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Original Articles

Association between miR-124 rs531564 and miR-100 rs1834306 polymorphisms and cervical cancer: a meta-analysis

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Summary

Aim: To explore the correlations between miR-124 rs531564 and miR-100 rs1834306 polymorphisms and cervical cancer (CC). *Materials and Methods:* Relevant studies were searched from the electronic databases Embase, Cochrane library, and PubMed updated to January 2017, as well as through literature tracing. Studies were selected based on strict criteria, followed by the included studies which were conducted with quality assessment using Newcastle-Ottawa Scale (NOS). With odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) as effect indicators, meta-analysis for exploring the correlations between rs531564 and rs1834306 polymorphisms and CC was performed using R 3.12 software. Using Egger's test, publication bias was elevated for the included studies. In addition, sensitivity analysis was carried out. *Results:* There were a total of four eligible studies, involving 3,707 participators (including 1,592 CC patients and 2,115 healthy controls). The NOS scores of the included studies were 5-7, indicating a high quality. Meta-analysis showed that all genetic models of rs531564 were statistically significant ($p < 0.05$), indicating that rs531564 was associated with the occurrence of CC. Nevertheless, the situation for rs1834306 was exactly the opposite. Egger's test for rs531564 showed no publication bias, suggesting that our results were reliable. Sensitivity analysis showed that the pooled results of rs531564 were stable in general. *Conclusion:* These indicated that rs531564 was correlated with the development of CC, but not rs1834306.

Key words: Cervical cancer; microRNAs; rs531564; rs1834306; Meta-analysis.

Introduction

As a type of cancer derived from the cervix, cervical cancer (CC) is characterized by pelvic pain, vaginal bleeding, or pain during sexual intercourse [1]. Over 90% of CC cases are induced by human papillomavirus (HPV) infection, and CC can also be caused by other risk factors such as weak immune system, smoking, engaging in sexual activity from an early age, contraceptive drugs, and having many sexual partners [2, 3]. CC is mainly consisted of squamous cell carcinomas and adenocarcinoma, which is diagnosed by cervical screening, biopsy, and medical imaging [4]. CC can be prevented by inoculating HPV vaccines, using condoms, and reducing sexual partners [5-7]. CC is the fourth most common cancer and the fourth leading cause of cancer mortality in women, which has approximately 528,000 new cases and results in 266,000 deaths globally in 2012 [2].

MicroRNAs (miRNAs) are a kind of small non-coding RNAs with 20-23 nucleotides, which can function in multiple biological processes via targeting mRNAs [8]. The processing processes of miRNAs include the generation of pre-miRNA from pri-miRNA and then the generation of mature miRNAs, which can be enhanced or impaired by the single nucleotide polymorphisms (SNPs) in miRNAs [9, 10]. MiR-124 is found to be a suppressor in various malignant tumors including CC, hematological malignancies, gastric cancer, and hepatocellular carcinoma [11-14]. Through regulating astrocyte-elevated gene-1 (AEG-1), miR-124 inhibits cell proliferation, invasion, and migration, and epithelial-mesenchymal transition (EMT) in CC [15]. Previous study reports that the miR-124 rs531564 C > G polymorphism is involved in the development of multiple cancers among Chinese [16]. Furthermore, miR-100 is found to be able to affect the carcinogenesis of CC via suppressing polo-like kinase1 (PLK1) [17]. Ubiquitin-specific protease 15 (USP15) expression mediated by miR-100 has influences on paclitaxel resistance in CC, indicating that USP15 and miR-100 can be used for the treatment of paclitaxel-resistant CC [18]. MiR-100 rs1834306 is reported to be related to the development and progression of human tumors, such as esophageal squamous cell carcinoma [19] and colon cancer [20]. To reveal the correlations between rs531564 and rs1834306 polymorphisms and CC, this study performed meta-analysis for case-control studies.

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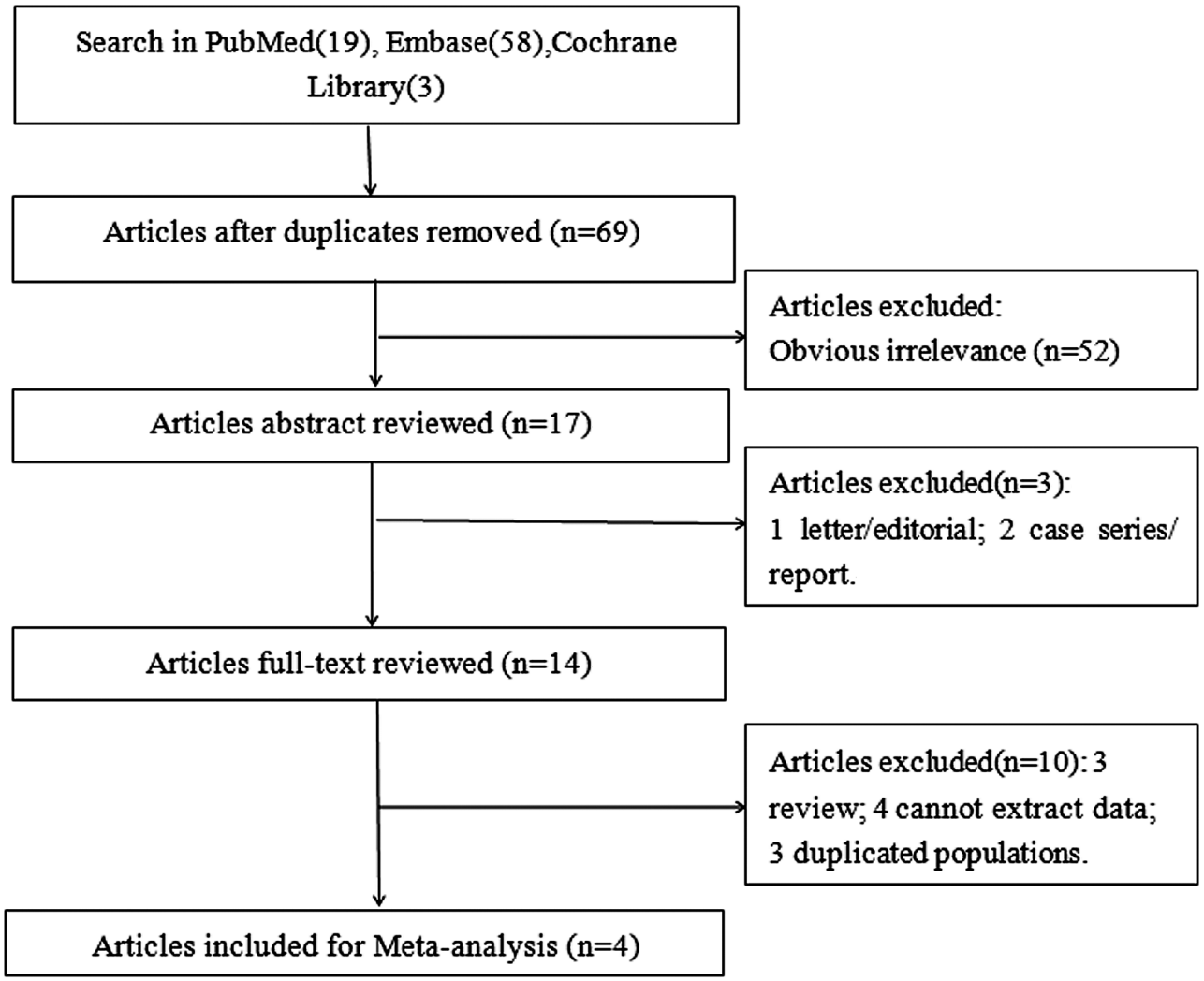

Figure 1. — The process of literature selection.

Materials and Methods

Using "cervical cancer" OR "carcinoma of uterine cervix" OR "cervical neoplasia" AND miR-124 OR miRNA-124 OR microRNA-124 OR rs531564 OR miR-100 OR miRNA-100 OR microRNA-100 OR rs1834306 as searching words, the authors retrieved the electronic databases Embase (http://www.embase.com), Cochrane library (http://www. cochranelibrary.com/), and PubMed (http://www.ncbi.nlm.nih. gov/pubmed/) updated to January 2017, without language restriction. Furthermore, literature tracing was also conducted to identify more relevant researches.

The inclusion criteria for selecting the eligible studies were: (1) the study involves the frequency distribution of rs531564 and rs1834306 in CC patients and normal controls, (2) the study could provide the exact frequencies of genotypes or alleles, and (3) the study was case-control study. On the other hand, the exclusion criteria were as follows: (1) the study had no complete data and that could not be used for statistical analysis was excluded, (2) non-theoretical literatures such as letters, reviews, or comments were excluded, and (3) for the same population data or repeatedly published data used for several researches, only the latest study or the most comprehensive study was included and the others were excluded.

Two reviewers selected the eligible studies and extracted relevant data independently. The extracted contents were: first author's name, publication year, geographic area, study year, the detection methods of single nucleotide polymorphisms (SNPs), the case numbers of disease group (CC group) and control group (healthy control group), the genes associated with rs531564 and rs1834306, the case number of each genotype in CC and control groups, and some demographic characteristics (including HPV infection and smoking status-smoker). Based on Newcastle-Ottawa Scale (NOS) [21], the qualities of the eligible studies were assessed. The disagreements during data extraction and quality assessment were settled through the group discussion with a third reviewer.

Firstly, Hardy-Weinberg equilibrium (HWE) test [22] was carried out, with a $p < 0.05$ as the significant threshold of disequilibrium. Meta-analysis was performed using R 3.12 software (R Foundation for Statistical Computing, http://www.R-project.org), and the effect indicators were odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs). The heterogeneities among the eligible studies was detected using Cochran's Q-statistic [23] and I^2-test [24]. The random-effects model was

Table 1. — *The characteristics of the eligible studies.*

Author	Public Year	Location	Study Year	Detection method	SNP	NOS	Group	N	HPV infection	Smoking status-Smoker	SNP CC(AA)	SNP CG(AG)	SNP GG	HWE X^{2*}	HWE *p*
Xingdong X	2014	China	2008.11-2012.8	PCR-LDR	rs531564	6	Case	107	67	0	91	15	1	0.418	0.5181
							Control	208	34	5	151	51	6		
Henghui W	2014	China	2011.1-2013.7	PCR-LDR	rs531564	5	Case	158	145	1	134	22	2	1.564	0.2111
							Control	260	46	7	184	66	10		
Chuanyin L	2017	China	NA	PCR	rs531564	7	Case	609	NA	NA	17	144	448	0.038	0.8445
							Control	612	NA	NA	7	118	458		
					rs1834306		Case	615	NA	NA	139	299	171	0.007	0.9345
							Control	618	NA	NA	126	289	168		
Xingdong X	2013	China	2009.2-2012.7	PCR-LDR	rs1834306	6	Case	103	81	2	27	38	38	0.125	0.7233
							Control	417	34	22	87	203	127		

*PCR-LDR: polymerase chain reaction-ligation detection reaction; HPV: human papilloma virus; SNP: single nucleotide polymorphism; *: likelihood-ratio X^2; NOS: Newcastle-Ottawa Scale; N: total number of including; HWE: Hardy-Weinberg equilibrium tests of control.*

Table 2. — The results of meta-analysis for genes associated with rs531564 and rs1834306.

SNP	Gene model	Sample size K	Cases	Control	Test of association *OR(95%CI)*	*Z*	*p*	Model	Test of heterogeneity[a,b] *Q*	*p*	I^2 (%)	Publication bias[c] *t*	*p* value
rs531564	G *vs.* C	3	1748	2102	0.5792 [0.4038; 0.8309]	2.97	0.0030	R	4.67	0.10	57.1	2.7280	0.2237
	GC *vs.* CC	3	423	877	0.4753 [0.3278; 0.6891]	3.92	<0.0001	F	0.04	0.98	0.0	1.2570	0.4278
	GG *vs.* CC	3	693	816	0.3483 [0.1693; 0.7164]	2.87	0.0042	F	0.24	0.89	0.0	1.3415	0.4078
	GG *vs.* CC+GC	3	874	1061	0.7220 [0.5568; 0.9363]	2.46	0.0140	F	1.79	0.41	0.0	4.7664	0.1317
	GG+GC *vs.* CC	3	874	1061	0.4427 [0.3093; 0.6336]	4.45	<0.0001	F	0.04	0.98	0.0	0.3086	0.8094
rs1834306	G *vs.* A	2	1424	2000	0.9744 [0.8450; 1.1236]	0.36	0.7212	F	0.12	0.73	0.0	-	-
	GA *vs.* AA	2	503	705	0.8552 [0.6611; 1.1064]	1.19	0.2338	F	1.92	0.17	47.8	-	-
	GG *vs.* AA	2	375	508	0.9327 [0.7054; 1.2332]	0.49	0.6247	F	0.02	0.89	0.0	-	-
	GG *vs.* AA+GA	2	712	1000	1.0402 [0.8346; 1.2965]	0.35	0.7257	F	1.52	0.22	34.2	-	-
	GG+GA *vs.* AA	2	712	1000	0.8860 [0.6967; 1.1267]	0.99	0.3236	F	0.62	0.43	0.0	-	-

[a]Random-effects model was used when the p for heterogeneity test< 0.05, otherwise the fixed-effect model was used. [b]p < 0.05 is considered statistically significant for Q statistics. [c]Egger's test to evaluate publication bias, p < 0.05 is considered statistically significant; OR: odds ratio; CI: confidence interval. K: The number of included studies. R: random; F: fixed.

used when heterogeneity test showed significant difference ($p < 0.05$, $I^2 > 50\%$), otherwise, the fixed-effects model was used ($p > 0.05$, $I^2 < 50\%$) [25]. Combined with Egger's test [26], publication bias was elevated for the eligible studies. Through ignoring one study per time, sensitivity analysis was carried out.

Results

The processes of literature selection are shown in Figure 1. According to the search strategy, 19, 58, and three relevant studies were selected from PubMed, Embase, and Cochrane library, respectively. A total of 69 studies remained after removing 11 duplicates. Followed by 52 studies were filtered out through browsing tittle. Then, three studies were excluded after browsing abstract. Furthermore, ten studies were eliminated through full text reading. Finally, four studies were selected as eligible studies and included in the present meta-analysis [27-30].

The characteristics of the four eligible studies are presented in Table 1. The included studies involved a total of 3,707 participators (including 1,592 CC patients and 2115 healthy controls). The publication years of the included studies varied from 2013 to 2017, and their geographic areas all were in China. The detection method of SNPs mainly was polymerase chain reaction-ligation detection reaction (PCR-LDR). In HPV infection, the prevalence of CC patients was greater than that of normal controls. However, the two groups had no significant difference in smoking status-smoker. The NOS scores of the eligible studies were 5-7, indicating a high quality. The results of HWE test suggested that all of the objects in the control group con-

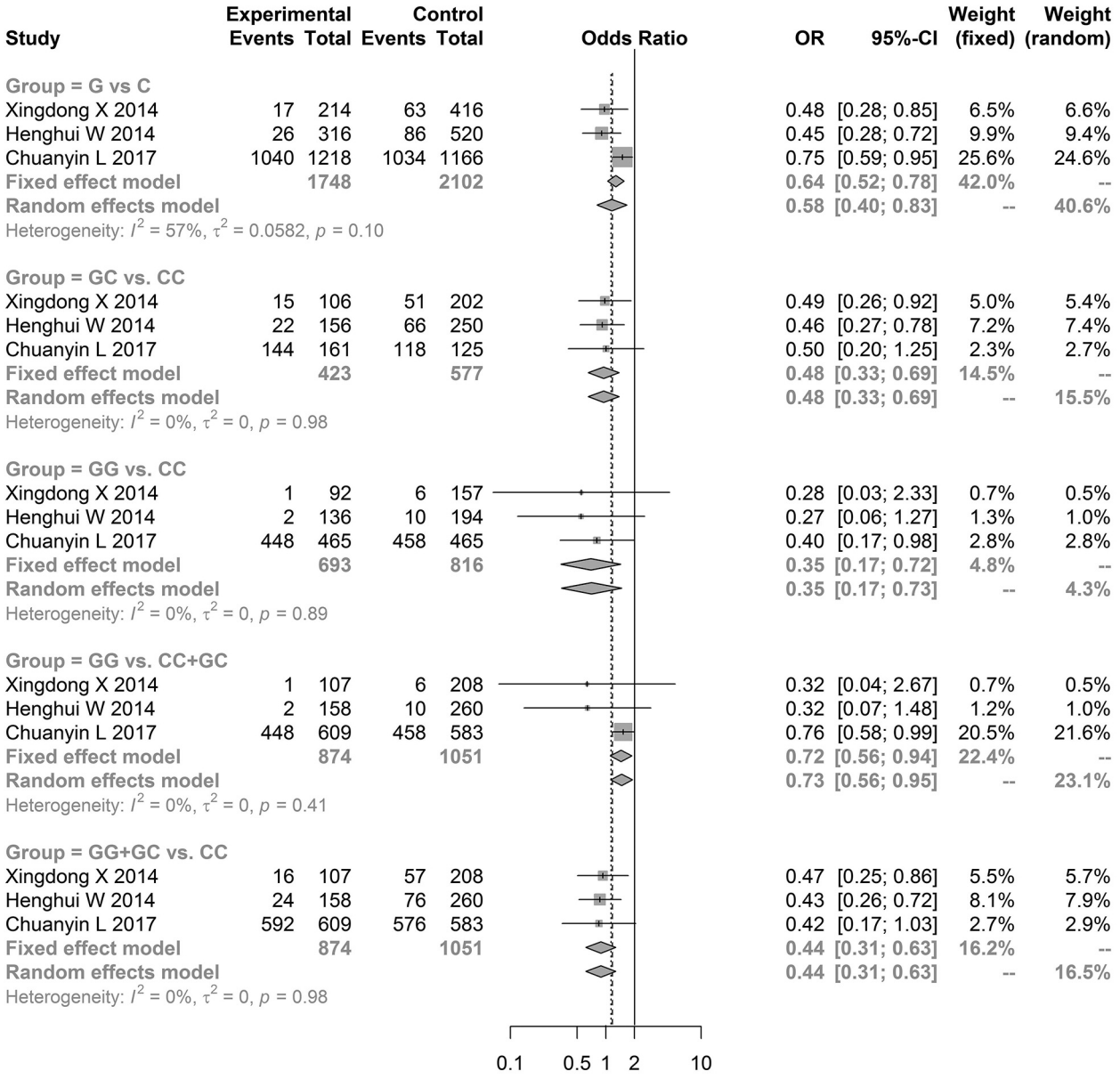

Figure 2.— Forest plots of the correlation between rs531564 and cervical cancer under "G *vs.* C" model, "GC *vs.* CC" model, "GG *vs.* CC" model, "GG *vs.* CC + GC" model, and "GG + GC *vs.* CC" model.

formed to HWE.

This meta-analysis analyzed different genetic models (allele genetic model, additive genetic model, recessive genetic model, and dominance genetic model) for genes associated with rs531564 and rs1834306. Heterogeneity test was conducted, and then suitable effect model was selected for merging effect indicators. There was heterogeneity outcome ($p < 0.05$, $I^2 > 50\%$) in the "G *vs.* C" model of rs531564-associated gene, therefore, random-effects model was utilized for calculating the pooled results. For the others, the fixed-effects model was used to merge the effect indicators ($p > 0.05$, $I^2 < 50\%$) (Table 2).

The meta-analysis of rs531564 SNP showed that all genetic models of rs531564 were statistically significant ($p < 0.05$), indicating that rs531564 was associated with the occurrence of CC. Both OR and 95% CI were less than 1, and thus rs531564 was a protective factor (Figure 2, Table 2). Meanwhile, the meta-analysis of rs1834306 SNP showed that all genetic models of rs1834306 had no statistical significance. Therefore, rs1834306 was not related to the development of CC (Figure 3, Table 2).

The Egger's test for rs531564 showed that there was no publication bias. Thus, the present results were reliable (Table 2). Only two studies involving rs1834306 were included, therefore, quantitative evaluation of publication bias could not be performed for rs1834306.

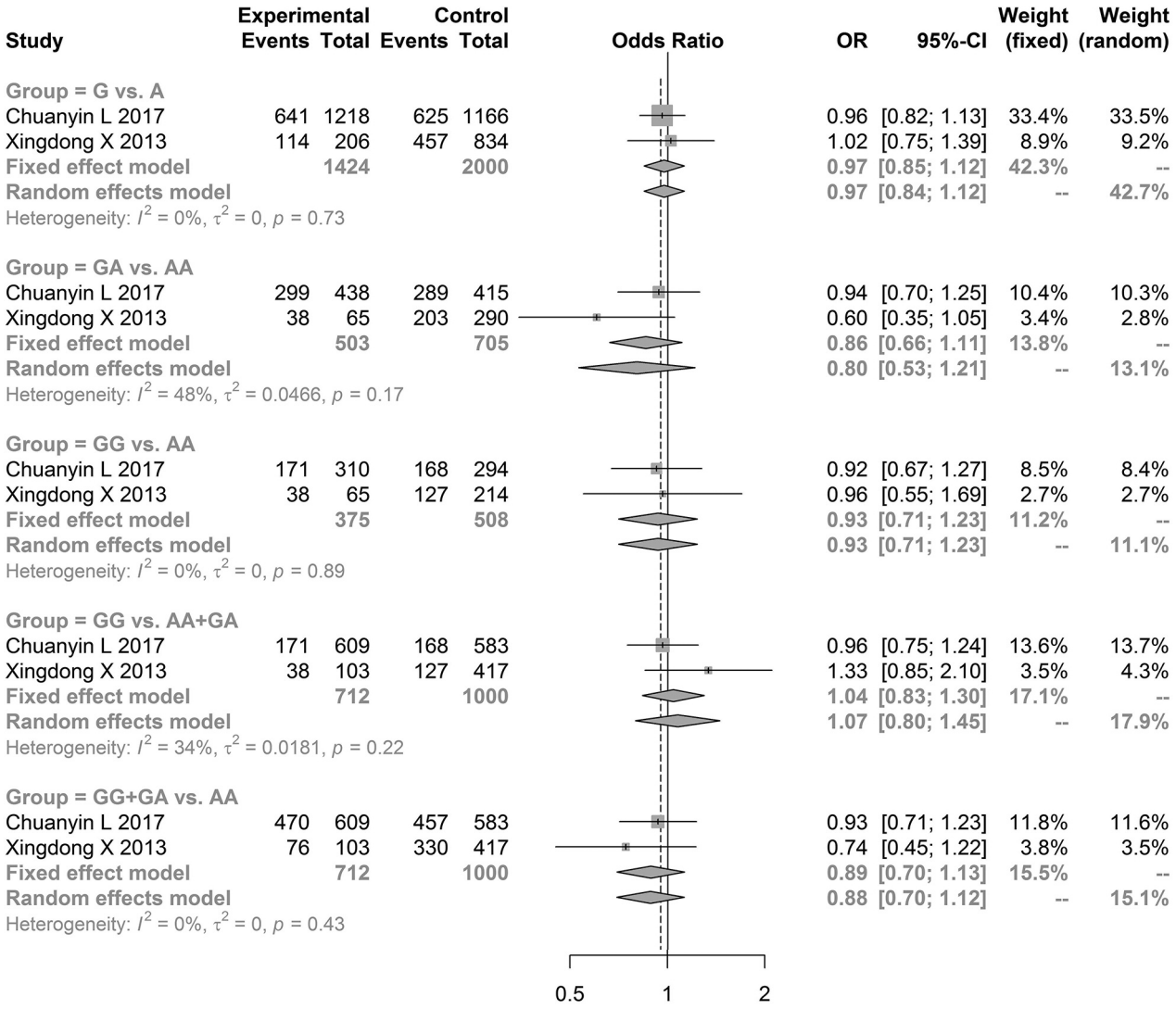

Figure 3. — Forest plots of the correlation between rs1834306 and cervical cancer under "G *vs.* A" model, "GA *vs.* AA" model, "GG *vs.* AA" model, "GG *vs.* AA + GA" model, and "GG + GA *vs.* AA" model.

Sensitivity analysis showed that the pooled results for the "GG *vs.* CC + GC" model of rs531564 were reversed after ignoring the study of Li *et al.* [27], and the pooled results for other models had no changes (Figure 4). Therefore, the pooled results of rs531564 were stable in general. Only two studies were included for rs1834306, and thus no sensitivity analysis was conducted for rs1834306.

Discussion

CC threatens the health and life safety of women worldwide. This meta-analysis was aimed to explore the correlations between rs531564 and rs1834306 polymorphisms and CC. In the present meta-analysis, 4 eligible studies were included, which involved a total of 3,707 participators (including 1,592 CC patients, and 2,115 healthy controls). The NOS scores indicated that the included studies had high qualities. HWE test suggested that all of the objects in the control group conformed to HWE. Different genetic models (allele genetic model, additive genetic model, recessive genetic model, and dominance genetic model) were analyzed in this study. Meta-analysis showed that all genetic models of rs531564 were statistically significant, indicating that rs531564 was associated with the occurrence of CC. However, all genetic models of rs1834306 had no statistical significance, and thus rs1834306 was not related to the development of CC. Egger's test for rs531564 showed no publication bias. Sensitivity analysis showed that the pooled results of rs531564 were stable in general. Only two studies were included for rs1834306, and thus no publication bias and sensitivity analysis was conducted for rs1834306.

Among the four eligible studies, a study explored the influences of pri-miR-100 rs1834306, pre-miR-27a

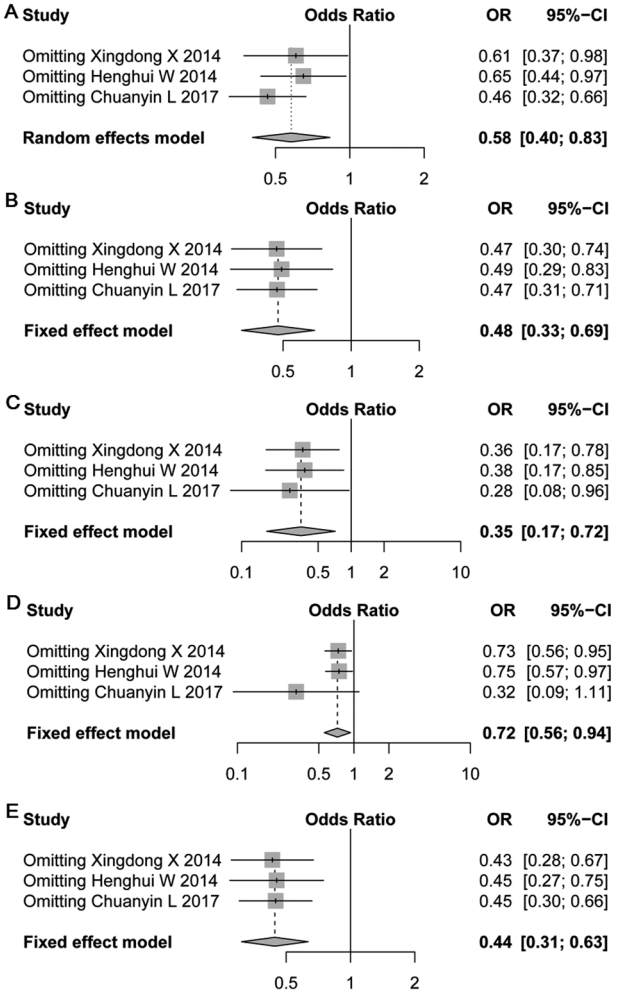

Figure 4. — Sensitivity analysis for rs531564 under "G *vs.* C" model (A), "GC *vs.* CC" model (B), "GG *vs.* CC" model (C), "GG *vs.* CC + GC" model (D), and "GG + GC *vs.* CC" model (E).

rs895819, and pri-miR-26a-1 rs7372209 on individual susceptibility to CC, finding that only miR-27a rs895819 is related to a reduced risk of CC in southern Chinese women [30]. Li *et al.* found that pri-miR-124-1 rs531564 and pri-miR-218-2 rs11134527 had associations with CC and cervical intraepithelial neoplasia in Chinese Hans, but not pri-miR-100 rs1834306 [27]. In Chinese Han women, the miR-124 rs531564 polymorphism is reported to act in determining CC susceptibility [28]. MiR-124 rs531564 may be correlated with CC risk in Chinese Han women, and G allele has an association with a decreased CC risk [29]. These studies had differences in sample sizes and study population, and thus a quantitative assessment of their diversity was performed by this meta-analysis. Pri-miR-124-1 rs531564 has correlations with the elevated incidences of CC in females [12] and esophageal cancer in males [31]. Wu *et al.* explore the influences of five miRNA polymorphisms (miR-100 rs1834306, miR-146a rs2910164, miR-196a2 rs11614913, miR-125a rs12976445, and miR-26a1 rs7372209) on the prognosis of esophageal squamous cell carcinoma patients, finding there is no correlation between miR-100 rs1834306 polymorphism and the disease [32]. These supported that not rs1834306 but rs531564 was related to the development of CC.

This meta-analysis used different genetic models (allele genetic model, additive genetic model, recessive genetic model, and dominance genetic model) to investigate the correlations between rs531564 and rs1834306 polymorphisms and CC. However, there were some limitations in this study. Because of the incomplete data and the small number of included studies, covariate correction and subgroup analysis had not been performed. There were only two studies among the included studies were correlated with rs1834306, therefore, publication bias and sensitivity analysis could not be conducted for rs1834306. Sensitivity analysis for rs531564 showed that the pooled results for the "GG *vs.* CC + GC" model were reversed after ignoring the study of Li *et al.* [27], indicating that more studies were still needed to support the present results. Moreover, the geographic areas of the included studies all were in China, which might cause some bias. Although the above limitations existed, the present results were accurate due to the high qualities of the eligible studies.

In conclusion, the present findings suggested that rs531564 was related to the occurrence of CC and served as a protective factor. On the contrary, rs1834306 had no correlation with the development of CC. However, the present results should be confirmed by more studies with high qualities and large samples in the future.

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