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Relationship between metabolic enzyme polymorphism and colorectal cancer

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Abstract

AIM: To clarify the influence of genetic polymorphisms on colorectal cancer.

METHODS: The results of 42 related studies from 1990 to 2001 were analyzed by meta-analysis. Mantel-Haenzel fixed-effect model or Dersimonian-Laird random-effect model and ReviewManager 4.1 statistical program were applied in processing the data.

RESULTS: Meta analysis of these studies showed that GSTT1 deletion (pooled *OR* = 1.42), N-acetyltransferase 2 (NAT2)-rapid acetylator phenotype and genotye (pooled *OR* = 1.08) and NAT2-rapid acetylator phenotype (pooled *OR* = 1.15) had a significantly increased risk for colorectal cancer ($P<0.05$), other genotypes like GSTM1 deletion, GSTP1 1le105Val, NAT1*10, NAT2-rapid acetylator genotype CYP1A1 L1e462Val, CYP1A1 MspI*C, MTHFR C677T and MTR A2759G had no significant relationship with colorectal cancer ($P>0.05$).

CONCLUSION: Risks for colorectal cancer are significantly associated with the genetic polymorphisms of GSTT1 deletion, NAT2-rapid acetylator phenotype and genotye and NAT2-rapid acetylator phenotype.

Key words: Colorectal cancer; Glutathione S-transferase T1; N-acetyltransferase; Polymorphism

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers, and several factors affect its progress. Some risk factors for colorectal cancer can be ascribed to the environmental factors associated with fatty food and dietary fibers[1]. Exterior substances must be activated or inactivated by metabolic enzymes in the body, and metabolic pathways may be modified by polymorphisms in relevant genes. There is some evidence that the general host metabolic status can provide a milieu that enhances or reduces cancer progression[2]. Most metabolic enzymes have several genetic polymorphisms, which can affect their activities[3]. Different alleles of metabolic enzymes contribute to different colorectal cancer susceptibility[4]. Marugame *et al*[5] have suggested that the genotype might be involved in all stages of colorectal carcinogenesis. It is now widely accepted that the development of colorectal cancer is determined by a complex interaction of both genetic polymorphisms and environmental factors[6]. Recently, many studies have focused on the relationship between the genetic polymorphisms and risks of colorectal cancer. However, the overall results of such studies are inconsistent[7-15]. Understanding the role of genetic polymorphisms and host susceptibility would help us with screening, treatment, surveillance, and prevention of CRC. In order to provide overall possible information on association between genetic polymorphisms of metabolic enzymes and risks of colorectal cancer, we performed this meta-analysis of 42 published studies from January 1990 to December 2001.

MATERIALS AND METHODS

Selection of studies

The published literatures of case-control or cohort studies that have information on colorectal cancer and genetic polymorphisms of metabolic enzymes were collected by retrieving MEDLINE, CBmdisc and Chinese Medical Current Contents (CMCC), American Association for Cancer Research (AACRC), and retrospective searching over the period of January 1990 to December 2001. The citations in identified articles and in review articles were also examined. The criteria for acceptance of the literature were as follows. (1) Independent case-control or cohort studies published in journals from January 1990 to December 2001 were included. (2) Each study should have the synthetic statistical index, namely odds ratio (*OR*) or risk ratio (*RR*). (3) Each study should have the similar research goal with the identical study method. (4) The main factors of these studies should be related to the genetic polymorphisms of metabolic enzymes and colorectal cancer. (5) The latest ones were chosen among those with the same data available in more than one studies or the data overlapping with those in other studies. (6) Duplicated, poor quality reports or those with little information were discarded. The data were input doubly into computer to be checked, and the database was then established. Therefore, 42 articles were collected by screening in this way.

Grouping

All literatures were divided into two groups by the integrity of information in the literature. Group A included all literatures, and group B contained those literatures that could acquire all details about the number of exposed and non-exposed persons in both case and control groups. So the literatures in group A covered those in group B.

Statistical analysis

To take into account the possibility of heterogeneity across the studies, a statistical test for heterogeneity (test for equal variance) by different genetic polymorphisms across the studies was performed. In group A, whether Mantel-Haenzel fixed-effect model or Dersimonian-Laird random-effect model was used to calculate the pooled OR based on the result of test for heterogeneity. If there was an equal variance (P>0.05) in the result of the test, then the model of Mantel-Haenzel fixed-effects was chosen; otherwise, the Dersimonian-Laird random-effect model should be selected. The ReviewManager 4.1 statistical program was employed in processing the literatures in group B.

The two steps in the meta-analysis were as follows:

(1) Test for heterogeneity (test for equal variance)

$$Q=\sum_{i=1}^{m} W_{MH_i}(ln(OR_i)-ln(OR_{MH}))^2$$

$$OR_{MH}=\frac{\sum_{i=1}^{m} W_{MH_i} OR_i}{\sum_{i=1}^{m} W_i}$$

$$W_{MH_i}=\frac{1}{Variances_i}$$

$$Variances_i=\left(\frac{ln(OR_i)-ln(OR_{iL})}{1.96}\right)^2$$

The statistics of Q was in accordance with the chi-square distribution (degree of freedom: m-1).

(2) Calculation of synthetic OR-value

The formula for the calculation of data in group A was Mantel -Haenzel fixed-effect model (M-H model)

The calculating process of ORMH was as following:

$$OR_L = OR_{MH} \times e^{-1.96\times\sqrt{VarOR_{MH}}}$$

$$OR_U = OR_{MH} \times e^{1.96\times\sqrt{VarOR_{MH}}}$$

$$VarOR_{MH} = \frac{1}{\sum_{i=1}^{m} W_{MH_i}}$$

Dersimonian-Laird random-effect model (D-L model).

$$D=\begin{cases} 0 & (\text{if } Q>m-1) \\ \dfrac{[Q-(m-1)]\sum_{i=1}^{m} W_{MH_i}}{\left(\sum_{i=1}^{m} W_{MH_i}\right)^2-\sum_{i=1}^{m} W^2{}_{MH_i}} & (\text{if } Q\le m-1) \end{cases}$$

$$W_i=\frac{1}{D+\frac{1}{W_{MH_i}}}, i=1,2,3,\ldots,m$$

$$\ln(OR_{DL})=\frac{\sum_{i=1}^{m} W_i \ln(OR_i)}{\sum_{i=1}^{m} W_i}$$

$$Variance_{DL} = \frac{1}{\sum_{i=1}^{m} W_i}$$

$$OR_{DLL} = OR_{MH} \times e^{-1.96\times\sqrt{Variance_{DL}}}$$

$$OR_{DLU} = OR_{MH} \times e^{1.96\times\sqrt{Variance_{DL}}}$$

Data of literatures in group B were input into the Review Manager 4.1 statistical program to be analyzed.

RESULTS

Four types of metabolic enzymes correlated with colorectal cancer are summarized in Table 1 by different genetic polymorphisms.

Table 1 References to colorectal cancer and polymorphisms of metabolic enzymes

References	Gene and polymorphism[1]	Grouping[2]	References	Gene and polymorphism[1]	Grouping[2]
Carcinogenesis. 1991; 12(1): 25-8	1	B	Pharmacogenetics. 1999; 9(2): 165-9	6	B
Carcinogenesis. 1993; 14(9): 1821-4 (abstract)	1	B	Cancer-Res 1995; 55(16): 3537-42	3	B
Carcinogenesis. 1995; 16(7): 1655-7 (abstract)	1,2		Am-J-Epi 1997;145 (abstract)	4	
Carcinogenesis. 1996; 17(4): 881-4	1,2	B	Cancer-Res. 1998; 58(15): 3307-11	3,5	B
Carcinogenesis. 1996; 17(9): 1855-9	1,2	B	Int-J-Cancer. 1990; 46(1): 22-30	4	B
Carcino-Terato-Muta 1996; 8(6): 326-332	1	B	Cancer-Res. 1991; 51(8): 2098-100	4	B
Can-Epi-Bio-Prev. 1998; 7(11): 1001-5	1,2	B	Can-Epi-Bio-Prev. 1994; 3(8): 675-82	4	
J-Toxicol-Sci. 1998; 23 Suppl 2140-2 (abstract)	1		Cancer. 1994; 74(12): 3108-12	4	B
Can-Epi-Bio-Prev. 1998; 7(12): 1079-84 (abstract)	1,5		Lancet. 1996; 347(9012): 1372-4	4	
Zhengjiang Yixueyuan Xuebao 1998; 8(4): 446-447	1	B	Cancer res on prevention and treatment 1999; 26(3): 232-233	4	B
Cancer-Epidemiol-Biomarkers-Prev. 1999; 8(1): 15-24	1,4	B	Gut. 1997; 41(2): 229-34	5	B
Cancer-Lett. 1999; 142(1): 97-104	1,2	B	Carcinogenesis. 1997l; 18(7): 1351-4	5	B
Exp-Toxicol-Pathol. 1999; 51(4-5): 321-5 (abstract)	1		Carcinogenesis. 1998; 19(1): 37-41	5	B
Can-Epi-Bio-Prev. 1999; 8(4 Pt 1): 289-92	1,2,6	B	Pharmacogenetics. 1998; 8(6): 513-7	5	
J-UOEH. 1999; 21(2): 133-47	1,2,3,5,6	B	Cancer-Res. 1996; 56(21): 4862-4	9	B
Jiangshu Linchuangyixue Zazhi 2000; 4(2): 90-91	1,2	B	Cancer-Res. 1997; 57(6): 1098-102	9	B
Anticancer-Res. 2000; 20(1B): 519-22 (abstract)	1		Genet-Test. 1999; 3(2): 233-6	9	B
J-Gast-Hepatol. 2001; 16(6): 631-5 (abstract)	2		Can-Epi-Bio-Prev. 1999; 8(6): 513-8	9	
Carcinogenesis. 2001; 22(7): 1053-60	1,2,5,6	B	Can-Epi-Bio-Prev. 1999; 8(9): 825-9	10	B
Gastroenterology 1997: 112: A542 (abstract)	2	B	Can-Epi-Bios-Prev. 2000 ; 9(8): 855-6	7,8	B
			Carcinogenesis. 2001; 88(8): 1323-6	7,8	B

[1]Note: 1-GSTM1 deletion, 2-GSTT1 deletion, 3-NAT1*10, 4-NAT2-rapid acetylator phenotype, 5-NAT2-rapid acetylator genotype, 6-GSTP1 lle105Val, 7-CYP1A1 Lle462Val, 8-CYP1A1 MspI*C, 9-METHFR C677T, 10-MTR A2759G [2]Note, Grouping B: The literatures in group B, grouping A: The literatures in group B.

Table 2 lists the results of meta-analysis in group A for the genetic polymorphisms of metabolic enzymes related with colorectal cancer. Since there was no equal variance in the genotype of GSTM1 deletion, GSTT1 deletion, CYP1A1 MspI*C, they were analyzed by D-L model. Other genetic polymorphisms of metabolic enzymes were processed by M-H model. The pooled OR values of GSTM1 deletion, GSTT1 deletion, GSTP1 1le105Val, NAT1*10, NAT2-rapid acetylator phenotype and genoype and NAT2-rapid acetylator phenotype, NAT2-rapid acetylator genotypes CYP1A1 L1e462Val,CYP1A1 MspI*C, MTHFR C677T and MTR A2759G were 1.08, 1.42, 1.09, 1.25, 1.08, 1.15, 1.05, 1.26, 1.30, 0.83, 0.60 respectively. Among these genetic polymorphisms, GSTT1 deletion, NAT2-rapid acetylator phenotype and genotye and NAT2-rapid acetylator phenotype had significant relationships with colorectcal cancer (pooled OR>1.08, P<0.05), while the others had no relationship with colorectal cancer (P>0.05).

Table 3 shows the results of meta-analysis in group B for the genetic polymorphisms of metabolic enzymes related with colorectal cancer. Genetic polymorphisms other than CYP1A1 MspI*C had the equal variance. Therefore the genotype of CYP1A1 MspI*C was analyzed by D-L model, and others were analyzed by M-H model. The pooled OR values of GSTM1 deletion, GSTT1 deletion, GSTP1 1le105Val, NAT1*10, NAT2-rapid acetylator phenotype and genotye and NAT2-rapid acetylator phenotype, NAT2-rapid acetylator genotypes CYP1A1 L1e462Val, CYP1A1 MspI*C, MTHFR C677T and MTR A2759G were 1.07, 1.20, 1.08, 1.20, 1.02, 1.06, 0.95, 1.21, 1.17, 0.69, and 0.60. Only the genotpyes of GSTT1 deletion and MTHFR C677T had a significant association with colorectal cancer (P<0.05), and the genotype of GSTT1 deletion was a risk factor (OR>1.00) while MTHFR C677T was a protective factor (OR<1.00) for colorectal cancer.

There was a significant difference when the synthetic OR values in two groups were calculated by paired test (t = 5.080, P = 0.000). When the number of literatures was the same, there was no significance (P>0.05).

DISCUSSION

The pathogenesis of colorectal cancer can be ascribed to multiple factors, such as environmental substance and family history[16]. Metabolic enzymes are responsible for the activation or detoxification of mutagenic xenobiotics. Chemical carcinogens generally require metabolic activation in order to bind to DNA and contribute to cancer formation. Cancer susceptibility might be resulted from differences in the expression of metabolic enzymes[15]. Most of the human metabolic enzymes are genetically polymorphic, and these polymorphisms may affect the enzyme

Table 2 Results of meta-analysis of polymorphisms and risk for colorectal cancer in group A

Gene and polymorphism	Study numbers	Cumulative cases	Cumulative controls	Test of heterogeneity		Statistical method	OR	95%CI	Significance P
				Q	P				
GSTM1 deletion	18	5 455	6 853	31.1	<0.05	Random	1.08	0.96-1.20	>0.20
GSTT1 deletion	11	1 348	1 792	29.79	<0.001	Random	1.42[b]	1.21-1.66	<0.001
GSTP1 *Ile*105*Val*	4	612	755	4.06	0.2	Fixed	1.09	0.87-1.37	>0.30
NAT1*10	3	520	433	5.43	0.10-0.20	Fixed	1.25	0.96-1.63	>0.10
NAT2-rapid acetylator p&g	18	6 741	8 015	22.86	0.20-0.30	Fixed	1.08[a]	1.00-1.16	<0.05
NAT2-rapid acetylator p	8	2 182	2 861	14.24	0.10-0.20	Fixed	1.15[a]	1.02-1.31	<0.05
NAT2-rapid acetylator g	10	4 559	5 154	7.71	>0.50	Fixed	1.05	0.94-1.14	>0.20
CYP1A1 *Lle*462*Val*	2	235	280	1.77	>0.30	Fixed	1.26	0.77-2.08	0.05-0.1
CYP1A1 MspI*C	2	234	250	8.36	<0.02	Random	1.3	0.82-2.06	>0.30
METHFR C677T	4	1 949	3 099	3.11	0.30-0.50	Fixed	0.83	0.68-1.01	>0.10
MTR A2759G	3	613	1 189	0	0.9	Fixed	0.6	0.28-1.29	0.10-0.20

Fixed: Fixed-effect model, Random: Random-effects model. [a]P<0.05, [b]P<0.01.

Table 3 Results of meta-analysis of polymorphisms and risk for colorectal cancer in group B

Gene and polymorphism	Study numbers	Cumulative cases	Cumulative controls	Test of heterogeneity		Statistical method	OR	95%CI	Significance P
				χ	P				
GSTM1 deletion	14	3 002	3 911	20.54	0.08	Fixed	1.07	0.97-1.17	0.2
GSTT1 deletion	8	1 029	1 492	12.52	0.085	Fixed	1.20[a]	1.00-1.44	0.05
GSTP1 *Ile*105*Val*	4	609	755	3.63	0.3	Fixed	1.08	0.86-1.35	0.5
NAT1*10	3	520	433	5.2	0.07	Fixed	1.2	0.92-1.56	0.18
NAT2-rapid acetylator p&g	12	3 121	3 697	13.61	0.26	Fixed	1.02	0.92-1.13	0.7
NAT2-rapid acetylator p	6	2 038	2 546	8.91	0.11	Fixed	1.06	0.94-1.20	0.3
NAT2-rapid acetylator g	6	1 083	1 151	3.62	0.61	Fixed	0.95	0.79-1.13	0.5
CYP1A1 *Lle*462*Val*	2	235	280	1.62	0.2	Fixed	1.17	0.71-1.91	0.5
CYP1A1 MspI*C	2	234	280	5.01	0.03	Random	1.21	0.77-1.90	0.4
METHFR C677T	3	546	1 413	1.38	0.5	Fixed	0.69[a]	0.51-0.94	0.02
MTR A2759G	2	356	476	0	0.98	Fixed	0.6	0.28-1.29	0.19

Fixed: Fixed-effect model, Random: Random-effects model. [a]P<0.05.

activity or inducibility. Individuals carrying some "high-risk" alleles have a strikingly increased risk for colorectal cancer[3]. Some genotypes of metabolic enzymes might be a useful prognostic biomarker for colorectal cancer[17].

The results of this study show that GSTT1 deletion was a risk factor for colorectal cancer. Glutathione S-transferases (GSTs) are a family of enzymes widely expressed in mammalian tissues and have a broad substrate specificity. It has been found that most GST substrates are xenobiotics or products of oxidative stress, including some environmental carcinogens[18]. The genes glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) code for cytosolic enzymes glutathione S-transferase (GST)-mu and GST-theta respectively, which are involved in phase 2 metabolism[19,20]. GSTs could contribute to protection against the formation of carcinogens, and GSTT1 null genotype might exhibit a greater predisposition to colorectal cancer[21,22]. GSTs could detoxify activated carcinogen metabolites by catalysis of their reaction with GSH. Individuals who have the risk to develop CRC might be possibly due to inefficient hepatic detoxification of N-acetoxy-PhIP[23].

NAT2-rapid acetylator phenotype and genotype and NAT2-rapid acetylator phenotype have been proved to have a significant relationship with colorectal cancer in this study. N-acetyltransferase (NAT2) is involved in the metabolism of several compounds relevant in pharmacology or toxicology. The results of this study have confirmed that NAT2-rapid acetylator phenotype and genotye and NAT2-rapid acetylator phenotype are risk factors for colorectal cancer. Frazier *et al*[24] reported that NAT2 genotypes might be an important factor in tumorigenesis of colorectal cancer. The effect of NAT1 and NAT2 genotypes on cancer varies with organ site, probably reflecting tissue-specific expression of NAT1 and NAT2. The frequency of some NAT2 genotypes in population might be relatively high[25].

Among the eleven genetic polymorphisms of metabolic enzymes in this study, only three enzymes had a significant relationship with colorectal cancer. The results of this study have some difference with what was reported[3,4,25]. One of the possible reasons is the interaction of diet and other factors. It has been testified that NAT2 alone could not be a risk factor for colonic cancer[26]. Heterocyclic amines (HCA) that are taken during consumption of meat and fish could increase the risk for rectal cancer in men, but does not appreciably affect the risk for rectal cancer in women or for colonic cancer in either sex[27]. It has been indicated p53 is involved in the tumorigenesis of colorectal cancer[28]. An increased frequency of p53 gene mutations, including G:C to A:T transitions at non-CpG sites, is associated with an increased risk for colorectal carcinogenesis in cigarette smokers[29]. De *et al*[30] advised that description of the exact relations between polymorphisms and colorectal cancer susceptibility with an adequate power must take into account relevant dietary and lifestyle habits and other factors. Most recently, great interests have been focused on the possibility that the risk associated with smoking could be modified by polymorphisms of metabolic enzymes. It has been hypothesized that GST functional variants associated with less effective detoxification of potential carcinogens may confer an increased susceptibility to cancer, especially in the presence of environmental stresses such as smoking. Slattery *et al*[31] reported a significant association between the risks for colorectal cancer and the interaction of GSTM1 polymorphism and smoking. All these results suggest that some risk factors susceptible to colorectal cancer have a relationship with genetic polymorphisms of metabolic enzymes, and colorectal cancer is also associated with several environmental and dietary risk factors. Diet and other factors must be considered when the relationship between genetic polymorphisms of metabolic enzymes and colorectal cancer is studied.

The other reason might be the bias of analysis and the information in these literatures. Meta analysis has been extended quickly from social sciences to medical sciences. Two ways were used in the calculation of pooled OR value in this study, but the statistic principle and method of these two ways are similar. Since there is no significant difference when the number of literature is same in two ways, the bias of different ways could be eliminated. However, the potential confounding factors might have not well controlled due to the limited number of literature is, therefore the results may be affected. Further study is required.

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