RESEARCH ARTICLE

Cyclooxygenase-2 Promoter 765C Increase of Digestive Tract Cancer Risk in the Chinese Population: a Meta-analysis

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Abstract

Background: To evaluate relationship between the cyclooxygenase-2 promoter 765G/C polymorphism and digestive cancer risk in China. Materials and Methods: A literature search through February 2014 was performed using PubMed, Chinese Biomedical Literature Database (CBM) and China National Knowledge Infrastructure (CNKI) databases, and a meta-analysis was performed with RevMan 5.2 software for odds ratios and 95% CIs. Results: In total, 9 articles with 3,263 cases and 4,858 controls were included in this meta-analysis.The pooled OR (95% CIs) in the co-dominant model (GC *vs* GG) was 1.56 [1.19, 2.06], and in the dominant model ((CC+GC) *vs* GG), the pooled OR was 1.59 [1.21, 2.09] in overall cancers. In the subgroup analysis, stratified by cancer type, significant associations were found that the-765C allele had increased pancreatic cancer and gastric risk. No significant liver cancer and colorectal cancer risk of COX-2 -765G/C polymorphism was found. Conclusions: These findings suggest that COX-2-765*C is related to cancer susceptibility and may increase gastric and pancreatic cancer risk.

Keywords: Digestive tract cancer - cyclooxygenase-2 - polymorphism - meta-analysis

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Introduction

It has been suggested that environmental factors and genetic predisposition may affect the individual's susceptibility and play an important role in the development of tumors (Cocos et al., 2012; Rubin et al., 2012; Arzumanyan et al., 2013; Hardbower et al., 2013), though the risk attributable to each is unclear. In recent years, a good many genes have been identified as potential digestive tract cancer susceptibility genes. An important one is Cyclooxygenase-2 (COX-2), which works as a multi-functional cytokine that plays a key role in cellular growth, proliferation (Wu et al., 2010) and differentiation (Rizzo et al., 2011), prognosis (Hedieh et al., 2013). So far several polymorphisms in the COX-2 gene have been reported and found to affect COX-2 protein expression. Among them, a functional single nucleotide polymorphism at the 765th nucleotide in the promoter region, with a G to C change, has been shown to vary greatly among different ethnic groups and may result in an altered transcriptional regulation and thereby influence the development and severity of COX-2-related diseases. As for -765G/C polymorphism of COX-2, conflicting results were reported, partially because of the relatively small sample size in each of the published studies. Therefore, we performed a meta-analysis of the published studies to derive a more precise estimation of the association between COX-2, 765G/C polymorphism and the digestive cancers susceptible risk.

Materials and Methods

Publication search

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 (last search was updated on 1 January 2014) 'Cyclooxygenase-2' or 'COX-2', 'polymorphism' and 'digestive tract cancer' or 'colorectal cancer' or 'gastric cancer' or 'pancreatic cancer' or 'liver cancer'. Only published studies with full text articles were included. When overlapping data of the same patient population were included in more than one publication, only the most recent or complete study was used in this meta- analysis.

Inclusion criteria

The inclusion criteria were (1) evaluation of COX-2 -765G/C polymorphism and digestive tract cancer risk; (2) case-control studies; (3) genotype frequency was available; (4) published in English or Chinese; (5) full-text articles. When overlapping data of the same patient

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population were included in more than one publication, only the most recent or complete study was used in this meta-analysis; (6) sufficient published data for estimating an ORs with 95%CIs.

Data extraction

Two investigators (Bo Zhao and Hui Li) independently extracted data and reached a consensus on all of the items (Table 1). The following information was extracted from each enrolled references: first author, year of publication, numbers of cases and controls with the GC, CC and GG genotypes, tumor types, source of control, respectively.

Quantitive analysis

There was statistical significance (Table 2) among different genotypes.The main results of the meta-analysis are listed in Table 3. The association between COX-2-765 G/C polymorphism and cancer risk was estimated in two comparison models: a co-dominant model (GC *vs* GG) and a dominant model [(CC+GC) *vs* GG]. In the co-dominant model, we found associations of this SNP with cancer risk in overall cancer susceptibility (OR=1.56, 95%CI=[1.19, 2.06], p=0.001), gastric cancer (OR=1.75, 95%CI=[1.31, 2.32], p=0.0002), liver cancer (OR=1.03, 95%CI=[0.51, 2.07], p=0.94), colorectal cancer (OR=1.27, 95%CI=[0.62, 2.57], p=0.52), pancreatic cancer (OR=2.51, 95%CI= [1.73, 3.66], p<0.00001). In the dominant model, we found associations of this SNP with cancer risk in overall cancer susceptibility (OR=1.59, 95%CI=[1.21, 2.09], p=0.0008), gastric cancer (OR=1.76, 95%CI=[1.33, 2.33], p<0.0001), colorectal cancer (OR=1.47, 95%CI=[1.09, 1.98], p=0.01), liver cancer (OR=1.08, 95%CI=[0.49, 2.36], p=0.86), pancreatic cancer (OR=2.51, 95%CI=[1.73, 3.66], p<0.00001) (Figrue 1-4).

Publication bias

Begger's funnel plot and Egger's test were conducted

Table 2. Genotype and Allels Frequencies of COX-2 765G/C Polymorphism in Case and Control

COX-2 polymorphism	Case (%)	Control (%)	Chi-square	p value
Genotype				
GG	2856(87.5)	4506(92.6)	66.999	0.000
GC	385(11.8)	343(7.1)		
CC	22(1.7)	9(0.3)		
Allels				
G	6097(93.4)	9355(96.3)	68.920	0.000
C	429(6.6)	361(3.7)		

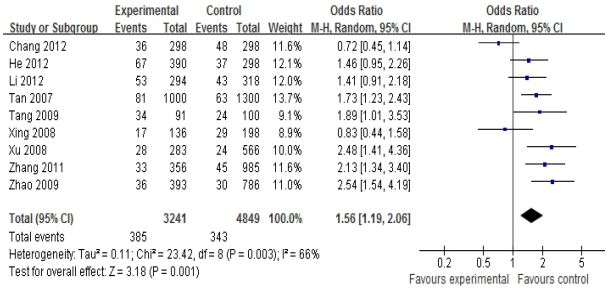

Figure 1. Forest Plots of Odds Ratios for GC *vs* GG of Digestive Cancer Associated with COX-2 Gene Promoter -765G/C

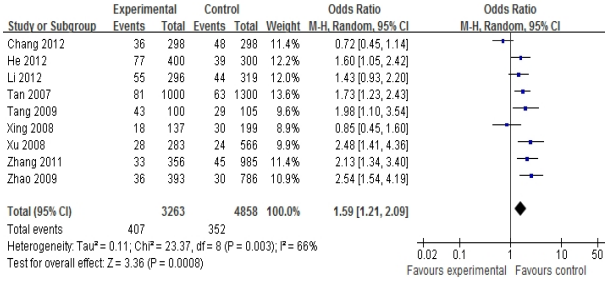

Figure 2. Forest Plots of Odds Ratios for GC+CC *vs* GG of Digestive Cancer Associated with COX-2 Gene Promoter -765G/C

Table 1. Characteristics of Studies of -765G/C Polymorphism with Digestive Cancer Included in this Meta-Analysis

First author	Cases			Controls			Type	Source of control
	GC	CC	GG	GC	CC	GG		
Tan et al., 2007	81	0	919	63	0	1237	colorectal cacer	population
Xing et al., 2008	17	1	119	29	1	169	colorectal cancer	hospital
Chang et al., 2012	36	0	262	48	0	250	liver cancer	hospital
He et al., 2012	67	10	323	37	2	261	liver cancer	hospital
Tang et al., 2009	34	9	57	24	5	76	gasteric cancer	population
Li et al., 2012	53	2	241	43	1	275	gasteric cancer	population
Zhang et al., 2011	33	0	323	45	0	940	gasteric cancer	hospital
Zhao et al., 2009	36	0	357	30	0	756	pancreatic cancer	hospital
Xu et al., 2008	28	0	255	24	0	542	pancreatic cancer	population

Table 3. Stratified Analyses of the COX-2 765G/C Polymorphism on Colorectal Cancer Risk

Type	No	Case/Control	GC *vs* GG			GC+CC *vs* GG		
			OR(95%CI)	p	Heterogeneity	OR(95%CI)	p	Heterogeneity
total	9	3263/4858	1.56(1.19, 2.06)	0.001	0.003	1.59(1.21, 2.09)	0.0008	0.003
gc	3	752/1409	1.75(1.31, 2.32)	0.0002	0.42	1.76(1.33, 2.33)	<0.0001	0.42
l c	2	698/598	1.03(0.51, 2.07)	0.94	0.68	1.08(0.49, 2.36)	0.86	0.01
p c	2	676/1352	2.51(1.73, 3.66)	<0.00001	0.95	2.51(1.73, 3.66)	<0.00001	0.95
crc	2	1137/1499	1.27(0.62, 2.57)	0.52	0.05	1.47(1.09, 1.98)	0.48	0.05

gc:gastric cancer ; lc:liver cancer; pc:pancreatic cancer; crc:colorectal cancer

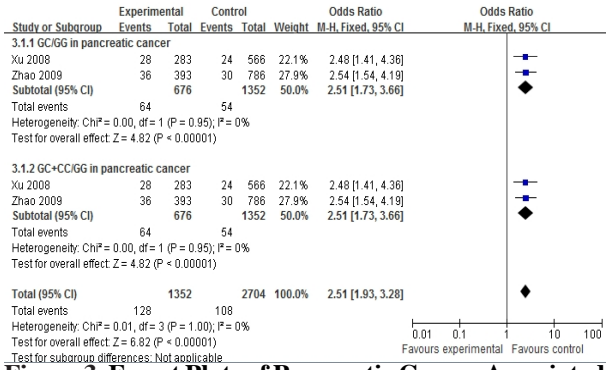

Figure 3. Forest Plots of Pancreatic Cancer Associated with COX-2 Gene Promoter -765G/C

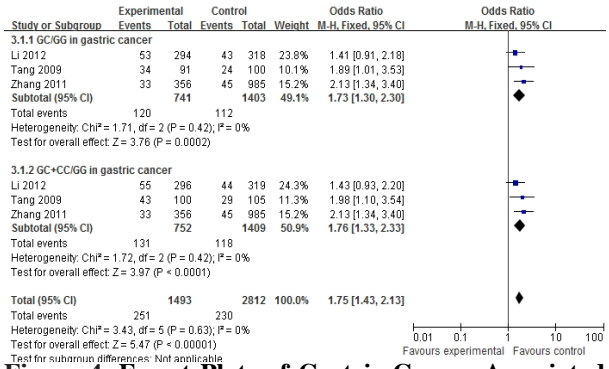

Figure 4. Forest Plots of Gastric Cancer Associated with COX-2 Gene Promoter -765G/C

to assess the publication bias of literatures. The shape of funnel plots did not reveal any evidence of funnel plot symmetry. The statistical results still did not show publication bias (p>0.05, for all).

Results and Discussion

Although CRC human digestive carcinogenesis is a complex, multistep and multigenetic process. Cyclooxygenase-2, a key enzyme in arachidonic acid metabolism, is overexpressed in several epithelial malignacies. Analysis of potentially functional polymorphisms in candidate genes has emerged as a powerful approach in deciphering the complex relationship between genotype and phenotype.

In this context, the present met-analysis, including 3263 cases and 4853 controls from 9 published case-control studies (Tan et al., 2007; Xing et al., 2008; Xu et al., 2008; Tang et al., 2009; Zhao et al., 2009; He et al., 2011; Zhang et al., 2011; Chang et al., 2012; Li et al., 2012) in Chinese population, explored the role of genetic polymorphisms of the COX-2 promoter -765G/C in susceptibility to digestive tract cancers. Significant association between COX-2-765G/C and the susceptibility risk of overall tumors were found. In the stratified analysis by tumor, we found that significant association between COX-2-765G/C and the susceptibility risk of pancreatic cancer. Among 9 articles, genotype GC, GC+CC had significantly increased cancer susceptibility risk, researched by Tan et al. (2007), Xu et al. (2008), Tang et al. (2009), Zhao et al. (2009), Zhang et al. (2011). At present, a meta-analysis included 3322 colorectal cancer cases and 5166 controls (Cao et al., 2010) was inconsistent with our meta-analysis, which the -765C allele of the COX-2 gene may be a potential risk factor for colorectal cancer in Asians. In recent study, Akkız et al. (2011) showed that COX-2 -765 C allele carriers had lower susceptibility to liver cancer, but in this research, we did not find this relationship. COX-2 -765 C allele carriers may be a protective factor between COX-2 -765G/C polymorphism and susceptibility of liver cancer. Our results are in line with those of Khorshidi et al. (2014) for colorectal cancer. This meta-analysis is the first research, between COX-2 -765G/C polymorphism and digestive system tumor susceptibility in Chinese population, which suggesting a possible role of ethnic differences in genetic background and the environment they lived in.

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, while a more precise analysis might be conducted if individual data were available, which could allow for an adjusted estimation by sex, age, smoking, drinking, environmental factors and tumor stage. Third, as cancer is a multifactorial and complex disease, the influence of the COX-2 -765G/C 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 addition, our researches came from domestic, studies are needed to further validate ethnic difference in the effect of the polymorphism on cancer risk. If considering these factors, our results should be interpreted with caution.

In spite of these limitation, our meta-analysis had several advantages. First, substantial number of cases and controls were pooled from different studies in China, which significantly increased the statistical power of the analysis. Second, no publication biases were detected, indicating that the whole pooled results may be unbiased. Although further research is needed, this present meta-analysis validates a significant association between COX-2 -765G/C polymorphism and cancer genetic susceptibility, especially in gastric cancer, liver cancer and colorectal cancer in the Chinese population. To determine a precise association between the COX-2-765G/C and cancer genetic susceptibility, it is essential to design and perform scientific and rigorous studies with large sample sizes in the future.If confirmed in future studies, this genotype may be used by clinicians to select individuals for early diagnosis and treatments.

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