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RESEARCH ARTICLE

Associations of CYP2E1 rs2031920 and rs3813867 polymorphisms with colorectal cancer risk: a systemic review and meta-analysis

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Abstract Cytochrome P450 2E1 (CYP2E1) is a natural enzyme involved in the metabolic activation of many carcinogens, and the functional polymorphisms in the CYP2E1 gene might have impacts on colorectal cancer risk. Many studies were published to assess the associations of CYP2E1 rs2031920 and rs3813867 polymorphisms with colorectal cancer risk, but no consistent findings were reported. A systemic review and meta-analysis of eligible studies was performed to comprehensively assess the associations above. Odds ratios (ORs) with 95 % confidence interval (95 % CIs) were used to assess the strength of the associations. Seventeen studies from 15 publications with 17,082 individuals were finally included into this meta-analysis. Meta-analysis of the 13 studies on CYP2E1 rs2031920 polymorphism showed that there was a significant association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk under two genetic models (c2 versus c1: OR=1.19, 95 % CI 1.03–1.37, *P*=0.022; c2c2/c2c1 versus c1c1: OR=1.16, 95 % CI 1.00–1.35, *P*=0.046). Meta-analysis of those four case–control studies on CYP2E1 rs3813867 polymorphism showed that there was no significant association between CYP2E1 rs3813867 polymorphism and colorectal cancer risk under all contrast models (c2 versus c1: OR=0.96, 95 % CI 0.80–1.16, *P*=0.672; c2c2 versus c1c1: OR=1.26, 95 % CI 0.43–3.67, *P*=0.672; c2c2/c1c2 versus c1c1: OR=0.95, 95 % CI 0.78–1.16, *P*=0.114; and c2c2 versus c1c2/c1c1: OR=1.17, 95 % CI 0.41–3.36, *P*=0.775). Therefore, the findings from this meta-analysis suggest that CYP2E1 rs2031920 polymorphism is associated with colorectal cancer risk, but CYP2E1 rs3813867 polymorphism is not associated with colorectal cancer risk. In addition, more well-designed studies with large sample size are needed to provide a more precise evaluation on the associations above.

Keywords CYP2E1 · Colorectal cancer · Associations · Meta-analysis

Introduction

Colorectal cancer is the second most commonly diagnosed cancer with over 1.2 million new cases and 608,700 deaths in 2008 [1, 2]. The highest incidence rate of colorectal cancer is found in Australia, Europe, and North America [2]. In addition, the incidence rate of colorectal cancer is rapidly increasing in a number of countries within Eastern Asia, such as China [2]. Though the definite mechanism of colorectal cancer is still unknown, it has been well accepted that smoking, obesity, red meat consumption, and excessive alcohol consumption are risk factors for colorectal cancer [3, 4]. However, only a small part of individuals exposing to these risk factors develop colorectal cancer, suggesting that genetic susceptibility also plays an important role in the development of colorectal cancer [3–5]. *N*-nitrosamines present in tobacco and red meat are well-recognized carcinogens involved in the development of colorectal cancer [6, 7]. Cytochrome P4502E1 (CYP2E1) is a member of the cytochrome P450 superfamily and is involved in the metabolic activation of many carcinogens such as *N*-nitrosamines and aniline [8–10]. There are several polymorphisms found in the CYP2E1 gene which may have some impacts on susceptibility to colorectal cancer [11, 12]. The CYP2E1 rs2031920 (RsaI) and rs3813867 (PstI) polymorphisms in the 5′-flanking promoter region of the

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CYP2E1 gene are reported to affect the transcriptional activity of CYP2E1 gene [11, 12]. For CYP2E1 rs2031920 and rs3813867 polymorphisms, the three different genotypes are named the homozygous wild-type genotype (c1c1), heterozygous genotype (c1c2), and homozygous rare genotype (c2c2), respectively. Currently, many studies were published to assess the associations of CYP2E1 rs2031920 and rs3813867 polymorphisms with colorectal cancer risk, but no consistent findings were reported [13–24]. A systemic review and meta-analysis of eligible studies was performed to comprehensively assess the associations between CYP2E1 rs2031920 and rs3813867 polymorphisms and colorectal cancer risk.

Materials and methods

Publication search and eligible criteria

PubMed, Embase, Web of Science, and China National Knowledge Infrastructure (CNKI) were searched for case–control studies on the associations between CYP2E1 rs2031920 and rs3813867 polymorphisms and colorectal cancer risk. The following keywords were used in the literature search: ("colorectal cancer"' or "colon cancer" or "rectal cancer") and ("CYP2E1" or "CYP4502E1" or "rs2031920" or "rs3813867"). All studies included into this meta-analysis must meet the following eligibility criteria: (1) case–control study; (2) assessing the associations between CYP2E1 rs2031920 and rs3813867 polymorphisms and colorectal cancer risk; and (3) providing sufficient data on the genotype frequencies of CYP2E1 rs2031920 and rs3813867 polymorphisms to estimate the odds ratio (OR) with 95 % confidence interval (95 % CI). When two or more publications were performed on the same population, only the study with the largest or the most recent data was included into this meta-analysis.

Data extraction

The following information was extracted from those included studies: the first author's name, publication year, country of the studied population, ethnicity of the studied population, genotyping methods, and genotype frequencies of CYP2E1 rs2031920 and rs3813867 polymorphisms in both cases and controls. The ethnicities of the studied population were categorized as Caucasians, Asians, and others.

Statistical analysis

The pooled OR with 95 % CI was calculated to assess the associations of CYP2E1 rs2031920 and rs3813867 polymorphisms with colorectal cancer risk. For both rs2031920 and rs3813867 polymorphisms, the ORs with their 95 % CIs were calculated for the allele model (c2 versus c1), the codominant model (c2c2 versus c1c1), the dominant model (c2c2/c1c2 versus c1c1), and the recessive model (c2c2 versus c1c2/c1c1), respectively. The statistical heterogeneity among studies was assessed with the I^2 test, and a I^2 value ≥50 % was considered to represent significant heterogeneity [25]. When there was obvious between-study heterogeneity, the random effect model (DerSimonian–Laird method) was used to calculate the pooled OR [26]. When there was no obvious between-study heterogeneity, the fixed effect model (Mantel–Haenszel method) was used to calculate the pooled OR [27]. Subgroup analysis based on ethnicity was also performed. Publication bias was tested by a funnel plot. All statistical analyses were undertaken using Stata version 12.0 (StataCorp, College Station, TX, USA). All the P values in this meta-analysis were two-sided, and a P value less than 0.05 was defined statistically significant.

Results

Study characteristics

There were a total of 20 studies preliminarily identified by searching the PubMed, Embase, Web of Science, and CNKI databases [13–24, 28–35]. According to the eligible criteria, five studies were further excluded including three studies for other CYP2E1 polymorphism, one for case-only studies and the other one for the lack of useful data [31–35]. At last, 17 studies from 15 publications with 17,082 individuals were finally included into this meta-analysis [13–24, 28–30]. There were 14 studies with a total of 5,291 cases and 6,477 controls on the association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk. Besides, there were four studies with 2,312 cases and 3,002 controls on the association between CYP2E1 rs3813867 polymorphism and colorectal cancer risk. Among those 15 studies, the polymerase chain reaction restriction fragment length polymorphism was the most common method used to analyze the genotype frequencies of those two polymorphisms.

Meta-analysis outcomes

Meta-analysis of the 13 studies on CYP2E1 rs2031920 polymorphism showed that there was a significant association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk under two genetic models (c2 versus c1: OR=1.19, 95 % CI 1.03–1.37, P=0.022; c2c2/c2c1 versus c1c1: OR=1.16, 95 % CI 1.00–1.35, P=0.046) (Table 1, Figs. 1 and 2). However, subgroup analysis by ethnicity showed that there was no obvious association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk in both Caucasians and Asians (Table 1).

Table 1 Association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk

Contrast models	Number of studies	OR (95 % CI)	P_{OR}	Model	I^2 (%)
Total studies					
c2 vs. c1	13	1.19 (1.03-1.37)	0.022	Random	61.9
c2c2 vs. c1c1	13	1.40 (0.92-2.14)	0.121	Random	54.9
c2c2/c2c1 vs. c1c1	13	1.16 (1.00-1.35)	0.046	Random	51.8
c2c2 vs. c1c1/c2c1	13	1.35 (0.90-2.03)	0.147	Random	52.4
Caucasians					
c2 vs. c1	8	1.24 (0.97-1.60)	0.086	Random	61.4
c2c2 vs. c1c1	8	1.36 (0.86-2.16)	0.186	Fixed	37.5
c2c2/c2c1 vs. c1c1	8	1.23 (0.95-1.60)	0.116	Random	59.1
c2c2 vs. c1c1/c2c1	8	1.38 (0.87-2.19)	0.166	Fixed	33.3
Asians					
c2 vs. c1	5	1.15 (0.95-1.39)	0.152	Random	69.3
c2c2 vs. c1c1	5	1.31 (0.76-2.24)	0.333	Random	73.0
c2c2/c2c1 vs. c1c1	5	1.07 (0.95-1.20)	0.276	Random	47.9
c2c2 vs. c1c1/c2c1	5	1.25 (0.75-2.10)	0.391	Random	71.5

OR odds ratio; *CI* confidence interval, P_{OR} *P* value of OR

Meta-analysis of those four case–control studies on CYP2E1 rs3813867 polymorphism showed that there was no significant association between CYP2E1 rs3813867 polymorphism and colorectal cancer risk under all contrast models (c2 versus c1: OR=0.96, 95 % CI 0.80–1.16, *P*=0.672; c2c2 versus c1c1: OR=1.26, 95 % CI 0.43–3.67, *P*=0.672; c2c2/c1c2 versus c1c1: OR=0.95, 95 % CI 0.78–1.16, *P*=0.114; and c2c2 versus c1c2/c1c1: OR=1.17, 95 % CI 0.41–3.36, *P*=0.775) (Table 2). In addition, subgroup analysis by ethnicity suggested there was no obvious association between the CYP2E1 rs3813867 polymorphism and colorectal cancer risk in both Caucasians and Asians (Table 2).

A funnel plot was performed to estimate the publication bias of literatures in this meta-analysis. The shapes of funnel

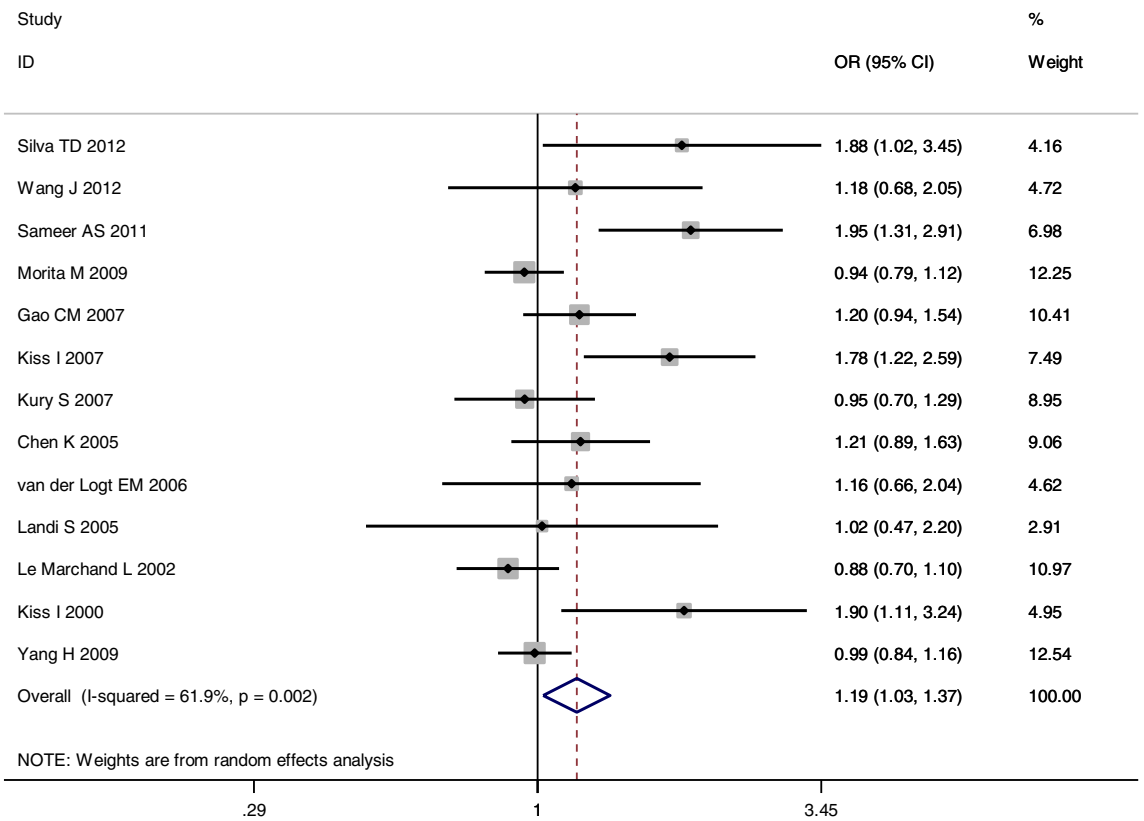

Fig. 1 Forest plot showing significant association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk under the allele model

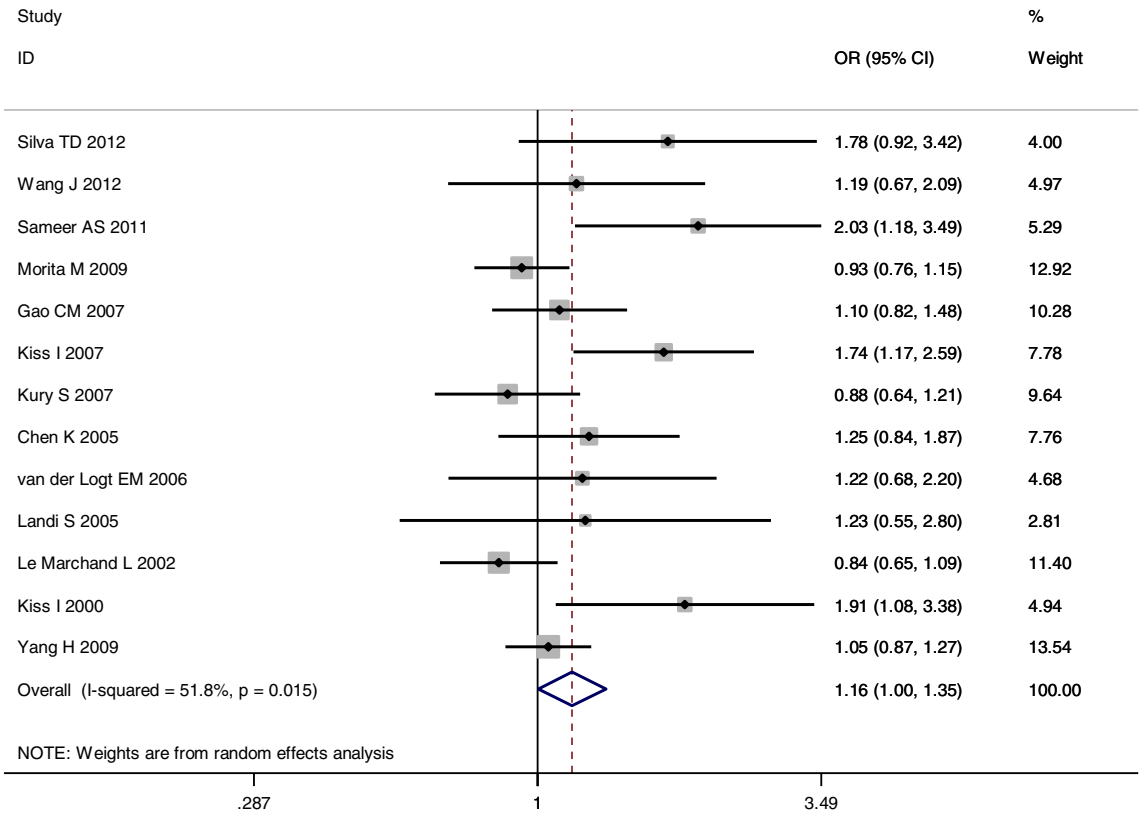

Fig. 2 Forest plot showing significant association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk under the dominant model

plots for all contrast models in the meta-analysis of the association between the CYP2E1 rs2031920 polymorphism and colorectal cancer risk revealed obvious evidence of asymmetry (Fig. 3). However, the shapes of funnel plots for all contrast models in the meta-analysis of the association between the CYP2E1 rs3813867 polymorphism and colorectal cancer risk also did not reveal evidence of asymmetry. Therefore, there was risk of publication bias in the meta-analysis of the

Table 2 Association between CYP2E1 rs3813867 polymorphism and colorectal cancer risk

Contrast models	Number of studies	OR (95 % CI)	P_{OR}	Model	I^2 (%)
Total studies					
c2 vs. c1	4	0.96 (0.80-1.16)	0.672	Fixed	0.0
c2c2 vs. c1c1	4	1.26 (0.43-3.67)	0.672	Fixed	0.0
c2c2/c2c1 vs. c1c1	4	0.95 (0.78-1.16)	0.614	Fixed	16.7
c2c2 vs. c1c1/c2c1	4	1.17 (0.41-3.36)	0.775	Fixed	0.0
Caucasians					
c2 vs. c1	3	0.87 (0.69-1.09)	0.216	Fixed	0.0
c2c2 vs. c1c1	3	1.49 (0.25-8.88)	0.659	Fixed	0.0
c2c2/c2c1 vs. c1c1	3	0.86 (0.68-1.08)	0.184	Fixed	0.0
c2c2 vs. c1c1/c2c1	3	1.51 (0.25-8.95)	0.653	Fixed	0.0
Asians					
c2 vs. c1	1	1.23 (0.87-1.74)	0.241	Fixed	–
c2c2 vs. c1c1	1	1.14 (0.29-4.40)	0.854	Fixed	–
c2c2/c2c1 vs. c1c1	1	1.34 (0.88-2.08)	0.167	Fixed	–
c2c2 vs. c1c1/c2c1	1	1.01 (0.26-3.85)	0.993	Fixed	–

OR odds ratio, *CI* confidence interval, P_{OR} *P* value of OR

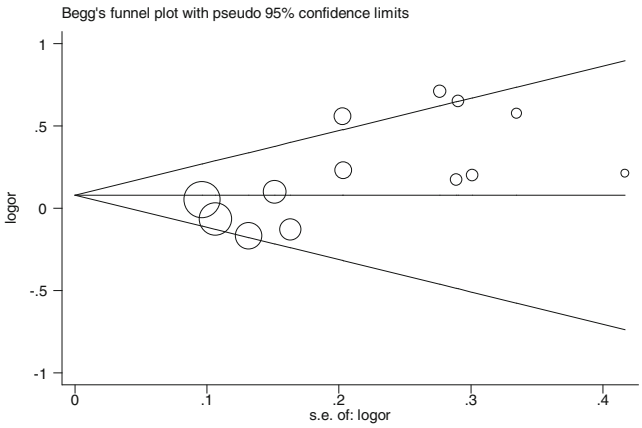

Fig. 3 Funnel plot showing obvious evidence of asymmetry in the meta-analysis of CYP2E1 rs2031920 polymorphism under the dominant model

association between the CYP2E1 rs2031920 polymorphism and colorectal cancer risk.

Discussion

In the present meta-analysis, we provided the most comprehensive assessment of the associations of CYP2E1 rs2031920 and rs3813867 polymorphisms with colorectal cancer risk. Seventeen studies from 15 publications with a total of 17,082 individuals were finally included into this meta-analysis [13–24, 28–30]. Meta-analysis of the 13 studies on CYP2E1 rs2031920 polymorphism showed that there was a significant association between CYP2E1 rs2031920 polymorphism and colorectal cancer risk under two genetic models (Table 1). Meta-analysis of those four case–control studies on CYP2E1 rs3813867 polymorphism showed that there was no significant association between CYP2E1 rs3813867 polymorphism and colorectal cancer risk under all contrast models (Table 2). Therefore, the findings from this meta-analysis suggest that CYP2E1 rs2031920 polymorphism is associated with colorectal cancer risk, but CYP2E1 rs3813867 polymorphism is not associated with colorectal cancer risk.

Currently, though smoking, obesity, red meat consumption, and excessive alcohol consumption have been identified as risk factors of colorectal cancer, the definite mechanism of colorectal cancer is still unclear [36, 37]. However, there is no doubt that genetic susceptibility also plays an important role in the development of colorectal cancer [38–40]. There are many genetic polymorphisms which have been identified as risk factors of colorectal cancer, and many of them are involved in the metabolism of carcinogens, such as the glutathione S-transferase superfamily [38, 41]. N-nitrosamines present in tobacco and red meat are well-recognized carcinogens involved in the development of colorectal cancer. As a member of the cytochrome P450 superfamily, CYP2E1 is involved in the metabolic activation of many carcinogens such as *N*-nitrosamines and aniline, and it has important roles in the host's susceptibility to colorectal cancer [40].

There are a number of polymorphisms found in the CYP2E1 gene which may have some impacts on susceptibility to colorectal cancer. The CYP2E1 rs2031920 (RsaI) and rs3813867 (PstI) polymorphisms in the 5′-flanking promoter region of the CYP2E1 gene are reported to affect the transcriptional activity of CYP2E1 gene. These two polymorphisms have some impacts on the activity of CYP2E1 enzyme and may further result in some inevitable influences on the host's ability to metabolizing the carcinogens. Therefore, there are some possibilities for the obvious associations between CYP2E1 rs2031920 and rs3813867 polymorphisms and colorectal cancer risk. Many studies were published to assess the associations of CYP2E1 rs2031920 and rs3813867 polymorphisms with colorectal cancer risk, but no consistent findings were reported. So we performed this systemic review and meta-analysis of eligible studies to comprehensively assess the associations between CYP2E1 rs2031920 and rs3813867 polymorphisms and colorectal cancer risk. At last, the findings from this meta-analysis suggest that CYP2E1 rs2031920 polymorphism is associated with colorectal cancer risk, but CYP2E1 rs3813867 polymorphism is not associated with colorectal cancer risk.

There are three limitations when interpreting the findings from the meta-analysis. Firstly, there were only four studies with 2,312 cases and 3,002 controls on the association between CYP2E1 rs3813867 polymorphism and colorectal cancer risk. The limited number of included studies on this association may increase the risk of bias in the meta-analysis. To get a more precise estimation on the association between CYP2E1 rs3813867 polymorphism and colorectal cancer risk, more studies with large number of participants are needed. Secondly, this present meta-analysis was based on unadjusted estimates. There is no doubt that the real estimation between CYP2E1 rs3813867 polymorphism and colorectal cancer risk could be biased by the confounding factors. To obtain a more precise estimation on the associations between CYP2E1 rs2031920 and rs3813867 polymorphisms and colorectal cancer risk, we need carry out more studies with the consideration of confounding factors, such as age, tobacco smoking, and other environment factors. Finally, the shapes of funnel plots for all contrast models in the meta-analysis of the association between the CYP2E1 rs2031920 polymorphism and colorectal cancer risk revealed obvious evidence of asymmetry (Fig. 3). As was shown in Fig. 3, the studies with large sample size tend to show negative findings on the association between the CYP2E1 rs2031920 polymorphism and colorectal cancer risk, while the studies with relative small sample size tend to show obvious findings on the association above. Therefore, to get a more precise estimation on the association

between CYP2E1 rs2031920 polymorphism and colorectal cancer risk, more well-designed studies with large sample size are needed to provide a more precise evaluation on the association above.

In conclusion, the findings from this meta-analysis suggest that CYP2E1 rs2031920 polymorphism is associated with colorectal cancer risk, but CYP2E1 rs3813867 polymorphism is not associated with colorectal cancer risk. In addition, more well-designed studies with and large sample size are needed to provide a more precise evaluation on the associations above.

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Conflicts of interest None

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