



Association between Long Non-coding RNA POLR2E rs3787016 Polymorphism and Cancer Susceptibility: A Meta-analysis of 8725 Cancer Cases and 10710 Controls

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Received 2020 February 25; Revised 2020 September 02; Accepted 2020 September 04.

Abstract

Objectives: Several studies have reported a correlation between the *POLR2E* rs3787016 polymorphism and cancer development, but findings are inconsistent. Therefore, we designed the current study to understand how rs3787016 polymorphism impacts cancer susceptibility.

Methods: We searched the Scopus, Web of Science, and PubMed databases for studies related to the topic of interest published up to March 2019. A total of 11 relevant studies, encompassing 8,761 cancer cases and 10,534 controls, were retrieved and subject to quantitative analysis. The strength of the relationship was evaluated using the pooled odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Overall, the findings proposed a positive association between rs189037 polymorphism and susceptibility to cancer in homozygous (OR = 1.32, 95% CI = 1.11 - 1.57, P = 0.002, TT vs. CC), recessive (OR = 1.21, 95% CI = 1.06-1.39, P = 0.005, TT vs. CT + CC), and allele (OR = 1.12, 95% CI = 1.02-1.22, P = 0.021, T vs. C) genetic models. Stratified analysis showed that rs3787016 increased the risk of prostate and breast cancer. In addition, we found a significant association between the variant and increased cancer risk in Asian and Caucasian populations.

Conclusions: In summary, the findings of the current meta-analysis suggest that the *POLR2E* rs3787016 polymorphism is an indicator of cancer susceptibility.

Keywords: *POLR2E*, Polymorphism, Cancer, lncRNA, Meta-analysis

1. Context

Cancer constitutes one of the most important global health concerns (1). The precise mechanisms of carcinogenesis remain largely elusive, but both genomic and environmental factors have been recognized to contribute to cancer development (2-7). Over the years, it has become evident that certain specific single nucleotide polymorphisms (SNPs) are related to cancer predisposition (6, 8-11).

Long non-coding RNAs (lncRNAs), mainly the transcripts of RNA polymerase II, are a class of specific non-coding RNA molecules with a length of more than 200 nucleotides (nt) (12, 13). Accumulating evidence reveals that lncRNA plays an imperative role in numerous biological processes and signaling pathways, such as cell cycle progression, apoptosis, transcription, splicing, transla-

tion, epigenetics, and regulation of gene expression (12-15). It has been proposed that alterations in the expression of lncRNAs are involved in cancer development and progression (16-19).

The *POLR2E* lncRNA gene is mapped to chromosome 19 (19p13). Several investigations have focused on identifying a relationship between the *POLR2E* rs3787016 polymorphism and the risk of cancer in various populations (20-28), but, overall, the findings have been inconsistent and conflicting. To comprehensively assess the correlation between the *POLR2E* rs3787016 polymorphism and cancer susceptibility, we designed and performed the current meta-analysis. Three recent meta-analyses have focused on *POLR2E* rs3787016 polymorphism and cancer. Chu et al. covered only four studies about *POLR2E* rs3787016 polymorphism, while in the current meta-analysis, we cov-

ered 11 manuscripts; therefore, our study is much more comprehensive and conclusive. Chen et al. investigated POLR2E rs3787016 polymorphism in liver and lung cancer and used five articles in their meta-analysis (25); therefore, our meta-analysis with 11 articles is more conclusive and covers more types of cancers. Huang et al. investigated POLR2E rs3787016 polymorphism in prostate cancer, while our meta-analysis covered all types of cancers and investigated POLR2E rs3787016 polymorphism in these cancers. Therefore, the current meta-analysis on POLR2E rs3787016 polymorphism in cancer would be the most comprehensive investigation on the evaluation of POLR2E rs3787016 polymorphism and the risk of cancer.

2. Methods

2.1. Literature Search

Our team performed an extensive literature review using the Scopus, Web of Science, and PubMed electronic databases to retrieve papers of interest published up to March 2019. The search keywords were “POLR2E” and “rs3787016 or variation or mutation or polymorphism” and “cancer or tumor or carcinoma or neoplasms”. We considered studies eligible if they examined the relationship between POLR2E rs3787016 and cancer risk.

2.2. Inclusion and Exclusion Criteria

We applied similar methods as used in our previous investigations to identify the relevant literature for the current meta-analysis (29). Briefly, eligible articles were incorporated in this meta-analysis if they met the following criteria: a) Evaluation of the relationship between POLR2E rs3787016 polymorphism and susceptibility to cancer, b) Appropriate data for estimating the odds ratios (ORs) and 95% confidence intervals (CIs), and c) Sufficient data representing the genotype and allele frequency of cases and controls. Accordingly, studies with the following criteria were excluded: a) Duplicate publications and overlapping data, b) Reviews, conference papers, case reports, letters, and case-only studies, and c) Inadequate information for data extraction.

2.3. Data Extraction

Two of our investigators independently and blindly extracted the following information from each eligible study: The first author's name, publication year, country of origin, the ethnicity of the study population, genotyping methods, total number of cases and controls, distributions of genotypes and alleles in cases and controls, and p-value of the Hardy-Weinberg Equilibrium (HWE) (Table 1).

2.4. Statistical Analysis

The χ^2 test was performed to assess whether the genotype distribution in the controls was in the HWE. The strength of the association between the presence of POLR2E rs3787016 polymorphism and cancer risk was evaluated by calculating pooled ORs and corresponding 95% CIs in six genetic models. The significance of the pooled ORs was assessed by the Z-test. The results with a P value < 0.05 were considered statistically significant.

The heterogeneity among studies was determined by the χ^2 test-based Q statistics. A P_Q value less than 0.10 indicated the presence of inter-study heterogeneity, in which the random-effects model was used to determine the ORs. Otherwise, the fixed-effects model was applied.

Publication bias was evaluated using Begg's funnel plots and Egger's tests. Sensitivity analysis was performed by sequentially eliminating one single study at a time to examine its effect on the pooled ORs. All statistical analyses were conducted using STATA 14.1 software.

3. Results

A flow diagram of the literature selection procedure is illustrated in Figure 1. Ultimately, a total of 11 case-control studies from nine articles (20-28), comprising 8,761 cancer cases and 10,534 controls, were subject to the pooled analysis. The main characteristics of eligible studies are presented in Table 1.

3.1. Quantitative Data Analysis

We examined the association between the POLR2E rs3787016 polymorphism and the risk of cancer through a meta-analysis of the overall population (Table 2). Our findings revealed that the rs3787016 polymorphism significantly increased the risk of cancer in homozygous (OR = 1.32, 95% CI = 1.11-1.57, $P = 0.002$, TT vs. CC), recessive (OR = 1.21, 95% CI = 1.06-1.39, $P = 0.005$, TT vs. CT + CC), and allele (OR = 1.12, 95% CI = 1.02-1.22, $P = 0.021$, T vs. C) genetic models (Figure 2).

Subgroup analysis based on cancer type showed that the polymorphism was associated with the risk of PCa (OR = 1.16, 95% CI = 1.07-1.25, $P = 0.000$, CT vs. CC; OR = 1.38, 95% CI = 1.20 - 1.59, $P = 0.000$, TT vs. CC; OR = 1.19, 95% CI = 1.11-1.28, CT + TT vs. CC), and breast cancer (OR = 1.64, 95% CI = 1.25-2.16, $P = 0.000$, TT vs. CC; OR = 1.40, 95% CI = 1.14 - 1.72, $P = 0.001$, TT vs. CT + CC; OR = 1.25, 95% CI = 1.10 - 1.43, $P = 0.001$, T vs. C) (Table 3). In addition, stratified analysis by ethnicity (Table 3) revealed that rs3787016 was associated with increased cancer risk particularly in Asian (OR = 1.31,

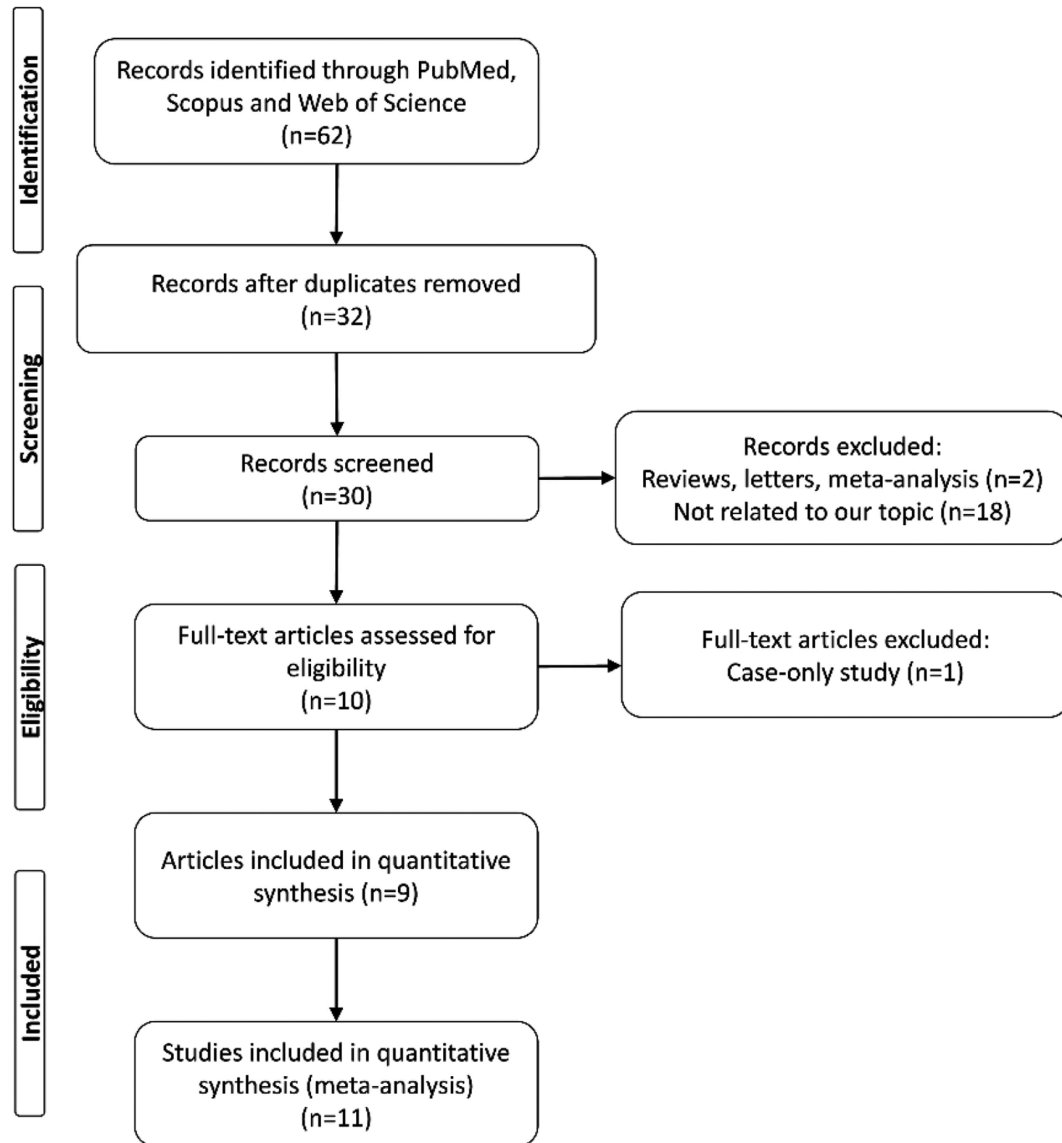


Figure 1. Flowchart of the study selection procedure

95% CI = 1.05-1.63, $P = 0.019$, TT vs. CC; OR = 1.20, 95% CI = 1.02-1.41, $P = 0.031$, TT vs. CT + CC) and Caucasian (OR = 1.38, 95% CI = 1.17-1.64, $P = 0.000$, TT vs. CC; OR = 1.30, 95% CI = 1.10-1.53, $P = 0.002$, TT vs. CT + CC; OR = 1.25, 95% CI = 1.10 - 1.43, $P = 0.001$, T vs. C) populations.

3.2. Heterogeneity and Publication Bias

As shown in Table 2, inter-study heterogeneity was detected in all genetic models; therefore, the random-effects model was applied for pooled analysis. In the meta-

analysis of the overall population, the Begg's funnel plot and Egger's tests did not indicate the presence of publication bias (Figure 3 and Table 2).

3.3. Sensitivity Analysis

We did not find any significant changes in the pooled OR and corresponding 95% CI in the homozygous and recessive genetic models (Figure 4) when individual study results were sequentially omitted, verifying the stability and reliability of the pooled results.

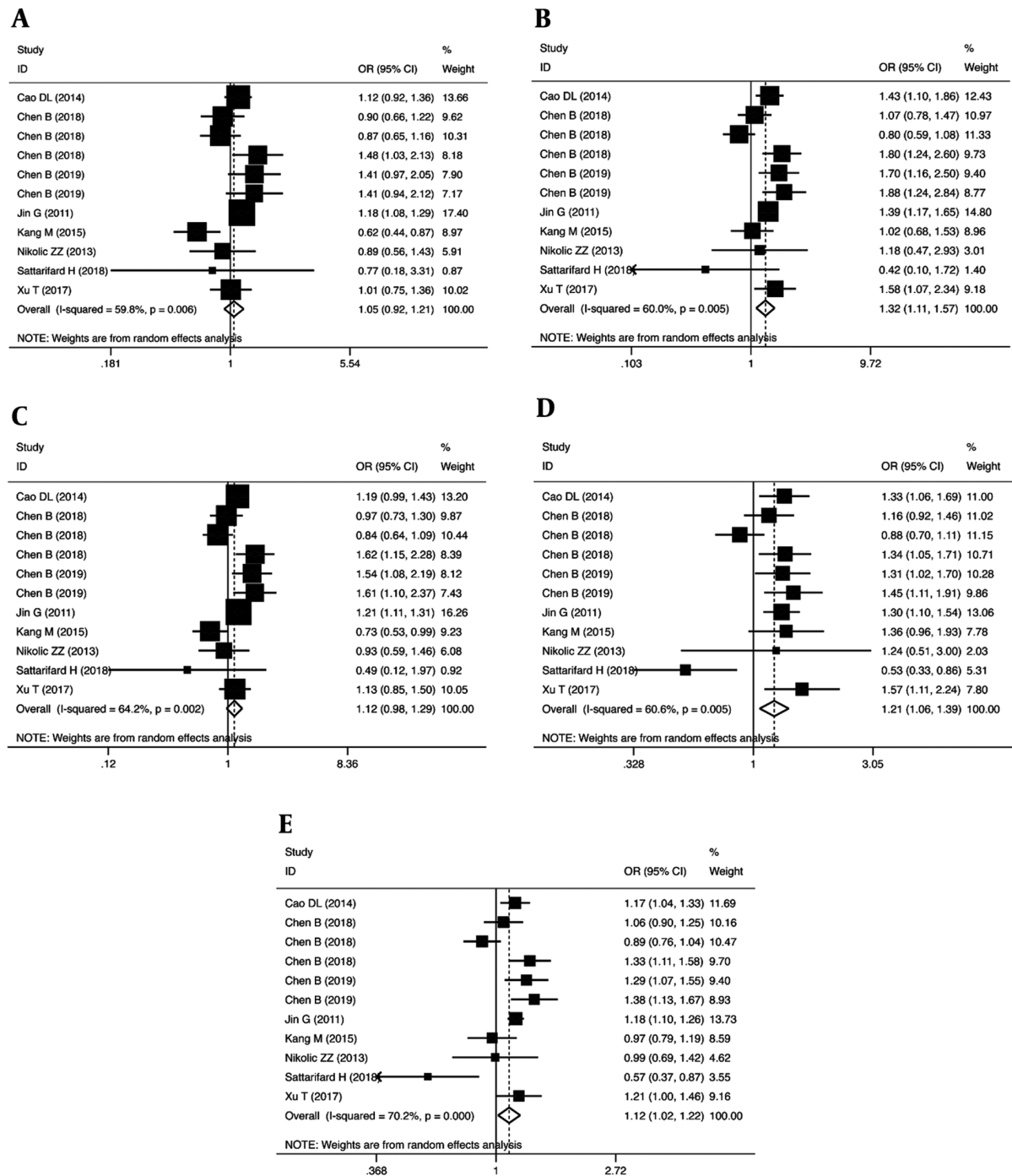


Figure 2. Forest plot representing the association between the rs3787016 polymorphism and overall cancer risk in heterozygous (A), homozygous (B), dominant (C), recessive (D), and allele (E) genetic models.

Table 1. Characteristics of All Studies Included in the Meta-analysis (*POLR2E* 3787016)

Author	Year	Country	Ethnicity	Cancer Type	Source of Control	Genotyping Method	Case/Control	Cases					Controls					HWE (P)
								CC	CT	TT	C	T	CC	CT	TT	C	T	
Cao DL (21)	2014	China	Asian	Prostate cancer	PB	PCR-RFLP	1015/1032	313	513	189	1139	891	357	524	151	1238	826	0.064
Chen B (25)	2018	China	Asian	Liver cancer	HB	PCR-RFLP	480/800	92	200	188	384	576	150	364	286	664	936	0.075
Chen B (25)	2018	China	Asian	Lung cancer	HB	PCR-RFLP	550/800	119	250	181	488	612	150	364	286	664	936	0.075
Chen B (26)	2018	China	Asian	Thyroid cancer	HB	PCR-RFLP	409/800	51	183	175	285	533	150	364	286	664	936	0.075
Chen B (28)	2019	China	Asian	Breast Cancer	HB	PCR-RFLP	480/588	60	218	202	338	622	90	232	178	412	588	0.287
Chen B (28)	2019	China	Asian	Cervical cancer	HB	PCR-RFLP	348/588	46	167	171	259	509	90	232	178	412	588	0.287
Jin G (20)	2011	USA	Caucasian	Prostate cancer	PB	TaqMan assay	4196/5007	2261	1638	297	6160	2232	2930	1800	277	7660	2354	0.997
Kang M (23)	2015	China	Asian	Esophageal cancer	HB	PCR-RFLP	369/370	130	149	90	409	329	105	194	71	404	336	0.268
Nikolic ZZ (22)	2013	Serbia	Caucasian	Prostate cancer	HB	TaqMan assay	261/106	140	100	21	380	142	55	44	7	154	58	0.544
Sattarifard H (24)	2018	Iran	Asian	Prostate cancer	HB	PCR-RFLP	178/180	6	51	121	63	293	3	33	144	39	321	0.468
Xu T (27)	2017	China	Asian	Breast cancer	PB	MassARRAY	439/439	137	209	93	483	395	149	226	64	524	354	0.144

Table 2. The Pooled Odds Ratios and 95% Confidence Intervals for the Association Between *POLR2E* Polymorphism and Cancer Susceptibility

Genetic Model	Test Of Association			Heterogeneity (I^2 (%), P)			Publication Bias Tests	
	OR (95%CI)	Z	P	χ^2	I^2 (%)	P	Egger's Test P	Begg's Test P
CT vs. CC	1.05 (0.92 - 1.21)	0.72	0.474	24.89	59.8	0.006	0.291	0.697
TT vs. CC	1.32 (1.11 - 1.57)	3.09	0.002	24.99	60.0	0.005	0.640	0.938
CT + TT vs. CC	1.12 (0.98 - 1.29)	1.63	0.104	27.96	64.2	0.002	0.438	0.935
TT vs. CT + CC	1.21 (1.06 - 1.39)	2.82	0.005	25.36	60.6	0.005	0.570	0.938
T vs. C	1.12 (1.02 - 1.22)	2.30	0.021	33.53	70.2	0.000	0.265	0.586

4. Discussion

lncRNAs, a novel class of RNAs, have recently become a hot topic of attention due to their fundamental functions, which might be related to their oncogenic and/or tumor-suppressive activities (30, 31) in cellular and molecular mechanisms that drive cancer (18). lncRNAs interact with biological macromolecules (DNA, RNA, and protein) to partake in diverse regulatory activities, such as chromatin remodeling, RNA splicing, and editing (32, 33), as well as the regulation of gene expression at the epigenetic and post-transcription levels (34-36). Genome-wide Association Studies (GWAS) have revealed that lncRNAs have an important role in cancer initiation and progression (37, 38). The expression and function of lncRNAs could be affected by genetic variations in the lncRNAs gene. In this regard, numerous investigations have examined the re-

lationship between the *POLR2E* rs3787016 polymorphism and various cancers, including squamous cell carcinoma (ESCC) (23), prostate (20-22, 24), thyroid (26), breast (27, 28), cervical (28), liver, and lung cancer (25). In the current study, we conducted a meta-analysis to address the precise role of *POLR2E* rs3787016 in overall cancer susceptibility. The pooled analysis of 11 eligible studies encompassing 8,761 cancer cases and 10,534 controls revealed that the rs3787016 polymorphism of the *POLR2E* gene significantly increased the risk of overall cancer in homozygous, recessive, and allele genetic models. Further stratified analyses indicated that this variant was particularly associated with the risk of prostate and breast cancer and increased overall cancer susceptibility in Asian and Caucasian populations. In line with our findings, a previous meta-analysis of four studies (comprising 5,841 cases and 6,702 controls) pro-

Table 3. Stratified Analysis of Variants on Susceptibility to Cancer

Genetic Model	No.	Test of Association			Heterogeneity Test		
		OR (95%CI)	Z	P	χ^2	I ² (%)	P
Cancer Type							
Prostate cancer	4						
CT vs. CC		1.16 (1.07 - 1.25)	3.71	0.000	1.77	0.0	0.622
TT vs. CC		1.38 (1.20 - 1.59)	4.44	0.000	2.93	0.0	0.402
CT+TT vs. CC		1.19 (1.11 - 1.28)	4.64	0.000	2.81	0.0	0.423
TT vs. CT + CC		1.07 (0.77 - 1.51)	0.41	0.678	12.56	76.1	0.006
T vs. C		1.05 (0.89 - 1.25)	0.58	0.562	11.75	74.5	0.008
Breast cancer	2						
CT vs. CC		1.17 (0.84 - 1.62)	0.92	0.356	1.90	47.4	0.168
TT vs. CC		1.64 (1.25 - 2.16)	3.53	0.000	0.07	0.0	0.791
CT + TT vs. CC		1.29 (0.96 - 1.74)	1.70	0.089	1.74	42.7	0.187
TT vs. CT + CC		1.40 (1.14 - 1.72)	3.18	0.001	0.66	0.0	0.415
T vs. C		1.25 (1.10 - 1.43)	3.33	0.001	0.22	0.0	0.638
Ethnicity							
Asian	9						
CT vs. CC		1.04 (0.87 - 1.25)	0.43	0.670	20.56	61.1	0.008
TT vs. CC		1.31 (1.05 - 1.63)	2.35	0.019	24.51	67.4	0.002
CT + TT vs. CC		1.12 (0.93 - 1.36)	1.19	0.234	25.51	68.6	0.001
TT vs. CT + CC		1.20 (1.02 - 1.41)	2.16	0.031	24.81	67.8	0.002
T vs. C		1.11 (0.98 - 1.25)	1.62	0.106	31.87	74.9	0.000
Caucasian	2						
CT vs. CC		1.13 (0.94 - 1.37)	1.32	0.186	1.29	22.5	0.256
TT vs. CC		1.38 (1.17 - 1.64)	3.73	0.000	0.12	0.0	0.728
CT + TT vs. CC		1.17 (1.00 - 1.38)	1.91	0.056	1.22	17.9	0.270
TT vs. CT + CC		1.30 (1.10 - 1.53)	3.08	0.002	0.01	0.0	0.914
T vs. C		1.25 (1.10 - 1.43)	3.33	0.001	0.22	0.0	0.638

posed an association between rs3787016 polymorphism and cancer susceptibility(39), whereas another seven studies (including 7,310 cases 8,554 controls) revealed a correlation with overall cancer risk (25). The statistical power of our meta-analysis is higher than that of previously published meta-analyses due to the inclusion of a larger sample size.

Our current investigation has several weaknesses that should be considered: 1) Heterogeneity existed between studies, which may be the result of differences in cancer type and/or ethnic background, 2) The number of studies used for stratified analyses was relatively small (four studies for prostate cancer, two studies for breast cancer, and two studies for Caucasian population), rendering limited

statistical power, and 3) Only one SNP in the *POLR2E* gene was analyzed. Due to these limitations, the findings should be interpreted with caution.

In conclusion, our meta-analysis suggests that the rs3787016 polymorphism of *POLR2E* is associated with increased cancer susceptibility. Well-designed, large-scale, case-control studies are warranted to further verify and validate our results.

Footnotes

Authors' Contribution: Mohsen Taheri: literature research, data extraction, data analysis, manuscript editing and approval of final version. Saeid Ghavami: literature research, data extraction, data analysis, manuscript editing

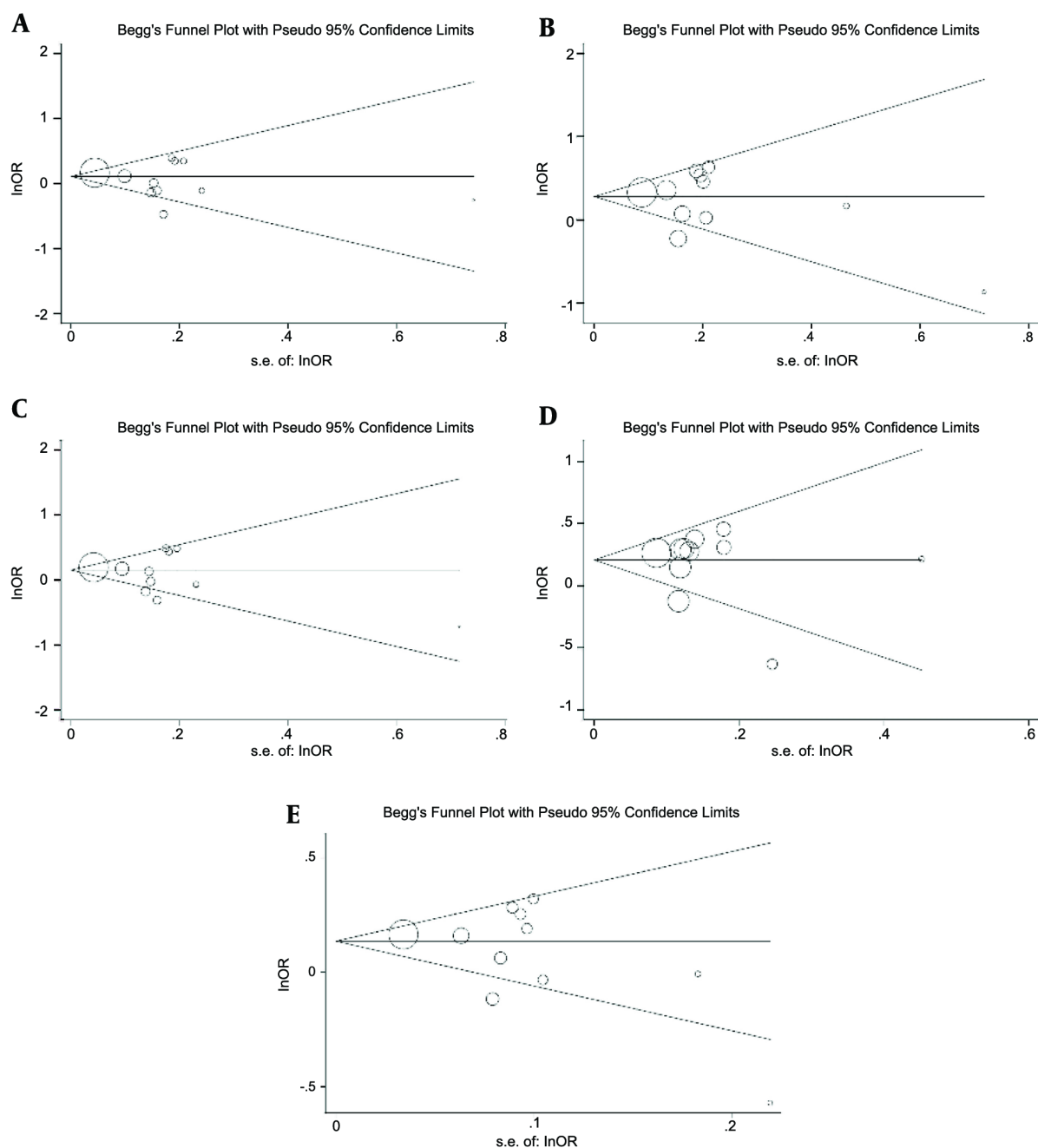


Figure 3. Begg's funnel plot testing publication bias for the association between the rs3787016 polymorphism and overall cancer risk assessed in heterozygous (A), homozygous (B), dominant (C), recessive (D), and allele (E) genetic models.

and approval of final version. Mohammad Hashemi: study concepts, study screening, statistical analysis, manuscript drafting.

Conflict of Interests: The authors declare that they have no conflict of interest.

Ethical Approval: Ethical approval was not required in this study.

Funding/Support: The authors confirm that the project was not supported by any funding agency and operating grants.

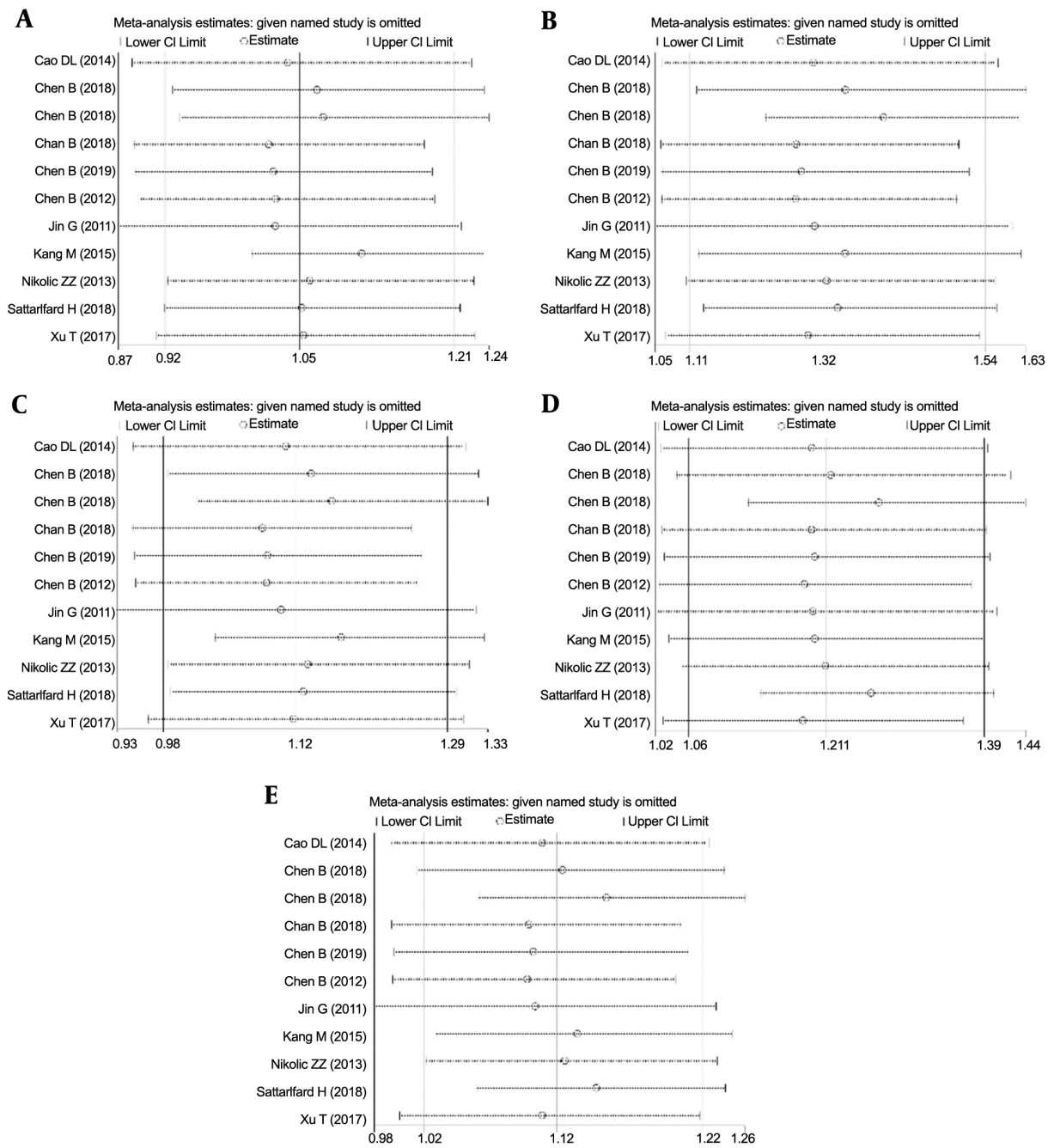


Figure 4. Sensitivity analyses for studies on the association of rs3787016 polymorphism with cancer risk determined in heterozygous (A), homozygous (B), dominant (C), recessive (D), and allele (E) genetic models.

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