INPLASY PROTOCOL

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None declared.

Different effects of miRNA-499 polymorphism on digestive tract cancers susceptibility in eastern and western China：a meta-analysis and trial sequential analysis

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Review question / Objective: **In the Chinese population, the association between miRNA-499 T > C polymorphism and susceptibility to digestive tract cancers is still inconclusive. We included 15 case-control studies with 7230 cases and 8740 controls to reveal this relationship, and the trial sequential analysis (TSA) was also performed to demonstrate that the sample size in this meta-analysis was adequate.**
Condition being studied: **In this article, we followed the PRIMSA guidelines and ultimately pooled 15 case-control studies to obtain a precise result, which demonstrated that miRNA-499 C variant are more likely to develop digestive tract cancers compared to T allele carriers. In view of the significant differences between eastern China and western China on occurrence and development of cancers, subgroup analysis based on Chinese region was performed to ascertain the association between miRNA-499 T>C polymorphism and digestive tract cancers risk. This is the first work to examine the effect of miRNA-499 T>C polymorphism in relation to Chinese regional factors, and we found there was evident correlation between miRNA-499 T>C variant and digestive tract cancers risk in eastern China but not in western China. Some conjectures about gene polymorphism and environmental factors were also proposed to explain the results. These findings promoted the development of the miRNA-499 gene for the prediction of digestive tract cancers and introduced regionalism into miRNA-499 gene therapy for digestive tract cancers.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 May 2022 and was last updated on 02 May 2022 (registration number INPLASY202250006).

INTRODUCTION

Review question / Objective: **In the Chinese population, the association between miRNA-499 T > C polymorphism and susceptibility to digestive tract cancers is still inconclusive. We included 15 case-control studies with 7230 cases and 8740 controls to reveal this relationship, and the trial sequential analysis (TSA) was also**

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METHODS

Participant or population: Chinese population.

Intervention: digestive tract cancers patients.

Comparator: digestive tract cancers patients.

Study designs to be included: We firstly calculated the value of Hardy-Weinberg equilibrium (HWE) by using the chi-square goodness-of-fit test, and the valueC polymorphism and susceptibility to digestive tract cancers. When there was no heterogeneity among included studies (P>0.1 and I2<50%), the fixed-effects model (Mantel-Haenszel method) was performed; if there was a huge statistical heterogeneity among studies (P50%), we used t.

Eligibility criteria: Inclusion criteria(1) evaluation of the miRNA-499 rs3746444 T>C polymorphism and cancer risks; (2) a case-control study; (3) sufficient data were provided for the computation of odds ratios (ORs) and its 95% confidence intervals (CIs); (4) alleles or genotypes frequencies could be received from the study.Exclusion criteria(1) the object of study was not Chinese population; (2) not relevant to digestive tract cancers; (3) studies represented duplicates of previous publications; (4) the distribution of genotypes was not in accord with Hardy-Weinberg equilibrium (HWE).

Information sources: Eligible studies were searched in Cochrane Library database, EMBASE, Pudmed, Web of science, China National Knowledge Infrastructure and Wanfang database.

Main outcome(s): Overall, miRNA-499 T > C polymorphism increased the risk of developing digestive tract cancers in the Chinese population (C vs. T, OR = 1.18, 95% CI: 1.08-1.30, P = 0.001). In the subgroup analysis by region of China, the miRNA-499 T > C polymorphism only increased susceptibility to digestive tract cancers in eastern China (C vs. T, OR = 1.22, 95% CI: 1.10–1.35, P = 0.001), and the TSA result confirmed the finding. In western China, the effect of the miRNA-499 T > C polymorphism on digestive tract cancers appeared to be concealed. Furthermore, we found that the miRNA-499 TC genotype may be the risk factor for developing HCC (TC vs. TT, OR = 1.25, 95% CI: 1.09–1.44, P = 0.002) and OSCC (TC vs. TT, OR = 1.56, 95% CI: 1.12-2.18, P = 0.008).

Quality assessment / Risk of bias analysis: We used the Newcastle-Ottawa Quality Assessment Scale (the NOS scale) to evaluate the quality of included studies, and the articles were defined as high quality (scores≥7 stars) and low quality (scores<7 stars).

Strategy of data synthesis: We firstly calculated the value of Hardy-Weinberg equilibrium (HWE) by using the chi-square goodness-of-fit test, and the valueC

polymorphism and susceptibility to digestive tract cancers. When there was no heterogeneity among included studies (P>0.1 and I2<50%), the fixed-effects model (Mantel-Haenszel method) was performed; if there was a huge statistical heterogeneity among studies (P50%), we used the random-effect model (DerSimonian and Laird method) to calculate pooled ORs. The significance of the pooled OR was determined by the Z-test, and P<0.05 was considered that the results are significant. The genetic contrast models were allelic model (Cvs.T), homozygote model (CCvs.TT), heterozygote model (TCvs.TT), recessive model (CCvs.TT+TC), and dominant model (TC+CCvs.TT). Subgroup analyses were done by the region of China, cancer type and source of control. Furthermore, publication bias of literatures was evaluated by funnel plots and Egger's test, and each time one document was removed for sensitivity analysis. Statistical analysis was done by Review Manager 5. 4. 1 Software. All the P-values are two-sided in our meta-analysis.

Subgroup analysis: Subgroup analysis of the correlation between miRNA-499 T>C polymorphism and the susceptibility to digestive tract cancers in different region of China. For eastern China subgroup, 8 studies with a total of 5651 cases and 7908 controls were included, respectively. There was evident correlation between the miRNA-499 T>C variant and digestive tract cancers risk in the eastern China (C vs. T, OR=1.22, 95% CI:1.10-1.35, PC polymorphism was not found in west of China (P>0.05) . Subgroup analysis of the correlation between miRNA-499 T>C polymorphism and 4 digestive tract cancers susceptibility. The pooled results suggested that miR-499 T>C polymorphism was not associated with the susceptibility of GC and CRC (P>0.05). However, for HCC and OSCC, we found that individuals with the TC variant had a significantly higher risk of developing corresponding cancer compared to those with TT genotype .

Sensitivity analysis: We conducted the sensitivity analysis by removing each individual document from the analysis at a time to evaluate the stability. It revealed that there were no marked changes for each study, implying that our findings were reliable and consistent.

Language: None.

Country(ies) involved: China.

Keywords: miRNA-499, eastern China, digestive tract cancers, meta-analysis, trial sequential analysis.

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