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Growth arrest-specific 5 (GAS5) insertion/deletion polymorphism and cancer susceptibility in Asian populations

A meta-analysis

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Abstract

Background: Previous studies have reported the association of an insertion/deletion (Ins/Del) polymorphism (rs145204276 AGGCA/-) in the promoter region of growth arrest-specific 5 (GAS5) with the risk of cancer, such as breast cancer, gastric cancer, and hepatocellular carcinoma. However, the results are still controversial. We aimed to clarify the association of GAS5 rs145204276 polymorphism with cancer risk by meta-analysis.

Methods: PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang, and Cochrane Library were searched for studies concerning GAS5 and cancer published up to November 25, 2019. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate cancer risk.

Results: A total of 12 case–control studies with 8729 cases and 10,807 controls were included in this meta-analysis. We found that the GAS5 rs145204276 polymorphism was not significantly associated with cancer risk (Del vs Ins: OR = 0.96, 95% CI: 0.81–1.13; Del/Del vs Ins/Ins: OR = 1.00, 95% CI: 0.70–1.43; Ins/Del vs Ins/Ins: OR = 0.92, 95% CI: 0.78–1.08; Ins/Del and Del/Del vs Ins/Ins: OR = 0.93, 95% CI: 0.76–1.13; Del/Del vs Ins/Del and Ins/Ins: OR = 1.04, 95% CI: 0.78–1.38). In the stratified analyses, significant effects on gastric cancer were found (Del vs Ins: OR = 0.79, 95% CI: 0.72–0.86; Del/Del vs Ins/Ins: OR = 0.65, 95% CI: 0.52–0.82; Ins/Del vs Ins/Ins: OR = 0.76, 95% CI: 0.68–0.86; Ins/Del + Del/Del vs Ins/Ins: OR = 0.74, 95% CI: 0.66–0.83; Del/Del vs Ins/Ins + Ins/Del: OR = 0.74, 95% CI: 0.59–0.91).

Conclusion: Our meta-analysis showed that GAS5 rs145204276 polymorphisms were not related to overall cancer risk. However, the GAS5 rs145204276 polymorphism may be a protective factor for gastric cancer in the stratification analyses.

Abbreviations: CIs = confidence intervals, GAS5 = growth arrest-specific 5, HWE = Hardy–Weinberg equilibrium, Ins/Del = insertion/deletion, lncRNAs = long non-coding RNAs, ORs = odds ratios.

Keywords: cancer, GAS5, meta-analysis, polymorphism

1. Introduction

Cancer is one of the world's major public health problems, and global cancer incidence and mortality rates have increased in 2018.[1] The exact mechanisms of cancer development and progression are currently not well clarified.[2] However, more and more evidence shows that genetic susceptibility is significantly associated with the risk of individual cancer development.[3,4] This may be a direction for cancer diagnosis and treatment in the future.

Long non-coding RNAs (lncRNAs) are characterized as a group of endogenous RNAs, which are more than 200 nucleotides in length and have no protein-encoding function.[5]

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They play an important role in regulating gene expression, and their biological and regulatory networks are complex and unclear.[6] However, they play an important role in the development of disease. A meta-analysis has recently proven that the dysregulated expression of lncRNAs serves as a diagnostic biomarker of type 2 diabetes mellitus.[7] Several studies also showed that the abnormal expression of lncRNAs is often associated with tumor cell proliferation, migration, and even poor prognosis.[8–10] LncRNAs have a great potential to become a new biomarker in cancer diagnosis.

The lncRNA human growth arrest-specific transcript 5 (GAS5) is a multismall nucleolar RNA host gene located on chromosome 1q25.1. It is 630 nt in length and contains 12 exons and 11 introns, and mature GAS5 was primarily identified as a tumor suppressor in human cancers.[11] GAS5 is involved in a variety of biological functions, such as cell proliferation, apoptosis, migration, invasion, epithelial–mesenchymal transition, and DNA repair, and it is a fascinating lncRNA widely expressed in cancers.[12] The relationship between an insertion/deletion (Ins/Del) polymorphism (rs145204276 AGGCA/-) in the promoter region of GAS5 and cancer susceptibility has been studied in detail, but the results of published studies vary and are even contradictory.[13–24] Since GAS5 plays an important role in carcinogenesis, a meta-analysis is needed to accurately determine the relationship between lncRNA GAS5 rs145204276 polymorphism and cancer susceptibility.

2. Materials and methods

2.1. Search strategy

Two investigators (Daozhang Mo and Zhouyan Lan) independently searched for all publications in PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang, and Cochrane Library up to November 25, 2019, by using the following search terms: "growth arrest-specific 5" or "GAS5" in combination with "polymorphism" or "variant" or "mutation" in combination with "cancer" or "tumor". The articles in the reference list were also manually searched. Only human studies were searched, and published studies that were in the English or Chinese language were identified.

2.2. Inclusion and exclusion criteria

The following criteria were used to choose studies for inclusion: studies that evaluated the correlation between GAS5 rs145204276 polymorphism and cancer risk; case–control or cohort design studies; and studies that have data that can be extracted to calculate odds ratios (ORs), 95% confidence intervals (CIs), and Hardy–Weinberg equilibrium (HWE). The exclusion criteria were as follows: review articles, letters, case reports, editorials, and conference abstracts; family-based studies; studies where in the genotype frequency cannot be obtained; and duplicated publications or samples.

2.3. Data extraction

The basic data included the first author's name, publication date, country, ethnicity, source of control, genotyping method, and sample sizes of case group and control group. The genotype frequencies for GAS5 rs145204276 were independently extracted from the included studies by 2 investigators (Daozhang Mo and Zhouyan Lan). To ensure accuracy, the information extracted by the 2 investigators should be the same. If there was any discrepancy, the data were checked again. If the 2 investigators were unable to reach an agreement, the dispute was submitted to a third reviewer (Xiaoyong Guan) for ruling. The quality of the studies was rigorously assessed using the Newcastle-Ottawa Quality Assessment Scale. The following aspects of each study were evaluated: selection of cases and controls, comparability, and outcome or exposure. Quality scores ranged from 0 to 9 points. A study was considered high quality when the Newcastle-Ottawa Quality Assessment Scale checklist score was ≥6 points.[25]

2.4. Statistical analysis

The association between GAS5 rs145204276 Ins/Del polymorphisms and cancer susceptibility was evaluated on the basis of ORs and their corresponding 95% CIs. The pooled ORs were estimated for the allele contrast (Del vs Ins), homozygous (Del/Del vs Ins/Ins), heterozygous (Ins/Del vs Ins/Ins), dominant (Ins/Del and Del/Del vs Ins/Ins), and recessive (Del/Del vs Ins/Del and Ins/Ins) models. Heterogeneity was assessed by the chi-squared Q-test and I-square statistics. If $PQ > 0.1$ or $I^2 < 50\%$, we considered that the heterogeneity is not significant, and a fixed-effects model was applied using the Mantel–Haenszel method. Otherwise, the summary OR and the corresponding 95% CI were calculated with the random-effects model (the DerSimonian and Laird method). Subgroup analysis was carried out and stratified by genotyping method, source of the controls, and cancer type. Sensitivity analysis was performed to examine such influence by removing studies one by one and recalculating the pooled OR and 95% CI. To determine publication bias, Begg funnel plot and Egger test were used, and $P < .05$ was considered significant. The statistical analysis was performed using STATA software (version 12.0; Stata Corporation, College Station, TX). Since this is a meta-analysis based on previous studies, ethical approval was not required.

3. Results

3.1. Literature selection and study characteristics

After conducting a systematic literature search in the above-mentioned databases and performing a manual search in other sources, a total of 152 potentially relevant articles were selected. Among them, 110 articles were excluded after reading the abstract, 30 articles were excluded after reading the full text, and the remaining 12 eligible studies were included in the meta-analysis on the basis of the inclusion and exclusion criteria. Figure 1 shows the flow of studies in this meta-analysis based on the inclusion and exclusion criteria; 12 case–control studies with 8729 cases and 10,807 controls were suitable for the meta-analysis. All the studies were on Asians. Three studies were on gastric cancer; 2 studies were on colorectal cancer. There is only 1 study each on prostate cancer, breast cancer, glioma, osteosarcoma, lung cancer, hepatocellular carcinoma, and cervical cancer. The source of the control population of 10 studies was hospital-based, and that of the other 2 studies was public-based. Polyacrylamide gel electrophoresis was used in 7 studies and TaqMan probe technology (TaqMan) was used in 2 studies. HWE was calculated on the basis of the genotype of the control population, and 1 study did not fall in the HWE. The quality

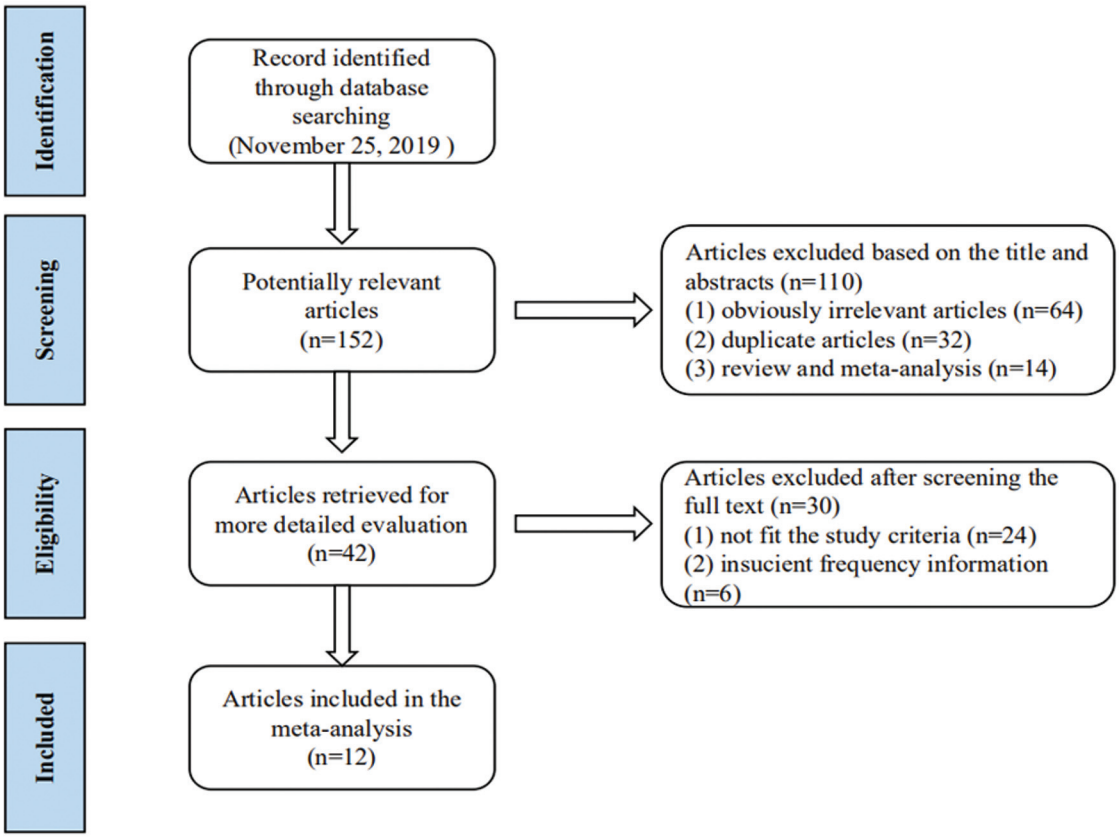

Figure 1. Flow chart of the study selection procedure in this meta-analysis.

score indicated that all 12 studies were "high quality". The characteristics of the included studies are listed in Table 1. The distributions of genotypes and allele frequencies of the GAS5 rs145204276 polymorphism in the cases and controls are shown in Table 2, and which is a supplement to Table 1.

3.2. Meta-analysis results

Because the heterogeneity between studies was significant, a random effects model was applied to all the comparative models. In the overall analysis, the GAS5 rs145204276 polymorphism was not associated with cancer risk in the allele contrast model (Del vs Ins: OR = 0.96, 95% CI: 0.81–1.13, $P = .599$), homozygous model (Del/Del vs Ins/Ins: OR = 1.00, 95% CI: 0.70–1.43, $P = .991$), heterozygous model (Ins/Del vs Ins/Ins: OR = 0.92, 95% CI: 0.78–1.08, $P = .313$), dominant model (Ins/Del and Del/Del vs Ins/Ins: OR = 0.93, 95% CI: 0.76–1.13, $P = .452$), and recessive model (Del/Del vs Ins/Del and Ins/Ins: OR = 1.04, 95% CI: 0.78–1.38, $P = .795$). Therefore, no significant association with cancer risk was found in all the models. The forest plot of

Table 1

Characteristics of the eligible studies included in the meta-analysis (n = 12).

First author	Year	Country	Ethnicity	Cancer type	Source of controls	Genotyping method	Number (case/control)	HWE	NOS score
Lin et al	2019	China	Asian	Prostate cancer	HB	TaqMan	579/579	Yes	8
Tang et al	2018	China	Asian	Breast cancer	HB	PAGE	575/602	Yes	8
Aminian et al	2018	Iran	Asian	Gastric cancer	HB	ARMS-PCR	130/230	Yes	7
Li et al	2018	China	Asian	Gastric cancer	PB	PAGE	853/954	Yes	7
Yuan et al	2018	China	Asian	Glioma	HB	MassArray system	440/820	Yes	8
Xu et al	2018	China	Asian	Osteosarcoma	HB	PAGE	132/1270	Yes	7
Li et al	2018	China	Asian	Gastric cancer	PB	TaqMan	1253/1354	Yes	7
Li et al	2017	China	Asian	Lung cancer	HB	Real-time PCR	600/600	Yes	8
Zheng et al	2016	China	Asian	Colorectal cancer	HB	PAGE	1400/1400	Yes	8
Tao et al	2015	China	Asian	HCC	HB	PAGE	1034/1054	Yes	8
Zhu et al	2017	China	Asian	Cervical cancer	HB	PAGE	920/1018	No	7
Zhu et al	2016	China	Asian	Colorectal cancer	HB	PAGE	813/926	Yes	8

ARMS-PCR = tetra-primer amplification refractory mutation system polymerase chain reaction, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle-Ottawa Quality Assessment Scale, PAGE = polyacrylamide gel electrophoresis, PB = public-based, TaqMan = TaqMan probe technology.

Table 2

GAS5 rs145204276 polymorphism genotype distribution and allele frequency in cases and controls.

		Genotype (*n*)								Allele frequency (*n*)				
		Case				Control				Case		Control		
First author	Year	Total	Del/Del	Ins/Del	Ins/Ins	Total	Del/Del	Ins/Del	Ins/Ins	Del	Ins	Del	Ins	HWE
Lin et al	2019	579	64	252	263	579	72	270	237	380	778	414	744	0.756
Tang et al	2018	575	45	220	310	602	62	261	279	310	840	385	819	0.496
Aminian et al	2018	130	6	36	88	230	20	84	126	48	212	124	336	0.271
Li et al	2018	853	58	334	461	954	85	415	454	450	1256	585	1323	0.476
Yuan et al	2018	440	52	198	154	820	55	346	419	302	506	456	1184	0.144
Xu et al	2018	132	10	42	80	1270	111	543	616	62	202	765	1775	0.575
Li et al	2018	1253	88	483	682	1354	123	593	638	659	1847	839	1869	0.376
Li et al	2017	600	43	270	287	600	62	292	246	356	844	416	784	0.068
Zheng et al	2016	1400	112	550	738	1400	151	610	639	774	2026	912	1888	0.763
Tao et al	2015	1034	140	480	414	1054	82	468	504	760	1308	632	1476	0.062
Zhu et al	2017	920	123	433	364	1018	73	459	486	679	1161	605	1431	0.011
Zhu et al	2016	813	109	387	317	926	73	409	444	605	1021	555	1297	0.112

GAS5 = growth arrest-specific 5, HWE = Hardy–Weinberg equilibrium, Ins/Del = insertion/deletion.

effect estimates for the GAS5 rs145204276 polymorphism and overall cancer susceptibility under the heterozygote genetic model (Ins/Del vs Ins/Ins) are shown in Figure 2.

In the stratified analysis shown in Table 3, a significant association between GAS5 rs145204276 polymorphism and gastric cancer risk was found in all the models when stratified by cancer type (Del vs Ins: OR = 0.79, 95% CI: 0.72–0.86; Del/Del vs Ins/Ins: OR = 0.65, 95% CI: 0.52–0.82; Ins/Del vs Ins/Ins: OR = 0.76, 95% CI: 0.68–0.86; Ins/Del + Del/Del vs Ins/Ins: OR = 0.74, 95% CI: 0.66–0.83; Del/Del vs Ins/Ins + Ins/Del: OR = 0.74, 95% CI: 0.59–0.91). In subgroups formed according to genotyping method, significantly decreased risks were observed in the TaqMan analysis in all the comparison models (Del vs Ins: OR = 0.82, 95% CI: 0.74–0.91; Del/Del vs Ins/Ins: OR = 0.72, 95% CI: 0.57–0.90;

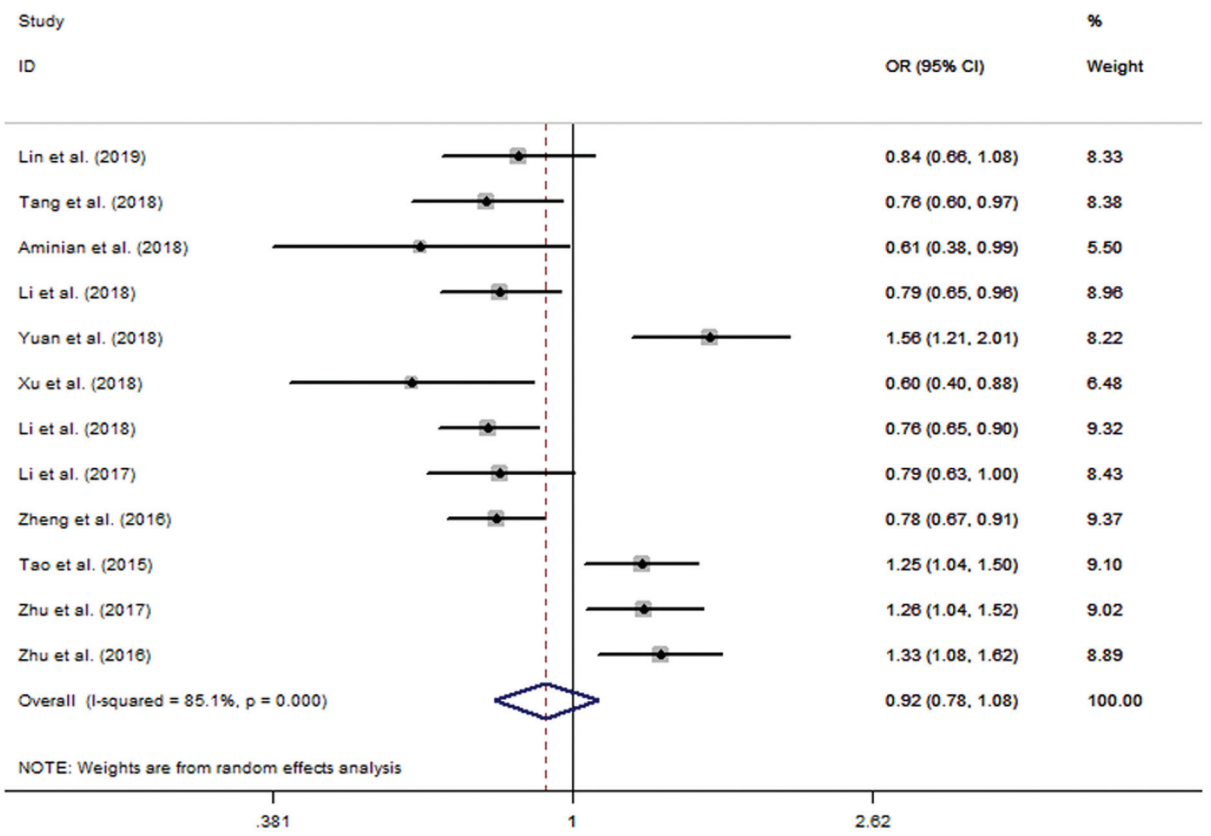

Figure 2. Forest plot illustrating the association between GAS5 rs145204276 polymorphism and cancer risk (heterozygote genetic model Ins/Del vs Ins/Ins). CI = confidence interval, GAS5 = growth arrest-specific 5, Ins/Del = insertion/deletion, OR = odds ratio.

Table 3

Analysis of the GAS5 rs145204276 polymorphism and risk of cancer.

		Allelic (Del vs Ins)			Homozygote (Del/Del vs Ins/Ins)			Heterozygote (Ins/Del vs Ins/Ins)			Dominant (Ins/Del + Del/Del vs Ins/Ins)			Recessive (Del/Del vs Ins/Ins + Ins/Del)		
Variables	**n**	**OR (95% CI)**	I^2, %	P_{OR}	**OR (95% CI)**	I^2, %	P_{OR}	**OR (95% CI)**	I^2, %	P_{OR}	**OR (95% CI)**	I^2, %	P_{OR}	**OR (95% CI)**	I^2, %	P_{OR}
Overall	12	0.96 (0.81–1.13)	92.8	.599	1.00 (0.70–1.43)	91.0	.991	0.92 (0.78–1.08)	85.1	.313	0.93 (0.76–1.13)	90.7	.452	1.04 (0.78–1.38)	86.7	.795
Cancer type																
GC	3	**0.79 (0.72–0.86)**	0.00	.000	**0.65 (0.52–0.82)**	0.00	.000	**0.76 (0.68–0.86)**	0.00	.000	**0.74 (0.66–0.83)**	0.00	.000	**0.74 (0.59–0.91)**	0.00	.005
CRC	2	1.04 (0.60–1.81)	97.3	.876	1.15 (0.36–3.67)	96.6	.808	1.01 (0.60–1.70)	94.0	.960	1.04 (0.55–1.96)	96.4	.906	1.14 (0.46–2.80)	95.0	.783
Others	7	1.03 (0.82–1.29)	92.3	.811	1.17 (0.71–1.90)	90.5	.532	0.98 (0.77–1.23)	84.9	.830	1.00 (0.76–1.32)	90.3	.990	1.18 (0.81–1.73)	85.9	.387
Genotyping method																
PAGE	7	1.00 (0.8–1.25)	93.9	.992	1.11 (0.69–1.81)	92.5	.661	0.94 (0.76–1.17)	86.8	.596	0.97 (0.75–1.26)	92.0	.802	1.14 (0.77–1.68)	89.1	.502
TaqMan	2	**0.82 (0.74–0.91)**	0.00	.000	**0.72 (0.57–0.90)**	0.00	.005	**0.79 (0.69–0.90)**	0.00	.000	**0.77 (0.68–0.88)**	0.00	.136	**0.80 (0.64–1.00)**	0.00	.050
Others	3	0.93 (0.54–1.59)	94.5	.777	0.91 (0.29–2.86)	92.7	.865	0.93 (0.54–1.60)	89.7	.799	0.92 (0.49–1.74)	93.2	.800	0.93 (0.38–2.28)	88.7	.880
Source of control																
HB	10	0.99 (0.81–1.20)	92.9	.921	1.08 (0.72–1.64)	91.2	.703	0.95 (0.79–1.15)	85.4	.614	0.97 (0.77–1.22)	90.9	.770	1.11 (0.80–1.54)	87.0	.523
PB	2	**0.80 (0.73–0.88)**	0.00	.000	**0.67 (0.53–0.84)**	0.00	.001	**0.77 (0.68–0.88)**	0.00	.000	**0.76 (0.67–0.85)**	0.00	.000	**0.75 (0.60–0.94)**	0.00	.011
HWE																
Yes	11	0.92 (0.78–1.10)	92.1	.361	0.92 (0.64–1.33)	89.8	.669	0.89 (0.75–1.06)	84.3	.182	0.89 (0.73–1.09)	89.9	.264	0.98 (0.73–1.30)	84.7	.862

CI = confidence interval, CRC = colorectal cancer, GAS5 = growth arrest-specific 5, GC = gastric cancer, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, Ins/Del = insertion/deletion, OR = odds ratio, PAGE = polyacrylamide gel electrophoresis, PB = public-based, TaqMan = TaqMan probe technology.

Ins/Del vs Ins/Ins: OR = 0.79, 95% CI: 0.69–0.90; Ins/Del + Del/Del vs Ins/Ins: OR = 0.77, 95% CI: 0.68–0.88; Del/Del vs Ins/Ins + Ins/Del: OR = 0.80, 95% CI: 0.64–1.00). Moreover, the stratified analysis by source of control showed evidence of the association between GAS5 rs145204276 polymorphism and overall cancer risk (Del vs Ins: OR = 0.80, 95% CI: 0.73–0.88; Del/Del vs Ins/Ins: OR = 0.67, 95% CI: 0.53–0.84; Ins/Del vs Ins/Ins: OR = 0.77, 95% CI: 0.68–0.88; Ins/Del + Del/Del vs Ins/Ins: OR = 0.76, 95% CI: 0.67–0.85; Del/Del vs Ins/Ins + Ins/Del: OR = 0.75, 95% CI: 0.60–0.94). After excluding a study that was deviated from HWE, the pooled ORs of all the models did not change significantly. The forest plots show the association between GAS5 rs145204276 polymorphism and cancer risk by cancer type subgroup under the heterozygote genetic model (Fig. 3).

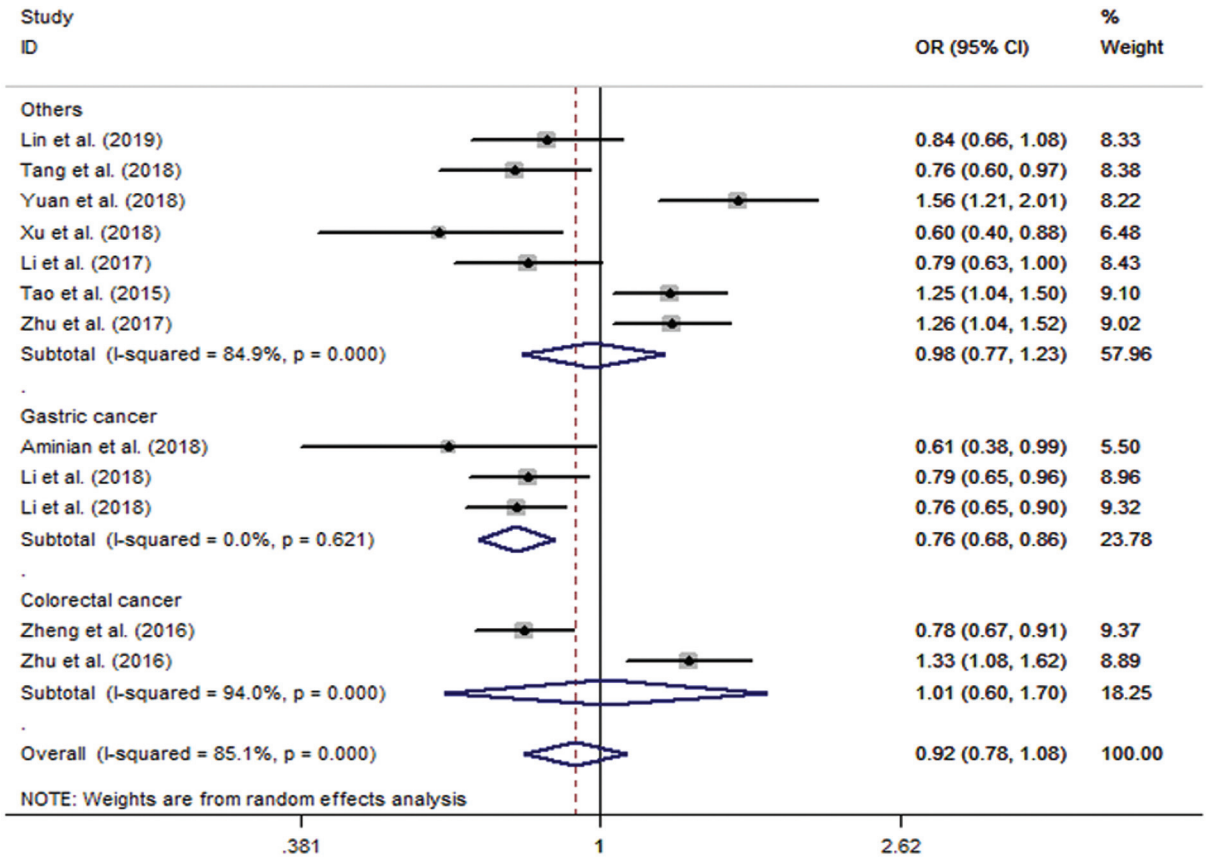

Figure 3. Forest plot show the association. CI = confidence interval, OR = odds ratio.

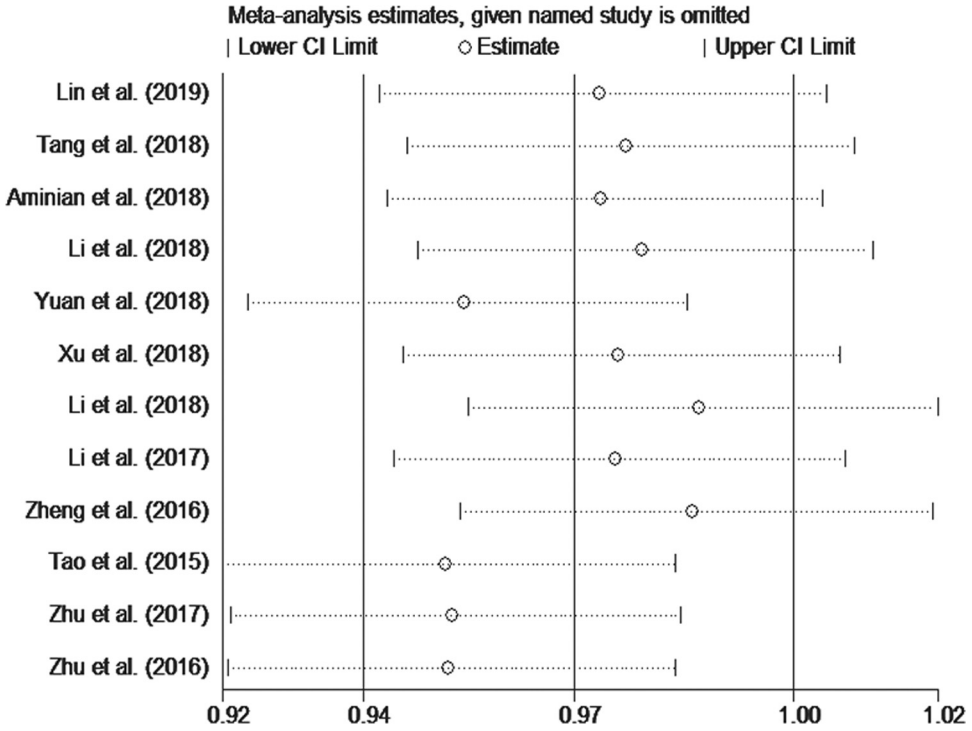

Figure 4. Sensitivity analysis of the GAS5 rs145204276 polymorphism and cancer risk (heterozygote genetic model Ins/Del vs Ins/Ins). CI = confidence interval, GAS5 = growth arrest-specific 5, Ins/Del = insertion/deletion.

3.3. Sensitivity analyses

Sensitivity analyses were carried out to confirm the effect of every study on the overall OR, and they were performed by excluding the studies one by one. The heterozygote genetic model is shown in Figure 4, and no separate study has a qualitative impact on the combined OR, indicating that this meta-analysis result was stable and reliable.

3.4. Publication bias

The potential publication bias of studies for our meta-analysis was determined using Begg funnel plot and Egger test. The results showed that our meta-analysis has no publication bias (Table 4), and the statistical results for Egger test also showed evidence of funnel plot symmetry ($P > 0.05$); this suggested that the meta-analysis was reliable.

4. Discussion

The occurrence of cancer is a complex result of the interaction between environmental and genetic factors. LncRNA has been a research hotspot recently in the genetics of cancer. It forms a variety of transcripts that regulate cellular functions through interactions with proteins, chromatin, and even RNA itself.[25] LncRNA GAS5 is down-regulated in many types of cancer, thereby regulating cellular processes, such as cell proliferation, apoptosis, and invasion. In addition, the low-level expression of GAS5 generally enhances proliferation capacity and plays an important role in cancer diagnosis, treatment, and prognosis.[26]

In this study, we analyzed the association between GAS5 rs145204276 gene polymorphism and cancer risk through a comprehensive meta-analysis. On the basis of 12 eligible publications and a total of 19,536 participants, we found that GAS5 rs145204276 polymorphisms are not associated with

Table 4

Publication bias analysis of the meta-analysis.

Genetic model	Test	*t*	95% CI	*P*
Del vs Ins	Begg test			.631
	Egger test	−0.59	−11.53, 6.67	.565
Del/Del vs Ins/Ins	Begg test			.945
	Egger test	−0.52	−9.96, 6.19	.613
Ins/Del vs Ins/Ins	Begg test			.537
	Egger test	−0.47	−7.85, 5.14	.652
Ins/Del + Del/Del vs Ins/Ins	Begg test			.451
	Egger test	−0.39	−9.76, 6.82	.701
Del/Del vs Ins/Ins + Ins/Del	Begg test			.996
	Egger test	−0.58	−8.26, 4.86	.577

CI = confidence interval, Ins/Del = insertion/deletion.

genetic susceptibility to human cancer in Asian populations. Heterogeneity is a major issue in all the models in this meta-analysis. Therefore, we performed a stratified analysis based on cancer type, genotyping method, and control source. Reduced heterogeneity was observed in gastric cancer, TaqMan, and population-based studies in all 5 genetic models. These results suggest that the type of cancer, genotyping method, and control source may partly explain the source of heterogeneity. After excluding studies that deviated from HWE, the pooled ORs of all the models did not change significantly, suggesting that HWE may not be a source of heterogeneity.

Gene insertions and deletions are common, which will cause gene polymorphisms, affect gene functions and biological characteristics, and are often associated with the occurrence of cancer.[27,28] Some studies showed that GAS5 polymorphisms may reduce cancer risk. Tang et al[14] showed that the rs145204276 del allele induced promoter activity by binding to transcriptional factor specificity protein 1, thereby preventing the development of breast cancer and ultimately leading to higher expression levels of GAS5. There is also a study indicating that GAS5 can regulate the cell cycle by regulating the P21 and CDK6 proteins and thus inhibit the growth of gastric cancer cells.[29] Furthermore, Ye et al[30] showed that lncRNA GAS5 serves as a competitive endogenous RNA for miR-221 and inhibits cell growth and epithelial–mesenchymal transition in osteosarcoma by regulating the miR-221/aplasia Ras homologue member I pathway, thereby reducing the risk of cancer. However, there are other studies that present different perspectives. Tao et al[22] proved that rs145204276 may promote the occurrence of hepatocarcinogenesis by affecting the methylation status of the GAS5 promoter and its transcriptional activity. The reason for these conflicting conclusions may be related to the different types of cancer, or the interaction between the environment and genes was not considered. In conclusion, the exact mechanism by which GAS5 regulates cancer occurrence and development remains unclear.

Our study has some limitations, and the results of this meta-analysis should be interpreted with caution. First, the small number of studies included may be the biggest limitation of this study. Second, the interaction between GAS5 gene polymorphisms and environmental factors was not considered. Some confounding factors such as family medical history, smoking history, drinking status, and menopause status may affect the results of the meta-analysis. Third, only Chinese and English publications were screened, excluding studies published in other languages and unpublished data. In addition, the results of the meta-analysis were not representative because all the studies selected were from Asian populations. The absence of other races, such as Caucasians and Africans, undermines the generality of the conclusions.

In summary, the results of our meta-analysis suggest that GAS5 rs145204276 polymorphisms may not be related to cancer susceptibility in Asian populations, but subgroup analysis confirms that GAS5 rs145204276 variants may be potential protective factors for gastric cancer. Larger sample sizes and well-designed case–control experiments are needed in the future to strengthen our conclusions.

Author contributions

GG designed the study. LCM wrote the draft paper. LXL and GXY assessed studies for inclusion and analysed the data. All authors have approved the final version. GG is the guarantor and takes responsibility for the content of this article.

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References

[1] Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53.
[2] Fitzmaurice C, Akinyemiju TF, Al Lami FH, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2018;4:1553–68.
[3] Wang Y, Yang SH, Hsu PW, et al. Impact of WNT1-inducible signaling pathway protein-1 (WISP-1) genetic polymorphisms and clinical aspects of breast cancer. Medicine 2019;98:e17854.
[4] Shen M, Lin L. Functional variants of autophagy-related genes are associated with the development of hepatocellular carcinoma. Life Sci 2019;235:116675.
[5] Lv X, Li Y, Li Y, et al. FAL1: a critical oncogenic long non-coding RNA in human cancers. Life Sci 2019;236:116918.
[6] Zhang Y, Tao Y, Liao Q. Long noncoding RNA: a crosslink in biological regulatory network. Brief Bioinform 2018;19:930–45.
[7] Zhang W, Zheng J, Hu X, Chen L. Dysregulated expression of long noncoding RNAs serves as diagnostic biomarkers of type 2 diabetes mellitus. Endocrine 2019;65:494–503.
[8] Matsunaga N, Wakasaki T, Yasumatsu R, Kotake Y. Long noncoding RNA, ANRIL, regulates the proliferation of head and neck squamous cell carcinoma. Anticancer Res 2019;39:4073–7.
[9] Wang L, Su K, Wu H, Li J, Song D. LncRNA SNHG3 regulates laryngeal carcinoma proliferation and migration by modulating the miR-384/WEE1 axis. Life Sci 2019;232:116597.
[10] Kamel LM, Atef DM, Mackawy AMH, Shalaby SM, Abdelraheim N. Circulating long non-coding RNA GAS5 and SOX2OT as potential biomarkers for diagnosis and prognosis of non-small cell lung cancer. Biotechnol Appl Biochem 2019;66:634–42.
[11] Yu Y, Hann SS. Novel tumor suppressor lncRNA growth arrest-specific 5 (GAS5) in human cancer. Onco Targets Ther 2019;12:8421–36.
[12] Goustin AS, Thepsuwan P, Kosir MA, Lipovich L. The growth-arrest-specific (GAS)-5 long non-coding RNA: a fascinating lncRNA widely expressed in cancers. Noncoding RNA 2019;5:46.
[13] Lin CY, Wang SS, Yang CK, et al. Impact of GAS5 genetic polymorphism on prostate cancer susceptibility and clinicopathologic characteristics. Int J Med Sci 2019;16:1424–9.
[14] Tang Y, Wang Y, Wang X, Liu Y, Zheng K. A genetic variant of rs145204276 in the promoter region of long noncoding RNA GAS5 is associated with a reduced risk of breast cancer. Clin Breast Cancer 2019;19:e415–21.
[15] Aminian K, Mashayekhi F, Mirzanejad L, Salehi Z. A functional genetic variant in GAS5 lncRNA (rs145204276) modulates p27(Kip1) expression and confers risk for gastric cancer. Br J Biomed Sci 2019;76:83–5.
[16] Li Q, Ma G, Sun S, Xu Y, Wang B. Polymorphism in the promoter region of lncRNA GAS5 is functionally associated with the risk of gastric cancer. Clin Res Hepatol Gastroenterol 2018;42:478–82.
[17] Yuan J, Zhang N, Zheng Y, Chen Y-D, Liu J, Yang M. LncRNA GAS5 indel genetic polymorphism contributes to glioma risk through interfering binding of transcriptional factor TFAP2A. DNA Cell Biol 2018;37:750–7.
[18] Xu L, Xia C, Xue B, Sheng F, Xiong J, Wang S. A promoter variant of lncRNA GAS5 is functionally associated with the development of osteosarcoma. J Bone Oncol 2018;12:23–6.

[19] Li QJ, Ma G, Guo HM, Sun SH, Xu Y, Wang BJ. The variant rs145204276 of GAS5 is associated with the development and prognosis of gastric cancer. J Gastrointestin Liver Dis 2018;27:19–24.
[20] Li W, Huang K, Wen F, Cui G, Guo H, Zhao S. Genetic variation of lncRNA GAS5 contributes to the development of lung cancer. Oncotarget 2017;8:91025–9.
[21] Zheng Y, Song D, Xiao K, et al. LncRNA GAS5 contributes to lymphatic metastasis in colorectal cancer. Oncotarget 2016;7: 83727–34.
[22] Tao R, Hu S, Wang S, et al. Association between indel polymorphism in the promoter region of lncRNA GAS5 and the risk of hepatocellular carcinoma. Carcinogenesis 2015;36:1136–43.
[23] Zhu Z, Feng L, Li F, Xue Y, Li C, Wang H. A novel functional indel polymorphism within long non-coding RNAs growth arrest specific 5 conferred risk for cervical squamous cell carcinoma in Chinese Han populations. Transl Cancer Res 2017;6:424–31.
[24] Zhu Z, Xue Y, Fu W, et al. Functional indel polymorphism within lncRNA GAS5 and colorectal carcinoma risk. Int J Clin Exp Pathol 2016;9:11767–73.
[25] Begolli R, Sideris N, Giakountis A. LncRNAs as chromatin regulators in cancer: from molecular function to clinical potential. Cancers 2019;11:
[26] Ji J, Dai X, Yeung SJ, He X. The role of long non-coding RNA GAS5 in cancers. Cancer Manag Res 2019;11:2729–37.
[27] Raad M, Bayat A, Sharafshah A, Amiri AZ, Zohour MM, Ahmadvand M. Association and in silico investigations of miR-302c insertion/deletion variant as a novel biomarker with susceptibility to gastric cancer. J Cell Biochem 2019;120:18946–55.
[28] Benenemissi IH, Sifi K, Sahli LK, Semmam O, Abadi N, Satta D. Angiotensin-converting enzyme insertion/deletion gene polymorphisms and the risk of glioma in an Algerian population. Pan Afr Med J 2019;32:197.
[29] Guo X, Deng K, Wang H, et al. GAS5 inhibits gastric cancer cell proliferation partly by modulating CDK6. Oncol Res Treat 2015; 38:362–6.
[30] Ye K, Wang S, Zhang H, Han H, Ma B, Nan W. Long noncoding RNA GAS5 suppresses cell growth and epithelial-mesenchymal transition in osteosarcoma by regulating the miR-221/ARHI pathway. J Cell Biochem 2017;118:4772–81.