ORIGINAL RESEARCH

Association of *GEMIN4* gene polymorphism and the risk of cancer: a meta-analysis

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Abstract: Gem-associated protein 4 (*GEMIN4*) gene is a key regulator for the miRNA biogenesis processes. Recent studies have demonstrated that some single-nucleotide polymorphisms (SNPs) in *GEMIN4* gene are associated with the risk of cancer, but the results are still controversial. Therefore, we conducted a meta-analysis to analyze the association between three major SNPs (rs2740348, rs7813, and rs3744741) in the *GEMIN4* gene and the risk of cancer. Relevant articles were searched in Web of Science, PubMed, Cochrane Library, Chinese Wan Fang, and Chinese National Knowledge Infrastructure databases. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to quantitatively estimate the association. Publication bias and sensitivity analyses were undertaken to evaluate the stability of the results. Overall, the pooled results showed that rs2740348 involving 3,604 cases and 3,770 controls was significantly associated with increased cancer risk (GG vs GC/CC: OR =1.16, 95% CI =1.05–1.29, *P*=0.004) and rs7813 involving 4,729 cases and 4,562 controls was also related to increased cancer risk (TT vs TC/CC: OR =1.12, 95% CI =1.03–1.22, *P*=0.009). However, there was no significant association between rs3744741 and cancer risk under overall genetic models. In conclusion, our study has demonstrated that rs2740348 and rs7813 are associated with increased risk of cancer, and they may be new biomarkers for predicting cancer risk.

Keywords: gem-associated protein 4, single-nucleotide polymorphism, cancer, meta-analysis

Introduction

Cancer is a major serious challenge to human health worldwide. According to the latest report from American Cancer Society, 1,688,780 new cancer cases and 600,920 cancer deaths are expected to occur in the United States in 2017.[1] Cancer is considered as a multi-genetic disease caused by substantial accumulation of DNA mutations.[2] Genetic variations will induce the activation of oncogenes and inactivation of tumor suppressor genes, subsequently resulting in unrestrained cell proliferation and neoplasm formation.[3,4] With cancer genome sequencing widely applied, identifying the mutations in an individual patient may contribute to preventing cancer efficiently.[5]

MicroRNA (miRNA), a type of noncoding RNA containing approximately 22 nucleotides, participates in regulating gene expression at the post-transcriptional level.[6] miRNA biogenesis is a sophisticated process involving several steps. To be specific, miRNA is initially transcribed into a 300- to 1,000-nucleotide-length pri-miRNA,[7] and then the pri-miRNA is processed into two-nucleotide strands precursor-miRNA (pre-miRNA) in the nucleus in collaboration with a nuclear protein known as DiGeorge Syndrome Critical Region 8 (DGCR8).[8] Finally, the pre-miRNA is further cut by the RNase III enzyme Dicer in the cytoplasm to generate a mature miRNA.[9] Gem-associated protein 4 (GEMIN4), encoded by *GEMIN4* gene, along with the mature miRNA, Argonaute (Ago) protein and gem-associated protein 3 (GEMIN3)

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participates in the formation of the miRNA-induced silencing complex (RISC), which promotes the mature miRNAs to bind to their target mRNAs and then regulates the expression of target genes.[10,11]

Recent studies have found that miRNAs are generally dysregulated in cancer and function as oncogenes or tumor suppressor genes.[12,13] Furthermore, the alteration in miRNA biogenesis genes may be associated with susceptibility to cancer probably by influencing the function of miRNAs.[14] Furthermore, a body of evidence has indicated that some single-nucleotide polymorphisms (SNPs) in the *GEMIN4* gene, a major miRNA biogenesis gene, are associated with the risk of several types of cancer,[15–19] but the published results are inconsistent.[15–17] Therefore, in the present study, we undertook a meta-analysis to analyze the association between three major SNPs in the *GEMIN4* gene (rs2740348, rs7813, and rs3744741) and the risk of cancer based on published articles.

Methods
Literature search
Relevant articles published prior to July 20, 2017 were mainly identified through searches of Web of Science, PubMed, Cochrane Library, Chinese Wan Fang, and Chinese National Knowledge Infrastructure databases online. The key terms of literature search included "genetic polymorphism," "single nucleotide polymorphism," "genetic variants," "nuclear organelle associated protein 4," "*GEMIN4*," "cancer," "carcinoma," "malignancy," and "tumor." Furthermore, manual retrieval was undertaken additionally by browsing the references from eligible articles. Each retrieved article including title, abstract, and full text was comprehensively evaluated by two independent authors to determine whether it could be included in the final analysis. If their opinions were not consistent, other authors critically assessed whether the retrieved article should be included.

Eligibility criteria
The qualified articles should simultaneously meet three major inclusion criteria as follow: 1) concerning the association between the *GEMIN4* polymorphism and cancer; 2) case–control study; and 3) complete data concerning the frequencies of genotype or sufficient original data for calculating the frequencies of genotype. Retrieved articles were excluded if they met one of the two major exclusion criteria as follows: 1) duplicated or retracted articles, 2) review, case report, letter, or short commentary. In addition, the healthy control should be free of any type of cancer.

Data extraction
Information about the eligible article including the author's name, publication date, characteristics of case and control, methods of genotyping, *P*-value of the Hardy–Weinberg equilibrium (HWE) test, sample size of the study, and number of genotype was extracted from full text by two independent authors separately. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of included studies as described previously.[20]

Statistical analysis
Firstly, the distribution of genotype in the control was evaluated to ascertain whether it conformed to the HWE through the chi-square goodness-of-fit test. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to estimate the association between the *GEMIN4* polymorphism and risk of cancer. Cochran's Q statistic in combination with the I-squared (I^2) metric was used to assess heterogeneity. Specifically, $P<0.10$ or $I^2>50\%$ was considered as indicative of significant heterogeneity. The random-effects model was used to estimate the pooled OR with significant heterogeneity existing; otherwise, the fixed-effects model was developed. The best-fitting genetic model was chosen to estimate the association between the *GEMIN4* polymorphism and the risk of cancer, according to previously published articles.[21] Subgroup analysis was further undertaken based on ethnicity. Publication bias was evaluated through funnel plots in combination with Egger's linear regression test. Publication bias was considered significant when the *P*-value of Egger's test was less than 0.05. Sensitivity analysis was conducted to evaluate the stability of pooled results through omitting a single study each time to examine its influence on the total OR value. Statistical data analyses were conducted by using STATA 11.0 (STATA Corp., College Station, TX, USA).

Results
Characteristics of the included studies
In general, 70 relevant articles were originally chosen from different electronic databases. According to the inclusion and exclusion criteria, 55 articles were eliminated and 15 qualified articles (9 articles referring to rs2740348,[15,18,22,28] 11 articles referring to rs7813,[15–17,19,22–25,29–31] and 5 articles referring to rs3744741[15,16,22–24]) were finally included in the meta-analysis (Figure 1). Specifically, details of the eliminated articles are shown in Table S1.

The main characteristics of all qualified studies are listed in Tables 1–3, respectively. Each included study got no less
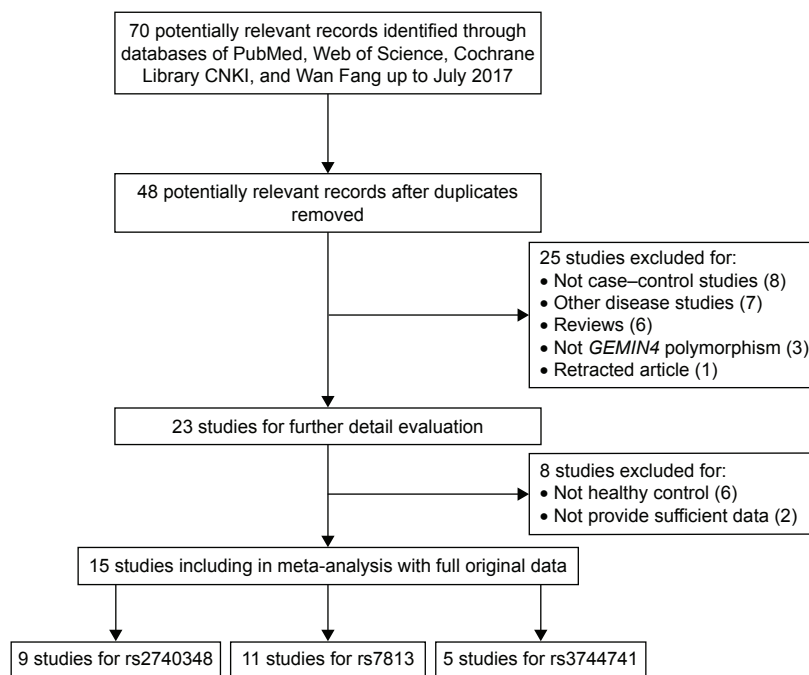
Figure 1 Flow chart of the study selection process.

than 7 points referring to the NOS score, and the genotype distribution in the control conformed to HWE.

Quantitative data synthesis

For rs2740348, the pooled result with 3,604 cases and 3,770 controls showed that it was significantly associated with increased risk of cancer in the recessive model (GG vs GC/CC: OR =1.16, 95% CI =1.05–1.29, P=0.004; Figure 2A). The result of subgroup analysis by ethnicity showed that rs2740348 was significantly associated with increased risk of cancer in a mixed population (GG vs GC/CC: OR =1.23, 95% CI =1.05–1.43, P=0.009; Figure 2A), but not in Caucasians (GG vs GC/CC: OR =1.20, 95% CI =0.95–1.52, P=0.127; Figure 2A) and Asians (GG vs GC/CC: OR =1.07, 95% CI =0.90–1.27, P=0.423; Figure 2A).

For rs7813, the pooled result with 4,729 cases and 4,562 controls also indicated that rs7813 was related to increased risk of cancer in the recessive model (TT vs TC/CC: OR =1.12, 95% CI =1.03–1.22, P=0.009; Figure 2B). Subgroup analysis by ethnicity further indicated that rs7813 significantly increased susceptibility to cancer in Asians (TT vs TC/CC: OR =1.14, 95% CI =1.02–1.27, P=0.019; Figure 2B) rather than Caucasians (TT vs TC/CC: OR =1.09, 95% CI =0.95–1.25, P=0.206; Figure 2B).

As for rs3744741, the pooled result with 2,167 cases and 2,143 controls suggested no association existed between rs3744741 and the risk of cancer in the recessive model

(CC vs CT/TT: OR =1.04, 95% CI =0.92–1.18, P=0.509; Figure 2C). Furthermore, no association was found in other genetic models (Table S2).

Sensitivity analysis and publication bias

To evaluate the stability of the pooled results, sensitivity analysis was conducted. The result of sensitivity analysis showed the pooled OR value did not significantly change when omitting any single study (Figure 3). To evaluate the publication bias, the funnel plot and Egger's linear regression test were applied. Funnel plots of rs2740348, rs7813, and rs3744741 were visually symmetrical (Figure 4) and, furthermore, the result of Egger's test showed no evidence of publication bias (P=0.769, 95% CI: −2.90, 2.24 for rs2740348, P=0.751, 95% CI: −3.61, 4.83 for rs7813, P=0.557, 95% CI: −4.03, 6.14 for rs3744741, respectively).

Discussion

GEMIN4 gene is located on the human chr17. Genetic variants in the *GEMIN4* gene might lead to a decreased inhibitory effect on the proliferation of hepatocarcinoma cells and simultaneously have an impact on the DNA repair system by altering the expression of proliferation-associated genes and DNA repair genes.[32] Several studies have found that genetic variants in the *GEMIN4* gene not only alter the susceptibility to cancer,[15–19] but also influence the survival time of patients with cancer.[33,34] However, as far as we know,

Table 1 Main characteristics of studies included in the meta-analysis for rs2740348

Studies	Country	Ethnicity	Age, year (case/control)	Male, % (case/control)	Cancer type	Genotype method	NOS score	HWE test (control)	Simple size (case/control)	Genotype (case/control)	
										GG	GC + CC
Ye et al[22]	USA	Caucasian	63.3±11.0/63.2±10.63	88.4/88.4	Esophageal cancer	SNPlex assay	8	Yes	346/346	238/238	108/108
Jiang et al[23]	China	Asian	NA	0/0	Breast cancer	TaqMan assay	8	Yes	863/888	665/682	198/206
Liu et al[15]	China	Asian	71.43±9.38/71.15±9.64	100/100	Prostate cancer	HRM method	8	Yes	300/244	246/182	54/62
Kim et al[24]	Korea	Asian	61.5±10.9/61.5±11.3	80/80	Lung cancer	Spectrometry-based	8	Yes	92/90	74/71	18/19
Gutiérrez-Malacatt et al[26]	Mexico	Mixed	40.52±8.46/44.87±14.88	56/56	Chronic myeloid leukemia	TaqMan assay	7	Yes	312/469	203/291	109/178
Horikawa et al[25]	USA	Caucasian	60.29±10.57/60.46±10.88	67/67	Renal cell carcinoma	SNPlex assay	8	Yes	276/278	192/168	84/110
Xie et al[27]	China	Asian	NA	72.3/72.5	Gastric cancer	PCR-LDR	7	Yes	137/140	110/115	27/25
Zhao et al[28]	China	Asian	NA	57.1/65.5	Colon cancer	PCR-LDR	7	Yes	163/142	128/114	35/28
Mullany et al[18]	USA	Mixed	NA	NA	Colon cancer	PCR-RFLP	8	Yes	1,115/1,173	798/782	317/391

Note: Data presented as mean ± standard deviation.
Abbreviations: HWE, Hardy–Weinberg equilibrium; NA, not available; NOS, Newcastle–Ottawa Scale.

Table 2 Main characteristics of studies included in the meta-analysis for rs7813

Studies	Country	Ethnicity	Age, year (case/control)	Male, % (case/control)	Cancer type	Genotype method	NOS score	HWE test (control)	Simple size (case/control)	Genotype (case/control)	
										TT	TC + CC
Ye et al[22]	USA	Caucasian	63.3±11.0/63.2±10.63	88.4/88.4	Esophageal cancer	SNPlex assay	8	Yes	346/346	112/105	234/241
Jiang et al[23]	China	Asian	NA	0/0	Breast cancer	TaqMan assay	8	Yes	866/885	397/402	469/483
Liu et al[15]	China	Asian	71.43±9.38/71.15±9.64	100/100	Prostate cancer	HRM method	8	Yes	300/244	192/144	108/100
Kim et al[24]	Korea	Asian	61.5±10.9/61.5±11.3	80/80	Lung cancer	Spectrometry-based	8	Yes	98/99	42/47	56/52
Sung et al[16]	Korea	Asian	46.5±10.9/46.0±12.4	0/0	Breast cancer	TaqMan assay	8	Yes	558/567	236/218	322/349
Qu et al[29]	China	Asian	NA	67.2/64.3	Esophageal squamous cell carcinoma	PCR-RFLP	8	Yes	381/426	163/186	218/240
Fang et al[17]	China	Asian	56.26±11.71/56.13±11.64	0/0	Lung cancer	TaqMan assay	8	Yes	473/395	242/153	231/242
Horikawa et al[25]	USA	Caucasian	60.29±10.57/60.46±10.88	67/67	Renal cell carcinoma	SNPlex assay	8	Yes	277/278	96/75	181/203
Nikolić et al[19]	Serbia	Caucasian	NA	100/100	Prostate cancer	TaqMan assay	7	Yes	355/319	114/101	241/218
Liang et al[30]	USA	Caucasian	NA	0/0	Ovarian cancer	Illumina	8	Yes	339/267	123/93	216/174
Yang et al[31]	USA	Caucasian	63.5±10.9/63.3±10.6	79/79	Bladder cancer	SNPlex assay	8	Yes	736/736	225/222	511/514

Note: Data presented as mean ± standard deviation.
Abbreviations: HWE, Hardy–Weinberg equilibrium; NA, not available; NOS, Newcastle–Ottawa Scale.

Table 3 Main characteristics of studies included in the meta-analysis for rs3744741

Studies	Country	Ethnicity	Age, year (case/control)	Male, % (case/control)	Cancer type	Genotype method	NOS score	HWE test (control)	Simple size (case/control)	Genotype (case/control)		
										CC	CT	TT
Ye et al[22]	USA	Caucasian	63.3±11.0/63.2±10.63	88.4/88.4	Esophageal cancer	SNPlex assay	8	Yes	346/346	268/250	73/88	5/8
Jiang et al[23]	China	Asian	NA	0/0	Breast cancer	TaqMan assay	8	Yes	862/887	440/466	353/354	69/67
Liu et al[15]	China	Asian	71.43±9.38/71.15±9.64	100/100	Prostate cancer	HRM method	8	Yes	300/244	188/142	92/82	20/20
Kim et al[24]	Korea	Asian	61.5±10.9/61.5±11.3	80/80	Lung cancer	Spectrometry-based	8	Yes	100/99	56/60	38/34	6/5
Sung et al[16]	Korea	Asian	46.5±10.9/46.0±12.4	0/0	Breast cancer	TaqMan assay	8	Yes	559/567	331/327	198/207	30/33

Note: Data presented as mean ± standard deviation.
Abbreviations: HWE, Hardy–Weinberg equilibrium; NA, not available; NOS, Newcastle–Ottawa Scale.

most of these studies are small-scale case–control studies. Although a meta-analysis conducted by Zhu et al firstly showed that rs2740348 and rs7813 polymorphisms were associated with increased risk of cancer, the total number of subjects in their meta-analysis was also limited.[35] Compared with previous meta-analysis, one advantage of our meta-analysis is that it included larger sample size, nearly double that of studies earlier. In addition, another new finding of our study is that it firstly evaluates the association between the rs3744741 polymorphism and the risk of cancer.

The rs2740348 polymorphism is a C/G mutation located in the exon region of the *GEMIN4* gene. Liu et al found that rs2740348 was associated with decreased risk of prostate cancer.[15] A similar protective effect was also shown in colon cancer.[18] However, Zhao et al suggested no association existed in colorectal cancer.[28] Moreover, there was no association with lung cancer,[24] chronic myeloid leukemia, and gastric cancer.[26,27] More interestingly, Yang et al found that a haplotype of the *GEMIN4* gene including rs2740348 was associated with increased risk of bladder cancer.[31] In our present meta-analysis, we found that rs2740348 was significantly associated with increased risk of cancer in the general population under the recessive model (GG vs GC/CC), which agreed with the result reported by Zhu et al.[35] However, this conclusion was only confirmed in a mixed population, but not in Asians and Caucasians. Therefore, the discrepancy of the results might be partly attributed to the difference of the study population.

The rs7813 polymorphism is a C/T mutation located in the exon region of the *GEMIN4* gene. Liu et al found that rs7813 was associated with an increased risk of prostate cancer,[15] and Nikolić et al also found a significant association between rs7813 and the risk of prostate cancer progression.[19] However, Fang et al found that rs7813 was associated with decreased risk of lung cancer.[17] A similar protective effect was found in ovarian and breast cancers.[30,34] In addition, some studies did not report any significant association between rs7813 and the risk of breast cancer,[23] lung cancer, and esophageal squamous cell carcinoma.[24,32] In the present study, we reported that rs7813 was related to an increased risk of cancer in the general population under the recessive model (TT vs TC/CC), but this conclusion was only confirmed in Asians, not in Caucasians, which is contrary to a previous meta-analysis.[35] Thus, we inferred that the discrepancy might be explained by the diversity of study population and tumor types.

The rs3744741 polymorphism is a C/T mutation located in the exon region of the *GEMIN4* gene. Liu et al found that
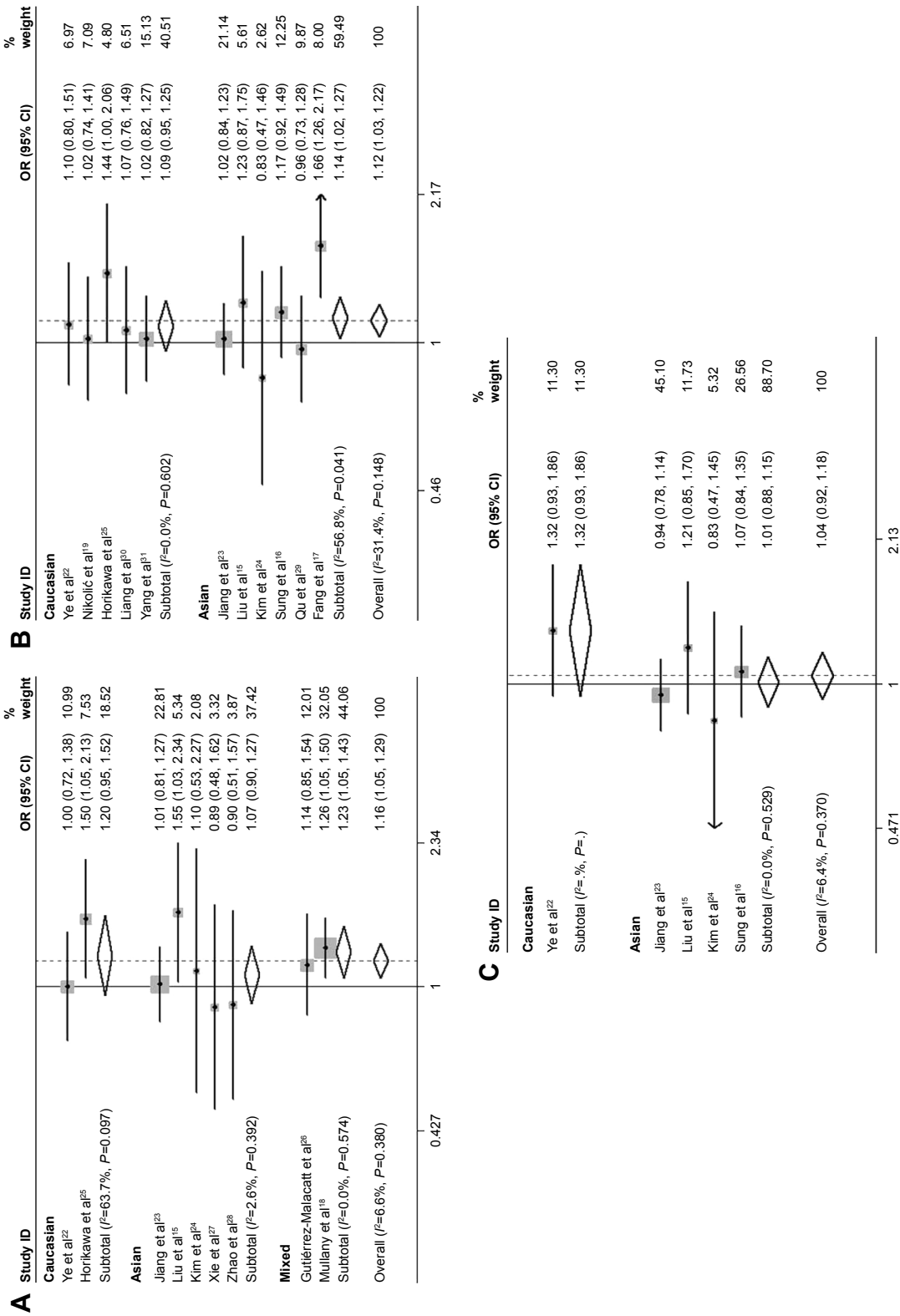
A

Study ID	OR (95% CI)	% weight
Caucasian		
Ye et al[22]	1.00 (0.72, 1.38)	10.99
Horikawa et al[25]	1.50 (1.05, 2.13)	7.53
Subtotal (I^2=63.7%, P=0.097)	1.20 (0.95, 1.52)	18.52
Asian		
Jiang et al[23]	1.01 (0.81, 1.27)	22.81
Liu et al[15]	1.55 (1.03, 2.34)	5.34
Kim et al[24]	1.10 (0.53, 2.27)	2.08
Xie et al[27]	0.89 (0.48, 1.62)	3.32
Zhao et al[28]	0.90 (0.51, 1.57)	3.87
Subtotal (I^2=2.6%, P=0.392)	1.07 (0.90, 1.27)	37.42
Mixed		
Gutiérrez-Malacatt et al[26]	1.14 (0.85, 1.54)	12.01
Mullany et al[18]	1.26 (1.05, 1.50)	32.05
Subtotal (I^2=0.0%, P=0.574)	1.23 (1.05, 1.43)	44.06
Overall (I^2=6.6%, P=0.380)	1.16 (1.05, 1.29)	100

0.427   1   2.34

B

Study ID	OR (95% CI)	% weight
Caucasian		
Ye et al[22]	1.10 (0.80, 1.51)	6.97
Nikolić et al[19]	1.02 (0.74, 1.41)	7.09
Horikawa et al[25]	1.44 (1.00, 2.06)	4.80
Liang et al[30]	1.07 (0.76, 1.49)	6.51
Yang et al[31]	1.02 (0.82, 1.27)	15.13
Subtotal (I^2=0.0%, P=0.602)	1.09 (0.95, 1.25)	40.51
Asian		
Jiang et al[23]	1.02 (0.84, 1.23)	21.14
Liu et al[15]	1.23 (0.87, 1.75)	5.61
Kim et al[24]	0.83 (0.47, 1.46)	2.62
Sung et al[16]	1.17 (0.92, 1.49)	12.25
Qu et al[29]	0.96 (0.73, 1.28)	9.87
Fang et al[17]	1.66 (1.26, 2.17)	8.00
Subtotal (I^2=56.8%, P=0.041)	1.14 (1.02, 1.27)	59.49
Overall (I^2=31.4%, P=0.148)	1.12 (1.03, 1.22)	100

0.46   1   2.17

C

Study ID	OR (95% CI)	% weight
Caucasian		
Ye et al[22]	1.32 (0.93, 1.86)	11.30
Subtotal (I^2=%, P=)	1.32 (0.93, 1.86)	11.30
Asian		
Jiang et al[23]	0.94 (0.78, 1.14)	45.10
Liu et al[15]	1.21 (0.85, 1.70)	11.73
Kim et al[24]	0.83 (0.47, 1.45)	5.32
Sung et al[16]	1.07 (0.84, 1.35)	26.56
Subtotal (I^2=0.0%, P=0.529)	1.01 (0.88, 1.15)	88.70
Overall (I^2=6.4%, P=0.370)	1.04 (0.92, 1.18)	100

0.471   1   2.13

Figure 2 Quantitative analysis for the association between *GEMIN4* gene polymorphism and the risk of cancer.
Notes: (**A**) Forest plot of rs2740348 polymorphism and the risk of cancer under the recessive model (GG vs GC/CC). (**B**) Forest plot of rs7813 polymorphism and the risk of cancer under the recessive model (TT vs TC/CC). (**C**) Forest plot of rs3744741 polymorphism and the risk of cancer under the recessive model (CC vs CT/TT).
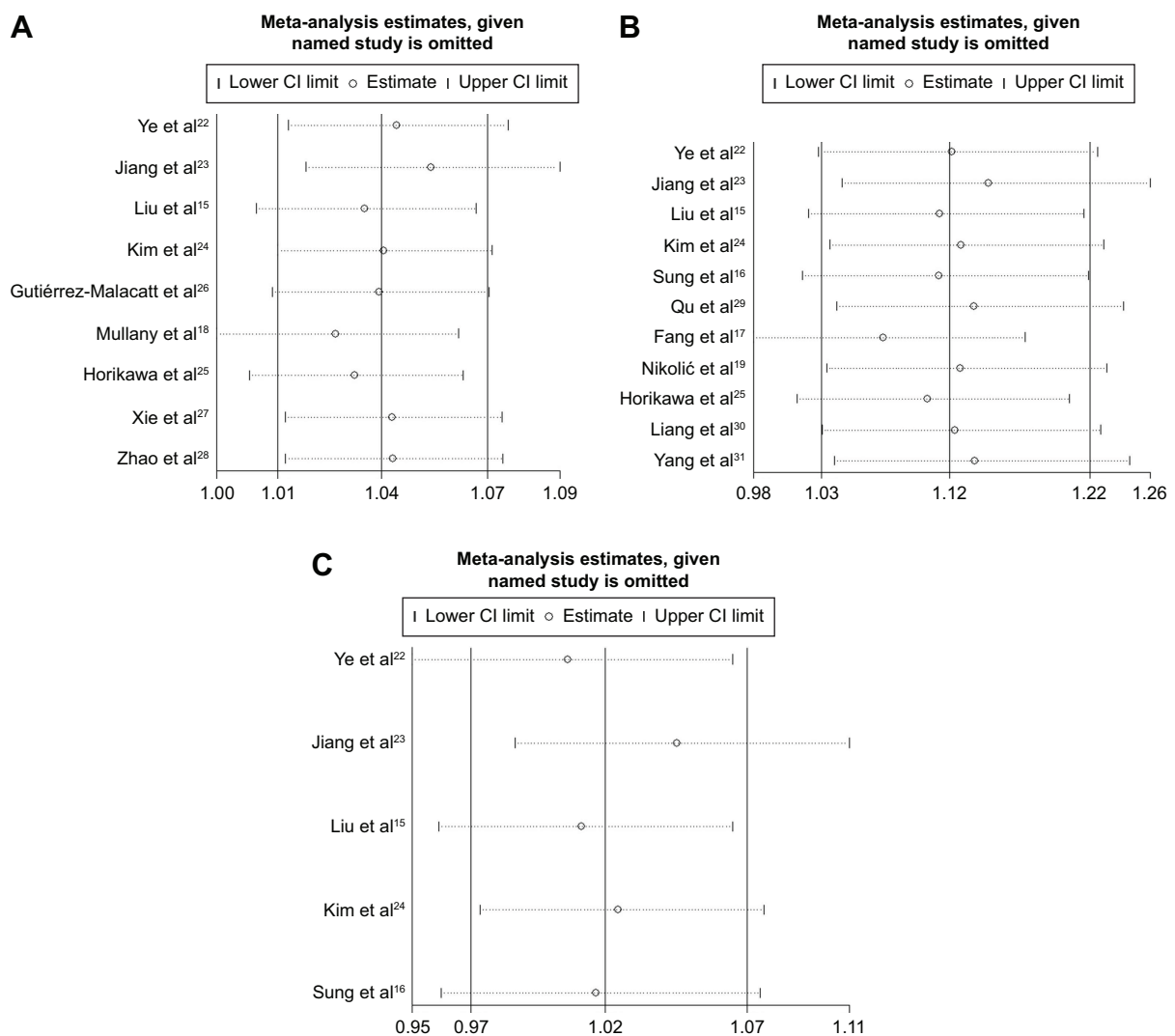
A

Meta-analysis estimates, given
named study is omitted

| Lower CI limit ○ Estimate | Upper CI limit

Ye et al[22]

Jiang et al[23]

Liu et al[15]

Kim et al[24]

Gutiérrez-Malacatt et al[26]

Mullany et al[18]

Horikawa et al[25]

Xie et al[27]

Zhao et al[28]

1.00   1.01   1.04   1.07   1.09

B

Meta-analysis estimates, given
named study is omitted

| Lower CI limit ○ Estimate | Upper CI limit

Ye et al[22]

Jiang et al[23]

Liu et al[15]

Kim et al[24]

Sung et al[16]

Qu et al[29]

Fang et al[17]

Nikolić et al[19]

Horikawa et al[25]

Liang et al[30]

Yang et al[31]

0.98   1.03   1.12   1.22   1.26

C

Meta-analysis estimates, given
named study is omitted

| Lower CI limit ○ Estimate | Upper CI limit

Ye et al[22]

Jiang et al[23]

Liu et al[15]

Kim et al[24]

Sung et al[16]

0.95   0.97   1.02   1.07   1.11

Figure 3 Sensitivity analysis for the association of *GEMIN4* gene polymorphism with the risk of cancer.
Notes: (**A**) Sensitivity analysis for rs2740348 polymorphism and the risk of cancer under the recessive model (GG vs GC/CC). (**B**) Sensitivity analysis for rs7813 polymorphism and the risk of cancer under the recessive model (TT vs TC/CC). (**C**) Sensitivity analysis for rs3744741 polymorphism and the risk of cancer under the recessive model (CC vs CT/TT).

the T allele of rs3744741 was associated with decreased risk of III/IV stage of prostate cancer,[15] but no significant association between rs7813 and the risk of cancer was reported in breast and lung cancers.[23,24] Moreover, we did not find any significant associations between rs7813 and the risk of cancer, neither in Asians nor in Caucasians under overall genetic models. Considering that the sample size was relatively small (2,167 cases and 2,143 controls), this conclusion should be further validated by some more large-scale studies.

Certainly, several limitations still existed in our meta-analysis. Firstly, the sample size of our meta-analysis, especially for rs3744741, was still relatively small. The conclusion should be reconfirmed by more large-scale studies. Secondly, the characteristics of included studies, such as age and gender,

were diverse and might affect the results of meta-analysis. Due to a lack of valid data pertaining to age and gender for all included studies, we could not evaluate their impacts on the pooled OR value. Finally, our study only evaluated the impact of these three SNPs on the risk of cancer separately and ignored the interaction effects of multiple SNPs, which was a deficit we must acknowledge.

Conclusion

Our study has demonstrated that rs2740348 and rs7813 polymorphism in *GEMIN4* gene are risk factors for cancer, but rs3744741 polymorphism is not associated with the risk of cancer. These findings should be further reconfirmed by more large-scale studies.
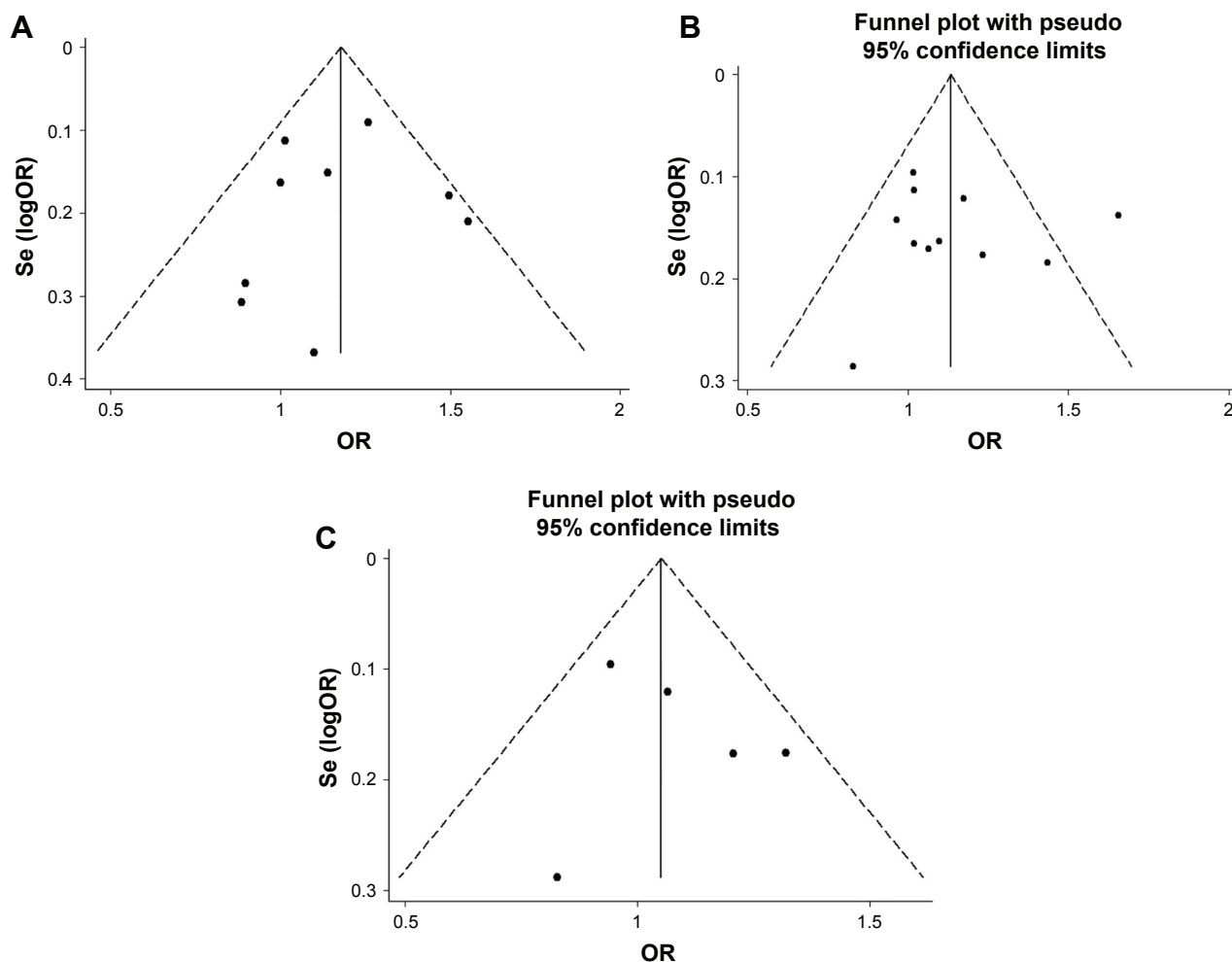
Figure 4 Funnel plot of *GEMIN4* gene polymorphism and the risk of cancer.
Notes: (**A**) Funnel plot of rs2740348 polymorphism and the risk of cancer under the recessive model (GG vs GC/CC). (**B**) Funnel plot of rs7813 polymorphism and the risk of cancer under the recessive model (TT vs TC/CC). (**C**) Funnel plot of rs3744741 polymorphism and the risk of cancer under the recessive model (CC vs CT/TT).

Disclosure

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