Transforming Growth Factor Beta-1 C-509T Polymorphism and Cancer Risk: A Meta-analysis of 55 Case-control Studies

Yang Liu, Xian-Fan Lin, Chun-Jing Lin, Si-Si Jin, Jin-Ming Wu*

Abstract

Aim: To investigate the association of transforming growth factor-beta 1 (TGF-β1) C-509T polymorphism and susceptibility to cancer by means of meta-analysis. Methods: An extensive search was performed to identify eligible case-control studies investigating such a link. The strength of the association between TGF-β1 C-509T polymorphism and cancer risk was assessed by pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) in fixed or random effects models. Results: 55 published case-control studies with a total number of 21,639 cases and 28,460 controls were included. Overall, there was no association between TGF-β1 C-509T and cancer risk in all genetic comparison models (TT vs. CC: OR=1.01, 95% CI=0.89-1.15; T vs. C: OR=1.01, 95% CI=0.94-1.07). However, a stratified analysis by cancer type indicated -509 T allele was significantly associated with decreased risk of colorectal cancer (CRC) (TT vs. CT/CC: OR=0.85, 95% CI=0.76-0.95), especially for Caucasians (TT vs. CT/CC: OR=0.83, 95% CI=0.71-0.98) and for population-based studies (TT vs. CT/CC: OR=0.78, 95% CI=0.68-0.89). Conclusion: This meta-analysis suggested that TGF-β1 C-509T polymorphism might contribute to a decreased risk on colorectal cancer susceptibility, especially for Caucasians.

Keywords: TGF-β1 - polymorphism - cancer risk- meta-analysis

Introduction

Cancer is thought to be a multifactorial, multigenetic, and multistage disease resulting from complex interactions between environmental and genetic factors (Pharoah et al., 2004). According to recent Cancer Statistics, over 1,638,000 new cancer cases and 577,000 deaths were expected to occur in the United States in 2012 (Siegel et al., 2012). Cytokines, as the product of host responses to inflammation, play an important role in the defense against carcinogenesis. As a multifunctional cytokine that influence the process of cell cycle regulation, cell differentiation, migration and vascularization, TGF-β1 has been extensively studied for many years. It belongs to the transforming growth factor beta family and is the most frequently up-regulated forms in tumor cells, functioning as both a tumor suppressor and promoter of tumor progression (Blobe et al., 2000; Massague et al., 2000; Derynck et al., 2001).

Cancer heritability is related not only to the rare deleterious gene defects but also to the polymorphic variations in the DNA sequence. Single nucleotide polymorphism (SNP) is the most common sources of human genetic variation and can be served as prognostic markers of cancer. The commonly studied C-509T polymorphism (rs1800469), which is located in the promoter region of TGF-β1 gene, may directly influence the expression profiles. Compared with -509 C allele, the -509 T allele is associated with an increased transcriptional activity (Luedecking et al., 2000), which leads to a higher plasma concentration of TGF-β1 among T homozygous than in heterozygote individuals in a dose-response effect (Grainger et al., 1999). Given the important roles of TGF-β1 in multiple biological functions, it is plausible that TGF-β1 C-509T polymorphism may modulate the cancer risk.

Recently, a proliferation of original articles have investigated the role of the TGF-β1 C-509T polymorphism in the etiology of various cancers. Although these studies attempted to link TGF-β1 C-509T polymorphism to cancer, data from literature reports were not often reproducible. Hence, we performed this meta-analysis to provide a quantitative approach for combining different results and estimate the association specifically.

Materials and Methods

Identification and eligibility of relevant studies

Relevant studies were identified by searching the electronic literature on PubMed, Chinese Biomedical Literature Database (CBM) and China National Knowledge Infrastructure (CNKI) using search terms “transforming growth factor beta 1”, “TGF-β1”, “polymorphism” and “cancer” (last search update July 2012). Additional studies were identified by a hand search of references of original or review articles on this topic. Studies were
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Yang Liu et al calculated for additive model (T vs. C), codominant model (CC vs. TT, CT vs. CC) and recessive model (TT vs. CT + CC), respectively. The significance of pooled ORs was tested by Z test (P<0.05 was considered significant). The Q statistic was used to test for heterogeneity among the studies included in the meta-analysis (P≤0.1 was considered significant). All P-values were two-sided. When studies were shown to be homogenous, fixed effect model was used for the meta-analysis otherwise random effect model was applied. Publication bias was examined by inspection of symmetry of Begg’s funnel plot and Egger-regression test. Hardy–Weinberg equilibrium (HWE) was tested by Chi-square test. All analyses were performed using Stata version 11.0 software (Stata, College Station, TX, USA).

Results

Characteristics of Studies

55 relevant studies with a total number of 21,639 cases and 28,460 controls were included in the meta-analysis. Characteristics of the included studies were shown in Table 1. With the exception of 5 studies (Nikolova et al., 2007; Li et al., 2008; Saltzman et al., 2008; Guan et al., 2009; Guo et al., 2011), the distribution of genotypes for the 5-C90T polymorphism in the controls of all studies was consistent with Hardy–Weinberg equilibrium.

Table 1. Characteristics of Studies Included in the Meta-analysis

| Study (ref.) | Location | Ethnicity | Histology | Source of control | Cases | Controls | HWE in | ORs with 95% CIs were calculated to assess the strength of association between TGF–β1 C–509T polymorphism and cancer. Since no available evidence favored any genetic models of inheritance for the polymorphism under investigation, the pooled ORs were calculated for additive model (T vs. C), codominant model (TT vs. CC, CT vs. CC), dominant model (CT + TT vs. CC), and recessive model (TT vs. CT +CC), respectively. The significance of pooled ORs was tested by Z test (P<0.05 was considered significant). The Q statistic was used to test for heterogeneity among the studies included in the meta-analysis (P≤0.1 was considered significant). All P-values were two-sided. When studies were shown to be homogenous, fixed effect model was used for the meta-analysis otherwise random effect model was applied. Publication bias was examined by inspection of symmetry of Begg’s funnel plot and Egger-regression test. Hardy–Weinberg equilibrium (HWE) was tested by Chi-square test. All analyses were performed using Stata version 11.0 software (Stata, College Station, TX, USA). |

| Data extraction |

Two investigators (Liu Y and Lin XF) independently extracted data and reached a consensus on all of the items. The following information was extracted from each enrolled references: first author, year of publication, location, ethnicity, histology, genotype frequency. Different ethnicity was categorized as Asian, Caucasian, and mixed population. Different case-control groups in one study were considered as independent studies (Table 1).

Statistical analysis

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Publication bias

As shown in Figure 2, the shapes of Begg’s funnel plot did not reveal any evidence of obvious asymmetry.

**Figure 1. Forest Plot for the Association Between C-509T Polymorphism and Colorectal Cancer Risk**

**Quantitative Data Synthesis**

Overall, there was no association between TGF-β1 C-509T polymorphism and cancer risk in all genetic models (T vs. C: OR=1.01, 95% CI=0.94-1.07; TT vs. CC: OR=1.01, 95% CI=0.89-1.15; CT vs. CC: OR=0.98, 95% CI=0.90-1.06; CT+TT vs. CC: OR=0.98, 95% CI=0.88-1.08; TT vs. CT+CC: OR=1.00, 95% CI=0.91-1.10; Table 2). When stratifying the source of controls and cancer type, we failed to find any vital effects for the polymorphism on cancer risk except CRC. As shown in Table 3, the possession of the -509T allele was associated with a decreased risk of colorectal cancer as compared with individuals of the C allele (TT vs. CT/CC: OR=0.85, 95% CI=0.76-0.95; Figure 1), especially for Caucasian (TT vs. CT/CC: OR=0.83, 95% CI=0.71-0.98; TT vs. CC: OR=0.80, 95% CI=0.67-0.95; T vs. C: OR=0.92, 95% CI=0.85-0.99) and for population-based studies (TT vs. CT/CC: OR=0.78, 95% CI=0.68-0.89; TT vs. CC: OR=0.73, 95% CI=0.63-0.80; T vs. C: OR=0.86, 95% CI=0.76-0.96).

**Figure 2. Funnel Plot for C-509T Polymorphism and Cancer Risk for Publication Bias**

Egger’s test suggested the absence of publication bias (TT vs. CT/CC: P=0.419).

**Discussion**

This meta-analysis, including 21,639 cases and 28,460 controls from 55 studies of 53 publications, explored the association between the TGF-β1 C-509T polymorphism and cancer risk. We found that variant homozygotes or heterozygotes of the C-509T polymorphism were not associated with cancer risk in overall comparisons; the insignificance of this relationship holds up under various genetic models.

In the stratification analysis of cancer types, we found no significant associations between TGF-β1 C-509T polymorphism and cancer susceptibility except for colorectal cancer. CRC is the third most commonly diagnosed cancer in males and in the second females (Jemal et al., 2011), and is especially common in the North America, Australia and Western Europe, while the incidence tends to be low in Africa and Asia (Kamangar et al., 2006). Several lines of evidence suggest that the abnormalities in the TGF-β pathway may be involved in the development of colorectal carcinoma (Xu et al., 2007).
The over expression of TGF-β1 inhibits cell proliferation and induces apoptosis through its downstream cell-cycle checkpoint genes, including CDKN1A, CDKN1B and CDKN2B, acting as a tumor suppressor in early stages of tumor development (Massague et al., 2000). Consistent with these observations, we found individuals with T/T genotype were associated with a lower colorectal cancer risk than subjects with at least a C allele. The findings were also in line with the results of studies in animal models (Tang et al., 1998) and another meta-analysis (Liu et al., 2012). However, the effect of -509 T/T genotype was unfavorable toward the development of breast and gastric cancer, as shown in previous studies (Huang et al., 2011; Niu et al., 2012). The inconsistent results among different cancers may involve the mechanisms by which TGF-β1 regulates cell proliferation or apoptosis in different cancer cells. Also, it is conceivable that TGF-β1 C-509T polymorphism might be linked to a causal variant or interacts with others to produce the final disease phenotype (Niu et al., 2010). Moreover, different cancers may be influenced by different environmental factors, which may strengthen or weaken the association with this polymorphism. In addition, the difference could also be due to limited statistical power as a result of a relatively small sample size in some tumor site subgroups.

Genotype frequency of various polymorphic loci may manifest racial differences. To clarify the association between the TGF-β1 C-509T polymorphism and cancer in different genetic background, subgroup analysis by ethnicity was performed. No evidence was found for the association between this polymorphism and cancer susceptibility among the racial groups, except for -509 T allele with colorectal cancer risk in Caucasians. Considering the possible small effect size of genetic polymorphism to CRC and the relatively small population in these studies, the discrepancy will be apparent since some of the studies may be underpowered to detect the association. So it will be necessary to perform further experiments on larger samples to verify the results. In addition, no study on African population was found. Additional studies are needed to further validate ethnic difference in the effect of the polymorphism on cancer risk, especially in Africans.

When stratifying the source of controls, we also found the association of significantly decreased CRC risk with T/T genotype was more pronounced in studies with population-based controls than hospital-based controls. The possible explanation may be that population-based controls were more representative of the general population and thus have a greater statistical power to detect the effect of the C-509T polymorphism. Therefore, the use of proper controls was very important in reducing biases in such genotype association studies.

Heterogeneity is a potential problem when interpreting the results of the meta-analysis. In our study, significant heterogeneity was detected in overall comparisons as well as some of the subgroup analyses. The following aspects may provide some reasonable interpretations. First, cancer type was an important potential factor. Different TGF-β1 regulation mechanisms and microenvironment in different tissues may explain why the same polymorphism plays different roles in different cancers. Ethnicity was another causal factor. The same polymorphism may play different roles in different populations as they have different genetic backgrounds and be exposed to different environment factors. Moreover, matching criteria and selection bias could also contributed to heterogeneity. In addition, stages of the tumors should yet be considered.

There are still some limitations in this meta-analysis. First, all the eligible studies were limited to English and Chinese papers. It is likely that some relevant studies in other languages meeting the inclusion criteria were missed. Second, our results were based on unadjusted estimates, which should be adjusted by other potentially covariates if possible. Third, as cancer is a multifactorial and complex disease, the influence of the TGF-β1 -509 T variants may be masked by the presence of other as-yet-unidentified genes involved in carcinogenesis. Therefore, the combined analysis of gene-gene interaction might be more powerful than the analysis of single allele effect.

In summary, this meta-analysis showed evidence that TGF-β1 C-509T polymorphism was associated with decreased risk of colorectal cancer, especially for Caucasians. To further evaluate gene-to-gene and gene-to-environment interactions on TGF-β1 C-509T polymorphism and cancer risk, more well designed studies based on larger sample size are needed to verify our findings.

References


