0.084	48.4	1.03 (0.85-1.24)	0.802	0.0	1.11 (0.94-1.30)	0.050	54.9
Caucasian	2 (902/991)	0.85 (0.56-1.31)	0.821	0.0	0.98 (0.81-1.18)	0.610	0.0	0.85 (0.55-1.32)	0.901	0.0	1.00 (0.82-1.22)	0.539	0.0	0.96 (0.82-1.13)	0.744	0.0
Postmenopausal	9 (3286/3739)	1.14 (0.98-1.32)	0.444	0.0	1.01 (0.91-1.12)	0.835	0.0	1.18 (0.99-1.41)	0.928	0.0	0.99 (0.88-1.10)	0.721	0.0	1.04 (0.97-1.12)	0.680	0.0
Asian	6 (1243/1262)	1.14 (0.96-1.35)	0.163	36.5	1.12 (0.92-1.37)	0.886	0.0	1.23 (0.98-1.55)	0.739	0.0	1.07 (0.86-1.32)	0.637	0.0	1.10 (0.98-1.23)	0.637	0.0
Caucasian	3 (2043/2477)	1.13 (0.86-1.49)	0.992	0.0	0.98 (0.86-1.10)	0.568	0.0	1.11 (0.84-1.47)	0.973	0.0	0.96 (0.84-1.09)	0.547	0.0	1.00 (0.90-1.10)	0.679	0.0
Source of control																
HB	14 (5026/6927)	1.19 (1.07-1.31)	0.389	5.8	1.02 (0.93-1.12)	0.815	0.0	1.16 (1.01-1.32)	0.682	0.0	0.98 (0.89-1.08)	0.964	0.0	1.06 (0.99-1.12)	0.385	6.2
Asian	8 (2679/3040)	1.17 (1.05-1.31)	0.307	15.6	1.09 (0.95-1.24)	0.802	0.0	1.19 (1.02-1.39)	0.380	6.5	1.02 (0.89-1.17)	0.956	0.0	1.10 (1.02-1.19)	0.342	11.3
Caucasian	6 (2347/3887)	1.25 (1.01-1.56)	0.397	3.1	0.95 (0.84-1.09)	0.763	0.0	1.03 (0.77-1.38)	0.994	0.0	0.94 (0.82-1.08)	0.684	0.0	0.98 (0.88-1.08)	0.911	0.0
PB	6 (4963/4832)	0.96 (0.85-1.10)	0.825	0.0	0.99 (0.91-1.08)	0.088	47.8	0.97 (0.84-1.14)	0.271	21.6	1.00 (0.91-1.09)	0.063	52.2	0.99 (0.93-1.05)	0.348	10.5
Asian	1 (1102/1167)	0.96 (0.81-1.14)	-	100	1.11 (0.89-1.37)	-	100	1.06 (0.83-1.34)	-	100	1.14 (0.91-1.44)	-	0.0	1.01 (0.90-1.14)	-	0.0
Caucasian	5 (3861/3665)	0.97 (0.80-1.18)	0.707	0.0	0.97 (0.89-1.07)	0.076	52.8	0.92 (0.76-1.13)	0.223	29.7	0.97 (0.88-1.07)	0.064	54.9	0.98 (0.91-1.05)	0.250	25.7

P_h *P* values for heterogeneity from *Q* test. I^2, the percentage of variability in OR attributes to heterogeneity. Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-model was used.

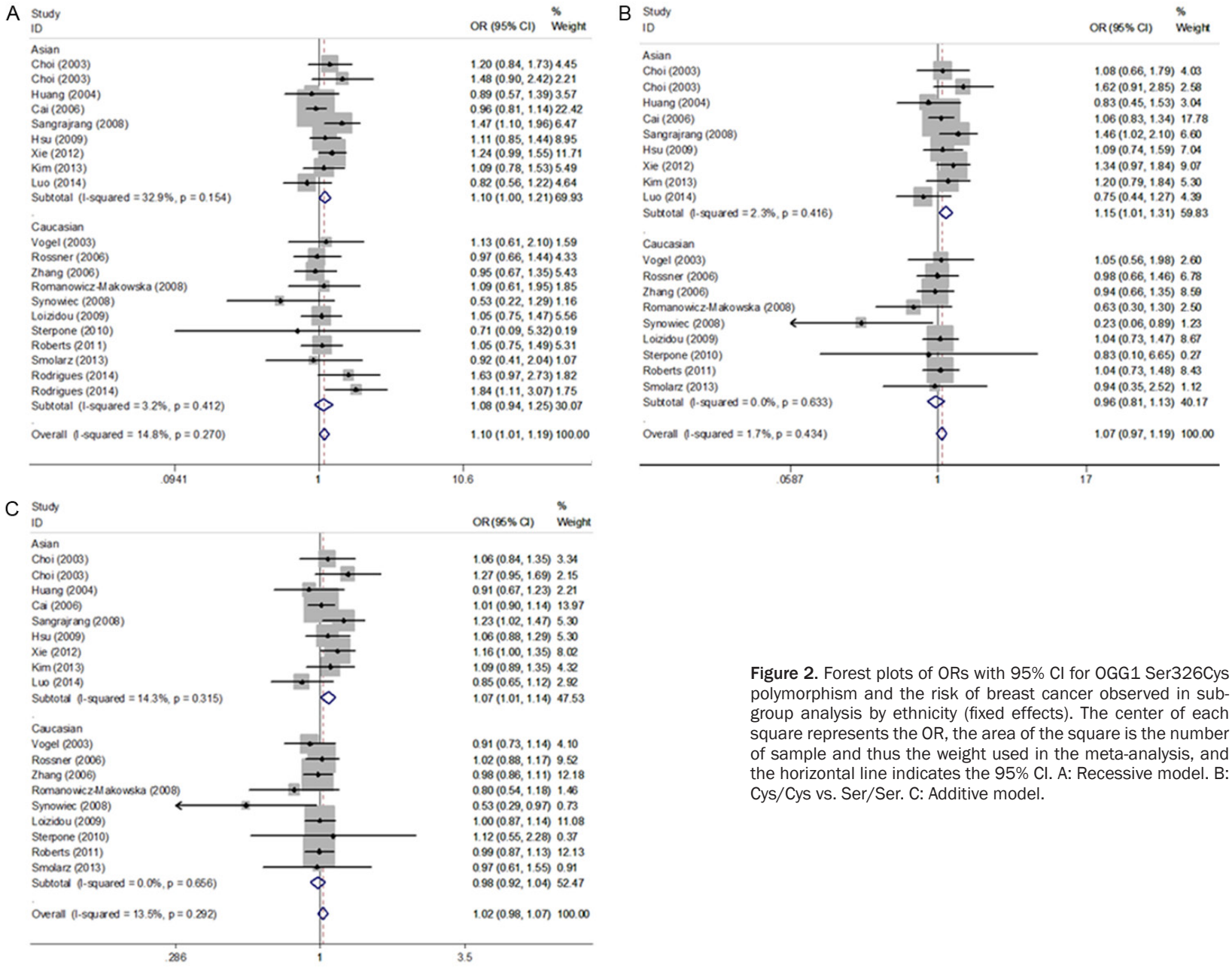

Figure 2. Forest plots of ORs with 95% CI for OGG1 Ser326Cys polymorphism and the risk of breast cancer observed in subgroup analysis by ethnicity (fixed effects). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. A: Recessive model. B: Cys/Cys vs. Ser/Ser. C: Additive model.

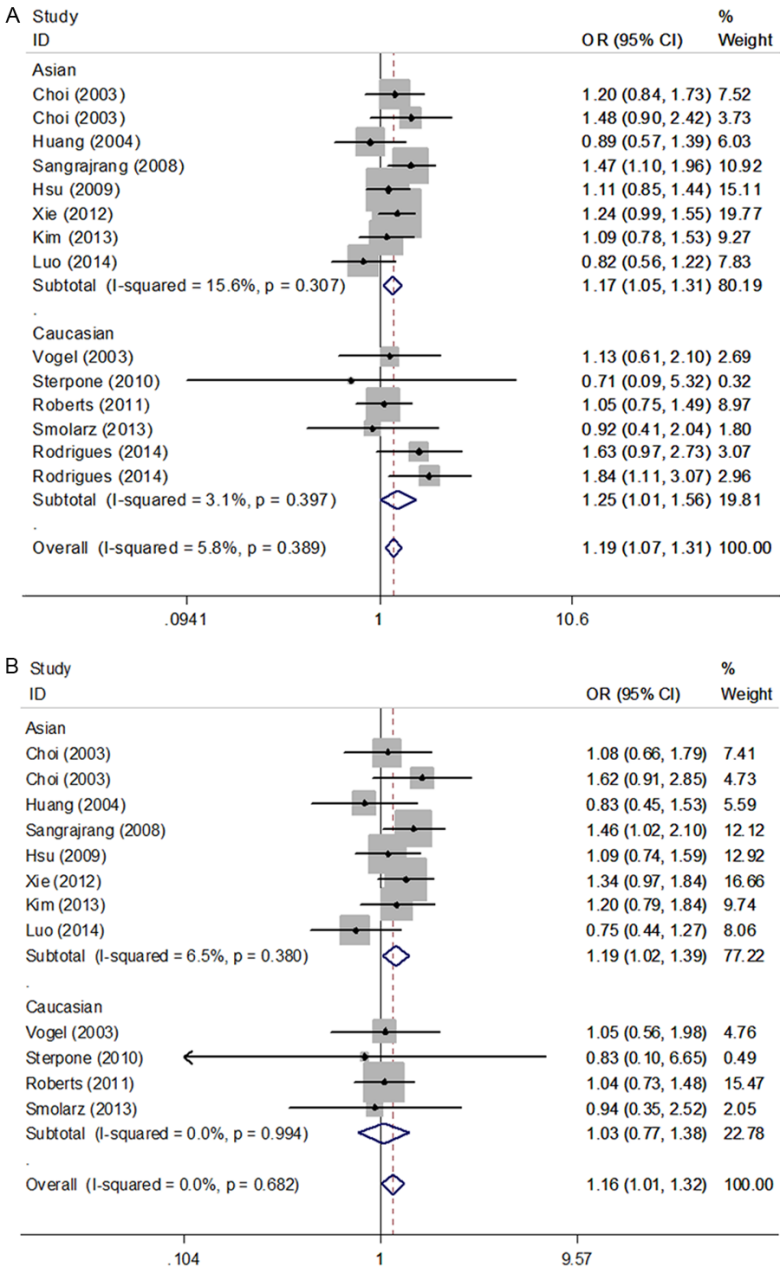

Figure 3. Forest plots of ORs with 95% CI for OGG1 Ser326Cys polymorphism and the risk of breast cancer observed in hospital-based controls (fixed effects). The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. A: Recessive model. B: Cys/Cys vs. Ser/Ser.

morphism in **Figure 4**. And the results of Egger's test still did not suggest any evidence of publication bias (P=0.319 for dominant model, P=0.971 for recessive model, P=0.066 for homozygote model, P=0.199 for heterozygote model, and P=0.329 for additive model).

Discussion

In mammalian cells, they can utilize different pathways to repair diverse types of DNA damage, and thus conserve genome stability and integrity. Base excision repair is an important DNA repair pathway responsible for the repair of base damage resulting from X-rays, oxygen radicals, and alkylating agents, which is initiated by recognition and excision of damaged base by the specific DNA glycosylase. The human OGG1 (hOGG1) is one of central players in the BER pathway, which catalyzes the cleavage of the glycosylic bond between the modified base and the sugar moiety, leaving an abasic apurinic/apyrimidinic site in DNA. And the resulting apurinic/apyrimidinic site is then incised, and the repair is completed by successive actions of a phosphodiesterase, a DNA polymerase, and a DNA ligase [39, 40]. To date, although many functional studies have reported that the possible function of OGG1 Ser326Cys polymorphism in the development of breast cancer, the results of epidemiological studies still remains contradictory. Previous meta-analyses even provided some conflicting results due to different sample sizes and different classification on the ethnicity. And the discrepancies across these studies motivated the present meta-analysis.

In the present meta-analysis, we performed a quantitative synthesis of the evidence on the association between OGG1 Ser326Cys polymorphism and the risk of breast cancer based on 20 case-control studies with 9989 cases and 11759 controls. The combined results

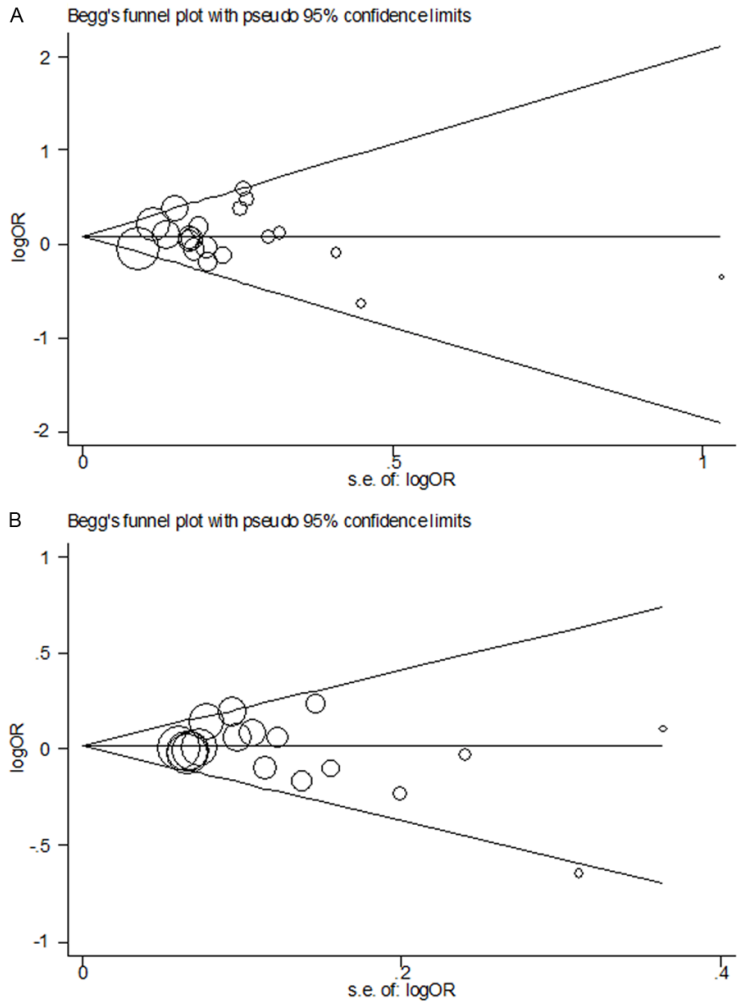

Figure 4. Begg's funnel plots of OGG1 Ser326Cys polymorphism and breast cancer risk for publication bias test. Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, means effect size. A: Recessive model. B: Additive model.

revealed that OGG1 Ser326Cys polymorphism was significantly associated with an increased risk of breast cancer in the whole population, which was inconsistent with all the previous meta-analyses [31-33, 41]. When stratified by ethnicity, our results showed that Ser326Cys polymorphism might contribute to the susceptibility of breast cancer among Asians, but not Caucasians, which were differed from the conclusions drawn by Gu *et al*. [31] and Yuan *et al*. [32] in their meta-analyses. Interestingly, several meta-analyses suggested that Ser326Cys polymorphism may increase the predisposition to esophageal cancer [42] among Asians, whereas it may confer significantly increased risks of lung cancer [43] or colorectal cancer [44] among Caucasians. However, Xu *et al*. [43] proved that Ser326Cys polymorphism was significantly associated with increased risk of lung cancer in both Asians and Caucasians. Moreover, no evidence of Ser326Cys polymorphism with the risk of gastric cancer [45], pancreatic cancer [46] and gallbladder cancer [47] was observed in both Asians and Caucasians. Several factors may contribute to the results that the same polymorphism plays different roles in cancer risk among different ethnic populations. First of all, ethnic variation in the distribution of genotypes of this polymorphism has been demonstrated, which indicate that this polymorphism may modify the risk of cancer in different ethnicities. Meanwhile, this apparent difference on cancer susceptibility might be partially owing to the existence of gene-to-gene or gene-to-environment interactions. The fact that the low penetrance genetic effects of single polymorphism usually depends on the interaction with other polymorphisms and/or a particular environmental exposure including dietary and lifestyle factors can explain that other as-yet-unidentified causal genes involved in carcinogenesis might disguise the influence of the genetic variant. Thus, further investigations are warranted to validate ethnic differences in the effect of this functional polymorphism on cancer risk, especially in Asians.

Furthermore, subgroup analyses based on the source of control showed that individuals who carried Cys allele might have a significantly increased risk of breast cancer among the hospital-based studies but not the population-based. The reason may be that hospital-based studies have some bias. Because these controls may suffer certain begin disease which have different risks of developing malignancy and may not be very representative of the general population. Thus, the use of a proper and representative cancer-free control subjects is

very important in reducing biases in such case-control studies. While stratified analyses by ethnicities in hospital-based studies, the result indicated that significant associations were observed among both Asians and Caucasians, implying that source of controls may affect the overall results in the whole population. Additionally, there was no evidence for the association between Ser326Cys polymorphism and breast cancer risk in both premenopausal and postmenopausal females, which was inconsistent with the conclusion drawn by Peng *et al.* [33]. Similarly, Ser326Cys polymorphism is not associated with increased breast cancer risk in either premenopausal or postmenopausal females among different ethnicities.

Previous meta-analysis by Yuan *et al.* [32] reported that 326Cys allele might have significant protective effects on breast cancer among Caucasian women. However, the meta-analyses by Gu *et al*. [31] and Peng *et al*. [33] did not show the significant results of Caucasian population. In addition, the studies by Yuan *et al*. [31] and Zhou *et al*. [41] did not conduct with all published case-control studies, which may interfere with the results. In the published studies, one study showed a significantly increased risk of postmenopausal females in dominant model [23], but the other studies provided inconsistent results [13-15, 20, 27, 28]. Studies with small sample sizes may have insufficient statistical power to detect any slight effect, so a positive association between this polymorphism and breast cancer might therefore not be ruled out. But in this update meta-analysis, the sample size was large enough to detect a moderate statistical significance of Ser326Cys polymorphism. For example, the subgroup analysis of Asians, including 9 studies (3781 cases and 4207 controls), the sample size was enough to ascertain the association strength of Ser326Cys polymorphism with breast cancer risk. With the accumulating evidence and enlarged sample size, we enhance statistical power to provide more precise and reliable risk estimates than the previous meta-analyses. First, sensitivity analyses revealed that the results were robust. Second, there was no significant heterogeneity in most of the comparisons. Third, funnel plots and Egger's tests found no significant publication bias.

In interpreting our results of the present meta-analysis, several limitations merit consideration. First, the number of published studies was not sufficiently large for stratified analysis by menopausal status in different ethnicities. Our results were hindered because of limited available data for the Caucasian population. Larger studies are needed to clarify whether OGG1 Ser326Cys polymorphism affects the risk of breast cancer in both premenopausal and postmenopausal females from different ethnicities. Second, these results for hospital-based studies should be interpreted with caution because the controls were not uniformly defined. Some studies used a healthy population as the control group, whereas others selected hospital patients without cancer. Therefore, non-differential misclassification bias is possible because these studies may have included the individuals who have different risks of developing breast cancer. Third, our results were based on single-factor estimates without adjustment for other risk factors such as smoking status, drinking consumption, environmental factors and other variables, which might have caused serious confounding bias.

In conclusion, our meta-analysis suggested that OGG1 Ser326Cys polymorphism was significantly associated with increased risk of breast cancer. Nevertheless, large-scale, well-designed and population-based studies are needed to further evaluate gene-environment interaction on Ser326Cys polymorphism and breast cancer risk. Additional studies exploring the combined effects of different polymorphisms in genes involved in DNA repair pathway should be investigated.

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Disclosure of conflict of interest

None.

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