Review Article

Tumor Necrosis Factor-α T-857C (rs1799724) Polymorphism and Risk of Cancers: A Meta-Analysis

Ping Wang,¹ June Wang,¹,² Mingxia Yu,¹ and Zhiqiang Li³

¹Department of Clinical Laboratory and Center for Gene Diagnosis, Zhongnan Hospital of Wuhan University, Wuhan 430071, China
²Guangdong Provincial Key Laboratory of Medical Molecular Diagnostics, Guangdong Medical University, Dongguan 523808, China
³Department of Neurosurgery, Zhongnan Hospital of Wuhan University, Wuhan 430071, China

Correspondence should be addressed to Zhiqiang Li; lizq0766@163.com

Received 6 September 2016; Revised 4 December 2016; Accepted 6 December 2016

Academic Editor: Hubertus Himmerich

Copyright © 2016 Ping Wang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objectives. To investigate the potential association of tumor necrosis factor-α T-857C polymorphism with susceptibility to the five common malignant tumors. Materials and Methods. A comprehensive search of PubMed/Medline, Embase, and Web of Science databases was performed up to November 2015. Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to assess the strength of the association. Subgroup analysis, heterogeneity analyses, and publication bias were also tested in the meta-analysis. Results. A total of twenty-two publications involving 5215 cases and 6755 controls were recruited. Overall, the meta-analysis revealed an increased risk between the TNF-α T-857C polymorphism and gastric cancer susceptibility in T versus C model, heterozygote genetic model, and dominant genetic model. An increased risk between the TNF-α T-857C polymorphism and hepatocellular cancer susceptibility in homozygote genetic model and recessive genetic model was also found. No significant association was found between the TNF-α T-857C polymorphism and colorectal cancer, cervical cancer, and prostate cancer.

Conclusions. Our meta-analyses suggest that TNF-α T-857C polymorphism may be associated with increased risk of gastric cancer and hepatocellular cancer development. Therefore, the TNF-α T-857C polymorphism could be considered as one possible risk factor of gastric cancer and hepatocellular cancer according to our study.

1. Introduction

Cancer has been a disease which endangers human physical and psychosocial wellbeing, causing a significant public health and economic burden all over the world. Cancer is a multifactorial disease, and the etiology of these cancers is extremely complex. In order to understand its pathology, numerous susceptibility genes and external environmental factors appear to be considered.

Chronic inflammation has long been associated with the development of cancer. Recent evidences have reignited the interest of cancer researchers in the exciting concept of an association between chronic inflammation and cancer. Rather than protecting against cancer, growing evidence indicates that TNF-α can promote the development of cancer [1]. Previously our study also found that targeting TNF-α suppressed breast cancer growth and TNF-α monoclonal antibody exerted effectively antitumor activity [2], which further supported this assertion.

The length of TNF gene is 12 kilobases (kb) and it is located on the short arm of chromosome 6 (p21.1–p21.3) [3]. As transcription of TNF-α is regulated under genetic control, recent studies have shown that its promoter polymorphisms at TNF-α G-238A (rs361525), TNF-α G-308A (rs1800629), TNF-α T-857C (rs1799724), and TNF-α T-1031C (rs1799964) positions could regulate TNF-α production, thus affecting the risk of cancers [4–7]. Therefore, genetic polymorphisms of TNF-α gene have been supposed as candidate risk factors of cancer.

There are a large number of studies on the association between TNF-α G-308A (rs1800629), TNF-α G-238A (rs361525), and cancers [8, 9]; TNF-α G-308A (rs1800629)
and TNF-α G-238A (rs361525) have been successfully identified as risk factors of cancer. Molecular epidemiological research suggests that TNF-α T-857C (rs1799724) polymorphisms may be associated with an increased risk of cancers [10–13], but results remain controversial. TNF-α T-857C is a C to T transition in the promoter at position −857, and previous data have shown that TNF-α T-857C allele T increases the transcription of TNF-α [14–16]. Therefore, TNF-α T-857C polymorphism may be associated with cancer risk and represents candidate risk marker of cancers. To explore a more precise estimation of the relationship between TNF-α T-857C polymorphism and cancers, we performed a meta-analysis.

2. Materials and Methods

2.1. Study Selection. To identify eligible studies published before November 2015, we applied a systematic literature search strategy to the following electronic databases: PubMed/Medline, Embase, and Web of Science. We used the following keywords and subject headings in combination to identifying relevant articles in electronic databases: (tumor necrosis factor alpha OR TNF-α OR 857 C/T OR rs1799724) AND (polymorphism OR variant OR genotype OR mutation) AND (cancer OR carcinoma OR neoplasm). Duplicate articles were manually filtered using the “find duplicate function” of EndNote X7. Two of the authors reviewed results of each of the database searches to make sure that published papers were not missed.

2.2. Inclusion and Exclusion Criteria. The following inclusion criteria were used for the literature selection: (1) genotype distributions of both cases and controls were available; (2) the studies might be cohort or case-control studies; (3) articles about TNF-α T-857C polymorphism and cancer risk; (4) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI); (5) when several publications were available for the same study group, we retained the most recent one for analysis. We excluded publications as follows: (1) based on pedigree data that were excluded; (2) retrospective or cross sectional studies; (3) nonoriginal research (reviews, editorials, or commentaries), abstracts, unpublished studies, and duplicated studies; and (4) studies on animals.

2.3. Data Extraction. Two authors (Ping Wang and June Wang) independently extracted characteristics of studies and resolved any uncertainty through discussion. If these two authors could not reach a consensus, a third author was consulted to resolve the dispute and a final majority decision was made. After excluding the overlap studies and including the additional ones, this meta-analysis covered a total of 22 articles on TNF-α T-857C polymorphism. From each identified article, we extracted the first author’s name, publication year, country, ethnicity, type of disease, sample size, source of control, genotyping method, and Hardy-Weinberg equilibrium (HWE) for controls.

2.4. Statistical Analysis. The Hardy-Weinberg equilibrium (HWE) in the controls was tested by the Chi-square test for goodness of fit. The following contrasts for the associations between TNF-α T-857C polymorphism and the cancers mentioned above were evaluated: T allele versus C allele, homozygote comparison (TT versus CC), heterozygote comparison (TC versus CC), and recessive (TT versus TC + CC) and dominant (TT + TC versus CC) genetic model, respectively. The strength of association between TNF-α T-857C polymorphism and cancer risk was assessed using the pooled odds ratio (OR) with 95% confidence intervals (CIs). If the number of included studies was applicable, subgroup analysis was performed based on HWE status of controls, ethnicity, source of control, and genotyping method. The heterogeneity of the data was quantified using Chi-square statistics. Heterogeneity among studies was considered significant when $P < 0.1$ or $I^2 > 50\%$. If there was significant heterogeneity among studies, the random effects model (DerSimonian and Laird) was used; otherwise, the fixed-effects model (Mantel and Haenszel) was acceptable. We plotted Begg’s funnel plot to examine the underlying publication bias. We conducted sensitivity analysis by deleting each included study in turn.
to evaluate the overall robustness of the study’s results. All analyses were conducted using Review manager 5.3 and Stata 12.0. All the P values were two-sided.

3. Results

3.1. Study Selection and Characteristic. There were 723 papers relevant to the search words. The flowchart of selection of studies and reasons for exclusion is presented in Figure 1. Finally, a total of 22 studies were included in this meta-analysis. All those 22 studies were reported in English. The details of included studies were shown in Table 1. In the initial search, 723 articles were retrieved, and 553 studies were excluded after reading titles and abstracts. 5215 cases and 3.2. Quantitative Synthesis. The summary results of meta-analysis of the association between the TNF-α T-857C polymorphism and cancer risk are displayed in Table 2.

3.2.1. Association between the TNF-α T-857C Polymorphism and Gastric Cancer Risk. A total of 9 relevant studies, consisting of 1897 patients and 3219 controls, were examined for the association between the TNF-α T-857C polymorphism and gastric cancer risk. In all subjects, meta-analysis showed an increased risk between the TNF-α T-857C polymorphism and gastric cancer susceptibility in three genetic models (T versus C: OR = 1.12, 95% CI = 1.01–1.25, P = 0.04, I² = 0%, fixed-effects model; TC versus CC: OR = 1.16, 95% CI = 1.02–1.33, P = 0.02, I² = 0%, fixed-effects model; TT + TC versus CC: OR = 1.16, 95% CI = 1.02–1.32, P = 0.02, I² = 0%, fixed-effects model, Figure 2). Further stratified analyses based on ethnic subgroups revealed similar results in Asian populations for the T versus C model, TC versus CC model, and the dominant model. The sensitivity analysis showed the results without substantive change (Figure 3 for TT + TC versus CC model).
### Table 2: Results of overall and subgroups analyses.

<table>
<thead>
<tr>
<th></th>
<th>No T vs C</th>
<th>TT vs CC</th>
<th>TC vs CC</th>
<th>TT vs TC+CC</th>
<th>TT+TC vs CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td>Total</td>
<td>9</td>
<td>0.04</td>
<td>1.12 [0.79, 1.58]</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>HWE, yes</td>
<td>7</td>
<td>0.96</td>
<td>&lt;0.01 [1.42, 0.95]</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>HWE, no</td>
<td>2</td>
<td>0.96</td>
<td>0.64 [0.57, 0.32]</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>1</td>
<td>0.10</td>
<td>0.84 [0.66, 0.12]</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1</td>
<td>0.94</td>
<td>0.38 [0.14, 2.22]</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>HCC</td>
<td>1</td>
<td>0.99</td>
<td>0.71 [1.34, 0.23]</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>HB</td>
<td>1</td>
<td>0.90</td>
<td>0.15 [1.04, 2.34]</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>1</td>
<td>0.99</td>
<td>0.71 [0.14, 2.32]</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>PCR-RFLP</td>
<td>1</td>
<td>0.16</td>
<td>0.38 [0.10, 3.77]</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>TaqMan</td>
<td>1</td>
<td>1.07</td>
<td>0.44 [0.89, 1.61]</td>
<td>0.70</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Total</td>
<td>1</td>
<td>0.16</td>
<td>0.27 [0.08, 2.57]</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>HWE, yes</td>
<td>1</td>
<td>0.36</td>
<td>0.48 [0.05, 2.29]</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>HBE</td>
<td>1</td>
<td>0.92</td>
<td>0.09 [0.10, 3.60]</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>1</td>
<td>1.85</td>
<td>0.51 [0.60, 2.17]</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>PCR-RFLP</td>
<td>2</td>
<td>1.24</td>
<td>0.46 [0.02, 2.35]</td>
<td>0.70</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Total</td>
<td>3</td>
<td>0.75</td>
<td>0.44 [0.23, 1.54]</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Prostate cancer</td>
<td>Total</td>
<td>2</td>
<td>1.05</td>
<td>0.57 [0.11, 1.20]</td>
</tr>
</tbody>
</table>

*P* was derived from Chi-square statistics.
### Study or subgroup

<table>
<thead>
<tr>
<th>Event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Experimental</td>
</tr>
<tr>
<td>de Oliveira et al. 2015</td>
<td>105</td>
</tr>
<tr>
<td>Hou et al. 2007</td>
<td>78</td>
</tr>
<tr>
<td>Lee et al. 2004</td>
<td>112</td>
</tr>
<tr>
<td>Ohyama et al. 2004</td>
<td>107</td>
</tr>
<tr>
<td>Shirai et al. 2006</td>
<td>66</td>
</tr>
<tr>
<td>Sugimoto et al. 2007</td>
<td>39</td>
</tr>
<tr>
<td>Wu et al. 2004</td>
<td>56</td>
</tr>
<tr>
<td>Yang et al. 2009</td>
<td>35</td>
</tr>
<tr>
<td>Zambon et al. 2005</td>
<td>46</td>
</tr>
</tbody>
</table>

#### Total (95% CI)

<table>
<thead>
<tr>
<th>Event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Experimental</td>
</tr>
<tr>
<td>1897</td>
<td>644</td>
</tr>
</tbody>
</table>

### Heterogeneity:

- $\chi^2 = 6.04$, df = 8 ($P = 0.64$);
- $I^2 = 0$

Test for overall effect: $Z = 2.30$ ($P = 0.02$)

### Test for subgroup differences:

- $\chi^2 = 1.14$, df = 1 ($P = 0.29$), $I^2 = 12.3$

### Figure 2: Continued.
807 cases and 1510 controls were included in this analysis. All these four studies are based on Asian population. A significant increase in hepatocellular cancer risk was observed in the Asian population in two gene models (TT versus CC: \( OR = 1.65, 95\% CI = 1.06–2.57, P = 0.03, I^2 = 46\% \), fixed-effects model; TT versus TC + CC: \( OR = 1.61, 95\% CI = 1.04–2.49, P = 0.03, I^2 = 37\% \), fixed-effects model, Figure 4). Furthermore, analysis by excluding studies with control inconsistent with HWE showed elevated cancer risk in homozygote comparison and recessive genetic model (TT versus CC: \( OR = 2.29, 95\% CI = 1.16–4.51, P = 0.02, I^2 = 46\% \), fixed-effects model; TT versus TC + CC: \( OR = 2.21, 95\% CI = 1.12–4.93, P = 0.02, I^2 = 37\% \), fixed-effects model). Sensitivity analyses were also conducted, and no conspicuous change of the pooled ORs was detected.

3.2.3. Association between the TNF-α T-857C Polymorphism and Colorectal Cancer Risk. We included four studies to describe the association between the TNF-α T-857C polymorphism and colorectal cancer risk (Figure 5). However, our analysis showed no association between the polymorphism and colorectal cancer risk. The result of stratified analyses based on ethnic subgroups also revealed negative association. The sensitivity analysis showed the results without substantive change.

3.2.4. Association between the TNF-α T-857C Polymorphism and Cervical Cancer and Prostate Cancer Risk. Of all the included studies, only three case-control studies involving 480 cases and 520 controls focused on cervical cancer and two studies involving 1336 cases and 2517 controls on prostate cancer. Meta-analysis of our result revealed negative association between the polymorphism and these two cancers. Table 2 showed the result of our analysis.

3.3. Publication Bias. Due to limitations of the quantity of included studies, we just test the publication bias between target gene polymorphism and gastric cancer. Funnel plots were conducted to assess the publication bias, and no evidence of asymmetry was observed (Figure 6 for TT + TC versus CC model). This result was further supported by the analysis using Egger’s test (TT versus C: \( P = 0.06 \); TT versus
4. Discussion

Genetic factors have been shown to influence the susceptibility of patients to various diseases and have attracted increasing attention. Chronic inflammation and cytokines are thought to play the most important role in tumor promotion and progression by driving angiogenesis, cell metastasis, and immune-suppression. TNF is an important infectious agent in inflammation progression as well as cancer development [39]. In our meta-analysis, we aggregated data from published studies to estimate genetic associations between the TNF-α T-857C polymorphism and the susceptibility of five common cancers. Our analysis provided some evidence to support an elevated risk between the TNF-α T-857C polymorphism and gastric cancer and hepatocellular cancer susceptibility. But no associations were found in the remained three cancers (colorectal cancer, cervical cancer, and prostate cancer). In the stratified analysis by ethnicity for the TNF-α T-857C polymorphism and gastric cancer susceptibility, we found a significant risk in Asian populations rather than Caucasian populations, suggesting that the increased gastric risk may be ethnoscific. In the stratified analysis based on HWE, we found an elevated risk between the TNF-α T-857C polymorphism and hepatocellular cancer susceptibility. The results of HWE indicated that studies out of HWE might bias the result. Hence, more high quality primary studies are needed. We did not found any meaningful associations in the stratified analysis in all included cancer types by source of control and genotyping method.

To date, numerous related studies have been conducted to investigate the association between the TNF-α T-857C polymorphism and disease risk; however, the exact role of TNF-α T-857C as a carcinogen is still controversial. The previous meta-analysis by Wei et al. in 2011 also investigated the relationship between the TNF-α T-857C polymorphism and hepatocellular cancer susceptibility [40]. However, no association was observed between TNF-α T-857C polymorphism
and hepatocellular cancer susceptibility in their study. Compared with their study, our meta-analysis had a larger sample size than them, which increased the statistic power. We included 4 studies, consisting of 807 patients and 1510 health controls, and revealed that TNF-α T-857C polymorphism is associated with a significant increased risk of HCC in homozygote model and recessive genetic model. With regard to the TNF-α T-857C polymorphism and gastric cancer susceptibility, the study of Cen and Wu [41] was published in 2013. Compared with the previous meta-analysis, we retained the most recent study which increased new cases for analysis when two publications [25, 42] were available. Moreover, in our meta-analysis, we conducted four subgroups analysis based on ethnicity, source of control, genotyping method, and HWE for controls and explained these roundly, while they just conducted subgroups analysis based on race. Thus, our results are more reliable and dependable. Hence, this is the most comprehensive meta-analysis that investigated the relationship between the TNF-α T-857C polymorphism and gastric cancer susceptibility.

It is important to note the limitations of our meta-analysis. First, heterogeneity is one of the important issues in genetic association meta-analysis. In our study, some genetic models showed clear homogeneity while others had various heterogeneities, either in total populations or in subgroup analysis. Heterogeneity may be caused by different environment or lifestyle; however, we could not study these factors due to lack of individual data. Second, it should be noted that publication bias is a potential threat to the validity of our meta-analysis because of limitations of the quantity of included studies. In addition, only articles published in English were selected and this may result in language bias leading to an overestimation of effect sizes. Therefore, the statistic power of this meta-analysis might be affected and false positive or false negative rate might occur. Third, in some cancer types, since the number of relevant original documents was limited, there was not enough power to identify the relationship between TNF-α T-857C variant and cancer risk. Thus, further identification based on well-designed studies with large sample sizes is needed. Fourth, as we know, cancer is a multifactorial disease and genetic mutations, environmental changes, lifestyle, diet, age, and gender may be factors in the development of cancer. Like all meta-analyses, it is a secondary retrospective study; therefore, we could not explain the fundamental underlying mechanisms clearly due to unadjusted data.

5. Conclusions

This meta-analysis with published data suggested that the TNF-α T-857C polymorphism is a risk factor for gastric cancer, especially in Asian populations. Our result also indicated that the TNF-α T-857C polymorphism also plays an important role in hepatocellular cancer development. There is lack of association between the TNF-α T-857C polymorphism and colorectal cancer, cervical cancer, prostate cancer, and breast cancer. However, considering the limited objectives of this meta-analysis, further studies providing adjusted data, large sample size, and gene-environment detailed information are needed to assess the findings.

Competing Interests

The authors have no financial conflict of interests.

Acknowledgments

This study was supported by National Natural Science Funds (nos. 81573459, 81472033, and 30901308), the National Science Foundation of Hubei Province (nos. 2013CFB233 and 2013CFB235), the project of Wuhan Science and Technology Bureau (nos. 2014070404010223 and 20140601010045), and Hubei Province Health and Family Planning Scientific Research Project (WJ2015Q021).

References


