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BRIEF ARTICLE

CYP2E1 Pst I /Rsa I polymorphism and colorectal cancer risk: A meta-analysis

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Abstract

AIM: To clarify the association between *CYP2E1 Pst I /Rsa I* polymorphism and susceptibility to colorectal cancer.

METHODS: A meta-analysis based on 10 eligible case-control studies involving 4979 cases and 6012 controls was carried out to summarize the data on the association between *CYP2E1 Rsa I /Pst I* polymorphism and colorectal cancer risk.

RESULTS: In comparison of the homozygote *c2c2* and *c2* carriers (*c1c2* + *c2c2*) and the homozygous wild-type genotype (*c1c1*), no association was found between *CYP2E1 Rsa I /Pst I* polymorphism and colorectal cancer risk [odds ratio (OR) = 1.24 (95% CI: 0.93-1.66) for *c2c2*; OR = 1.02 (95% CI: 0.88-1.19) for *c2* carriers]. In stratified analysis, Caucasians with *c2c2* homozygote appeared to have an increased risk of colorectal cancer (OR = 2.67, 95% CI: 1.03-6.89, *P* = 0.043), no significant associations were found in other groups.

CONCLUSION: *c2c2* homozygote of *CYP2E1 Pst I /Rsa I* polymorphism may be associated with the increased risk of colorectal cancer in Caucasians, which needs further investigations.

Key words: Cytochrome P450 2E1; *Pst I /Rsa I* polymorphism; Colorectal cancer; Cancer susceptibility; Meta-analysis

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INTRODUCTION

Colorectal cancer is one of the most common cancers in developed countries and getting more and more attentions in developing countries for its morbidity and mortality. The definite mechanism of its development is still unknown, but both environmental factors and genetic susceptibility are believed to contribute to the onset of colorectal cancer[1,2].

Cytochrome P450 2E1 (CYP2E1), a member of the cytochrome P-450 superfamily, is a naturally ethanol-inducible enzyme and primarily responsible for the metabolic activation of many low molecular weight carcinogens[3,4], including certain nitrosamines believed to participate in the carcinogenesis of digestive tract[5]. Based on the biological significance of CYP2E1, a hypothesis has been proposed that *CYP2E1* polymorphisms may

be associated with cancer susceptibility[6]. Of the many known genetic polymorphisms in the *CYP2E1* gene, two point mutations in the 5'-flanking region (*Pst I*, *Rsa I*), which are in close linkage disequilibrium, have drawn much interest as it is known to alter the transcriptional activity of the gene[7]. Three genotypes consisting of wild-type allele (*c1*) and variant-type allele (*c2*) of *Pst I* / *Rsa I* polymorphism are defined as homozygous wild-type genotype (*c1c1*), heterozygote (*c1c2*) and rare homozygote (*c2c2*), respectively[8].

Recently, meta-analyses showed that *c2* allele carriers had a significantly lower risk of lung cancer in the Asian population, but a higher risk of gastric cancer. However, the conclusion regarding colorectal cancer remains to be established. Though several studies focusing on *Pst I* / *Rsa I* polymorphism and susceptibility to colorectal cancer have been conducted, the results are inconsistent due to the small sample size of individual study or other factors such as race, diet and tumor location[9-18]. For better understanding this relationship, a meta-analysis was performed.

MATERIALS AND METHODS

Study identification and selection

Inclusion criteria was defined as follows: (1) articles evaluating the association between *CYP2E1 Pst I* /*Rsa I* polymorphism and colorectal cancer risk; (2) studies designed as case-control; (3) sufficient data available to estimate an odds ratio (OR) with its 95% CI.

A literature search of Medline and Embase (updated to January 1, 2010) was conducted using the following terms: 'cytochrome p450 2E1/ⅡE1' or 'CYP2E1/ⅡE1', 'colorectal' and 'cancer' or 'adencarcinoma', without restriction on language. The retrieved literatures were then read in their entirety to assess their appropriateness for the inclusion in this meta-analysis by the two authors (Zhou GW, Hu J) independently. The reference lists of reviews and retrieved articles were searched simultaneously to find additional eligible studies. If more than one article was published by the same author using the same case series, we selected the study with the largest size of samples. If there was an disagreement, it was resolved through discussion between the two authors.

Data extraction

The following variables were extracted from each study if available: first author's surname, publication year, country, ethnicity, source of controls (hospital-based or population-based), matching criteria, number of cases and controls, and number of cases and controls in different *Pst I* / *Rsa I* genotypes.

Statistical analysis

The strength of association between *CYP2E1 Pst I* /*Rsa I* polymorphism and colorectal cancer risk was assessed by odds ratio (OR) with the corresponding 95% CI. The pooled OR was calculated by a fixed-effects model (the Mantel-Haenszel method)[19] or a random-effects model (the DerSimonian and Laird method)[20] according to the heterogeneity. Heterogeneity among studies was checked by the Q test[21] and $P < 0.10$ was considered statistically significant. The ORs of colorectal cancer associated with *c2* allele carriers (*c1c2* + *c2c2*) and homozygous *c2* genotype (*c2c2*) for the *CYP2E1 Pst I* /*Rsa I* polymorphism were estimated using the homozygous wild-type (*c1c1*) as the reference group. Influence analysis was performed by omitting an individual study each time to find potential outliers to the pooled OR[22]; sensitivity analysis was also performed, if necessary, by excluding the Hardy-Weinberg equilibrium (HWE)-violating studies to check the robustness of the result. Departure from HWE was detected in the control populations, but a deviation from HWE was allowed in mixed control populations. Subgroup analyses for different ethnicities (Asian, Caucasian and mixed population) and cancer locations (colon cancer, rectum cancer) were conducted. The possible publication bias was examined visually in a funnel plot of log[OR] against its standard error (SE), and the degree of asymmetry was tested by Egger's test ($P < 0.05$ was considered a significant publication bias)[23]. Meta-analysis was performed using the STATA version 10.0 software.

RESULTS

Study characteristics

A total of 13 publications met the inclusion criteria. Of these studies, two studies[24,25] were excluded as another two included studies[14,16] were based on the same population with a larger sample size. With 14 more cases but less information on the relationship studied in this paper, Chen's study[26] published in 2005 overlapped with Yu's work[11], and it was excluded after discussion. As a result, a total of 10 publications[9-18] containing 4979 cases and 6012 controls were included into this meta-analysis. Table 1 lists the main characteristics of these studies. Of these publications, only one was not published in English but in Chinese[11]. The sample sizes ranged from 419 to 2144. All of the cases were histologically confirmed as colorectal cancer. Controls were mainly healthy populations, and matched with age, sex, or cancer-free. There were three groups of Asians, six groups of Caucasians and one group of mixed populations. Four studies[10,11,16,18] provided information on *Pst I* /*Rsa I* polymorphism status associated with tumor locations classified as colon cancer and rectum cancer. Four studies[10,15,16,18] investigated the significance of *Pst I* /*Rsa I* polymorphism interacting with environmental factors with regard to susceptibility to colorectal cancer. Genotype distributions in the controls of all studies were in agreement with HWE except for one study with mixed control populations[10], without conducting sensitivity analysis by excluding the HWE-violating studies.

Meta-analysis results

Table 2 lists the main results of this meta-analysis. When the homozygote *c2c2* and *c2* carriers (*c2c2* + *c1c2*) were compared with the homozygous wild-type genotype (*c1c1*), the pooled ORs for all the 10 studies were 1.24 (95% CI:

Table 1 Main characteristics of studies included in this meta-analysis

Author, yr	Ethnicity (country)	Source of controls	Matching criteria	Sample size (case/control)	Genotype (case/controls)			HWE
					c1c1	*c2c2*	*c1c2 + c2c2*	
Butler *et al*[9], 2001	Caucasian (Australian)	Population-based	Age, sex	219/200	147/194	NA/NA	2/6	NA
Le Marchand *et al*[10], 2002	Mixed (Japanese, Caucasian, Hawaiian)	Population-based	Age, sex, ethnicity	521/639	384/449	21/26	137/190	No[1]
Yu *et al*[11], 2004	Asian (Chinese)	Population-based	Cancer-free	126/343	69/209	3/8	57/129	Yes
Landi *et al*[12], 2005	Caucasian (Spanish)	Hospital-based	Cancer-free	377/326	323/283	1/1	18/16	Yes
van der Logt *et al*[13], 2006	Caucasian (Netherlander)	Population-based	Age > 18-yr, without (family) history of CRC	371/415	333/389	1/2	24/23	Yes
Kiss *et al*[14], 2007	Caucasian (Hungarian)	Both	Age, sex, red meat intake, smoking	500/500	428/456	7/2	72/44	Yes
Küry *et al*[15], 2007	Caucasian (French)	Population-based	Age, sex	1023/1121	940/1027	6/1	73/91	Yes
Gao *et al*[16], 2007	Asian (Chinese)	Population-based	Age, sex, ethnicity	315/439	185/266	22/13	128/167	Yes
Cotterchio *et al*[17], 2008	Caucasian (Canadian)	Population-based	Age, sex	842/1251	784/1162	0/0	48/85	Yes
Morita *et al*[18], 2009	Asian (Japanese)	Population-based	Sex, smoking, red meat intake, residence area	685/778	412/455	36/44	273/323	Yes

[1]The deviation from HWE was allowed in mixed control populations. HWE: Hardy-Weinberg equilibrium; NA: Not available.

Table 2 Results of meta-analysis for *CYP2E1 Pst I /Rsa I* polymorphism and colorectal cancer risk

Analysis	Number of cases/controls	*c1c2 + c2c2 vs c1c1*		*c2c2 vs c1c1*	
		OR (95% CI)	*P*/P_h	OR (95% CI)	*P*/P_h
Overall	4979/6012	1.02 (0.88, 1.19)	0.780/0.094	1.24 (0.93, 1.66)	0.148/0.148
Subgroup analysis for ethnicity					
Asian	1126/1560	1.03 (0.88, 1.21)	0.707/0.274	1.35 (0.66, 2.75)	0.414/0.072
Caucasian	3332/3813	1.05 (0.78, 1.41)	0.747/0.066	2.67 (1.03, 6.89)	0.043/0.389
Mixed	521/639	0.84 (0.65, 1.09)	0.196/NA	0.94 (0.52, 1.71)	0.850/NA
Subgroup analysis for tumor location					
Colon cancer	907/2188	1.09 (0.83, 1.43)	0.522/0.082	1.22 (0.85, 1.77)	0.279/0.809
Rectum cancer	739/2188	0.89 (0.75, 1.06)	0.206/0.241	0.97 (0.38, 2.43)	0.941/0.014

P_h: *P* values for heterogeneity from *Q* test.

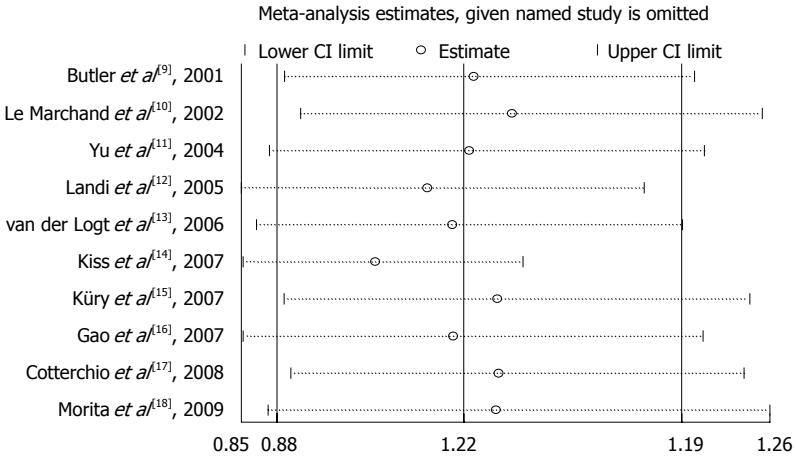

Figure 1 Influence analysis for *c1c2 + c2c2 vs c1c1* in the overall meta-analysis. It shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate its 95% CI. Each hollow round indicates the pooled OR when the left study is omitted in this meta-analysis. The two ends of each broken line represent the 95% CI.

0.93-1.66, *P* = 0.148) and 1.02 (95% CI: 0.88-1.19, *P* = 0.780), respectively. In the subgroup analysis of ethnicity, Caucasians with c2c2 homozygote appeared to have an increased risk of colorectal cancer (OR = 2.67, 95% CI: 1.03-6.89, *P* = 0.043), while no significant association was found among Asians and mixed populations. In the subgroup analysis of cancer locations, no significant associations were discovered in both colon cancer and rectum cancer.

Sensitivity analysis

Influence analysis was performed to assess the effects of each individual study on the pooled OR in each analysis, by removing an individual study each time. The results

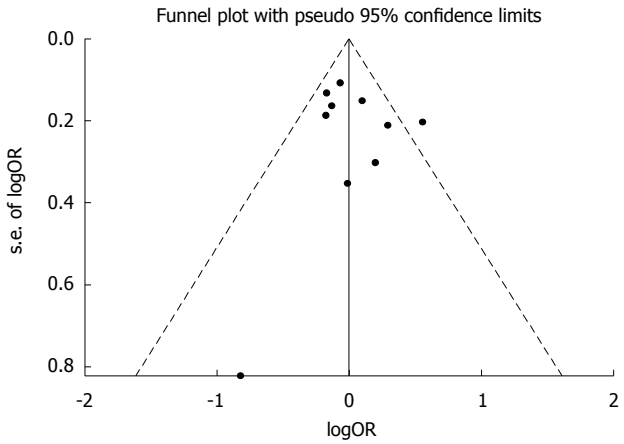

Figure 2 Funnel plot of *CYP2E1 Pst I /Rsa I* polymorphism and colorectal cancer risk for publication bias.

suggested that no individual study significantly affected the pooled ORs. Figure 1 shows the result of influence analysis for *c1c2 + c2c2 vs c1c1*.

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plot did not indicate any evidence of obvious asymmetry (Figure 2) and no publication bias was found in the Egger's test $P = 0.647$).

DISCUSSION

The relationship between *CYP2E1 Pst I /Rsa I* polymorphism and colorectal cancer susceptibility has been studied in several researches[9-18], and the results are controversial. Kiss and his colleagues[14] reported that *c2* variant allele significantly increased the risk of colorectal cancer, while Gao *et al*[16] suggested that only *c2c2* homozygote was associated with colorectal cancer, and no significant association was found in other studies[10,13]. This is the first systematic study of the meta-analysis of this relationship.

Ten case-control studies were included in this meta-analysis, involving 4979 cases and 6012 controls. The results strongly suggested that there was no significant association between *CYP2E1 Pst I /Rsa I* polymorphism and colorectal cancer susceptibility. By sequentially removing individual studies during influence analysis, it was confirmed that all results were not materially altered by an individual study. In addition, no significant publication bias was found.

Analysis based on the ethnic subgroup showed that Caucasians with *c2c2* homozygote had an increased risk of colorectal cancer. This may be explained by various frequency distributions of *Pst I /Rsa I c2* allele[27] and different living habits and environment in different ethnicity. However, no study regarding African populations was done.

Sensitivity of colon and rectum tissue to carcinogens is inconsistent. In contrast to studies involving rectal cancer, animal studies suggested that nitrosamines may have no correlation with the development of colon cancer[28]. Based on this phenomenon, it is proposed that differences may exist between colon and rectal cancer susceptibility with respect to *Pst I /Rsa I* polymorphism. Morita *et al*[18] found that *c2* allele may significantly reduce the risk of rectal cancer, while in a similar study, Gao's results[16] were completely the opposite. On the other hand, no association was revealed between *c2* allele and colon cancer in these two studies. But Yu *et al*[11] suggested that *c2* allele may increase the susceptibility to colon cancer. In this meta-analysis, a stratified analysis was performed by tumor location due to these conflicting results, and no association was revealed in neither the colon cancer group nor the rectal cancer group (Table 2). A very noteworthy point was that subjects investigated in this stratified analysis were mainly Asians, and studies on Caucasians are needed.

Although the result of this meta-analysis is suggestive, some limitations still exist. Firstly, heterogeneity among the studies, resulting from different defined controls or some other factors, may influence the results of this analysis. In some studies, the controls were selected randomly from a healthy population, and in other studies from hospital-based cancer-free patients. Furthermore, the matching criteria of the control group differed across studies in age and gender. The variant risks of colorectal cancer in these different populations may affect the results. Secondly, OR value was obtained without correction. More accurate OR should be corrected by age, gender and other factors. Thirdly, no African population was included in these ten studies, and the frequency distribution of *CYP2E1 Pst I /Rsa I* genotype in Africans was significantly different from that in Caucasians and Asians[27]. Therefore, the conclusion of this study is not applicable to the African population, and further investigations are required. Fourthly, the relationship between *CYP2E1* gene polymorphism and colorectal cancer risk was analyzed without consideration of gene-environment interactions. Although evidence supported that *c2* allele combined with smoking, drinking and consumption of red meat intake can significantly increase the susceptibility to colorectal cancer[10,15,16,18], this study failed to draw any concrete conclusions due to the different classification criteria of environmental factors in these studies. In addition, there has been no study on the association between *Pst I /Rsa I* polymorphism gene-gene interactions and colorectal cancer risk, and this should be further investigated.

COMMENTS

Background

Cytochrome P450 2E1 (CYP2E1) is a member of the cytochrome P-450 superfamily, and its gene polymorphisms are supposed to be associated with cancer susceptibility. Several studies focusing on *CYP2E1 Pst I /Rsa I* polymorphism and colorectal cancer susceptibility have been conducted.

Research frontiers

The relationship between *CYP2E1 Pst I /Rsa I* polymorphism and cancer susceptibility has been studied in different tumor types. Recently, meta-analyses showed that c2 allele carriers had a significantly lower risk of lung cancer in Asian population but a higher risk of gastric cancer. However, the relationship with colorectal cancer remains controversial and no meta-analysis has been conducted.

Innovations and breakthroughs

This is the first meta-analysis which systemically studied the relationship between *CYP2E1 Pst I /Rsa I* polymorphism and colorectal cancer susceptibility, and suggested that Caucasians with *c2c2* homozygote may have a higher risk of colorectal cancer.

Applications

This study provided a potential biomarker for identifying high-risk populations of colorectal cancer in Caucasians.

Peer review

The article is meritoriously and methodologically well written. The presentation is rigorous and the approach used is robust.

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