Association Between LncRNA MALAT1 Polymorphisms and Cancer Risk: A Meta-Analysis Based on 7007 Cases and 8791 Controls

Lei Zheng (zhenglei0825@163.com)  
Zhengzhou University First Affiliated Hospital  
https://orcid.org/0000-0003-2326-9873

Lijuan Rong  
Zhengzhou University First Affiliated Hospital

Zhenyun Cheng  
Zhengzhou University First Affiliated Hospital

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Abstract

Background: LncRNA metastasis associated with lung adenocarcinoma transcript-1 (MALAT1) was involved in pathogenesis and progress of diverse cancers. To investigate the association of MALAT1 and cancer susceptibility, this meta-analysis was appraised.

Methods: 12 studies including 7007 cancer patients and 8791 controls were selected for this meta-analysis. Ratio radiation (ORS) and 95% confidence interval (CIS) were used to assess cancer susceptibility.

Results: There was no significant association between rs3200401 polymorphism and the risk of cancer. However, rs3200401 was correlated with an increased risk of digestive cancer in allelic model (OR=1.15, 95%CI=1.04-1.28, P=0.009) and dominant model (OR=1.16, 95%CI=1.02-1.31, P=0.02). There was a borderline association between rs664589 and cancer susceptibility under the dominant model (OR=1.17, 95%CI=1.00-1.38, P=0.05). Rs619586 was associated with decreased cancer risk in all populations under four models (G vs A: OR=0.86, 95%CI=0.78-0.94, P=0.001; GG vs AA: OR=0.60, 95%CI=0.42-0.84, P=0.003; GG+AG vs AA: OR=0.87, 95%CI=0.78-0.97, P=0.009; GG vs AG+AA: OR=0.61, 95%CI=0.44-0.84, P=0.003). Moreover, rs1194338 was decreased associated with cancer susceptibility (A vs C: OR=0.89, 95%CI=0.80-0.98, P=0.01; AA vs CC: OR=0.77, 95%CI=0.62-0.96, P=0.02; AA+AC vs CC: OR=0.87, 95%CI=0.77-1.00, P=0.04; AA vs AC+CC: OR=0.82, 95%CI=0.67-1.00, P=0.05).

Conclusion: Our results suggest that rs619586 and rs1194338 are associated with decreased cancer risk, while rs3200401 and rs664589 correlated with increased digestive cancer risk.

1. Background

Cancer is the major cause of death worldwide, which would be the most important obstacle to prolonging life expectancy in the world in the 21st century, and has great economic impact on both developed and developing countries [1, 2]. Approximately 18.1 million new patients (17.0 million excluding nonmelanoma skin cancer (NMSC)) were diagnosed with cancer, and 9.6 million people died (9.5 million excluding NMSC) due to cancer worldwide in 2018 [3]. Due to the high rate of recurrence and metastasis, the 5-year survival rate of most tumors is still poor. It is very important to understand their specific pathogenesis. Cancer is caused by the mutations of susceptibility gens [4]. However, the mechanism of many polymorphic genes is still largely unknown.

Long non-coding RNAs (lncRNAs), which are nonprotein coding RNA molecules with more than 200 nucleotides, have been found to be involved in the regulation of cell proliferation and apoptosis [5, 6]. Previous studies have shown that lncRNAs may be the key regulators of different cellular process. In addition, IncRNAs have been identified to be connected with many cellular cancer pathways and differently expressed in tumor tissues [7–10]. Metastasis associated with lung adenocarcinoma transcript-1 (MALAT1), as an highly conserved lncRNA gene and consisting of approximately 8.7 kb and maps to chromosome 11q13 [11], was abnormally expressed in various cancers [12, 13]. As the most common genetic variants, single nucleotide polymorphisms (SNPs) are mostly located in the non-coding region and probably affect lncRNAs expression and its function [8]. Kumar et al. found that 75% of the SNPs influence the lncRNA expression, but not for the adjacent protein coding genes [14]. More and more studies have found that MALAT1 is abnormally overexpressed in various tumors, suggesting the critical role in the tumorigenesis [12, 15, 16]. It has been reported that genetic variants of lncRNA MALAT1 were associated with increased risk of some cancers [17–19]. On the contrary, MALAT1 rs619586 and rs1194338 showed a decreased effect on hepatocellular carcinoma and colorectal cancer [20, 21]. These inconsistent research results may be due to the different mechanisms of different cancer types. Therefore, we applied this meta-analysis to investigate the association between MALAT1 polymorphisms (rs3200401, rs664589, rs619586 and rs1194338) and overall cancer risk.

2. Materials And Methods

2.1. Search strategy

Eligible studies were screened from PubMed, Web of Science and Embase database up to March 01, 2020. Eligible studies were determined to evaluate the association of lncRNA MALAT1 and cancer risk by the following keywords: cancer/tumor/carcinoma/neoplasm/malignancy and LncRNA MALAT1/MALAT1 and polymorphism/variant/variation.

2.2. Study selection criteria

The included criteria for the meta-analysis were as follows: (1) case-control study design investigating association between lncRNA MALAT1 polymorphisms and cancer risk; (2) studies with detailed genotyping data; (3) all cancer patients were diagnosed by histology or pathology. The studies without controls and reviews were excluded. The smaller sample size was excluded when two or more studies had overlapped subjects [22, 23].
2.3. Data extraction and quality assessment

The information of each study was extracted by two authors, including first author, the year of publication, country, ethnicity, cancer types, sample size, genotyping methods, source of controls and genotype frequencies in cases and controls. Sources of controls were categorized as population-based (PB) and hospital-based (HB). Genotyping methods were classified as Taqman and others. Furthermore, included studies were sorted as digestive cancer and others by cancer types. Quality assessment was performed by two authors using Newcastle-Ottawa scale (NOS). 0 to 4 points represent low-quality studies; 5 to 10 points represent high-quality studies.

2.4. Statistical analysis

Statistical analyses were conducted using review manager version 5.0 software (RevMan) and STATA 12.0. The association of IncRNA MALAT1 polymorphism and susceptibility to cancer was assessed by odds ratio (OR) with 95% confidence interval (CI). The significance of pooled ORs was measured by the Z test with P < 0.05. We assessed the association by 5 genetic models: homozygous model (aa VS AA), heterozygote model (aa + Aa VS AA), dominant model (aa + Aa VS AA) and allelic model (a vs A, “a”: variant allele; “A”: wild-type allele). The heterogeneity among studies was detected by Cochran Q test and I^2 test [23]. The fixed effects model was used to calculate the pooled OR of studies when the P value of heterogeneity test was > 0.1 (P > 0.10) or I^2 was < 50%; if not, the random effects model was applied [22, 24]. The publication bias was assessed by Funnel plot, egger's test and sensitivity analysis.

3. Results

3.1. Characteristics of eligible studies

Based on the selection criteria, 12 studies [17–21, 25–31] were included in this meta-analysis (Fig. 1). The characteristics of these studies were presented in Table 1. In total, there were studies on hepatocellular carcinoma (HCC; n = 4), colorectal cancer (CC; n = 3), endometrial cancer (n = 1), esophageal squamous cell carcinoma (ESCC; n = 1), melanoma skin cancer (n = 1), thyroid cancer (n = 1) and breast cancer (n = 1), including 7007 cancer patients and 8791 controls. Among these studies, one was performed in Caucasian from Italy; one was carried out in African from Egypt; others were based on Chinese. Besides, there were 5 studies with PB and 7 studies with HB. Additionally, from the perspective of genotyping methods, 8 studies were Taqman methods and 4 were other methods. All quality scores of studies were > 5 on the basis of NOS.

| Study | Year | Country | Ethnicity | Cancer type | Genotyping method | Controls | Total (n) | Quality score | Citation |
|-------|------|---------|-----------|-------------|-------------------|----------|-----------|--------------|---------|
| Chen  | 2019 | China   | Chinese   | EC          | Taqman           | HB       | 229       | 446          | 8       |
| Li    | 2017 | China   | Chinese   | CC          | MassARRAY       | PB       | 818       | 853          | 10      |
| Liu   | 2012 | China   | Chinese   | HCC         | Taqman           | PB       | 1300      | 1344         | 10      |
| Motawi| 2019 | Egypt   | African   | HCC         | Taqman           | HB       | 70        | 70           | 8       |
| Orlandi| 2019 | Italy   | Caucasian | Melanoma skin cancer | PCR-RFLP | PB       | 334       | 291          | 9       |
| Peng  | 2017 | China   | Chinese   | Breast cancer | PCR-RFLP | PB       | 487       | 489          | 9       |
| Qu    | 2019 | China   | Chinese   | ESCC        | Taqman           | HB       | 245       | 490          | 8       |
| Wang  | 2019 | China   | Chinese   | HCC         | AS-PCR           | HB       | 518       | 806          | 8       |
| Wen   | 2019 | China   | Chinese   | Thyroid cancer | Taqman     | HB       | 1134      | 1228         | 9       |
| Wu    | 2019 | China   | Chinese   | CC          | Taqman           | HB       | 1078      | 1175         | 9       |
| Yuan  | 2019 | China   | Chinese   | HCC         | Taqman           | PB       | 394       | 1199         | 9       |
| Zhao  | 2018 | China   | Chinese   | CC          | Taqman           | HB       | 400       | 400          | 8       |

EC: Endometrial cancer; CC: Colorectal cancer; HCC: Hepatocellular carcinoma; ESCC: Esophageal squamous cell carcinoma; HB: Hospital controls; PB: Population controls; PCR-RFLP: polymerase chain reaction and restriction fragment length polymorphism; AS-PCR: allele specific-polymerase chain reaction.
3.2. Associations between lncRNA MALAT1 polymorphisms and cancer susceptibility

The genotypes and allele distributions of rs3200401, rs664589, rs619586 and rs1194338 were shown in Table 2.

| Genotype (N) | Allele frequency (N) |
|--------------|----------------------|
|              | Case | Control |       | Case | Control |
|              | aa   | Aa     | AA    | Total|         | a   | A   | a   | A   |
| rs3200401    |      |        |       |      |         |     |     |     |     |
| Orlandi 2019 | 19   | 125    | 190   | 334  | 21       | 96  | 174 | 291 | 163 | 505 |
| Peng 2017    | 10   | 120    | 357   | 487  | 6        | 145 | 338 | 489 | 140 | 834 |
| Qu 2019      | 18   | 79     | 148   | 245  | 19       | 133 | 338 | 490 | 115 | 375 |
| Wen 2019     | 23   | 302    | 808   | 1133 | 31       | 322 | 872 | 1225| 348 | 1918|
| Wu 2019      | 33   | 294    | 751   | 1078 | 27       | 292 | 856 | 1175| 360 | 1796|
| Yuan 2019    | 14   | 117    | 263   | 394  | 50       | 347 | 802 | 1199| 145 | 643 |
| Zhao 2018    | 15   | 102    | 283   | 400  | 10       | 96  | 294 | 400 | 132 | 668 |
| rs664589     |      |        |       |      |         |     |     |     |     |     |
| Chen 2019    | 9    | 26     | 214   | 249  | 4        | 73  | 369 | 446 | 44  | 454 |
| Qu 2019      | 22   | 117    | 106   | 245  | 49       | 236 | 205 | 490 | 161 | 329 |
| Wu 2019      | 25   | 195    | 858   | 1078 | 8        | 168 | 999 | 1175| 245 | 1911|
| rs619586     |      |        |       |      |         |     |     |     |     |     |
| Liu 2012     | 5    | 169    | 1094  | 1268 | 12       | 202 | 1116| 1330| 179 | 2357|
| Motawi 2019  | 4    | 16     | 50    | 70   | 7        | 17  | 46  | 70  | 24  | 116 |
| Orlandi 2019 | 0    | 25     | 309   | 334  | 0        | 17  | 274 | 291 | 25  | 643 |
| Peng 2017    | 7    | 65     | 415   | 487  | 10       | 93  | 386 | 489 | 79  | 895 |
| Qu 2019      | 28   | 132    | 85    | 245  | 65       | 248 | 177 | 490 | 188 | 302 |
| Wang 2018    | 1    | 83     | 434   | 518  | 9        | 113 | 684 | 806 | 85  | 951 |
| Wen 2019     | 1    | 131    | 1002  | 1134 | 10       | 167 | 1051| 1228| 133 | 2135|
| Yuan 2019    | 3    | 61     | 330   | 394  | 10       | 175 | 1014| 1199| 67  | 721 |
| Zhao 2018    | 5    | 65     | 330   | 400  | 10       | 82  | 308 | 400 | 75  | 725 |
| rs1194338    |      |        |       |      |         |     |     |     |     |     |
| Li 2017      | 72   | 357    | 389   | 818  | 95       | 377 | 381 | 853 | 501 | 1135|
| Yuan 2019    | 47   | 175    | 172   | 394  | 152      | 537 | 510 | 1199| 269 | 519 |
| Zhao 2018    | 50   | 156    | 194   | 400  | 64       | 172 | 164 | 400 | 256 | 544 |

a: variant allele; A: wild-type allele

The association of rs3200401 and cancer risk was performed in 7 studies with 4071 cases and 5269 controls. As shown in Table 3, no significant association between rs3200401 and cancer risk was found in all population under every genetic model. In the cancer types subgroup analysis, rs3200401 was associated with an increased risk of digestive cancer in two genetic models (allelic model: OR = 1.15, 95%CI = 1.04–1.28, P = 0.009; dominant model: OR = 1.16, 95%CI = 1.02–1.31, P = 0.02; Fig. 2). Besides, homozygous model (OR = 1.35, 95%CI
0.99–1.84, P = 0.05) and heterozygote model (OR = 1.14, 95%CI = 1.00-1.29, P = 0.05) showed borderline risk of digestive cancer susceptibility.
| Comparisons  | n  | a vs A | aa vs AA | Aa vs AA | aa + Aa vs AA | aa vs Aa + AA |
|--------------|----|--------|----------|----------|---------------|---------------|
|              |    | OR(95%CI) | P  | OR(95%CI) | P  | OR(95%CI) | P  | OR(95%CI) | P  | OR(95%CI) | P  |
| rs3200401    |    |          |      |          |      |          |      |          |      |          |      |
| Over all     | 7  | 1.06(0.98–1.15) | 0.12 | 1.15(0.90–1.46) | 0.26 | 1.06(0.97–1.17) | 0.21 | 1.07(0.98–1.17) | 0.15 | 1.12(0.88–1.42) | 0.37 |
| Caucasian    | 1  | 1.04(1.80–1.35) | 0.78 | 0.83(0.43–1.59) | 0.57 | 1.19(0.85–1.67) | 0.30 | 1.13(0.82–1.55) | 0.46 | 0.78(0.41–1.47) | 0.44 |
| Chinese      | 6  | 1.07(0.98–1.16) | 0.12 | 1.21(0.93–1.57) | 0.15 | 1.05(0.96,1.16) | 0.32 | 1.06(0.97–1.17) | 0.20 | 1.18(0.92–1.53) | 0.20 |
| Digestive cancer | 4  | 1.15(1.04–1.28) | 0.009 | 1.35(0.99–1.84) | 0.05 | 1.14(1.00–1.29) | 0.05 | 1.16(1.02–1.31) | 0.02 | 1.30(0.96–1.77) | 0.09 |
| Others       | 3  | 0.96(0.86–1.09) | 0.56 | 0.90(0.61–1.32) | 0.58 | 1.06(0.97–1.17) | 0.76 | 0.97(0.85–1.11) | 0.65 | 0.88(0.60–1.29) | 0.52 |
| Taqman       | 5  | 1.09(1.00–1.19) | 0.04 | 1.19(0.91–1.55) | 0.21 | 1.09(0.99–1.21) | 0.09 | 1.10(1.00–1.22) | 0.06 | 1.15(0.88–1.51) | 0.29 |
| Others       | 2  | 0.95(0.79–1.14) | 0.58 | 1.00(0.58–1.73) | 0.99 | 0.93(0.75–1.16) | 0.53 | 0.94(0.76–1.16) | 0.54 | 0.97(0.57–1.66) | 0.92 |
| rs664589     |    |          |      |          |      |          |      |          |      |          |      |
| Over all     | 3  | 1.13(0.81–1.59) | 0.47 | 2.16(0.72–6.47) | 0.17 | 0.97(0.64–1.47) | 0.88 | 1.17(1.00–1.38) | 0.05 | 2.17(0.74–6.39) | 0.16 |
| Digestive cancer | 2  | 1.20(0.76–1.89) | 0.44 | 1.72(0.42–7.04) | 0.45 | 1.16(0.83–1.62) | 0.38 | 1.26(1.06–1.51) | 0.01 | 1.69(0.45–6.44) | 0.44 |
| Endometrial cancer | 1  | 0.97(0.66–1.43) | 0.88 | 3.88(1.18–12.75) | 0.03 | 0.61(0.38–0.99) | 0.05 | 0.78(0.51–1.21) | 0.27 | 4.14(1.26–13.60) | 0.02 |
| rs619586     |    |          |      |          |      |          |      |          |      |          |      |
| Over all     | 9  | 0.86(0.78–0.94) | 0.001 | 0.60(0.42–0.84) | 0.003 | 0.90(0.81–1.00) | 0.06 | 0.87(0.78–0.97) | 0.009 | 0.61(0.44–0.84) | 0.003 |
| Caucasian    | 1  | 1.29(0.69–2.42) | 0.42 | - | - | 1.30(0.69–2.47) | 0.41 | 1.30(0.69–2.47) | 0.41 | - | - |
| Chinese      | 7  | 0.85(0.77–0.94) | 0.001 | 0.60(0.42–0.86) | 0.005 | 0.89(0.80–1.00) | 0.04 | 0.86(0.77–0.96) | 0.007 | 0.61(0.44–0.86) | 0.005 |
| African      | 1  | 0.73(0.40–1.32) | 0.29 | 0.53(0.14–1.91) | 0.33 | 0.87(0.39–1.91) | 0.72 | 0.77(0.37–1.57) | 0.47 | 0.55(0.15–1.95) | 0.35 |
| Digestive cancer | 6  | 0.90(0.80–1.00) | 0.06 | 0.66(0.45–0.95) | 0.03 | 0.96(0.90–1.09) | 0.49 | 0.92(0.81–1.04) | 0.19 | 0.66(0.46–0.94) | 0.02 |
| HCC          | 4  | 0.91(0.79–1.04) | 0.17 | 0.47(0.25–0.90) | 0.02 | 0.97(0.83–1.13) | 0.70 | 0.93(0.80–1.09) | 0.38 | 0.48(0.25–0.91) | 0.02 |
| CC           | 1  | 0.71(0.52–0.97) | 0.03 | 0.47(0.16–1.38) | 0.17 | 0.74(0.52–1.06) | 0.10 | 0.71(0.50–1.01) | 0.05 | 0.49(0.17–1.46) | 0.20 |
| Others       | 3  | 0.76(0.64–0.90) | 0.002 | 0.38(0.17–0.88) | 0.02 | 0.80(0.66–0.97) | 0.02 | 0.77(0.64–0.93) | 0.006 | 0.41(0.18–0.93) | 0.03 |
| Taqman       | 6  | 0.85(0.76–0.95) | 0.003 | 0.63(0.43–0.91) | 0.01 | 0.89(0.79–1.01) | 0.07 | 0.86(0.76–0.97) | 0.01 | 0.63(0.44–0.91) | 0.01 |
| Others       | 3  | 0.87(0.72–1.06) | 0.17 | 0.46(0.20–1.07) | 0.07 | 0.93(0.75–1.16) | 0.54 | 0.90(0.73–1.11) | 0.32 | 0.48(0.21–1.12) | 0.09 |
| PB           | 4  | 0.85(0.74–0.98) | 0.03 | 0.60(0.32–1.12) | 0.11 | 0.87(0.75–1.02) | 0.09 | 0.86(0.74–1.00) | 0.05 | 0.62(0.33–1.16) | 0.14 |

a: variant allele; A: wild-type allele; CI: confidence interval; OR: odds ratio; HB: Hospital controls; PB: Population controls; CC: Colorectal cancer; HCC: Hepatocellular carcinoma;
Polymorphisms (Fig. 28).

Funnel plot and Egger’s test was used to evaluate the publication bias. No obvious asymmetry was found in the funnel plots of MALAT1.

In the sensitivity analysis, after removing anyone study, the associations of rs619586 (Fig. 6B) polymorphisms with cancer susceptibility were significant as before.

The heterogeneity of researches was performed by Q test and I² in all genetic models and subgroup analysis of lncRNA MALAT1 polymorphism. If P value of heterogeneity was < 0.1, random effects model was applied. If not, the fixed effects model was used.

In the sensitivity analysis, after removing anyone study, the associations of rs619586 (Fig. 6A) and rs1194338 (Fig. 6B) polymorphisms with cancer susceptibility were significant as before.

Funnel plot and Egger’s test was used to evaluate the publication bias. No obvious asymmetry was found in the funnel plots of MALAT1 polymorphisms. Moreover, no publication bias existed in the further egger’s test result of this meta-analysis.
4. Discussion

A large number of SNPs have been found in many IncRNAs, and increasing research has focused on the association between IncRNA polymorphisms and cancer risk. More and more evidence has showed that SNPs in the promoter of IncRNAs regulated the expression of IncRNAs by affecting the binding of transcription factors [32]. MALAT1 with rs664589 G allele altered the binding affinity to miR-194-5p in the nucleus, resulting in the increased MALAT1 expression and the development of CRC [30]. At the same time, MALAT1 rs664589 polymorphism was associated with a decreased risk of HCC [28]. Hence, the particular mechanism of IncRNA MALAT1 in different cancer types is still unclear. In consideration of the inconsistent results, we performed this meta-analysis to systematically investigate the association of MALAT1 polymorphisms and cancer susceptibility.

In this meta-analysis, no association was found between MALAT1 rs3200401 polymorphism and cancer susceptibility in the all population. However, rs3200401 polymorphism was associated with an increased risk of digestive cancers. Similarly, Qu et al. found that rs3200401 C > T was associated with increased risk of ESCC [19]. Conversely, it had been reported that rs3200401 T allele was associated with a better survival for advanced lung adenocarcinoma patients [33]. The rs3200401 C > T variant was located at the region M of MALAT1 (6008–7011 nts), one of the binding sites to SRSF2 [34]. At the same time, C > T variation of rs3200401 caused 1.62 kcal/mol minimal free energy (MFE, ΔG) change, which may alter structural features of MALAT1, resulting in weaken interaction of MALAT1 and its binding protein SRSF2 [33]. In summary, rs3200401 may affect gene expression levels which are involved in the tumorgenesis and cancer development.

It's reported that rs664589 was associated with increased colorectal cancer susceptibility [30]. Other studies have mentioned that rs664589 polymorphisms were not associated with ESCC risk and coronary atherosclerotic heart disease [19, 35]. Only a borderline significance was found between rs664589 polymorphism and cancer risk. The secondary structure of IncRNAs was vital due to their function, and SNPs of IncRNAs may affect the folding structure [36, 37]. Besides, SNPfold algorithm had significantly altered the secondary structure along with rs664589 [30].

LncRNAs could accommodate gene expression through isolating miRNAs and preventing them from binding to targets. Rs619586 was a functional SNP which changed the function of MALAT1 on miRNAs, leading to the regulation of mRNA expression [38]. Wen et al. have showed that rs619586 polymorphism induced the epithelial to mesenchymal transition (EMT) cells process, a vital mechanism of tumorgenesis [27, 39]. In addition, MALAT1 induced EMT and suppressed cell apoptosis via Wnt/β-catenin signaling pathway [40]. Consistent with one previous meta-analysis including 2 studies for rs619586 [41], we found it was associated with decreased cancer risk in all populations. Nonetheless, no association was found between rs619586 and melanoma risk [29]. Overall, the results indicate that rs619586 may have different effects on carcinogenesis in different organs.

For rs1194338 polymorphism of cancer susceptibility, significant association was found in four genetic model except for the heterozygote model. Rs1194338 was located in the promoter of MALAT1. It was reported that genetic variation in promoter region will influence transcriptome expression, stability and subcellular localization, leading to functional changes and the occurrence of disease [42]. However, rs1194338 polymorphism did not alter the MALAT1 expression levels in colorectal cancer tissues [26]. In addition, there was no statistically significant difference in MALAT1 expression between CC genotype and AA genotype [43]. It is possible that common variations could change gene expression at the single cell level, rather than affecting the average level of gene expression in the tissues [44]. Through the application of pathophysiologically immune stimulation, it is helpful to analyze functional genetic variation and specific regulatory genes related to cancer [45].

There were several defects should be acknowledged in this meta-analysis. First, some information, such as age, gender, smoking and drinking status and others, was not considered. Second, the results were just based on the individual unadjusted ORs. Third, some studies with small sample size were contained, which may decrease the statistical power of meta-analysis. Finally, there were only 3 studies for rs664589 and rs1194338. The current data were possibly insufficient for reliable evaluation.

In conclusion, this meta-analysis indicated that rs619586 and rs1194338 had decreased association with cancer risk, while rs3200401 and rs664589 had increased association with digestive cancers. For all that, further studies with different ethnic groups and larger sample size were required to verify the associations.

Declarations

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Ethics approval and consent to participate
Not applicable.

**Consent for publication**

Not applicable.

**Data and materials availability**

All data generated or analyzed during this study are available from the corresponding author on reasonable requirements.

**Competing interest**

All authors declare that no competing interests exist in this study.

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**Authors’ contributions**

ZL designed this study. RLJ and CZY performed data extraction, analysis and quality assessment. The writing of this article was accomplished by CZY and ZL. The final manuscript was approved by all authors.

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**Figures**

106 of records identified through database searching

38 of records after duplicates removed

38 records screened the title and abstract

16 records were excluded

10 full-text articles excluded: 3 reviews or meta-analysis; 5 not MALAT1 polymorphism in cancer; 1 not case-control study, 1 without detail genotype frequency.

22 full-text articles assessed for detail review

12 studies included in this meta-analysis

**Figure 1**

The flow diagram of eligible studies.
### Figure 2

Forest plots of the association between rs3200401 and cancer risk in the cancer types subgroup (TT+CT vs CC).

| Study or Subgroup | Events | Control | Odds Ratio |
|-------------------|--------|---------|------------|
| Qu                | 97     | 245     | 1.46 [1.06, 2.01] |
| Wu                | 327    | 1078    | 1.17 [0.97, 1.40] |
| Yuan              | 131    | 394     | 1.01 [0.79, 1.28] |
| Zhao              | 117    | 400     | 1.15 [0.84, 1.56] |
| Subtotal (95% CI) | 2117   | 3264    | 1.16 [1.02, 1.31] |

Total events: 672 - 974

Heterogeneity: $\chi^2 = 3.30, df = 3 (P = 0.35); I^2 = 9%$

Test for overall effect: $Z = 2.36 (P = 0.02)$

### Figure 3

Forest plots of rs664589 polymorphism and cancer risk (GG+CG vs CC).

| Study or Subgroup | Events | Control | Odds Ratio |
|-------------------|--------|---------|------------|
| Orandi            | 144    | 334     | 1.13 [0.82, 1.55] |
| Peng              | 130    | 467     | 0.82 [0.62, 1.09] |
| Weng              | 325    | 1133    | 0.99 [0.83, 1.19] |
| Subtotal (95% CI) | 1954   | 2005    | 0.97 [0.85, 1.11] |

Total events: 599 - 621

Heterogeneity: $\chi^2 = 2.43, df = 2 (P = 0.30); I^2 = 18%$

Test for overall effect: $Z = 0.45 (P = 0.65)$

Test for subgroup differences: $\chi^2 = 3.63, df = 1 (P = 0.06), I^2 = 72.6%$
Figure 4

Forest plots of rs619586 polymorphism and cancer susceptibility in the cancer types subgroup (GG+AG vs AA).

Figure 5

Forest plots of the association between rs1194338 polymorphism and cancer risk (AA+CA vs CC).
Figure 6

Sensitivity analysis. A: Dominant model for rs619586 (GG+AG vs AA); B: Dominant model for rs1194338 (AA+CA vs CC).
Figure 7

Funnel plots for publication bias. A: rs3200401 (TT+CT vs CC); B: rs664589 (GG+CG vs CC); C: rs619586 (GG+AG vs AA); D: rs1194338 (AA+CA vs CC).