Meta-analysis of the association between long non-coding RNA maternally expressed gene 3 polymorphisms and cancer susceptibility

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Abstract. The long non-coding RNA (lncRNA) maternally expressed gene 3 (MEG3) polymorphism is associated with cancer risk, however, the results have been inconsistent. Therefore, the present meta-analysis aimed to explore the associations between MEG3 polymorphisms and cancer risk. Online databases were searched and reviewed up to December 2024 for eligible studies. Odds ratios (ORs) and corresponding 95% CIs were calculated to assess the underlying association with genetic models. Furthermore, heterogeneity tests, sensitivity and accumulative analysis and publication bias assessment were conducted to evaluate the robustness of the results. There were 24 publications comprising 45 independent case-control studies included in the present meta-analysis. The pooled results revealed a markedly increased cancer risk with the A allele of the MEG3 rs7158663 G>A variant [for example, GA + AA vs. GG (OR, 1.34; 95% CI, 1.14-1.56; P<0.01; I^2=78.8%)] and consistent findings across several subgroups such as in in both Hardy-Weinberg Equilibrium (HWE-yes and HWE-no groups, and both in East Asian and Middle Eastern individuals. Furthermore, a notable association was observed between rs11160608 A>C and cancer risk [for example, AC + CC vs. AA (OR, 1.16; 95% CI, 1.01-1.33; P=0.04; I^2=2.7%)], particularly in East Asian populations. No notable associations were identified for other polymorphic loci and cancer risk. In summary, the present meta-analysis suggested that the MEG3 rs7158663 G>A polymorphism may be a risk factor for cancer development.

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Introduction

Cancer ranks as one of the leading causes of death worldwide, following cardiovascular and cerebrovascular disease (1). In 2022, there were >20 million novel cancer cases and 9.7 million cancer-associated deaths were reported worldwide (2), accounting for nearly 16.8% of all global deaths and 22.8% of fatalities from non-communicable disease (2), driven by population aging and global development imbalances. Various factors, including environmental pollution, viral infection, obesity, genetic variation and unhealthy lifestyles, are implicated in cancer development (3-6). However, the specific pathogens and mechanisms remain to be elucidated.

Gene mutation, aberrant expression and epigenetic modifications can disrupt normal biological functions, which leads to tumorigenesis. Long non-coding RNAs (lncRNAs) are a type of non-protein-coding RNA that include >200 nucleotides. lncRNAs regulate gene expression at transcriptional, epigenetic and post-transcriptional levels, and are involved in key processes such as chromosomal silencing, genomic imprinting, transcriptional interference and intranuclear transport (7). Aberrant lncRNA expression is observed in various cancer types, such as oral cancer, lung cancer and gastric cancer, which not only reflect clinical aspects but also predict prognosis in patients with malignant disease. The maternally expressed gene 3 (MEG3), a 32-kb imprinted gene located on chromosome 14q32.3, encodes lncRNA MEG3 expression in diverse tissues, such as cancerous tissues, normal tissues, and blood (8). It was reported as the ortholog of gene trap locus 2 in mice by Schuster-Gossler *et al* (9) and identified in humans in 2000 (10). To date, numerous studies have demonstrated that MEG3 serves as a tumor suppressor and is involved in cancer-associated processes such as cell proliferation, differentiation, metastasis, immune response, metabolism and apoptosis, which serve an important role in tumor initiation and progression (11-13). MEG3 is a key component of the p53 and mouse double minute 2 (MDM2) signaling pathways,

where it inhibits carcinogenesis by increasing p53 expression (14). MEG3 expression is typically reduced or absent in a variety of cancer types, including acute myeloid leukemia (15), serous ovarian cancer (16) and head and neck cancer (17), which suggests MEG3 may serve as a tumor suppressor and target for cancer prevention and treatment.

Genetic alterations, such as single nucleotide polymorphisms (SNPs), serve a key role in cancer susceptibility. In lncRNAs, SNPs lead to aberrant transcript splicing and structural changes, which impairs lncRNA function. Cao *et al* (18) reported that individuals with the AA genotype in the MEG3 rs7158663 G>A polymorphism have a markedly higher risk of colorectal cancer compared with those with the GG genotype. Since then, several case-control studies have examined the association between MEG3 polymorphisms and cancer risk, although the results remain inconclusive (19,20). Therefore, the present meta-analysis aimed to clarify the potential associations between MEG3 polymorphisms and cancer risk.

Materials and methods

Study design. The present meta-analysis was conducted in accordance with the guidelines of PRISMA (21). All data were extracted from previously published studies and no ethical concerns were involved.

Literature search strategy. A total of five online databases (PubMed (pubmed.ncbi.nlm.nih.gov/?Db=pubmed), Excerpta Medica Database (embase.com/landing?status=grey), Web of Science (https://www.webofscience.com/wos/), China National Knowledge Infrastructure (https://www.cnki.net/) and Wanfang (https://www.wanfangdata.com.cn/)) were mined for studies that examined the association between MEG3 gene polymorphisms and cancer susceptibility from inception up to December 2024. Additionally, the references of all included studies were reviewed to identify additional relevant studies (Table SI).

Eligibility criteria. Inclusion criteria were as follows: i) Observational studies focusing on MEG3 gene polymorphisms; ii) studies with sufficient genotype data on allele, homozygous and heterozygote for each polymorphism locus; iii) studies published in English or Chinese. The exclusion criteria were as follows: i) Case reports, letters and reviews; ii) duplicate reports or those with overlapping data; iii) studies lacking sufficient data to calculate odds ratios (ORs) and 95% CI and iv) fundamental studies and others using animal models or cell lines.

Data extraction. Two authors reviewed all included studies and extracted the following data: Surname of first author, publication year, country or region of study, ethnicity differences, control group origin, sample sizes of patients and controls, frequency of genotype distribution and genotyping method. Disagreements were resolved through discussion with a third author.

Quality assessment. A total of two authors evaluated the quality of all included studies with a modified version of the Newcastle-Ottawa Quality Assessment Scale (NOS; Table SII) (22). The NOS evaluates six key aspects: Case representativeness, control source, Hardy-Weinberg equilibrium (HWE) status in controls, genotyping procedure, sample size and the assessment of the association. Studies were scored on a scale of 0 to 11, with a score ≥8 indicating high quality.

Statistical analysis. Crude OR and 95% CIs were calculated to evaluate the statistical strength of the associations between MEG3 polymorphisms and cancer risk. A total of five genetic models were examined for the rs7158663 G>A polymorphism: Allele contrast (A vs. G), codominant models including heterozygote model (GA vs. GG) and homozygote model (AA vs. GG), dominant model (AG + AA vs. GG) and recessive model (AA vs. GG + GA). Similar genetic models were applied to other loci (rs4081134 G>A, rs11160608 A>C, rs3087918 T>G, rs3783355 G>A, rs2281511 G>A and rs12431658 T>C). Potential heterogeneity between the included studies was assessed using the Cochran's χ^2-based test (23). According to the recommendations of Cochrane Handbook for Systematic Reviews of Interventions, a random-effects model (DerSimonian and Laird method) was used to guarantee the statistical power (24,25). Subgroup analyses based on ethnicity, source of controls, genotyping method and cancer subtypes were conducted when there were multiple studies on the same theme. Cumulative analyses were conducted to observe the trends in results when more studies were added. Sensitivity analyses were conducted to assess the robustness of the pooled results through gradual exclusion of studies. Publication bias was evaluated with Egger's bias test and Begg's funnel plots (26). All statistical analyses were conducted using STATA (version 14.0; StataCorp LP). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Overall results. A total of 458 potential publications were identified through a comprehensive search (Fig. 1). First, 78 duplicate articles were excluded, 343 irrelevant articles were removed after title and abstract screening and 13 articles were removed for reasons such as reviews, fundamental research or lacking sufficient genotype data. In total, 24 publications comprising 45 independent case-control studies with 7,423 patients and 9,118 controls were included in (18-20,27-47). Of these, 16 studies were conducted in East Asia (based solely on a Chinese population) and eight were conducted in the Middle East (Egypt and Iran; Table I). There were 21 studies that focused on rs7158663 G>A polymorphism (18-20,27-38,41-46); seven studies focused on rs4081134 G>A polymorphism (19,20,27,28,38-40), six focused on s11160608 A>C polymorphism (30,33,38-40,47), three focused on rs3087918 T>G polymorphism (30,33,38) and two each focused on rs3783355 G>A (39,40), rs2281511 G>A (39,40), rs12431658 T>C (39,40) and rs10132552 T>C (32,42) polymorphisms, respectively. A total of five case-control studies exhibited deviation from HWE across multiple loci (Table I).

rs7158663 G>A polymorphism and cancer risk. In total, 21 case-control studies involving 6,502 patients and 7,649 controls were included to investigate the association between

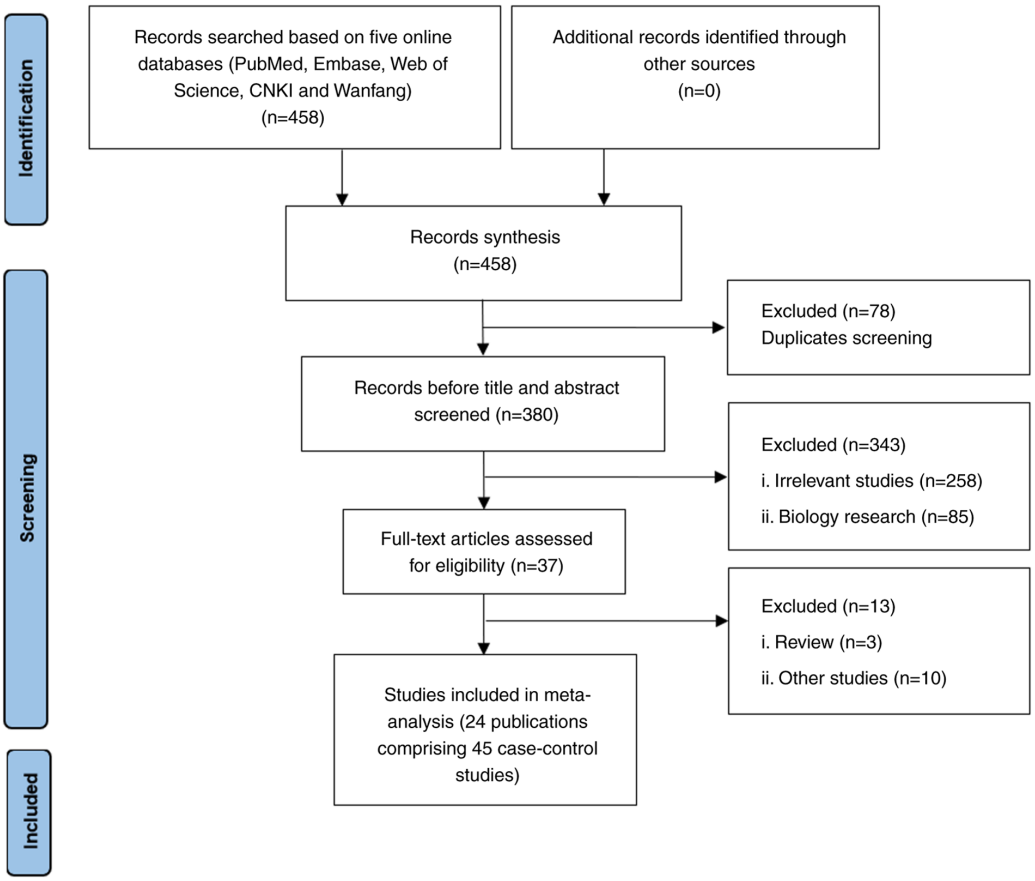


Figure 1. Flow diagram of the study selection process.

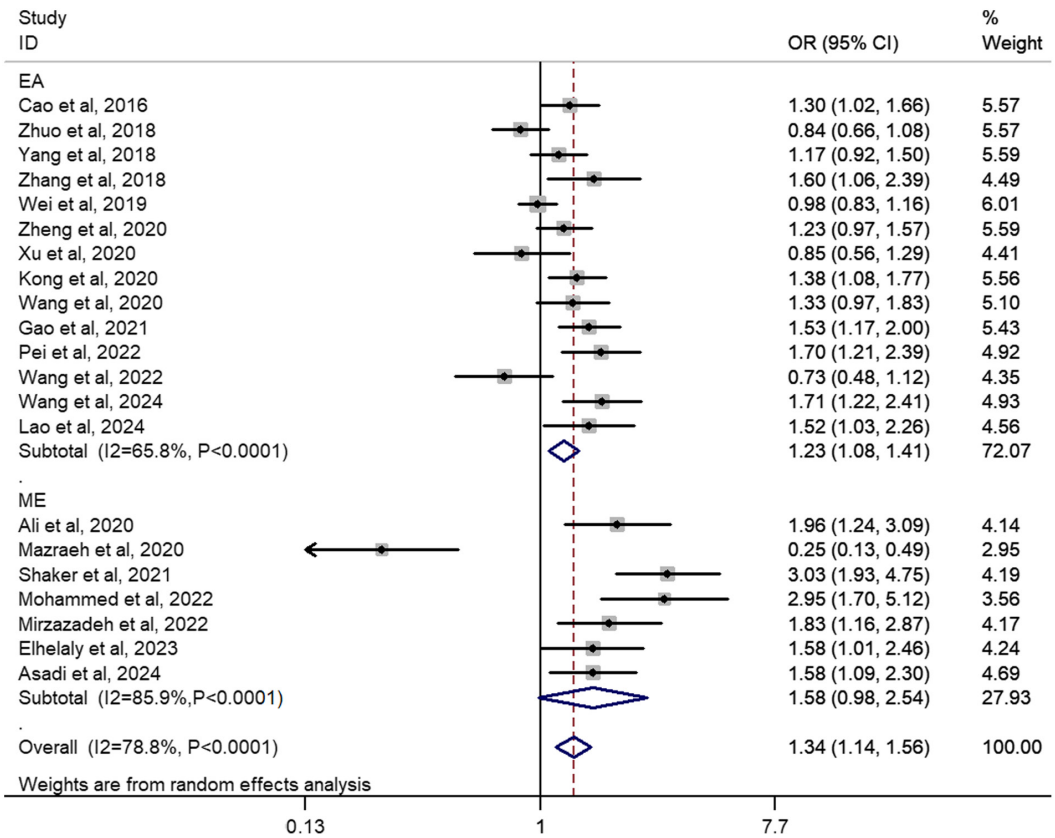


Figure 2. OR and 95% CI of the associations between MEG3 rs7158663 G>A polymorphism and cancer susceptibility in GA + AA vs. GG model. OR, odds ratio; MEG3, maternally expressed gene 3; EA, East Asia; ME, Middle East.

Table I. Characteristics of studies on MEG3 polymorphisms and cancer risk.

A, rs7158663 G>A

First author, year	Country	Ethnicity	Source of controls	Case, n	Control, n	Genotype distribution						Genotyping method	Cancer	P-value for HWE	NOS	(Refs.)
						Case (%)			Control (%)							
						GG	GA	AA	GG	GA	AA					
Cao *et al*, 2016	China	EA	HB	516	517	264 (51)	200 (39)	52 (10)	298 (58)	188 (36)	31 (6)	TaqMan™	Colorectal cancer	0.85	9	(18)
Zhuo *et al*, 2018	China	EA	HB	392	783	233 (59)	141 (36)	18 (5)	433 (55)	296 (38)	54 (7)	TaqMan	Neuro-blastoma	0.72	9	(19)
Yang *et al*, 2018	China	EA	HB	526	526	268 (51)	219 (42)	39 (7)	289 (55)	204 (39)	33 (6)	TaqMan	Lung cancer	0.71	9	(20)
Zhang *et al*, 2018	China	EA	HB	172	224	83 (48)	74 (43)	15 (9)	128 (57)	76 (34)	10 (4)	TaqMan	Gastric cancer	0.76	7	(27)
Wei *et al*, 2019	China	EA	PB	1,118	1,248	717 (64)	349 (31)	51 (5)	795 (64)	391 (31)	62 (5)	TaqMan	Liver cancer	0.13	9	(28)
Ali *et al*, 2020	Egypt	ME	HB	150	154	57 (38)	63 (42)	30 (20)	84 (55)	63 (41)	7 (5)	TaqMan	Breast cancer	0.26	7	(29)
Zheng *et al*, 2020	China	EA	PB	434	700	224 (52)	170 (39)	33 (8)	403 (58)	250 (36)	47 (7)	Mass-ARRAY®	Breast cancer	0.33	9	(30)
Xu *et al*, 2020	China	EA	HB	165	200	98 (59)	54 (33)	13 (8)	111 (56)	78 (39)	11 (6)	TaqMan	Prostate cancer	0.57	9	(31)
Kong *et al*, 2020	China	EA	HB	474	543	215 (45)	198 (42)	61 (13)	290 (53)	203 (37%)	50 ( )	TaqMan	Gastric cancer	0.10	9	(32)
Mazraeh *et al*, 2020	Iran	ME	HB	100	100	43 (43)	36 (36)	21 (21)	16 (16)	48 (48)	36 (36)	PCR-RFLP	Leukemia	1.00	6	(33)
Wang *et al*, 2020	China	EA	HB	319	306	163 (51)	121 (38)	35 (11)	178 (58)	110 (36)	18 (6)	PCR-RFLP	Lymphoma	0.85	8	(34)
Gao *et al*, 2021	China	EA	HB	430	445	202 (47)	185 (43)	43 (10)	256 (58)	159 (36)	30 (7)	TaqMan	Colorectal cancer	0.43	8	(35)
Shaker *et al*, 2021	Egypt	ME	HB	180	150	63 (35)	70 (39)	47 (26)	93 (62)	24 (16)	33 (22)	TaqMan	Breast cancer	<0.01	6	(36)

Table I. Continued.

A, rs7158663 G>A

First author, year	Country	Ethnicity	Source of controls	Case, n	Control, n	Genotype distribution						Genotyping method	Cancer	P-value for HWE	NOS	(Refs.)
						Case (%)			Control (%)							
						GG	GA	AA	GG	GA	AA					
Mohammed *et al*, 2022	Egypt	ME	HB	114	110	33 (29)	54 (47)	27 (24)	60 (55)	45 (41)	5 (5)	TaqMan	Hepatocellular cancer	0.34	7	(37)
Pei *et al*, 2022	China	EA	HB	266	266	118 (44)	119 (45)	29 (11)	153 (58)	96 (36)	17 (6)	TaqMan	Leukemia	0.71	10	(38)
Mirzazadeh *et al*, 2022	Iran	ME	HB	175	175	46 (26)	111 (63)	18 (10)	69 (39)	95 (54)	11 (6)	PCR Tetra-ARMS	Lymphoma	0.04	7	(41)
Wang *et al*, 2022	China	EA	HB	118	345	72 (61)	39 (33)	7 (6)	184 (53)	135 (39)	26 (8)	TaqMan	Cervical cancer	0.86	6	(42)
Elhelaly *et al*, 2023	Egypt	ME	HB	160	160	78 (49)	50 (31)	32 (20)	96 (60)	56 (35)	8 (5)	TaqMan	Colorectal cancer	0.96	7	(43)
Asadi *et al*, 2024	Iran	ME	HB	230	240	75 (33)	132 (57)	23 (10)	104 (43)	127 (53)	9 (4)	PCR-Tetra ARMS	Breast cancer	<0.01	7	(44)
Wang *et al*, 2024	China	EA	PB	271	267	120 (44)	123 (45)	28 (10)	154 (58)	96 (36)	17 (6)	PCR-sequencer	Hepatocellular cancer	0.60	8	(45)
Lao *et al*, 2024	China	EA	HB	200	200	87 (44)	76 (38)	37 (19)	108 (54)	71 (36)	21 (11)	TaqMan	Nasopharyngeal cancer	0.08	7	(46)

B, rs4081134G>A

Zhuo *et al*, 2018	China	EA	HB	392	783	200 (51)	165 (42)	27 (7)	443 (57)	294 (38)	46 (6)	TaqMan	Neuroblastoma	0.76	9	(19)
Yang *et al*, 2018	China	EA	HB	526	526	349 (66)	161 (31)	16 (3)	314 (60)	182 (35)	30 (6)	TaqMan	Lung cancer	0.59	9	(20)
Hou *et al*, 2018	China	EA	HB	444	984	243 (55)	169 (38)	16 (4)	598 (61)	332 (34)	54 (5)	Illumina®	Oral cancer	0.38	7	(39)
Zhang *et al*, 2018	China	EA	HB	172	224	102 (59)	58 (34)	12 (7)	135 (60)	73 (33)	16 (7)	TaqMan	Gastric cancer	0.17	7	(27)

Table I. Continued.

First author, year	Country	Ethnicity	Source of controls	Case, n	Control, n	Genotype distribution: Case (%) GG	GA	AA	Control (%) GG	GA	AA	Genotyping method	Cancer	P-value for HWE	NOS	(Refs.)
B, rs4081134G>A																
Yunho *et al*, 2019	China	EA	HB	98	86	47 (48)	35 (36)	16 (16)	39 (45)	33 (38)	14 (16)	PCR-RFLP	Oral cancer	0.13	8	(40)
Wei *et al*, 2019	China	EA	HB	1,118	1,248	533 (48)	461 (41)	120 (11)	604 (48)	537 (43)	103 (8)	TaqMan	Liver cancer	0.28	9	(28)
Pei *et al*, 2022	China	EA	HB	266	266	141 (53)	107 (40)	18 (7)	149 (56)	101 (38)	16 (6)	TaqMan	Leukemia	0.84	10	(38)
C. rs11160608 A>C																
Hou *et al*, 2018	China	EA	HB	444	984	112 (25)	237 (53)	93 (21)	308 (31)	485 (49)	191 (19)	Illumina	Oral cancer	1.00	7	(39)
Yunho *et al*, 2019	China	EA	HB	98	86	55 (56)	30 (31)	13 (13)	44 (51)	28 (33)	14 (16)	PCR-RFLP	Oral cancer	0.02	8	(40)
Zheng *et al*, 2020	China	EA	PB	434	700	126 (29)	218 (50)	80 (18)	227 (32)	341 (49)	132 (19)	Mass-ARRAY	Breast cancer	0.84	9	(30)
Mazraeh *et al*, 2020	Iran	ME	HeB	100	100	28 (28)	58 (58)	14 (14)	39 (39)	48 (48)	13 (13)	ARMS-PCR	Leukemia	0.77	6	(33)
Pei *et al*, 2022	China	EA	HB	266	266	80 (30)	137 (52)	49 (18)	85 (32)	131 (49)	50 (19)	TaqMan	Leukemia	0.97	10	(38)
Abdi *et al*, 2024	Iran	ME	HB	396	399	107 (27)	184 (46)	104 (26)	107 (27)	203 (51)	89 (22)	Illumina	Gastric cancer	0.70	7	(47)
D, rs3087918 T>G																
Zheng *et al*, 2020	China	EA	PB	434	700	171 (39)	207 (48)	47 (11)	259 (37)	334 (48)	107 (15)	Mass-ARRAY	Breast cancer	0.97	9	(30)
Mazraeh *et al*, 2020	Iran	ME	HB	100	100	52 (52)	36 (36)	12 (12)	41 (41)	52 (52)	7 (7)	PCR-RFLP	Leukemia	0.08	6	(33)
Pei *et al*, 2022	China	EA	HB	266	266	105 (39)	129 (48)	32 (12)	98 (37)	128 (48)	40 (15)	TaqMan	Leukemia	0.86	10	(38)

Table I. Continued.

First author, year	Country	Ethnicity	Source of controls	Case, n	Control, n	Genotype distribution: Case (%) GG	GA	AA	Control (%) GG	GA	AA	Genotyping method	Cancer	P-value for HWE	NOS	(Refs.)
E, rs3783355 G>A																
Hou *et al*, 2018	China	EA	HB	444	984	272 (61)	142 (32)	24 (5)	626 (64)	319 (32)	39 (4)	Illumina	Oral cancer	0.84	7	(39)
Yunho *et al*, 2019	China	EA	HB	98	86	51 (52)	29 (30)	18 (18)	47 (55)	22 (26)	17 (20)	PCR-RFLP	Oral cancer	<0.01	7	(40)
F, rs2281511 G>A																
Hou *et al*, 2018	China	EA	HB	444	984	299 (67)	134 (30)	11 (2)	673 (68)	269 (27)	42 (4)	Illumina	Oral cancer	0.03	7	(39)
Yunho *et al*, 2019	China	EA	HB	98	86	63 (64)	23 (23)	12 (12)	58 (67)	16 (19)	15 (17)	PCR-RFLP	Oral cancer	<0.01	8	(40)
G, rs12431658 T>C																
Hou *et al*, 2018	China	EA	HB	444	984	390 (88)	50 (11)	3 (1)	839 (85)	139 (14)	6 (1)	Illumina	Oral cancer	0.93	7	(39)
Yunho *et al*, 2019	China	EA	HB	98	86	74 (76)	19 (19)	5 (5)	67 (78)	16 (19)	3 (3%)	PCR-RFLP	Oral cancer	0.12	8	(40)
H. rs10132552 T>C																
Kong *et al*, 2020	China	EA	HB	474	543	239 (50)	207 (44)	28 (6)	278 (51)	219 (40)	46 (8)	TaqMan	Gastric cancer	0.76	9	(32)
Wang *et al*, 2022	China	EA	HB	118	345	82 (69)	32 (27)	4 (3)	187 (54)	142 (41)	16 (5)	TaqMan™	Cervical cancer	0.09	6	(42)

MEG3, maternally expressed gene 3; HWE, Hardy-Weinberg equilibrium; HB, hospital-based; PB, population-based; EA, East Asian; ME, Middle Eastern; Tetra-ARMS, tetra amplification-refractory mutation system; RFLP, restriction fragment length polymorphism; NOS, Newcastle-Ottawa Quality Assessment Scale.

Table II. ORs and 95% CIs of MEG3 polymorphisms and cancer risk.

A, rs7158663 G>A

Characteristic	n	A vs. G				GA vs. GG				AA vs. GG				GA + AA vs. GG				AA vs. GG + GA			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	21	1.30	1.14-1.48	<0.01	82.3	1.26	1.09-1.45	<0.01	72.0	1.74	1.31-2.32	<0.01	77.3	1.34	1.14-1.56	<0.01	78.8	1.55	1.23-1.96	<0.01	67.9
HWE																					
Yes	18	1.26	1.09-1.45	<0.01	83.3	1.17	1.03-1.34	0.02	64.2	1.64	1.20-2.25	<0.01	79.2	1.25	1.07-1.47	0.01	77.3	1.53	1.18-1.98	<0.01	71.1
No	3	1.58	1.33-1.88	<0.01	14.2	2.15	1.17-3.95	0.01	80.4	2.46	1.65-3.68	<0.01	0	2.05	1.38-2.99	<0.01	59.5	1.64	1.13-2.38	0.03	32.2
Ethnicity																					
EA	14	1.21	1.08 1.35	<0.01	70.4	1.18	1.05-1.33	0.01	51.7	1.47	1.18-1.83	<0.01	53.1	1.23	1.08-1.41	<0.01	65.8	1.33	1.16-1.53	<0.01	34.7
ME	7	1.53	1.04-2.23	0.03	88.8	1.44	0.89-2.34	0.14	84.3	2.70	1.12-6.52	0.03	88.3	1.58	0.98-2.54	0.06	85.9	2.30	1.13-4.68	0.02	84.5
Genotyping method																					
TaqMan	15	1.35	1.16-1.58	<0.01	82.5	1.27	1.08-1.50	<0.01	71.5	1.84	1.35-2.52	<0.01	75.1	1.37	1.15-1.64	<0.01	78.4	1.49	1.29-1.71	<0.01	69.1
PCR series	5	1.16	0.80-1.58	0.44	87.6	1.16	0.75-1.79	0.52	81.3	1.54	0.62-3.81	0.35	87.1	1.18	0.73-1.91	0.51	86.0	1.43	1.07-1.91	0.02	75.5
Cancer type																					
Gastrointestinal tract	5	1.40	1.26-1.55	<0.01	0	1.32	1.15-1.51	<0.01	0	2.00	1.57-2.54	<0.01	29.6	1.43	1.25-1.63	<0.01	0	1.78	1.41-2.25	<0.01	43.1
Liver	3	1.55	0.90-2.6	0.11	92.6	1.45	0.90-2.33	0.13	82.3	2.44	0.75-7.93	0.14	89.9	1.63	0.89-2.97	0.11	89.9	1.96	0.74-5.17	0.17	85.9
Breast	4	1.59	1.20-2.09	<0.01	75.3	1.75	1.10-2.78	0.02	81.2	2.56	1.34-4.92	0.01	74.8	1.79	2.22-2.63	<0.01	76.9	1.99	1.06-3.74	0.03	75.4
Blood	4	1.09	0.67-1.76	0.73	90.4	1.06	0.60-1.88	0.84	85.5	1.27	0.44-3.69	0.66	88.9	1.07	0.57-2.01	0.84	89.2	1.29	0.65-2.57	0.46	77.4
Other	5	1.02	0.82-1.28	0.85	72.0	0.97	0.80-1.19	0.78	40.4	1.11	0.69-1.79	0.66	62.5	0.99	0.78-1.26	0.96	62.1	1.12	0.74-1.69	0.59	52.7

Table II. Continued.

B, rs4081134 G>A

Characteristic	n	A vs. G				GA vs. GG				AA vs. GG				GA + AA vs. GG				AA vs. GG + GA			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	7	1.02	0.91-1.15	0.70	47.7	1.04	0.94-1.15	0.44	35.5	0.99	0.74-1.32	0.93	44.6	1.04	0.91-1.19	0.57	41.6	0.97	0.74-1.29	0.86	43.6
Oral cancer	2	1.04	0.88-1.24	0.61	0	1.20	0.98-1.50	0.11	3.3	0.79	0.49-1.27	0.33	0	1.14	0.92-1.42	0.24	0	0.78	0.48-1.20	0.25	0

C, rs11160608 A>C

Characteristic	n	C vs. A				AC vs. AA				CC vs. AA				AC + CC vs. AA				CC vs. AA + AC			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	6	1.09	1.00-1.19	0.57	0	1.15	1.10-1.33	0.05	0	1.17	0.94-1.40	0.10	0	1.16	1.01-1.33	0.04	2.7	1.08	0.92-1.26	0.35	0
Ethnicity																					
EA	4	1.08	0.98-1.20	0.13		1.19	1.01-1.41	0.04	0	1.15	0.93-1.42	0.20	0	1.18	1.01-1.37	0.04	0	1.03	0.86-1.23	0.77	0
ME	2	1.12	0.93-1.33	0.23		1.17	0.64-2.12	0.61	66.5	1.22	0.85-1.74	0.28	0	1.19	0.74-1.94	0.47	55.1	1.22	0.90-1.65	0.19	0
Cancer type																					
Oral	2	1.05	0.77-1.43	0.76	50.0	1.26	0.99-1.61	0.07	36.5	1.24	0.91-1.68	0.17	37.4	1.13	0.71-1.79.79	0.61	57.1	1.07	0.82-1.39	0.68	0
Leukemia	2	1.09	0.89-1.35	0.40	0	1.25	0.90-1.74	0.18	0	1.13	0.73-1.75	0.57	0	1.22	0.90-1.67	0.20	24.3	1.11	0.68-1.47	1.00	0

Table II. Continued.

D, rs3087918 T>G

Characteristic	n	G vs. T				TG vs. TT				GG vs. TT				TG + GG vs. TT				GG vs. TT + TG			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	3	0.86	0.75-0.99	0.04	0	0.88	0.72-1.08	0.22	30.5	0.74	0.54-0.99	0.05	0	0.85	0.70-1.03	0.09	0	0.77	0.59-1.03	0.08	39.4

E, rs3783355 G>A

Characteristic	n	A vs. G				GA vs. GG				AA vs. GG				AG + AA vs. GG				AA vs. GG + GA			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	2	1.08	0.91-1.30	0.37	0	1.04	0.83-1.31	0.71	0	1.25	0.81-1.94	0.31	0	1.07	0.86-1.33	0.52	0	1.22	0.79-1.86	0.37	0

F, rs2281511 G>A

Characteristic	n	A vs. G				GA vs. GG				AA vs. GG				AG + AA vs. GG				AA vs. GG + GA			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	2	0.96	0.80-1.16	0.70	0	1.14	0.90-1.44	0.27	0	0.64	0.38-1.08	0.10	0	1.05	0.84-1.31	0.68	0	0.61	0.37-1.03	0.7	0

G, rs12431658 T>C

Characteristic	n	C vs. T				TC vs. TT				CC vs. TT				TG + GG vs. TT				GG vs. TT + TG			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	2	0.88	0.67-1.16	0.37	16.5	0.82	0.60-1.12	0.22	0	1.27	0.47-3.44	0.64	0	0.84	0.63-1.14	0.30	0	1.28	0.47-3.50	0.64	0

Table II. Continued.

H, rs10132552 T>C

Characteristic	n	C vs. T				TC vs. TT				CC vs. TT				TG + GG vs. TT				GG vs. TT TG			
		OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]	OR	95% CI	P-value	I^2, %[a]
Total	2	0.79	0.50-1.22	0.29	77.4	0.77	0.37-1.62	0.49	87.4	0.68	0.43-1.08	0.10	0	0.75	0.38-1.47	0.40	85.7	0.69	0.44-1.07	0.10	0

[a]Test for heterogeneity. OR, odds ratio; MEG3, maternally expressed gene 3; HWE, Hardy-Weinberg equilibrium; ME, Middle Eastern; EA, East Asian.

rs7158663 G>A polymorphism and cancer risk. A significant association was observed in the overall population of A vs. G (OR, 1.30; 95% CI, 1.14-1.48; P<0.01; I^2=82.3%), GA vs. GG (OR, 1.26; 95% CI, 1.09-1.45; P<0.01; I^2=72.0%) AA vs. GG (OR, 1.74; 95%CI, 1.31-2.32; P<0.01; I^2=77.3%), GA + AA vs. GG (OR, 1.34; 95% CI, 1.14-1.56; P<0.01; I^2=78.8%; Fig. 2) and AA vs. GG + GA (OR, 1.55; 95% CI, 1.23-1.96; P<0.01; I^2=67.9%; Table II). Subgroup analyses revealed significantly elevated cancer risk associated with the rs7158663 G>A polymorphism in both HWE-yes groups [A vs. G (OR, 1.26; 95% CI, 1.09-1.45; P<0.01; I^2=83.3%); GA vs. GG (OR, 1.17; 95% CI, 1.03-1.34; P=0.02; I^2=64.2%); AA vs. GG (OR, 1.64; 95% CI, 1.20-2.25; P<0.01; I^2=79.2%); AG + AA vs. GG (OR,1.25; 95% CI, 1.07-1.47; P=0.01; I^2=77.3%) and AA vs. GG + GA (OR, 1.53; 95% CI, 1.18-1.98; P<0.01; I^2=71.1%)] and HWE-no groups [A vs. G (OR, 1.58; 95% CI, 1.31-1.91; P<0.01; I^2=14.2%); GA vs. GG (OR, 2.15; 95% CI, 1.17-3.95; P=0.01; I^2=80.4%); AA vs. GG (OR, 2.46; 95% CI, 1.65-3.68; P<0.01; I^2=0%); AG + AA vs. GG (OR, 2.05; 95% CI, 1.38-2.99; P<0.01; I^2=59.5%) and AA vs. GG + GA (OR, 1.69; 95% CI, 1.05-2.72; P=0.03; I^2=32.2%)]. For ethnic diversity, the similar increased risks were observed across both East Asian and Middle Eastern individuals (Table II). Furthermore, similar results were found in the genotyping subgroup using the TaqMan™ method (Table II). Increased tumorigenic risks were observed in gastrointestinal tract cancer groups [A vs. G (OR, 1.40; 95% CI, 1.26-1.55; P<0.01; I^2=0%); GA vs. GG (OR, 1.32; 95% CI, 1.15-1.51; P<0.01; I^2=0%); AA vs. GG (OR, 2.04; 95% CI, 1.51-2.75; P<0.01; I^2=29.6%); GA + AA vs. GG (OR, 1.43; 95% CI, 1.25-1.63; P<0.01; I^2=0%); and AA vs. GG + GA (OR, 1.85; 95% CI, 1.33-2.56; P<0.01; I^2=43.1%)] and breast cancer groups [A vs. G (OR, 1.59; 95% CI, 1.20-2.09; P<0.01; I^2=75.3%); GA vs. GG (OR, 1.75; 95% CI, 1.10-2.78; P=0.02; I^2=81.2%); AA vs. GG (OR, 2.56; 95% CI, 1.34-4.92; P=0.01; I^2=74.8%); GA + AA vs. GG (OR, 1.79; 95% CI, 2.22-2.63; P<0.01; I^2=76.9%) and AA vs. GG + GA (OR, 1.99; 95% CI, 1.06-3.74; P=0.03; I^2=75.4%; Table II)].

Cumulative analyses in the general population, which revealed that the first statistically significant association emerged when the study by Kong *et al* (2020) (32) was incorporated. This positive finding specifically demonstrated an association between the rs7158663 G>A polymorphism and cancer susceptibility (Fig. 3; GA + AA vs. GG).Furthermore, sensitivity analyses demonstrated a consistent and stable result when each study was removed step-by-step (Fig. 4; GA + AA vs. GG).

Funnel plot and Egger's test confirmed that there was no significant publication bias in the general population [A vs. G (P=0.13); GA vs. GG (P=0.30); AA vs. GG (P=0.10); GA + AA vs. GG (P=0.18; Fig. 5) and AA vs. GG + GA (P=0.03)].

rs4081134 G>A polymorphism and cancer risk. A total of seven case-control studies involving 3,016 patients and 4,117 controls were included to examine the association between the rs4081134G>A polymorphism and cancer risk. No significant cancer risk was found overall [A vs. G (OR, 1.02; 95% CI, 0.91-1.15; P=0.70; I^2=47.7%); GA vs. GG (OR, 1.05; 95% CI, 0.91-1.20; P=0.52; I^2=35.5%); AA vs. GG (OR, 0.99; 95% CI, 0.74-1.32; P=0.93; I^2=44.6%); AG + AA vs. GG (OR, 1.04; 95% CI, 0.91-1.19; P=0.57; I^2=41.6%) and AA vs. GG + GA

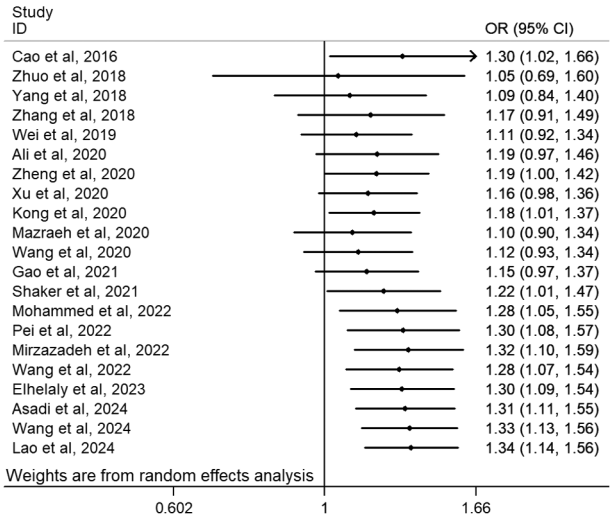


Figure 3. Cumulative meta-analyses according to publication year in GA + AA vs. GG model of MEG3 rs7158663 G>A polymorphism. OR, odds ratio; MEG3, maternally expressed gene 3.

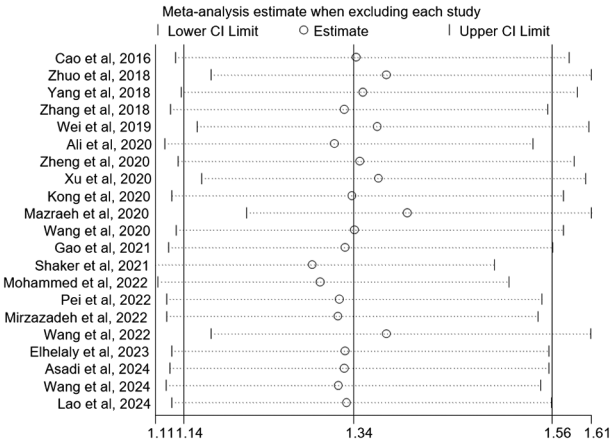


Figure 4. Sensitivity analysis through deleting each study to reflect the influence of the individual dataset on the pooled ORs in GA + AA vs. GG model of MEG3 rs7158663 G>A polymorphism. OR, odds ratio; MEG3, maternally expressed gene 3.

(OR, 0.97; 95% CI, 0.74-1.29; P=0.86; I^2=43.6%)] or in the subgroup analysis for oral cancer (Table II).

Cumulative and sensitivity analyses demonstrated fluctuations when studies were added or removed. No publication bias was observed and the results were further supported by Egger's test [A vs. G (P=0.61); GA vs. GG (P=0.95); AA vs. GG (P=0.19); AG + AA vs. GG (P=0.87) and AA vs. GG + GA (P=0.14); data not shown].

rs11160608 A>C polymorphism and cancer risk. A total of six case-control studies involving 1,725 patients and 2,535 controls were included to examine the association between rs11160608 A>C polymorphism and cancer risk. Overall, a significantly increased risk of tumorigenesis was observed [AC + CC vs. AA (OR, 1.16; 95% CI, 1.01-1.33; P=0.04; I^2=2.7%); Fig. S1; Table II].

Cumulative (Fig. S2; AC + CC vs. AA model) and sensitivity analyses (Fig. S3; AC + CC vs. AA model) demonstrated no significant differences when each study was added or

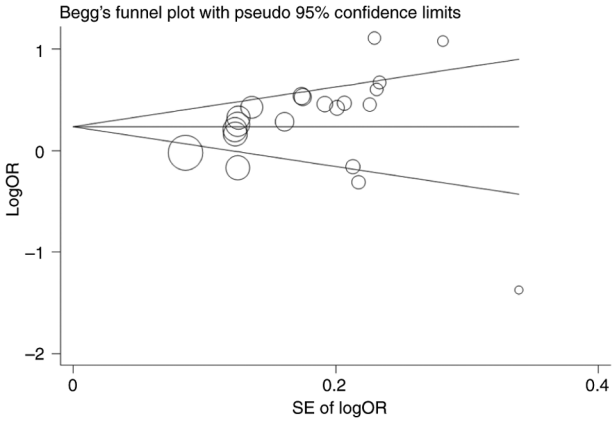


Figure 5. Funnel plot analysis to detect publication bias for GA + AA vs. GG model of MEG3 rs7158663 G>A polymorphism. Circles represent the weight of the studies. MEG3, maternally expressed gene 3

removed. Furthermore, no publication bias was observed and the results were further supported by Egger's test [C vs. A (P=0.51); AC vs. AA (P=0.84); CC vs. CC (P=0.48); AC + CC vs. AA (P=0.75); CC vs. AA + AC (P=0.35; Fig. S4)].

Other polymorphisms and cancer risk. No significant association was observed between rs3087918 T>G, rs3783355 G>A, rs2281511 G>A, rs12431658 T>C, rs10132552 T>C polymorphisms and cancer risk (Table II).

Discussion

Cancer is the leading cause of death globally and imposes notable economic and emotional burdens on both society and individuals (48). It is predicted that the global cancer burden will rise to 28.4 million cases by 2040, which marks a 47% increase from 2020 (49). Despite advances in understanding cancer, its etiology and pathogenesis remain incompletely understood.

lncRNA is one of the most important ncRNAs, serve key roles in various biological processes, including the regulation of histone modification, DNA methylation, transcriptional regulation and post-transcriptional regulation (50,51). Increasing evidence highlights that aberrant expression of lncRNAs is associated with metastasis, recurrence and prognosis across multiple types of cancer (52,53).

MEG3, located in the imprinting region of the Δ-like 1 homolog-MEG3 locus on chromosome 14q32.3 in humans, has garnered increasing attention as a tumor suppressor involved in tumorigenesis (8,21). Dysregulated expression of MEG3 restricts the cancer cell proliferation, invasion and metastasis while promoting apoptosis (54,55). Previous studies have suggested that lower MEG3 expression in patients with cancer is associated with worse pathological grade, enhanced tumor invasion and worse prognosis (56,57). Several signaling pathways, including p53, MDM2, VEFG, Wnt/β-catenin and TGF-β, have been implicated in these processes (14). MEG3 inhibits carcinogenesis by interacting with microRNAs (miRNAs or miRs), such as miR-148a-3p and miR-155, within both the intracellular and extracellular microenvironment (3,4), which offers potential strategies for cancer diagnosis and treatment.

SNPs are the most common forms of genetic mutations and serve a notable regulatory role in tumorigenesis. SNPs alter the secondary structure of lncRNAs and affect the binding affinity between lncRNAs and other molecules. The nucleotide substitution in the MEG3 rs7158663 G>A polymorphism modifies the folding structures and minimum free energy (5,58). Ghaedi *et al* (59) revealed that the rs7158663 polymorphism disrupts binding sites for miR-4307 and miR-1265 within MEG3. These alterations impact miRNA-lncRNA interactions, which modify binding sites for specific miRNAs and indirectly regulate gene expression.

Cao *et al* (18) performed a first case-control study in a Chinese population and reported a markedly increased risk for colorectal cancer associated with the MEG3 rs7158663 G>A polymorphism (OR, 1.31; 95% CI, 1.08-1.59; P=0.007). Numerous studies have examined the association between the MEG3 rs7158663 G>A polymorphism and various cancer types (18-20), however, the results were inconsistent. Ali *et al* (29) investigated the impact of the rs7158663 G>A polymorphism on breast cancer and found that individuals with the AA genotypes exhibited a markedly higher cancer risk compared with those with the GG genotype (OR, 6.32; 95% CI, 2.59-15.44; P<0.01). Kong *et al* (32) identified an increased susceptibility to gastric cancer in patients carrying the A allele at rs7158663 (OR, 1.41; 95% CI, 1.14-1.74; P<0.01). Mazraeh *et al* (33) reported that both the mutated homozygous and heterozygous genotypes are more likely to develop acute myeloid leukemia compared with the GG genotype. However, other studies, such as those by Zhuo *et al* (19), Yang *et al* (20) and Xu *et al* (31), found no notable association between the rs7158663 G>A polymorphism and cancer risk. Similar inconsistencies were observed for the rs4081134 G>A polymorphism and other loci (38). These discrepancies may be attributed to several factors, such as small sample sizes for each polymorphism locus, ethnic differences between studies, inconsistent quality of each study and deviation of HWE in controls in some studies.

To the best of our knowledge, the present systematic review and meta-analysis encompassed all relevant studies on the association between multiple lncRNA MEG3 polymorphisms and cancer susceptibility. The rs7158663 G>A polymorphism markedly contributed to cancer development in the general population, as well as in various subgroup analyses. The present findings suggested that both East Asian and Middle Eastern populations carrying the A allele are more susceptible to cancer: Ethnic differences appear to influence cancer susceptibility associated with these polymorphisms, with individuals from East Asia and the Middle East exhibiting heightened cancer risk. The majority of observational studies were conducted in East Asia and the Middle East (19,20,43). Furthermore, the present meta-analysis highlighted the potential role of the rs11160608 A>C polymorphism as a tumorigenic factor; however, the limited number of original studies warrants caution in drawing definitive conclusions.

Numerous limitations in the present meta-analysis should be addressed. First, ethnic bias could not be avoided, since most studies were conducted in East Asia (based solely on Chinese populations) and the Middle East. This raises concerns regarding the generalizability of the present results to other ethnic groups. Second, several interacting factors, such as viral infection, environmental pollution, unhealthy lifestyle and dietary habits are known to influence cancer susceptibility (60,61). However, a comprehensive assessment of the impact of these factors was not possible, as data on these variables were not extracted from all included studies, which may have introduced deviation. Third, although multiple loci in MEG3 were examined, the interactive assessment with other genes was not conducted, which may limit understanding of the tumorigenic mechanisms associated with these polymorphism loci. Fourth, heterogeneity existed between genetic models, which was alleviated in the subgroup analysis, particularly based on ethnicity and cancer subtypes.

Despite these limitations, a comprehensive and systematic search strategy was employed, yielding a large sample size. Rigorous statistical methods, including cumulative and sensitivity analysis and publication bias assessment, were used to evaluate potential bias and subgroup analyses based on HWE status, ethnicity, genotyping method and tumor subtypes were performed to explore potential associations.

In conclusion, the present meta-analysis indicated that MEG3 rs7158663 G>A polymorphism may serve a key role in the development of cancer, particularly in East Asian and Middle Eastern populations and numerous types of cancer. Furthermore, future case-control studies with larger sample sizes across diverse ethnic groups are warranted to confirm these associations in the future.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YN and YH conceived and designed the study, analyzed data and wrote and reviewed the manuscript. RC performed the experiments and wrote the manuscript. XL analyzed data. All authors have read and approved the final manuscript. YN and YH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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