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*Original Article*

# TGF-β1 C-509T and T869C polymorphisms and cancer risk: a meta analysis

You-You Gu[1*], Huan Wang[2,3*], Su Wang[1]

*[1]Department of Endocrinology, The Fifth Central Hospital of Tianjin, China; [2]Community Health Service Center of Hu Jiayuan Street, Binhai New District, Tianjin, China; [3]Graduate School of Tianjin Medical University, China. [*]Equal contributors.*

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**Abstract:** Objective The association between polymorphism of TGF-β1 and cancer risk has been discussed. Method A comprehensive electronic search was performed to identify articles published up until 12 December 2014 in Medline and Embase databases. The statistical analysis was performed by STATA 11.0 software and Review Manager 5.1 software. Results: In the present meta analysis, for C-509T (31 studies, 12944 cases and 15530 controls), no significant cancer risk was found in the overall analysis. In subgroup analysis, C-509T polymorphism was associated with decreased cancer risk in Asian population (OR=0.73 and 95% CI=0.59-0.90 for CT vs. CC), and there were no significant risks in gastric cancer, breast cancer, and other cancers. For T869C (11 studies, 2730 cases and 2973 controls), significantly increased risks of cancer were observed, and the ORs (95% CI) were 1.81 (1.18-2.78) for CC vs. TT, 1.50 (1.07-2.09) for TC vs. TT, 1.61 (1.13-2.30) for TC+CC vs. TT and 1.38 (1.11-1.73) for C-allele vs. T-allele, respectively. Subgroup analyses stratified by ethnicity and types of cancer were also performed, and the results indicated that T869C polymorphism was associated with cancer risk in Caucasion [1.93 (1.52-2.46) for TC vs. TT], but not in Asian [1.23 (0.80-1.90) for TC vs. TT]. We also observed that the T869C was associated with increased risk of squamous cell cancer of head and neck (SCCHN) [1.34 (1.07-1.67) for TC vs. TT]. Conclusion Decreased cancer risk association was observed in Asian for C-509T and significantly increased risk of cancer was observed for T869C.

**Keywords:** TGF-β1, polymorphism, cancer, meta-analysis

## Introduction

Cancer is thought to be a multifactorial, multigenetic, and multistage disease resulting from complex interactions between environmental and genetic factors. Transforming growth factor beta-1 (TGF-β1), as a multifunctional cytokine, it influences the process of cell cycle regulation, cell differentiation, migration and vascularization, which has been extensively studied for many years. The TGF-β1 gene is located at 19q13.1-q13.3, and contains several single nucleotide polymorphisms (SNPs), which affect the gene function [1]. The commonly studied C-509T and T869C polymorphisms, which are located in the promoter region of TGF-β1 gene, may directly influence the expression profiles. The relationship between TGF-β1 polymorphism and risk of cancer remains inconclusive [2]. Therefore, we chose to perform a meta analysis to assess the association between TGF-β1 polymorphism and cancer risk.

## Materials and methods

### *Search strategy, inclusion criteria, exclusion criteria, and information extracted*

A comprehensive electronic search was performed to identify articles published up until 12 December 2014 in Medline and Embase databases by two investigators (Y. Gu and H. Wang). The keywords we used were: "TGF-β1", "C-509T", "T869C", "polymorphism", "cancer", "neoplasm", "carcinoma", "tumor", and references of all the included articles were also hand searched. Studies included in our meta analysis had to meet the following inclusion criteria: 1) prospective cohort or case control studies, 2) studies investigating with TGF-β1 polymorphism and cancer risk, and 3) containing available genotype frequency. The exclusion criteria: 1) no control group, 2) duplicate Publication, 3) no available data, 4) low quality research. Information regarding the following

**Table 1.** Characteristics of primary studies for C-509T in the meta-analysis

| Author | Years | Country | Ethnicity | Type of cancer | Genotype distribution | | | | | | T allele (frequency) | | Quality score | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | case | | | control | | | | | | |
| | | | | | TT | CT | CC | TT | CT | CC | case | control | | |
| Amirghofran | 2009 | Iran | Asian | Colorectal cancer | 29 | 54 | 51 | 41 | 64 | 33 | 41.79% | 52.90% | 9 | 0.41 |
| Babyshkina | 2011 | Siberian | Caucasian | Breast cancer | 21 | 108 | 89 | 54 | 133 | 103 | 34.40% | 41.55% | 7 | 0.34 |
| Berndt | 2007 | America | Caucasian | Colorectal cancer | 74 | 319 | 340 | 52 | 345 | 356 | 31.86% | 29.81% | 5 | 0.01 |
| Bhayal | 2011 | India | Caucasian | Gastric cancer | 9 | 35 | 26 | 6 | 42 | 52 | 37.86% | 27.00% | 5 | 0.51 |
| Chung | 2007 | Korea | Asian | Colorectal cancer | 30 | 69 | 53 | 53 | 137 | 60 | 42.43% | 48.60% | 9 | 0.13 |
| Cingeetham | 2013 | India | Caucasian | Breast cancer | 23 | 66 | 64 | 22 | 36 | 70 | 36.60% | 31.25% | 5 | 0.00 |
| Crivello | 2006 | Italy | Caucasian | Colorectal cancer | 14 | 29 | 19 | 22 | 58 | 44 | 45.97% | 41.13% | 6 | 0.70 |
| David | 2007 | America | Caucasian | Breast cancer | 89 | 506 | 600 | 154 | 723 | 786 | 28.62% | 31.00% | 6 | 0.51 |
| Dunning | 2003 | UK | Caucasian | Breast cancer | 328 | 1391 | 1617 | 284 | 1441 | 1727 | 30.68% | 29.10% | 8 | 0.49 |
| Falleti | 2008 | Italy | Caucasian | Hepatocellular cancer | 53 | 85 | 50 | 22 | 61 | 57 | 50.80% | 37.50% | 7 | 0.40 |
| Gu | 2010 | China | Asian | Gastric cancer | 132 | 250 | 202 | 133 | 225 | 110 | 44.01% | 52.46% | 5 | 0.43 |
| Hu | 2012 | China | Asian | Nasopharyngeal cancer | 80 | 224 | 208 | 172 | 337 | 203 | 37.50% | 47.82% | 5 | 0.17 |
| Jin | 2007 | China | Asian | Esophageal cancer | 47 | 57 | 119 | 156 | 321 | 119 | 33.86% | 53.10% | 9 | 0.05 |
| JinG | 2007 | China | Asian | Gastric cancer | 161 | 228 | 247 | 156 | 321 | 199 | 43.24% | 46.82% | 9 | 0.23 |
| Kang | 2005 | Korea | Asian | Lung cancer | 104 | 197 | 131 | 105 | 223 | 104 | 46.88% | 50.12% | 8 | 0.50 |
| Li | 2008 | China | Asian | Gastric cancer | 49 | 87 | 31 | 51 | 76 | 66 | 55.39% | 46.11% | 5 | 0.00 |
| Lin | 2010 | China | Asian | Gastric cancer | 61 | 119 | 94 | 60 | 139 | 78 | 43.98% | 46.75% | 7 | 0.90 |
| Peng | 2009 | China | Asian | Hepatocellular cancer | 92 | 198 | 89 | 93 | 156 | 50 | 50.40% | 57.19% | 5 | 0.26 |
| Qi | 2009 | China | Asian | Colorectal cancer | 45 | 69 | 36 | 140 | 257 | 106 | 53.00% | 53.38% | 6 | 0.55 |
| Qianren | 2004 | Germany | Caucasian | Breast cancer | 26 | 161 | 204 | 38 | 214 | 256 | 27.24% | 28.54% | 6 | 0.46 |
| Quarmby | 2002 | UK | Caucasian | Breast cancer | 7 | 45 | 49 | 9 | 37 | 56 | 29.21% | 26.96% | 6 | 0.43 |
| Shin | 2005 | China | Asian | Breast cancer | 299 | 559 | 260 | 318 | 628 | 260 | 51.74% | 52.40% | 8 | 0.13 |
| Singh | 2009 | India | Caucasian | Cervical cancer | 34 | 65 | 51 | 28 | 81 | 53 | 44.33% | 42.28% | 8 | 0.76 |
| Vishnoi | 2008 | India | Caucasian | Gallbladder cancer | 24 | 72 | 30 | 34 | 96 | 60 | 47.62% | 43.16% | 8 | 0.68 |
| Wei | 2007 | China | Asian | Esophageal cancer | 69 | 122 | 56 | 63 | 124 | 73 | 52.63% | 48.08% | 5 | 0.47 |
| WeiY | 2007 | China | Asian | Nasopharyngeal cancer | 45 | 46 | 17 | 31 | 60 | 29 | 62.96% | 50.83% | 9 | 0.99 |
| WU | 2010 | China | Asian | Pancreatic cancer | 16 | 63 | 78 | 9 | 53 | 55 | 30.25% | 30.34% | 9 | 0.44 |
| Wu | 2009 | China | Asian | Colorectal cancer | 8 | 40 | 24 | 9 | 53 | 55 | 38.89% | 30.34% | 8 | 0.44 |
| Yan | 2007 | China | Asian | Gastric cancer | 63 | 90 | 103 | 76 | 149 | 78 | 42.19% | 49.67% | 6 | 0.77 |
| Zhang | 2009 | China | Asian | Colorectal cancer | 50 | 91 | 65 | 278 | 391 | 168 | 46.36% | 56.57% | 7 | 0.15 |
| Zhang | 2008 | China | Asian | Gastric cancer | 92 | 200 | 122 | 99 | 209 | 106 | 46.38% | 49.15% | 7 | 0.84 |

HWE *P* value for Hardy-Weinberg equilibrium in controls.

aspect was carefully retrieved from each study by two reviewers (Y. Gu and H. Wang): author name, year and country of the study, and ethnicity, type of cancer, genotyping method and numbers of genotyped cases and controls, and the evidence of Hardy-Weinberg equilibrium (HWE) in the controls.

The New castle Ottawa scale (NOS) was used for quality evaluation of all included articles, and the articles were graded by two researchers independently. Quality scores ranged from 0 to 9, with a higher score indicating better quality [3].

*Statistic analyses*

The odds ratio (OR) and its 95% confidence interval (95% CI) were used to investigate the strength of the association. The significance of pooled ORs was tested by Z test ($P<0.05$ was considered significant). The heterogeneity between the individual studies was calculated by Q test, and the significance was $P<0.05$ level. We also calculated the $I^2$ that represents the percentage of total variation across studies.

We used the fixed effects model when no heterogeneity of the results of studies; otherwise, the random effects model was adopted. The departure of frequencies from those expected under Hardy-Weinberg equilibrium was assessed by chi-square goodness-of-fit tests in control subjects. The potential publication bias was estimated by Egger's linear regression test and Begg and Mazumdar adjusted rank correlation test, and we adopt sensitivity analyses to assess the stability of the results. The statisti-

**Table 2.** Characteristics of primary studies for T869C in the meta-analysis

| Author | Years | Country | Ethnicity | Type of cancer | Genotype distribution | | | | | | C allele (frequency) | | Quality score | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | case | | | control | | | | | | |
| | | | | | CC | TC | TT | CC | TC | TT | case | control | | |
| Carneiro | 2012 | Brazil | Caucasian | SCCHN | 22 | 29 | 11 | 20 | 19 | 23 | 58.87% | 47.58% | 5 | 0.00 |
| Crivello | 2006 | Italy | Caucasian | Digestive tract cancer | 35 | 23 | 4 | 41 | 61 | 22 | 75.00% | 57.66% | 7 | 0.93 |
| Gu | 2010 | China | Asian | Digestive tract cancer | 137 | 257 | 190 | 135 | 229 | 104 | 45.46% | 53.31% | 8 | 0.71 |
| Hu | 2012 | China | Asian | SCCHN | 127 | 266 | 129 | 171 | 354 | 187 | 49.81% | 48.88% | 5 | 0.89 |
| Kang | 2005 | Korea | Asian | Lung cancer | 107 | 200 | 125 | 108 | 218 | 106 | 47.92% | 50.23% | 6 | 0.85 |
| Li | 2008 | China | Asian | Digestive tract cancer | 55 | 89 | 23 | 46 | 82 | 65 | 59.58% | 45.08% | 5 | 0.05 |
| Poonam | 2011 | India | Caucasian | SCCHN | 31 | 58 | 51 | 11 | 39 | 70 | 42.86% | 25.42% | 6 | 0.12 |
| Quarmby | 2002 | UK | Caucasian | Breast cancer | 9 | 48 | 44 | 7 | 41 | 54 | 32.67% | 26.96% | 9 | 0.84 |
| Teixeira | 2011 | Portugal | Caucasian | Lung cancer | 53 | 165 | 87 | 44 | 166 | 170 | 44.43% | 33.42% | 8 | 0.72 |
| Wei | 2007 | China | Asian | Digestive tract cancer | 77 | 123 | 47 | 64 | 114 | 82 | 56.07% | 46.54% | 9 | 0.06 |
| WeiY | 2007 | China | Asian | SCCHN | 43 | 49 | 16 | 29 | 61 | 30 | 62.50% | 49.58% | 6 | 0.85 |

HWE *P* value for Hardy-Weinberg equilibrium in controls, SCCHN squamous cell cancer of head and neck.

cal analysis was performed by STATA 11.0 software (College Station, TX) and Review Manage 5.1 software (The Cochrane Collaboration, Oxford, UK).

## Results

### *Eligible studies*

A total of 31 studies for C-509T [4-34] and 11 ones for T869C [10, 14, 15, 18, 19, 24, 28, 29, 35-37] met the inclusion criteria. For C-509T, these studies encompassed 19 with Asian and 12 with Caucasian; and each subgroup (including breast cancer, colorectal cancer, gastric cancer) had 7 studies and other cancers had 10 studies. Six studies with Asian and 5 studies with Caucasian were included in the analysis for T869C polymorphism, and there were 4 studies focused on digestive tract cancer, 4 on SCCHN and 3 on other cancers (**Tables 1-3**).

### *TGF-β1 C-509T*

We did not find significant association between cancer risk and TGF-β1 C-509T. Pooled ORs were 0.90 (95% CI=0.75-1.07, $P_h$<0.00001, $I^2$=79%), 0.86 (95% CI=0.75-1.00, $P_h$<0.00001, $I^2$=83%), 0.88 (95% CI=0.76-1.02, $P_h$<0.00001, $I^2$=85%) and 0.95 (95% CI=0.86-1.03, $P_h$< 0.00001, $I^2$=82%), respectively, for TT vs. CC, CT vs. CC, TT+CT vs. CC and T-allele vs. C-allele comparisons. We used subgroup analyses for ethnic group and cancer type to avoid heterogeneity influence. In the stratified analysis, C-509T polymorphism was associated with decreased cancer risk in Asian population (OR=0.73 and 95% CI=0.59-0.90 for CT vs. CC), but not in Caucasion (OR=1.03 and 95% CI=0.96-1.10 for CT vs. CC). And there were no significantly risks with gastric cancer, breast cancer, and other cancers. Three studies were found with significant deviation from HWE (Berndt 2007, Cingeetham 2013, Li 2008) (**Table 3**; **Figure 1**).

### *TGF-β1 T869C*

We observed significantly increased risk of cancer with TGF-β1 T869C, and the Ors (95% CI) were 1.81 (1.18, 2.78) for CC vs. TT, 1.50 (1.07, 2.09) for TC vs. TT, 1.61 (1.13, 2.30) for TC+CC vs. TT, 1.38 (1.11, 1.73) for C-allele vs. T-allele. And, in the stratified analysis, robust increased risk of SCCHN was observed (OR= 2.14, 95% CI=1.07-4.29, $P_h$=0.004, $I^2$=77% for CC vs. TT; OR=1.34, 95% CI=1.07-1.67, $P_h$= 0.05, $I^2$=62% for TC vs. TT; OR=1.81, 95% CI=1.08-3.04, $P_h$=0.008, $I^2$=75% for TC+CC vs. TT; OR=1.54, 95% CI=1.03-2.29, $P_h$=0.0006, $I^2$=83% for C-allele vs. T-allele). But it conferred no significant risks with digestive tract cancer and other cancers. In the subgroup analysis by ethnicity, T869C were estimated as 1.93 (95% CI=1.52-2.46, $P_h$=0.70, $I^2$=0%) for TC vs. TT in Caucasion, which showed significant association of the T869C with increased cancer risk in Caucasion, but not in Asian One study was found with significant deviation from HWE (Carneiro 2012). The results of the meta analysis were not altered after exclusion of studies of HWD (**Table 3**; **Figure 2**).

### *Publication bias, sensitivity analyses*

Sensitivity analyses indicated that no individual study significantly alter the pooled ORs, demon-

**Table 3.** Meta-analysis of the associations between TGF-β1 C-509T and T869C polymorphisms and cancer risk

| C-509T | *N* | Sample size | TT vs. CC | | | | CT vs. CC | | | | TT+CT vs. CC | | | | T-allele vs. C-allele | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Case/control | OR (95% CI) | *P* | $P_h$ | $I^2$ (%) | OR (95% CI) | *P* | $P_h$ | $I^2$ (%) | OR (95% CI) | *P* | $P_h$ | $I^2$ (%) | OR (95% CI) | P | $P_h$ | $I^2$ (%) |
| Total | 31 | 12944/15530 | 0.90 [0.75, 1.07] R | 0.24 | <0.01 | 79 | 0.86 [0.75, 1.00] R | 0.05 | <0.01 | 83 | 0.88 [0.76, 1.02] R | 0.08 | <0.01 | 85 | 0.95 [0.86, 1.03] R | 0.22 | <0.01 | 82 |
| Ethnicities | | | | | | | | | | | | | | | | | | |
| Asian | 19 | 6221/7918 | 0.77 [0.63, 0.96] R | 0.02 | <0.01 | 77 | 0.73 [0.59, 0.90] R | <0.01 | <0.01 | 83 | 0.75 [0.61, 0.92] R | <0.01 | <0.01 | 85 | 0.86 [0.77, 0.97] R | 0.02 | <0.01 | 82 |
| Caucasian | 12 | 6723/7612 | 1.16 [0.90, 1.50] R | 0.25 | <0.01 | 67 | 1.03 [0.96, 1.10] F | 0.48 | 0.09 | 38 | 1.09 [0.96, 1.24] R | 0.17 | 0.01 | 53 | 1.08 [0.97, 1.21] R | 0.15 | <0.01 | 66 |
| Type of cancer | | | | | | | | | | | | | | | | | | |
| Breast cancer | 7 | 6512/7349 | 0.89 [0.70, 1.14] R | 0.36 | <0.01 | 66 | 1.00 [0.93, 1.07] F | 0.99 | 0.09 | 45 | 1.00 [0.93, 1.07] F | 0.8 | 0.06 | 51 | 1.02 [0.92, 1.13] R | 0.67 | 0.03 | 58 |
| Colorectal cancer | 7 | 1594/2722 | 0.84 [0.55, 1.28] R | 0.41 | <0.01 | 74 | 0.81 [0.70, 0.93] F | 0.01 | 0.11 | 42 | 0.77 [0.59, 1.00] R | 0.05 | <0.01 | 66 | 0.88 [0.73, 1.07] R | 0.2 | <0.01 | 72 |
| Gastric cancer | 7 | 2401/2431 | 0.89 [0.65, 1.22] R | 0.47 | <0.01 | 73 | 0.83 [0.58, 1.17] R | 0.28 | <0.01 | 84 | 0.86 [0.62, 1.18] R | 0.35 | <0.01 | 84 | 0.86 [0.74, 1.00] R | 0.04 | <0.01 | 69 |
| Other cancer[a] | 10 | 2437/3028 | 1.02 [0.64, 1.61] R | 0.95 | <0.01 | 87 | 0.87 [0.57, 1.33] R | 0.52 | <0.01 | 90 | 0.93 [0.61, 1.42] R | 0.74 | <0.01 | 91 | 1.00 [0.78, 1.30] R | 0.98 | <0.01 | 90 |
| HWE | 28 | 11891/14456 | 0.85 [0.71, 1.02] R | 0.07 | <0.01 | 79 | 0.81 [0.70, 0.94] R | <0.01 | <0.01 | 82 | 0.83 [0.72, 0.96] R | 0.01 | <0.01 | 84 | 0.91 [0.88, 0.95] R | <0.01 | <0.01 | 82 |
| Publication bias tests | | | | | | | | | | | | | | | | | | |
| Begg and Mazumdar's P | | | 0.592 | | | | 0.103 | | | | 0.002 | | | | 0.541 | | | |
| Egger's P | | | 0.558 | | | | 0.299 | | | | 0.345 | | | | 0.928 | | | |
| T869C | *N* | Sample size | CC vs. TT | | | | TC vs. TT | | | | TC+CC vs. TT | | | | C-allele vs. T-allele | | | |
| | | Case/control | OR (95% CI) | *P* | $P_h$ | $I^2$ (%) | OR (95% CI) | *P* | $P_h$ | $I^2$ (%) | OR (95% CI) | *P* | $P_h$ | $I^2$ (%) | OR (95% CI) | P | $P_h$ | $I^2$ (%) |
| Total | 11 | 2730/2973 | 1.81 [1.18, 2.78] R | <0.01 | <0.01 | 85 | 1.50 [1.07, 2.09] R | 0.02 | <0.01 | 83 | 1.61 [1.13, 2.30] R | <0.01 | <0.01 | 87 | 1.38 [1.11, 1.73] R | 0.005 | <0.01 | 87 |
| Ethnicities | | | | | | | | | | | | | | | | | | |
| Asian | 6 | 2060/2185 | 1.39 [0.82, 2.35] R | 0.22 | <0.01 | 88 | 1.23 [0.80, 1.90] R | 0.35 | <0.01 | 87 | 1.30 [0.82, 2.06] R | 0.27 | <0.01 | 90 | 1.18 [0.90, 1.54] R | 0.23 | <0.01 | 89 |
| Caucasian | 5 | 670/788 | 2.67 [1.91, 3.72] F | <0.01 | 0.54 | 0 | 1.93 [1.52, 2.46] F | <0.01 | 0.7 | 0 | 2.09 [1.66, 2.62] F | <0.01 | 0.57 | 0 | 1.70 [1.46, 1.98] F | <0.01 | 0.31 | 16 |
| Type of cancer | | | | | | | | | | | | | | | | | | |
| Digestive tract cancer | 4 | 1060/1045 | 1.95 [0.70, 5.46] R | 0.2 | <0.01 | 93 | 1.59 [0.67, 3.76] R | 0.34 | <0.01 | 91 | 1.76 [0.70, 4.43] R | 0.23 | <0.01 | 93 | 1.40 [0.83, 2.37] R | 0.21 | <0.01 | 93 |
| SCCHN | 4 | 832/1014 | 2.14 [1.07, 4.29] R | 0.03 | <0.01 | 77 | 1.34 [1.07, 1.67] F | 0.01 | 0.05 | 62 | 1.81 [1.08, 3.04] R | 0.02 | <0.01 | 75 | 1.54 [1.03, 2.29] R | 0.03 | <0.01 | 83 |
| Other cancer[b] | 3 | 838/914 | 1.43 [0.66, 3.10] R | 0.37 | <0.01 | 82 | 1.29 [0.69, 2.40] R | 0.05 | <0.01 | 87 | 1.32 [0.70, 2.51] R | 0.39 | <0.01 | 89 | 1.23 [0.82, 1.84] R | 0.31 | <0.01 | 86 |
| HWE | 10 | 2668/2911 | 1.78 [1.14, 2.79] R | 0.01 | <0.01 | 86 | 1.42 [1.01, 1.99] R | 0.04 | <0.01 | 84 | 1.55 [1.07, 2.24] R | 0.02 | <0.01 | 88 | 1.08 [1.08, 1.74] R | <0.01 | <0.01 | 88 |
| Publication bias tests | | | | | | | | | | | | | | | | | | |
| Begg and Mazumdar's P | | | 0.755 | | | | 0.436 | | | | 0.161 | | | | 0.640 | | | |
| Egger's P | | | 0.291 | | | | 0.803 | | | | 0.040 | | | | 0.838 | | | |

$P_h$: *P* Values for heterogeneity from Q test, P: *P* values for pooled ORs tested by Z test; R: random-effect model, F: fixed-effect model; SCCHN squamous cell cancer of head and neck; [a]Other cancer including hepatocellular cancer, nasopharyngeal cancer, esophageal cancer, lung cancer, cervical cancer, gallbladder cancer, pancreatic cancer; [b]Other cancer including breast cancer and lung cancer.

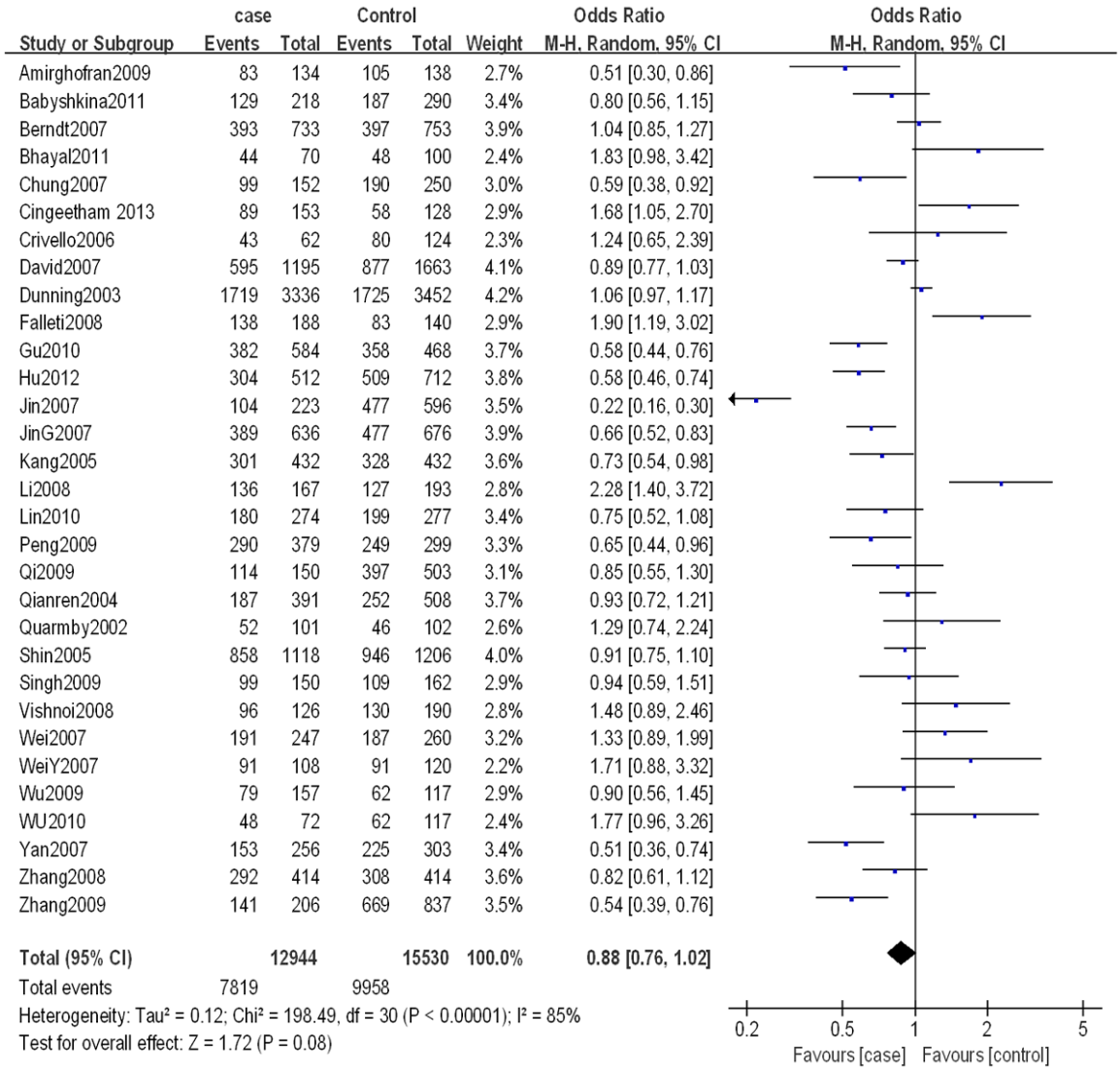


**Figure 1.** Forest plot of the meta-analysis for TGF-β1 C-509T polymorphism associated with overall cancer risk (TT+CT vs. CC). Random effect model was made.

strating the results of this meta analysis were stable (**Figures 3**, **4**). The results of Begg and Egger's test did not identify obvious publication bias for C-509T and T869C (**Table 3**).

## Discussion

It is well recognized that there is individual susceptibility to cancer risk even with the same environmental exposure. Host factors, including polymorphisms of genes involved in cancer, may have accounted for this difference [34]. Therefore, genetic factors are considered to be strong disease determinants, and this has encouraged researchers to search for the responsible genes. In recent years, constant efforts have been made for TGF-β1 gene. As we know, TGF-β1 plasma concentrations have been correlated with the development of several diseases. Polymorphisms in the TGF-β1 gene may alter the mRNA expression levels and influence the plasma protein concentration. Thus, all of these render TGF-β1 a particularly interesting candidate gene.

In the present meta analysis, we combined the evidence on the association of the TGF-β1 gene C-509T and T869C promoter polymorphisms and susceptibility to cancer risk. The results exhibited no significant cancer risk in cancer patients compared with normal controls between for TGF-β1 C-509T polymorphism. When

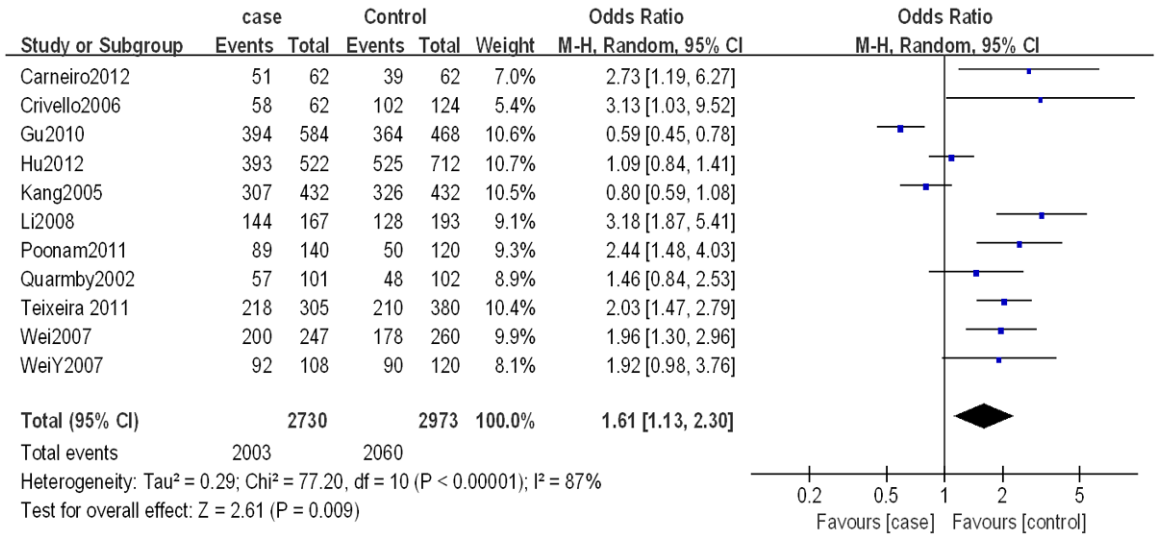


**Figure 2.** Forest plot of the meta-analysis for TGF-β1 T869C polymorphism associated with overall cancer risk (TC+CC vs. TT). Random effect model was made.

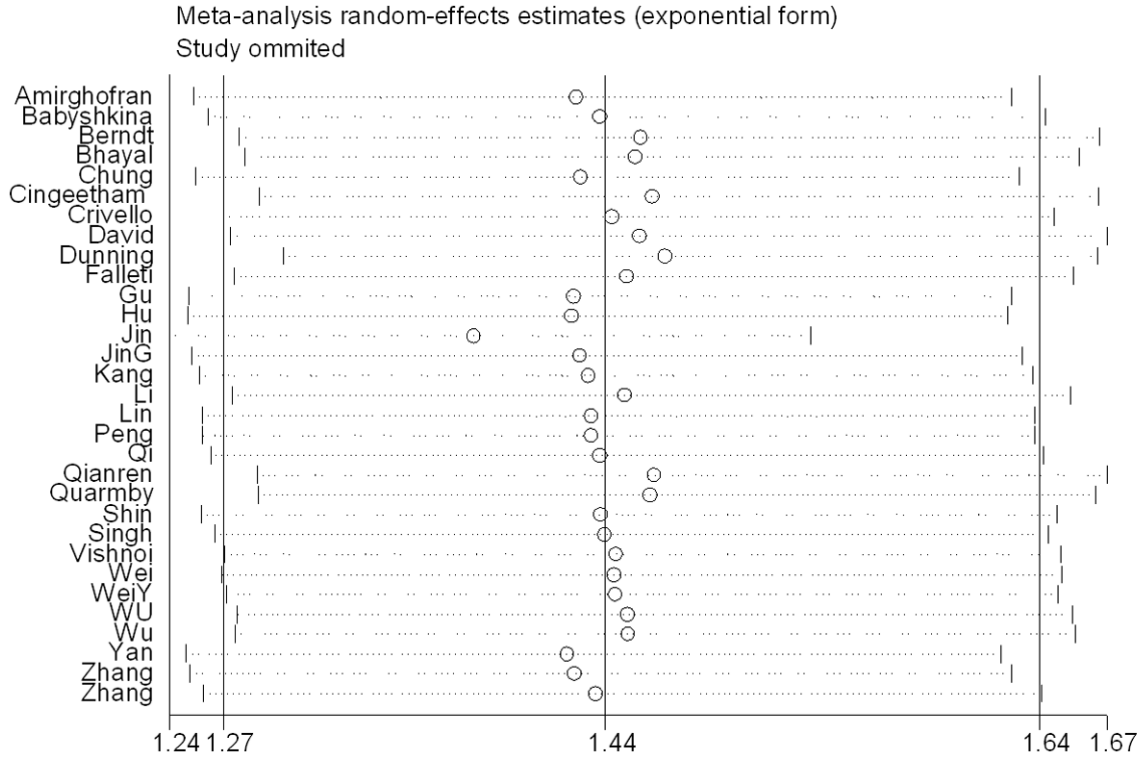


**Figure 3.** One-way sensitivity analysis of the pooled ORs and 95% CI for TGF-β1 C-509T (TT+CT vs. CC), omitting each dataset in the meta-analysis. Random effect model was made.

stratified by race, decreased cancer risk association was observed only in Asian population, but not in Caucasians. These discrepancies might be due to the different ethnicities. Additionally, we did not detect an association between TGF-β1 C-509T polymorphism and gastric cancer, breast cancer, and other cancers. For T869C, significantly increased risk of cancer was observed. Subgroup analyses stratified by ethnicity and types of cancer were also performed, and results indicated that T869C polymorphism was associated with risk of can-

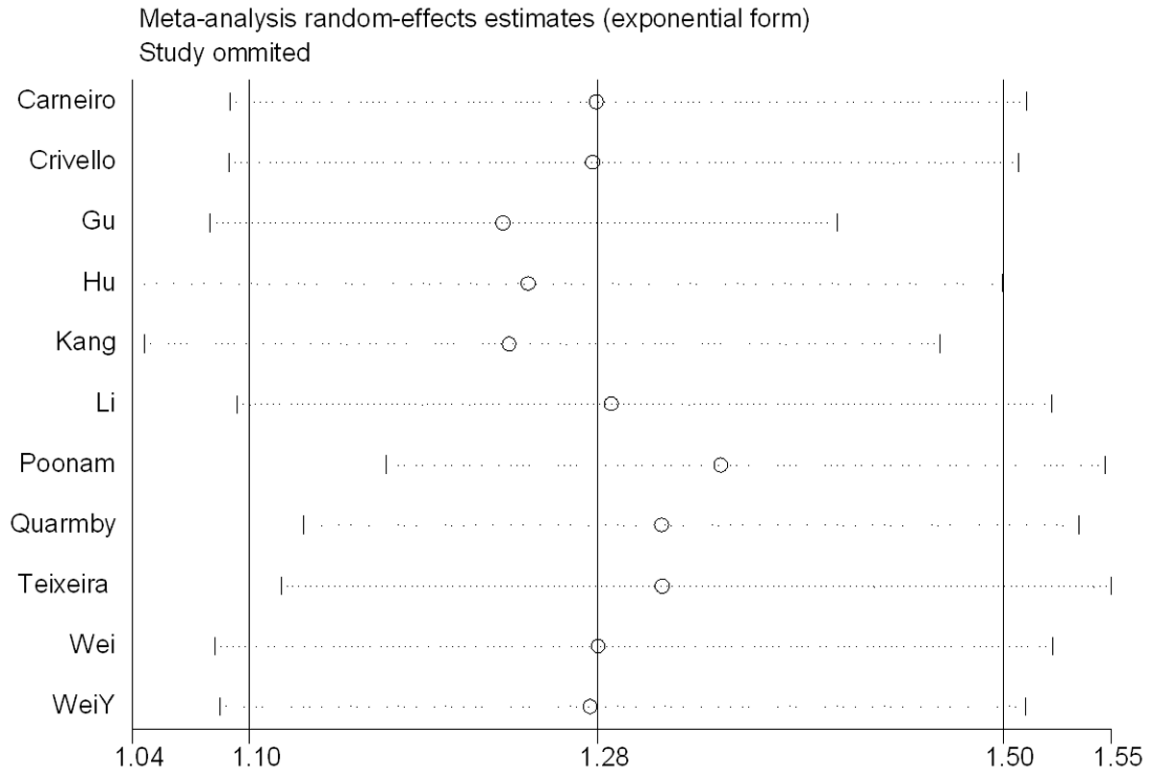


**Figure 4.** One-way sensitivity analysis of the pooled ORs and 95% CI for TGF-β1 T869C (TC+CC vs. TT), omitting each dataset in the meta-analysis. Random effect model was made.

cer in Caucasion, but not in Asian. And we also observed that the T869C was associated with increased risk of SCCHN.

There were some limitations to this meta analysis. Firstly, the value of this meta analysis was limited by the small number of included studies that addressed the effect of TGF-β1 C-509T and T869C polymorphisms with cancer, and it is possible that some related unpublished studies were missed. Secondly, publication bias might have been present, even though statistical analysis indicated this not to be the case. Thirdly, our results were based on unadjusted estimates and a more precise analysis could have been conducted if individual data were available, which would allow for adjustment by other covariates such as age, ethnicity, environmental factors, and life style.

To further evaluate gene-to-gene and gene-to-environment interactions on TGF-β1 C-509T and T869C polymorphism and cancer risk, more well designed studies based on larger sample size are needed to verify our findings.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Su Wang, Department of Endocrinology, The Fifth Central Hospital of Tianjin, Zhejiang road 41, Binhai New Area of Tianjin, Tianjin 300450, China. Tel: +86-18722002011; E-mail: wsrealm@126.com

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