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RAPID COMMUNICATION

CYP2E1 Rsa I polymorphism impacts on risk of colorectal cancer association with smoking and alcohol drinking

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Abstract

AIM: To investigate associations between the *Rsa* I polymorphism of *CYP2E1* and risk of colorectal cancer.

METHODS: A case-control study was conducted with 315 colorectal cancer cases (105 colon, 210 rectal) and 439 population-based controls in Jiangsu Province of China. Genomic DNA samples were assayed for restriction fragment length polymorphisms in *CYP2E1* by PCR amplification followed by digestion with *Rsa* I. Information on smoking and alcohol drinking was collected using a questionnaire. Odds ratios (ORs) were estimated with an unconditional logistic model.

RESULTS: The proportional distribution of the *CYP2E1 Rsa* I c1/c1, c1/c2 and c2/c2 genotypes were 61.4%, 35.6% and 3.0% in controls, 60.6%, 33.7% and 5.8% in colon cancer cases, and 58.4%, 34.0% and 7.7% in rectal cancer cases, respectively. A significant difference was noted between controls and rectal cancer cases (P = 0.029), the c2/c2 genotype being associated with elevated OR (adjusted age, sex and status of the smoking and alcohol drinking) for rectal cancer (1.64, 95% CI, 1.12-2.41, *vs* c1 allele carriers), but not for colon cancer. In interaction analysis between the *CYP2E1 Rsa* I genotype and smoking and drinking habits, we found a significant cooperative action between the c2/c2 genotype and alcohol drinking in the sex-, age-adjusted ORs for both colon (4.74, 95% CI, 1.10-20.40) and rectal (5.75, 95% CI, 1.65-20.05) cancers. Among non-smokers, the *CYP2E1 Rsa* I c2/c2 genotype was also associated with elevated ORs in the two sites (1.95, 95% CI, 0.99-3.86 and 2.30, 95% CI, 1.32-3.99).

CONCLUSION: The results of the present study suggest that the *CYP2E1* c2/c2 genotype increases susceptibility to rectal cancer and the gene-environmental interactions between the *CYP2E1* polymorphism and smoking or alcohol drinking exist for colorectal neoplasia in general.

Key words: *CYP 2E1*; Gene polymorphism; Smoking; Alcohol drinking; Colorectal cancer

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INTRODUCTION

CYP2E1, a member of the cytochrome P450 superfamily, is involved in the metabolic activation of many low-molecular-weight compounds such as N-nitrosamines, aniline, vinyl chloride, urethane and alcohol[1]. N-nitrosamines present in tobacco and diet are well-recognized carcinogens involved in tumor development at various sites. Functional *CYP2E1* gene polymorphisms might therefore impact on susceptibility to cancer development.

A substitution polymorphism (G1259C) detected using the restriction enzymes *Pst* I or *Rsa* I has been associated

with decreased *CYP2E1* activity/inducibility[2-5]. The *Dra* I polymorphism is also associated with altered activity of *CYP2E1*, although *Dra* I is located in intron 6 and is not thought to affect gene transcription[6]. Activity of *CYP2E1* is also modulated by various physiological determinants, such as obesity[7], fasting[7] and liver dysfunction[8] and can be induced by ethanol[9]. In contrast, dietary isothiocyanates[10] and garlic[11,12], as well as some drugs, such as disulfiram[13] and chlormethiazole[14], inhibit its activity. A number of environmental factors may thus modify the cancer risk through altered *CYP2E1* enzyme activity.

Previous studies have shown inconsistent findings on *CYP2E1* polymorphism associations with cancer risk. Some studies demonstrated the common genotype or alleles to confer greater risk of oral[15], pharyngeal[15], esophageal[16,17] liver[18] and lung[19,20] cancers. On the other hand, increased risk of oral[21], nasopharyngeal[22], liver[23] and colorectal[24,25] cancers was observed with the rare genotype or allele carriers in other studies. Furthermore, some case-control studies failed to find a significant association between *CYP2E1* polymorphisms and risk of neoplasia of the oral cavity and pharynx[26], esophagus[27], stomach[28,29], lung[30-33], bladder[34] and colorectum[35]. The reasons for these inconsistent results are not clear, but one problem is a lack of sufficient investigation of gene-environmental interactions, including links with dietary and smoking habits. We hypothesized that environmental factors may alter the enzyme activity of *CYP2E1* and therefore modify cancer susceptibility due to *CYP2E1* polymorphisms. One earlier study in our laboratory showed that gene-environment interactions between the *CYP2E1* polymorphism and smoking have the potential to alter susceptibility to gastric cancer[36].

To investigate possible relations between *CYP2E1 Rsa* I polymorphisms and environmental factors (smoking and alcohol drinking) on the risk of colorectal cancers, we conducted a population-based case-control study in Jiangsu province, China.

MATERIALS AND METHODS

Subjects

We recruited colorectal cancer cases using data of Cancer Registries in Huian and Jintan Cities of Jiangsu Province of China, and also recruited cases who visited Jiangsu Province Cancer Hospital from these cities from August 2000 to September 2002. All were histopathologically diagnosed as having a primary colorectal cancer. Physicians at the hospital asked eligible cases to participate in our study, and doctors or nurses interviewed the subjects and collected blood samples from a peripheral vein after obtaining informed consent. Population-based controls were selected from healthy residents in eight villages or towns of Huian and Jintan Cities. Doctors of the public health center randomly selected one or two controls for each case, after matching for ethnicity, sex and age within 2 years using the records of residents at the local governmental office, and then asked eligible residents for their participation. Interviews and blood collection were performed as for the cancer cases. A few patients and residents refused to participate in our study, but the response rates were 97% for cases and 93% for controls. The ethics committee of Jiangsu Province Institute of Cancer Research approved this study.

Environmental factors

The items of our questionnaire covered smoking and drinking habits. Smokers were divided into never- and ever-smokers (current and former). Drinkers also were divided into two groups ($\geq$ 2 times/mo and < 2 times/mo) according to drinking frequency.

DNA extraction and genotyping of the CYP2E1

Whole blood was collected into EDTA-coated tubes and centrifuged for 15 min, and the buffy coat layer was isolated. Genomic DNA was extracted from 200 μL of buffy coat using a Qiagen QIAamp DNA Blood Mini Kit (QIAGEN Inc., Valencia, CA). The method for genotyping of the *CYP2E1* has been previously described[30]. In brief, PCR was used to amplify the transcription regulation region of *CYP2E1* that includes the *Rsa* I enzyme recognition site[3]. The primers were 5'-CCAGTCGAGTCTACATTGTCA and 5'-TTCATTCT GTCTTCTAACTGG. The PCR product was subjected to *Rsa* I restriction enzyme digestion and samples were then analyzed by electrophoresis in 5% polyacrylamide gels. There were three genotypes of *CYP2E1* resulting from digestion with the restriction enzyme *Rsa* I : the common homozygote c1/c1; the heterozygote c1/c2; and the rare homozygote c2/c2. Among 754 examined samples, PCR products could not be visualized for 2 cases and 6 controls.

Statistical analysis

Associations between the *Rsa* I polymorphism and colorectal cancer risk were estimated by OR, using the unconditional logistic regression model. We calculated adjusted ORs for age (continuous), sex, smoking and drinking habits. To investigate gene-environmental interactions, we also calculated (stratified analysis) ORs according to combinations of the *CYP2E1* genotypes and habits of the smoking and drinking, with *Rsa* I c1 allele carriers as the reference. The procedure LOGISTIC from the statistical package SAS was employed for the calculations. The probability of Hardy-Weinberg equilibrium was assessed by the χ^2 test.

RESULTS

Numbers of subjects were 190 male and 125 female with colorectal cancer, and 223 male and 216 female controls (Table 1). The proportion of females in controls was significant higher than in colorectal cases but the mean age did not differ between cases and controls. The proportional distributions of smokers and alcohol drinkers were significant higher in colorectal cancer cases than in controls.

The distributions of *CYP2E1 Rsa* I c1/c1, c1/c2 and c2/c2 genotypes were 61.4%, 35.6% and 3.0%, respectively, in controls, 59.1%, 33.9% and 7.0% in colorectal cases, 60.6%, 33.7% and 5.8% in colon cancer cases, and 58.4%, 34.0% and 7.7% in rectal cancer cases (Table 1). The proportional distribution significantly differed

Table 1 Background characteristics of colorectal cancer cases and their controls

	Controls *n* (%)	Colorectal cancer *n* (%)	Colon cancer *n* (%)	Rectal cancer *n* (%)
All of the subjects	439 (100.0)	315 (100.0)	105 (100.0)	210 (100.0)
Gender				
Males	223 (50.8)	190 (60.3)	65 (61.9)	125 (59.5)
Females	216 (49.2)	125 (39.7)	40 (38.1)	85 (40.5)
χ^2_{MH} (*P*)		6.70 (0.010)	4.19 (0.041)	4.34 (0.037)
Age (yr)				
< 40	42 (9.6)	44 (14.0)	14 (13.3)	30 (14.3)
40-49	75 (17.1)	54 (17.1)	15 (14.3)	39 (18.6)
50-59	150 (34.2)	88 (27.9)	30 (28.6)	58 (27.6)
60-69	131 (29.8)	85 (29.0)	26 (24.8)	59 (28.1)
> 70	41 (9.3)	44 (14.0)	20 (19.1)	24 (11.4)
χ^2_{MH} (*P*)		9.37 (0.053)	10.23 (0.037)	5.69 (0.224)
Mean age ± SD	55.7 ± 11.0	55.3 ± 12.7	56.4 ± 13.4	54.7 ± 12.3
P (*t* test)		0.6172	0.6325	0.3159
Smoking status				
Nonsmoker	284 (64.7)	176 (55.9)	61 (58.1)	115 (54.8)
Courrent and former	155 (35.3)	139 (44.1)	44 (41.9)	95 (45.2)
χ^2_{MH} (*P*)		5.99 (0.014)	1.59 (0.208)	5.91 (0.015)
Alcohol status				
Nondrinker	327 (74.5)	176 (55.9)	65 (61.9)	120 (57.1)
Current and former	112 (25.5)	139 (44.1)	50 (38.1)	90 (42.9)
χ^2_{MH} (*P*)		28.58 (0.000)	14.19 (0.000)	19.90 (0.000)
CYP 2E1 genotypes[1]				
c1/c1	266 (61.4)	185 (59.1)	63 (60.6)	122 (58.4)
c1/c2	154 (35.6)	106 (33.9)	35 (33.7)	71 (34.0)
c2/c2	13 (3.0)	22 (7.0)	6 (5.8)	16 (7.7)
χ^2_{MH} (*P*)		6.58 (0.037)	1.91 (0.385)	7.07 (0.029)

[1]Six controls and two cases were excluded because of unknown CYP2E1 genotype.

Table 2 CYP2E1 genotypes and risk of colorectal cancer

	Genotype	Cases (*n*)	Controls (*n*)	OR[1] (95% CI)	OR[2] (95% CI)
Colorectal cancer					
	c1/c1	185	266	1.00	1.00
	c1/c2	106	154	0.99 (0.72-1.35)	0.99 (0.72-1.35)
	c2/c2	22	13	1.54 (1.07-2.19)	1.55 (1.08-2.22)
Colon Cancer					
	c1/c1	63	266	1.00	1.00
	c1/c2	35	154	0.96 (0.61-1.52)	0.95 (0.60-1.51)
	c2/c2	6	13	1.36 (0.82-2.25)	1.40 (0.84-2.33)
Rectal cancer					
	c1/c1	122	266	1.00	1.00
	c1/c2	71	154	1.01 (0.71-1.44)	1.01 (0.71-1.44)
	c2/c2	16	13	1.61 (1.09-2.36)	1.64 (1.12-2.41)

[1]ORs were adjusted for age and sex in a logistic regression model. [2]ORs were adjusted for age, sex and status of smoking and alcohol drinking.

between control and colorectal (χ^2_{MH} = 6.58, P = 0.037) or rectal (χ^2_{MH} = 7.07, P = 0.029) cancer cases. The allelic distribution of the *Rsa* I polymorphism for controls was in Hardy-Weinberg equilibrium (χ^2 = 2.77, P > 0.05). It shows that the controls from general population are representative. The *CYP2E1 Rsa* I c2/c2 genotype was associated with significantly increased ORs for colorectal cancer (sex-, age- and habits of smoking and alcohol drinking adjusted OR = 1.55, 95% CI, 1.08-2.22) and rectal cancer (adjusted OR = 1.64, 95% CI, 1.12-2.41) (Table 2).

Table 3 shows the results of the multivariable analysis of smoking, alcohol drinking and *CYP2E1 Rsa* I c2/c2 genotypes and risk of colorectal cancer. The smoking habit was not associated with any increased OR for colon or rectal cancer, but alcohol drinking was linked with elevated ORs for colon (1.68, 95% CI, 0.97-2.89) and rectal (2.08,

Table 3 Logistic regression analysis on smoking, alcohol drinking and CYP2E1 c2/c2 genotypes and risk of colorectal cancer

	Colorectal cancer OR[1] (95% CI)	Colon cancer OR[1] (95% CI)	Rectal cancer OR[1] (95% CI)
Smoking	1.01 (0.69-1.47)	0.84 (0.49-1.44)	1.08 (0.70-1.67)
Alcohol drinking	1.91 (1.31-2.80)	1.68 (0.97-2.89)	2.08 (1.36-3.19)
CYP2E1 c2/c2	1.50 (1.05-2.15)	1.34 (0.81-2.23)	1.58 (1.08-2.32)

[1]Logistic regression model included age (continuous), sex, smoking (nonsmoker, current + former smoker), alcohol drinking (nondrinker, current + former drinker) and *CYP2E1* genotype (c1/c1 + c1/c2, c2/c2).

Table 4 Interaction between the *CYP2E1* genotype and the status of smoking and alcohol drinking, and the odds ratios (ORs) for colorectal cancer

	CYP2E1 genotype	Controls	Colorectal cancer		Colon cancer		Rectal cancer	
		n	*n*	OR[1] (95% CI)	*n*	OR[1] (95% CI)	*n*	OR[1] (95% CI)
Smoker								
No	c1/c1 + c1/c2	275	162	1.00	57	1.00	105	1.00
No	c2/c2	5	14	2.20 (1.31-3.70)	4	1.95 (0.99-3.86)	10	2.30 (1.32-3.99)
Yes	c1/c1 + c1/c2	145	129	1.34 (0.93-1.92)	41	1.11 (0.66-1.88)	88	1.48 (0.98-2.25)
Yes	c2/c2	8	8	1.41 (0.50-3.96)	2	0.91 (0.18-4.57)	6	1.75 (0.57-5.42)
Drinker								
No	c1/c1 + c1/c2	313	174	1.00	62	1.00	112	1.00
No	c2/c2	9	10	1.41 (0.89-2.24)	2	1.09 (0.50-2.38)	8	1.55 (0.95-2.53)
Yes	c1/c1 + c1/c2	107	117	1.86 (1.28-2.68)	36	1.50 (0.89-2.55)	81	2.07 (1.37-3.14)
Yes	c2/c2	4	12	5.42 (1.65-17.40)	4	4.74 (1.10-20.40)	8	5.75 (1.65-20.05)

[1]ORs were adjusted for age and sex.

95% CI, 1.36-3.19) cancers. The *CYP2E1 Rsa* I c2/c2 genotype significantly increased the OR for rectal cancer (1.58, 95% CI, 1.08-2.32).

Table 4 shows the results of interaction analysis of the *CYP2E1 Rsa* I polymorphism with smoking and alcohol drinking habits. Among nonsmokers, *Rsa* I c2/c2 was associated with elevated ORs for colon (1.95, 95% CI, 0.99-3.86) and rectal (2.30, 95% CI, 1.32-3.99) cancers. Among smokers with the *Rsa* I c2/c2 genotype, no increase in the OR for colon cancer was observed, and the slightly increased OR for rectal cancer also was not statistically significant.

Among carriers of the *Rsa* I c1 allele, alcohol drinking was significantly associated with an elevated OR for rectal cancer (2.07, 95% CI, 1.37-3.14). As compared with non-drinkers with the *Rsa* I c1 allele, drinkers with RsaI c2/c2 genotype had significant increased ORs for colon cancer (4.74, 95% CI, 1.10-20.40) and rectal cancer (5.75, 95% CI, 1.65-20.05).

DISCUSSION

The present study revealed a significant association between the *CYP2E1 Rsa* I c2/c2 genotype and risk of rectal cancer, as well as a notable interaction with smoking or alcohol drinking as environmental factors.

Previous investigations showed inconsistent findings. As regards colorectal cancer, Kiss *et al*[24] found the *CYP2E1* c2 allele to be significantly associated with colorectal cancer (OR: 1.91, 95% CI, 1.05-3.52) in a Hungarian population. Yu *et al*[25] found the *CYP2E1 Pst* I c2 allele to be a susceptibility factor for colorectal cancer, especially for colon cancer, and there is an apparent gene-environment interaction with salted food in a Chinese population. In a study from the Netherlands, although calculation of crude ORs revealed an increased risk for colorectal cancer associated with the variant *CYP2E1* genotype (OR: 2.2, 95% CI: 1.3-3.8), this was no longer evident after adjustment for age and gender[35].

The reason for the inconsistent findings for the *CYP2E1* polymorphism is unknown but clearly variation with ethnicity and gender could contribute to differences in influence on neoplasia. The rare *Rsa* I allele is considered to result in increased transcriptional activation of the *CYP2E1* gene[2,3], with elevated expression levels of *CYP2E1* mRNA and protein[3,37]. However, several studies demonstrated common genotype carriers to have the higher *CYP2E1* enzyme activity[4,5]. Differences in *CYP2E1* activity by ethnicity and gender have also been reported, females showing 25% lower activity than males[7,38]. Japanese appear to demonstrate 30%-40% lower activity of *CYP2E1* than Caucasians, even after taking account differences in body size[39].

In the present study, we found a gene-environmental interaction between the *CYP2E1* polymorphism and smoking. Thus, increased risk of colon or rectal cancer was associated with the *CYP2E1 Rsa* I c2/c2 genotype among smokers, but not non-smokers. A similar phenomenon was also found in another study[40]. It has been shown that among non-smokers, urinary styrene metabolites are significantly decreased in subjects with c1/c1 alleles of *CYP2E1* as compared with those with the c1/c2 genotype, whereas no significant differences in urinary metabolites were noted among smokers[41].

We found alcohol drinking to significantly increase risk of cancer development, especially in the rectum, and there was a significant interaction with the *CYP2E1 Rsa* I c2/c2 genotype in both the colon and rectum. Our results are consistent with previous investigations indicating that alcohol consumption is associated with an increased risk for cancers of many organs, such as oral cavity, pharynx, larynx, esophagus, breast, liver, ovary; colon, rectum, stomach and pancreas[42]. Chronic ethanol consumption may promote carcinogenesis by (1) production of acetaldehyde, which is a weak mutagen and carcinogen; (2) induction of *CYP2E1* and associated oxidative stress and conversion of pro-carcinogens to carcinogens; (3) depletion of S-adenosylmethionine and, consequently, induction of global DNA hypomethylation; (4) induction of increased production of inhibitory guanine nucleotide regulatory proteins and components of extracellular signal-regulated kinase-mitogen-activated protein kinase signaling; (5) accumulation of iron and associated oxidative stress; (6) inactivation of the tumor suppressor gene BRCA1 and increased estrogen responsiveness (primarily in breast); and (7) impairment of retinoic acid metabolism[43]. Alcohol also can affect the pharmacokinetics of drugs by altering gastric emptying

or liver metabolism by inducing *CYP2E1*[43]. *CYP2E1* is the key microsomal enzyme that metabolizes alcohol in the non-alcohol dehydrogenase pathway. Choi *et al*[44] also discovered that "ever"-drinking women with the *CYP2E1* c2 allele containing genotypes had an increased risk of developing breast cancer compared to non-drinkers with the *CYP2E1* c1/c1 genotype in the Korean population.

Finally, some limitations require discussion. Because the frequency of the *CYP2E1 Rsa* I c2/c2 genotype is lower in subjects, only relatively small numbers were available for subgroup analyses, with consequent reduction in the magnitude of statistical power and increase in the potential for random error. Another possible problem is selection bias for controls, these being recruited by local health staff, albeit from the general population with a high response rate. The proportional distribution of female in controls was higher than that in colorectal cases, which may have caused a lower prevalence of smokers and alcohol drinkers in the present controls, though we adjusted for sex and age in all statistical analyses.

In summary, the present study revealed a link between the *CYP2E1 Rsa* I polymorphism and increased risk of rectal cancer, with a significant interaction between the *Rsa* I polymorphism and smoking and alcohol drinking habits regarding development of both colon and rectal cancers. The data provide support for our hypothesis that cancer susceptibility with the *CYP2E1* polymorphisms may be altered by background environmental factors.

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COMMENTS

Background

Colorectal cancer is the fifth most commonly occurring cancer in China. Cytochrome P450 (CYP) enzymes in epithelial cells lining the alimentary tract play an important role in both the elimination and activation of (pro-) carcinogens. To estimate the role of *CYP2E1* in colorectal cancer development, we conducted a population based case-control study of colorectal cancer in Jiangsu Province of China.

Research frontiers

A lot of carcinogens from environment must be metabolized for their elimination and activation. Genetic polymorphisms of metabolizing enzymes may affect the metabolism of carcinogens and the risk of cancer formation in humans. Susceptibility to cancer is generally thought to be the sum of complex interactions between environmental and genetic factors. Thereby, how interaction between environmental and genetic factors is a hotspot of cancer epidemiological study. We Regarding to the hotspot, we studied interactions between *CYP2E1* and habits of smoking and alcohol drinking in colorectal cancer development.

Innovations and breakthroughs

In present study, we demonstrate a correlation between *CYP2E1 Rsa* I polymorphism in c2/c2 genotype is associated with rectal and not colon cancer. This increased risk associated with this polymorphism was negated in smokers. Furthermore, a significant cooperative action was seen between the c2/c2 genotype and alcohol consumption in both colon and rectal cancers.

Applications

This research exposes a screenable genetic risk factor and the effects of gene-environment interactions in identifying individuals at risk for colon or rectal cancer. These results have some theoretical and application values in the etiology and prevention of colorectal cancer.

Terminology

CYP2E1: cytochrome P450 2E1. *CYP2E1 Rsa* I polymorphism: *Rsa* I enzyme recognized polymorphism in *CYP2E1* gene.

Peer review

Gao *et al* demonstrate a correlation between *CYP2E1 Rsa* I polymorphisms in c2/c2 genotypes are associated with rectal and not colon cancer. This increased risk associated with this polymorphism was negated in smokers. Furthermore, a significant cooperative action was seen between the c2/c2 genotype and alcohol consumption in both colon and rectal cancers. The experiments contain appropriate controls and weightings of the data taking into consideration age, sex, smoking status and alcohol consumption. This research exposes a screenable genetic risk factor and the effects of gene-environment interactions in identifying patients at risk for colon or rectal cancer.

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