

RESEARCH COMMUNICATION

The Myeloperoxidase-463 G>A Polymorphism Influences Risk of Colorectal Cancer in Southern China: a Case-control Study

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Abstract

Objective: Oxidative stress may be involved in colorectal carcinogenesis. Myeloperoxidase (MPO) is an endogenous oxidant enzyme that generates reactive oxygen species (ROS). We hypothesized that the MPO -463 locus polymorphism might therefore contribute to genetic susceptibility to colorectal adenomas. **Methods:** RFLP-PCR analysis identified the MPO genotypes in 325 Chinese colorectal adenomas cases and 345 controls matched by age, sex, smoking status, and alcohol use. An epidemiological interview elicited detailed information on demographic data and lifestyle characteristics. **Results:** Individuals with a GA/AA genotype had a significantly lower risk of colorectal cancer (adjusted OR = 0.57, 95% CI, 0.41-0.79) than those with the GG genotype. On stratification analysis, the decreased risk was more pronounced among older subjects (adjusted OR = 0.56, 95% CI, 0.39-0.81), males (0.47, 0.33-0.68), smokers (0.54, 0.35-0.85), and ever-drinkers (0.44, 0.27-0.71). **Conclusion:** For a similar level of exposure to established carcinogens, individuals with MPO A-allele genotypes appear to have a reduced risk of colorectal adenomas in southern Chinese population, especially among older subjects, men, smokers, and ever-drinkers.

Keywords: Myeloperoxidase - polymorphism - colorectal cancer

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Introduction

Colorectal cancer (CRC) is the second most common cause of cancer mortality among men and women worldwide, with an incidence of approximately 1 million cases per year and more than 500,000 deaths (World Gastroenterology Organization/International Digestive Cancer Alliance, 2007). CRC in Asia has been increasing to North American and European levels. An investigation in China including 169,871 men and women demonstrated that colorectal cancer was in the fifth place among the five leading causes of death from cancer (He et al., 2005).

Cancer is a multifactorial disease that results from complex interactions between the genetic background and environmental factors. Published studies have identified that colorectal cancer is known to be associated with polymorphisms in the KRAS, APC, p53 and DCC genes (Chiang et al., 1998), but many people are exposed to these risk factors, only a fraction of exposed individuals develop colorectal cancer, suggesting that there is an individual variation in susceptibility to exposure-related colorectal carcinogenesis. In general, no single factor can be identified as the only causative factor in cancer etiology. Colorectal cancer has also been considered to be a result of gene-environment interactions, which is a complex

multifactorial and multistage process .

The lysosomal enzyme myeloperoxidase (MPO) is found in neutrophils and monocytes (Riley et al., 1995). Exposure to cigarette smoke stimulates the recruitment of neutrophils into human lung tissue, resulting in local release of MPO. For its microbicidal activity, MPO produces hypochlorous acid, a strong oxidant that can attack nucleic acids, proteins and unsaturated lipids through the concomitant release of reactive oxygen species (Ohnishi et al., 2002). A frequently occurring polymorphism in the promoter region of the MPO gene is a -463 G>A transition, which is located in the consensus binding site of the SP1 transcription factor. The MPO G wild-type allele confers about 25 times higher transcriptional activation compared to the -463 A variant in vitro, and the former has been associated with increased MPO mRNA and protein levels in myeloid leukemia cells (Kiyohara et al., 2005). This polymorphism has been reported to be associated with cancer risk at lung (Yang et al., 2007), breast (Yang et al., 2007), gastric (Steenport et al., 2007), and laryngeal cancer (Cascorbi et al., 2000). However, there is no report of association between the MPO -463 locus polymorphism and risk of human colorectal cancer.

In the present study, we hypothesized that MPO

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-463 locus polymorphism might contribute to genetic susceptibility to colorectal cancer. To test this hypothesis, we genotyped the polymorphism and assessed its association with risk of colorectal cancer in our ongoing, hospital-based, case-control study in a Chinese population.

Materials and Methods

Subjects

A total of 325 subjects newly diagnosed with colorectal cancer and 345 healthy controls were consecutively recruited from The First Affiliated Hospital of Nanjing Medical University between January 2003 and February 2008. Every subject participating in the study was genetically unrelated ethnic Han Chinese, permanently residing in Jiangsu province in China. The diagnoses of colorectal cancer were all confirmed by endoscopic biopsy or surgical specimens with histological confirmed adenocarcinoma. All patients consented to participate in the study, and donated 5 ml of blood. Control subjects living in the same residential areas had no current or previous diagnosis of cancer and genetic disease and were frequency-matched to the cases on age, sex, smoking status, and alcohol use. Individuals that smoked once a day for over 1 year were defined as ever smokers, and those that consumed three or more alcohol drinks per week for at least 1 year were considered ever drinkers. Each subject was informed about the aims and requirements of this study, and informed consent for participation was obtained in accordance with institutional guidance at Nanjing Medical University. A structured questionnaire was filled by interviewers to collect information on demographic data and lifestyle characteristics. The research protocol was approved by the institutional review board.

Genotyping

Genomic DNA was isolated from frozen leukocyte pellet using standard phenol-chloroform extraction. The MPO -463 G>A polymorphism was detected by polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP). A 350 bp DNA fragment containing the polymorphic site was amplified by PCR in the T1 Thermocycler (Biometra, Goettingen, Germany) using the forward primer 5'-CGG TAT AGG CAC ACA ATGGTG AG-3' and the reverse primer 5'-GCA ATG GTT CAA GCG ATT CTTC-3'. The PCR reaction was performed in a total volume of 20 ml containing 2 ml 10×PCR buffer, 1.5 mM MgCl₂, 0.2 mM dNTPs, 0.375 mM each primer, 200 ng of genomic DNA and 1 U of Taq DNA polymerase (MBI Fermentas). The PCR conditions were 94°C for 5 min, followed by 35 cycles of 60 s at 94°C, 60 s at 56°C and 60 s at 72°C, with a final elongation at 72°C for 10 min. An aliquot of 10 ml of the PCR product was digested with 5 U of Aci (New England BioLabs) in 2 ml of 10×NEB buffer 3 (100 mM NaCl, 50 mM Tris-HCl, 10 mM MgCl₂ and 1 mM dithiothreitol) and 7.5 ml dH₂O at 37°C overnight. The DNA fragments were separated on a 2% agarose gel containing 0.5 mg/ml ethidium bromide. The G homozygous yields three bands at 169, 120 and 61 bp, and the A homozygous produces two bands at 289 and 61 bp, where the heterozygote (GA) has four bands

at 289, 169, 120 and 61 bp. Approximately 10–15% of the samples were randomly selected for repeated assays, and the results were 100% concordant.

Statistical Analysis

Two-sided χ^2 test was used to evaluate the frequency distributions of select demographic variables, smoking status, alcohol use, and alleles and genotypes of MPO polymorphism between the test subjects and controls. The associations between MPO genotypes and the risk of colorectal cancer were estimated by computing the crude and adjusted odds ratios (ORs) and their 95% confidence intervals (95% CIs) from logistic regression analyses. The genotype data were further stratified by subgroups of age, sex, smoking status, and alcohol use. The multivariate analysis adjusted for age, sex, smoking status, and alcohol use. Two-sided tests of statistical significance were performed by using the SAS software (version 8.2; SAS Institute, Inc., Cary, North Carolina).

Results

Characteristics of the Study Population

The frequency distributions of select characteristics of the cases and controls are presented in Table 1. The cases and controls appeared to be well matched on age, sex. There was no significant difference in the frequency distributions of age and sex between the cases and controls ($P = 0.243$ for age and $P = 0.376$ for sex). However, there

Table 1. Frequencies Distributions of Selected Variables between the Colorectal Cancer Cases and Controls

Variables	Cases (n = 325)	Controls (n = 345)	P ^a	
Age	≤ 55	66 (20.3)	83 (24.1)	0.243
	> 55	259 (79.7)	262 (75.9)	
Sex	Male	266 (81.9)	273 (79.1)	0.376
	Female	59 (18.2)	72 (20.9)	
Smoking status	Never	112 (34.5)	204 (59.1)	<0.001
	Ever	213 (65.5)	141 (40.9)	
Drinking status	Never	130 (40.0)	195 (64.1)	<0.001
	Ever	195 (60.0)	124 (35.9)	

^aTwo-sided χ^2 test for the frequency distributions of selected variables between the cases and controls

Table 2. Genotype and Allele Frequencies of the MPO Polymorphism among the Cases and Controls

Genotypes	Cases	Control ^a	P ^b	Adjusted OR ^c (95% CI)
GG	206 (63.4)	175 (50.7)	0.002	1.00
GA	99 (30.5)	149 (43.2)		0.54 (0.38-0.76)
AA	20 (6.1)	21 (6.1)		0.82 (0.41-1.63)
GA/AA	119 (36.6)	170 (49.3)		0.57 (0.41-0.79)
A allele	0.214	0.277	0.009	

^aThe observed genotype frequencies among the control subjects were in agreement with the Hardy-Weinberg equilibrium ($\chi^2 = 2.137$, $P = 0.144$ for -463 G>A); ^bTwo-sided chi-square test for either genotype distributions or allele frequencies between the cases and controls; ^cOdds ratios (ORs) were obtained from a logistic regression model with adjustment for age, sex, smoking, and drinking status; 95% CI, 95% confidence interval. cOdds ratios (ORs) were obtained from a logistic regression model with adjustment for age, sex, smoking, and drinking status; 95% CI, 95% confidence interval

Table 3. Stratification Analyses between the MPO Polymorphism and Colorectal Cancer Risk

Variables n(case/control)	-463 G/A genotypes (case/control)		Pa	Crude OR (95% CI)	Adjusted OR ^b (95% CI)		
	GG	GA/AA					
Total	325/345	206/175 (63.4/50.7)	119/170 (36.6/49.3)	<0.001	0.60 (0.44-0.81)	0.57 (0.41-0.79)	
Age (years)	≤ 55	66/83	48/49 (72.7/59.0)	18/34 (27.3/41.0)	0.082	0.54 (0.27-1.08)	0.52 (0.25-1.09)
	> 55	259/262	158/126 (61.0/48.1)	101/136 (39.0/51.9)	0.003	0.59 (0.42-0.84)	0.56 (0.39-0.81)
Sex	Male	266/273	177/138 (66.5/50.5)	89/135 (33.5/49.5)	<0.001	0.51 (0.36-0.73)	0.47 (0.33-0.68)
	Female	59/72	29/37 (49.2/51.4)	30/35 (50.9/48.6)	0.800	1.09 (0.55-2.18)	1.30 (0.61-2.79)
Smoking status	Never	112/204	69/102 (61.6/50.0)	43/102 (38.4/50.0)	0.048	0.62 (0.39-0.99)	0.60 (0.37-1.01)
	Ever	213/141	137/73 (64.3/51.8)	76/68 (35.7/48.2)	0.019	0.60 (0.39-0.92)	0.54 (0.35-0.85)
Drinking status	Never	130/221	81/119 (62.3/53.9)	49/102 (37.7/46.2)	0.122	0.71 (0.45-1.10)	0.72 (0.46-1.13)
	Ever	195/124	125/56 (64.1/45.2)	70/68 (35.9/54.8)	<0.001	0.46 (0.29-0.73)	0.44 (0.27-0.71)

^aTwo-sided chi-square test for the distributions between the cases and controls; ^bOdds ratios (ORs) were obtained from a logistic regression model with adjustment for age, sex, smoking status, and alcohol use; 95% CI, 95% confidence interval

were more ever smokers (65.54%) and ever alcohol users (60.00%) among the cases than among the controls (40.9% and 35.9%, respectively), and these differences were statistically significant ($P < 0.001$ for both the tobacco smoking and alcohol use). Therefore, these variables were further adjusted in the multivariate logistic regression analysis to assess the main effect of the MPO -463 G>A polymorphism on risk of colorectal cancer.

Genotype Distributions of MPO Polymorphisms among the Cases and Controls

The genotype and allele frequencies of the MPO polymorphism and its association with risk of colorectal cancer are summarized in Table 2. The results revealed a significant association of MPO with the risk of colorectal cancer. For the MPO polymorphism, the GG, GA, and AA genotype frequencies were 63.4, 30.5, and 6.1%, respectively, among the cases and 50.7, 43.2, and 6.1%, respectively, among the controls. As a protective factor, the GA genotype frequency of MPO was lower among the cases (30.5%) than among the controls (43.2%), and this difference was significant ($P = 0.002$). The combined genotype GA/AA frequency of MPO was lower among the cases (36.6%) than among the controls (49.3%), and the difference was also significant. As shown in Table 2, the MPO allele frequencies was 0.214 among the cases and 0.277 among the controls, and the differences was also statistically significant ($P = 0.009$). The genotype distributions of the MPO polymorphisms among the controls was in agreement with the Hardy-Weinberg equilibrium ($\chi^2 = 2.137, P = 0.144$ for -463 G>A).

Association and Stratification Analysis between MPO Polymorphisms and Colorectal Cancer Risk

As shown in Table 3, individuals with GA/AA genotype had a significantly decreased risk of colorectal cancer (adjusted OR = 0.57, 95% CI, 0.41-0.79) than those with GG genotype. In the stratification analysis, we found that the decreased risk was more pronounced among older subjects (adjusted OR = 0.56, 95% CI, 0.39-0.81), men (0.47, 0.33-0.68), smokers (0.54, 0.35-0.85), and ever-drinkers (0.44, 0.27-0.71).

Discussion

In this hospital-based, case-control study, we assessed

the role of the MPO -463 A polymorphism in colorectal cancer susceptibility in Chinese population. The results indicated that the MPO -463 G to A variant was associated with the reduced risk of colorectal cancer especially among older subjects, men, smokers, and ever-drinkers.

As an important component of the neutrophil's antimicrobial armory, MPO catalyses the oxidation of chloride by hydrogen peroxide to produce bactericidal compound HOCl, and other reactive byproducts generated by MPO can also lead to damage to bystander cells and host DNA, which could drive the inflamed epithelia to malignancy at inflammatory sites (McKenzie et al., 1996; Whiteman et al., 1999). Since the MPO -463 G>A polymorphism was reported in 1993 by Austin et al (1993), it has been considered to be associated with a decreased risk of many human malignancies (Xu et al., 2002; Schabath et al., 2002). It has also been confirmed that the G to A variant appears to decrease expression of MPO for the loss of a SP1 transcription factor binding site (Piedrafita et al., 1996). A number of studies have shown the MPO GA/AA genotype to be associated with decreased susceptibility to lung cancer (Cascorbi et al., 2000; Schabath et al., 2002), while other studies have failed to replicate this inverse association (Le Marchand et al., 2000; Skuladottir et al., 2005). Findings by Hung et al (2004) suggested that individual susceptibility of bladder cancer may be modulated by MPO -463 G>A polymorphisms (OR .031; 95% CI, 0.12-0.80). Having at least one A allele was found to be associated with an overall 13% reduction in breast cancer risk (Ahn et al., 2004). Compared with wild-type GG, a protective factor of mutant genotype (AA + GA) was also found in laryngeal cancer patients (OR,0.63;95% CI,0.43-0.92;P= 0.017) (Cascorbi et al., 2000).

In this study, a significant difference of the MPO -463 G/A genotype distribution was found between colorectal cancer cases and controls. We observed 43 % reduced risk of colorectal cancer in individuals with MPO -463 GA/AA compared with the GG carriers (adjusted OR = 0.57, 95% CI, 0.41-0.79).

In the study, our findings also showed that MPO -463 G>A polymorphism had a significant decreased effect in risk of colorectal cancer in older subjects (age >55 years) than in younger subjects. Cascorbi et al (2000) reported that a significant decreased risk of lung cancer and laryngeal cancer was found in older subjects (age

>63 years) with GA or AA genotype. In older subjects, colorectal mucosal inflammation may decrease because of the progression of colorectal atrophy and metaplasia. In addition, a lower serum MPO level was exhibited in individuals with MPO -463 A allele. Therefore, MPO may promote the colorectal mucosal inflammation at an early stage in life, whereas it may not in older subjects. Conversely, Schabath et al (2002) observed a 72% reduced risk of lung cancer in younger subjects (age<61 years) (GA + AA versus GG) compared with a nonsignificant 22% reduced risk in older subjects. Relative high level exposure to carcinogens and weak immune system in older individuals may account for these. The reason for the different observations remains unclear.

We also found an interaction between MPO genotype and sex. The adjusted OR was 0.47 for GA/AA genotype compared with GG genotype among male individuals. But the OR was not statistically significant among female individuals. Our findings were consistent with previous observations of studies concerning lung cancer, laryngeal cancer, or gastric cancer (Yang et al., 2007; Steenport et al., 2007; Cascorbi et al., 2000). Reynolds et al (2000) reported that the Alu-HRE (Alu hormone responsive element (HRE)) from the MPO A allele, with the -463A, was bound by estrogen receptor whereas the -463G element was not bound. And estrogen could increase MPO -463 A promoter activity by several times, while has no significant effect on MPO -463 G promoter activity. Thus it is a reasonable hypothesis that the absence of protective effect of the MPO -463 A variant in female subjects may be due to the elevation of MPO -463 A promoter activity by estrogen.

Tobacco smoke contains hundreds of chemicals, some of which are carcinogens, such as polycyclic aromatic hydrocarbons and N-nitroso compounds. Our results suggested that the MPO mutant genotype had a significant protective effect on colorectal cancer risk for current smokers. Schabath et al (2002) observed that the MPO mutant genotype had a significant protective effect on lung cancer risk for current smokers. Similar interactions were documented by Lu et al (2002) and Hung et al (2004). However, other data could not find the interaction between MPO genotype and smoking status. MPO can participate in the activation of carcinogens in tobacco smoke, such as BP (Benzo(a)pyrene) to BPDE (Benzo(a)pyrene diol-epoxide), its ultimate carcinogen (Petruska et al., 1992) in vivo formation of BPDE-DNA adducts in the skin of patients treated with a similar dose of coal tar was significantly affected by MPO genotypes. Individuals with the MPO -463 (GA or AA) variant had 4-fold lower BPDE-DNA adduct levels compared to those with the wild-type MPO (Rojas et al., 2001). Compounds in smoke, such as 2-naphthylamine and 4-aminobiphenyl, can cause genotoxic events in the colorectal epithelium (Zhu et al., 2006; Cascorbi et al., 2000; Petruska et al., 1992). In addition, the chemicals in cigarette smoke can result in carcinogenic events in colorectal epithelium. Tobacco smoking enhances cellular proliferation and may have a synergistic effect on colorectal carcinogenesis (Johansson et al., 1997; Lijinsky et al., 1992).

Alcohol consumption is a factor in the onset of

colorectal cancer (Moskal et al., 2007). The primary breakdown product of ethanol in the body, acetaldehyde, has been shown to cause damage to the DNA, thereby contributing to cancer risk (Boffetta and Hashibe, 2006). Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells (Pöschl et al., 2004). Our results suggested that the MPO mutant genotype had a significant protective effect on colorectal cancer risk for ever-drinkers. The effects of alcohol may be mediated through the production of the generation of free radical oxygen species. MPO -463 G>A polymorphism in the promoter region of the gene results in reduced gene expression which, in turn, decrease enzymes, implying a lower susceptibility of colorectal cancer in mutant carriers (Pöschl et al., 2004). Shama (2008) observed that the MPO mutant genotype had a significant protective effect on oral cancer risk for ever-drinkers. However, other data could not find the interaction between MPO genotype and drinking status. So the mechanism is still unclear. The hypothesis and mechanism both need to be further tested in larger studies.

In conclusion, our results showed that the MPO -463 G>A variant may be associated with the decreased risk of colorectal cancer in Chinese population, suggesting that the polymorphism of MPO -463 G>A is involved in the colorectal carcinogenesis. The interactions between the MPO -463 G>A genotype and sex, age, tobacco smoking, alcohol use and colorectal cancer also have been demonstrated in this study. These findings, after validation by larger studies, may help identify at-risk populations for primary cancer prevention. Larger studies with more detailed environmental exposure data and more detailed clinical information about tumors are needed.

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