Association between TGFBR1 Polymorphisms and Cancer Risk: A Meta-Analysis of 35 Case-Control Studies

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Abstract

Background: Numerous epidemiological studies have evaluated the association between TGFBR1 polymorphisms and the risk of cancer, however, the results remain inconclusive. To derive a more precise estimation of the relation, we conducted a comprehensive meta-analysis of all available case-control studies relating the TGFBR1*6A and IVS7+24G>A polymorphisms of the TGFBR1 gene to the risk of cancer.

Methods: Eligible studies were identified by search of electronic databases. Overall and subgroup analyses were performed. Odds ratio (OR) and 95% confidence interval (CI) were applied to assess the associations between TGFBR1*6A and IVS7+24G>A polymorphisms and cancer risk.

Results: A total of 35 studies were identified, 32 with 19,767 cases and 18,516 controls for TGFBR1*6A polymorphism and 12 with 4,195 cases and 4,383 controls for IVS7+24G>A polymorphism. For TGFBR1*6A, significantly elevated cancer risk was found in all genetic models (dominant OR = 1.11, 95% CI = 1.04~1.18; recessive: OR = 1.36, 95% CI = 1.11~1.66; additive: OR = 1.13, 95% CI = 1.05~1.20). In subgroup analysis based on cancer type, increased cancer risk was found in ovarian and breast cancer. For IVS7+24G>A, significant correlation with overall cancer risk (dominant: OR = 1.39, 95% CI = 1.15~1.67; recessive: OR = 2.23, 95% CI = 1.26~3.92; additive: OR = 1.43, 95% CI = 1.14~1.80) was found, especially in Asian population. In the subgroup analysis stratified by cancer type, significant association was found in breast and colorectal cancer.

Conclusions: Our investigations demonstrate that TGFBR1*6A and IVS7+24G>A polymorphisms of TGFBR1 are associated with the susceptibility of cancer, and further functional research should be performed to explain the inconsistent results in different ethnicities and cancer types.

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Introduction

Cancer is a disease resulting from complex interactions between environmental and genetic factors [1–3]. Genetic factors, including the sequence alterations and organization aberrations of the cellular genome that range from single-nucleotide substitutions to gross chromosome, could modulate several important biological progress and alert susceptibility to cancer consequently.

The transforming growth factor-β (TGF-β) signaling pathway has been the focus of extensive research since it was first discovered in 1981 [4,5]. It has now been well established that this signaling pathway is an important modulator of several biological processes, including cell proliferation, differentiation, migration and apoptosis [6]. Alterations of the TGF-β signaling pathway are frequently found in many diseases including human cancers in breast, colon, prostate or pancreas [7–10]. As overall TGF-β signaling may be determined by genetic polymorphisms in several TGF-β pathway genes, an increasing number of studies have pointed to the effects of TGF-β pathway gene variants on cancer risk. As the central propagator of TGF-β signaling pathway, TGF-β receptor type I (TGFBR1) has been the hot spot of research.

TGFBR1 gene locates on chromosome 9q22 [11]. Two commonly studied polymorphisms of TGFBR1 gene are TGFBR1*6A (rs1466445), which results from the deletion of three alanines within a nine-alanine (*9A) stretch in exon 1 [12] and IVS7+24G>A (rs334354), which represents a G to A transversion in the +24 position of the donor splice site in intron 7. Although the functional role of IVS7+24G>A is unclear yet, TGFBR1*6A has been suggested to be responsible for efficiency in mediating TGF-β growth inhibitory signals [13]. Therefore, it is biologically reasonable to hypothesize that polymorphisms of TGFBR1 gene may play a functional role in carcinogenesis.

A number of studies have investigated the association between TGFBR1 polymorphisms and cancer risk, but results are somewhat controversial and underpowered. For TGFBR1*6A, a recent meta-analysis in 2010 by Liao et al. [14] found significant
association with overall cancer, however, several new papers are further available [15–23]. With respect to IVS7+24G>A polymorphism, only 2 meta-analysis on this issue had ever appeared [24,25]. Zhang [24] found the IVS7+24G>A carriers had a 76% increase of risk of cancer (OR = 1.76, 95% CI = 1.33–2.34) with only 440 cases and 706 controls in 3 studies. Meanwhile, Zhang et al. [25] limited the investigation on colorectal cancer and found that there was a significantly increased risk for homozygosity A/A carriers compared to heterozygosity and homozygosity of the allele G carriers (OR = 1.71, 95% CI = 1.17–2.51). To derive a more precise estimation of the relationship between TGFBR1 polymorphisms and cancer risk, we carried out an updated meta-analysis of all available case-control studies relating the TGFBR1*6A and/or IVS7+24G>A polymorphisms of the TGFBR1 gene to the risk of cancer. To the best of our knowledge, this is the most comprehensive meta-analysis regarding the TGFBR1 polymorphisms and cancer risk.

**Materials and Methods**

**Identification and Eligibility of Relevant Studies**

This study was performed according to the proposal of Meta-analysis of Observational Studies in Epidemiology group (MOOSE) [26]. A systematic literature search was performed for articles regarding TGFBR1 SNPs associated with cancer risk. The MEDLINE, Embase, and Chinese National Knowledge Infrastructure (CNKI) were used simultaneously, with the combination of terms “TGFBR1 or transforming growth factor receptor 1 or Type I TGF-beta receptor”, “polymorphism or variant or SNP” and “cancer or neoplasm or carcinoma” (up to May 12, 2012). Reference lists of the identified articles were also examined and the literature retrieval was performed in duplication by two independent reviewers (Yong-qiang Wang and Xiao-wei Qi). Studies that were included in the meta-analysis had to meet all of the following criteria: (1) the publication was a case-control study referring to the association between TGFBR1 polymorphisms (TGFBR1*6A and/or IVS7+24G>A) and cancer, (2) the papers must offer the sample size, distribution of alleles, genotypes or other information that can help us infer the results, (3) when multiple publications reported on the same or overlapping data, we used the most recent or largest population as recommended by Little et al. [27], and (4) publication language was confined to English and Chinese.

**Data Extraction**

Two investigators (Yong-qiang Wang and Xiao-wei Qi) independently extracted the data from eligible studies selected according to the pre-specified criteria and the results were compared. Disagreements were resolved by discussion or by involving a third reviewer (Qiao-nan Guo). The following information of each study was collected: first author, reference year, name of studies, total number of cases and controls, studied polymorphisms, ethnicity of subjects, source of controls, and distribution of genotypes in case and control groups. For studies with inadequate information, authors were contacted for further support by E-mail if possible.

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186 articles identified initially

81 articles potentially considered for inclusion

56 articles for further evaluation

43 articles relevant to TGFBR1 polymorphisms and cancer risk were for data extraction

Finally, 35 studies were included in this meta-analysis

21 were not for cancer research
62 were not about TGFBR1
22 were not about SNP research

24 were not case-control study
1 article were registered both in pubmed and CNKI

9 reviews
4 meta-analysis studies

3 for not about the two polymorphisms
3 for no useful data
2 were not consistent with HWE

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Figure 1. Flow diagram of study identification. doi:10.1371/journal.pone.0042899.g001
**Table 1.** Characteristics of case-control studies included in TGFBR1 TGFBR1*6A polymorphism and cancer risk.

| First author | Year | Country | Ethnicity | Cancer type | Sample size (case/control) | Case 9A/9A | 6A/9A | 6A/6A | Control 9A/9A | 6A/9A | 6A/6A |
|--------------|------|---------|-----------|-------------|---------------------------|------------|-------|-------|---------------|-------|-------|
| Pasche [36]  | 1999 | USA     | Mixed     | Colon       | 111/732                   | 90          | 17    | 4     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | USA     | Mixed     | Ovarian     | 47/732                    | 39          | 7     | 1     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | USA     | Mixed     | Breast      | 152/732                   | 128         | 24    | 0     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | USA     | Mixed     | Germ cell cancer | 56/732                   | 49          | 5     | 2     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | USA     | Mixed     | Lung        | 94/732                    | 82          | 11    | 1     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | USA     | Mixed     | Prostate    | 59/732                    | 51          | 8     | 0     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | USA     | Mixed     | Pancreas    | 14/732                    | 12          | 2     | 0     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | USA     | Mixed     | Bladder     | 77/732                    | 67          | 10    | 0     | 654           | 78    | 0     |
| Pasche [36]  | 1999 | Italy   | Caucasian | Bladder     | 234/50                    | 199         | 35    | 0     | 38            | 12    | 0     |
| Pasche [36]  | 1999 | Italy   | Caucasian | Breast      | 65/50                     | 57          | 8     | 0     | 38            | 12    | 0     |
| Chen [37]    | 1999 | USA     | NS        | Cervical    | 37/38                     | 29          | 7     | 1     | 34            | 4     | 0     |
| Chen [37]    | 1999 | Jamaica | African   | Cervical    | 29/30                     | 26          | 3     | 0     | 27            | 3     | 0     |
| van Tilborg [38] | 2001 | Netherlands | Caucasian | Bladder | 146/183                    | 121         | 25    | 0     | 148           | 32    | 3     |
| Stefanovska [39] | 2001 | Macedonia | Caucasian | Colorectal | 117/200                    | 108         | 8     | 1     | 179           | 20    | 1     |
| Samowitz [40] | 2001 | USA     | Mixed     | Colon       | 250/358                   | 202         | 46    | 2     | 295           | 58    | 5     |
| Baxter [41]  | 2002 | UK      | Caucasian | Breast      | 355/248                   | 268         | 83    | 4     | 207           | 39    | 2     |
| Baxter [41]  | 2002 | UK      | Caucasian | Ovarian     | 304/248                   | 236         | 62    | 6     | 207           | 39    | 2     |
| Chen [12]    | 2004 | USA     | Mixed     | Renal       | 88/138                    | 71          | 15    | 2     | 112           | 25    | 1     |
| Chen [12]    | 2004 | USA     | Mixed     | Bladder     | 63/138                    | 49          | 13    | 1     | 112           | 25    | 1     |
| Kaklamani [42] | 2004 | USA     | Mixed     | Prostate    | 442/465                   | 380         | 59    | 3     | 402           | 62    | 1     |
| Reiss [43]   | 2004 | USA     | Mixed     | Breast      | 98/91                     | 87          | 11    | 0     | 77            | 14    | 0     |
| Ellis [43]   | 2004 | USA     | Ashkenazi Jews | Colon | 767/766                   | 655         | 108   | 4     | 663           | 100   | 3     |
| Caldes [43]  | 2004 | Spain   | Caucasian | Breast      | 271/292                   | 214         | 56    | 1     | 250           | 42    | 0     |
| Caldes [43]  | 2004 | Spain   | Caucasian | Colorectal | 235/292                   | 183         | 50    | 2     | 250           | 42    | 0     |
| Offit [43]   | 2004 | USA     | NS        | Breast      | 462/330                   | 391         | 67    | 4     | 291           | 38    | 1     |
| Northwestern [43] | 2004 | USA     | NS        | Breast, Ovarian | 86/123                  | 74          | 12    | 0     | 105           | 17    | 1     |
| Northwestern [43] | 2004 | USA     | NS        | Colon       | 35/123                    | 30          | 5     | 0     | 105           | 17    | 1     |
| Jin [44]     | 2004 | Finland | Caucasian | Breast      | 221/234                   | 177         | 38    | 6     | 171           | 60    | 3     |
| Jin [44]     | 2004 | Poland  | Caucasian | Breast      | 170/202                   | 140         | 28    | 2     | 176           | 26    | 0     |
| Suarez [45]  | 2005 | USA     | Mixed     | Prostate    | 534/488                   | 441         | 87    | 6     | 407           | 79    | 2     |
| Spillman [46] | 2005 | USA     | Mixed     | Ovarian     | 578/607                   | 468         | 100   | 10    | 497           | 104   | 6     |
| Kaklamani [47] | 2005 | USA     | Mixed     | Breast      | 611/690                   | 515         | 92    | 4     | 612           | 77    | 1     |
| Chen [48]    | 2006 | USA     | Mixed     | Breast      | 115/130                   | 92          | 23    | 0     | 111           | 18    | 1     |
| Feigelson [49] | 2006 | USA     | Mixed     | Breast      | 481/484                   | 387         | 94    | -     | 384           | 100   |       |
| You [50]     | 2007 | China   | Asian     | Lung        | 252/250                   | 217         | 35    | 0     | 219           | 31    | 0     |
| Cox [51]     | 2007 | USA     | NS        | Breast      | 1187/1673                 | 968         | 207   | 12    | 1352          | 302   | 19    |
| Song [52]    | 2007 | Sweden  | Caucasian | Breast      | 763/852                   | 598         | 152   | 13    | 682           | 160   | 10    |
| Skoglund [53] | 2007 | Sweden  | Caucasian | Colorectal | 1040/852                  | 827         | 203   | 10    | 682           | 160   | 10    |
| Skoglund Lundin [54] | 2009 | Sweden  | Caucasian | Colorectal | 213/852                   | 167         | 42    | 4     | 682           | 160   | 10    |
| Castillejo [55] | 2009 | Spain   | Caucasian | Bladder     | 1094/1014                 | 887         | 199   | 8     | 812           | 191   | 11    |
| Jakubowska [56] | 2010 | Poland  | Caucasian | Breast      | 318/290                   | 282         | 33    | 3     | 252           | 38    | 0     |
| Jakubowska [56] | 2010 | Poland  | Caucasian | Ovarian     | 144/279                   | 122         | 22    | 0     | 244           | 35    | 0     |
| Colloran [57] | 2009 | Ireland | Caucasian | Breast      | 960/958                   | 796         | 154   | 10    | 785           | 160   | 13    |
| Dai [15]     | 2009 | Germany | Caucasian | ALL         | 458/552                   | 390         | 61    | 7     | 456           | 88    | 8     |
Meta-analysis was performed as described previously [28, 29]. Hardy-Weinberg equilibrium (HWE) in the controls for each study was calculated using goodness-of-fit test (chi-square or Fisher’s exact test). It was considered statistically significant when $P < 0.05$. Studies deviated from HWE were removed.

Crude odds ratios (ORs) with their 95% CIs were used to assess the strength of association between polymorphisms of TGFBR1 and cancer risk. The pooled ORs were performed for dominant model (1:1+1:2 vs. 2:2), recessive model (1:1 vs. 1:2+2:2), additive model (1 vs. 2) respectively. 1 and 2 represent the minor and the major allele respectively. Stratified analysis was also performed by ethnicity and cancer type. Leukemia, lymphoma and MM (multiple myeloma) were merged as hematologic cancer. For ethnicity classification, African, Jews and the ethnicity not stated in original study were merged as others.

Heterogeneity assumption was assessed by chi-based Q-test. The heterogeneity was considered statistically significant if $P < 0.10$ [30]. With lacking of heterogeneity among studies, the pooled OR was calculated by the fixed effects model (Mantel–Haenszel) [31]. Otherwise, the random effects model (DerSimonian and Laird) was used [32, 33]. We also calculated the quantity $I^2$ that represents the percentage of total variation across studies that is a result of heterogeneity rather than chance. Values of less than 25% may be considered “low”, values of about 50% may be considered “moderate”, and values of more than 75% may be high.

### Table 1. Cont.

| First author       | Year | Country | Ethnicity | Cancer type | Sample size (case/control) | Case | Control |
|--------------------|------|---------|-----------|-------------|---------------------------|------|---------|
| Carvajal-Carmona   | 2010 | UK      | Caucasian | Colorectal  | 913/828                   | 746  | 159     |
|                    |      |         |           |             | 673                        | 145  | 10      |
| Carvajal-Carmona   | 2010 | UK      | Caucasian | Colorectal  | 933/990                   | 772  | 152     |
|                    |      |         |           |             | 843                        | 140  | 7       |
| Carvajal-Carmona   | 2010 | UK      | Caucasian | Colorectal  | 1152/1333                 | 938  | 201     |
|                    |      |         |           |             | 1119                      | 200  | 14      |
| Forsti [17]        | 2010 | Sweden  | Caucasian | Colorectal  | 293/558                   | 218  | 69      |
|                    |      |         |           |             | 635                        | 115  | 8       |
| Hu [18]            | 2010 | China   | Asian     | Osteosarcoma| 168/168                   | 107  | 51      |
|                    |      |         |           |             | 103                        | 31   | 3       |
| Abuli [19]         | 2011 | Spain   | Caucasian | Colorectal  | 509/513                   | 427  | 78      |
|                    |      |         |           |             | 405                        | 103  | 5       |
| Dong [20]          | 2011 | China   | Asian     | Esophageal  | 482/584                   | 409  | 69      |
|                    |      |         |           |             | 499                        | 79   | 6       |
| Guo [21]           | 2011 | China   | Asian     | Gastric     | 468/584                   | 393  | 70      |
|                    |      |         |           |             | 499                        | 79   | 6       |
| Joshi [22]         | 2011 | India   | Asian     | Breast      | 167/222                   | 163  | 4       |
|                    |      |         |           |             | 213                        | 9    | 0       |
| Joshi [22]         | 2011 | India   | Asian     | Breast      | 42/169                    | 33   | 8       |
|                    |      |         |           |             | 148                        | 19   | 2       |
| Martinez-Canto     | 2012 | Spain   | Caucasian | Colorectal  | 521/404                   | 442  | 72      |
|                    |      |         |           |             | 334                        | 67   | 3       |

*The combination of Leukemia, lymphoma and MM (multiple myeloma).

**This study was excluded from the combined allelic effect and recessive model because of insufficient data on the frequencies of 9A/6A and 6A/6A genotype.

NS: not stated, ALL: acute lymphocytic leukemia.

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### Table 2. Characteristics of case-control studies included in TGFBR1 IVS7+24G>A polymorphism and cancer risk.

| First author | Year | Country | Ethnicity | Cancer type | Sample size (case/control) | Case | Control |
|--------------|------|---------|-----------|-------------|---------------------------|------|---------|
| Chen [37]    | 1999 | USA, Netherlands | Mixed | Cervical | 16/38 | 9    | 7   | 0    | 24  | 12  | 2   |
| Chen [12]    | 2004 | USA     | Mixed | Renal     | 86/113 | 46   | 36   | 4    | 81  | 32  | 0   |
| Chen [12]    | 2004 | USA     | Mixed | Bladder   | 65/113 | 33   | 28   | 4    | 81  | 32  | 0   |
| Chen [12]    | 2006 | USA     | Mixed | Breast    | 223/153 | 120  | 92   | 11   | 113 | 37  | 3   |
| Song [52]    | 2007 | Sweden  | Caucasian | Breast | 767/853 | 500  | 238  | 267  | 559 | 265 | 29  |
| Castillejo [58] | 2009 | Spain   | Caucasian | Colorectal | 504/504 | 296 | 178  | 30   | 333 | 156 | 15  |
| Lundin [54]  | 2009 | Sweden  | Caucasian | Colorectal | 262/856 | 135  | 67   | 12   | 559 | 265 | 29  |
| Zhang [59]   | 2009 | China   | Asian  | Colorectal | 206/838 | 60   | 103  | 43   | 245 | 431 | 162 |
| Dai [15]     | 2009 | Germany | Caucasian | ALL       | 456/551 | 285  | 147  | 24   | 356 | 170 | 25  |
| Forsti [17]  | 2010 | Sweden  | Caucasian | Colorectal | 308/585 | 220  | 68   | 14   | 382 | 179 | 20  |
| Dong [20]    | 2011 | China   | Asian  | Esophageal | 482/584 | 296  | 163  | 23   | 402 | 168 | 14  |
| Guo [21]     | 2011 | China   | Asian  | Gastric   | 468/584 | 291  | 155  | 22   | 402 | 168 | 14  |
| Hu [60]      | 2011 | China   | Asian  | Osteosarcoma | 168/168 | 100  | 57   | 11   | 115 | 48  | 5   |

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**Table 3.** Pooled analysis of association of TGFBR1 TGFBR1*6A (rs1466445) and cancer risk.

| Cancer type | N   | Case/Control | OR (95% CI) | \( \rho_h \) | \( \chi^2 \) |
|-------------|-----|--------------|------------|-------------|-------------|
|             |     |              |            |             |             |
| **Total**   | 58  | 19767/18516  | 1.105 (1.035–1.181) | 0.024 | 28.7% |
| **Cancer type** | | | | | |
| Colorectal  | 15  | 7154/8851   | 1.076 (0.956–1.212) | 0.048 | 41.2% |
| Ovarian  | 4   | 1071/1866   | 1.218 (0.983–1.510) | 0.526 | 0.0% |
| Breast  | 17  | 6421/7647   | 1.122 (0.978–1.287) | 0.023 | 45.2% |
| Lung  | 2   | 346/982     | 1.173 (0.782–1.759) | 0.861 | 0.0% |
| Prostate  | 3   | 1035/1685   | 1.073 (0.848–1.358) | 0.865 | 0.0% |
| Bladder  | 5   | 1461/2117   | 0.936 (0.780–1.112) | 0.536 | 0.0% |
| Hematologic  | 2   | 686/1284   | 1.185 (0.575–2.440) | 0.007 | 86.2% |
| Cervical  | 2   | 66/68       | 1.732 (0.619–4.849) | 0.454 | 0.0% |
| **Ethnicity** | | | | | |
| Mixed  | 20  | 4108/4183   | 1.145 (1.049–1.251) | 0.640 | 0.0% |
| Caucasian  | 25  | 11477/9980 | 1.037 (0.941–1.142) | 0.011 | 43.8% |
| Others  | 7   | 2603/2960  | 1.208 (1.083–1.347) | 0.668 | 0.0% |
| Asian  | 6   | 1579/1393  | 1.272 (0.951–1.702) | 0.089 | 47.7% |

**Publication bias test**

| Egger's test | P = 0.001 |
| Egger's test | P = 0.129 |

\( \rho_h \): test for heterogeneity, OR: odds ratio, CI: confidence interval, N: number of data sets.

\( \chi^2 \): the percentage of total variation across studies that is a result of heterogeneity rather than chance.

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**Table 4.** Pooled analysis of association of IVS7+24G>A (rs334354) and cancer risk.

| Cancer type | N   | Case/Control | OR (95% CI) | \( \rho_h \) | \( \chi^2 \) |
|-------------|-----|--------------|------------|-------------|-------------|
|             |     |              |            |             |             |
| **Total**   | 13  | 4195/4383   | 1.385 (1.146–1.673) | 0.000 | 75.9% |
| **Cancer type** | | | | | |
| Colorectal  | 4   | 1226/2776 | 1.030 (0.779–1.362) | 0.016 | 71.0% |
| Breast  | 2   | 1228/1006  | 1.989 (1.673–2.365) | 0.345 | 0.0% |
| **Ethnicity** | | | | | |
| Caucasian  | 5   | 2481/2489 | 1.194 (0.854–1.669) | 0.000 | 88.2% |
| Asian  | 4   | 1324/1590 | 1.206 (1.116–1.505) | 0.410 | 0.0% |
| Mixed  | 4   | 390/304 | 2.283 (1.694–3.082) | 0.820 | 0.0% |

**Publication bias test**

| Egger's test | P = 1.00 |
| Egger's test | P = 0.867 |

\( \rho_h \): test for heterogeneity, OR: odds ratio, CI: confidence interval, N: number of data sets.

\( \chi^2 \): the percentage of total variation across studies that is a result of heterogeneity rather than chance.

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considered “high”. A value of 0 (zero) indicates no observed heterogeneity, and larger values show increasing heterogeneity.

Sensitivity analysis was carried out by removing each study at a time to evaluate the stability of the results. Publication bias was analyzed by performing funnel plots qualitatively, and estimated by Begg’s and Egger’s test quantitatively [34,35].

All statistical analysis was conducted using STATA software (version 11.0; STATA Corporation, College Station, TX). Two-sided P-values<0.05 were considered statistically significant.

Figure 2. Forest plot (random effects model) describing the association of the TGFBR1*6A polymorphism with risk of cancer. The TGFBR1*6A polymorphism was associated with increased risk of cancer in additive model. Each study is shown by the point estimate of the OR (the size of the square is proportional to the weight of each study) and 95% CI for the OR (extending lines).

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Figure 3. Forest plot (random effects model) describing the association of the IVS7+24G>A polymorphism with risk of cancer. The IVS7+24G>A polymorphism was associated with increased cancer risk in additive model.
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Figure 4. Funnel plot analysis (recessive model of TGFBR1*6A polymorphism) to detect publication bias. Each point represents an individual study for the indicated association. LogOR, natural logarithm of OR. Perpendicular line, mean effect size.
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Results

Study Characteristics

After comprehensive searching, a total of 186 publications were identified. We reviewed the titles, abstracts and the full texts of all retrieved articles through defined criteria as shown in Figure 1. Finally, the pool of eligible studies included 35 studies [12,15–23,36–60], among which 32 with 19,767 cases and 18,516 controls were for TGFBR1*6A polymorphism and 12 with 4,195 cases and 4,383 controls for IVS7+24G>A polymorphism. Each study in one publication was considered as a data set separately for pooling analysis. Table 1 and Table 2 list the main characteristics of these data sets about these two polymorphisms.

Quantitative Synthesis

The main results of this meta-analysis and the heterogeneity test were shown in Table 3 and 4. With respect to TGFBR1*6A polymorphism, a total of 58 data sets in 32 studies were included in this meta-analysis. Of these data sets, 25 were Caucasian, 6 were Asian, 20 were mixed population and 7 were others. Overall, significantly elevated cancer risk was found in all genetic models (dominant model: OR = 1.11, 95% CI = 1.04–1.18; recessive model: OR = 1.36, 95% CI = 1.11–1.66; additive model: OR = 1.13, 95% CI = 1.05–1.20, Figure 2). The heterogeneity was significant in all genetic models except for recessive model (P = 0.34). In the subgroup analysis stratified by ethnicity, significantly increased cancer risk was suggested among mixed ethnicity from US studies (dominant model: OR = 1.15, 95% CI = 1.05–1.25; recessive model: OR = 1.85, 95% CI = 1.26–2.72; additive model: OR = 1.22, 95% CI = 1.10–1.36) but not among Caucasian or Asian population in all genetic models. In the subgroup analysis by cancer type, no significant association with cancer risk was demonstrated in overall population with colorectal, lung, prostate, bladder, hematological and cervical cancer. For ovarian cancer, significantly increased risk was observed in recessive model (OR = 2.30, 95% CI = 1.01–5.22) and additive model (OR = 1.25, 95% CI = 1.02–1.52). With respect to breast cancer, significantly increased risk was found only in additive model (OR = 1.15, 95% CI = 1.01–1.31).

With respect to IVS7+24G>A polymorphism, a total of 12 studies with 13 data sets were included. Of these data sets, 5 were European, 4 were Asian and 4 were from USA with mixed ethnicity. Similar to TGFBR1*6A polymorphism, significantly elevated cancer risk was associated with IVS7+24G>A in all genetic models (dominant model: OR = 1.39, 95% CI = 1.15–1.67; recessive model: OR = 2.23, 95% CI = 1.26–3.92; additive model: OR = 1.43, 95% CI = 1.14–1.80, Figure 3). The heterogeneity was significant in all genetic models (P < 0.1). In the subgroup analysis by ethnicity, significantly increased risk was found in Asian population (dominant model: OR = 1.30, 95% CI = 1.12–1.51; recessive model: OR = 1.58, 95% CI = 1.07–2.34; additive model: OR = 1.27, 95% CI = 1.09–1.48) but not in Caucasian in all genetic models. In the subgroup analysis stratified by cancer type, significantly increased risk was detected in all genetic models in breast cancer (dominant model: OR = 1.99, 95% CI = 1.67–2.37; recessive model: OR = 5.96, 95% CI = 1.59–22.33; additive model: OR = 2.54, 95% CI = 2.10–3.08). With respect to colorectal cancer, significant association was found only in recessive model (OR = 1.38; 95% CI = 1.04–1.84).

Publication Bias and Sensitivity Analysis

The shapes of the funnel plots did not reveal any evidence of obvious asymmetry for TGFBR1*6A polymorphism in all genetic models, except for recessive model (Figure 4). The Begg’s and Egger’s test also suggested the same results (dominant model: \( P_{\text{Begg}} = 0.54; \ P_{\text{Egger}} = 0.26 \); recessive model: \( P_{\text{Begg}} = 0.00 (7.13 \times 10^{-4}); \ P_{\text{Egger}} = 0.00 (2.23 \times 10^{-5}) \); additive model: \( P_{\text{Begg}} = 0.52; \ P_{\text{Egger}} = 0.13 \)). For IVS7+24G>A polymorphism, publication bias was not ruled out not only through visual inspection of asymmetry in funnel plots but also through statistical evidence of the Begg’s and Egger’s test (dominant model: \( P_{\text{Begg}} = 1.00; \ P_{\text{Egger}} = 0.87 \); recessive model: \( P_{\text{Begg}} = 0.25; \ P_{\text{Egger}} = 0.89 \); additive model: \( P_{\text{Begg}} = 0.36; \ P_{\text{Egger}} = 0.58 \)).
Discussion

In the present study, we explored the association between the TGFBR1*6A and IVS7+24G>A polymorphisms and cancer risk, involving 35 eligible case–control studies. For TGFBR1*6A polymorphism, 19,767 cases and 18,516 controls were included. We found that individuals with the TGFBR1*6A allele showed an increased risk of cancer. In the stratified analysis by cancer type, significantly elevated risks were more pronounced among ovarian cancer and breast cancer. However, no significant correlation of polymorphism TGFBR1*6A with colorectal cancer was found. These findings, though including the latest publications, were consistent with a recent meta-analysis study conducted by Liao et al. [14]. While according to Colleran’s study [57], TGFBR1*6A is not associated with breast cancer. This discrepancy may be due to data missing of some important studies, which was exclusively elaborated by Zhang et al. [61]. Another meta-analysis performed by Zhang et al. [25] found TGFBR1*6A is statistically associated with an increased colorectal cancer risk in dominant model. One factor that may contribute to the differences is that we excluded Castillejo’s study [62] for HWE deviation and included two latest studies [22,23]. Moreover, a significantly increased risk was found among mixed ethnicity from US studies but not among Caucasian and Asian, and this was the first study evaluating the relation between TGFBR1 polymorphism and overall cancer risk among different populations.

With respect to IVS7+24G>A polymorphism, a previous meta-analysis conducted by Zhang [24] with only 440 cases and 706 controls found that the IVS7+24G>A carriers had a 76% increase of cancer risk. Another meta-analysis conducted by Zhang et al. [25] found that IVS7+24G>A polymorphism had significant effects on colorectal cancer risk in recessive model. However, there were defects in their meta-analysis [25] for mistaking adenoma cases of Lundin’s study [54] as colorectal cancer cases. For the current meta-analysis, 4,195 cases and 4,383 controls were found that the IVS7+24G>A polymorphism was strongly associated with colorectal cancer. The results were in line with Zhang et al. [25]. Besides, we also found strong association between IVS7+24G>A polymorphism and breast cancer risk, indicating that potentially functional IVS7+24G>A polymorphism may play a low penetrance role in development of breast cancer. Significant association was found in Asian but not in Caucasian, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in. To some extent, limitations of this meta-analysis should be addressed. First, the sample sizes of several included studies [12,37] were rather small and not adequate enough to detect the possible risk for TGFBR1 polymorphisms. Second, cancer is a complex disease with multifactorial etiology. The gene–environment and gene–gene interactions should be further evaluated. Third, haplotype association analysis is the most powerful method to explore the intrinsic effects of gene, but most of the literatures identified in our present meta-analysis were focused on the relation between the two TGFBR1 SNPs and tumor susceptibility, which made it difficult to investigate the TGFBR1 haplotype effects on carcinogenesis. Last but not least, most of US studies were mixed ethnicity, which made it hard to obtain the effects of specific ethnicity on the associations between TGFBR1 polymorphisms and cancer risk.

In summary, this meta-analysis provided evidence that the TGFBR1*9A/6A polymorphism is associated with overall cancer susceptibility and seem to be more susceptible to ovarian and breast cancer. Meanwhile, IVS7+24G>A polymorphism is also associated with increased overall cancer risk especially in colorectal and breast cancer. More well-designed epidemiological studies on specific ethnicity and cancer types, which were not well covered by existing studies, will be necessary to validate the findings identified in the current meta-analysis. Further studies regarding other SNPs (or haplotypes) in the TGFBR1 gene and cancer risk are also encouraged to better understand the role of TGFBR1 in carcinogenesis.

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Author Contributions

Conceived and designed the experiments: QG JJ. Performed the experiments: WQ XQ FW. Analyzed the data: WQ XQ FW. Contributed reagents/materials/analysis tools: WQ XQ FW. Wrote the paper: WQ XQ QG.

References

1. Bredberg A (2011) Cancer: More of polygenic disease and less of multiple mutations? A quantitative viewpoint. Cancer 117: 440–445.
2. Horváthák JB (2001) Genome maintenance mechanisms for preventing cancer. Nature 411: 366–374.
3. Pharoah PDP, Dunning AM, Ponder BAJ, Easton DF (2004) Association studies for finding cancer-susceptibility genetic variants. Nat Rev Cancer 4: 850–860.
4. Moses HL, Brannum EL, Proper JA, Robinson RA (1981) Transforming growth factor production by chemically transformed cells. Cancer Res 41: 2048–2054.
5. Roberts AB, Anzano MA, Lamb LC (1981) New class of transforming growth factors potentiated by epidermal growth factor: Isolation from non-neoplastic tissues. Proc Natl Acad Sci U S A 78: 5339–5343.
6. Gordon KJ, Blobe GC (2008) Role of transforming growth factor-beta signaling pathways in human disease. Biochim Biophys Acta 1782: 197–220.
7. Benson JR (2004) Role of transforming growth factor-beta in breast carcinogenesis. Lancet Oncol 5: 229–239.
8. Elliot RL, Blobe GC (2005) Role of transforming growth factor beta in human polyps. J Clin Oncol 23: 2078–2093.
9. Bierie B, Moses HL (2006) Tumour microenvironment - TGF-B: The molecular Jekyll and Hyde of cancer. Nat Rev Cancer 6: 506–520.
10. Gallaher AJ, Neil JR, Schiemann WP (2006) Role of transforming growth factor-beta in cancer progression. Future Oncol 2: 743–763.
11. Psachos C, Duan Y, Tao P, Saperstein D, Etzioni R, et al. (2006) Type I transforming growth factor (beta) receptor maps to 9q22 and exhibits a polymorphism and a rare variant within a polyalanine tract. Cancer Res 66: 7277–7273.
12. Chen T, Jackson C, Costello B, Singer N, Colligan B, et al. (2004) An intrinsic variant of the TGFBR1 gene is associated with carcinomas of the kidney and bladder. Int J Cancer 112: 430–435.
13. Psachos C, Kobilac TB, Tian Y, Liu J, Phukan S, et al. (2005) Somatic acquisition and signaling of TGFBR1*6A in cancer. JAMA 294: 1634–1646.
14. Liao KY, Mao C, Qin LX, Ding H, Chen Q, et al. (2010) TGFBR1*6A/9A polymorphism and cancer risk: A meta-analysis of 13,662 cases and 14,147 controls. Mol Biol Rep 37: 3227–3232.
20. Dong ZM (2011) Correlation of TGF-
17. Forsti A, Li X, Wagner K, Tavelin B, Enquist K, et al. (2010) Polymorphisms in
16. Carvajal-Carmona LG, Churchman M, Bonilla C, Walther A, Lefèvre JH, et al. (2010) Comprehensive assessment of variation at the transforming growth factor
(beta) type 1 receptor locus in colorectal cancer predisposition. Pro Natl Acad Sci U S A 107: 7535–7562.
15. Dai L, Gaat A, Horsk A, Schrappe M, Bartram CR, et al. (2009) A case-study of childhood acute lymphoblastic leukemia and polymorphisms in the TGF-(beta) and receptor genes. Pediatr Blood Cancer 52: 819–825.
14. Carvajal-Carmona LG, Churchman M, Bonilla C, Walther A, Lefèvre JH, et al. (2010) Comprehensive assessment of variation at the transforming growth factor
(beta) type 1 receptor locus and colorectal cancer predisposition. Pro Natl Acad Sci U S A 107: 7535–7562.
13. Forsti A, Li X, Wagner K, Tavelin B, Enquist K, et al. (2010) Polymorphisms in
12. Dong ZM (2011) Correlation of TGF-
11. Abuli A, Fernandez-Rozadilla C, Giradlez MD, Mous J, Gonzalez V, et al. (2011) A two-phase case-control study for colorectal cancer genetic susceptibility: Candidate genes from chromosomal regions 8q22 and 8p22. Br J Cancer 105: 870–875.
10. Dong ZM (2011) Correlation of TGF-
9. Joshi NN, Kale MD, Hoke SS, Kannan S (2011) Transforming growth factor (beta) signaling pathway associated gene polymorphisms may explain lower breast cancer risk in western Indian women. PLoS One 6: e21866.
8. Martinez-Canto A, Castillo E, Mata-Balaguera T, Castillo MI, Hernandez-Ilhan E, et al. (2012) TGFBR1 intracellular epistatic interaction as a risk factor for colorectal cancer. PLoS One 7: e30812.
7. Zhang HT (2003) Int7G24A variant of the TGFBR1 gene and cancer risk: A meta-analysis of three case-control studies. Lancet Cancer 49: 419–420.
6. Zhang X, Wu L, Sheng Y, Zhou W, Huang Z, et al. (2012) The association of polymorphisms on TGFBR1 and colorectal cancer risk: a meta-analysis. Mol Biol Rep 39: 2567–2574.
5. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, et al. (2000) Meta-analysis of observational studies in epidemiology: A proposal for reporting. JAMA 283: 2000–2012.
4. Little J, Bradley I, Bray MS, Clyne M, Dorman J, et al. (2002) Reporting, appraising, and integrating data on genotype prevalence and gene-disease associations. Am J Epidemiol 156: 300–310.
3. Qi X, Ma X, Yang X, Fan L, Zhang Y, et al. (2010) Methylenetetrahydrofolate reductase polymorphisms and breast cancer risk: A meta-analysis from 11 studies with 16,680 cases and 22,385 controls. Breast Cancer Res Treat 123: 499–506.
2. Qi X, Ma X, Yang X, Fan L, Zhang Y, et al. (2010) Transforming growth factor-beta1 polymorphisms and breast cancer risk: A meta-analysis based on 27 case-control studies. Breast Cancer Res Treat 122: 273–279.
1. Lau J, Ioannidis JP, Schmid CH (1997) Quantitative synthesis in systematic reviews. Annu Intern Med 127: 820–826.

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