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.

Quantitative 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<0.0001). 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<0.0001) (Figure 1-4).

Publication bias

Begg’s funnel plot and Egger’s test were conducted

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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       |               |                   |
| Tan et al., 2007   | 81    | 0        | 919           | colorectal cancer |
|                   |       |          |               | population        |
| Xing et al., 2008  | 17    | 1        | 119           | colorectal cancer |
|                   |       |          |               | hospital          |
| Chang et al., 2012 | 36    | 0        | 262           | liver cancer      |
|                   |       |          |               | hospital          |
| He et al., 2012    | 67    | 10       | 323           | liver cancer      |
|                   |       |          |               | hospital          |
| Tang et al., 2009  | 34    | 9        | 57            | gasteric cancer   |
|                   |       |          |               | population        |
| Li et al., 2012    | 53    | 2        | 241           | gasteric cancer   |
|                   |       |          |               | population        |
| Zhang et al., 2011 | 33    | 0        | 323           | gasteric cancer   |
|                   |       |          |               | hospital          |
| Zhao et al., 2009  | 36    | 0        | 357           | pancreatic cancer |
|                   |       |          |               | hospital          |
| Xu et al., 2008    | 28    | 0        | 255           | pancreatic cancer |
|                   |       |          |               | population        |

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

| Genotype | Case (%) | Control (%) | Chi-square | p value |
|----------|----------|-------------|------------|---------|
| 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)     |         |       |

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 |
| gc   | 3              | 1.56(1.19, 2.06) | 0.001 | 0.003 | 1.59(1.21, 2.09) | 0.0008 | 0.003 |
| l c  | 2              | 1.75(1.31, 2.32) | 0.0002 | 0.42 | 1.76(1.33, 2.33) | <0.0001 | 0.42 |
| p c  | 2              | 1.03(0.51, 2.07) | 0.94 | 0.68 | 1.08(0.49, 2.36) | 0.86 | 0.01 |
| crc  | 2              | 2.51(1.73, 3.66) | <0.0001 | 0.95 | 2.51(1.73, 3.66) | <0.0001 | 0.95 |

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

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

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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 malignancies. 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 meta-analysis, including 3263 cases and 4853 controls from 9 published case-control studies (Tan et al., 2007; Xing et al., 2008; Xu et al., 2010; Tang et al., 2009; Zhao et al., 2009; Li et al., 2011; Zhang 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-2-765C 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-2-765C polymorphism and digestive system tumor susceptibility in Chinese population, 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-2-765C 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 may be used by clinicians to select individuals for early diagnosis and treatments.

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-2-765C 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-2-765C/C and cancer risk. If considering these factors, our results should be interpreted with caution.

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