COX-2-765G>C Polymorphism Increases the Risk of Cancer: A Meta-Analysis

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Abstract

Background: Chronic inflammation has been regarded as an important mechanism in carcinogenesis. Inflammation-associated genetic variants have been highly associated with cancer risk. Polymorphisms in the gene cyclooxygenase-2 (COX-2), a pro-inflammation factor, have been suggested to alter the risk of multiple tumors, but the findings of various studies are not consistent.

Methods: A literature search through February 2013 was performed using PubMed, EMBASE, and CNKI databases. We used odds ratios (ORs) with confidence intervals (CIs) of 95% to assess the strength of the association between the COX-2-765G>C polymorphism and cancer risk in a random-effect model. We also assessed heterogeneity and publication bias.

Results: In total, 65 articles with 29,487 cancer cases and 39,212 non-cancer controls were included in this meta-analysis. The pooled OR (95% CIs) in the co-dominant model (GC vs. GG) was 1.11 (1.02–1.22), and in the dominant model (CC vs. GG), the pooled OR was 1.12 (1.02–1.23). In the subgroup analysis, stratified by cancer type and race, significant associations were found between the 765C allele and higher risk for gastric cancer, leukemia, pancreatic cancer, and cancer in the Asian population.

Conclusion: In summary, the COX-2-765 C allele was related to increased cancer susceptibility, especially gastric cancer and cancer in the Asian population.

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Introduction

Cancer is a complicated disease resulting from the combined effect of genetic susceptibility and external elements such as lifestyle and inflammation [1,2]. The role of inflammation in carcinogenesis is a pivotal issue. Studies have demonstrated that inflammation-associated molecules are associated with a majority of cancer types, and these molecules are activated by various elements related to environment and lifestyle [3]. Signs of inflammation, including cytokines, chemokines, and immune cells, have been identified in many precancerous and cancerous tissues [4]. Several models have typically demonstrated that inflammation induces certain cancers: chronic intestinal inflammation has been associated with colon cancer; Helicobacter pylori (HP) with gastric cancer; human papilloma virus (HPV) infection with cervical carcinoma; and hepatitis B virus (HBV) infection with hepatocellular carcinoma [5-8]. Chronic inflammation of the colon (e.g., ulcerative colitis) markedly increases the risk of developing colon cancer [9]. The persistent presence of pathogenic microorganisms causes chronic inflammation that raises the likelihood of some cancers [10].

Cyclooxygenase-2 (COX-2), known as prostaglandin-endoperoxide synthase 2 (PTGS2), is a rate-limiting enzyme produced during the production of prostaglandins, and prostaglandins play an important role in inflammation, tumor progression, and metastasis [11]. COX-2 is often undetectable in normal tissue, whereas in tumor tissue specimens its expression is observably higher [12]. It has been reported that COX-2 overexpression contributes to carcinogenesis by increasing cell proliferation, suppressing apoptosis, enhancing invasiveness, and inducing chronic activation of immune responses [13,14].

Genetic variants may affect the expression of COX-2, and the underlying mechanism is considered to occur through self-regulated transcriptional activity resulting from variations in the capability of its promoter region to bind with certain nuclear proteins [15]. The single-nucleotide polymorphism (SNP) COX-2-765G>C (rs20417) is a functional, extensively studied polymorphism that features guanine (G) converting to cytosine (C) at position-765 bp of the promoter region, altering the transcription activity of the COX-2 gene. Several studies have demonstrated the COX-2-765 G>C polymorphism to be associated with increased risk of human cancers such as gastric cancer, colorectal cancer,
prostate cancer, breast cancer, and others [16–18]. However, in other studies, the COX-2-765 C allele was not observed to be associated with cancer risk [19]. To further ascertain the relationship between COX-2-765 G>C and cancer risk, several further meta-analyses were performed, but regrettably, the results among studies have varied for different cancer types [20–22]. Recently, additional studies of the COX-2-765 G>C polymorphism in several cancer types have been reported; therefore, we conducted this meta-analysis to synthesize the results of these studies and to establish a more durable conclusion.

**Methods**

**Publication Search**

A systematic literature search through February 12, 2013, was performed using the databases of PubMed and EMBASE and searching for the following terms: (cyclooxygenase-2 or COX-2 or PTGS2) and (polymorphism or polymorphisms or variant or variants or genotype) and (cancer or carcinoma or neoplasm). To expand our investigation, we also searched China National Knowledge Infrastructure (CNKI) database using the following terms in Chinese: COX-2, cancer risk, and polymorphism. References for these articles and eligible literature from review articles were also collected.

**Inclusion and Exclusion Criteria and Data Extraction**

Article selection for the meta-analysis used the following inclusion criteria: 1) information on the evaluation of COX-2-765G>C (rs20417) polymorphism and cancer risk; 2) case-controlled study; 3) human subjects; and 4) sufficient genotype data to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). When the same or overlapping populations were included in several publications, the studies with larger sample size were selected. When pertinent data were not included or data presented were unclear, we contacted the authors to collect more data or to clarify the study results. Exclusion criteria were the following: 1) no controls; 2) overlapping study populations; 3) not enough pertinent data; and 4) departure from the Hardy-Weinberg equilibrium (HWE) method in control subjects.

The following data were extracted from all eligible publications: the first author, publication year, cancer type, country and race of the study population, control source (population-based (PB), hospital-based (HB) and family-based (FB)), total number of cases and controls studied, number of cases and controls with the wild-type, heterozygous, and homozygous genotypes, and with the minor allele frequency (MAF). Ethnic subgroups were categorized as Caucasian, Asian, American, and African. For case-control studies with subjects of different races, data were extracted separately for each ethnic group whenever possible. When a study did not include detailed genotypes of each ethnic group, or if it was difficult to discriminate the ethnicity of participants according to the data presented, the study was termed “mixed”. If the study was performed in different counties or regions and the subgroups were indistinguishable in the report, the study was termed “ multicenter”. All data were independently extracted by two investigators according to these selection criteria. Disagreement was resolved by discussion.

**Statistical Methods**

We utilized odds ratios (ORs) with 95% (confidence intervals) CIs to assess the strength of association between the COX-2-765G>C polymorphism and cancer risk. The pooled ORs with 95% CIs were calculated in a co-dominant model (variant homozygote vs. heterozygote) and a dominant model (variant homozygote + heterozygote vs. wild-type homozygote). Subgroup analyses were stratified by ethnicity and cancer type.

We used the goodness-of-fit $\chi^2$ test to evaluate HWE for control subjects in each study, and we considered $P<0.05$ to representative.
Table 1. Main characteristics of studies involved in this meta-analysis for an association between COX-2-765 G>C polymorphism and cancer risk.

| First author | Year | Cancer type       | Country | Race     | Study design | Genotype method | Case | Control | MAF of controls | HWE(P) |
|--------------|------|-------------------|---------|----------|--------------|----------------|------|---------|-----------------|--------|
| Gao          | 2007 | Breast            | China   | Asian    | PB           | PCR-RFLP       | 601  | 643     | 0.05            | 0.70   |
| Cox          | 2007 | Breast            | America | mixed    | PB           | PCR-RFLP       | 1243 | 1715    | 0.17            | 0.58   |
| Piranda      | 2010 | Breast            | Brazilian | American | HB           | PCR-RFLP       | 308  | 264     | 0.29            | 0.21   |
| Dossus       | 2010 | Breast            | Multicenter | mixed   | PB           | PCR-RFLP       | 6254 | 8092    | 0.84            | 0.13   |
| Tan          | 2007 | Colorectal carcinoma | China   | Asian    | PB           | PCR-RFLP       | 1000 | 1300    | 0.02            | 0.37   |
| Hamajima     | 2001 | Colorectal carcinoma | Japan   | Asian    | HB           | PCR-CTPP       | 148  | 241     | 0.02            | 0.70   |
| Xing         | 2008 | Colorectal carcinoma | China   | Asian    | HB           | PCR-RFLP       | 137  | 199     | 0.08            | 0.84   |
| Koh          | 2004 | Colorectal carcinoma | Singapore | Asian    | PB           | PCR-RFLP       | 310  | 1177    | 0.05            | 0.43   |
| Iglesias     | 2009 | Colorectal carcinoma | Spain   | Caucasian | HB           | PCR-RFLP       | 284  | 123     | 0.21            | 0.48   |
| Gong         | 2009 | Colorectal carcinoma | America | American | PB           | PCR-RFLP       | 162  | 211     | 0.23            | 0.67   |
| Wang         | 2012 | Colorectal carcinoma | Multicenter | mixed   | FB           | PCR-RFLP       | 305  | 359     | 0.18            | 0.49   |
| Daraei       | 2012 | Colorectal carcinoma | Iran    | Caucasian | PB           | PCR-RFLP       | 110  | 120     | 0.32            | 0.20   |
| Cox          | 2004 | Colorectal carcinoma | Spain   | Caucasian | HB           | PCR-RFLP       | 220  | 257     | 0.19            | 0.73   |
| Hoff         | 2009 | Colorectal carcinoma | Netherlands | Caucasian | HB           | PCR-RFLP       | 326  | 369     | 0.17            | 0.26   |
| Andersen     | 2009 | Colorectal carcinoma | Denmark | Caucasian | PB           | QPCR²           | 359  | 765     | 0.14            | 0.61   |
| Pereira      | 2010 | Colorectal carcinoma | Portugal | Caucasian | HB           | PCR-RFLP       | 117  | 256     | 0.19            | 0.37   |
| Thompson     | 2009 | Colorectal carcinoma | America | American | PB           | PCR-RFLP       | 421  | 479     | 0.16            | 0.29   |
| Ulrich       | 2005 | Colorectal adenoma | America | American | PB           | PCR-RFLP       | 494  | 584     | 0.17            | 0.37   |
| Ueda         | 2008 | Colorectal adenoma | Japan   | Asian    | PB           | PCR-RFLP       | 455  | 1051    | 0.03            | 0.32   |
| Gunter       | 2006 | Colorectal adenoma | America | American | HB           | PCR-RFLP       | 210  | 196     | 0.15            | 0.46   |
| Kristinsson  | 2009 | Esophageal adenoma | Netherlands | Caucasian | PB           | PCR-RFLP       | 222  | 236     | 0.18            | 0.47   |
| Upadhyay     | 2009 | Esophageal adenoma | India   | Asian    | HB           | PCR-RFLP       | 174  | 216     | 0.18            | 0.09   |
| Zhang        | 2005 | Esophageal adenoma | China   | Asian    | HB           | PCR-RFLP       | 1026 | 1270    | 0.02            | 0.43   |
| Moons        | 2007 | Esophageal adenoma | Netherlands | Caucasian | PB           | PCR-RFLP       | 140  | 495     | 0.12            | 0.24   |
| Bye          | 2011 | Esophageal adenoma | South Africa | African | PB           | Taqman         | 347  | 462     | 0.51            | 0.94   |
| Bye          | 2011 | Esophageal adenoma | South Africa | mixed   | PB           | Taqman         | 190  | 422     | 0.32            | 0.91   |
| Shin         | 2012 | Gastric           | Korea   | Asian    | HB           | PCR-RFLP       | 100  | 100     | 0.05            | 0.60   |
| Li           | 2012 | Gastric           | China   | Asian    | PB           | PCR-RFLP       | 296  | 319     | 0.07            | 0.62   |
| Hou          | 2007 | Gastric           | Poland  | Caucasian | PB           | PCR-RFLP       | 290  | 409     | 0.16            | 0.90   |
| Liu          | 2006 | Gastric           | China   | Asian    | PB           | PCR-DHPLC      | 247  | 427     | 0.05            | 0.27   |
| Tang         | 2009 | Gastric           | China   | Asian    | PB           | PCR-RFLP       | 100  | 105     | 0.16            | 0.11   |
| Zhang        | 2011 | Gastric           | China   | Asian    | PB           | PCR-RFLP       | 357  | 985     | 0.02            | 0.46   |
| Sitarz       | 2008 | Gastric           | Netherlands | Caucasian | PB           | PCR-sequence   | 241  | 100     | 0.25            | 0.14   |
| Pereira      | 2006 | Gastric           | Portugal | Caucasian | HB           | PCR-RFLP       | 73   | 210     | 0.22            | 0.28   |
| Saxena       | 2008 | Gastric           | India   | Asian    | HB           | PCR-RFLP       | 62   | 241     | 0.16            | 0.42   |
| Chang        | 2012 | HCC¹              | China   | Asian    | HB           | PCR-RFLP       | 298  | 298     | 0.08            | 0.13   |
| He           | 2012 | HCC               | China   | Asian    | HB           | PCR-RFLP       | 300  | 300     | 0.07            | 0.59   |
significant departure from HWE [23]. The heterogeneity assumption was verified using the χ²-based Q-test. Q-test results of P ≥ 0.05 suggested a lack of heterogeneity among studies, so the pooled OR of all studies was calculated using the fixed-effect model based on the Mantel–Haenszel method. Otherwise, we used the random-effect model, based on the DerSimonian–Laird method, which provides a larger pool of 95% CIs from studies differing among themselves [24,25].

We also conducted a sensitivity analysis by excluding each study, one at a time, and recalculating the ORs and 95% CIs to assess the effects of each study on the pooled risk of cancer [26].

Then we performed an estimate of potential publication bias using the funnel plot, in which the standard error of log (OR) of every study was plotted against its log (OR) [27], and an asymmetric plot indicated a potential publication bias. We assessed funnel-plot asymmetry using Egger’s linear regression test, a linear regression method of evaluating funnel plot asymmetry on the natural logarithm scale of the OR [28]. The significance of the intercept was determined using the t-test suggested by Egger, and p ≥ 0.05 was considered representative of statistically significant publication bias [29,30]. In cases of publication bias, the Duval and Tweedie nonparametric “trim and fill.” method was performed to adjust for it [31]. All of the statistical tests were performed using STATA version 10.0 (Stata Corporation, College Station, TX).

Results

Eligible Studies Characteristics

A total of 579 publications from the MEDLINE, EMBASE, and CNKI databases were reviewed using the specified key words.

Table 1. Cont.

| First author | Year | Cancer type | Country   | Race       | Study design | Genotype method | Case | Control | MAF² of controls | HWE¹(P) |
|--------------|------|-------------|-----------|------------|--------------|-----------------|------|---------|-----------------|---------|
| Peters       | 2009 | HNC         | Netherlands | Caucasian | HB           | PCR-RFLP        | 428  | 433     | 0.14            | 0.12    |
| Ben          | 2009 | HNC¹²       | Tunisia    | Caucasian | HB           | PCR-RFLP        | 180  | 169     | 0.13            | 0.93    |
| Mittal       | 2010 | HNC         | India      | Asian     | HB           | PCR-RFLP        | 176  | 96      | 0.32            | 0.08    |
| Chiang       | 2008 | HNC         | China      | Asian     | HB           | PCR-RFLP        | 178  | 205     | 0.10            | 0.13    |
| Wang         | 2010 | Leukemia    | China      | Asian     | HB           | PCR-RFLP        | 266  | 266     | 0.06            | 0.30    |
| Zheng        | 2011 | Leukemia    | China      | Asian     | PB           | PCR-RFLP        | 446  | 725     | 0.02            | 0.56    |
| Coskunpinar  | 2011 | lung        | Turkey     | Caucasian | HB           | PCR-RFLP        | 231  | 118     | 0.50            | 0.20    |
| Liu          | 2010 | lung        | China      | Asian     | HB           | QPCR            | 358  | 716     | 0.07            | 0.06    |
| Campa        | 2004 | lung        | Norway     | Caucasian | PB           | PCR-RFLP        | 250  | 214     | 0.10            | 0.19    |
| Monroy       | 2011 | Lymphoma    | America    | American  | HB           | PCR-RFLP        | 100  | 100     | 0.87            | 0.48    |
| Hoefl        | 2008 | Lymphoma    | Germany    | Caucasian | PB           | PCR-RFLP        | 668  | 661     | 0.15            | 0.18    |
| Chang        | 2009 | Lymphoma    | America    | American  | PB           | PCR-RFLP        | 454  | 354     | 0.19            | 0.39    |
| Agachan      | 2010 | Ovarian     | Turkey     | Caucasian | HB           | PCR-RFLP        | 57   | 111     | 0.32            | 0.38    |
| Pinheiro     | 2010 | Ovarian     | Multicenter | mixed     | PB           | PCR-RFLP        | 1264 | 1756    | 0.17            | 0.26    |
| Zhao         | 2009 | Pancreatic  | China      | Asian     | PB           | PCR-RFLP        | 393  | 786     | 0.02            | 0.59    |
| Xu           | 2008 | Pancreatic  | China      | Asian     | HB           | PCR-RFLP        | 283  | 566     | 0.02            | 0.61    |
| Cheng        | 2007 | Prostate    | America    | African   | HB           | PCR-RFLP        | 89   | 88      | 0.35            | 0.61    |
| Cheng        | 2007 | Prostate    | America    | Caucasian | HB           | PCR-RFLP        | 416  | 417     | 0.16            | 0.98    |
| Murad        | 2009 | Prostate    | UK         | Caucasian | PB           | PCR-RFLP        | 1592 | 3028    | 0.16            | 0.06    |
| Catsburg     | 2012 | Prostate    | America    | American  | PB           | PCR-RFLP        | 1431 | 756     | 0.21            | 0.21    |
| Wu           | 2011 | Prostate    | China      | Asian     | HB           | PCR-RFLP        | 218  | 436     | 0.08            | 0.06    |
| Joshi        | 2012 | Prostate    | America    | American  | PB           | PCR-RFLP        | 935  | 756     | 0.21            | 0.21    |
| Panguluri    | 2004 | Prostate    | Nigeria    | African   | PB           | Pyrosequencing  | 146  | 108     | 0.14            | 0.12    |
| BalsiFeresi  | 2010 | Prostate    | Italy      | Caucasian | HB           | PCR-RFLP        | 50   | 125     | 0.30            | 0.19    |
| Vogel        | 2007 | Skin        | Denmark    | Caucasian | PB           | QPCR            | 304  | 315     | 0.12            | 0.93    |
| Lira         | 2007 | Skin        | Italy      | Caucasian | PB           | PCR-RFLP        | 105  | 129     | 0.18            | 0.59    |
| Cocos        | 2012 | Skin        | Romania    | Caucasian | HB           | PCR-RFLP        | 174  | 80      | 0.22            | 0.44    |
| Pandey       | 2010 | Cervical    | India      | Asian     | HB           | PCR-RFLP        | 200  | 200     | 0.10            | 0.09    |
| Schwartzbaum | 2005 | Glioblastoma| Sweden     | Caucasian | PB           | PCR-DASH        | 108  | 399     | 0.15            | 0.65    |
| Biramijamal  | 2011 | Colorectal&  | Iran       | Caucasian | PB           | PCR-RFLP        | 60   | 103     | 0.18            | 0.26    |

¹HCC: hepatocellular carcinoma; ²HNC: head and neck cancer. ³MAF: minor allele frequency; ⁴HWE: Hardy-Weinberg equilibrium. ⁵QPCR: quantitative PCR.
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1HCC: hepatocellular carcinoma; 2HNC: head and neck cancer. 3MAF: minor allele frequency; 4HWE: Hardy-Weinberg equilibrium.
After a review of titles and abstracts, 494 publications were excluded according to our criteria. From the remaining 85 studies on COX-2-765G>C polymorphism and susceptibility to cancer that met our inclusion criteria, we eliminated 5 publications due to insufficient genotype data, 11 due to deviation from Hardy-Weinberg equilibrium in controls, and 4 due to overlap with other studies. Finally, 65 articles, including with 29,487 cancer cases and 39,212 non-cancer controls, were included in this meta-analysis. A flow chart of the study selection procedure is shown in Fig. 1.

The main characteristics of the studies are listed in Table 1. The respective studies focused on the following cancer types: 13 studies investigated colorectal carcinoma [17,32–43], 9 gastric cancer [16,44–51], 8 prostate cancer [18,52–57], 6 esophageal cancer [58–62], 3 colorectal adenoma [63–65], 4 breast cancer [19,70–72], 3 skin cancer [79–81], 2 pancreatic cancer [84,85], and 2 ovarian cancer [86,87].

The main results of the meta-analysis are listed in Table 2. 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). The analysis used a random pooling model because the heterogeneity among studies was significant in the co-dominant model and in the dominant model (p<0.001). In the co-dominant model, the overall pooled effect indicated that the-765 G allele was associated with a significantly increased overall cancer susceptibility (OR = 1.12, 95% CI = 1.02–1.23, P = 0.01). In stratification analyses by cancer type and ethnicity, the association was maintained in gastric cancer (OR = 1.53, 95% CI = 1.04–2.24, p = 0.03), leukemia (OR = 1.86, 95% CI = 1.32–2.62, P<0.01), and cancer in the Asian population (OR = 1.42, 95% CI = 1.15–1.76, p<0.01) (Fig. 2A and B). Notably, the association between the COX-2-765 C allele and decreased cancer risk was found in the Caucasian population (OR = 0.91, 95% CI = 0.83–1.00, P = 0.04). However, this difference may have been the result of different ethnic subjects and bias from different genotyping methods. In the dominant model, we found significant associations of this SNP with cancer risk in overall cancer susceptibility (OR = 1.12, 95% CI = 1.02–1.23, P = 0.01), gastric cancer (OR = 1.60, 95% CI = 1.02–2.50, P = 0.04), leukemia (OR = 0.91, 95% CI = 1.36–2.69, P<0.01), and pancreatic cancer (OR = 2.51, 95% CI = 1.73–3.66, P<0.01), and

### Table 2. Quantitative synthesis of the associations between COX-2-765 G>C polymorphism and cancer risk in two models.

| Ethnicity | No of studies | Cancer type | No of studies | Cancer type | No of studies | Cancer type |
|-----------|--------------|-------------|--------------|-------------|--------------|-------------|
| Asian     | 25           | Gastric     | 9            | Leukemia    | 2            | Prostate    |
|           |              |             |              |             |              | Esophageal  |
|           |              |             |              |             |              | HNC         |
|           |              |             |              |             |              | Breast      |
|           |              |             |              |             |              | Colorectal adenoma |
|           |              |             |              |             |              | Skin        |
|           |              |             |              |             |              | Lung        |
|           |              |             |              |             |              | Lymphoma    |
|           |              |             |              |             |              | HCC         |
|           |              |             |              |             |              | Ovarian     |
|           |              |             |              |             |              | Other*      |
| Caucasian | 25           | Gastric     | 9            | Leukemia    | 2            | Prostate    |
|           |              |             |              |             |              | Esophageal  |
|           |              |             |              |             |              | HNC         |
|           |              |             |              |             |              | Breast      |
|           |              |             |              |             |              | Colorectal adenoma |
|           |              |             |              |             |              | Skin        |
|           |              |             |              |             |              | Lung        |
|           |              |             |              |             |              | Lymphoma    |
|           |              |             |              |             |              | HCC         |
|           |              |             |              |             |              | Ovarian     |
|           |              |             |              |             |              | Other*      |
| African   | 3            | Gastric     | 9            | Leukemia    | 2            | Prostate    |
|           |              |             |              |             |              | Esophageal  |
|           |              |             |              |             |              | HNC         |
|           |              |             |              |             |              | Breast      |
|           |              |             |              |             |              | Colorectal adenoma |
|           |              |             |              |             |              | Skin        |
|           |              |             |              |             |              | Lung        |
|           |              |             |              |             |              | Lymphoma    |
|           |              |             |              |             |              | HCC         |
|           |              |             |              |             |              | Ovarian     |
|           |              |             |              |             |              | Other*      |
| American  | 9            | Gastric     | 9            | Leukemia    | 2            | Prostate    |
|           |              |             |              |             |              | Esophageal  |
|           |              |             |              |             |              | HNC         |
|           |              |             |              |             |              | Breast      |
|           |              |             |              |             |              | Colorectal adenoma |
|           |              |             |              |             |              | Skin        |
|           |              |             |              |             |              | Lung        |
|           |              |             |              |             |              | Lymphoma    |
|           |              |             |              |             |              | HCC         |
|           |              |             |              |             |              | Ovarian     |
|           |              |             |              |             |              | Other*      |
| Mixed     | 5            | Gastric     | 9            | Leukemia    | 2            | Prostate    |
|           |              |             |              |             |              | Esophageal  |
|           |              |             |              |             |              | HNC         |
|           |              |             |              |             |              | Breast      |
|           |              |             |              |             |              | Colorectal adenoma |
|           |              |             |              |             |              | Skin        |
|           |              |             |              |             |              | Lung        |
|           |              |             |              |             |              | Lymphoma    |
|           |              |             |              |             |              | HCC         |
|           |              |             |              |             |              | Ovarian     |
|           |              |             |              |             |              | Other*      |

*Cancers studied in only one article were combined and termed “other.”

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cancer in the Asian population (OR = 1.42, 95% CI = 1.15–1.76, P<0.01) (Fig. 2C and D).

Heterogeneity, Sensitivity Analysis, and Publication Bias

Heterogeneity was determined using the χ²-based Q-test, and heterogeneity was found in two pooling models (P<0.01 in both models), so the random model was utilized to generate a larger pool of studies with 95% CIs. We performed the sensitivity analysis by assessing the influence of an individual study on the overall OR. No individual study affected the pooled OR markedly, since omission of any single study made no substantial difference. Also, we conducted Begger’s funnel plot and Egger’s test to assess the publication bias of all eligible literature. The shapes of the funnel plot seemed symmetrical in two comparison models, and statistical results from Egger’s test still did not show publication bias (p = 0.36 in co-dominant model and p = 0.34 in dominant model). These findings demonstrated that publication bias, if any, did not significantly affect the results of our meta-analysis for the association between COX-2-765G>C and cancer risk.

Discussion

COX-2-765G>C is a functional polymorphism, located at 765 bp upstream (-765 bp) from the transcription start site. It changes a putative stimulatory protein (Sp1) binding site in the promoter of COX-2 between -766 and -761 bp [93], but it creates an E2 promoter factor (E2F) binding site, leading to high transcription activity, which may be the mechanism of COX-2-765G>C polymorphism increasing cancer risk [15].

The current meta-analysis explored the role of COX-2-765G>C polymorphism in the susceptibility of cancer among 65 articles with 29487 cancer cases and 39212 non-cancer controls. We found that C-allele carriers had an increased risk of cancer, especially gastric cancer, leukemia, and pancreatic cancer in the Asian population (OR = 1.42, 95% CI = 1.15–1.76, P<0.01) (Fig. 2C and D).
carriers. Our results show that COX-2-765 C carriers are at significantly increased risk for gastric cancer, leukemia, and pancreatic cancer but not other cancer types. One possible explanation is that different types of cancer have various mechanisms of carcinogenesis. Additionally, it is possible that the significant difference effects are casual, because studies with small sample sizes have deficient statistical power to disclose a slight effect. Interestingly, our meta-analysis revealed an association between the COX-2-765 C allele and decreased cancer risk in Caucasian population. In this Caucasian subgroup, a large study sample with 6254 cases and 8092 controls (two thirds of all subjects between the COX-2-765 C allele and decreased cancer risk in effect. Interestingly, our meta-analysis revealed an association sample sizes have deficient statistical power to disclose a slight. Additionally, this extremely high MAF value may have resulted from bias induced by experimental procedure and methods. Our study differed from previous meta-analyses in the subgroup analysis of gastric and colorectal cancer. Zhu reported a significant association between-765GC polymorphisms and colorectal carcinoma, but not in gastric cancer, contrary to the results of our present study [94]. In other studies, researchers analyzed the role of COX-2-765GC polymorphism in diverse cancer types. No convincing association between the C allele and risk of prostate cancer [22,93], breast cancer [21], and colorectal cancer [96] respectively, were revealed, but a significant association was reported between C allele and risks for gastric cancer [97] and esophageal cancer [98]. However, the number of subjects included in previous studies was not as large, and our meta-analysis includes the latest studies. Furthermore, we analyzed at least twice as many studies as meta-analyses published previously [94]. In summary, our findings provide the most current and powerful conclusion among analyses of this type.

Limitations encountered in this analysis should be considered as these results are interpreted. First, the CC genotype frequency in many studies was zero, so we assumed a co-dominant model and a dominant model. For some polymorphisms, this model might not be the most suitable for a clear assessment of the gene-disease interaction. Secondly, the results of the subgroup stratification analysis must be interpreted with caution because of the limited number of published studies. For example, only two reports for leukemia and pancreatic cancer were included. Thirdly, there is marked heterogeneity among studies in overall and some subgroup analyses, which may derive from ethnic groups and types of cancer, may have skewed our results. Finally, this systematic review was based on unadjusted data, as the genotype information stratified for the main confounding variables was not available in the original papers and the confounding factors addressed across the different studies varied. Adjusted estimates might provide more precise and stronger associations, as they reduced the impact of possible confounding factors. To determine a precise association between the COX-2-765GC and cancer genetic susceptibility, it is essential to design and perform scientific and rigorous studies with large sample sizes in the future.

Although further research is needed, this present meta-analysis validates a significant association between COX-2-765GC polymorphism and genetic cancer susceptibility, especially in gastric cancer, leukemia, pancreatic cancer, and cancer in the Asian population. If confirmed in future studies, this genotype may be used by clinicians to select individuals for early diagnosis and treatments.

Author Contributions
Conceived and designed the experiments: WG. Wrote the paper: XW MH. Extracted and analyzed the data: XW MH. Polished the English writing: NZ RH.

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