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• ESOPHAGEAL CANCER •

NQO1 C609T polymorphism associated with esophageal cancer and gastric cardiac carcinoma in North China

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Abstract

AIM: To investigate the association of the *NQO1* (C609T) polymorphism with susceptibility to esophageal squamous cell carcinoma (ESCC) and gastric cardiac adenocarcinoma (GCA) in North China.

METHODS: The *NQO1* C609T genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis in 317 cancer patients (193 ESCC and 124 GCA) and 165 unrelated healthy controls.

RESULTS: The *NQO1* C609T C/C, C/T and T/T genotype frequency among healthy controls was 31.5 %, 52.1 % and 16.4 % respectively. The *NQO1* T/T genotype frequency among ESCC patients (25.9 %) was significantly higher than that among healthy controls (χ^2=4.79, *P*=0.028). The *NQO1* T/T genotype significantly increased the risk for developing ESCC compared with the combination of C/C and C/T genotypes, with an age, sex and smoking status adjusted odds ratio (OR) of 1.78 (1.04-2.98). This increased susceptibility was pronounced in ESCC patients with family histories of upper gastrointestinal cancers (UGIC) (adjusted OR=2.20, 95 % CI=1.18-3.98). Similarly, the susceptibility of the *NQO1* T/T genotype to GCA development was also observed among patients with family histories of UGIC, with an adjusted odds ratio of 2.55 (95 % CI=1.21-5.23), whereas no difference in *NQO1* genotype distribution was shown among patients without family histories of UGIC.

CONCLUSION: Determination of the *NQO1* C609T genotype may be used as a stratification marker to predicate the individuals at high risk for developing ESCC and GCA in North China.

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INTRODUCTION

China is a country with high incidence regions of esophageal squamous cell cancer (ESCC) and gastric cardiac adenocarcinoma (GCA). Chemical carcinogenesis existed in consumed alcohol and tobacco or ingested food[1,2], nutrition deficiency[3], unhealthy living habits[2] and pathogenic infections[4-6] are in general considered as the risk factors for developing these two cancers. However, not all individuals exposed to the above exogenous risk factors will develop ESCC or GCA, indicating that the host susceptibility factors may play an important role in the cancer development. The role of a genetic background in developing these cancers was also strongly suggested by the familial clustering of upper gastrointestinal cancer (UGIC) patients in high incidence regions[7,8].

In recent years, many polymorphic genes encoded carcinogen metabolic enzymes have been found to be associated with susceptibility to chemically induced cancers such as esophageal cancer and gastric cancer[9-13]. NAD(P)H: quinone oxidoreductase 1 (NQO1) is a cytosolic enzyme which catalyzes the two-electron reduction of quinone compounds and prevents the generation of semiquinone free radicals and reactive oxygen species, thus protecting cells from oxydative damage[14]. On the other hand, NQO1 catalyzes the reductive activation of quinoid chemotherapeutic agents and of environmental carcinogens such as nitrosamines, heterocyclic amines and cigarette smoke condensate[15]. The activity of the NQO1 enzyme may be influenced by a single C to T substitution at nucleotide 609 of exon 6 of the *NQO1* cDNA that causes the Pro187Ser amino acid change[16]. The homozygous wild-type (C/C) encodes NQO1 protein with complete enzyme activity, whereas the protein encoded by the heterozygous phenotype (C/T) has approximately three-fold decreased activity and the homozygous mutant (T/T) phenotype has a complete lack of enzyme activity[15-18]. The *NQO1* C609T polymorphism is correlated with the susceptibility to several chemical carcinogen induced tumors such as lung cancer[19,20] and leukemia[21,22]. The association of *NQO1* C609T polymorphism with the susceptibility to ESCC and GCA has not been reported so far. Therefore, the current study investigated the *NQO1* C609T genotype distribution in ESCC and GCA patients and healthy controls from North China.

MATERIALS AND METHODS

Subjects

This case-control study recruited 317 patients with histologically confirmed cancers (193 esophageal cancer and 124 gastric cardiac cancer) and 165 unrelated healthy controls. The cancer patients were hospitalized for tumor resection in the Fourth Affiliated Hospital of Hebei Medical University between 2001 and 2002. The histological pattern of the resected samples was determined by pathologists of the same hospital according to the international standard[23]. The healthy controls were unrelated blood donors or voluntary staff of Hebei Cancer

Institute. All of the patients and controls were from Shijiazhuang city or its surrounding regions. The information about sex, age, smoking habits and family history was obtained from the cancer patients by their hospital recordings and from the healthy controls by interview directly after bleeding. The smokers were defined as ex- or current smoking 5 cigarettes per day for at least two years. The individuals with at least one first-degree relative or at least two second-degree relatives having esophageal/cardiac/gastric cancer were defined as having family histories of upper gastrointestinal cancers (UGIC). The informed consent was obtained from all the recruited subjects. The study was approved by the Ethics Committee of the Hebei Cancer Institute. The demographic data of the cancer patients and healthy controls are presented in Table 1.

DNA extraction

Five ml of venous blood from each subject was drawn in vacutainer tubes containing EDTA. The genomic DNA was extracted within one week after bleeding using proteinase K digestion followed by a salting out procedure.

NQO1 genotyping

NQO1 genotyping of healthy controls and ESCC patients was performed at the Molecular Laboratory of the Institute of Pathology, Heinrich-Heine University, Duesseldorf. The genotyping of the GCA patients was performed at the Molecular Biology Laboratory of the Hebei Cancer Institute with the same reagents and the same methods. The base change (C to T) at nucleotide 609 of *NQO1* cDNA created a *Hinf I* restriction site. Therefore, the *NQO1* C609T genotyping was performed by PCR and subsequent restriction fragment analysis. PCR was performed in a 25 μl volume containing 100 ng DNA template, 2.5 μl 10×PCR-buffer, 1 U Hotstar Taq-DNA-polymerase (Qiagen, Hilden, Germany), 200 μmol dNTPs and 10 pmol sense primer (5' AAGCCCAGACCAACTTCT-3') and antisense primer (5' -ATTTGAATTCGGGCGTCTGCTG-3'). Initial denaturation for 14 min at 94 ℃ was followed by 40 cycles at 94 ℃ for 1 min, at 56 ℃ for 1 min, and at 72 ℃ for 2 min. The PCR products were subsequently digested with 20 units of *Hinf* I (Boehringer, Mannheim, Germany) for 3 h at 37 ℃ and separated on a 2 % agarose gel (Figure 1). The *NQO1* wild-type allele showed a 172-bp PCR product resistant to enzyme digestion, whereas the null allele showed a 131-bp and a 41-bp band. For quality control, each PCR reaction used distilled water instead of DNA as a negative control, and 10 % of the samples were analyzed twice.

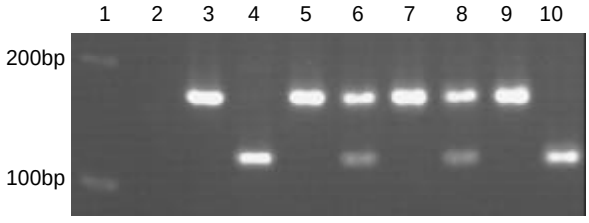

Figure 1 Genotype patterns for *NAD(P)H: quinone oxidoreductase 1 (NQO1)* C609T polymorphism analyzed by PCR-*Hinf I* digestion. Lane 1, 100bp molecular marker; lane 2, negative control; lane 3, PCR fragment containing *NQO1* C609T polymorphism; lanes 4,10, homozygous null genotype (T/T); lanes 5,7,9, homozygous wild genotype (C/C); lanes 6,8, heterozygous genotype (C/T).

Statistical analysis

The comparison of *NQO1* genotype distribution in the study groups was performed by means of two-sided contingency tables using Chi-square test. Hardy-Weinberg analysis was performed to compare the observed and expected genotype frequencies using Chi-square test. A probability level of 5 % was made as statistically significant. The odds ratio (OR) and 95 % confidence interval (CI) were calculated and adjusted for age, sex and smoking status with the unconditional logistic regression model. Statistical analysis was made using SPSS software package (10.0 version).

RESULTS

As shown in Table 1, the composition of gender, age and the proportion of smokers in ESCC and GCA patients were compared with the healthy controls. Eighty-six (44.6 %) of the ESCC and 45 (36.3 %) of the GCA patients had family histories of UGIC. The proportion of age, sex and smoking status in ESCC and GCA patients with and without family histories of UGIC was also not significantly different (data not shown). None of the healthy controls had a family history of UGIC.

The *NQO1* C609T genotyping was successfully performed in all study subjects. The observed *NQO1* genotype frequencies were not significantly deviated from those expected from Hardy-Weinberg equilibrium in the healthy controls (χ^2=0.061; *P*=0.970), ESCC patients (χ^2=0.166; *P*=0.920) and GCA patients (χ^2=0.832; *P*=0.660). The *NQO1* C609T genotype distribution among healthy controls was 31.5 % (C/C), 52.1 % (C/T), and 16.4 % (T/T) respectively (Table 1). The genotype distribution was not correlated with gender, age and smoking status in each study group (data not shown).

Table 1 Demographic characteristics and *NQO1* polymorphism among ESCC, GCA patients and controls

Groups	Control *n* (%)	ESCC *n* (%)	GCA *n* (%)
Sex			
Male	109(66.1)	124(64.3)	92(74.2)
Female	56(33.9)	69(35.7)	32(25.8)
Mean age ±SD (yrs)	52±7.16	59±8.73	60±8.24
Smoking status			
Smoker	82(49.7)	104(53.9)	68(59.8)
Non-smoker	83(50.3)	89(46.1)	46(40.2)
Family history of UGIC			
Positive	0	86(44.6)	45(36.3)
Negative	165(100)	107(55.4)	79(63.7)
Genotype			
C/C	52(31.5)	51(26.4)	40(32.3)
C/T	86(52.1)	92(47.7)	55(44.3)
T/T	27(16.4)	50(25.9)[a]	29(23.4)
Allele type			
C	190(57.6)	194(50.3)	135(54.4)
T	140(42.4)	192(49.7)[b]	113(45.6)

Note. ESCC: esophageal squamous cell carcinoma; GCA: gastric cardiac adenocarcinoma; *NQO1: NAD(P)H: quinone oxidoreductase 1;* UGIC: upper gastrointestinal cancer; a. The genotype frequency was significantly higher than that in healthy controls (χ^2=4.79, *P*=0.028); b. The allele frequency was marginaly higher than that in healthy controls (χ^2=3.83, *P*=0.05).

The overall *NQO1* null-allele frequency among ESCC patients (49.7 %) was marginally higher than that among healthy controls (42.4 %) (χ^2=3.83, *P*=0.05). There was no difference in allele distribution between GCA patients and healthy controls (χ^2=0.567, *P*=0.451) (Table 1). The distribution of *NQO1* C/C and C/T genotypes among ESCC and GCA

patients was not significantly different from that among healthy controls (P>0.05) (Table 1).

Interestingly, in ESCC patients, the *NQO1* T/T genotype was significantly more frequent (25.9 %) than that among healthy controls (χ^2=4.79, P=0.028) (Table 2). The relative risk of the T/T genotype for the ESCC development was increased by about 1.8 fold compared with the combination of the C/C or C/T genotypes, with an age, sex and smoking status adjusted odds ratio of 1.78 (95 % CI=1.04-2.98). When stratified for the family history of UGIC, the *NQO1* T/T genotype was significantly more common among patients with family histories of UGIC (30.2 %) than that among healthy controls (χ^2=6.53, P=0.011). The T/T genotype significantly increased the risk for developing ESCC among patients with family histories of UGIC, compared with the C/C and C/T genotypes (adjusted OR=2.20, 95 % CI=1.18-3.98). In contrast, the *NQO1* T/T genotype frequency was not significantly different between ESCC patients without family history of UGIC (22.4 %) and healthy controls (χ^2=1.49, P=0.223) (Table 2).

In line with the result of ESCC, the *NQO1* T/T genotype significantly increased the risk for developing GCA compared with the C/C and C/T genotypes. However, this increased risk was only demonstrated when stratified for the family history. Thus, among GCA patients with family histories of UGIC, the T/T frequency (33.3 %) was significantly higher than that among healthy controls (χ^2=6.36, P=0.012). In this patient group, the relative risk of the T/T genotype for developing GCA was more than two-fold higher compared with the combination of C/C and C/T genotypes (adjusted OR=2.55, 95 % CI=1.21-5.23), whereas the *NQO1* T/T genotype frequency among the overall GCA patients (23.4 %) and GCA patients without family histories of UGIC (17.7 %) remained similar to that of the healthy controls (P>0.05) (Table 2).

Table 2 Relative risk of the *NQO1* C609T homogenous null for ESCC and GCA development

Groups	*NQO1* genotype		aOR (95%CI)[d]
	C/C+C/T *n* (%)	T/T *n* (%)	
Healthy controls	138(83.6)	27(16.4)	
ESCC patient	143(74.1)	50(25.9)[a]	1.78 (1.04-2.98)
Family history of UGIC			
Positive	60(69.8)	26(30.2)[b]	2.20 (1.18-3.98)
Negative	83(77.6)	24(22.4)	1.46 (0.79-2.63)
GCA patient	95(76.6)	29(23.4)	1.44 (0.86-2.30)
Family history of UGIC			
Positive	30(66.7)	15(33.3)[c]	2.55 (1.21-5.23)
Negative	65(82.3)	14(17.7)	1.10 (0.80-1.34)

Note. ESCC: esophageal squamous cell carcinoma; *NQO1:NAD (P)H: quinone oxidoreductase 1*; UGIC: upper gastrointestinal cancer; a,b,c. The genotype frequency was significantly higher than that in healthy controls (a. χ^2=4.79, P=0.028; b. χ^2=6.53, P=0.011; c. χ^2=6.36, P=0.012); d. The age, sex and smoking status adjusted relative risk of the *NQO1* C609T homogenous null genotype (T/T) against the combination of the heterozygote (C/T) and homozygous wild type (C/C).

To observe the different influence of the *NQO1* C609T polymorphism on the ESCC or GCA development among smokers and non-smokers, the genotype distribution was also stratified according to the smoking habits. No difference in *NQO1* genotype distribution among smoking or non-smoking ESCC and GCA patients was observed as compared with that of the healthy controls (data not shown).

DISCUSSION

Both of ESCC and GCA are characterized by a particularly poor prognosis since most of patients are diagnosed at advanced stages. Endoscopic examination is the only feasible way to detect ESCC and GCA at early and/or precancerous stages. However, the wide application of this method is limited by the high cost and painfulness of the examination. The laboratory identification of high-risk individuals, in combination with the clinical detection, will provide a promising way to detect the early tumors.

The present hospital based case control study suggests that *NQO1* C609T homozygous null genotype may increase the susceptibility to ESCC and GCA in the northern Chinese population. This result is consistent with the previous investigations, which showed that the *NQO1* homozygous null genotype increased the susceptibility to other tumor types such as lung cancer[19], leukemia[21,22] and cutaneous cancers[24]. The underlying mechanism of the correlation of *NQO1* C609T polymorphism with increased risk for developing various tumors may be related to the different enzyme activities encoded by the different *NQO1* genotypes. Thus, lack of NQO1 activity encoded by the homozygous null genotype results in a reduced detoxification of exogenous carcinogens and leads cells to be easily damaged by oxidation, and thereby increasing the susceptibility to chemically induced cancers such as ESCC and GCA. In addition, the recessive effect of the *NQO1* C609T null allele on the development of ESCC and GCA was suggested by the current study, since the heterozygous genotype frequency among tumor patients was similar to that among healthy controls. The result indicates that although the *NQO1* heterozygous genotype results in a three-fold decrease of the NQO1 enzyme activity, it may be sufficient for protecting cells from damage by exogenous carcinogens.

In this study, the increased risk of the *NQO1* C609T homozygous null genotype for developing both of ESCC and GCA was only evident in patients with family histories of UGIC, indicating that in families aggregated with UGIC patients, a predisposition to ESCC and GCA may be inherited by lack of *NQO1* enzyme activity. A strong association of increased risk for esophageal cancer with a positive family history of UGIC in the first-degree relatives has been reported in the high incidence regions of China[7,8]. The segregation analysis on the high-risk nuclear families suggested that the ESCC occurrence was best fit to the autosomal recessive Mendelian inheritance[8]. However, the underlying molecular mechanisms for the familial clustering of UGIC patients have not been elucidated so far. Our results suggested, that the *NQO1* C609T polymorphic gene, together with other possible susceptible genes, might give an opportunity to challenge the genetic mechanisms of cancer development in the UGIC clustered families and provide a chance to predict high-risk individuals in the high-incidence regions. In addition, the consistent association of *NQO1* C609T polymorphism with the susceptibility to ESCC and GCA, as shown in this study, supports that there might be a common genetic background in the development of these two tumor types. However, the result should be interpreted cautiously, since the number of cases, especially in the subgroup analyses, was probably too small to draw a final conclusion.

In summary, our preliminary data suggest that the *NQO1* C609T gene polymorphism may influence the susceptibility to ESCC and CAC in a northern Chinese population. Determination of *NQO1* C609T genotype may provide a useful genetic marker in predicating high-risk individuals for the development of ESCC and CAC. It is worthwhile conducting additional population-based studies including enlarged subjects before its clinical application.

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