Original Article

Association of Catalase Genotype with Oxidative Stress in the Predication of Colorectal Cancer: Modification by Epidemiological Factors*

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Abstract

Objective This paper aims to assess the interaction between common variations in catalase (CAT) polymorphic gene and environmental factors for antioxidant defense enzyme in modulating individual susceptibility to colorectal cancer (CRC).

Methods A case-control study with 880 colorectal cancer cases and 848 controls was conducted to investigate whether variations in the catalase (*CAT*) gene, one of the genes involved in scavenging oxidative stress, influenced susceptibility to CRC.

Results The interaction between life style and genotypes as well as with their effects on colorectal cancer was deduced from the present study. Significant difference (P=0.01) was identified in the distribution of *CAT* genotype between the colorectal cancer cases and the controls. The CRC cases had significantly lower mean activity than the controls (P<0.01). Correlation analyses revealed statistically significant correlations between CAT activity and *CAT* genotype (P<0.01).

Conclusion The risk of CRC was associated with smoking, low vegetable consumption, high pork and poultry consumptions, and low or high BMI. This is the first study reporting an association of polymorphism *CAT*-21A>T with colorectal cancer. Low CAT activity was associated with an increased risk of CRC; however, no evidence was found to support an association between *CAT*-21A>T polymorphism and CRC risk.

Key words: Colorectal cancer (CRC); Oxidative stress; Catalase (CAT) gene; Epidemiological factors

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INTRODUCTION

The risk of colorectal cancer is mainly associated with lifestyle factors and may be modulated by several genetic factors of low penetrance. Genetic variants represented by single nucleotide polymorphisms in genes encoding key players in the colorectal cancer sequence may contribute to variation in susceptibility to colorectal cancer. Cancer development is nurtured by the

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sustained relationship of two pathological processes, oxidative stress and chronic inflammation[1-2]. Oxidative stress may play a significant role in the risk of colorectal cancer[3-5].

Reactive oxygen species (ROS) have been related to one of the etiological agents in carcinogenesis as they are known to be mitogenic and capable of tumor promotion[6-8]. Transient fluctuations in reactive oxygen species have important regulatory functions, but when at high and/or sustained levels, reactive oxygen species can cause severe damage to DNA, protein, and lipids. In view of these findings, reactive oxygen species are considered as an important class of carcinogens. Their effect is balanced by the antioxidant action of nonenzymatic antioxidants (e.g., glutathione, vitamins C, and E), as well as antioxidant defense enzymes (e.g., catalase). Catalase (CAT), a heme enzyme that plays a predominant role in controlling hydrogen peroxide concentration in human cells, by converting H_2O_2 into H_2O and O_2, protecting cells from oxidative stress. Activity levels of catalase are likely to be affected by functional polymorphisms in the gene encoding.

The present study aims to confirm the role of CAT with a much larger sample size and to evaluate the association between common variants in catalase activity and CAT gene coding which are modified by demographic characteristics and lifestyle factors, and susceptible to colorectal cancer.

MATERIALS AND METHODS

Subjects

A case-control study design (880 colorectal cancer cases and 848 controls) was used to test the association between catalase activity and polymorphisms of *CAT* and the risk of colorectal cancer. Colorectal cancer patients recruited to this case-control study were incident, pathologically confirmed colorectal cancer cases, diagnosed from 2007 to 2010. Colorectal cancer cases were recruited from the First Affiliated Hospital and the Third Affiliated Hospital of Harbin Medical University. All the patients agreed to participate in this study and signed written informed consents. The eligible pool of control subjects was restricted to the individuals of the same age (±2 years) and sex as case subjects. The controls were pair-matched into a 1 to 1 ratio in terms of those cases studied. Exclusion criteria for the case-control study included a previous history of cancer. Trained interviewers conducted face-to-face interviews. Information was collected on life-long smoking, diet habits, physical activity, and family history of colorectal cancer.

Catalase Activity Assay

Serum samples collected from the participants were assayed for catalase activity according to the procedure of Aebi et al.[5]. The concentrations of catalase activity were measured with spectrophotometric method.

Genotypic Assay

Genomic DNA was extracted from lymphocytes of the participants as previously descried (9). The genotypes of *CAT* were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis: a -21A>T point mutation in the promoter region of the catalase gene. PCR was done for *CAT* by using primers 5’-AAT CAG AAG GCA GTC CTC CC-3’ and 5’-TCG GGG AGC ACA GAG TGT AC-3’. The restriction enzyme is *Hin*fI. DNA amplification was carried out in a final volume of 50µL, by using 0.35 µg of genomic DNA and 1 nmol of each of the primers. Four deoxynucleotides were present in a final concentration of 200 µmol/L. The amplification reaction was started by adding 0.5 units of *Taq* polymerase. Annealing, extension and denaturing were carried out by using an automatic thermal cycler (MJ 100, USA). The primers were designed to amplify a 250 base pair (bp) fragment of the catalase gene (Figure 1).

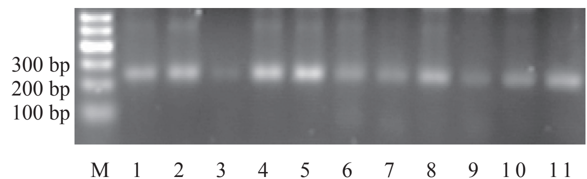

Figure 1. PCR results for *CAT* gene. Lane 1-11 PCR products observed in catalase gene (250 bp).

The PCR products were digested at 37 °C for 4 h by using 25 µL of each PCR amplified product with 10 units of the restriction enzyme (New England Biolabs, Inc., Beverly, MA, USA).

The polymerase chain reaction products were electrophoresed at 75 V for 1.0 h through a 1.5% agarose gel. The gels were stained with ethidium bromide and visualized by ultraviolet light. All genotyping results were reviewed manually for quality control. Controls for genotype and two nontemplate controls were included on each plate.

In the *CAT* gene, the mutant allele has no *Hin*fI restriction site. All laboratory staffs were blinded to case/control status (Figure 2).

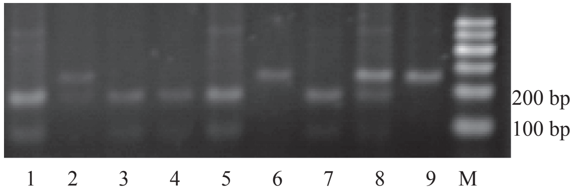

Figure 2. PCR-RFLP analysis for *CAT* polymorphism. Lane 1, 3, 4, 5, 7 PCR products observed in homozygous genotype (176 bp/74 bp); Lane 6, 9 PCR products observed in mutant homozygous genotype (250 bp); Lane 2, 8 PCR products observed in heterozygous genotype (250 bp /176 bp/74 bp).

Statistical Analysis

All analyses were conducted with SPSS 13.0. The Wilcoxon rank sum test and the x^2 test were adopted to verify the hypothesis that the distribution of baseline characteristics was the same for cases and controls. Hardy-Weinberg equilibrium tests for *CAT* genotype were performed on the control participants. Linear trend analyses for catalase activity were conducted by creating a variable using activity scores based on the median values of activity for the first, second, and third activity tertiles. Unconditional logistic regression was used to calculate odds ratios (ORs; an estimate of relative risk) and 95% confidence intervals (95% CI) to evaluate the association between genotype and tertiles of catalase activity after adjustment for potential confounders of colorectal cancer. Modification of the effect of genotype and CAT activity on the risk of colorectal cancer by age, sex, smoking status, body mass index (BMI), beef, mutton, pork and poultry consumption, and vegetable consumption (*P*s for interactions) was examined by statistical tests of the first order interaction term in the logistic regression models. Correlation analyses were conducted to evaluate the correlations between CAT activity and *CAT* genotype. All of the *P*s reported are two-sided.

RESULTS

CAT Genotype and Subject Characteristics

There was no significant difference in mean age between the cases (58.6±11.85) and the controls (58.6±11.85). Table 1 describes selected characteristics of the study population. There was no difference between the cases and the controls in age, sex, and BMI. However, there was significant difference between the cases and the controls in current smoking status, meat consumption and vegetable consumption. In addition, significant difference (*P*=0.01) was also found in the distribution of *CAT* genotype between the colorectal cancer cases and the controls. Examination of the CAT enzymatic activity in serums reveals that colorectal cancer cases had significantly lower mean activity than the controls (3.50±0.95 in the cases compared with 6.00±1.87 in the controls; *P*<0.01). Genotype data were available for 880 colorectal cancer patients and 848 control individuals. For the *CAT* genotypes, the Hardy-Weinberg equilibrium assumption was tested in the subjects by using a χ^2 test. No deviation was found in the control individuals (*P*=0.56) and in the case individuals (*P*=0.09) from equilibrium. The frequency of the *CAT* variant TT homozygous genotype in the cases was different from that in the controls (17.3% and 12.3%, respectively; *P*=0.01) while the T allele in the former was not different from that in the latter (0.43 and 0.40, respectively; *P*=0.12).

Table 1. Selected Characteristics of Colorectal Cancer Cases and Controls

Characteristic	Cases (*n*=880)	Controls (*n*=848)	*P*[a]
Age (y)			
<40	56	56	
40-49	160	176	
50-59	264	208	0.14
60-69	280	288	
≥70	120	120	
Sex			
Male (M)	504	472	0.53
Female (F)	376	376	
Smoking status			
Current	368	408	0.01
Never or former	512	440	
Body mass index[b] (BMI, Kg/m²)			
BMI≤19 (M) or BMI≤18 (F)	48	64	
19<BMI≤22 (M) or 18<BMI≤21 (F)	312	264	0.06
BMI>22 (M) or BMI>21 (F)	520	520	
Beef and mutton consumption (grams/week)			

(continued)

Characteristic	Cases (*n*=880)	Controls (*n*=848)	P^a
0	432	464	
0.1-250	328	264	0.06
250.1-1 000	96	96	
>1000	24	24	
Pork consumption (grams/week)			
0	152	160	
0.1-250	288	312	0.00
250.1-1 000	320	320	
>1 000	120	56	
Poultry consumption (grams/week)			
0	400	488	
0.1-250	376	224	0.00
250.1-1 000	72	104	
>1 000	32	32	
Vegetable consumption (grams/day)			
0-100	96	96	
100.1-500	584	480	0.00
>500	200	272	
Genotype			
CAT AA	280 (31.%)	272 (32.1%)	
CAT AT	448 (50.9%)	472 (55.7%)	0.01
CAT TT	152 (17.3%)	104 (12.3%)	
T allele[c]	0.43	0.40	0.12
P^d	0.09	0.56	
CAT activity[e] (Units/mL)	3.50±0.95	6.00±1.87	<0.000

Note. [a]*P*s as determined by Wilcoxon rank-sum tests and Fisher's exact test for categorical variables. [b]Body mass index (BMI, Kg/m^2) was grouped based on Asia-Pacific standard 2000. [c]χ^2=2.47; *P*=0.12 from χ^2 test for the T allele frequencies between cases and controls. [d]The observed genotype frequency in both the control and the case subjects was in agreement with Hardy-Weinberg equilibrium. [e]Data are mean±SD. *P*<0.01 *vs* healthy subjects.

CAT Genotype, Phenotype, and Subject Characteristics Stratified by Lifestyle Factors among Colorectal Cancer Patients and Controls

The association between *CAT* polymorphism and colorectal cancer risk was estimated by the odds ratio (OR), by using the unconditional logistic regression models. We calculated the values adjusted for age, sex, BMI, smoking, and diet habits to control the effect of potential confounding environmental factors. Since the *CAT* AA genotype was considered to have the highest effective enzymatic activity, this genotype was used as reference for colorectal cancer risks. Thus, the ORs for the *CAT* AT and *CAT* TT types relative to the *CAT* AA were calculated. The OR for the *CAT* AT+TT type versus the *CAT* AA was also calculated because both the *CAT* AT and the *CAT* TT type could potentially influence the individual repair activity.

Table 2 shows the relationship between *CAT* genotype and phenotype in relation to colorectal cancer risks. Based on logistic regression analyses, neither the homozygous TT [adjusted OR 0.88; 95% confidence interval (CI) 0.64-1.22] nor the heterozygous AT (adjusted OR, 0.82; 95% CI 0.58-1.14) genotypes was shown to be associated with colorectal cancer risks after adjustment for age, sex, current smoking status, BMI, meat consumption and vegetable consumption.

Table 2 also provides in detail *CAT* activity among colorectal cancer patients and controls. *CAT* activity data were available for 880 colorectal cancer patients and 848 control individuals. Tertiles of activity were derived from the distribution of CAT activity in both the control and the case population. The median higher CAT activity tertiles were associated with reduced risks of colorectal cancer (OR, 0.08; 95% CI, 0.06-0.10) compared with the lowest activity tertile. The subjects with increasing CAT activity had reduced risk of CRC. There were no subjects in the highest CAT activity tertiles. Current smoking status, BMI, pork and poultry consumptions and vegetable consumption had effects on colorectal cancer risks except for beef and mutton consumption. The direction of the ORs indicates elevated risks of colorectal cancer with increasing pork consumption (*P*<0.01) and increasing poultry consumption, and the difference had statistical significance (*P*<0.01). When vegetable consumption was considered, the two groups with more vegetable consumption had reduced risks of colorectal cancer (OR, 0.39; 95% CI, 0.26-0.60 and OR, 0.55; 95% CI, 0.42-0.71 for the second and third groups of vegetable consumption, respectively) compared with the group with the least vegetable consumption. Smoking increased risks of colorectal cancer (*P*<0.01). High BMI was a risk factor of colorectal cancer (OR, 1.41; 95% CI, 1.14-1.74) and suitable BMI was a protective factor of colorectal cancer (OR, 0.56; 95% CI, 0.37-0.88).

Table 3 shows the relationship among catalase activities by CAT genotype. The difference of catalase activities by *CAT* genotype was among those with the AA and TT genotypes. The lowest catalase activity

Table 2. Association between *CAT* Genotype, Enzyme Activity, Subject Characteristics, and Odds of Colorectal Cancer[a]

Characteristic	Cases/ controls	Odds ratio (95% confidence interval)	P
Genotype			
CAT AA	280/272	1.0 (Reference)	
CAT AT	448/472	0.82 (0.58-1.14)	0.48
CAT TT	152/104	0.88 (0.64-1.22)	
CAT AT+ TT	600/576	1.07 (0.87-1.32)	0.51
CAT activity[b]			
Tertile 1 (1.22-3.63)	680/128	1.0 (Reference)	
Tertile 2 (3.64-5.46)	200/464	0.08 (0.06-0.10)	0.00
Tertile 3 (5.47-11.08)	0/256	-	
Smoking status			
Current	368/408	1.0 (Reference)	0.00
Never or former	512/440	0.60 (0.49-0.73)	
Body mass index (BMI, Kg/m^2)			
BMI≤19 (M) or BMI≤18 (F)	48/64	1.0 (Reference)	
19<BMI≤22 (M) or 18<BMI≤21 (F)	312/264	0.56 (0.37-0.88)	0.00
BMI>22 (M) or BMI>21 (F)	520/520	1.41 (1.14-1.74)	
Beef and mutton consumption (grams/week)			
0	432/464	1.0 (Reference)	
0.1-250	328/264	2.07 (0.88-4.90)	0.09
250.1-1 000	96/96	2.47 (1.04-5.86)	
>1 000	24/24	2.46 (1.01-5.98)	
Pork consumption (grams/week)			
0	152/160	1.0 (Reference)	
0.1-250	288/312	1.97 (1.74-2.28)	0.00
250.1-1 000	320/320	2.05 (1.80-2.38)	
>1 000	120/56	3.26 (2.53-5.32)	
Poultry consumption (grams/week)			
0	400/488	1.0 (Reference)	
0.1-250	376/224	3.36 (1.76-6.41)	0.00
250.1-1 000	72/104	7.73 (4.02-14.85)	
>1 000	32/32	2.27 (1.11-4.62)	
Vegetable consumption (grams / day)			
0-100	96/96	1.0 (Reference)	
100.1-500	584/480	0.39 (0.26-0.60)	0.00
>500	200/272	0.55 (0.42-0.71)	

Note. [a]Unconditional logistic regression models adjusted for age, sex, current smoking status, BMI, beef and mutton consumption, pork consumption, poultry consumption and vegetable consumption. [b]Tertiles derived from distribution among cases and controls with the first tertile used as the reference group. Activity units are units/mL.

levels were among those with TT genotypes and the highest catalase activity levels were among those with AA genotypes. Correlation analyses revealed statistically significant correlations between CAT activity and *CAT* genotype(r=-0.372, P<0.01). However, as shown by correlation coefficient, there was no close inverse correlativity between *CAT* genotype and catalase activities.

Table 3. Catalase Activity by *CAT* Genotype

Characteristic Genotype[c]	n	Catalase Activity	R_p[a]	P[b]
CAT AA[d]	96	3.95±1.10		
CAT AT[d]	144	3.84±0.98	-0.203	0.001
CAT TT[d]	18	3.31±0.23		

Note. [a]Correlation Coefficient R_p= -0.203 shows there is no close inverse correlativity between *CAT* genotype and catalase activity. [b]Correlation is significant at the 0.01 level.[c]The mean difference of catalase activity is significant at the 0.05 level by different *CAT* genotype group, P<0.01.[d]The mean difference of catalase activity is significant at the 0.05 level between *CAT AA* and *CAT TT* and is not significant between *CAT AA* and *CAT AT*, *CAT AT* and *CAT TT*.

DISCUSSIONS

In this study, we determined both genotype and phenotype for CAT, and evaluated their association with colorectal cancer risks. We found no significant association between *CAT* genotype and colorectal cancer risks in the Chinese people. However, when CAT activity was examined in relation to colorectal cancer risks, there was a clear association between low CAT activity and colorectal cancer risks. There was also evidence supporting that increased pork and poultry consumption and reduced vegetable consumption were associated with colorectal cancer risks.

Missing data are likely to have introduced bias as there were more missing values in controls than in cases. However, unless the missing genotypes were random with respect to genotype category and related to case-control status, missing data would not bias the results. The loss of data will result in a little loss of statistical power. Missing data are more likely to be important for a balanced case-control design, but it seems unlikely that the adjustment used for missing values was inadequate.

There are a number of pathological factors, including reactive oxygen species (ROS) involved

in the process of colorectal cancer initiation and progression[10]. ROS play an important role in pathophysiological process in several chronic diseases or types of cancers. It is suggested that oxidative stress may greatly contribute to the development of colorectal cancer[5]. CAT is one of the most important antioxidases and plays a significant part in normal metabolism and health states of human bodies[11], which is located primarily in peroxisomes and reduces H_2O_2 to water. There are reports on the associations of catalase phenotype and genotype with breast cancer patients[12-14] and miners exposed to coal dust[15]. In the present study, we found no association between the *CAT* -21A>T polymorphism and CRC risks, but evident association of catalase phenotype with colorectal cancer patients. Our findings suggest that this common polymorphism may not play a major role in the etiology of CRC.

One reason for discrepant results in case-control studies is that the selection of the controls may be biased in terms of biomarkers of interest. This study is the first to evaluate the CAT -21A>T polymorphism in relation to colorectal cancer risks. It is shown in our study that there was significant difference (P=0.01) in the distribution of *CAT* genotype between the colorectal cancer cases and the controls, and the correlation analyses revealed statistically significant correlations between CAT activity and *CAT* genotype(r=-0.203, P=0.001). No literature information on relation between *CAT* gene polymorphism and colorectal cancer is make available to support our study. It was only reported that the frequency of -21AA genotype of the *CAT* gene was significantly higher in patients with allergic (OR, 0.47; 95% CI, 0.25-0.92; P=0.024) and nonallergic (OR, 0.32; 95% CI, 0.14-0.71; P=0.004) asthma in comparison with controls[16]. There is no sufficient support for *CAT* to detect smaller risk breast cancer estimates[14].

Our findings illustrate the effects of genes and internal and external factors on cancer risks, and specifically suggest a role of reduced repair of oxidative DNA damage in colorectal cancer. Lower activity of CAT (the internal factor), possibly determined by genetic factors, leads to a reduced ability to repair oxidative DNA damage and, as a result, the rate of mutation increases in association with a higher estimated relative risk of cancer. This study provides an example of interaction of dietary habits, BMI and smoking status (the external factors) with the risk of CRC. The risk of CRC is associated with current smoking status, high or low BMI, high pork and poultry consumptions. The reduced risk of CRC associated with high vegetable consumption is shown in our study, which is consistent with the report that the women with low vegetable and fruit intake (<median) appeared to be associated with raised breast cancer risks[12,14,17]. Current smoking status, BMI, pork and poultry consumptions and vegetable consumption had effects on colorectal cancer risks except beef and mutton consumption.

Our data indicate that reduced CAT activity is associated with CRC and that reduced activity is a statistically significant risk factor for this cancer. This conclusion is supported by the following considerations: 1) The mean CAT activity values for case patients were statistically significantly lower than those for control subjects. 2) The odds ratios of CRC associated with low CAT activity were large and highly statistically significant. In addition to indicating a strong association, this result also argues the possibility of a selection bias in the control group. 3) The odds ratios for CAT activity as a risk factor for CRC were statistically significant after adjustments for possible confounding effects of sex, age, BMI, smoking status, and dietary factors.

In conclusion, this study provides an example of a gene-environment interaction in which catalase phenotype is affected by the individual genetic background and dietary practices. Moreover, because catalase activity is closely linked to endogenous antioxidant activity, these data provide a plausible biological explanation for our previous findings of the association between the *CAT* -21A>T genotypes and the risks for colorectal cancer and other diseases. More importantly, the finding that associations between genotype and activity are modified by demographic and lifestyle factors (age, gender, BMI, smoking status, and dietary habits) has implications for molecular epidemiological studies. We did not find evidence to support an association between *CAT* -21A>T polymorphism and colorectal cancer risks in our study population. Future research in this area should include more detailed coverage of polymorphisms within the genes implicated in this study, as well as other genes involved in the mediation of oxidative stress response.

The present study demonstrates that phenotype related to genotype is modified by dietary habits. The viewpoint could support the notion that some of the inconsistencies in molecular epidemiological studies could be due to differences in the study populations and underlying characteristics, rather than due to the relationship between genetic polymorphisms and the actual in vivo phenotypes. One reason for discrepant results in case-control studies is that the selection of

the controls may be biased in terms of biomarkers of interest. The limitation of our study lies in the hospital-based study design, as we cannot rule out the possibility of selection bias of subjects. Given many genes are involved in the repair of oxidative damage[15-16], it is essential to perform genotype and phenotype correlation analyses and to conduct a comprehensive study of the entire repair pathway. To improve the research in the field of molecular epidemiology, parallel studies may be helpful for elucidating the complex relationships among genetic polymorphisms, phenotypic effects, and cancer risks.

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