Meta-Analysis of Observational Studies In Epidemiology

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Association between polymorphisms of epidermal growth factor 61 and susceptibility of lung cancer

A meta-analysis

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Abstract

To explore the association between epidermal growth factor (EGF) 61A/G polymorphism and lung cancer.

All eligible case-control studies published up to August, 2019 were identified by searching PubMed, The excerpta medica database, China Academic Journals Full-text Database, China Biology Medicine, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Wanfang databases. Two researchers independently identified the literature, extracted data, and evaluated quality according to inclusion and exclusion criteria. Meta-analysis was performed by Stata 15.0.

A total of 6 studies is included, including 1487 cases and 2044 control subjects. Compared with allele A, allele G was considered to have no association with the risk of lung cancer, odds ratio = 1.07 (95% confidence interval: 0.98–1.15). GG recessive genotype, GG + GA dominant genotype, GG homozygote genotype and GA heterozygote genotype were found out that all of them are not associated with the risk of lung cancer. No association between EGF 61A/G polymorphism and lung cancer was found out by ethnical subgroup analysis. However, in view of the limitations of this study, such as the results of quantitative and sensitivity analysis may be lack of accuracy, so the conclusions of allele model and recessive gene model should be made carefully.

It suggested that there was no association between polymorphism of EGF 61A/G and susceptibility of lung cancer.

Abbreviations: CBM = China Biology Medicine, CI = confidence interval, CJFD = China Academic Journals Full-text Database, \ = China National Knowledge Infrastructure, EGF = epidermal growth factor, Embase = The excerpta medica database, ERK = extracellular regulated protein kinases, Mek = mitogen-activated protein kinase, OR = odds ratio, VIP = China Science and Technology Journal Database.

Keywords: epidermal growth factor, gene polymorphism, lung cancer, meta-analysis

1. Introduction

According to the data of global statistical report, up to now, the incidence and mortality of lung cancer rank first among all kinds of malignant tumors, seriously threatening the quality of life and life span of human beings.[1] In the past 30 years, the incidence of lung cancer had increased nearly 4 times. According to the World Health Organization forecast, the annual incidence of lung cancer in China will be as high as 1 million by 2025.[1] The main causes of lung cancer are genetic and environmental factors, but the specific pathogenesis has not yet been elucidated. At present, it is believed that smoking is the main cause of lung cancer,[2] but not all patients with lung cancer smoke, which also suggests that genetic variation is also involved in the occurrence and development of lung cancer. Now the general point is that the occurrence and development of lung cancer is the result of the interaction between environment and gene.[3] As an endocrine growth factor, epidermal growth factor (EGF) plays an important role in regulating cell proliferation, differentiation, and vascular production by binding to specific epidermal grow factor receptor.[4–6] EGF is located on chromosome 4. There is a correlation between the functional polymorphism of 61 A/G locus and susceptibility of various malignant tumors, such as gastric cancer, liver cancer, colorectal cancer, and so on.[6–8] In the study of Peng et al[6–8] on EGF 61A/G polymorphism and susceptibility of gastric cancer, the results of a meta-analysis of 6 case-control studies showed that compared with AA genotypes, GG and GG + GA genotypes increased the risk of gastric cancer, especially among Asian people. The correlation between EGF 61 A/G locus and lung cancer susceptibility has also been studied, but the conclusions are not consistent. In this study, case-control studies on EGF 61A/G polymorphism and lung cancer risk were collected for meta-analysis, and the correlation between EGF 61A/G polymorphism and lung cancer risk was comprehensively evaluated.

2. Materials and methods

2.1. Literature retrieval

All studies from establishment to publication at August, 2019 were identified by searching PubMed, The excerpta medica

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database, China Academic Journals Full-text Database, China Biology Medicine, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Wanfang databases. The research object is limited to human beings and language is not limited. English and Chinese retrieval is based on "epidermal growth factor or EGF," "polymorphism or SNP or variant," and "lung carcinoma/cancer," supplemented by literature review.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria. Study on the correlation between polymorphism of EGF 61A/G and susceptibility of lung cancer;

Case-control study;

Data in the literature are complete, or statistical indicators odds ratio (OR) and 95% confidence interval (CI) can be provided directly or indirectly.

2.2.2. Exclusion criteria. Literature on case-only studies, case reports, reviews, and comments;

Republished and incomplete literature;

Control group in the literature not satisfied with Hardy-Weinberg (H-W) genetic balance.

2.3. Data extraction

Two researchers independently identified the literature and extracted data. When disagreements arise, they are resolved through discussion or with the assistance of a third researcher. Data extraction included author, publication year, ethnicity, source of control, total number of cancer group and control group, distribution of genotypes, and H-W balance of control group. If $P < .05$, it is considered that it was not in accordance with H-W balance.

2.4. Literature quality evaluation

Newcastle–Ottawa scale criteria was used.[9] Star-level criteria was used to evaluate 3 parts.

Study objects selection of case group and control group;

Comparability of study objects between case group and control group;

Exposure to risk factors.

Studies with scores greater than or equal to 7 were identified as high-quality studies.

2.5. Statistical methods

Stata 15.0 was used for meta-analysis. OR and its 95% CI were selected as the combined effect quantities. Heterogeneity test was conducted for the included studies, Q test and I statistics were used. If $P > .05$ or $I^2 < 50\%$, it suggests that there is no heterogeneity among the studies. Fixed-effect model was used for combined analysis.[10] On the contrary, the random-effect model was adopted. Sensitivity analysis excludes individual literature in turn and then re-conducts meta-analysis to estimate the size of the comprehensive effect. Publication bias was quantitatively detected by Egger regression method, if $P < .05$, it was considered that there was publication bias.

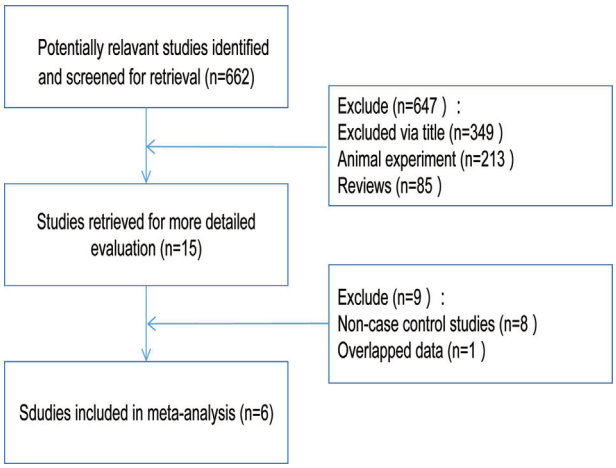

Figure 1. A flow diagram of the study selection process.

3. Results

3.1. Literature retrieval

A total of 6 relevant literature was found out by searching, all of which could extract data. Therefore, this study included 6 papers, including 1487 cases and 2044 controls. All the 6 papers were in English. Two papers were about Korean population,[11,12] 2 about Portuguese population,[13,14] 1 about Indian population,[15] and 1 about Brazilian population.[16] Except for 1 literature in which the control group came from the community, the rest came from the hospital. Through H-W genetic balance test, the results indicated that in the test of the 6 literature control groups, P were greater than .05, which satisfied the genetic balance. The specific process of literature screening can be found in Figure 1, and the data characteristics of literature can be found in Table 1.

Table 1

Characters of included studies.

Study	Year	Country	Ethnicity	Source of control	Sample size (case/control)	Cases			Controls			Study quality	HWE (control)
						GG	AG	AA	GG	AG	AA		
Yun Jeong Lim et al	2004	Korea	Asian	Hospital	122/132	64	48	10	42	55	35	8	0.059
Hyo-Gyoung Kang et al	2007	Korea	Asian	Population	432/432	197	191	44	198	185	49	8	0.562
Ataman et al	2011	Portugal	Caucasian	Hospital	52/150	16	23	13	42	64	44	7	0.073
Ramon Andrade de Mello et al	2012	Portugal	Caucasian	Hospital	112/126	28	58	26	23	52	51	8	0.139
Mirza Masroor et al	2015	India	Asian	Hospital	100/100	20	63	17	13	51	36	7	0.441
Ana Carolina Laus et al	2019	Brazil	Caucasian	Hospital	669/1104	169	317	183	255	570	279	8	0.272

Table 2

Results of meta-analysis for EGF 61A/G polymorphism and lung cancer risk.

Genetic models	n	Model for analysis	OR (95% CI)	I^2 (%)	*P* for heterogeneity	*P* for bias
Allelic model	6	FEM	1.07 (0.98–1.15)	35.9	.168	.043
Asian	3	FEM	1.11 (0.98–1.25)	58.7	.089	.197
Caucasian	3	FEM	1.04 (0.93–1.15)	14.9	.309	.44
Dominant model	6	FEM	1.04 (0.94–1.15)	0	.554	.024
Asian	3	FEM	1.09 (0.93–1.28)	0	.425	.046
Caucasian	3	FEM	1.01 (0.88–1.15)	0	.421	.422
Recessive model	6	FEM	1.13 (0.98–1.30)	0	.44	.132
Asian	3	FEM	1.14 (0.93–1.39)	53.8	.115	.355
Caucasian	3	FEM	1.12 (0.92–1.36)	0	.79	.54
Homozygous model	6	FEM	1.12 (0.96–1.31)	24.2	.253	.029
Asian	3	FEM	1.18 (0.94–1.47)	52.3	.123	.089
Caucasian	3	FEM	1.07 (0.87–1.32)	3	.357	.443
Heterozygous model	6	FEM	1.04 (0.92–1.19)	0	.467	.024
Asian	3	FEM	1.14 (0.92–1.14)	0	.484	.042
Caucasian	3	FEM	0.99 (0.85–1.17)	6.8	.342	.423

CI = confidence interval, EGF = epidermal growth factor, FEM = fixed-effect model, OR = odds ratio.

3.2. Heterogeneity test

The risk between the polymorphism of EGF 61A/G and the susceptibility of lung cancer can be seen in Table 2. Heterogeneity of EGF 61A/G polymorphism was tested in 5 genetic models, as well as in ethnic subgroups. The results showed that the *P* value of heterogeneity test of all models was greater than .05, so the fixed effect model was selected for analysis.

3.3. Results of meta-analysis

Table 2 shows the combined OR value of lung cancer and the risk of EGF 61A/G locus polymorphism. In allele comparison (G vs A), OR = 1.07 (95% CI: 0.98–1.15); in dominant genetic model (GG + GA vs AA), OR = 1.04 (95% CI: 0.94–1.15); in recessive genetic model (GG vs GA + AA), OR = 1.13 (95% CI: 0.98–1.30); in homozygote model (GG vs AA), OR = 1.12 (95% CI: 0.96–1.31). In the heterozygote model (GA vs AA), OR = 1.04 (95% CI: 0.92–1.19). The 95% CI of all OR values contains 1, indicating that the difference is not statistically significant. Subgroup analysis of races showed that the results of Asian and Caucasian analysis also failed to produce a statistically significant genetic model. Five gene models and forest graphs of subgroup analysis are shown in Figure 2. This indicates that the polymorphism of EGF 61A/G cannot be considered to be associated with the risk of lung cancer.

3.4. Publication bias

The assessment results of publication bias are shown in Funnel Figure 3, and the results of Egger' test are showed in Table 2. The results showed that among the 5 genotypes, except the *P* value in the recessive gene model was .132, the rest were all less than .05, which was not very symmetrical on funnel map, indicating that there was publication bias. However, from the specific value of *P* value, the allele model *P* = .043, approaching .05, indicating that publication bias is almost not exist.

3.5. Sensitivity analysis

The 6 papers included in this study were published in high-quality academic journals. The results of sensitivity analysis was showed in Figure 4. It showed that, in the allele model, after removing the large proportion of the study of Laus et al,[16] the difference was statistically significant. In the recessive gene model, after the removal of the study of Kang et al,[12] the difference was statistically significant. The results of meta-analysis of the other 3 genotypes showed that the combined effects of genetic models did not change significantly. Therefore, the conclusions of allele model and recessive gene model should be made carefully.

4. Discussion

Since the past decade, the EGF 61A/G polymorphism has been studied and considered as a risk factor for cancer,[17] such as liver cancer, gastric cancer, malignant melanoma,[18,19] and so on. In the study of EGF 61A/G polymorphism and malignant melanoma,[17] the authors pointed out that the EGF 61G/A locus was close to the regulatory region of EGF gene, which can also explain the high expression of serum EGF biologically. In September, 2011, at the European Multidisciplinary Conference held in Stockholm, the association between EGF A/G polymorphism and non-small cell lung cancer[13,14] was demonstrated for the first time in the Portuguese population. This is inconsistent with previous studies by Kang et al[11,12] and other people. The reason for this inconsistency may be ethnic differences. Current studies have indicated that the presence of the EGF 61G allele is indeed considered as a key point in the carcinogenic process, because it can increase serum EGF, thus stimulating proliferation, angiogenesis, and cancer cell metastasis. This interaction between serum EGF and its receptor is very important in the framework of non-small cell lung cancer. It induces tumor invasion through 4 main pathways:

phospholipase C γ;
phosphatidylinositol 3-kinase;
signal transduction and activation factor;
Ras, Raf, MEK, ERK, mitogen-activated protein kinase.[20]

However, another Korean study conducted by Lim et al[11,12] and other people showed that EGF + 61A/G polymorphism was associated with lung cancer. Therefore, the conclusions are inconsistent between different studies. Thus, to evaluate the relation between EGF 61A/G locus and susceptibility of lung cancer, this study collected case-control studies on the relation between EGF 61A/G polymorphism and lung cancer in recent years, and conducted a Meta-analysis to comprehensively

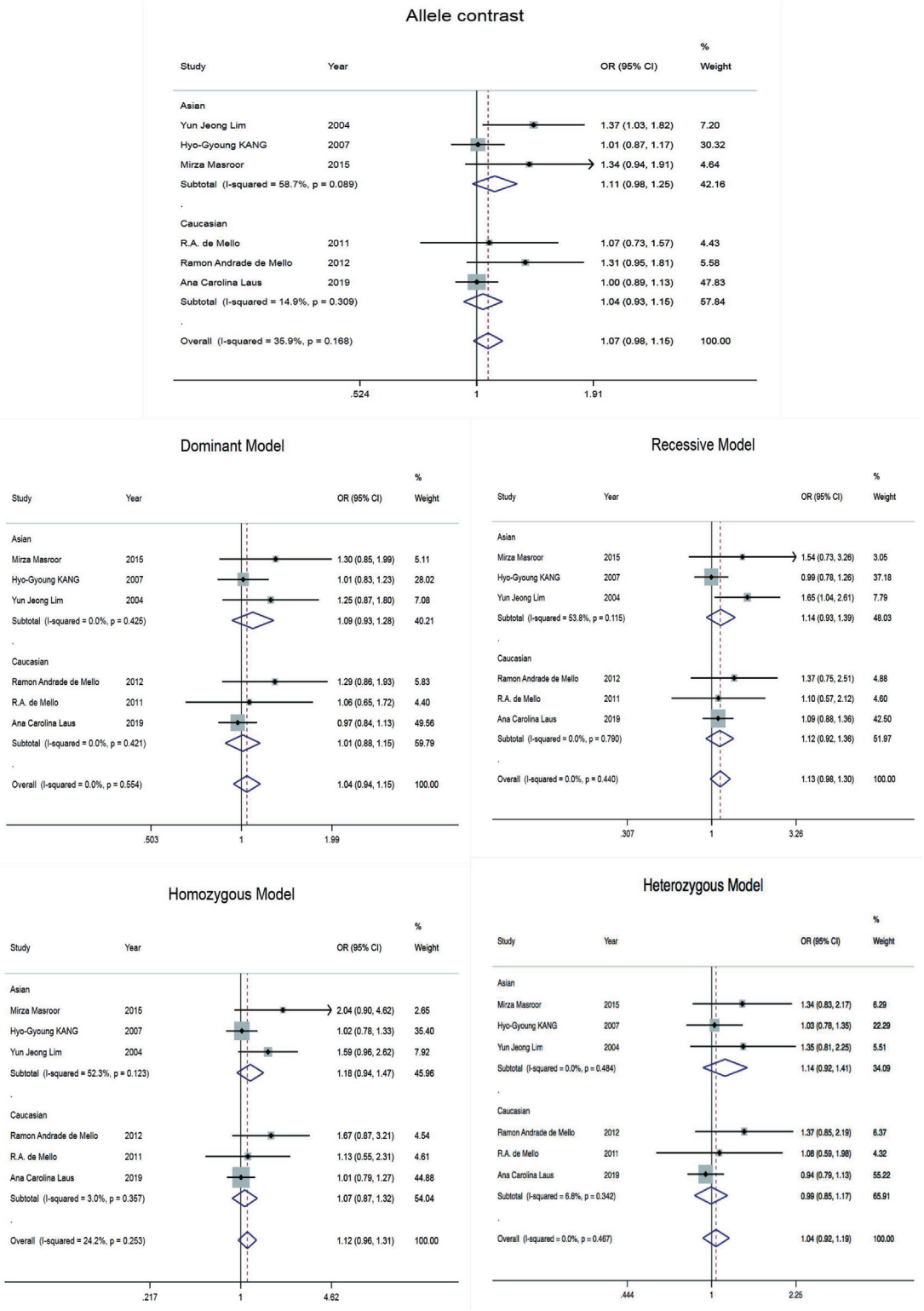

Figure 2. Forest plot for the association between EGF 61A/G polymorphism and lung cancer risk in 5 gene models. EGF = epidermal growth factor.

evaluate the correlation between EGF 61A/G polymorphism and lung cancer risk.

Different from the studies on EGF 61A/G polymorphism and malignant tumors like gastric cancer, liver cancer, and melanoma, the studies on the association between EGF 61A/G polymorphism and lung cancer are not enough. At present, there are only 6 literature that can extract data and meet the research requirements. Only Asians and Caucasians have had some study on this topic, while Africans have not. From the overall results, the EGF 61A/G allele G related to allele A, OR =

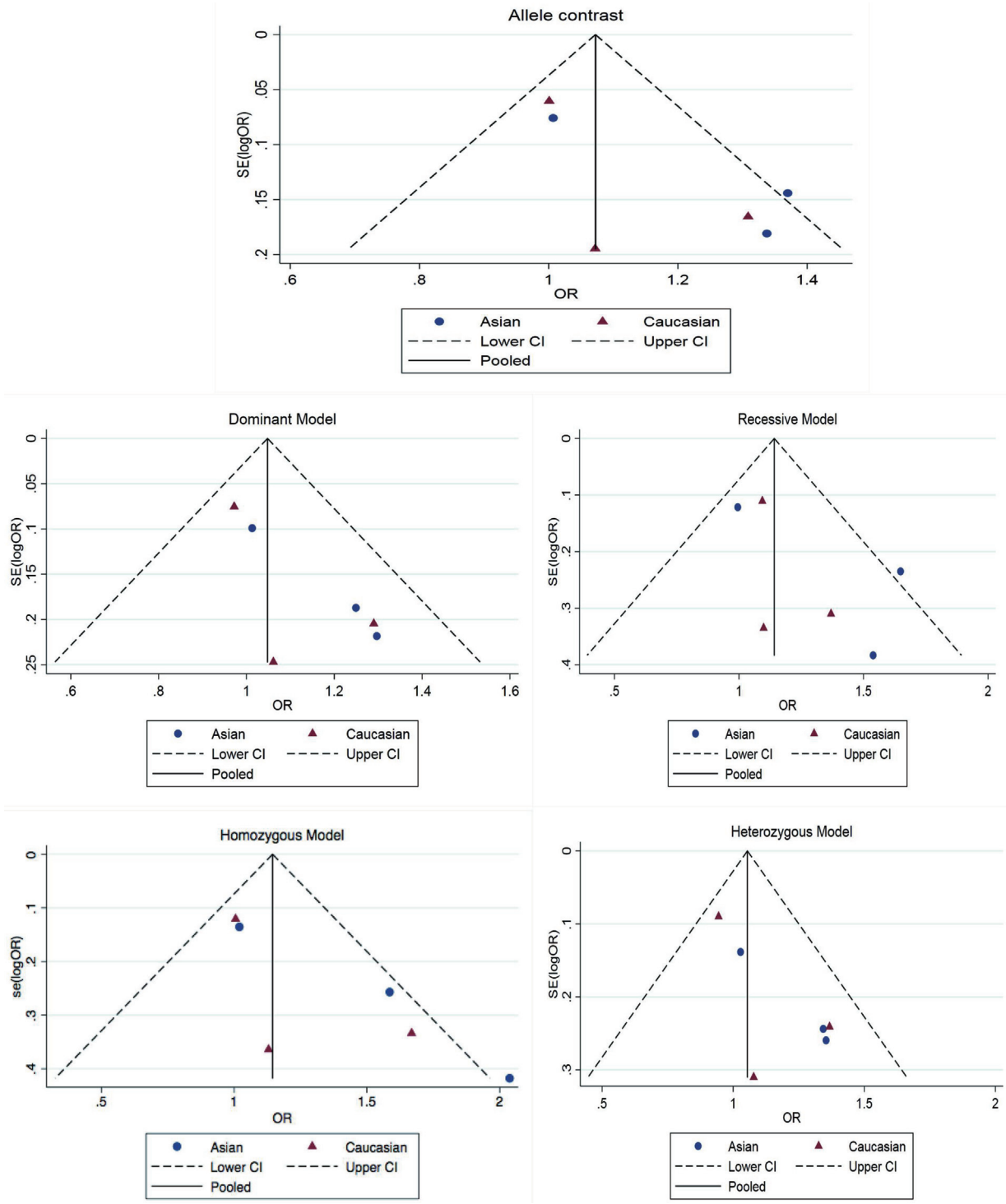

Figure 3. Funnel plot for the assessment of publication bias.

1.07, 95% CI is 0.98 to 1.05, the interval contained 1. In dominant gene model, recessive gene model, homozygote model, and heterozygote model, 95% CI contained 1, and the difference is not statistically significant.

Of course, this study also has limitations.

The number of papers included is not enough, and there are few studies on the association between EGF 61 polymorphism and lung cancer. From the first study in 2004, up to now, there are only 6 papers. From the test results of publication bias, there is significant bias;

the number of cases and the control group is only 1487 and 2044, and the sample size is relatively small;

The research scope is narrow, only Asian and Caucasian studies, not Africans;

The sensitivity of allele model and recessive gene model is poor;

The influence of gender, diet and other factors is not included.

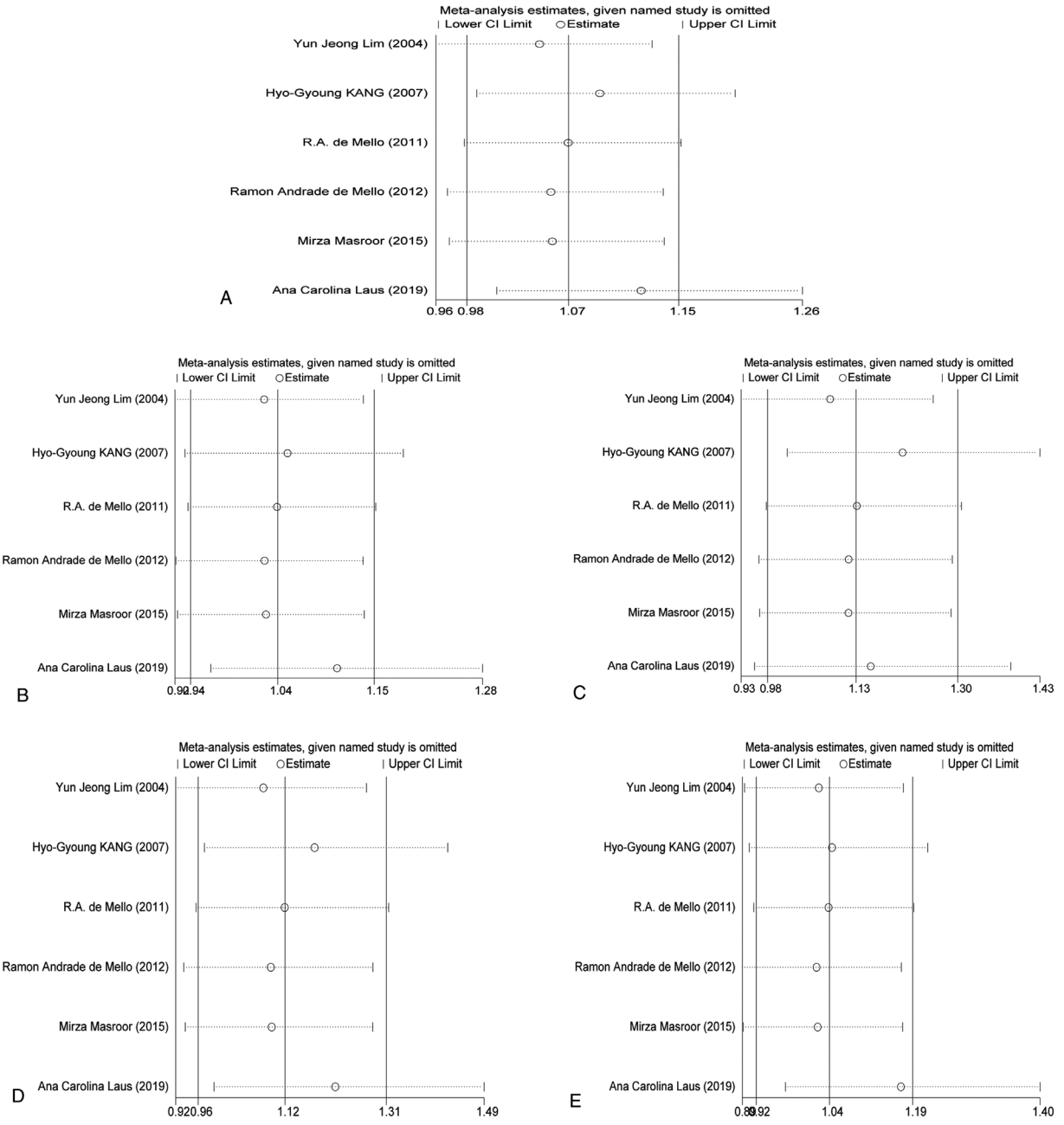

Figure 4. Sensitivity analysis results.

Although the current results of meta-analysis shows that there is no association between the polymorphism of EGF 61A/G and the risk of lung cancer, in term of the limitations of the study, this conclusion still need more researches to support, and more studies are needed to be conducted. Up to now, no meta-analysis is conducted on the association between EGF 6A/G polymorphism and lung cancer susceptibility, so it is meaningless to compare with the results of other researchers. Of course, the occurrence of cancer is caused by multiple factors, especially the influence of genes and environment. Therefore, in the future, a lot of researches still should be done to study the interaction between genes and genes, genes and environment, environment and environment, and explore the association between EGF polymorphism and susceptibility of lung cancer from a broader and deeper perspective.

Author contributions

Study concept and design: Quan Chen, Pengcheng Wang.
Acquisition of data: Quan Chen, Yiming Zheng, Bingbing Wu, Xia Chen, Pengfei Ge, Pengcheng Wang.
Analysis and interpretation of data: Quan Chen, Pengcheng Wang.
Drafting of the manuscript: Quan Chen, Pengcheng Wang; Critical revision of the manuscript for important intellectual content: Quan Chen, Pengcheng Wang.

Statistical analysis: Quan Chen, Yiming Zheng, Bingbing Wu, Xia Chen, Pengfei Ge, Pengcheng Wang.
Administrative, technical, and material support: Quan Chen, Yiming Zheng, Bingbing Wu, Xia Chen, Pengfei Ge, Pengcheng Wang.
Study supervision: Quan Chen, Pengcheng Wang.
All authors have read and approved the manuscript.

Correction

In the original version, R.A. de Mello et al appeared incorrectly in Table 1 and is now appearing correctly as Ataman et al.

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