Association between tumor necrosis factor alpha gene polymorphisms and multiple myeloma risk: an updated meta-analysis

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\begin{abstract}
\textbf{Objective:} This study aimed to investigate the relationship between tumor necrosis factor alpha (TNFa) polymorphisms and multiple myeloma (MM) risk.

\textbf{Methods:} Eligible studies were retrieved from PubMed, the Cochrane Library, Embase, CNKI and the Wanfang database. Polymorphisms of TNFa-308 G/A, TNFa-857 C/T, and TNFa-238 G/A were analyzed based on the allele, recessive, dominant, and additive-dominant models. The meta-analysis was conducted using R 3.12 software. Odds ratio (OR) and 95% confidence intervals (CI) were used as evaluation indicators. Heterogeneity among studies was detected. Publication bias was evaluated. Sensitivity and power analyses were also conducted.

\textbf{Results:} Significant associations existed between ‘TT vs. CC’ (OR = 2.3752, 95% CI = 1.1342–4.9740) and ‘TT vs. CC + TC’ (OR = 2.0802, 95% CI = 1.0250–4.2218) models of the TNFa-857 C/T gene and MM risk. There were no significant differences in other genetic models of TNFa-857 C/T or any genetic models of TNFa-308 G/A and TNFa-238 G/A. No significant publication bias existed among the studies. In addition, sensitivity analyses showed that meta-analysis results of all genetic models of the TNFa-857 C/T gene did not change after omitting one of these studies, but most models of TNFa-857 C/T and TNFa-308 G/A exhibited significant changes.

\textbf{Conclusion:} Our findings indicate that the ‘TT vs. CC’ and ‘TT vs. CC + TC’ of TNFa-857 C/T are correlated with MM risk. TNFa-857 C/T may be a risk factor for MM development. There is no association between TNFa-238/-308 polymorphisms and MM risk.
\end{abstract}

\section*{Introduction}

Multiple myeloma (MM) is a type of hematologic tumor that features an abnormal growth of malignant plasma cells in the bone marrow [1,2] and accounts for approximately 10%–15% of all hematologic malignancies and 1% of total malignancies [3,4]. MM has a multifactorial etiology that is influenced by various environmental and genetic factors [5–7]. Recent evidences have confirmed the association between genetic polymorphisms and MM risk [8–10].

Tumor necrosis factor alpha (TNFa) is one of the most important cytokines and can function as a prominent mediator of immune regulation [11]. An autocrine function for TNFa has been implicated in lymphoproliferative diseases, such as chronic lymphocytic leukemia and plasma cell myeloma [12]. In MM, TNFa is a key regulator in the generation of malignant plasma cells [13,14], and an enhanced expression of TNFa is correlated with an increased aggressiveness of MM [15].

Accumulating evidence has confirmed that TNFa polymorphisms are associated with increased MM risk. For example, TNFa-238 G/A is involved in MM development and prognosis following treatment [14]. TNFa-857 T allele, or TT genotype, is correlated with a risk of developing MM among the Chinese population of Shangdong area [16]. However, Basmaci et al. revealed that TNFa-308 GG polymorphism was lowly expressed in MM patients and might play a key role in MM pathogenesis, but TNFa-238/857 polymorphisms did not exhibit any difference between MM patients and healthy controls [10]. Moreover, a previous meta-analysis has shown that TNFa-238/-308 polymorphisms cannot influence MM risk [17]. These findings indicate that there remains a great controversy regarding the association between TNFa polymorphisms and MM risk. In addition, the previous meta-analysis did not analyze the link between TNFa-857 polymorphisms and MM risk. These findings prompted us to perform this updated meta-analysis. The findings of this study will provide new evidence for explaining the significance of TNFa polymorphisms in predicting MM risk.

\section*{Materials and methods}

\textbf{Search strategy}

Relevant studies were searched for via Embase (http://www.embase.com), PubMed (http://www.ncbi.nlm.nih.gov).
Key words used for retrieving studies were ‘multiple myeloma’ OR ‘MM’ OR ‘Kahler’s disease’ OR ‘Huppert’s disease’ AND ‘tumor necrosis factor alpha’ OR ‘TNFα-308’ OR ‘TNFα-238’ OR ‘TNFα-857’ AND ‘polymorphi*’. The deadline for retrieval was 12 April 2018.

**Study selection criteria**

Inclusion criteria for eligible studies were (1) studies reported the distributions of TNFα-308 G/A, TNFα-238 G/A and TNFα-857 C/T polymorphisms in MM and non-MM patients; (2) accurate genotype or allele frequency data were available in the studies; (3) studies were case–control studies.

Exclusion criteria were (1) data were incomplete and could not be used for statistical analysis; (2) studies were reviews, reports, comments, letters, editorials, etc.; (3) repetitive publications and studies with data applied in several articles, except for one study with the latest research or the most complete information.

**Data extraction**

Useful data were independently extracted from retrieved articles by two investigators and included the first author’s name; publication year; geographical location; number and demographic data characteristics, including sex and age of participants in case and control groups; and the number of patients and controls with each gene polymorphism in each study. The Newcastle–Ottawa Scale (NOS) provided by the Agency for Healthcare Research and Quality was used for assessing the quality of the studies included [18]. Divergences in data extraction and quality assessment were settled through discussion with a third investigator.

**Statistical analysis**

The Hardy–Weinberg equilibrium (HWE) was assessed in control participants using chi-squared ($\chi^2$) test [19]. A meta-analysis was conducted using R 3.12 software. Odds ratio (OR) and 95% confidence intervals (CI) were applied as evaluation indicators to estimate data [20]. Heterogeneity among studies was detected using chi-squared $Q$ statistic [21] and $I^2$ value. If $P < 0.05$ or $I^2 > 50\%$, then heterogeneity was considered significant, and the random-effects model was thus applied to pool the effect sizes; otherwise, the fixed-effects model was chosen [22]. Publication bias was evaluated using Egger’s method [23]. Sensitivity analyses were conducted by omitting one study at a time. Power analyses were performed using Power Analysis and Sample Size (PASS) 2008 Statistical Software [24].

**Results**

**Characteristics of eligible studies**

Based on the preliminary search strategy outlined above, study selection was conducted according to the flow chart shown in Figure 1. Briefly, 83 articles were retrieved from PubMed, Embase, Cochrane Library, CNKI, and the Wanfang database. After removing duplicates, 52 articles were included for abstract review. Of these, 18 articles were excluded due to obvious irrelevance. Of the remaining 34 articles, 10 additional articles were excluded due to repetitive publications or lack of data. Finally, 13 articles were included for meta-analysis.

**Figure 1.** Flowchart of the literature search and study selection.
were initially recruited from PubMed [20], Embase [24], the Cochrane Library [3], CNKI [15] and the Wanfang database [21]. Of these, 31 articles from repeated search results and 18 obviously irrelevant articles were removed. After reading the abstracts, three letters/editorials, three case series/reports, and four animal/cell studies were excluded. Upon further review of the full text of the remaining 24 articles, three reviews, five studies from which data could not be extracted, and three studies with duplicated populations were excluded. Finally, 13 eligible studies were included [10,14,16,25–34].

The eligible studies were published between 2000 and 2016. A total of 4110 participants, including 2421 MM patients and 1689 non-MM participants, were included from China, U.S.A., Turkey, U.K., Hungary, Italy, Russia, Sweden, and Germany. With regard to demographic characteristics, participants were middle-aged, and the distribution of men and women was evenly balanced, except for a study reported by Brown et al. [31]. Single nucleotide polymorphisms (SNPs) were detected using PCR-RFLP and PCR-LDR. In addition, results of quality assessment showed that the NOS score was 3–8 points, indicating that the quality of most included studies was acceptable. Among the articles, 10 had an NOS score of ≥ 6 and the others had low quality. According to the results of the HWE test, all participants in the control group were in line with the HWE (Table 1), indicating that the population representativeness was good.

**Summary results of the meta-analysis**

This meta-analysis investigated the relationship between MM risk and the allele model (TNFα-308, A vs. G; TNFα-238, A vs. G; TNFα-857, T vs. C), additive-dominant model (TNFα-308, AA vs. GG, AG vs. GG; TNFα-238, AA vs. GG, AG vs. GG; TNFα-857, TT vs. CC, TT vs. CC), recessive model (TNFα-308, AA vs. GG + AG; TNFα-238, AA vs. GG + AG; TNFα-857, TT vs. CC + TC, and dominant model (TNFα-308, AA + AG vs. GG; TNFα-238, AA + AG vs. GG; TNFα-857, TT + TC vs. CC), respectively.

A heterogeneity test was conducted to select a suitable effect model to pool the effect sizes. As shown in Table 2, significant heterogeneity existed in the ‘A vs. G’, ‘AG vs. GG’, and ‘AA + AG vs. GG’ models of the TNFα-308 G/A gene and the ‘T vs. C’ and ‘TT + TC vs. CC’ models of the TNFα-857 C/T gene; thus, the random-effects model was applied to combine the effect sizes of these models. Other models used the fixed-effects model.

The results of the meta-analysis with regard to the relationship between TNFα polymorphisms and MM risk showed that significant associations existed between ‘TT vs. CC’ (OR = 2.3752, 95% CI = 1.1342–4.9740) and ‘TT vs. CC + TC’ (OR = 2.0802, 95% CI = 1.0250–4.2218) of TNFα-857 C/T and MM risk, indicating that TNFα-857 C/T might be a risk factor for MM development (Table 2 and Figure 2). However, no genetic models of TNFα-238 G/A and TNFα-308 G/A exhibited significant associations with MM risk (Table 2 and Figures 3 and 4), indicating that these two TNFα polymorphisms do not result in MM development.

The results of Egger’s test did not display a significant publication bias among studies of the above three TNFα polymorphisms (Table 2), confirming that our conclusions were more reliable.

In addition, sensitivity analysis results showed that the meta-analysis results for all genetic models of the TNFα-238 G/A gene did not markedly change after omitting one of these studies. However, meta-analysis results of the ‘AA vs. GG’, ‘AG vs. GG’, and ‘AA vs. GG + AG’ models of the TNFα-308 G/A gene and the ‘TT vs. CC’, ‘TT vs. CC + TC’, and ‘TT + TC vs. CC’ models of the TNFα-857 C/T gene exhibited significant changes (data not shown).

Further power analyses showed that all genetic models of the above three TNFα polymorphisms had a low statistical power (all power values <0.80), particularly TNFα-238 G/A. The power value of all genetic models of TNFα-238 G/A was <0.20.

**Discussion**

The present meta-analysis evaluated the relationship between TNFα polymorphisms and MM risk. The results showed that ‘TT vs. CC’ and ‘TT vs. CC + TC’ models of the TNFα-857 C/T gene had significant associations with MM risk. There were no significant differences in other genetic models of TNFα-857 C/T and any genetic models of TNFα-308 G/A and TNFα-238 G/A. These data suggest that TNFα-857 C/T polymorphisms are causative factors for MM.

Increasing evidences have reported that several proinflammatory cytokines, particularly TNFα, play crucial roles in the pathology of MM [35,36]. In addition, TNFα polymorphisms have been shown to influence TNFα production [37,38]. Consistent with the findings of Liu et al. that TNFα-857 T allele, or TT genotype, is associated with MM risk in the Chinese population of the Shangdong area [16], our results showed that ‘TT vs. CC’ and ‘TT vs. CC + TC’ models of the TNFα-857 C/T gene have significant associations with MM risk. Although Basmaci et al. did not conclude any association of TNFα-857 polymorphism with MM risk, our analysis prompts us to speculate that TNFα-857 C/T is a risk factor for MM development. In addition, although previous studies have confirmed that TNFα-238 site variations are associated with a favorable overall response rate following thalidomide and dexamethasone therapy [32] and that the TNFα-308 polymorphism might play a key role in MM pathogenesis [10],...
| Author       | Year | Location | Detection | NOS | Group | Male/Female | Age-median (Min-Max)/mean ± SD | TNF-308 G/A | HWE | TNF-238 G/A | HWE | TNF-857 C/T | HWE | χ² | P       |
|--------------|------|----------|-----------|-----|-------|-------------|---------------------------------|-------------|-----|-------------|-----|-------------|-----|-----|---------|
| Au WY 2006   | China | PCR-RFLP | 6         | MM  | 82    | 47/35       | 64 (29–91)                      | 67          | 15  | 0           | 1.000 | NA          | NA  | NA  | NA      |
|              |      |          |           | Co  | 98    | NA          | 80                              | 18          | 0    | NA          | NA  | NA          | NA  | NA  | NA      |
| Basmaci C 2016 | Turkey | PCR-RFLP | 7         | MM  | 77    | NA          | 59 (31–81)                      | 59          | 18  | 0           | 0.5856 | 64          | 13  | 0   | 1.000   |
|              |      |          |           | Co  | 77    | 31/46       | 42                              | 35          | NA  | 0           | NA  | NA          | NA  | NA  | NA      |
| Brown EE 2007 | U.S.A. | TaqMan   | 6         | MM  | 127   | 0/127       | 21–84                           | 99          | 23  | 3           | 1.724 | 0.0000000001192 | 0 |    |         |
|              |      |          |           | Co  | 536   | 0/536       | 21–84                           | 388         | 137 | 18          |        | NA          | NA  | NA  | NA      |
| Davis FE 2000 | U.K. | PCR      | 5         | MM  | 198   | 112/86      | Median: 67                      | 116         | 79  | 3           | 1.563 | 0.2112 |        | NA  | NA  | NA      |
|              |      |          |           | Co  | 250   | 134/116     | NA                              | 167         | 78  | 5           |        | NA          | NA  | NA  | NA      |
| Du J 2010    | China | PCR-RFLP | 6         | MM  | 210   | 144/66      | 28–81                           | 182         | 26  | 2           | 0.0841 | 191         | 18  | 1   | 1.000   |
|              |      |          |           | Co  | 218   | NA          | 170                             | 48          | 0    | NA          | NA  | NA          | NA  | NA  | NA      |
| Kadar k 2008 | Hungary | PCR-RFLP | 7         | MM  | 94    | 28/66       | 68.0 (59.0–73.0)                | 85          | 9   | 0           | 1.000 | 103         | 12  | 0   | 1.791   |
|              |      |          |           | Co  | 141   | 81/60       | 68.9 (62.9–74.0)                | 111         | 30  | 0           |        | 448         | 56  | 4   | NA      |
| Liu YH 2012  | China | PCR-LDR  | 3         | MM  | 86    | 50/36       | 55 (21–77)                      | 73          | 13  | 0           | 0.6075 | 80          | 6   | 0   | 0.286   |
|              |      |          |           | Co  | 172   | 100/72      | 54 (21–78)                      | 153         | 29  | 0           |        | 153         | 18  | 1   | 141     |
| Lu ZM 2007   | China | PCR-RFLP | 3         | MM  | 35    | 19/16       | 55 (27–70)                      | 24          | 9   | 2           | 0.068  | 0.7947 |        | NA  | NA  | NA      |
|              |      |          |           | Co  | 38    | 20/18      | 36.6 (20–45)                    | 28          | 9   | 1           |        | NA          | NA  | NA  | NA      |
| Martino A 2012 | Italy,Germany | TaqMan | 8         | MM  | 202   | 108/94     | 61.6 ± 9.9                      | 153         | 44  | 5           | 0.108  | 0.7419 |        | NA  | NA  | NA      |
|              |      |          |           | Co  | 235   | 129/106    | 58.8 ± 10.9                     | 189         | 44  | 2           |        | NA          | NA  | NA  | NA      |
| Morgan GJ 2005 | U.K. | IHR,PCR  | 6         | MM  | 181   | NA         | NA                              | 141         | 36  | 3           | 1.667  | 0.1966 | 161    | 18  | 1 | 1.084   |
|              |      |          |           | Co  | 233   | NA         | 158                             | 64          | 11  | 11          |        | 217         | 15  | 1   | 200     |
| Neben K 2002 | Germany | NA      | 7         | MM  | 255   | NA         | NA                              | 184         | 57  | 14          | 0.0865 | 236         | 19  | 0   | 1.000   |
|              |      |          |           | Co  | 200   | NA         | 142                             | 57          | 1    | NA          |        | 177         | 23  | 0   | NA      |
| Yakupova EV 2003 | Russia | PCR      | 6         | MM  | 69    | NA         | 32–75                           | 49          | 19  | 1           | 0.176  | 0.6749 |        | NA  | NA  | NA      |
|              |      |          |           | Co  | 94    | NA         | 72                              | 20          | 2    | NA          |        | NA          | NA  | NA  | NA      |
| Zheng CY 2000 | Sweden | PCR      | 6         | MM  | 73    | 33/40      | 67 (34–89)                      | 52          | 21  | 2           | 0.460  | 0.4976 |        | NA  | NA  | NA      |

Note: PCR-LDR: polymerase chain reaction-ligation detection reaction; IHG: induced heteroduplex generator analysis; PCR-RFLP: restriction fragment length polymorphism polymerase chain reaction; MM: multiple myeloma group; Co: control group; NOS: Newcastle-Ottawa Scale; N: total number of including; HWE: Hardy–Weinberg equilibrium tests of control.

*Likelihood-ratio χ²*.
### Table 2. Summary results of meta-analysis.

| SNP     | Gene model | Sample size | Test of association | Test of heterogeneity | Publication bias |
|---------|------------|-------------|---------------------|-----------------------|-----------------|
|         |            |             | Z       | P        | Q          | I² (%) | t     | P value | Power |
| TNFα-308 G/A | A vs. G    | 13          | 3376    | 0.8834  | [0.7074, 1.0303] | 1.09 | 0.2741 | R       | 29.23 <0.01 | 58.9 | 0.5172 | 0.6152 | 0.3015 |
|          | AA vs. AG  | 9           | 1035    | 1.2878  | [0.9076, 1.0978] | 0.66 | 0.5068 | F       | 12.63 0.13 | 36.7 | 0.7064 | 0.9028 | 0.1047 |
|          | AA vs. GG + AG | 9     | 1349    | 1.3349  | [0.8205, 2.1718] | 1.16 | 0.2447 | F       | 12.36 0.14 | 35.3 | 0.5647 | 0.5899 | 0.1262 |
|          | AA + AG vs. GG | 13   | 1688    | 0.8400  | [0.6550, 1.0771] | 1.37 | 0.1693 | R       | 29.76 <0.01 | 59.7 | 0.4228 | 0.6806 | 0.4597 |
| TNFα-238 G/A | A vs. G    | 6           | 1846    | 0.9407  | [0.7104, 1.2456] | 0.43 | 0.6694 | F       | 0.77 0.33 | 13.4 | 0.2053 | 0.8474 | 0.1335 |
|          | AA vs. GG  | 4           | 537     | 1.0224  | [0.2356, 4.0271] | 0.03 | 0.9747 | F       | 0.84 0.84 | 0    | 0.5243 | 0.6524 | 0.0870 |
|          | AA vs. GG + AG | 4   | 591    | 1.0248  | [0.2598, 4.0426] | 0.03 | 0.9721 | F       | 0.81 0.85 | 0    | 0.5255 | 0.6516 | 0.0862 |
|          | AA + AG vs. GG | 6   | 923    | 0.9450  | [0.7059, 1.2652] | 0.38 | 0.7042 | F       | 5.51 0.36 | 9    | 0.3061 | 0.7748 | 0.1096 |
| TNFα-857 C/T | TC vs. CC | 3          | 320     | 1.1497  | [0.7904, 1.6275] | 0.73 | 0.4656 | F       | 3.09 0.21 | 35.3 | 1.6502 | 0.3468 | 0.1492 |
|          | TT vs. CC  | 3           | 277     | 2.3752  | [1.1342, 4.9740] | 2.29 | 0.0218 | F       | 1.45 0.48 | 0    | 0.7981 | 0.5712 | 0.7613 |
|          | TT vs. CC + TC | 3   | 343    | 2.0802  | [0.2356, 4.0271] | 2.03 | 0.0425 | F       | 1.64 0.44 | 0    | 1.0002 | 0.4999 | 0.7344 |
|          | TT + TC vs. CC | 3  | 343    | 1.3113  | [0.7932, 2.1676] | 1.06 | 0.2907 | R       | 4.03 0.14 | 50.3 | 2.8997 | 0.2114 | 0.4630 |

Note: OR: odds ratio; CI: confidence interval; K: number of included studies; MM: multiple myeloma group; Co: control group; R: random-effects model; F: fixed-effects model.

*Random-effects model was used when P for heterogeneity test was <0.05, otherwise the fixed-effects model was used; P < 0.05 is considered statistically significant for Q statistics; Egger’s test to evaluate publication bias, P < 0.05 is considered statistically significant.

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**Figure 2.** Meta-analysis of associations between genetic models of tumor necrosis factor alpha-857 C/T polymorphisms and multiple myeloma risk.
our results were in line with the findings of a previous meta-analysis [17] and we still cannot infer any association between TNFα-308/238 polymorphisms and MM risk.

Similar to other meta-analyses, significant heterogeneity existed among the articles included in the present meta-analysis in relation to the ‘A vs. G’, ‘AG vs. GG’, and ‘AA + AG vs. GG’ models of the TNFα-308 G/A gene and the ‘T vs. C’ and ‘TT + TC vs. CC’ models of the TNFα-857 C/T gene. For this meta-analysis, studies from different geographical regions, including China, U.S.A., Turkey, U.K., Hungary, Italy, Russia, Sweden and Germany, were included, which may explain the heterogeneity of genetic diversity caused by differences in regional living habits and living environments as well as disparities in economic development levels. Other confounding factors, such as sex and age, may also play a role in this heterogeneity.

Several limitations should be considered when explaining our results. First, because data from some
studies were incomplete, particularly demographic data, the covariates were not calibrated in this study. These incomplete data may be potentially confounding factors affecting the results of this meta-analysis. Second, sensitivity analysis showed that meta-analysis results for the partial models of TNFα-
308 G/A and TNFα-857 C/T exhibited significant changes after omitting one of these studies. Thus, more relevant studies are required to confirm our findings. Third, power analysis showed that all genetic models of the above three TNFα polymorphisms had a low statistical power, particularly in genetic models of TNFα-238 G/A, with all power values being <0.20. These data imply that further research is needed to support our results. Therefore, in future, more studies with bigger sample sizes should be conducted for further evaluation of any associations.

Taken together, the present meta-analysis reveals that the ‘TT vs. CC’ and ‘TT vs. CC + TC’ of TNFα-857 C/T are correlated with MM risk. TNFα-857 C/T may be a risk factor for MM development. There is no association between TNFα-238 or TNFα-308 polymorphisms and MM risk.

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