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Association between three exonuclease 1 polymorphisms and cancer risks: a meta-analysis

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Abstract: To date, the results of studies exploring the relation between exonuclease 1 (*Exo1*) polymorphisms and cancer risks have differed. In this study, we performed a meta-analysis to investigate the effect of the three most extensively studied *Exo1* polymorphisms (Pro757Leu, Glu589Lys, and Glu670Gly) on cancer susceptibility. The related studies published before August 5, 2015, were collected by searching the PubMed and EMBASE databases. We found 16 publications containing studies that were eligible for our study, including 10 studies for Pro757Leu polymorphism (4,093 cases and 3,834 controls), 12 studies for Glu589Lys polymorphism (6,479 cases and 6,550 controls), and 7 studies for Glu670Gly polymorphism (3,700 cases and 3,496 controls). Pooled odds ratios and 95% confidence intervals were used to assess the strength of the associations, and all the statistical analyses were calculated using the software program STATA version 12.0. Our results revealed that the Pro757Leu polymorphism was significantly associated with a reduced cancer risk, whereas an inverse association was found for the Glu589Lys polymorphism. Furthermore, subgroup analysis of smoking status indicated that the Glu589Lys polymorphism was significantly associated with an increased cancer risk in smokers, but not in nonsmokers. However, no evidence was found for an association between the Glu670Gly polymorphism and cancer risk. In conclusion, this meta-analysis suggests that the Pro757Leu polymorphism may provide protective effects against cancer, while the Glu589Lys polymorphism may be a risk factor for cancer. Moreover, the Glu670Gly polymorphism may have no influence on cancer susceptibility. In the future, large-scaled and well-designed studies are needed to achieve a more precise and comprehensive result.

Keywords: exonuclease 1, polymorphism, cancer risks, meta-analysis

Introduction

Cancer, caused by complex factors including genetics and environment, as well as by the interactions between these two factors, is a severe global public-health problem.[1,2] DNA damage may lead to human cancer, while DNA repair pathways such as mismatch repair (MMR) in mammals may play a role in repairing such damage.[3,4] Genetic variations in DNA repair genes may influence repair efficiency and alter cancer risks.[5]

The exonuclease 1 (*Exo1*) gene, belonging to the MMR system and the RAD2/XPG nuclease family, encodes an 846 amino acid protein, which functions in DNA repair, replication, and homologous recombination.[6–9] Exo1 can interact physically with the MMR proteins MLH1 and MSH2 and participate in mismatch-provoked excision repair by forming a ternary complex of Exo1-MLH1-PMS2 or Exo1-MSH2-MSH6.[10–12]

Several nonsynonymous coding polymorphisms in the *Exo1* gene have been identified. These polymorphisms may lead to amino acid changes and may affect the interactions between the Exo1 protein and other MMR proteins, resulting in altered DNA repair capacity and influencing cancer risks.[13,14] In consideration of the possible

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influence of the genetic variants on the repair efficiency of the MMR system and cancer susceptibilities, many studies have assessed the relationship between *Exo1* polymorphisms and cancer risks.

To date, three single-nucleotide polymorphisms (SNPs) of the *Exo1* gene – Pro757Leu (rs9350, C/T) at exon 13, Glu589Lys (rs1047840, G/A), and Glu670Gly (rs1776148, A/G) at exon 11 – have been the most widely investigated in epidemiological studies.[15–30] Not all of these studies, however, reached the same conclusion, which may be partly due to the limitations of individual studies. Therefore, we carried out this meta-analysis of all eligible case-control studies to draw a more reliable conclusion of the association between *Exo1* polymorphisms (Glu589Lys, Pro757Leu, and Glu670Gly) and cancer susceptibility.

Materials and methods

Study identification and inclusion criteria

We searched the PubMed and EMBASE databases for relevant studies (last search was updated on August 5, 2015). Without applying search filters, the following keywords were used for the literature search: (Exo1 or "Exonuclease 1"), (cancer or carcinoma or tumor or neoplasm), and (polymorphism or variant or variation or mutation). Furthermore, the references in the retrieved articles were also manually screened to ensure that no relevant publication was missed.

All studies used in our meta-analysis were carefully examined to meet the following criteria: case–control studies conducted on human subjects, with full text articles that investigated the association between cancer risk and at least one of three *Exo1* gene polymorphisms (Pro757Leu, Glu589Lys, or Glu670Gly). Another requirement of these studies was the inclusion of an odds ratio (OR) with 95% confidence intervals (CIs) or the provision of sufficient raw data to calculate these measures. A request letter for the original genotype frequency data was sent to the corresponding author when such data were unavailable in relevant articles. If studies had overlapping data, only the more complete study was used.

Data extraction

Two investigators collected the following items from each eligible study, independently: name of the first author, year of publication, ethnicity, country, cancer types, genotyping method, source of controls, numbers of cases and controls, genotype frequency of cases and controls, and the demographic data – if available – including smoking status.

Statistical analysis

This meta-analysis was performed for a recessive model (aa vs Aa+AA, where "A" was the major allele and "a" was the minor allele), dominant model (aa+Aa vs AA), homozygote comparison (aa vs AA), heterozygote comparison (Aa vs AA), and additive model (a vs A). We used ORs with 95% CIs to evaluate the strength of association between *Exo1* polymorphisms and cancer risk, while pooled ORs were obtained by calculating a weighted average of OR from each study.[31] Between-study heterogeneity, measured by a Q-statistic test[32] and I^2 statistic,[33] was assessed to determine whether a fixed-effects or random-effects model should be applied. When the P_h value of the Q-test is smaller than 0.05, which indicated a significant heterogeneity among the studies, a random-effects model[34] was used to calculate the pooled ORs; otherwise the fixed-effects model[35] was used.

Subgroup analyses were performed by ethnicity, source of controls, cancer types, and smoking status to explore the effect of heterogeneity among the studies. Univariate meta-regression analysis was used to further clarify the potential reasons for heterogeneity ($P<0.05$ was considered significant).[36] Studies were split into large sample size or small sample size using the cut-point of 600 participants. By sequentially omitting each study, sensitivity analysis was used to assess the stability of the results. Begg's funnel plot and Egger's linear regression test were carried out to estimate the potential publication bias, graphically and statistically, and $P<0.05$ was considered significant.[37]

A goodness-of-fit χ^2 test with 1 degree of freedom was applied to assess the Hardy–Weinberg equilibrium (HWE) in controls and a value of $P<0.05$ was considered as a significant disequilibrium. We used the software program STATA (version 12.0; StataCorp LP, College Station, TX, USA) for all the statistical analyses in this meta-analysis.

Results

Extraction process and study characteristics

On the basis of the inclusion criteria, 17 publications were preliminarily identified as eligible.[15–30,38] Among these, the study conducted by Yoshiya et al[38] was excluded because the data were the same as those for the earlier study by Yamamoto et al.[15] Thus, 16 articles were included in the final meta-analysis.[15–30] Table 1 summarizes the main characteristics of the selected studies, while Figure 1 shows the study selection process. The genotyping data in the study by Jin et al[19] were only analyzed in the additive genetic model because the data were limited. In addition, the data from Tang et al's study[30]

Table 1 Characteristics of studies included in the meta-analysis

Study	Ethnicity	Region	SNPs studied	Cancer types	Genotyping	Control source	Cases/controls
Yamamoto et al[15]	Asian	Japan	757	Colorectal	PCR-RFLP	PB	102/110
Zienolddiny et al[16]	Caucasian	Norway	589	Lung	TaqMan	PB	256/291
Kim et al[17]	Asian	Korea	757	Colorectal	DHPLC	HB	268/300
Chang et al[18]	Caucasian	USA	589, 670	Glioblastoma	Microarray	PB	112/110
Jin et al[19]	Asian	People's Republic of China	757, 589, 670	Lung	Illumina	HB	500/517
Bau et al[20]	Asian	Taiwan	757, 589, 670	Gastric	PCR-RFLP	HB	179/179
Hsu et al[21]	Asian	Taiwan	757, 589, 670	Lung	PCR-RFLP	HB	358/358
Tsai et al[22]	Asian	Taiwan	757, 589, 670	Oral	PCR-RFLP	HB	680/680
Wang et al[23]	Asian	Taiwan	757, 589, 670	Breast	PCR-RFLP	HB	1,272/1,272
Wang et al[24]	Mixed	Costa Rica	757	Cervical	TaqMan	PB	460/431
Haghighi et al[25]	Asian	Iran	757	Colorectal	PCR-RFLP	HB	90/98
Ibarrola-Villava et al[26]	Caucasian	Spain	757, 589, 670	Melanoma	Sequenom, TaqMan, Sequenom	HB	684/406, 599/379, 599/379
Bayram et al[27]	Caucasian	Turkey	589	Hepatocellular	PCR-RFLP	HB	224/224
Luo et al[28]	Asian	People's Republic of China	589	Cervical	PCR-RFLP	HB	126/278
Kabzinski et al[29]	Caucasian	Poland	589	Colorectal	TaqMan	NA	150/150
Tang et al[30]	Caucasian	Multiple Regions	589	Pancreatic	Illumina	Mixed	2,023/2,112

Abbreviations: SNP, single nucleotide polymorphism; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; TaqMan, real-time TaqMan analysis; DHPLC, denaturing high-performance liquid chromatography; Sequenom, genotyping was performed using the Sequenom platform; PB, population based; HB, hospital based; NA, not available.

were genome-wide association study data. In the pooled analyses, we included 4,093 cases and 3,834 controls from 10 studies for the Pro757Leu polymorphism, 6,479 cases and 6,550 controls from 12 studies for the Glu589Lys polymorphism, and 3,700 cases and 3,496 controls from 7 studies for the Glu670Gly polymorphism. Of these, six were studies of Caucasians, nine were studies of Asians, and one was a study of mixed population, while four were population based and ten were hospital based. In addition, there were three lung cancer studies,[16,19,21] four colorectal cancer studies,[15,17,25,29] two cervical cancer studies,[24,28] and seven others studies including glioblastoma,[18] gastric cancer,[20] oral cancer,[22] breast cancer,[23] melanoma,[26] hepatocellular cancer,[27] and pancreatic cancer.[30] Table 2 lists the genotype distribution and allele frequency of *Exo1* polymorphism among cancer cases and controls and the *P*-value of the HWE in the controls.

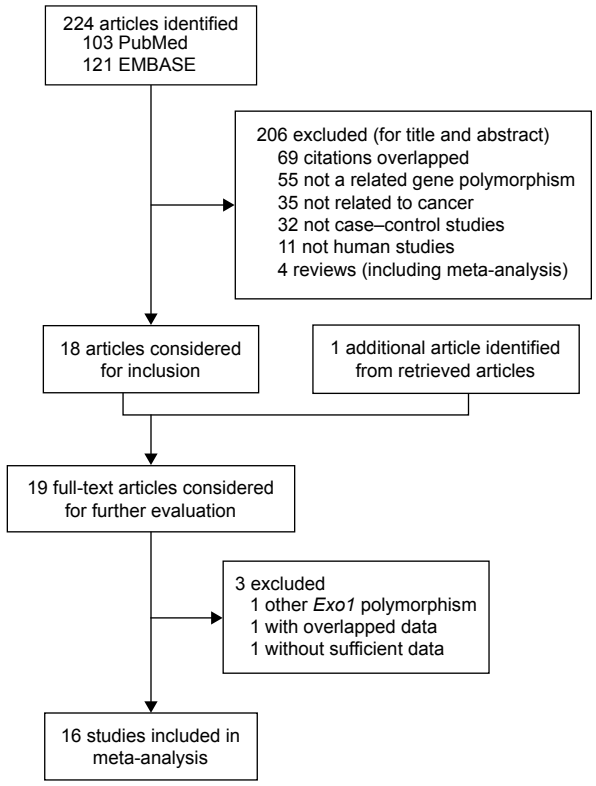

Figure 1 Studies included in this meta-analysis.

Meta-analysis results

The main results for the three *Exo1* polymorphisms of this meta-analysis are listed in Table 3. Overall, the combined results based on all eligible studies showed a significant association between the Pro757Leu polymorphism and reduced cancer risk (dominant model: OR =0.902, 95% CI =0.821–0.991, *P*=0.032; and heterozygote comparison: OR =0.894, 95% CI =0.809–0.988, *P*=0.027; Table 3). Moreover, in the stratified analysis, the results showed that the Pro757Leu polymorphism was associated with a reduced risk of cancer among Asians (dominant model: OR =0.852, 95% CI =0.765–0.949, *P*=0.004; heterozygote comparison: OR =0.847, 95% CI =0.755–0.951, *P*=0.005; and additive model: OR =0.932, 95% CI =0.871–0.997, *P*=0.039; Figure 2), but not among Caucasians. In the subgroup analysis by source of controls, a significant association was found between the Pro757Leu polymorphism and a reduced

Table 2 Genotype distribution of *Exo1* polymorphisms used in this study

Polymorphism	Disease	First author	Ethnicity	Sample size (case/control)	Case			Control			HWE	MAF
					AA	Aa	aa	AA	Aa	aa		
Pro757Leu	Colorectal	Yamamoto et al[15]	Asian	102/110	35	53	14	36	47	27	0.143	0.459
	Colorectal	Kim et al[17]	Asian	268/300	108	125	35	99	163	38	0.021	0.398
	Lung	Jin et al[19]	Asian	500/517	–	–	–	–	–	–	–	0.409
	Gastric	Bau et al[20]	Asian	179/179	62	78	39	56	84	39	0.479	0.453
	Lung	Hsu et al[21]	Asian	358/358	124	156	78	112	167	79	0.264	0.454
	Oral	Tsai et al[22]	Asian	680/680	235	297	148	214	313	153	0.061	0.455
	Breast	Wang et al[23]	Asian	1,272/1,272	433	563	276	402	596	274	0.057	0.450
	Cervical	Wang et al[24]	Mixed	460/431	175	214	71	169	217	45	0.042	0.356
	Colorectal	Haghighi et al[25]	Asian	90/98	60	28	2	51	37	10	0.402	0.291
	Melanoma	Ibarrola-Villava et al[26]	Caucasian	684/406	485	186	13	297	99	10	0.611	0.147
Glu589Lys	Lung	Zienolddiny et al[16]	Caucasian	256/291	115	106	35	116	145	30	0.117	0.352
	Glioblastoma	Chang et al[18]	Caucasian	112/110	55	42	15	29	59	22	0.419	0.468
	Lung	Jin et al[19]	Asian	500/517	304	172	24	355	138	24	0.030	0.180
	Gastric	Bau et al[20]	Asian	179/179	103	64	12	125	49	5	0.940	0.165
	Lung	Hsu et al[21]	Asian	358/358	214	125	19	251	97	10	0.865	0.163
	Oral	Tsai et al[22]	Asian	680/680	391	244	45	482	183	15	0.626	0.157
	Breast	Wang et al[23]	Asian	1,272/1,272	794	421	57	898	341	33	0.926	0.160
	Melanoma	Ibarrola-Villava et al[26]	Caucasian	599/379	234	282	83	136	175	68	0.373	0.410
	Hepatocellular	Bayram et al[27]	Caucasian	224/224	95	94	35	99	108	17	0.089	0.317
	Cervical	Luo et al[28]	Asian	126/278	73	48	5	196	77	5	0.412	0.156
	Colorectal	Kabzinski et al[29]	Caucasian	150/150	22	95	33	49	62	39	0.038	0.467
	Pancreatic	Tang et al[30]	Caucasian	2,023/2,112	827	910	286	815	993	304	0.956	0.379
Glu670Gly	Glioblastoma	Chang et al[18]	Caucasian	112/111	44	57	11	46	47	18	0.314	0.374
	Lung	Jin et al[19]	Asian	500/517	–	–	–	–	–	–	–	0.181
	Gastric	Bau et al[20]	Asian	179/179	131	39	9	135	36	8	0.011	0.145
	Lung	Hsu et al[21]	Asian	358/358	262	78	18	269	73	16	0.000	0.147
	Oral	Tsai et al[22]	Asian	680/680	497	148	35	511	138	31	0.000	0.147
	Breast	Wang et al[23]	Asian	1,272/1,272	941	267	64	958	255	59	0.000	0.147
	Melanoma	Ibarrola-Villava et al[26]	Caucasian	599/379	239	293	67	160	171	48	0.826	0.352

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; A, the major allele; a, the minor allele.

cancer risk in the dominant model and in the heterozygote comparison in the hospital-based controls (Leu/Leu+Pro/Leu vs Pro/Pro: OR =0.882, 95% CI =0.797–0.977, P=0.016; Pro/Leu vs Pro/Pro: OR =0.878, 95% CI =0.788–0.979, P=0.019; Table 3), but not in the population-based controls. Moreover, the Leu allele of the Pro757Leu polymorphism was significantly associated with a reduced risk of colorectal cancer (dominant model: OR =0.724, 95% CI =0.557–0.942, P=0.016; homozygote comparison: OR =0.633, 95% CI =0.417–0.961, P=0.032; and additive model: OR =0.782, 95% CI =0.648–0.943, P=0.010).

In terms of the *Exo1* Glu589Lys polymorphism, a statistically significant association was found between the *Exo1* Glu589Lys polymorphism and the risk of cancer in the homozygote comparison (Lys/Lys vs Glu/Glu: OR =1.447, 95% CI =1.028–2.035, P=0.034) and in the additive model (Lys vs Glu: OR =1.200, 95% CI =1.014–1.421, P=0.034) in the pooled analyses. For Asians, the results showed that the Glu589Lys polymorphism increased the cancer risk (recessive model: OR =1.876, 95% CI =1.444–2.436, P<0.001; dominant model: OR =1.555, 95% CI =1.401–1.726, P<0.001; homozygote comparison: OR =2.133, 95% CI =1.639–2.777, P<0.001; heterozygote comparison: OR =1.495, 95% CI =1.341–1.666, P<0.001; and additive model: OR =1.487, 95% CI =1.361–1.625, P<0.001), while no association was found among Caucasians. When stratified by the source of controls, a significantly elevated cancer risk was found among studies with hospital-based controls (recessive model: OR =1.683, 95% CI =1.097–2.581, P=0.017; dominant model: OR =1.405, 95% CI =1.180–1.674, P<0.001; homozygote comparison: OR =1.848, 95% CI =1.164–2.934, P=0.009; heterozygote comparison: OR =1.356, 95% CI =1.161–1.583, P<0.001; and additive model: OR =1.366, 95% CI =1.144–1.632, P=0.001), while in population-based studies, the results showed that the Glu589Lys polymorphism was associated with a reduced cancer risk only in the heterozygote comparison (OR =0.616, 95% CI =0.453–0.836, P=0.002). In terms of cancer types, no association was found for lung cancer. Furthermore, subgroup analysis was also performed by smoking status. The results

showed that the Glu589Lys polymorphism was significantly associated with an increased cancer risk in smokers (dominant model: OR =1.866, 95% CI =1.384–2.515, $P<0.001$; Table 4, Figure 3), but not in nonsmokers.

In terms of the *Exo1* Glu670Gly polymorphism, no evidence was found for an association between the Glu670Gly polymorphism and cancer risk for all genetic models (Table 3). Furthermore, the results in the subgroup analyses by ethnicity, source of controls, and cancer types revealed no association, either.

Test of heterogeneity

The heterogeneity test showed that no significant heterogeneity was found for the Pro757Leu and Glu670Gly polymorphisms in all comparisons (Table 3). However, there was significant between-study heterogeneity for the *Exo1* Glu589Lys polymorphism in all genetic models (Table 3). Subgroup analysis was performed to explore the potential sources of heterogeneity. After patients were stratified by ethnicity, no heterogeneity was found in the Asian population, which indicated that ethnicity may contribute to substantial heterogeneity for the Glu589Lys polymorphism. A series of univariate meta-regression analyses under all genetic models, with the covariates of ethnicity, publication year, sample size, and HWE, showed that only ethnicity had a significant influence on heterogeneity (recessive model: $P=0.029$; dominant model: $P=0.035$; homozygote comparison: $P=0.032$; and additive model: $P=0.004$; Table 5).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs. The results showed that the conclusions of this meta-analysis for the Glu670Gly polymorphism were relatively stable and credible because the overall ORs were not influenced excessively by omitting any single study (data not shown). However, the conclusions for the Pro757Leu and Glu589Lys polymorphism were not sufficiently stable. While excluding any one of the three studies,[17,22,23] the pooled ORs for the Pro757Leu polymorphism changed and the result became negative in all genetic models, indicating that the results were relatively unstable. In terms of the Glu589Lys polymorphism, when the study by Chang et al[18] was excluded, the association between the *Exo1* Glu589Lys polymorphism and the risk of cancer became significant in all genetic models (recessive model: OR =1.399, 95% CI =1.048–1.866, $P=0.022$; dominant model: OR =1.333, 95% CI =1.086–1.637, $P=0.006$; homozygote comparison: OR =1.601, 95% CI =1.144–2.240, $P=0.006$; heterozygote comparison: OR =1.294, 95% CI =1.055–1.587, $P=0.013$; and additive model: OR =1.269, 95% CI =1.079–1.494, $P=0.004$), suggesting that this study significantly influenced the result.

Publication bias

The publication bias of the literature was assessed by both Begg's funnel plot and Egger's test. The shapes of the funnel plots for each polymorphism showed no obvious asymmetry (Figure 4). Evidence of publication bias was not found using Egger's test for the Pro757Leu polymorphism (recessive model: $P=0.188$; dominant model: $P=0.357$; homozygote comparison: $P=0.188$; heterozygote comparison: $P=0.734$; and additive model: $P=0.178$), Glu589Lys polymorphism (recessive model: $P=0.093$; dominant model: $P=0.516$; homozygote comparison: $P=0.081$; heterozygote comparison: $P=0.556$; and additive model: $P=0.310$), and Glu670Gly polymorphism (recessive model: $P=0.679$; dominant model: $P=0.193$; homozygote comparison: $P=0.608$; heterozygote comparison: $P=0.098$; and additive model: $P=0.666$), respectively.

Discussion

Our meta-analysis is the first study to investigate the association between *Exo1* Pro757Leu and Glu670Gly polymorphisms of Exo1 and cancer susceptibility, and also the largest and most comprehensive assessment of the relationship between the Glu589Lys polymorphism and cancer risk. In our study, we conducted an analysis that included 10 studies relating to the Pro757Leu polymorphism (4,093 cases and 3,834 controls), 12 studies relating to the Glu589Lys polymorphism (6,479 cases and 6,550 controls), and 7 studies relating to the Glu670Gly polymorphism (3,700 cases and 3,496 controls). The final results showed that Pro757Leu conferred a protective effect against cancer, and the Glu589Lys polymorphism was associated with an increased cancer risk, but the Glu670Gly polymorphism was not statistically significantly associated with cancer risk. Interestingly, stratified analysis by ethnicity indicated that, among Asians, the Pro757Leu polymorphism was associated with a reduced risk of cancer under the dominant model, heterozygote comparison, and additive model, whereas the Glu589Lys polymorphism was significantly associated with increased cancer risk under all the genetic models. The differences between Asians and other races may be partly due to the different genetic backgrounds and environments or lifestyles.[39] The Leu allele frequency of the Pro757Leu polymorphism among the controls in the Asian population was 43.7% (95% CI =42.5%–44.8%), which was significantly higher than that

Table 3 Results of meta-analysis for *Exo1* polymorphisms and the risk of cancer

Genetic model		Recessive model			Dominant model		
Pro757Leu	**Number of studies (n of cases/ n of controls)**	**Leu/Leu vs Pro/Leu+Pro/Pro**			**Leu/Leu+Pro/Leu vs Pro/Pro**		
		OR (95% CI)	**P_h**	**I^2 (%)**	**OR (95% CI)**	**P_h**	**I^2 (%)**
Total	10 (4,593/4,351)	0.995 (0.883–1.122)	0.098	40.4	0.902 (0.821–0.991)	0.419	1.8
Ethnicity							
Asian	8 (3,449/3,514)	0.955 (0.842–1.084)	0.252	23.2	0.852 (0.765–0.949)	0.744	0.0
Caucasian	1 (684/406)	0.767 (0.333–1.766)	–	–	1.118 (0.850–1.471)	–	–
Mixed	1 (460/431)	1.566 (1.050–2.334)	–	–	1.050 (0.802–1.376)	–	–
CS							
PB	2 (562/540)	0.910 (0.292–2.838)	0.005	87.2	1.028 (0.805–1.312)	0.708	0.0
HB	8 (4,031/3,811)	0.972 (0.856–1.105)	0.600	0.0	0.882 (0.797–0.977)	0.347	10.8
Cancer							
Colorectal	3 (728/768)	0.717 (0.489–1.050)	0.053	66.0	0.724 (0.557–0.942)	0.435	0
Lung	2 (858/875)	0.984 (0.690–1.402)	–	–	0.859 (0.629–1.174)	–	–
HWE							
Yes	7 (3,365/3,103)	0.945 (0.830–1.076)	0.240	24.8	0.900 (0.810–0.999)	0.488	0.0
No	3 (1,228/1,248)	1.331 (0.978–1.812)	0.201	38.8	0.914 (0.739–1.129)	0.102	62.7
Glu589Lys	**n**	**Lys/Lys vs Glu/Lys+Glu/Glu**			**Lys/Lys+Glu/Lys vs Glu/Glu**		
		OR (95% CI)	**P_h**	**I^2 (%)**	**OR (95% CI)**	**P_h**	**I^2 (%)**
Total	12 (6,479/6,550)	1.320 (0.999–1.744)	0.000	71.6	1.237 (0.995–1.538)	0.000	86.6
Ethnicity							
Asian	6 (3,115/3,214)	1.876 (1.444–2.436)	0.194	32.2	1.555 (1.401–1.726)	0.650	0.0
Caucasian	6 (3,364/3,266)	1.000 (0.751–1.332)	0.019	62.9	0.936 (0.697–1.257)	0.000	81.0
CS							
PB	2 (368/401)	1.042 (0.687–1.580)	0.076	68.2	0.568 (0.264–1.221)	0.019	81.7
HB	8 (5,961/5,999)	1.683 (1.097–2.581)	0.000	74.0	1.405 (1.180–1.674)	0.004	66.9
Cancer							
Lung	3 (1,114/1,166)	1.338 (0.948–1.888)	0.436	0.0	1.231 (0.848–1.787)	0.010	78.2
HWE							
Yes	10 (5,829/5,883)	1.444 (1.039–2.005)	0.000	75.7	1.149 (0.908–1.454)	0.000	87.2
No	2 (650/667)	0.902 (0.610–1.334)	0.525	0.0	1.904 (0.972–3.727)	0.029	78.9
Glu670Gly	**n**	**Glu/Glu vs Gly/Glu+Gly/Gly**			**Glu/Glu+Gly/Glu vs Gly/Gly**		
		OR (95% CI)	**P_h**	**I^2 (%)**	**OR (95% CI)**	**P_h**	**I^2 (%)**
Total	7 (3,700/3,496)	0.989 (0.802–1.219)	0.683	0.0	1.094 (0.978–1.224)	1.000	0.0
Ethnicity							
Asian	5 (2,989/3,006)	1.111 (0.857–1.440)	0.999	0.0	1.093 (0.962–1.241)	0.994	0.0
Caucasian	2 (711/490)	0.796 (0.559–1.132)	0.341	0.0	1.099 (0.869–1.390)	0.984	0.0
CS							
PB	1 (112/111)	0.563 (0.253–1.254)	–	–	1.094 (0.640–1.868)	–	–
HB	6 (3,588/3,385)	1.032 (0.830–1.282)	0.900	0.0	1.094 (0.976–1.227)	0.999	0.0
Cancer							
Lung	2 (858/875)	1.132 (0.568–2.256)	–	–	1.107 (0.792–1.548)	–	–

Notes: Random-effects model was used when *P*-value for heterogeneity test <0.05; otherwise, fixed-model was used.
Abbreviations: CS, control source; PB, population based; HB, hospital based; P_h, *P*-values for heterogeneity from *Q*-test; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; 95% CI, 95% confidence interval; n, number.

in the Caucasian population (14.7%, 95% CI =12.2%–17.1%, $P<0.001$). On the contrary, the Lys and Gly allele frequency of the Glu589Lys and Glu670Gly polymorphisms in Asians was 16.3% (95% CI =15.4%–17.2%) and 15.3% (95% CI =14.3%–16.2%), which was significantly lower than that in Caucasians (38.3%, 95% CI =37.1%–39.5%, $P<0.001$, and 35.7%, 95% CI =32.7%–38.7%, $P<0.001$). In subgroup analysis of the different sources of controls, significant associations were found between the Pro757Leu polymorphism and reduced cancer risk, while evidence of an association between the Glu589Lys polymorphism and an increased cancer risk was found in the hospital-based studies, but not in the population-based studies. This may be because the hospital-based controls may have sickness that was connected with the genotypes under investigation, leading to potential biases.[40] Furthermore, there was a significantly

Homozygote			Heterozygote			Additive model		
Leu/Leu vs Pro/Pro			Pro/Leu vs Pro/Pro			Leu vs Pro		
OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)
0.920 (0.805–1.053)	0.154	33.0	0.894 (0.809–0.988)	0.530	0.0	0.960 (0.902–1.020)	0.188	27.9
0.872 (0.755–1.007)	0.410	1.9	0.847 (0.755–0.951)	0.809	0.0	0.932 (0.871–0.997)	0.341	11.4
0.796 (0.345–1.838)	–	–	1.151 (0.867–1.527)	–	–	1.068 (0.837–1.362)	–	–
1.524 (0.992–2.340)	–	–	0.952 (0.717–1.264)	–	–	1.141 (0.941–1.383)	–	–
0.953 (0.343–2.651)	0.023	80.7	0.986 (0.763–1.275)	0.565	0.0	1.056 (0.890–1.255)	0.080	67.5
0.884 (0.766–1.022)	0.592	0.0	0.878 (0.788–0.979)	0.417	0.9	0.946 (0.886–1.010)	0.330	12.8
0.633 (0.417–0.961)	0.135	50.2	0.766 (0.581–1.009)	0.315	13.5	0.782 (0.648–0.943)	0.208	36.2
0.892 (0.595–1.336)	–	–	0.844 (0.603–1.181)	–	–	0.988 (0.863–1.130)	0.450	0.0
0.872 (0.753–1.010)	0.407	2.4	0.906 (0.810–1.013)	0.532	0.0	0.933 (0.868–1.004)	0.283	19.3
1.210 (0.868–1.687)	0.091	64.9	0.847 (0.679–1.058)	0.193	41.0	1.027 (0.916–1.151)	0.207	36.5
Lys/Lys vs Glu/Glu			**Glu/Lys vs Glu/Glu**			**Lys vs Glu**		
OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)
1.447 (1.028–2.035)	0.000	79.0	1.208 (0.974–1.498)	0.000	84.8	1.200 (1.014–1.421)	0.000	86.7
2.133 (1.639–2.777)	0.161	36.8	1.495 (1.341–1.666)	0.903	0.0	1.487 (1.361–1.625)	0.330	13.3
1.016 (0.701–1.475)	0.002	73.1	0.931 (0.673–1.288)	0.000	82.5	0.954 (0.807–1.128)	0.004	71.0
0.674 (0.211–2.151)	0.016	82.6	0.616 (0.453–0.836)	0.058	72.1	0.734 (0.415–1.297)	0.013	83.8
1.848 (1.164–2.934)	0.000	76.5	1.356 (1.161–1.583)	0.033	54.0	1.366 (1.144–1.632)	0.000	78.9
1.346 (0.944–1.921)	0.362	1.5	1.188 (0.777–1.816)	0.004	81.5	1.230 (0.961–1.574)	0.046	67.5
1.451 (0.975–2.158)	0.000	82.1	1.104 (0.884–1.378)	0.000	84.0	1.181 (0.971–1.436)	0.000	88.8
1.434 (0.901–2.282)	0.298	7.8	2.135 (0.930–4.901)	0.011	84.6	1.298 (1.084–1.554)	0.884	0.0
Glu/Glu vs Gly/Gly			**Gly/Glu vs Gly/Gly**			**Glu vs Gly**		
OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)	OR (95% CI)	P_h	I^2 (%)
1.037 (0.837–1.286)	0.861	0.0	1.104 (0.978–1.245)	0.994	0.0	1.057 (0.971–1.151)	0.982	0.0
1.131 (0.871–1.468)	0.998	0.0	1.084 (0.944–1.244)	0.996	0.0	1.078 (0.977–1.189)	0.994	0.0
0.867 (0.595–1.263)	0.435	0.0	1.169 (0.913–1.497)	0.755	0.0	0.997 (0.840–1.182)	0.617	0.0
0.639 (0.271–1.504)	–	–	1.268 (0.720–2.232)	–	–	0.912 (0.620–1.342)	–	–
1.072 (0.859–1.339)	0.963	0.0	1.096 (0.969–1.240)	0.996	0.0	1.065 (0.976–1.162)	0.992	0.0
1.155 (0.577–2.313)	–	–	1.097 (0.764–1.575)	–	–	1.062 (0.890–1.267)	0.748	0.0

negative correlation between the Leu allele of the Pro757Leu polymorphism and colorectal cancer risk. However, this result should be interpreted with caution because only three studies (728 cases and 768 controls) were included in the analysis. Moreover, subgroup analysis was also performed under smoking conditions for the Glu589Lys polymorphism. The results showed that the Glu589Lys polymorphism was significantly associated with an increased cancer risk in smokers, but not in nonsmokers, which indicated that cigarette smoking can cause DNA damage and influence the DNA repair activity, which then alters the cancer risk. There was no evidence for an association between the Glu670Gly polymorphism and cancer risk in subgroup analyses based on ethnicity, source of controls, and cancer types. In the future, larger well-designed studies will be needed to validate these associations.

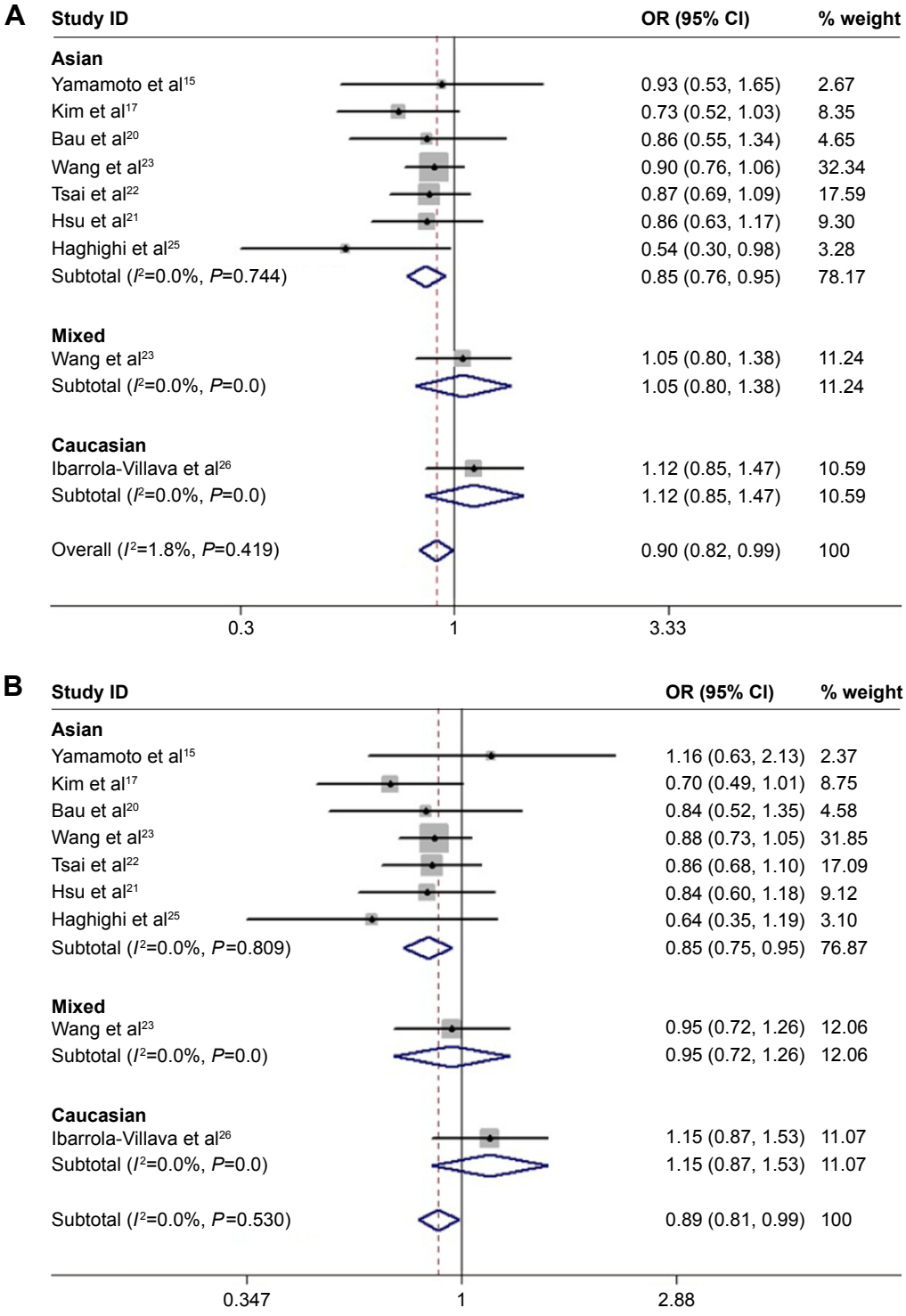

Figure 2 Forest plots of ORs with 95% CI for *Exo1* Pro757Leu polymorphism and the risk of cancer observed in subgroup analyses by ethnicity.
Notes: The center of each square represents the OR, the area of the square represents the sample number and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. (**A**) Dominant model; (**B**) heterozygote comparison.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

In this study, there was significant heterogeneity between studies relating to the Glu589Lys polymorphism, but not to the other two polymorphisms. To explore the sources of heterogeneity, studies were classified according to ethnicity, source of controls, cancer type, and sample size. The results showed that the heterogeneity was significantly reduced in the Asian population subgroup, which indicated that ethnicity could partly explain the source of heterogeneity. The studies for the Caucasian population yielded different results, with high heterogeneity, revealing the necessity for further study.

Table 4 Results of stratified analysis by smoking status for *Exo1* Glu589Lys polymorphism in dominant model (Lys/Lys+Glu/Lys vs Glu/Glu)

Smoking	Number of studies (n of cases/ n of controls)	Lys/Lys+Glu/Lys vs Glu/Glu		
		OR (95% CI)	P_h	I^2 (%)
Smokers	4 (1,268/1,151)	1.866 (1.384–2.515)	0.038	64.5
Nonsmokers	4 (449/583)	1.114 (0.862–1.440)	0.148	43.9

Notes: Random-effects model was used when *P*-value for heterogeneity test <0.05; otherwise, fixed-model was used.
Abbreviations: P_h, *P*-values for heterogeneity from *Q*-test; OR, odds ratio; 95% CI, 95% confidence interval; n, number.

Likewise, the metaregression analysis identified ethnicity as an important contributor to heterogeneity. Furthermore, the sensitivity analysis showed that the study by Chang et al[18] could have an influence on the overall results for Glu589Lys polymorphism because it was the only study to reveal that the Glu589Lys polymorphism was significantly related to reduced cancer risk. Although the three studies by Kim et al,[17] Tsai et al,[22] and Wang et al[23] may affect the overall results for the Pro757Leu polymorphism, none of the studies led to a change in conclusions for the Asian population, indicating that the results for the Asian population were relatively stable and credible. Additionally, the overall results for the Pro757Leu and Glu589Lys polymorphisms were dominated by the conclusions for the Asian population, which indicated that ethnicity was an important factor in Exo1 SNPs and should be carefully considered in future studies.

Many previous studies have investigated the association between the Pro757Leu polymorphism and cancer risk. Studies performed by Yamamoto et al,[15] Kim et al,[17] and Haghighi et al[25] revealed that the Leu/Leu genotype is associated with reduced risk of colorectal cancer in Asians, which concurred with our results of subgroup analysis on ethnicity and cancer types. However, the results of some studies differ from our own results,[19–22] which may be attributed to the limitation of sample size. Similarly, in terms of the Glu589Lys polymorphism, the studies for the Asian population uniformly showed that individuals with the Glu/Lys or Lys/Lys genotypes had a significantly increased cancer risk, including an increased risk of lung, gastric, breast, oral, and cervical cancer, which concurred with our own conclusion.[19–23,28] Moreover, some other studies found no statistical association between the Glu589Lys polymorphism and cancer risk in the Caucasian population, which was also in line with our own results for Caucasians.[16,26,30] In terms of the Glu670Gly polymorphism, we found no significant association with cancer risk, which was consistent with the results of previous studies.[18–23,26]

Interestingly, Bayram[41] and Duan et al[42] have conducted meta-analyses to identify whether there was any evidence of a relationship between the *Exo1* Glu589Lys polymorphism and cancer susceptibility. Their conclusions could be considered to be inconsistent, which may be partially attributable to the relatively small sample size. The meta-analysis by Bayram[41] showed that the Glu589Lys polymorphism was not associated with overall cancer susceptibility, which contrasted with our own results. However, we found that the data reported by Bayram[41] from the studies by Wang et al[23] and Ibarrola-Villava et al[26] were not the same as the original data. Another recent meta-analysis by Duan et al[42] concluded that the Glu589Lys polymorphism was significantly associated with increased cancer risk in all genetic

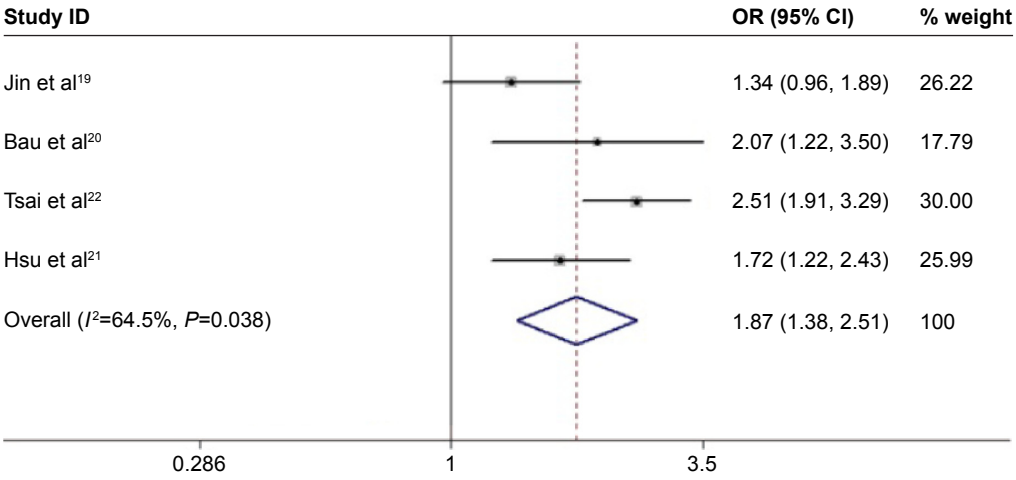

Figure 3 Forest plot of ORs with 95% CI for the *Exo1* Glu589Lys polymorphism and the risk of cancer for the dominant model (Lys/Lys+Glu/Lys vs Glu/Glu) in smokers.
Notes: The center of each square represents the OR, the area of the square represents the sample number and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. Weights are from random effects analysis.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Table 5 Univariate meta-regression analysis for heterogeneity of Glu589Lys polymorphism

Covariates	Recessive model		Dominant model		Homozygote		Heterozygote		Additive model	
	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value
Ethnicity	–0.638	0.029	–0.535	0.035	–0.768	0.032	–0.501	0.111	–0.456	0.003
Year	–0.044	0.493	0.052	0.408	0.015	0.859	0.063	0.330	0.007	0.867
SS	0.016	0.961	0.087	0.777	0.000	0.999	0.109	0.730	0.082	0.690
HWE	–0.464	0.275	0.506	0.205	0.008	0.989	0.636	0.114	0.099	0.718

Abbreviations: SS, sample size; HWE, Hardy–Weinberg equilibrium.

models, which differed from our own results. This may be explained by the relatively small sample size. At least four eligible studies[16,26,29,30] were not included in the meta-analysis by Duan et al,[42] while the study by Jin et al[19] was excluded because their controls deviated from the HWE. Compared with the previous study, five additional studies[16,19,26,29,30] – with 3,528 cases and 3,449 controls in total – were included in our meta-analysis, from which more solid evidence could be provided on the association between the Glu589Lys polymorphism and cancer risk.

Some limitations of our meta-analysis should also be considered when interpreting the results. First, there was an insufficient number of studies collected in this analysis to explore a true association between *Exo1* polymorphisms and cancer risk, especially in terms of the stratified analyses. Second, owing to lack of original data, an evaluation of gene–gene, gene–environment, and different polymorphism loci interactions, which may alter cancer risk, could not be carried out in our study. In fact, the study conducted by Yamamoto et al[15] had studied the combined effects of two SNPs of Exo1 on cancer risk. Third, serious confounding bias may exist because we calculated only unadjusted ORs; other risk factors such as age, sex, smoking status, and other variables were not adjusted. A more precise analysis should be conducted if more detailed personal data are available. Fourth, we used only published and English articles, which may bias the results, although the funnel plot and Egger's test did not indicate remarkable publication bias. Despite the limitations, the advantages of this meta-analysis should also be acknowledged. First, the statistical power was significantly

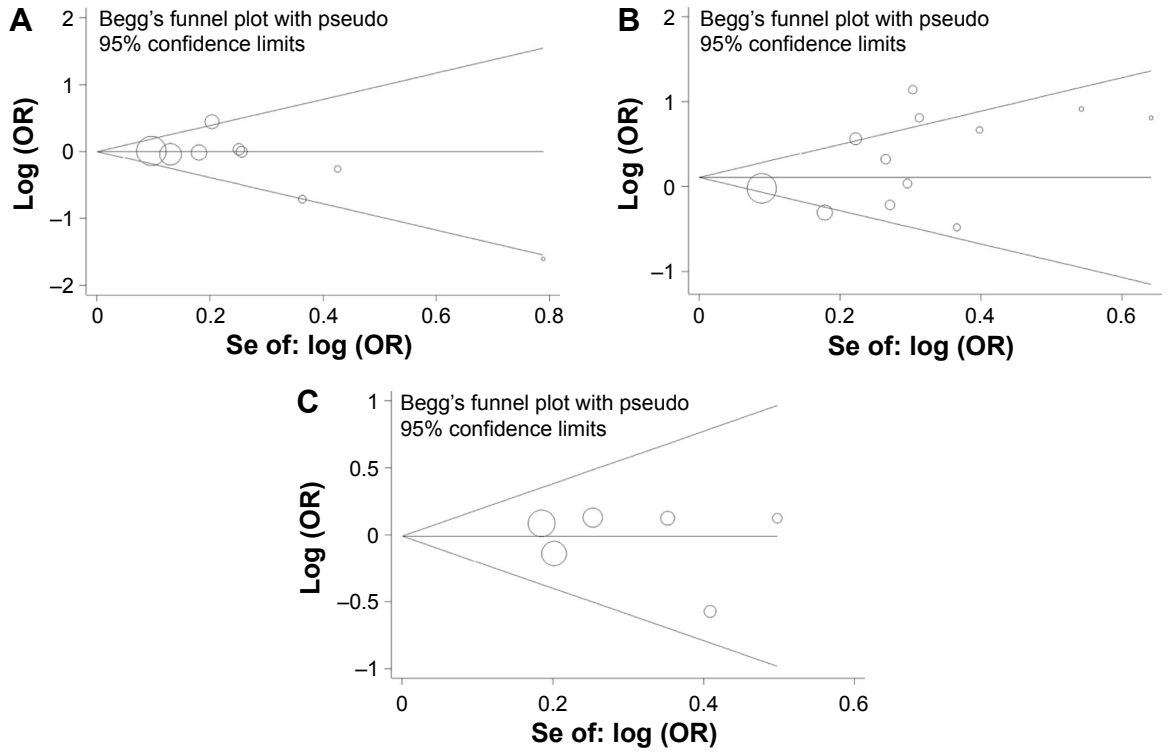

Figure 4 Begg's funnel plots for the *Exo1* polymorphisms and the risk of cancer for the publication bias test.
Notes: Each point represents a separate study for the indicated association. Log (OR); natural logarithm of OR. The horizontal line indicates the effect size. (**A**) Pro757Leu polymorphism; (**B**) Glu589Lys polymorphism; (**C**) Glu670Gly polymorphism.
Abbreviation: OR, odds ratio.

increased. Second, the studies included in this meta-analysis were satisfactory and met the inclusion criteria.

In conclusion, the results from this meta-analysis suggest that the *Exo1* Pro757Leu polymorphism contributes to reduced cancer susceptibility, especially in the Asian population, hospital-based studies, and colorectal cancer. However, the Glu589Lys polymorphism was found to be statistically associated with an increased cancer risk in the Asian population, smokers, and hospital-based studies. In addition, no evidence of an association was found between the Glu670Gly polymorphism and cancer risks. In the future, well-designed and population-based studies with larger sample sizes are needed to clarify the association between these polymorphisms and the risk of cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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