

Evaluation of association studies, a systematic review and meta-analysis of CYP1A1 polymorphisms, and colorectal cancer risk

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Abstract

Background: 37 publications and seven previous meta-analyses have been reported to investigate the correlation between CYP1A1 T3801C and A2455G polymorphisms with CRC risk. However, the results were contradictory. Original studies were not involved in previously published meta-analyses. Moreover, their meta-analyses did not evaluate positive results to identify multiple comparisons. **Objectives:** We performed an updated meta-analysis and systematically evaluated the published meta-analyses on the association between CYP1A1 T3801C and A2455G polymorphism with CRC susceptibility. **Results:** CYP1A1 T3801C polymorphism was not associated with CRC risk when all the selected studies were merged. However, subgroup analyses according to ethnicity, geographic region, location of CRC, gender and smoking, showed a significant association in rectal cancer and females. However, after BFDP correction, false significant associations were observed in rectal cancer (CC vs. TT: BFDP = 0.998; CC vs. (TT + TC): BFDP = 0.998; C vs. T: BFDP = 0.999) and females (TC vs. TT: BFDP = 0.999). A significantly increased CRC risk was yielded in overall analysis, Caucasians, Europe countries populations, and males for CYP1A1 A2455G polymorphism. After BFDP correction, associations still be significant only in Europe countries populations (AG vs. AA: BFDP = 0.680; (AG + GG) vs. AA: BFDP = 0.475; G vs. A: BFDP = 0.126). However, when we further performed a sensitivity analysis and BFDP test, false significant associations were observed in all analyses (BFDP > 0.8). **Conclusions:** In summary, this study suggests that these positive findings may result from false-positive results, rather than from true associations or biological factors.

Evaluation of association studies, a systematic review and meta-analysis of *CYP1A1* polymorphisms, and colorectal cancer risk

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Conclusions: In summary, this study suggests that these positive findings may result from false-positive results, rather than from true associations or biological factors.

Keywords: *CYP1A1* , polymorphism, colorectal cancer, meta-analysis

Introduction

Colorectal cancer (CRC) has been an public health problem for many years because of increasing incidence and high mortality rate despite some overall improvements in diagnosis and treatment [1, 2]. It is a common form of cancer, with more than 1.5 million new patients diagnosed every year worldwide [3] and more common in developed than developing countries [4]. Previously published studies have indicated that age over 60 years, alcohol consumption and tobacco habits may contribute to sporadic CRC risk [5, 6]. Moreover, the development of CRC is widely considered as a multi-step, multi-factorial process involving gene-gene and gene-environment interactions [7]. It has been suggested that inter-individual differences including single nucleotide polymorphism (SNP) might influence CRC risk [8, 9].

The cytochrome P450 enzymes (CYPs) take part in the metabolism of carcinogenic compounds in the human body [10]. *CYP1A1* is expressed in the large bowel [11]. Because of the involvement of *CYP1A1* in the metabolism of PAHs and estrogens, and perhaps cruciferous vegetables and heterocyclic amines [12], it might be expected that *CYP1A1* variants might influence the risk of colorectal cancer. A commonly studied SNP in the *CYP1A1* gene has been indicated to associate with CRC risk, which was localized on chromosome 15q22 [13]. The commonly reported the 3801T>C (also referred to as 2A, m1, or rs4646903) and A2455G polymorphisms (also known as E7, *2C, m2, rs1048943) with CRC risk [14]. The T3801C and A2455G polymorphisms might change the level of gene expression or messenger RNA stability, resulting in a highly inducible activity of the enzyme [15].

To date, 37 publications (supplemental Table 2) and seven previous meta-analyses [16-22] have been reported to investigate the correlation between the *CYP1A1* T3801C and A2455G polymorphisms with CRC risk. However, the results were inconsistent or even contradictory. In addition, a lot of original studies did not involve in previously published meta-analyses (supplemental Table 1). Moreover, previously published meta-analyses also did not evaluate positive results to identify multiple comparisons. Therefore, we performed an updated meta-analysis and systematically evaluated the published meta-analyses on the association between *CYP1A1* T3801C and A2455G polymorphism with CRC susceptibility.

Materials and Methods

The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [23].

Search strategy

We systematically searched the PubMed, Embase, China National Knowledge Infrastructure (CNKI), and Wan Fang databases (up to Sep 12, 2020) by using the following strategy: ('*CYP1A1* OR 'Cytochrome

P450 1A1') AND ('polymorphism' OR 'variant' OR 'variation' OR 'mutation' OR 'SNP' OR 'genome-wide association study' OR 'genetic association study' OR 'genotype' OR 'allele') AND ('colorectal' OR 'colon' OR 'rectal'). The language was not limited in this study. In addition, the reference lists was checked if the publications were relevant review and meta-analyses studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) case-control or cohort studies, (2) explored the correlation between the *CYP1A1* T3801C and A2455G polymorphisms and CRC risk, and (3) gave the genotype data of cases and controls or the odds ratio (OR) with their 95% confidence intervals (CI). Exclusion criteria were as follows: (1) review articles, (2) case reports, (3) editorials, (4) systematic review and meta-analyses, (5) other SNP, (6) other disease, (7) animal studies, and (8) duplicate data.

Data extraction and quality score assessment

Data was extracted and checked by two investigators independently. Disagreement was settled through discussion and consensus. The following information was collected: (1) first author name, (2) year of publication, (3) country, (4) geographic region, (5) ethnicity, (6) sample size, (7) source of controls, (8) type of control, (9) matching, (10) genotypes distribution, (11) location of CRC, (12) site of CRC, and (12) gender.

Scale for quality assessment criteria was shown in Table 1. All eligible studies quality was also independently assessed by two authors. Total scores ranged from 0 (worst) to 21 (best). If scores were < 13 (the eligible studies were regarded as low quality) and If scores of [?] 13 (the eligible studies were regarded as high quality).

Statistical analysis

Crude ORs and 95% CIs was applied to assess the association between the *CYP1A1* T3801C and A2455G polymorphism with CRC risk. The following genetic models were used: a dominant model (*CYP1A1* T3801C: (TC + CC) vs. TT and *CYP1A1* A2455G: (AG + GG) vs. AA), a recessive model (*CYP1A1* T3801C: CC vs. (TT + TC) and *CYP1A1* A2455G: GG vs. (AA + AG)), an additive model (*CYP1A1* T3801C: TC vs. TT and CC vs. TT; *CYP1A1* A2455G: AG vs. AA and GG vs. AA), and an allelic model (*CYP1A1* T3801C: V vs. T and *CYP1A1* A2455G: G vs. A).

Heterogeneity among studies was assessed to use $P_{\text{heterogeneity}}$ (P_h) and I^2 values [24]. A fixed-effects model (Mantel-Haenszel method) [25] was considered if P [?] 0.10 and/or I^2 [?] 50%; otherwise, a random-effects model (DerSimonian and Laird method) was regarded [26]. Subgroup analyses were calculated by ethnicity, geographic region, gender, location of CRC, and site of CRC. Sensitivity analyses were conducted to investigate the stability of results. The following two methods were considered: (1) One by one exclusion and (2) a data set was built only selecting high-quality and controls of Hardy-Weinberg equilibrium (HWE) studies. HWE was tested by a Chi-square goodness-of-fit test. If $P < 0.05$, the controls were considered as Hardy-Weinberg disequilibrium (HWD). Begg's funnel plot [27] and Egger's regression asymmetry test [28] were employed to assess publication bias. A nonparametric "trim and fill" method [29] was selected if a obvious publication bias was observed. In addition, a meta-regression analysis was employed to explore the sources of heterogeneity among studies. Furthermore, a Bayesian false discovery probability (BFDP) was used to assess the false positive results [30]. A cutoff value of BRDP was set up to be a level of 0.8 and a prior probability of 0.001 to evaluate whether the significant associations were the false positive. All statistical analyses were calculated applying Stata 12.0 software (STATA Corporation, College Station, TX).

Results

Study characteristics

A flow diagram was shown in Fig. 1. Overall, 37 publications were selected to analyze the *CYP1A1* T3801C and A2455G polymorphisms with CRC risk. The current and published meta-analyses involving studies were shown in supplemental Table 1. The eligible studies characteristics were listed in supplemental Table 2. Of

these, 27 studies (involving 9,672 cases and 12,689 controls; eight studies on Asians, fourteen on Caucasians, and five on mixed populations; ten studies on Asia; nine on Europe; five on North America, one on South America, and one on Ocean) for *CYP1A1* T3801C polymorphism and 24 studies (involving 8,933 cases and 11,692 controls; seven studies on Asians, twelve on Caucasians, and five on mixed populations; seven studies on Asia; nine on Europe; five on North America, two on South America, and one on Ocean) for *CYP1A1* A2455G polymorphism were performed in the current pooled analysis. Supplementary Tables 3-5 shows the study characteristics by location of CRC, gender, and site of CRC, respectively.

Quantitative synthesis

The *CYP1A1* T3801C polymorphism and CRC risk

Overall, the *CYP1A1* T3801C polymorphism was not associated with CRC risk when all the selected studies were merged, as shown in Table 2. Then, subgroup analyses according to ethnicity, geographic region, location of CRC, gender, and smoking, a significant association was only observed in rectal cancer (CC vs. TT: OR = 0.73, 95% CI: 0.55–0.97; CC vs. (TT + TC): OR = 0.75, 95% CI: 0.57–0.98; C vs. T: OR = 0.89, 95% CI: 0.80–1.00) and females (TC vs. TT: OR = 1.27, 95% CI: 1.00–1.62). However, after BFD correction, associations did not be observed in rectal cancer (CC vs. TT: BFD = 0.998; CC vs. (TT + TC): BFD = 0.998; C vs. T: BFD = 0.999) and females (TC vs. TT: BFD = 0.999).

The *CYP1A1* A2455G polymorphism and CRC risk

Tables 3 shows the pooled results on the association between the *CYP1A1* A2455G polymorphism and CRC risk. A significantly increased CRC risk was yielded in overall analysis (GG vs. AA: OR = 1.39, 95% CI: 1.03–1.88; GG vs. (AG + AA): OR = 1.32, 95% CI: 1.10–1.57). Then, Subgroups were conducted by ethnicity, geographic region, location of CRC, gender, and smoking. A significantly increased CRC risk was also found in Caucasians (AG vs. AA: OR = 1.26, 95% CI: 1.10–1.46; GG vs. AA: OR = 1.71, 95% CI: 1.00–2.93; (AG + GG) vs. AA: OR = 1.27, 95% CI: 1.04–1.54; G vs. A: OR = 1.27, 95% CI: 1.12–1.43), Europe countries populations (AG vs. AA: OR = 1.43, 95% CI: 1.20–1.70; (AG + GG) vs. AA: OR = 1.45, 95% CI: 1.23–1.72; G vs. A: OR = 1.43, 95% CI: 1.22–1.66), and males ((AG + GG) vs. AA: OR = 1.47, 95% CI: 1.12–1.94). after BFD correction, association was still significant in Europe countries populations (AG vs. AA: BFD = 0.680; (AG + GG) vs. AA: BFD = 0.475; G vs. A: BFD = 0.126).

Heterogeneity and sensitivity analyses

Significant heterogeneity was observed, as shown in Tables 2 and 3. We observed that ethnicity, HWE, and quality score were not source of source of heterogeneity. However, when we excluded Pereira Serafim PV et al. (supplemental Table 1), I^2 value dropped and significant association was found in overall analysis (G vs. A: OR = 1.15, 95% CI: 1.02–1.30) for *CYP1A1* A2455G polymorphism. Furthermore, after BFD correction, no significant association was observed in G vs. A (BFD = 0.998).

Sensitivity analysis was conducted using two methods. First, the results did not change when we applied one by one exclusion in the present study. Further, when we only involved high-quality and HWE in controls studies, a significant association was yielded in Asians (C vs. T: OR = 0.92, 95% CI: 0.85–1.00), Asia countries populations (C vs. T: OR = 0.92, 95% CI: 0.85–1.00), rectal cancer (CC vs. TT: OR = 0.73, 95% CI: 0.55–0.97; CC vs. (TT + TC): OR = 0.75, 95% CI: 0.57–0.98; C vs. T: OR = 0.89, 95% CI: 0.80–1.00), and females (TC vs. TT: OR = 1.27, 95% CI: 1.00–1.62) for the *CYP1A1* T3801C polymorphism, as also shown in Table 2; concerning the *CYP1A1* T2455G polymorphism, a significant association was observed in overall analysis, Asians, Caucasians, Asia countries populations, Europe countries populations, and males, as also shown in Table 3. However, after BFD correction, no significant associations were found in the above all analyses (all BFD > 0.8), as also listed in Tables 2-3.

Publication bias

No obvious publication bias was found on the *CYP1A1* A2455G polymorphism with CRC risk. However, a significant publication bias was observed on the *CYP1A1* T3801C (C vs. T: $P = 0.013$) polymorphism

with CRC risk. Figure 2 shows the non-parametric ‘trim and fill’ method funnel plot. The result did not revised in overall analysis (C vs. T: OR = 0.94, 95% CI: 0.84–1.04) indicating add studies can not affect the merging result.

Discussion

Hayashi S et al. In 1992 (Supplemental Table 1) first reported an association on the *CYP1A1* T3801C and A2455G polymorphisms and with CRC risk. So far, a lot of studies have performed the above two issues. However, the results are still inconsistent. Moreover, seven previously published meta-analyses [16– 22] have arrived at significant disagreement results, especially in different races, as list in supplemental Tables 6 and 7. Moreover, As far as we know that this is the first meta-analysis to investigate the significant results by BFDP test to avoid confounding factors.

The *CYP1A1* T3801C polymorphism was associated with rectal cancer risk in overall races and CRC risk in females; the *CYP1A1* A2455G polymorphism was associated with an increased CRC risk in overall analysis, Caucasians, Europe countries populations, and males. Five genetic model and several subgroup analyses was conducted, this analysis came at the cost of multiple comparisons, in this instance, the pooled OR with their 95% CI must be adjusted to avoid the false positive results [32]. Wakefield et al. [31] provided a precise Bayesian measure of false discovery to adjust the positive results. The method especially suited for SNP and disease susceptibility study. Therefore, we applied BFDP value to evaluate the positive results in this study. After we further performed a sensitivity analysis and BFDP test, BFDP > 0.8 were found in all analyses.

Therefore, these positive associations might most likely result from false-positive results, rather than from true associations or biological factors. The reason may be because some small sample and low-quality studies were easier to accept if there was a positive report. They tend to yield false-positive results because they may be not rigorous and are often of low-quality. In addition, controls of HWD may be genotype errors and selection bias in molecular epidemiological studies.

Therefore, we performed a sensitivity analysis restricted to studies that only included high-quality articles and controls of HWE.

Supplemental Tables 6– 7 list the results of seven previously published meta-analyses [16–22] on the *CYP1A1* T3801C and A2455G polymorphisms with CRC risk, respectively. The largest sample size study [19] was performed in 2014 involving 18 studies (7,171 cases and 8,957 controls) for the *CYP1A1* T3801C polymorphism; on the *CYP1A1* A2455G polymorphism, The largest sample size study [16] was reported in 2016 including 20 studies (8665 cases and 8853 controls). Several studies should be excluded in the above two studies [16, 29]. The present study included 27 studies (9,672 cases and 12,689 controls) on the *CYP1A1* T3801C polymorphism and 24 studies (8,933 cases and 11,692 controls) on the *CYP1A1* A2455G polymorphism with CRC risk. In addition, four previous meta-analyses [16, 18, 19, 21] reported the association on the *CYP1A1* T3801C polymorphism with CRC risk, only a meta-analysis [18] observed a significant decreased CRC risk in Chinese population; another three meta-analyses found that the *CYP1A1* T3801C polymorphism was not significantly associated with CRC risk; five published meta-analyses [16, 17, 20– 22] have been performed to investigate the association on the *CYP1A1* A2455G polymorphism with CRC risk. Of these, four studies [16, 20– 22] reported a significantly increased CRC risk in Asians and Caucasians and one study [17] observed a significantly increased CRC risk in Asia and Europe, but not in America. These results of previously published studies were not consistent, especially in ethnicity. An obvious inconsistency was found in classification of ethnic groups among these published meta-analyses, cells with red color in supplemental Table 1. Moreover, we still found a significant difference on the HWE of controls in these published studies (cells with blue color in supplemental Table 1). In addition, previously published meta-analyses involved incomplete studies and some repeat studies. All studies did not adjusted significant results for multiple comparisons. Therefore, their meta-analyses are still incredible.

Though all our efforts were made to improve our research, the current study still exist several limitations. First, only published articles were included while positive results are known to be published more readily than negative ones. Second, several subgroup analyses only included small sample size, such as in smoking

subgroups (Table 2 and Table 3), the results should be interpreted with caution and it is necessary that a well-designed large sample study to explore the true association. Third, we did not collect the adjusted data because the original study provided little information. Hence, a more precise analysis should be performed when enough data was available in future.

In summary, this study suggests that these positive findings may most likely result from false-positive results, rather than from true associations or biological factors.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution

L.X. was involved in the conception and design of the meta-analysis. X.H. contributed to study selection, data extraction, statistical analysis and writing of manuscript. L.X. and X.H. contributed to the preparation of the meta-analysis and literature review. X.W. critically revised the manuscript and all authors read and approved the manuscript.

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Table 1-3.pdf available at <https://authorea.com/users/374149/articles/491747-evaluation-of-association-studies-a-systematic-review-and-meta-analysis-of-cyp1a1-polymorphisms-and-colorectal-cancer-risk>