CAV1 rs7804372 (T29107A) polymorphism might be a potential risk for digestive cancers
A protocol for systematic review and meta-analysis
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Abstract
Background: Caveolin-1 (CAV1) is an essential structural component of caveolae, regulates cellular processes through complex cellular signaling pathways, and influences tumorigenicity. However, the role of the CAV1 (rs7804372) polymorphism in digestive cancers remains inconclusive. The meta-analysis was performed to evaluate the effect of CAV1 polymorphism on digestive cancer susceptibility and to provide a basis for precise treatment.

Methods: The databases of PubMed, EMBASE, Google Scholar and CNKI were used to retrieve the published studies on CAV1 (rs7804372) polymorphism and susceptibility to digestive cancers up to June 2020. Two researchers conducted study screening, data extraction, and methodological quality evaluation separately according to inclusion and exclusion criteria. Review Manager 5.3 software was used to conduct the meta-analysis.

Results: Six case-control studies were enrolled, including 2477 patients with digestive cancers and 2477 healthy controls. The pooled results showed that the CAV1 rs7804372 (T29107A) polymorphism increased the risk of digestive cancer occurrence in the allele (T vs. A; odds ratio (OR) 1.33, 95% confidence interval (CI): 1.15–1.53, \( P < .01 \)), homozygous (TT vs. AA; OR 1.72, 95% CI: 1.31–2.26, \( P < .01 \)), heterozygous (TA vs. AA; OR 1.47, 95% CI: 1.21–1.78, \( P < .01 \)), dominant (TT vs. TA + AA; OR 1.32, 95% CI: 1.18–1.48, \( P < .01 \)), and recessive comparing models (TT + TA vs. AA; OR 1.61, 95% CI: 1.26–2.07, \( P < .01 \)).

Conclusion: Our results indicate that the CAV1 (rs7804372) polymorphism may modify the occurrence of digestive cancers, and the presence of T allele or TT genotype of the CAV1 (rs7804372) may increase the risk of digestive cancers.

Abbreviations: CAV1 = Caveolin-1, CI = confidence interval, OR = odds ratio.

Keywords: CAV1, digestive cancers, meta-analysis, polymorphism

1. Introduction

The incidence of malignant cancers is increasing every year with the development of global aging and unhealthy lifestyle. Globally, the incidence of digestive malignant tumors ranks among the forefront of cancer incidence.\textsuperscript{[1]} Digestive cancers, especially esophageal carcinoma, gastric cancer, colorectal cancer, and hepatocellular cancer, are a global pivotal epidemiological health concern. Compared with other cancers, patients with digestive cancers not only are required to receive comprehensive treatment such as surgery, radiotherapy and chemotherapy but also face adverse reactions, such as malnutrition, diarrhea, constipation caused by gastrointestinal dysfunction, as well as body function and self-image changes caused by artificial stoma. These problems significantly influence the prognosis of patients with digestive cancer.\textsuperscript{[2]}

Caveolin-1 (CAV1) is the main membrane protein of caveolae, which are scaffolding proteins of plasma membrane invaginations.\textsuperscript{[3]} CAV1 is an essential structural component of caveolae, regulates cellular processes through complex cellular signaling pathways, and influences tumorigenicity. The structure and function of the caveolin-1 gene family are highly conserved in different species, indicating its essential role for maintaining cellular functions. CAV1 interacts with various signal transduction molecules through phosphorylation/dephosphorylation signaling.\textsuperscript{[4]} It plays an important role in cholesterol and lipid transport, membrane transport, signal transduction, and cell
adhesion.\textsuperscript{[15]} Additionally, CAV1 is involved in the regulation of various signaling pathways, such as cell proliferation, differentiation, apoptosis, migration, and angiogenesis, and is associated with the occurrence, development, invasion, and metastasis of various tumors.\textsuperscript{[6]} The carcinogenic role of CAV1 has been identified in several tumors, suggesting CAV1 as a novel therapeutic target for tumors. Several studies have explored the relationship between CAV1 polymorphisms and susceptibility to breast cancer,\textsuperscript{[7]} esophageal carcinoma,\textsuperscript{[8]} colorectal cancer,\textsuperscript{[9]} gastric cancer,\textsuperscript{[10,11]} hepatocellular cancer,\textsuperscript{[12]} and other cancers.\textsuperscript{[13,14]} However, the results of the CAV1 rs7804372 (T29107A) polymorphism and susceptibility to digestive cancer remain controversial. Thus, this meta-analysis was conducted to verify the contribution of the CAV1 rs7804372 (T29107A) polymorphism to digestive cancer susceptibility to provide evidence for precise clinical treatment.

2. Methods

Ethical review was not required since our manuscript is meta-analysis. This meta-analysis was conducted in comply with the guidelines for preferred reporting items for systematic reviews and meta-analyses (PRISMA statement).

2.1. Searching strategy and selection criteria

The literature related to the association of CAV1 (rs7804372) polymorphism and digestive cancer susceptibility was searched online through the PubMed, EMBASE, Google Scholar, CNKI, Wan Fang and VIP databases from their inception up to June 2020. The following terms were used for retrieving valuable articles: [(CAV1) or (Caveolin-1) or (caveolin)] and [rs7804372 OR T29107A] [polymorphism or genotype or mutation or variant] and [oral or esophageal or gastric or hepatocellular or colorectal]. The references of retrieved articles were manually reviewed for identifying other qualified articles.

Studies were enrolled according to the following criteria:

1. all published studies must have explored the association between the CAV1 rs7804372 (T29107A) polymorphism and digestive cancer;
2. case control studies;
3. genotype distribution in case and control can be directly acquired or calculated;
4. full text can be acquired directly.

The meta-analysis excluded studies according to the following criteria:

1. animal or cell line research;
2. systematic review, meta-analysis and repetitive reports;
3. unavailability of genotype data distribution.

2.2. Data extraction

Using a specified data extraction table, two investigators completed the study screening, data extraction, and sorted independently, discussed and negotiated the disputed parts, finally reached a consensus. Data extraction mainly includes the first author's name, publication year, sample size, tumor differentiation, clinical stage, and lymph node metastasis. The New Castle–Ottawa scale was used for assessing the quality of each study.

2.3. Statistical analyses

Review Manager 5.3 software was used for analyzing five genetic models of the CAV1 gene polymorphism, including allele (T vs. A), homozygous (TT vs. AA), heterozygous (TA vs. AA), dominant (TT vs. TA + AA), and recessive comparing models (TT + TA vs. AA), where TT is a homozygote of a wild-type allele, TA is a heterozygote, and AA is a homozygote of a mutant allele. The comparison between CAV1 (rs7804372) polymorphism and digestive cancer was expressed using pooled odds ratio (OR) and 95% confidence interval (CI). The $\chi^2$ test and $I^2$ statistics were used to judge whether there was heterogeneity among the studies; $P > .10$ and $I^2 < 50\%$ could be considered that there was no statistical heterogeneity between the research results, and the fixed effect model was selected for data consolidation; $P \leq .10$ and $I^2 \geq 50\%$ could be considered that there was statistical heterogeneity between the research results, and a random effect model was used for data consolidation. The Hardy–Weinberg equilibrium of the control group was evaluated using the $\chi^2$ test, and the expected and actual genotype frequencies of the control group were compared. In this meta-analysis, $P$-values of $\leq .05$ were considered statistically significant.

3. Results

3.1. Characteristics of enrolled studies

According to the inclusion and exclusion criteria, six case-control studies were included, including 2477 patients with digestive cancers and 2477 healthy controls. The positive rate of the T gene locus was 74.22% in patients and 68.21% in healthy controls (Tables 1 and 2).

3.2. Test of heterogeneity

$\chi^2$ test and $I^2$ statistics were used for assessing the heterogeneity of the enrolled studies. Results indicate that there was statistical heterogeneity in the heterozygous comparison model (TA vs. AA) and dominant (TT vs. TA + AA), the fixed effect model was used for evaluating the pooled OR and 95% CI for those comparisons. No statistical heterogeneity was discovered in the allele (T vs. A), homozygous comparison models (TT vs. AA) and recessive

Table 1: The main characteristics of included studies.

| First author | Ethnicity | Cancer type       | Case / control | Test method |
|--------------|-----------|-------------------|----------------|-------------|
| Zhang 2014   | Asian     | Gastric cancer    | 412/412        | Spectrometry |
| Lin 2014     | Asian     | Gastric cancer    | 358/358        | RT-PCR      |
| Wang 2014    | Asian     | Esophageal cancer | 427/427        | RT-PCR      |
| Hsu 2013     | Asian     | Hepatocellular cancer | 298/298        | RT-PCR      |
| Bau 2011     | Asian     | Oral cancer       | 620/620        | RT-PCR      |
| Yang 2010    | Asian     | Colorectal cancer | 363/362        | RT-PCR      |
comparison models (TT + TA vs AA), the random effect model was used for evaluating the pooled OR and 95% CI for those comparisons.

3.3. Sensitivity analysis and publication bias

A sensitivity analysis was performed for assessing the influence of each study on the overall result by eliminating every study step by step individually. The results suggested that there were no independent studies that significantly influenced the pooled ORs. Funnel charts were used for evaluating publication bias. The funnel chart did not show any significant asymmetry (Figure 1).

3.4. Meta-analysis of CAV1 (rs7804372) polymorphism and digestive cancer susceptibility

A summary of meta-analysis findings regarding the relationship between the CAV1 (rs7804372) polymorphism and digestive cancer is presented in (Table 3 and Figures 2–6) Overall pooled results revealed an increasing risk of CAV1 (rs7804372) polymorphism in digestive cancer in the allele (T vs A: OR 1.33, 95% CI: 1.15–1.53, P < .01), homozygous (TT vs AA: OR 1.72, 95% CI: 1.31–2.26, P < .01), heterozygous (TA vs AA: OR 1.47, 95% CI: 1.21–1.78, P < .01), dominant (TT vs TA + AA: OR 1.32, 95% CI: 1.18–1.48, P < .01), and recessive comparison models (TT + TA vs AA: OR 1.61, 95% CI: 1.26–2.07, P < .01).

4. Discussion

CAV1 is one of the critical components of the integral membrane protein that makes up caveolins. It has been reported to be associated with esophageal carcinoma,[15,16] prostate cancer,[17,18] colon cancer,[19] breast cancer,[20] bladder cancer,[21] lung cancer,[22] and others,[23,24] which can promote or suppress tumor occurrence and development.

| First Author | n   | TT  | AT  | AA  | T   | A   | TT  | AT  | AA  | T   | A   |
|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Zhang 2014   | 824 | 210 | 136 | 66  | 556 | 268 | 239 | 134 | 39  | 612 | 212 |
| Lin 2014     | 756 | 192 | 133 | 33  | 517 | 199 | 188 | 135 | 35  | 511 | 205 |
| Wang 2014    | 854 | 221 | 166 | 40  | 608 | 246 | 259 | 143 | 25  | 661 | 193 |
| Hsu 2013     | 596 | 152 | 98  | 48  | 402 | 194 | 166 | 93  | 39  | 425 | 171 |
| Bau 2011     | 1240| 306 | 206 | 108 | 818 | 422 | 363 | 193 | 64  | 919 | 321 |
| Yang 2010    | 724 | 179 | 120 | 63  | 478 | 246 | 216 | 117 | 29  | 549 | 175 |
| Total        | 4954| 1260| 859 | 358 | 3379| 1575| 1431| 815 | 231 | 3677| 1277|

Table 2

Allele frequency and genotype distribution of control and case in included studies.

Figure 1. Funnel plot for publication bias. A funnel chart was used for evaluating publication bias of the studies. The shape of the funnel chart did not show any evidence of significant asymmetry in the dominant model.
According to the results from BioMuta-single-nucleotide variations in the cancer database, 45 modified residues and two modified functional residues of the CAV1 polymorphism have been recorded, and some of them have been reported to be correlated with digestive cancers.\(^\text{[25]}\)

Yang et al\(^\text{[9]}\) first reported the correlation of CAV1 (rs7804372) polymorphism with colorectal cancer. Their results indicated that CAV1 (rs7804372) was related to a higher susceptibility to colorectal cancer, with joint effects with smoking status on colorectal cancer susceptibility, and the A allele of CAV1 (rs7804372) polymorphism might act as a potential biomarker for the early diagnosis, prediction, and targets for cancer therapy. Zhang et al\(^\text{[10]}\) reported the correlation of CAV1 (rs7804372) polymorphism with gastric cancer, and their results indicated that CAV1 (rs7804372) polymorphisms increased gastric cancer susceptibility and risk. Patients receiving the CAV1 (rs7804372) TT haplotype had a higher gastric cancer risk and susceptibility than those with AT or AA haplotypes. Bau et al\(^\text{[13]}\) reported that CAV1 (rs7804372) was involved in oral cancer, the A allele of CAV1 (rs7804372) played a protective role to prevent

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### Table 3

**Meta-analysis of Cav-1 rs7804372 gene polymorphism and tumor susceptibility of digestive system.**

| Genotype | n   | OR (95%CI) Z  |  |  |  |
|----------|-----|---------------|---|---|---|
| T vs A   | 9908| 1.33[1.15, 1.53] 3.92 <.01 12.83 <.01 61%  |
| TT vs AA | 3280| 1.72[1.31, 2.26] 3.90 <.01 10.60 <.01 53%  |
| TA vs AA | 2263| 1.47[1.21, 1.78] 3.92 <.01 5.75 .33 13%  |
| TT vs (TA+AA) | 4954| 1.32[1.18, 1.48] 4.87 <.01 6.80 .24 26%  |
| (TT+TA) vs AA | 4954| 1.61[1.26, 2.07] 3.81 <.01 9.33 .10 46%  |

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**Figure 2.** Forest plot of allele T vs A genotype. Overall pooled results revealed an increased risk of the CAV1 (rs7804372) polymorphism for digestive cancer in the allele comparing model (T vs A: odds ratio 1.33, 95% confidence interval: 1.15–1.53, \(P < .01\)), and heterogeneity among the included studies was observed (\(I^2 = 61\%, P = .03\)). Results showed that the risk of CAV1 (rs7804372) polymorphism T allele carriers was 1.33 times higher than that of A allele carriers.

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**Figure 3.** Forest plot of TT vs AA genotypes. Overall pooled results revealed an increased risk of the CAV1 (rs7804372) polymorphism for digestive cancer in the homozygous comparison model (TT vs AA: odds ratio 1.72, 95% confidence interval: 1.31–2.26, \(P < .01\)), and heterogeneity among the included studies was observed (\(I^2 = 53\%, P = .06\)). Results showed that the risk of CAV1 (rs7804372) polymorphism TT genotype carriers was 1.72 times higher than that of AA genotype carriers.
Figure 4. Forest plot of TA vs AA genotypes. Overall pooled results revealed an increased risk of CAV1 (rs7804372) polymorphism for digestive cancer in a heterozygous comparison model (TA vs AA: odds ratio 1.47, 95% confidence interval: 1.21–1.78, \(P < .01\)). No heterogeneity among the included studies was observed (I^2 = 13%, \(P = .33\)). Results showed that the risk of CAV1 (rs7804372) polymorphism TA genotype carriers was 1.47 times higher than that of AA genotype carriers.

Figure 5. Forest plot of TT vs (TA + AA) genotypes. Overall pooled results revealed an increased risk of the CAV1 (rs7804372) polymorphism for digestive cancer in the dominant comparison model (TT vs TA + AA: odds ratio 1.32, 95% confidence interval: 1.18–1.48, \(P < .01\)). Heterogeneity among the included studies was observed (I^2 = 26%, \(P = .24\)). Results showed that the risk of CAV1 (rs7804372) polymorphism TT genotype carriers was 1.31 times higher than that of (TA + AA) genotype carriers.

Figure 6. Forest plot of (TT + TA) vs AA genotypes. Overall pooled results revealed an increased risk of the CAV1 (rs7804372) polymorphism for digestive cancer in a recessive comparison model (TT + TA vs AA: odds ratio 1.61, 95% confidence interval: 1.26–2.07, \(P < .01\)). No heterogeneity among the included studies was observed (I^2 = 46%, \(P = .10\)). Results showed that the risk of CAV1 (rs7804372) polymorphism (TT + TA) genotype carriers was 1.61 times higher than that of the AA genotype carriers.
cancer occurrence and the T allele may be a risky factor. The TT genotype of CAVI (rs7804372) may be associated with risk for oral cancer. Moreover, Wang et al.[9] also reached the same conclusion for esophageal cancer. While different conclusions were obtained, Lin et al.[11] reported that there was no correlation between CAVI (rs7804372) polymorphism and gastric cancer susceptibility. Hsu et al.[12] evaluated the relationships between six single nucleotide polymorphism of the CAVI gene and hepatocellular cancer risk in a Taiwanese population. No significant association between rs7804372 polymorphism and hepatocellular cancer was observed. Owing to the inconsistent results between the CAVI (rs7804372) polymorphism and digestive system tumors, our team comprehensively searched all published studies on the CAVI (rs7804372) polymorphism with digestive cancer and performed a meta-analysis for obtaining a comprehensive correlation between them.

In our study, six studies were finally enrolled. To provide a more detailed overview of the relationship between CAVI (rs7804372) polymorphism and digestive cancer, five genetic models were used. Our results indicated that the CAVI (rs7804372) polymorphism was involved in risk for digestive cancer and influences the susceptibility to digestive cancer. The T allele, TT genotype, and TA of CAVI (rs7804372) induces an increasing risk of digestive cancers. This means that the CAVI (rs7804372) polymorphism can be regarded as a potential biomarker for early diagnosis, development, and prognosis prediction of digestive cancer.

Because of the few reported studies on the relationship between CAVI (rs7804372) gene polymorphism and digestive system tumor, the limitations of database retrieval and data collection, the relationship between the CAVI (rs7804372) gene polymorphism and age, sex, and clinical and pathological characteristics were not analyzed. Further studies with larger samples are needed for confirming the relationship between CAVI (rs7804372) gene polymorphism and digestive system tumors.

In conclusion, we confirmed that CAVI (rs7804372) can act as a valuable genetic susceptibility marker for digestive cancer. The presence of the allele T of CAVI (rs7804372) has a higher risk of digestive cancer than that of the allele A. There is a potential value of targeting the allele A for early diagnosis, prognosis prediction, and therapy for digestive cancers.

Author contributions

Data curation: Bai Xue, Ji -Ru Wang.
Methodology: Ji -Ru Wang.
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Writing – review & editing: Yu-ling Zhang.

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