

## RESEARCH ARTICLE

# Association between the TGFBR2 G-875A Polymorphism and Cancer Risk: Evidence from a Meta-analysis

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## Abstract

Disrupted transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling is involved in the development of various types of cancer and the TGF- $\beta$  receptor II (TGFBR2) is a key mediator of TGF- $\beta$  growth inhibitory signals. It is reported that the G-875A polymorphism in TGFBR2 is implicated in risk of various cancers. However, results for the association between this polymorphism and cancer remain conflicting. To derive a more precise estimation, a meta-analysis of 3,808 cases and 4,489 controls from nine published case-control studies was performed. Our analysis indicated that G-875A is associated with a trend of decreased cancer risk for allele A versus (*vs.*) allele G [odds ratio (OR) = 0.64, 95% confidence intervals (CI): 0.55-0.74], as well as for both dominant model [(A/A+G/A) *vs.* G/G, OR=0.76, 95% CI: 0.64-0.90] and recessive model [A/A *vs.* (G/G+G/A), OR=0.74, 95% CI: 0.59-0.93]. However, larger scale primary studies are required to further evaluate the interaction of TGFBR2 G-875A polymorphism and cancer risk in specific cancer subtypes.

**Keywords:** TGFBR2 - polymorphism - cancer risk - meta-analysis

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## Introduction

It has been suggested that environmental and genetic factors may affect the individual's susceptibility to cancer (Derynck et al., 2001). An important gene identified as cancer susceptibility one is transforming growth factor  $\beta$  (TGF- $\beta$ ), which exerts tumor-suppressive effects that cancer cells must elude for malignant evolution (Massague, 2008; Li et al., 2014). TGF- $\beta$  is a member of the transforming growth factor beta family and works as a multi-functional cytokine that plays a key role in cell proliferation, apoptosis and differentiation (Massague, 2008). Two transmembrane Serine/Threonine kinase receptors, known as TGF- $\beta$  receptor I (TGFBR1) and TGF- $\beta$  receptor II (TGFBR2), are required for TGF- $\beta$  signaling transduction. The TGF- $\beta$  ligand first binds to TGFBR2 at the plasma membrane, resulting in the formation of the TGFBR1-TGFBR2 complex. Then, TGFBR2 phosphorylates TGFBR1, and the activated TGFBR1 in turn phosphorylates Smad2 and Smad3. Finally, phosphorylated Smad2 and Smad3 form a complex with Smad4 and, when formed, this complex translocates to the nucleus to regulate target gene expression (Schmierer and Hill, 2007; Ikushima and Miyazono, 2010).

In 2001, Seijo et al. (Seijo et al., 2001) reported one polymorphic variant of TGFBR2, G-875A (rs3087465), caused a G $\rightarrow$ A transversion in the promoter region of

the gene. Furthermore, they found this base-pair change enhanced the activity of TGFBR2 transcription in normal epithelial cells and affected the specific binding with oligonucleotide probes (Seijo et al., 2001). On the basis of the important role of TGFBR2 in the carcinogenesis, this polymorphic variant identified may be functionally associated with cancer susceptibility.

Analysis of case-control studies is the most prevalent method of investigating the association between a disease and a specific gene polymorphism. Thus far, a number of studies have reported the role of TGFBR2 G-875A polymorphism in cancer risk, but the results remain inconclusive, partially because of the relatively small sample size in each of the published studies. Therefore, here we performed a meta-analysis of the published studies to derive a more precise estimation of the association between TGFBR2 G-875A polymorphism and the cancer risk.

## Materials and Methods

### Selection of studies

All of the case-control studies were identified by a computerized literature search of the PubMed, Web of Science, EBSCO, and CGEMS database (prior to July 2014) using the following words and terms: "TGFBR2", "polymorphism", and "cancer". References of the retrieved publications were also screened. Studies had to

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be based on an unrelated case-control design, so pedigree data were excluded. The genotype distribution of the control population of the studies had to be in Hardy-Weinberg equilibrium (HWE) ( $P>0.05$ ).

**Data extraction**

The following basic data were collected from the studies: first authors, journals, year of publications and cancer subtypes.

**Statistical analysis**

For each study, the OR was first calculated to assess the association between the polymorphisms and the disease in table 1. In meta-analysis, we examined the association between allele G of G-875A and the risk of cancer compare to that of allele A, as well as using recessive [A/A vs. (G/G+A/G)], and dominant [ (A/A+A/G) vs G/G] genetic models. There are three widely used methods of meta-analysis for dichotomous outcomes: two fixed effects methods (Mantel-Haenszel’s method and Peto’s method), which assume that studies are sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance; and one random effects method (DerSimonian and Laird’s method), which assumes that studies are taken from populations with varying effect sizes, calculating the study weights both from the in-study and between-study variance, considering the extent of variation, or heterogeneity. In our study, both Mantel-Haenszel’s fixed effects method and DerSimonian and Laird’s random effects method were used in Stata 10.0 software. A chi-square-based Q-statistic test was performed to evaluate the between-study heterogeneity of the studies. If  $P<0.10$ , the between-study heterogeneity was considered to be significant, we chose the random-effects model to calculate the OR. Otherwise, when  $P\geq 0.10$ , the between-study heterogeneity was not significant, then the fixed-effects model was suitable. In the absence of between-study heterogeneity, the two

methods yield similar results. In order to make a clear comparison, we present the OR of both the random-effects model and fixed-effects model for every meta-analysis. A pooled OR obtained by meta-analysis was used to give a more reasonable evaluation of the association. A Z test was performed to determine the significance of the pooled OR ( $P\leq 0.05$  suggests a significant OR). Funnel plots were used to access publication bias by the method of Egger’s regression test. A T test was performed to determine the significance of the asymmetry. An asymmetric plot suggested possible publication bias ( $P\geq 0.05$  suggests no bias). Hardy-Weinberg equilibrium was tested by the Chisquare test based on a program (<http://www.ihg.gsf.de/cgi-bin/hw/hwa1.pl>). Analyses were performed by Stata 10.0 software.

**Results**

**Study characteristics**

There are 9 studies (3, 808 cases and 4, 489 controls) analyzing the relation of TGFBR2 G-875A polymorphism and the risk of cancer. Each subpopulation in these articles was treated as a separate study in our meta-analysis. All the studies were published from Year 2001 to 2013. Populations were divided into different cancer subtypes and ethnic categories. All individual studies were in HWE. Table 1 shows the details of the cases and controls in the included studies, together with the ORs we calculated to make a primary evaluation. Table 2 is the summary of the meta-analysis of case-control studies examining the association between TGFBR2 G-875A polymorphism and cancer risk, with the comparison between different cancer subtypes and different ethnicities.

**Main results**

For each study we investigated the association between TGFBR2 G-875A polymorphism and cancer risk, assuming different inheritance models of the G24A allele

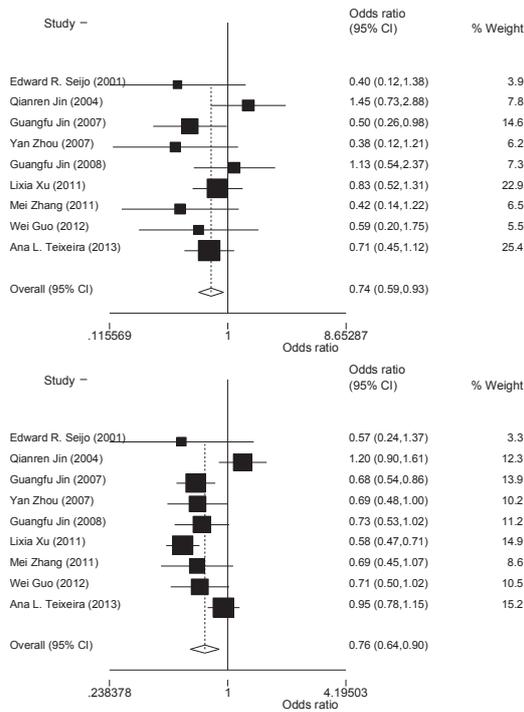
**Table 1. Characteristics of Studies Included in the Meta-analysis**

| Author              | Year | Cancer subtype              | Population | Genotype distribution of TGFBR2 G-875A polymorphism |      |    |     |         |    | OR(95%CI)       |                 | HWE (control P value) |          |
|---------------------|------|-----------------------------|------------|---|------|----|-----|---------|----|-----------------|-----------------|-----------------------|----------|
|                     |      |                             |            | GG  | Case |    |     | Control |    |                 | AA+GA/GG        |                       | AA/GA+GG |
|                     |      |                             |            |   | GA   | AA | GG  | GA      | AA |                 |                 |                       |          |
| Edward R. S(5)      | 2001 | Head and neck squamous cell | Caucasian  | 49  | 28   | 7  | 12  | 10      | 5  | 0.57(0.24-1.37) | 0.40(0.12-1.38) | 0.2847                |          |
| Qianren Jin(18)     | 2004 | Breast                      | Caucasian  | 247   | 122  | 20 | 282 | 120     | 15 | 1.2(0.90-1.61)  | 1.45(0.73-2.88) | 0.616                 |          |
| Guangfu Jin(11)     | 2007 | Gastric                     | Asian      | 463   | 160  | 13 | 436 | 213     | 27 | 0.68(0.54-0.86) | 0.50(0.26-0.98) | 0.8774                |          |
| Yan Zhou(12)        | 2007 | Gastric                     | Asian      | 190   | 62   | 4  | 202 | 89      | 12 | 0.69(0.48-1.00) | 0.38(0.12-1.21) | 0.5792                |          |
| Guangfu Jin(13)     | 2008 | Esophageal squamous cell    | Asian      | 159   | 54   | 10 | 436 | 213     | 27 | 0.73(0.53-1.02) | 1.13(0.54-2.37) | 0.8774                |          |
| Lixia Xu(14)        | 2011 | Gastric                     | Asian      | 702   | 222  | 39 | 478 | 268     | 38 | 0.58(0.47-0.71) | 0.83(0.52-1.31) | 0.9559                |          |
| Mei Zhang (15)      | 2011 | Breast                      | Asian      | 114   | 51   | 5  | 104 | 62      | 12 | 0.69(0.45-1.07) | 0.42(0.14-1.22) | 0.5095                |          |
| Wei Guo (16)        | 2012 | Gastric                     | Asian      | 140   | 52   | 4  | 355 | 180     | 19 | 0.71(0.50-1.02) | 0.59(0.20-1.75) | 0.5108                |          |
| Ana L. Teixeira(17) | 2013 | Prostate                    | Caucasian  | 562   | 295  | 34 | 541 | 287     | 46 | 0.95(0.78-1.15) | 0.71(0.45-1.12) | 0.3278                |          |

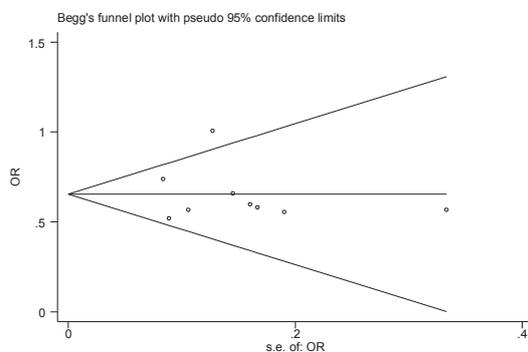
OR: Odds ratio, CI: confidence interval, HWE: Hardy-Weinberg equilibrium

**Table 2. Summary of the Meta-analysis of Case-control Studies Examining the Association between TGFBR2 G-875A Polymorphism and Cancer Risk**

| OR(95%CI)                       | A vs. G         | A/A vs. G/G     | G/A vs. G/G     | A/A vs. (G/G+G/A) | (A/A+G/A) vs. G/G |
|---------------------------------|-----------------|-----------------|-----------------|-------------------|-------------------|
| All of studies                  | 0.64(0.55-0.74) | 0.68(0.54-0.86) | 0.77(0.64-0.92) | 0.74(0.59-0.93)   | 0.76(0.64-0.90)   |
| All of Gastric Cancer studies   | 0.55(0.49-0.62) | 0.57(0.40-0.79) | 0.65(0.57-0.75) | 0.64(0.46-0.91)   | 0.64(0.56-0.73)   |
| All of Breast Cancer studies    | 0.76(0.42-1.36) | 0.81(0.21-3.14) | 1.01(0.79-1.31) | 0.98(0.56-1.72)   | 0.93(0.54-1.60)   |
| studiesAll of Caucasian studies | 0.80(0.70-0.91) | 0.84(0.58-1.21) | 1.02(0.87-1.21) | 0.84(0.58-1.20)   | 1.00(0.86-1.17)   |
| All of Asian studies            | 0.56(0.51-0.63) | 0.60(0.45-0.81) | 0.66(0.59-0.75) | 0.68(0.51-0.91)   | 0.89(0.81-0.97)   |



**Figure 1. Forest Plot of Cancer Risk Associated with the TGFBR2 Gene Polymorphism at G-875A.** The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. A. recessive genetic model [A/A vs. (G/G+A/G)] B. dominant genetic models [(A/A+A/G) vs. G/G]



**Figure 2. Begg's Funnel Plot of the Egger's Test for Publication Bias in Comparison of TGFBR2 G-875A Allele A vs. G**

Overall, when all the eligible studies were pooled into the meta-analysis, associations between TGFBR2 G-875A polymorphism and cancer susceptibility were observed in all genetic models. Significant associations were found for allele A vs. G (OR=0.64, 95% CI: 0.55-0.74,  $P=0.002$  for heterogeneity), A/A vs. G/G (OR=0.68; 95% CI: 0.54-0.86;  $P=0.182$  for heterogeneity), G/A vs. G/G (OR=0.77; 95% CI: 0.65-0.92;  $P=0.005$  for heterogeneity), A/A+G/A vs. G/G (OR=0.76; 95% CI: 0.64-0.90;  $P=0.003$  for heterogeneity) and A/A vs. G/A+G/G (OR=0.74; 95% CI: 0.59-0.93;  $P=0.266$  for heterogeneity) (Table 2). Subgroup analyses by ethnicity and cancer type also showed G-875A associated with a trend of decreased cancer risk (Table 2).

### Sensitivity analyses and publication bias

The results suggested the influences of the individual data set to the pooled ORs are all not significant. Funnel plots and Egger's test were performed to assess publication bias (Figure 2). The data suggested that there is no publication bias for the comparison of G-875A allele A vs. allele G ( $t=0.15$ ,  $P=0.888$ ).

## Discussion

TGF- $\beta$  is a multifunctional cytokine that is essential for maintaining homeostasis involving bone and muscle differentiation, immune response, and tumor suppression (Wu and Hill, 2009; Massague, 2012b; Li et al., 2014). Increased production of TGF- $\beta$  occurs in various tumor types and is correlated with severity of tumor grade (Massague, 2012a). There is also evidence that TGF- $\beta$  acts as a suppressor of tumor initiation but as a promoter of tumor progression when the growth inhibition effect of the TGF- $\beta$  signaling pathway has been overridden by other oncogenic mutations (Massague, 2008; Adorno et al., 2009).

Recently, several groups have used meta-analysis to investigate the association between cancer risk and gene Single nucleotide polymorphisms (SNP) involved in TGF- $\beta$  signaling (Huang et al., 2010; Huang et al., 2011; Liu et al., 2012). As one of the key effectors of TGF- $\beta$  signaling, TGFBR2 mediates the growth-inhibitory signals from TGF- $\beta$  through a complex with TGFBR1 (Derynck and Zhang, 2003; Ikushima and Miyazono, 2010). Though the functional role of the TGFBR2 G-875A variant in TGF- $\beta$  pathway has not yet to be well interpreted, several published clinic studies reported this variant was at decreased risk of developing various cancer (Jin et al., 2007; Zhou et al., 2007; Jin et al., 2008; Xu et al., 2011; Zhang et al., 2011; Guo et al., 2012; Teixeira et al., 2013). However, two published clinic studies reported this variant was not involved in the risk of cancer (Seijo et al., 2001; Jin et al., 2004). These conflicting studies based their conclusions on a small number of samples, so a meta-analysis of all available studies will help to establish a more convincing result. From our meta-analysis, G-875A in the combined population associated with a significant trend of decreased cancer risk. There is no publication bias among the total studies. In the stratified analysis by ethnicity and subtype of cancer, significant associations between TGFBR2 G-875A polymorphism and decreased cancer risk were also detected.

In conclusion, the research of the relationship of TGFBR2 G-875A polymorphism and cancer is very popular but remain conflicting at present. Our meta-analysis suggested that under recessive, dominant and other genetic models, the G-875A polymorphism associated with a decreased risk of cancer. However, the studies included in the subgroups analysis are still limited and the results are sensitive to study selection. More comparative studies are needed to evaluate interactions of TGFBR2 polymorphisms and cancer risk in specific cancer subtypes and ethnic subtypes.

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## References

- Adorno M, Cordenonsi M, Montagner M, et al (2009). A Mutant-p53/Smad complex opposes p63 to empower TGFbeta-induced metastasis. *Cell*, **137**, 87-98.
- Derynck R, Akhurst RJ, Balmain A (2001). TGF-beta signaling in tumor suppression and cancer progression. *Nat Genet*, **29**, 117-29.
- Derynck R, Zhang YE (2003). Smad-dependent and Smad-independent pathways in TGF-beta family signalling. *Nature*, **425**, 577-84.
- Guo W, Dong Z, Guo Y, et al (2012). Association of polymorphisms in transforming growth factor-beta receptors with susceptibility to gastric cardia adenocarcinoma. *Mol Biol Rep*, **39**, 4301-9.
- Huang Y, Hao Y, Li B, et al (2011). Lack of significant association between TGF-beta1-590C/T polymorphism and breast cancer risk: a meta-analysis. *Med Oncol*, **28**, 424-8.
- Huang Y, Li B, Qian J, et al (2010). TGF-beta1 29T/C polymorphism and breast cancer risk: a meta-analysis involving 25, 996 subjects. *Breast Cancer Res Treat*, **123**, 863-8.
- Ikushima H, Miyazono K (2010). TGFbeta signalling: a complex web in cancer progression. *Nat Rev Cancer*, **10**, 415-24.
- Jin G, Deng Y, Miao R, et al (2008). TGFB1 and TGFBR2 functional polymorphisms and risk of esophageal squamous cell carcinoma: a case-control analysis in a Chinese population. *J Cancer Res Clin Oncol*, **134**, 345-51.
- Jin G, Wang L, Chen W, et al (2007). Variant alleles of TGFB1 and TGFBR2 are associated with a decreased risk of gastric cancer in a Chinese population. *Int J Cancer*, **120**, 1330-5.
- Jin Q, Hemminki K, Grzybowska E, et al (2004). Polymorphisms and haplotype structures in genes for transforming growth factor beta1 and its receptors in familial and unselected breast cancers. *Int J Cancer*, **112**, 94-9.
- Li Z, Zhang LJ, Zhang HR, et al (2014). Tumor-derived transforming growth factor-beta is critical for tumor progression and evasion from immune surveillance. *Asian Pac J Cancer Prev*, **15**, 5181-6.
- Liu Y, Lin XF, Lin CJ, et al (2012). Transforming growth factor beta-1 C-509T polymorphism and cancer risk: a meta-analysis of 55 case-control studies. *Asian Pac J Cancer Prev*, **13**, 4683-8.
- Massague J (2008). TGFbeta in cancer. *Cell*, **134**, 215-30.
- Massague J (2012a). TGF-beta signaling in development and disease. *FEBS Lett*, **586**, 1833.
- Massague J (2012b). TGFbeta signalling in context. *Nat Rev Mol Cell Biol*, **13**, 616-30.
- Schmierer B, Hill CS (2007). TGFbeta-SMAD signal transduction: molecular specificity and functional flexibility. *Nat Rev Mol Cell Biol*, **8**, 970-82.
- Seijo ER, Song H, Lynch MA, et al (2001). Identification of genetic alterations in the TGFbeta type II receptor gene promoter. *Mutat Res*, **483**, 19-26.
- Teixeira AL, Gomes M, Nogueira A, et al (2013). Improvement of a predictive model of castration-resistant prostate cancer: functional genetic variants in TGFbeta1 signaling pathway modulation. *PLoS One*, **8**, 72419.
- Wu MY, Hill CS (2009). Tgf-beta superfamily signaling in embryonic development and homeostasis. *Dev Cell*, **16**, 329-43.

- Xu L, Zeng Z, Chen B, et al (2011). Association between the TGFB1 -509C/T and TGFBR2 -875A/G polymorphisms and gastric cancer: a case-control study. *Oncol Lett*, **2**, 371-7.
- Zhang M, Guo L, Cheng Z, et al (2011). A functional polymorphism of TGFBR2 is associated with risk of breast cancer with ER (+), PR (+), ER (+)PR (+) and HER2 (-) expression in women. *Oncol Lett*, **2**, 653-8.
- Zhou Y, Jin GF, Jiang GJ, et al (2007). Correlations of polymorphisms of TGFB1 and TGFBR2 genes to genetic susceptibility to gastric cancer. *Ai Zheng*, **26**, 581-5.