Association between cyclooxygenase-2 (COX-2) 8473 T > C polymorphism and cancer risk: a meta-analysis and trial sequential analysis

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**Abstract**

**Background:** Numerous studies have investigated the relationship between COX-2 8473 T > C polymorphism and cancer susceptibility, however, the results remain controversial. Therefore, we carried out the present meta-analysis to obtain a more accurate assessment of this potential association.

**Methods:** In this meta-analysis, 79 case-control studies were included with a total of 38,634 cases and 55,206 controls. We searched all relevant articles published in PubMed, EMBASE, OVID, Web of Science, CNKI and Wanfang Data, till September 29, 2017. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of the association. We performed subgroup analysis according to ethnicity, source of controls, genotyping method and cancer type. Moreover, Trial sequential analysis (TSA) was implemented to decrease the risk of type I error and estimate whether the current evidence of the results was sufficient and conclusive.

**Results:** Overall, our results indicated that 8473 T > C polymorphism was not associated with cancer susceptibility. However, stratified analysis showed that the polymorphism was associated with a statistically significant decreased risk for nasopharyngeal cancer and bladder cancer, but an increased risk for esophageal cancer and skin cancer. Interestingly, TSA demonstrated that the evidence of the result was sufficient in this study.

**Conclusion:** No significant association between COX-2 8473 T > C polymorphism and cancer risk was detected.

**Keywords:** COX-2 gene, 8473 T > C polymorphism, Cancer, Risk, Meta-analysis

**Background**

Currently, cancer is still considered as a global public health problem and the leading cause of human death [1], with an estimate of 14.1 million new cancer cases and 8.2 million cancer deaths in 2012 worldwide [2]. A large number of epidemiological and biological researches have demonstrated that cancer, as a multifactorial disease, is caused by a series of potential risk factors, including genetic and environmental factors [3]. However, the accurate mechanisms of carcinogenesis remained unclear. In recent years, many studies have pointed that the expression of tumor suppressor genes and oncogenes is closely associated with inflammation, which can also promote the transformation of cancer [4–6].

Cyclooxygenase-2 (COX-2), also called prostaglandin endoperoxide synthetase (PTGS-2), is an inducible isofrom of COX enzyme that converts arachidonic acid to prostaglandins, and prostaglandins are generally regarded as the effective mediators of inflammation [7]. By producing prostaglandins, COX-2 is considered to participate in several biological processes, such as carcinogenesis, cell proliferation, angiogenesis and mediating immune suppression. More and more evidence has pointed that increased expression of COX-2 is closely associated with malignant progression [8–10]. In addition, it is also shown that carcinogenesis could be prevented by using selective...
COX-2 inhibitors [11]. The human COX-2 gene, with a length of 8.3 kb and consisting of 10 exons, is located on chromosome 1q25.2-q25.3. Different polymorphism sites in the COX-2 gene have been clarified. One of these functional polymorphisms, the 8473 T > C polymorphism in the 3′-untranslated region (3′UTR) of COX-2 gene is the most widely investigated polymorphism.

Previous functional researches have indicated that 8473 T > C polymorphism is related to the alteration of the mRNA level of COX-2 gene via playing an important role in message stability and translational efficiency [12]. There are numerous case-control studies that have investigated the role of 8473 T > C polymorphism in cancer risk. However, the results of these studies remain inconclusive. Therefore, to draw a more precise conclusion, we conduct the present meta-analysis to evaluate the association of 8473 T > C polymorphism in COX-2 gene with cancer susceptibility.

Methods

Identification and eligibility of relevant studies

Literature in electronic databases, including PubMed, EMBASE, OVID and Web of Science, were systematically searched using the following terms: “cyclooxygenase-2 or COX-2 or PTGS2” and “polymorphism or variant or genotype” and “cancer or carcinoma or neoplasm”. To expand our investigation, we also searched China National Knowledge Infrastructure (CNKI) and Wanfang Data using the corresponding Chinese terms. Furthermore, references cited in each included study were also searched manually to identify potential additional relevant studies. When the information provided in the article was unclear, we contacted the author for detailed raw data. If data were overlapping, we adopted the most recent and comprehensive research for this meta-analysis. The last search date was September 29, 2017.

Inclusion and exclusion criteria

The inclusion criteria were as follows: studies investigating the association of COX-2 8473 T > C polymorphism with cancer risk; studies with essential information on genotype or allele frequencies to estimate ORs and 95% CIs; studies with human subjects; and case-controlled studies. Exclusion criteria included: reviews or meta-analyses; animal or cytology experiments; duplicate publications; studies not involving cancer; no controls, not according with Hardy-Weinberg equilibrium (P_{HWE} < 0.05) in the control group, and studies published neither in English nor Chinese.

Data extraction

From all eligible publications, the following data, including the first author, year of publication, population ethnicity, country, source of controls, cancer type, detection genotype methods of COX-2 8473 T > C polymorphism, and number of cases and controls, were carefully extracted by two authors (Qiuping Li and Chao Ma) independently. Inconsistencies were resolved after discussion, and a consensus was reached for all extracted data.

Quality assessment

The quality of the included studies was evaluated using the Newcastle–Ottawa scale (NOS) [13] with eight items (Additional file 1: Table S1). We awarded a study a maximum of nine star scale based on selection (four stars maximum), comparability (two stars maximum) and exposure (three stars maximum). Studies with NOS scores of 1–3, 4–6 and 7–9 were considered as low-quality, medium-quality and high-quality studies, respectively. Medium-quality and high-quality studies were included in the present meta-analysis.

Statistical analysis

We analyzed the association of COX-2 8473 T > C polymorphism with cancer risk using Stata software (Version 11.0; StataCorp, College Station, TX). Cumulative ORs and the corresponding 95% CIs were employed to measure the strength of associations. All p values were two-sided, and p < 0.05 was considered statistically significant. Heterogeneity was assessed using a Q statistic (considered significant heterogeneity among the studies if P value < 0.10) and an I-squared (I2) value [14]. When heterogeneity of studies was significant, the DerSimonian and Laird random-effects model [15] was performed to calculate the pooled ORs. Otherwise, the Mantel–Haenszel fixed-effects model was used [16]. We performed the sensitivity analysis to explore heterogeneity when significant heterogeneity was detected. Subgroup analysis was used to explore the effect of ethnicity, study design, cancer type and genotype method. Moreover, publication bias was evaluated quantitatively using Begg’s [17] and Egger’s [18] tests. Significant publication bias was indicated if P value < 0.05.

Trial sequential analysis

Type I errors may be caused by meta-analysis due to random error because of insufficient sample size in this meta-analysis. And the conclusions of the meta-analysis tended to be changed by later studies with a larger sample size [19]. When TSA was performed in a meta-analysis, both inadequate information size and false positive conclusions were revealed, and the above limitations were also overcome [19, 20]. Therefore, we used TSA software version 0.9 beta in this meta-analysis on the basis of two-sided tests, with an overall type I error risk of 5%, a statistical test power of 80%, and relative risk reduction of 10%. Trails were ignored in interim due to too low information to use (< 1.0%) by the TSA software. When the cumulative Z-curve in results crosses the TSA boundary.
or enters the insignificance area, a sufficient level of evidence has been reached, and no further studies are necessary. However, when the Z curve does not exceed any of the boundaries and the required sample size has not been reached, evidence to reach a conclusion is insufficient [21].

Results

Characteristics of the included studies
A detailed flow chart of included studies is shown in Fig. 1. A systematic search through five electronic databases yielded 652 citations after duplicate removal. After reviewing the titles, abstracts and full texts, articles that were not related with this analysis, meeting, animal or cytology experiments and reviews were removed, leading to the exclusion of 561 publications. The remaining 91 articles were further evaluated for eligibility. Finally, 65 full-text articles (79 studies) that met the inclusion criteria were included in the present meta-analysis.

The primary characteristics of the 79 included studies in this meta-analysis are summarized in Table 1. In our included studies, 38,634 cases and 55,206 controls surveyed the association between COX-2 8473 T > C polymorphism and cancer risk. Among these publications, there were 12 colorectal cancer [22–31], 1 ampulla of vater (AV) cancer [32], 4 bladder cancer [33–36], 13 breast cancer [37–46], 2 cervical cancer [47, 48], 1 endometrial cancer [49], 4 esophageal cancer [50–53], 1 extrahepatic bile duct (EHBD) cancer [32], 2 gallbladder cancer [32, 54], 4 gastric cancer [55–58], 1 glioma [59], 2 hepatocellular cancer (HCC) [60, 61], 1 head and neck (HN) cancer [62], 2 laryngeal cancer [50, 63], 11 lung cancer [64–74], 3 nasopharyngeal cancer [50, 75, 76], 3 oral cancer [50, 63, 77], 2 ovarian cancer [78], 1 pancreatic cancer [79], 6 prostate cancer [80–83] and 3 skin cancer [84–86]. Ethnic subgroups were divided into Asian, Caucasian, Australian and African. If it was difficult to distinguish the ethnicity of participants according to content included in the study, ethnicity of the study was termed “Mixed”. Study designs were categorized as PB and HB. The COX2 8473 T > C polymorphism was primarily detected by genotyping methods including TaqMan, PCR-RFLP and PCR-PIRA, in addition to the methods of SNPlex, SNP-IT, PCR-KASP, Invader, Illumina GoldenGate, Pyrosequencing and MassARRAY. We used subgroup analysis to search the effects of ethnicity, study design, genotype method and cancer type for the relationship of COX2 8473 T > C polymorphism with cancer risk.

Meta-analysis

Overall analysis
The main results of our meta-analysis are listed in Table 2. The association between COX2 8473 T > C polymorphism and cancer risk was evaluated in five comparison models: homozygote comparison, heterozygote comparison, dominant model, recessive model and allele analysis. When the homozygote and heterozygote comparisons were carried out, no significant association was found (CC vs. TT: OR = 1.01, 95% CI = 0.93–1.11, $p = 0.799$; TC vs. TT: OR = 0.99, 95% CI = 0.95–1.03, $p = 0.462$). Furthermore, neither dominant nor recessive model discovered significant associations of 8473 T > C polymorphism with cancer risk ((CC + TC) vs. TT: OR = 0.99, 95% CI = 0.95–1.03, $p = 0.644$; CC vs. (TC + TT): OR = 1.01, 95%CI = 0.94–1.09, $p = 0.779$).

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**Fig. 1 Flow chart of literature search and study selection**
| First author | Year | Ethnicity | Country | Control source | Cancer type | Genotype method | cases | controls | HWE | MAF |
|--------------|------|-----------|---------|----------------|-------------|----------------|-------|----------|------|-----|
| Cox, D.G.    | 2004 | Caucasian | Spain   | HB colorectal  | Invader     | 140 121 29     | 126 120 25 | 0.639 0.314 |
| Campa, D.    | 2004 | Caucasian | France  | PB lung        | TaqMan      | 31 107 112     | 65 99 50  | 0.304 0.465 |
| Hu, Z.       | 2005 | Asian     | China   | HB lung        | PCR-PIRA    | 234 83 5       | 209 107 7  | 0.113 0.187 |
| Sorensen, M. | 2005 | Caucasian | Denmark | PB lung        | TaqMan      | 127 111 18     | 115 126 27  | 0.377 0.336 |
| Campa, D.    | 2005 | Caucasian | France  | PB lung        | TaqMan      | 855 886 224    | 805 904 228 | 0.285 0.351 |
| Sakoda, L.C. | 2006 | Asian     | China   | PB AV          | TaqMan      | 30 11 4        | 541 216 21  | 0.920 0.166 |
| Gallicchio, L.| 2006| Mixed    | USA     | PB breast    | TaqMan      | 9 5 0          | 158 164 34  | 0.360 0.326 |
| Gallicchio, L.| 2006| Mixed    | USA     | PB breast    | TaqMan      | 29 26 11       | 396 416 95  | 0.353 0.334 |
| Siezen, C.L. | 2006| Caucasian | Netherlands | PB colorectal | Pyrosequencing | 97 83 20       | 190 163 35  | 0.996 0.300 |
| Siezen, C.L. | 2006| Caucasian | Netherlands | PB colorectal | Pyrosequencing | 216 171 55     | 339 281 73  | 0.198 0.308 |
| Sakoda, L.C. | 2006| Asian     | China   | PB EHBD       | TaqMan      | 70 51 5        | 541 216 21  | 0.920 0.166 |
| Sakoda, L.C. | 2006| Asian     | China   | PB gallbladder | TaqMan      | 165 61 10      | 541 216 21  | 0.920 0.166 |
| Park, J.M.   | 2006| Asian     | Korea   | HB lung       | PCR-PIRA    | 352 205 25     | 330 220 32  | 0.552 0.244 |
| Shahedi, K.  | 2006| Caucasian | Sweden  | PB prostate   | MassARRAY   | 571 618 158    | 306 363 88  | 0.208 0.356 |
| Cox, D.G.    | 2007| Mixed     | USA     | PB breast     | TaqMan      | 541 567 141    | 699 808 213 | 0.383 0.359 |
| Cox, D.G.    | 2007| Mixed     | USA     | PB breast     | TaqMan      | 140 131 30     | 270 259 81  | 0.134 0.345 |
| Gao, J.      | 2007| Asian     | China   | HB breast     | PCR-RFLP    | 404 179 18     | 429 194 20  | 0.733 0.182 |
| Vogel, U.    | 2007| Caucasian | Denmark | PB breast     | PCR-RFLP    | 167 150 44     | 155 165 41  | 0.770 0.342 |
| Lee, T.S.    | 2007| Asian     | Korea   | HB cervical   | SNP-IT      | 115 52 8       | 101 50 2   | 0.124 0.176 |
| Campa, D.    | 2007| Caucasian | France  | PB esophageal | TaqMan      | 64 84 11        | 389 377 87  | 0.756 0.323 |
| Jiang, G.J.  | 2007| Asian     | China   | HB gastric    | PCR-PIRA    | 159 86 9       | 199 96 9   | 0.525 0.188 |
| Hou, L.F.    | 2007| Caucasian | Poland  | PB gastric    | TaqMan      | 137 132 35     | 165 202 49  | 0.279 0.361 |
| Campa, D.    | 2007| Caucasian | France  | PB laryngeal  | TaqMan      | 139 120 22     | 313 321 77  | 0.694 0.334 |
| Campa, D.    | 2007| Caucasian | France  | PB nasopharyngeal | TaqMan | 41 47 11      | 313 321 77  | 0.694 0.334 |
| Campa, D.    | 2007| Caucasian | France  | PB oral       | TaqMan      | 72 70 11       | 313 321 77  | 0.694 0.334 |
| Cheng, I.    | 2007| African   | USA     | HB prostate   | TaqMan      | 12 39 38 11    | 49 29 162 0.601 |
| Cheng, I.    | 2007| Caucasian | USA     | HB prostate   | TaqMan      | 183 199 34     | 196 177 44  | 0.668 0.318 |
| Lira, M.G.   | 2007| Caucasian | Italy   | HB skin       | PCR-RFLP    | 44 47 12       | 64 51 15  | 0.330 0.312 |
| Vogel, U.    | 2007| Caucasian | Denmark | PB skin       | TaqMan      | 123 140 41     | 145 148 22  | 0.054 0.305 |
| Yang, H      | 2008| Mixed     | USA     | HB bladder    | SNPlex      | 279 268 76     | 236 312 85  | 0.255 0.381 |
| Song, D.K.   | 2008| Asian     | China   | HB bladder    | PCR-PIRA    | 132 39 4       | 113 61 5   | 0.337 0.198 |
| Ferguson, H.R.| 2008| Caucasian | UK      | HB esophageal | TaqMan      | 73 106 30      | 111 113 24  | 0.537 0.325 |
| Vogel, U.    | 2008| Caucasian | Denmark | PB lung       | PCR-RFLP    | 182 183 38     | 310 341 93  | 0.959 0.354 |
| Danforth, K.N.| 2008| Caucasian | USA     | PB prostate   | TaqMan      | 488 515 143    | 641 605 137 | 0.741 0.318 |
| Danforth, K.N.| 2008| Caucasian | USA     | PB prostate   | TaqMan      | 517 507 113    | 501 517 117 | 0.332 0.331 |
| Abraham, J.E.| 2009| Caucasian | UK      | PB breast     | TaqMan      | 927 985 260    | 996 1010 259 | 0.903 0.337 |
| Andersen, V  | 2009| Caucasian | Denmark | PB colorectal | TaqMan      | 147 178 34     | 315 355 95  | 0.745 0.356 |
| Gong, Z.H    | 2009| Mixed     | USA     | PB colorectal | PCR-RFLP    | 64 70 28       | 69 109 33  | 0.351 0.415 |
| Thompson, C.L.| 2009| Caucasian | USA     | PB colorectal | TaqMan      | 176 189 56     | 216 199 65  | 0.081 0.343 |
| Upadhyay, R. | 2009| Asian     | India   | HB esophageal | PCR-RFLP    | 63 89 22       | 81 102 33  | 0.924 0.389 |
| Srivastava, K.| 2009| Asian     | India   | HB gallbladder | PCR-RFLP    | 51 91 25       | 67 88 29  | 0.991 0.397 |
| Piranda, D.N.| 2010| Mixed     | Brazil  | PB breast     | TaqMan      | 125 149 20     | 120 99 25  | 0.496 0.305 |
The allele analysis also didn’t find significant association (C allele vs. T allele: OR = 1.00, 95% CI = 0.96–1.04, p = 0.921). Overall, the results of this meta-analysis showed no significant association between COX-2 8473 T > C polymorphism and cancer risk.

Subgroup analysis

In order to estimate the effects of specific study characteristics on the relationship between COX-2 8473 T > C polymorphism and cancer risk, we carried out subgroup analysis in control source, ethnicity, genotyping method, and cancer type.
| Genetic model | Group/subgroup | Studies | Heterogeneity test | Statistical model | Test for overall effect |
|---------------|----------------|---------|--------------------|-------------------|------------------------|
|               |                |         | I² (%) Phet OR (95% CI) |                    |                        |
|               |                |         |                    |                   |                        |
| CC vs. TT     | Overall        | 79      | 57.4 0             | R                 | 1.01 (0.93 – 1.11)    | 0.799                  |
|               | PB             | 42      | 58.6 0             | R                 | 1.01 (0.92 – 1.11)    | 0.870                  |
|               | HB             | 37      | 57.3 0             | R                 | 1.01 (0.83 – 1.23)    | 0.915                  |
|               | Asian          | 32      | 55.8 0             | R                 | 1.10 (0.88 – 1.37)    | 0.403                  |
|               | Caucasian      | 33      | 65.9 0             | R                 | 1.03 (0.90 – 1.18)    | 0.652                  |
|               | Taqman         | 41      | 63.9 0             | R                 | 1.08 (0.94 – 1.23)    | 0.272                  |
|               | PCR-RFLP       | 23      | 60.4 0             | R                 | 0.94 (0.74 – 1.20)    | 0.615                  |
|               | PCR-PIRA       | 5       | 0 0.802            | F                 | 0.83 (0.56 – 1.23)    | 0.345                  |
|               | bladder cancer | 4       | 13.1 0.327         | F                 | 0.74 (0.55 – 0.99)    | 0.040                  |
|               | breast cancer  | 13      | 53.5 0.012         | R                 | 1.01 (0.87 – 1.17)    | 0.939                  |
|               | cervical cancer | 2   | 82.6 0.016         | R                 | 1.04 (0.11 – 9.53)    | 0.971                  |
|               | colorectal cancer | 12 | 17.7 0.270         | F                 | 0.95 (0.86 – 1.06)    | 0.340                  |
|               | esophageal cancer | 4 | 61.1 0.052         | R                 | 1.30 (0.72 – 2.33)    | 0.390                  |
|               | gallbladder cancer | 2 | 0 0.532          | F                 | 1.28 (0.78 – 2.12)    | 0.326                  |
|               | gastric cancer | 4       | 52.4 0.098         | R                 | 1.34 (0.85 – 2.13)    | 0.210                  |
|               | HCC            | 2       | 59.9 0.114         | F                 | 1.54 (0.88 – 2.70)    | 0.128                  |
|               | laryngeal cancer | 2  | 67.3 0.080         | R                 | 0.98 (0.35 – 2.75)    | 0.973                  |
|               | lung cancer    | 11      | 80.5 0             | R                 | 0.97 (0.65 – 1.45)    | 0.883                  |
|               | nasopharyngeal cancer | 3 | 56.1 0.103         | F                 | 0.59 (0.40 – 0.86)    | 0.007                  |
|               | oral cancer    | 3       | 0 0.404            | F                 | 0.68 (0.40 – 1.16)    | 0.158                  |
|               | ovarian cancer | 2       | 51.6 0.151         | F                 | 0.84 (0.64 – 1.10)    | 0.205                  |
|               | prostate cancer | 6  | 42.8 0.120         | F                 | 1.10 (0.95 – 1.28)    | 0.192                  |
|               | skin cancer    | 3       | 42.6 0.175         | F                 | 1.51 (1.02 – 2.25)    | 0.041                  |
|               | TC vs. TT      | Overall | 79    | 33.1 0.003        | R                 | 0.99 (0.95 – 1.03)    | 0.462                  |
|               | PB             | 42      | 28.4 0.047         | R                 | 1.00 (0.96 – 1.04)    | 0.908                  |
|               | HB             | 37      | 37.7 0.012         | R                 | 0.96 (0.88 – 1.04)    | 0.303                  |
|               | Asian          | 32      | 43.4 0.005         | R                 | 0.98 (0.90 – 1.07)    | 0.675                  |
|               | Caucasian      | 33      | 23.1 0.119         | F                 | 0.99 (0.95 – 1.04)    | 0.679                  |
|               | Taqman         | 41      | 36.2 0.012         | R                 | 1.03 (0.97 – 1.09)    | 0.313                  |
|               | PCR-RFLP       | 23      | 11.6 0.303         | F                 | 0.97 (0.90 – 1.05)    | 0.494                  |
|               | PCR-PIRA       | 5       | 50.4 0.089         | R                 | 0.78 (0.61 – 0.99)    | 0.037                  |
|               | bladder cancer | 4       | 49.4 0.115         | F                 | 0.75 (0.62 – 0.90)    | 0.002                  |
|               | breast cancer  | 13      | 0 0.540            | F                 | 0.99 (0.94 – 1.04)    | 0.676                  |
|               | cervical cancer | 2  | 0 0.604            | F                 | 1.00 (0.74 – 1.37)    | 0.980                  |
|               | colorectal cancer | 12 | 3.8 0.408         | F                 | 0.97 (0.90 – 1.03)    | 0.305                  |
|               | esophageal cancer | 4 | 0 0.772          | F                 | 1.35 (1.10 – 1.66)    | 0.004                  |
|               | gallbladder cancer | 2 | 41.6 0.191         | F                 | 1.05 (0.80 – 1.38)    | 0.706                  |
|               | gastric cancer | 4       | 57.2 0.071         | R                 | 1.10 (0.89 – 1.36)    | 0.389                  |
|               | HCC            | 2       | 52.2 0.148         | F                 | 1.11 (0.85 – 1.44)    | 0.467                  |
|               | laryngeal cancer | 2  | 0 0.542            | F                 | 0.88 (0.69 – 1.13)    | 0.322                  |
|               | lung cancer    | 11      | 51.3 0.025         | R                 | 0.90 (0.79 – 1.03)    | 0.140                  |
|               | nasopharyngeal cancer | 3 | 33.3 0.223         | F                 | 0.84 (0.67 – 1.06)    | 0.135                  |
|               | oral cancer    | 3       | 0 0.867            | F                 | 0.88 (0.69 – 1.12)    | 0.307                  |
| Genetic model | Group/subgroup | Studies | Heterogeneity test | Statistical model | Test for overall effect |
|---------------|----------------|---------|--------------------|-------------------|------------------------|
|               | ovarian cancer | 2       | 14.7               | 0.279             | F                      |
|               | prostate cancer| 6       | 3.1                | 0.397             | F                      |
|               | skin cancer   | 3       | 0                  | 0.806             | F                      |
| (CC + TC) vs. TT| Overall      | 79      | 50.0               | 0                 | R                      |
|               | PB            | 42      | 46.4               | 0.001             | R                      |
|               | HB            | 37      | 53.9               | 0                 | R                      |
|               | Asian         | 32      | 57.0               | 0                 | R                      |
|               | Caucasian     | 33      | 51.5               | 0                 | R                      |
|               | Taqman        | 41      | 53.3               | 0                 | R                      |
|               | PCR-RFLP      | 23      | 43.4               | 0.015             | R                      |
|               | PCR-PIRA      | 5       | 48.8               | 0.099             | R                      |
|               | bladder cancer| 4       | 52.9               | 0.095             | R                      |
|               | breast cancer | 13      | 19.0               | 0.251             | F                      |
|               | cervical cancer| 2     | 0                  | 0.862             | F                      |
|               | colorectal cancer| 12  | 4.3                | 0.403             | F                      |
|               | esophageal cancer| 4  | 0                  | 0.414             | F                      |
|               | gallbladder cancer| 2 | 2.2                | 0.312             | F                      |
|               | gastric cancer | 4       | 65.6               | 0.033             | R                      |
|               | HCC           | 2       | 67.1               | 0.081             | R                      |
|               | laryngeal cancer| 2    | 7.3                | 0.299             | F                      |
|               | lung cancer   | 11      | 72.7               | 0                 | R                      |
|               | nasopharyngeal cancer| 3  | 47.0               | 0.152             | F                      |
|               | oral cancer   | 3       | 0                  | 0.856             | F                      |
|               | ovarian cancer | 2       | 0                  | 0.565             | F                      |
|               | prostate cancer| 6      | 21.0               | 0.275             | F                      |
|               | skin cancer   | 3       | 0                  | 0.979             | F                      |
| CC vs. (TC + TT) | Overall      | 79      | 52.6               | 0                 | R                      |
|               | PB            | 42      | 53.2               | 0                 | R                      |
|               | HB            | 37      | 53.3               | 0                 | R                      |
|               | Asian         | 32      | 52.9               | 0                 | R                      |
|               | Caucasian     | 33      | 58.5               | 0                 | R                      |
|               | Taqman        | 41      | 60.9               | 0                 | R                      |
|               | PCR-RFLP      | 23      | 55.3               | 0.001             | R                      |
|               | PCR-PIRA      | 5       | 0                  | 0.845             | F                      |
|               | bladder cancer| 4       | 25.9               | 0.256             | F                      |
|               | breast cancer | 13      | 53.4               | 0.012             | R                      |
|               | cervical cancer| 2     | 83.8               | 0.013             | R                      |
|               | colorectal cancer| 12  | 19.1               | 0.256             | F                      |
|               | esophageal cancer| 4  | 60.8               | 0.054             | R                      |
|               | gallbladder cancer| 2 | 13.5               | 0.282             | F                      |
|               | gastric cancer | 4       | 27.8               | 0.245             | F                      |
|               | HCC           | 2       | 42.5               | 0.187             | F                      |
|               | laryngeal cancer| 2    | 62.6               | 0.102             | F                      |
and type of cancer under a variety of genetic models. For control source subgroup, whether the source of controls was population-based (PB) or hospital-based (HB), no association between 8473 T > C polymorphism and cancer risk was found. When stratified according to ethnicity, we observed no significant associations in Asians or Caucasians. Stratified by genotyping method, no relationship was detected in TaqMan and PCR-RFLP. However, by comparison, we discovered statistically significant decreased cancer risk in PCR-PIRA (TC vs. TT: OR = 0.78, 95% CI: 0.61–0.99, p = 0.037; (CC + TC) vs. TT: OR = 0.79, 95% CI: 0.63–0.78, P = 0.035; C allele vs. T allele: OR = 0.84, 95% CI: 0.74–0.96, P = 0.010). According to cancer type, 8473 T > C polymorphism was associated with a statistically significant decreased risk for nasopharyngeal cancer except for heterozygote comparison (CC vs. TT: OR = 0.59, 95% CI: 0.40–0.86, P = 0.007; (CC + TC) vs. TT: OR = 0.79, 95% CI: 0.64–0.98, P = 0.030; CC vs. (TC + TT): OR = 0.65, 95%CI: 0.46–0.94, P = 0.020; C allele vs. T allele: OR = 0.80, 95% CI: 0.68–0.94, P = 0.007). In the group with bladder cancer, we also found a decreased risk in the homozygote comparison, heterozygote comparison and allele analysis (CC vs. TT: OR = 0.74, 95% CI = 0.55–0.99, P = 0.040; TC vs. TT: OR = 0.75, 95% CI = 0.62–0.90, P = 0.002; C allele vs. T allele: OR = 0.76, 95% CI = 0.60–0.96, P = 0.020), but not in the dominant model and

| Genetic model | Group/subgroup | Studies | Heterogeneity test | Statistical model | Test for overall effect |
|---------------|----------------|--------|-------------------|-------------------|------------------------|
|               | lung cancer    | 11     | 75.4              | 0                 | R                      | 0.99(0.70–1.38) 0.932 |
|               | nasopharyngeal cancer | 3 | 46.9              | 0.152             | F                      | 0.65(0.46–0.94) 0.020 |
|               | oral cancer    | 3      | 0                 | 0.388             | F                      | 0.71(0.42–1.18) 0.182 |
|               | ovarian cancer | 2      | 65.5              | 0.088             | R                      | 0.75(0.42–1.34) 0.336 |
|               | prostate cancer| 6      | 44.6              | 0.108             | F                      | 1.11(0.97–1.27) 0.137 |
|               | skin cancer    | 3      | 57.6              | 0.095             | R                      | 1.01(0.94–1.09) 0.454 |
|               | C allele vs. T allele Overall | 79 | 62.0              | 0                 | R                      | 1.00(0.96–1.04) 0.921 |
|               |                  | PB     | 42                | 59.9              | 0                       | 1.01(0.96–1.05) 0.810 |
|               |                  | HB     | 37                | 64.8              | 0                       | 0.98(0.90–1.07) 0.656 |
|               |                  | Asian  | 32                | 66.4              | 0                       | 1.00(0.91–1.09) 0.956 |
|               |                  | Caucasian | 33       | 66.9              | 0                       | 1.02(0.96–1.08) 0.573 |
|               |                  | Taqman | 41                | 66.5              | 0                       | 1.04(0.98–1.10) 0.239 |
|               |                  | PCR-RFLP | 23          | 61.4              | 0                       | 0.99(0.89–1.09) 0.794 |
|               |                  | PCR-PIRA | 5             | 39.9              | 0.155                  | F 0.84(0.74–0.96) 0.010 |
|               | bladder cancer  | 4      | 57.4              | 0.070             | R                      | 0.76(0.60–0.96) 0.020 |
|               | breast cancer   | 13     | 47.8              | 0.028             | R                      | 1.00(0.94–1.06) 0.938 |
|               | cervical cancer | 2      | 9.5               | 0.293             | F                      | 0.95(0.75–1.22) 0.699 |
|               | colorectal cancer | 12    | 12.8              | 0.319             | F                      | 0.97(0.93–1.02) 0.222 |
|               | esophageal cancer | 4     | 56.6              | 0.075             | R                      | 1.21(0.96–1.52) 0.100 |
|               | gallbladder cancer | 2   | 0                 | 0.759             | F                      | 1.07(0.88–1.31) 0.496 |
|               | gastric cancer  | 4      | 67.7              | 0.026             | R                      | 1.14(0.94–1.38) 0.195 |
|               | HCC             | 2      | 73.4              | 0.052             | R                      | 1.10(0.71–1.71) 0.658 |
|               | laryngeal cancer | 2      | 47.3              | 0.168             | F                      | 0.88(0.73–1.06) 0.183 |
|               | lung cancer     | 11     | 83.0              | 0                 | R                      | 0.96(0.82–1.14) 0.661 |
|               | nasopharyngeal cancer | 3 | 54.1              | 0.113             | F                      | 0.80(0.68–0.94) 0.007 |
|               | oral cancer     | 3      | 0                 | 0.669             | F                      | 0.85(0.70–1.03) 0.106 |
|               | ovarian cancer  | 2      | 0                 | 0.850             | F                      | 0.95(0.85–1.07) 0.428 |
|               | prostate cancer | 6      | 44.2              | 0.111             | F                      | 1.05(0.98–1.12) 0.188 |
|               | skin cancer     | 3      | 0                 | 0.589             | F                      | 1.21(1.02–1.45) 0.031 |

Abbreviations: OR odds ratios, CI confidence intervals, R random effects model, F fixed effects model, HB hospital based, PB population based, PCR-RFLP polymorphism chain reaction restriction fragment length polymorphism, PCR-PIRA polymorphism chain reaction based primer-introduced restriction analysis, HCC hepatocellular carcinoma

The results are in bold italic if P <0.05
recessive model. However, for the esophageal cancer group, the COX-2 8473 T > C polymorphism was significantly associated with an increased risk in the homozygote comparison and dominant model (TC vs. TT: OR = 1.35, 95% CI = 1.10–1.66, \( P = 0.004 \); (CC + TC) vs. TT: OR = 1.33, 95% CI = 1.10–1.63, \( P = 0.004 \)), but not in the homozygote comparison, recessive model and allele analysis. For the group of skin cancer, we also observed the association of a significantly increased risk in the homozygote comparison and allele analysis (CC vs. TT: OR = 1.51, 95% CI = 1.02–2.25, \( P = 0.041 \); C allele vs. T allele: OR = 1.21, 95% CI = 1.02–1.45, \( P = 0.031 \), respectively), but not in homozygote comparison, dominant model and recessive model. On the contrary, the result of breast cancer indicated no relationship with this polymorphism. Similarly, we also observed no significant association of 8473 T > C polymorphism with other cancers, including cervical cancer, colorectal cancer, gallbladder cancer, gastric cancer, HCC, lung cancer, oral cancer, ovarian cancer and prostate cancer. The detailed results were shown in Table 2.

**Test of heterogeneity and sensitivity analysis**
Significant heterogeneity was obvious in all the comparisons of COX-2 8473 T > C polymorphism (Table 2). Studies were excluded one by one to evaluate their influence on the test of heterogeneity and the credibility of our results. The results revealed that the corresponding pooled ORs and 95% CIs were not changed (Additional file 2: Figure S1, Additional file 3: Figure S2, Additional file 4: Figure S3 and Additional file 5: Figure S4), implying that the results of the present meta-analysis were credible and robust.

**Publication bias**
The Begg’s and Egger’s tests were performed to quantitatively assess the publication bias of this meta-analysis. \( P < 0.05 \) observed in the allelic genetic models was considered representative of statistically significant publication bias. The \( P \) details for bias were presented in Table 3. There was no significant publication bias in the overall analysis under each model. Moreover, the funnel plots quantitatively evaluating the publication bias did not reveal any evidence of obvious asymmetry in any model (Fig. 2).

**Table 3 Results of publication bias test**

| Compared genotype | Begg’s test | Egger’s test |
|-------------------|-------------|--------------|
|                   | \( z \) value | \( P \) value | \( t \) value | \( P \) value |
| CC vs. TT         | 1.10        | 0.273        | 0.34          | 0.734        |
| TC vs. TT         | −0.16       | 0.876        | −0.14         | 0.890        |
| (CC + TC) vs. TT  | 0.64        | 0.523        | 0.06          | 0.951        |
| CC vs. (TC + TT)  | 0.93        | 0.354        | 0.24          | 0.807        |
| C allele vs. T allele | 0.79    | 0.429        | 0.14          | 0.891        |

\( P \) value < 0.05 was considered as significant publication bias

**Trial sequential analysis (TSA) results**
As shown in Fig. 3, in order to prove the conclusions, the sample size required in the overall analysis was 50,558 cases for homozygote comparison, and 68,302 cases for heterozygote comparison. The results showed that the cumulative \( Z \)-cure didn’t exceed the TSA boundary, but the total number of cases and controls exceeded the required sample size, indicating that adequate evidence of our conclusions were established and no further relevant trials were needed.

**Discussion**
Inflammation has been considered as an acting element for the pathogenesis of cancer. Prostaglandins are important molecules in the inflammatory response, and they are produced from arachidonic acid through the catalytic activity of COX-2. COX-2 cannot be detected under normal conditions, but rapidly induced in response to various inflammatory stimuli [7]. The expression level of COX-2 gene is regulated by a series of regulatory elements located in COX-2 promoter region, including nuclear factor-kb(NF-kB)/nuclear factor interleukin-6 (NF-IL6)/CCAAT/enhancer-binding protein (C/EBP) binding sites, cyclic AMP-response element (CRE) and activation protein 1 (AP-1) [87]. Further studies indicated that 3′UTR of COX-2 gene of murine also contains several regulatory elements affecting the stability of mRNA and the efficiency of translation [12], which played vital roles in stabilization, degradation, and translation of the transcripts [88, 89]. According to the above studies, many researchers hypothesized that polymorphism sites in 3′UTR of COX-2 gene, with 8473 T > C polymorphism included, might increase the expression of COX-2 and affect the susceptibility of cancer. Therefore, the correlation between 8473 T > C polymorphism in 3′UTR of COX-2 gene and cancer susceptibility has been of great interest in polymorphism research. In this meta-analysis, not only did we try to make sure whether 8473 T > C polymorphism has any relationship with the susceptibility of overall cancer, but we also performed TSA to efficiently decrease the risk of type I error and evaluate whether our results were stable.

In the present meta-analysis, we comprehensively researched the association of the 8473 T > C polymorphism in the 3′UTR region of COX-2 with cancer risk in all population through 79 studies. The results showed that no significant association between 8473 T > C polymorphism we studied and overall cancer risk was detected under all five genetic comparisons. However, we discovered significant heterogeneity among studies, therefore, further sensitivity analyses were conducted. Though the studies were eliminated one by one, heterogeneity remained significant. Moreover, several subgroup analyses, performed according to control source, ethnicity, genotyping method...
and type of cancer in all compared genetic models, could not explain the source of heterogeneity. In control source subgroup, no statistical significance association was found neither in PB nor HB. For ethnicity subgroup, whether in Asians or Caucasians, the polymorphism had no influence on cancer risk. The results might indicate that different individuals in the studies have the same risk to cancer. Moreover, only in the subgroup of PCR-PIRA, 8473 T > C polymorphism was linked to decrease risk to overall cancer in heterozygote comparison, recessive model and allele analysis, suggesting that different genotype detecting methods used in studies might influence the results. In the stratification analysis by type of cancer, the results indicated that the 8473 T > C polymorphism was associated with a statistically significant decreased risk for nasopharyngeal cancer in other four models except for heterozygote comparison, and bladder cancer in the homozygote comparison, heterozygote comparison and allele analysis. However, we observed an increased risk for esophageal cancer in heterozygote comparison and dominant model, and for skin cancer in homozygote comparison and allele analysis. The factors that contributed to this contradiction might include the following three aspects. Firstly, inconsistent results might be attributed to the different pathogenesis of the cancer. Secondly, 8473 T > C polymorphism might play different roles in different cancers. Most importantly, the influence of COX-2 gene 8473 T > C polymorphism on cancer risk might be affected by complex interactions between gene and environment. For example, smoking, the most important risk factor of lung cancer, could induce COX-2 expression [90].

![Funnel plots for the publication bias test in the overall analysis](image)

**Fig. 2** a. Funnel plots for the publication bias test in the overall analysis under homozygote comparison. b. Funnel plots for the publication bias test in the overall analysis under heterozygote comparison. c. Funnel plots for the publication bias test in the overall analysis under dominant model. d. Funnel plots for the publication bias test in the overall analysis under recessive model. e. Funnel plots for the publication bias test in the overall analysis under allele analysis.
Currently, some meta-analysis have investigated the relationship of 8473 T > C polymorphism with susceptibility to some types of cancer. Interestingly, part of the previous studies found some strong associations inconsistent with the result of our meta-analysis. Such as the report by Liu et al. [91] indicated that COX-2 gene 8473 T > C polymorphism was a factor for suffering from lung cancer, and Zhu et al. [92] suggested that 8473 T > C polymorphism might cause a decreased risk of lung cancer. Like Pan et al. [93], the current study supports the view that no significant association between 8473 T > C polymorphism and lung cancer risk. The reasons for this result may be as follows, firstly, the quality of original studies directly influences the reliability of the meta-analysis. In our meta-analysis the quality assessment of all the studies related with cancer was performed by using NOS, and low-quality studies were excluded. Secondly, the studies with the most recent or larger sample size were included, we therefore carried out a more systematic review of all eligible studies on the COX-2 8473 T > C polymorphisms and risk of lung cancer. Thirdly, the result of this polymorphism on cancer susceptibility might be influenced by some environmental factors or other polymorphisms, such as smoking. Meanwhile, some significant correlations we found were not shown in previous meta-analysis. For example, 8473 T > C polymorphism was associated with a decreased risk in nasopharyngeal cancer. When later studies were included in the meta-analysis, the contradiction didn’t appear, suggesting that the conclusions of previous meta-analysis with less number of studies might be reliable. More studies are required to achieve a more reliable result.

**Fig. 3 a.** TSA for overall analysis under homozygote comparison. **b.** TSA for overall analysis under heterozygote comparison. The required information size was calculated based on a two side $\alpha = 5\%$, $\beta = 20\%$ (power 80%), and an anticipated relative risk reduction of 10%.
Obviously, we clarified the association in this meta-analysis, including more studies with the larger information size. Besides, it is the first TSA that comprehensively elaborated the influence of COX-2 8473 T > C polymorphism in response to cancer risk. However, several limitations should be taken into consideration in this meta-analysis. To begin with, only publications written in English or Chinese were included in our analysis. Therefore, selection bias might be inevitable. Secondly, there was significant heterogeneity in this meta-analysis between the polymorphism and cancer under all five genetic models. Moreover, the source of heterogeneity could not be explained by using subgroup and sensitivity analysis. Finally, as a complicated disease, the pathogenesis of cancer is strongly associated with environmental factors and the interactions with multifarious genetic factors rather than the effect of any single gene. Therefore, gene-to-environment interactions play a vital role in evaluating genetic polymorphisms. More original studies are required to estimate potential interactions between gene and gene, as well as gene and environment.

Conclusions

The results of this meta-analysis manifested that the association between COX-2 8473 T > C polymorphism and overall cancer was not detected under all five genetic comparisons. In the stratification analysis of cancer type, 8473 T > C polymorphism might be associated with a statistically significant decreased risk for nasopharyngeal cancer and bladder cancer, but an increased risk for esophageal cancer and skin cancer. And most importantly, in order to verify the conclusions of this analysis, further studies are needed to assess the potential gene-gene and gene-environment interactions.

Additional files

**Additional file 1:** Table S1. Results of Newcastle–Ottawa scale (NOS) assessment for the included studies. (DOCX 23 kb)

**Additional file 2:** Figure S1. A. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in H8 subgroup under homozygote comparison. B. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in PB subgroup under homozygote comparison. (TIF 4832 kb)

**Additional file 3:** Figure S2. A. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in Asians under homozygote comparison. B. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in Caucasians under homozygote comparison. (TIF 4809 kb)

**Additional file 4:** Figure S3. A. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in TaqMan under homozygote comparison. B. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in PCR-RFLP under homozygote comparison. (TIF 4661 kb)

**Additional file 5:** Figure S4. A. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in breast cancer under homozygote comparison. B. Sensitivity analysis of 8473 T > C polymorphism and cancer risk in lung cancer under homozygote comparison. (TIF 4758 kb)

**Abbreviations**

AV: Ampulla of vater; CI: Confidence intervals; EHBD: Extrahepatic bile duct; F: Fixed effects model; HB: Hospital based; HCC: Hepatocellular carcinoma; HN: Head and neck; HWE: Hardy-Weinberg equilibrium; IGG: Illumina GoldenGate; MAF: Minor allele frequency; OR: Odds ratios; PB: Population based; PCR-KASP: Polymorphism chain reaction based competitive allele specific; PCR-PIRA: Polymorphism chain reaction based primer-introduced restriction analysis; PCR-RFLP: Polymorphism chain reaction restriction fragment length polymorphism; R: Random effects model

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors’ contributions**

QPL and TJM were responsible for conception and design of the study. QPL and CM did the studies selection, data extraction and provided statistical expertise. QPL, WQZ and LZ contributed to the literature search, studies selection and figures. ZHZ and TJM reviewed and edited the manuscript extensively. All authors were involved in interpretation of results, read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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