Int7G24A polymorphism (rs334354) and cancer risk

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Abstract

Introduction: The transforming growth factor β (TGF-β) signaling system plays an important role in carcinogenesis. Alteration of TGF-β receptors is a potential mechanism in the development and progression of human cancers. Several studies have investigated the association between TGFBR1 gene Int7G24A and cancer risk, but the results are still inconclusive, so a meta-analysis is needed to verify the association.

Material and methods: We carried out a literature search using the PubMed database (up to January 2012) to identify all papers that investigated the association between the Int7G24A polymorphism (rs334354) and cancer risk. The inclusion criteria were: (1) evaluation of the Int7G24A polymorphism and cancer risk, (2) case-control studies, (3) sufficient published data about genotype frequency. Also the strength of the association between Int7G24A polymorphism and cancer was measured by odds ratio (OR), which was calculated according to the method of Woolf. A χ^2-based Q statistic test was performed to assess the between-study heterogeneity.

Results: There are 10 studies including 2398 cases and 3465 controls in the research. Our results indicate that the TGFBR1 gene Int7G24A polymorphism is associated with cancer risk (A vs. G: OR = 1.35, 95% CI = 1.10-1.66, A/A+G/A vs. G/G: OR = 1.34, 95% CI = 1.05-1.72).

Conclusions: This meta-analysis suggests that the TGFBR1 gene Int7G24A polymorphism might be associated with an increased risk of cancer.

Key words: TGFBR1, Int7G24A polymorphism, cancer risk, meta-analysis.

Introduction

The transforming growth factor β (TGF-β) signaling system plays an important role in carcinogenesis [1]. Alteration of TGF-β receptors is a potential mechanism of TGF-β growth inhibitory signals and the development and progression of human cancers [2]. The TGFBR1 gene is located on chromosome 9 [3]. One commonly studied polymorphism of TGFBR1 is Int7G24A (rs334354), which could lead to a G to A substitution in intron 7 [4, 5]. Several studies have investigated the association between Int7G24A and cancer risk, and a meta-analysis by Zhang 6 years ago found that Int7G24A was a low-penetrance tumor susceptibility allele that predisposes to carcinogenesis of non-small cell lung cancer (NSCLC), kidney and bladder malignancies [6]. However, there have been more studies about it, and the results are still inconclusive. So we performed a meta-analysis again to derive a more precise estimation of this relationship.

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Table I. Characteristics of case-control studies included in Int7G24A polymorphism and cancer risk

No.	First author	Year	Country	Cancer types	Cases			Controls		
					G/G	G/A	A/A	G/G	G/A	A/A
1	Chen [4]	1999	Holland	Cervical cancer	9	7	0	24	12	2
2	Zhang [5]	2003	China	Non-small cell lung cancer	18	24	11	31	52	6
3	Chen [11]	2004	USA	Renal cell carcinoma	46	36	4	81	32	0
4	Chen [11]	2004	USA	Transitional cell carcinoma	33	28	4	81	32	0
5	Chen [12]	2006	USA	Breast cancer	120	92	11	113	37	3
6	Song [13]	2007	Sweden	Breast cancer	500	238	29	559	265	29
7	Lundin [14]	2009	Sweden	Colorectal cancer	135	67	12	559	265	29
8	Castillejo [15]	2009	Spain	Colorectal cancer	296	178	30	333	156	15
9	Foresti [16]	2010	Sweden	Colorectal cancer	220	68	14	382	179	20
10	Hu [17]	2010	China	Osteosarcoma	100	57	11	115	48	5

Material and methods

Search strategy

We carried out a literature search using the PubMed database (up to January 2012) to identify all papers that investigated the association between the Int7G24A polymorphism (rs334354) and cancer risk in all ethnic groups, using combinations of the search terms "Int7G24A" and "polymorphism" and "cancer". We evaluated the titles and abstracts of all relevant publications, but excluded abstracts, case reports, editorials, and review articles.

Inclusion criteria

The inclusion criteria were: (1) evaluation of the Int7G24A polymorphism and cancer risk, (2) case-control studies, (3) sufficient published data about genotype frequency.

Data extraction

We followed a standard protocol for data extraction. The following data were collected from each study: the first author, publication date, country, ethnicity of the study population, cancer types, the number of cases and controls, and numbers of every genotype, respectively.

Statistical analysis

The strength of the association between Int7G24A polymorphism and cancer was measured by the

Table II. Summary ORs and 95% CI of TGFBR1 polymorphism and cancer risk

Analysis model	OR	95% CI	Value of p
A vs. G	1.35	1.10-1.66	0.004
A/A+G/A vs. G/G	1.34	1.05-1.72	0.02

Value of p for heterogeneity

odds ratio (OR), which was calculated according to the method of Woolf [7]. A χ^2-based Q statistic test was performed to assess the between-study heterogeneity [8]. Owing to the low power of the statistic, heterogeneity was considered significant for $p < 0.10$. A fixed effects model using the Mantel-Haenszel method or a random-effects model using the DerSimonian and Laird method was used to pool the results [9]. The significance of the pooled OR was determined by the Z-test. Publication bias was investigated by using a funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was further assessed by the method of Egger's linear regression test [10].

Results

Based on our search criteria, 9 publications were identified [4, 5, 11-17]. Among them, 1 publication included 2 case-control studies [11]. Hence, 9 publications including 10 studies were included in the final meta-analysis. In total, these studies included 2398 cases and 3465 controls. There were 2 studies concerning breast cancer, 3 concerning colorectal cancer, 1 concerning non-small lung cancer, 1 concerning renal cell carcinoma, 1 concerning transitional cell carcinoma, and 1 concerning osteosarcoma. All studies presented the numbers of G/G, G/A, and A/A genotypes separately. The characteristics of these studies are listed in Table I.

Meta-analysis results

The main results of this meta-analysis and the heterogeneity test are shown in Table II. When all 10 studies were pooled into the meta-analysis, significantly elevated cancer risk was associated with Int7G24A of TGFBR1 (A vs. G: OR = 1.35, 95% CI = 1.10-1.66, Figure 1; A/A+G/A vs. G/G: OR = 1.34, 95% CI = 1.05-1.72, Figure 2).
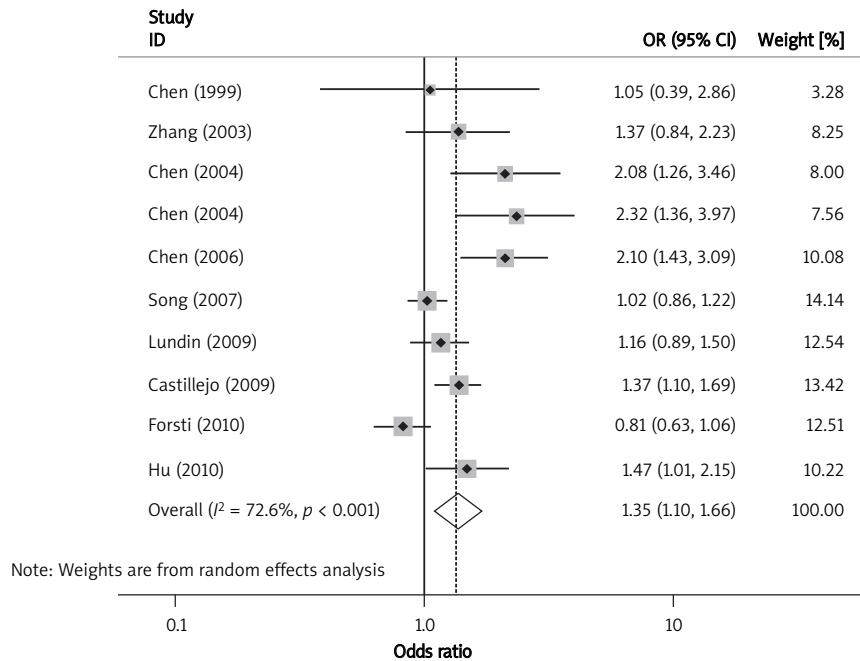
Figure 1. Forest plot for allele contrast (A vs. G) of the Int7G24A polymorphism in cancers
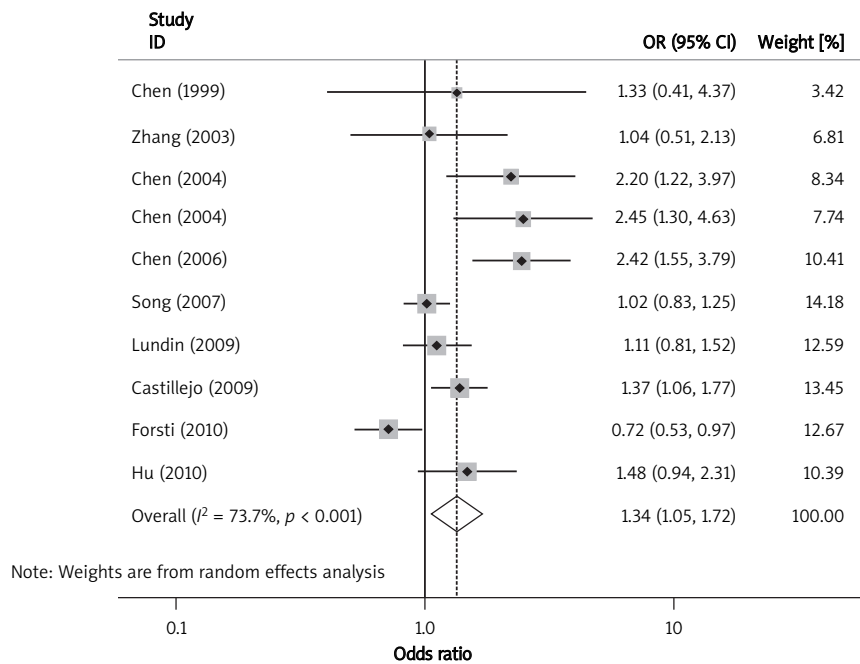

Figure 2. Forest plot for variant genotypes (A/A+G/A vs. G/G) of the Int7G24A polymorphism in cancers

Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set on the pooled ORs. None of the results were materially altered (data not shown).

Publication bias

The shapes of the funnel plots did not reveal obvious asymmetry (figures not shown). Also the

results of Egger's test did not suggest any evidence of publication bias ($p = 0.10$ for A vs. G, $p = 0.15$ for A/A+G/A vs. G/G).

Discussion

Cancer is one of the leading causes of mortality worldwide now. However, the mechanism of carcinogenesis, which may be triggered by genetic as well as environmental factors, is still not fully under-

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stood [18]. In recent years, many candidate genes have been reported to be involved in cancer susceptibility, including p53 [19], SPINK1 [20], TGF-β [1], and so on.

We all know the TGF-β signaling pathway is implicated in the pathogenesis of carcinogenesis. In this pathway, TGF-β binds directly to TGFBR2, and is then recognized by TGFBR1, which is phosphorylated and activated by TGFBR2 [21]. Upon binding of TGF-β to its receptors, receptor-regulated Smad2/3 proteins become phosphorylated and associate with Smad4, and then translocate to the nucleus, where they regulate transcription of specific genes [22,23].

TGFBR1 is crucial in the development and progression of cancer. A number of studies were reported to assess the effects of TGFBR1 polymorphism (TGFBR1*6A) on cancer risk [24], and this relationship was confirmed in a recent meta-analysis [25]. With respect to another single-nucleotide polymorphism (SNP), Int7G24A (rs334354), a meta-analysis by Zhang in 2005 showed that it is associated with increased cancer risk [6]. But there have been more studies about it, and the results are still inconclusive. Therefore, a meta-analysis was needed to confirm the association of the Int7G24A polymorphism with cancer risk.

Our pooled results, which included 2398 cases and 3465 controls, concerning seven kinds of cancers, indicated that the Int7G24A polymorphism was associated with cancer risk. The Int7G24A allele contrast (A) has a 35% increased risk of cancer, and the Int7G24A variant genotypes (both heterozygous G/A and homozygous A/A) have a 34% increased risk of cancer.

In conclusion, considering the limited studies and population numbers included in the meta-analysis, and the fact that studies with negative results are less likely to be published, further studies are encouraged to better identify these findings.

Despite these limitations, this meta-analysis confirms that Int7G24A polymorphism is associated with increased cancer risk.

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