Association between TCF7L2 Gene Polymorphism and Cancer Risk: A Meta-Analysis

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Abstract

Objective: The transcription factor 7-like 2 (TCF7L2) gene has been suggested to play an important role in the pathogenesis of cancer. However, the results have been inconsistent. In this study, we performed a meta-analysis to clarify the associations between TCF7L2 polymorphism and cancer risk.

Methods: Published literature from PubMed and EMBASE were retrieved. Pooled odds ratios (ORs) with 95% confidence interval (CIs) were calculated using fixed- or random-effects model.

Results: A total of 19 studies (14,814 cases and 33,856 controls) were identified for the analysis of the association between TCF7L2 polymorphism and cancer risk. The results showed that TCF7L2 polymorphism was associated with breast cancer (Homogeneous model: OR = 1.17, 95%CI = 1.02–1.35, 2 = 21.8%, p for heterogeneity = 0.276; Heterogeneous model: OR = 1.11, 95%CI = 1.03–1.20, 2 = 0.0%, p for heterogeneity = 0.543), prostate cancer (Homogeneous model: OR = 0.89, 95%CI = 0.84–0.96, 2 = 0.0%, p for heterogeneity = 0.640; Heterogeneous model: OR = 0.89, 95%CI = 0.84–0.95, 2 = 0.0%, p for heterogeneity = 0.871), and colon cancer (Homogeneous model: OR = 1.15, 95%CI = 1.01–1.31, 2 = 0.0%, p for heterogeneity = 0.658), but not with colorectal cancer, lung cancer, and ovarian cancer.

Conclusions: The present meta-analysis indicated that there were significantly associations between the TCF7L2 rs7903146 polymorphism and risk of breast, prostate and colon cancers, rather than colorectal cancer, lung cancer, and ovarian cancer.

Introduction

The transcription factor 7-like 2 (TCF7L2) gene, previously reported as TCF-4, has been found to be associated with type 2 diabetes. Rs7903146 variant of TCF7L2 gene was firstly identified as one susceptibility marker of type 2 diabetes by genome-wide association study [1]. The following studies further confirmed the association between TCF7L2 rs7903146 variant and type 2 diabetes [2]. In addition, individuals carrying T alleles of TCF7L2 rs7903146 variant demonstrated high risk of insulin resistance [3]. Alternatively, TCF7L2 may affect cancer independently of diabetes, as the TCF7L2 gene product is involved in the Wnt/β-catenin signaling pathway. TCF7L2 forms an active nuclear complex with β-catenin that binds and induces the expression of target genes involved in cellular proliferation, evasion of apoptosis, and tissue invasion and metastasis.

To date, many studies have been published investigating the association between TCF7L2 rs7903146 or rs12255372 (it is in high linkage disequilibrium with rs7903146) and several types of cancer, including breast cancer [4–8], prostate cancer [5,9–12], colorectal cancer [5,13–15], colon cancer [5,16], lung cancer [5] and ovarian cancer [6]. However, the conclusions have been conflicting. Therefore, we performed a meta-analysis to clarify the association between TCF7L2 rs7903146 variant and cancer risk.

Materials and Methods

Literature and Search Strategy

We searched the PubMed and EMBASE literature databases. The search strategy to identify all possible studies involved the use of the following key words: (TCF7L2 or transcription factor 7-like 2 or TCF-4) and (variant or variation or polymorphism or genotype) and (cancer or carcinoma or tumor). All related studies published in English language were included. The reference lists of retrieved articles were hand-searched. If more than one article were published using the same case series, only the study with the latest data was included. The literature search was updated on February 18, 2013.

Inclusion Criteria and Data Extraction

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) evaluates the associations of TCF7L2 polymorphism with cancer risk; (2) uses case–control or cohort design; and (3) provides sufficient data for calculation of odds ratio (OR) with 95% confidence interval (CI). The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity; (5) cancer type; (6) sample size of cases and controls; (7) covariates’...
adjusted OR with 95%CI under co-dominant model; (8) minor allele frequency in cases and controls; (9) \( p \) for Hardy Weinberg Equilibrium test in controls; and (10) studied polymorphism. The two authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements and reached a consistent decision.

**Statistical Analysis**

The association of \( TCF7L2 \) polymorphism with cancer risk was estimated by calculating pooled ORs and 95%CIs under a co-dominant model. The significance of pooled OR was determined by \( Z \) test (\( P<0.05 \) was considered statistically significant). Q test was performed to evaluate the between-study heterogeneity. A random- [DerSimonian-Laird method [17]] or fixed- [Mantel–Haenszel method] [18] effects model was used to calculate pooled OR in the presence (\( P\leq0.10 \)) or absence (\( P>0.10 \)) of heterogeneity, respectively. Subgroup analysis by cancer type was performed to address the between-study heterogeneity. Publication bias was assessed by Begg’s test [19] and Egger’s test [20] (\( P<0.05 \) was considered statistically significant). Data analysis was performed using STATA version 11 (StataCorp LP, College Station, TX, USA).

**Results**

**Characteristics of the Studies**

In this study, we followed the PRISMA Statement (Checklist S1). A flow chart describing the process of inclusion/exclusion of study is presented in Fig. 1. The literature search identified a total of 128 potentially relevant papers. Of them, 112 papers were excluded because of obvious irrelevance by reading the titles and abstracts. In addition, two papers were excluded because they were reviews. Then, 14 papers met the primary inclusion criteria. However, one paper was excluded because it did not provide sufficient data to calculate OR with 95%CI [21]. Since more than one study was included in two articles by Folsom et al [5] and

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**Figure 1. Flow chart of meta-analysis for exclusion/inclusion of individual articles (or studies).**

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### Table 1. Characteristics of included studies of association between TCF7L2 rs7903146 (or its proxy rs12255372) polymorphism and cancer risk.

| Study     | Country | Ethnicity | Cancer type   | Sample size | Homogeneous codominant model | Heterogeneous codominant model | MAF | P for HWE | Studied SNP |
|-----------|---------|-----------|---------------|-------------|------------------------------|-------------------------------|-----|-----------|-------------|
| Burwinkel,2006 | Germany | European | Breast cancer | 592/735     | 1.37 (0.91) 2.08             | 1.21 (0.97) 1.53             | 0.29 | 0.26     | rs12255372  |
| Agalli,2008   | USA     | European | Prostate cancer| 582/540     | 0.73 (0.44) 1.20           | 0.94 (0.72) 1.23             | 0.27 | 0.29     | rs12255372  |
| Folsom,2008a | USA     | Mixed    | Colorectal cancer| 180/1410 | 1.56 (0.97) 2.53           | 1.17 (0.85) 1.61             | 0.34 | 0.29     | rs7903146   |
| Folsom,2008b | USA     | Mixed    | Colon cancer | 128         | 2.15 (1.27) 3.64           | 1.25 (0.85) 1.83             | 0.36 | 0.29     | rs7903146   |
| Folsom,2008c | USA     | European | Lung cancer  | 177         | 1.59 (0.96) 2.63           | 1.63 (1.17) 2.25             | 0.37 | 0.29     | rs7903146   |
| Folsom,2008d | USA     | Black    | Lung cancer  | 62          | 0.62 (0.22) 1.76           | 0.75 (0.44) 1.3              | 0.26 | 0.29     | rs7903146   |
| Folsom,2008e | USA     | Mixed    | Breast cancer| 342         | 0.87 (0.57) 1.32           | 0.98 (0.78) 1.23             | 0.28 | 0.28     | rs7903146   |
| Folsom,2008f | USA     | Mixed    | Prostate cancer| 366        | 1.04 (0.72) 1.50           | 0.80 (0.64) 0.99             | 0.27 | 0.29     | rs7903146   |
| Hazra,2008    | USA     | European | Colorectal cancer| 357/814    | 0.63 (0.37) 1.08           | 0.90 (0.68) 1.18             | 0.25 | 0.29     | rs12255372  |
| Slattery,2008 | USA     | Mixed    | Colon cancer | 1573/1962  | 1.03 (0.80) 1.33           | 1.14 (0.99) 1.31             | 0.29 | 0.28     | rs7903146   |
| Goode,2009a  | USA     | European | Breast cancer | 779/830    | 0.92 (0.62) 1.36           | 1.16 (0.93) 1.43             | NA  | 0.28     | rs12255372  |
| Goode,2009b  | USA     | European | Ovarian cancer| 391/458     | 0.97 (0.56) 1.68           | 0.95 (0.71) 1.26             | NA  | 0.26     | rs12255372  |
| Tsilidis,2009 | USA     | Mixed    | Colorectal cancer| 202/354   | 1.44 (0.81) 2.57           | 1.13 (0.78) 1.66             | 0.32 | 0.28     | rs7903146   |
| Wang,2009    | USA     | Mixed    | Prostate cancer| 249/249    | 0.62 (0.32) 1.20           | 0.94 (0.62) 1.42             | 0.27 | 0.30     | rs7903146   |
| Meyer,2010   | USA     | Mixed    | Prostate cancer| 365/5757   | 0.88 (0.75) 1.03           | 0.88 (0.75) 1.03             | NA  | 0.30     | >0.05       |
| Machiela,2012 | USA    | European | Prostate cancer| 2782/4456  | 0.90 (0.83) 0.97           | 0.90 (0.83) 0.97             | NA  | 0.28     | >0.05       |
| Naidu,2012   | Malaysia| Southeast Asian | Breast cancer | 387/252    | 1.57 (0.829) 2.987         | 1.32 (0.948) 1.862           | 0.31 | 0.26     | rs12255372  |
| Sainz,2012   | Germany | European | Colorectal cancer| 1764/1749  | 1.28 (1.01) 1.63           | 1.13 (0.98) 1.30             | 0.31 | 0.28     | rs7903146   |
| Connor,2012  | USA     | Mixed    | Breast cancer | 3523/4209  | 1.24 (1.03) 1.49           | 1.09 (0.99) 1.20             | 0.26 | 0.23     | rs7903146   |

*Covariates’ adjusted estimate
b Estimate under an additive model.
MAF, minor allele frequency; NA, not available; HWE, Hardy Weinberg Equilibrium.
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Goode et al [6], they were considered as separate studies in the meta-analysis. In addition, since rs7903146 was in high LD with rs12255372, we combined all the included studies together. At last, 19 studies for the association between TCF7L2 polymorphism and cancer risk were included in the final meta-analysis. Of them, five were on breast cancer, five were on prostate cancer, four were on colorectal cancer, two were on colon cancer, two were on lung cancer, and one was on ovarian cancer. The characteristics of the included studies are listed in Table 1. It should be noted that because most studies provided covariates’ adjusted OR with 95%CI under a co-dominant model, we calculated the pooled estimate under this model only.

**Meta-analysis Results**

A total of 14814 cases and 33856 controls were identified for the analysis of the association between TCF7L2 polymorphism with cancer risk. The results indicated that TCF7L2 polymorphism might not be associated with cancer risk under co-dominant model (Homogeneous model: OR = 1.07, 95%CI = 0.95–1.21, \( I^2 = 61.4\% \), \( p \) for heterogeneity<0.001, Figure 2; Heterogeneous model: OR = 1.04, 95%CI = 0.97–1.12, \( I^2 = 58.1\% \), \( p \) for heterogeneity = 0.001, Figure 3). However, further subgroup analysis by cancer type suggested that the effect size was significant for breast cancer (Homogeneous model: OR = 1.17, 95%CI = 1.02–1.35, \( I^2 = 21.8\% \), \( p \) for heterogeneity = 0.276; Heterogeneous model: OR = 1.11, 95%CI = 1.03–1.20, \( I^2 = 0.0\% \), \( p \) for heterogeneity = 0.543), prostate cancer (Homogeneous model: OR = 0.89, 95%CI = 0.84–0.96, \( I^2 = 0.0\% \), \( p \) for heterogeneity = 0.640; Heterogeneous model: OR = 0.89, 95%CI = 0.84–0.95, \( I^2 = 0.0\% \), \( p \) for heterogeneity = 0.871), and colon cancer (Heterogeneous model: OR = 1.15, 95%CI = 1.01–1.31, \( I^2 = 0.0\% \), \( p \) for heterogeneity = 0.658), but not for colorectal cancer, lung cancer, and ovarian cancer (all \( p > 0.05 \), Table 2).

**Potential Publication Bias**

No publication bias could be detected under homogeneous co-dominant model (\( p = 0.780 \) for Begg’s test and \( p = 0.123 \) for
Figure 3. Meta-analysis of association between TCF7L2 rs7903146 polymorphism and cancer risk under heterogeneous co-dominant model.
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Table 2. Pooled ORs and 95%CIs of the association between TCF7L2 rs7903146 (or its proxy rs12255372) polymorphism and cancer risk.

| Contrasts                  | No. of studies (cases/controls) | Homogeneous co-dominant model | Heterogeneous co-dominant model |
|----------------------------|---------------------------------|-------------------------------|---------------------------------|
|                            |                                 | OR (95% CI)                   | %                              |
| All                        | 19 (14814/33856)                | 1.07 (0.95–1.21)              | 61.4                            |
| Cancer type                |                                 |                               |                                 |
| Breast cancer              | 5 (5623/17436)                 | 1.17 (1.02–1.35)              | 21.8                            |
| Prostate cancer            | 5 (4358/22493)                 | 0.89 (0.84–0.96)              | 0.0                             |
| Colorectal cancer          | 4 (2502/14327)                 | 1.18 (0.84–1.66)              | 59.1                            |
| Colon cancer               | 2 (1710/13372)                 | 1.43 (0.70–2.94)              | 83.6                            |
| Lung cancer                | 2 (239/11410)                  | 1.11 (0.45–2.73)              | 60.8                            |
| Ovarian cancer             | 1 (391/458)                    | 0.97 (0.56–1.68)              | –                               |

*Shared the same number of controls (n = 11410).
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Egger’s test) and heterogeneous co-dominant model ($p = 0.889$ for Begg’s test and $p = 0.274$ for Egger’s test).

**Discussion**

To the best of our knowledge, our meta-analysis represents the first one investigating the association between TCF7L2 rs7903146 polymorphism and cancer risk. The results suggested that TCF7L2 rs7903146 polymorphism might not be associated with cancer risk. However, further stratified analysis demonstrated the significant association with breast cancer, prostate cancer and colon cancer, rather than colorectal cancer, lung cancer, and ovarian cancer.

Interestingly, the T allele of rs7903146 polymorphism, which has been associated with increased risk of type 2 diabetes, showed the inverse association with prostate cancer based on our meta-analysis. The finding was consistent with those from the individual studies by Folsom et al. [5] and Machiela et al [12]. However, the other three included studies did not suggest any association [9–11]. In addition, we found positive association between rs7903146 polymorphism and breast cancer risk. Recently, Michailidou et al. [21] have found rs7904519 in intron 4 of TCF7L2 ($r^2 = 0.37$ with rs7904519/rs12255372), to be associated with breast cancer. Further studies are necessary to examine the potential different mechanisms of TCF7L2 polymorphism in various cancers.

Heterogeneity between studies is common in meta-analysis of genetic association studies. Although heterogeneity can be taken into account by performing a random-effects model, it would increase the odds of type I error [23]. We found significant between-study heterogeneity in the association of TCF7L2 rs7903146 polymorphism with cancer risk. Therefore, subgroup analysis by ethnicity because of the inverse association between TCF7L2 rs7903146 polymorphism with cancer risk. The current meta-analysis has several strengths. First, OR (95% CI) after covariates adjustment from individual study was used to calculate the pooled estimate, which increased the accuracy of effect estimate. Second, statistical power was greatly improved for the association study of TCF7L2 rs7903146 polymorphism in the pooled analysis. However, several limitations should also be noted. First, the case – control study design does not allow for the inference of causality between the gene polymorphism and the outcome. Second, the effect of gene – gene/gene – environment interactions was not addressed in this meta-analysis. Third, although ethnicity plays an important role in the association of TCF7L2 rs7903146 polymorphism with cancer risk, we did not perform the further subgroup analysis by ethnicity because of limited studies for each cancer type.

In conclusion, the results indicated that there was a significantly association between TCF7L2 rs7903146 polymorphism and the risk of breast cancer, prostate cancer and colon cancer, rather than colorectal cancer, lung cancer, and ovarian cancer. Further well-designed large-scale studies with the consideration of gene–gene and gene–environment interactions should be conducted to investigate the association in future.

**Supporting Information**

**Checklist S1 PRISMA Checklist.**

(DOC)

**Author Contributions**

Conceived and designed the experiments: PC. Performed the experiments: TY ML. Analyzed the data: JC PC. Contributed reagents/materials/analysis tools: TY ML. Wrote the paper: JC.

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