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Interactive Effect of Smoking and *NQO1* Haplotypes on Lung Cancer Risk

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The role of genetic polymorphisms of NAD(P)H:quinone oxidoreductase 1 (*NQO1*), which is known to be related to carcinogen metabolism and oxidative status, was evaluated for lung cancer development. The genotypes of two *NQO1* polymorphisms, namely, IVS1-27C>G and Ex6+40C>T, were determined in 616 lung cancer cases and 616 lung cancer-free controls and haplotypes composed of the two polymorphisms were estimated. In the evaluation of the effect of the *NQO1* genotypes or diplotypes, we did not find any significant association with lung cancer risk after adjusting for body mass index and smoking status. However, when we evaluated the effect of the *NQO1* diplotypes for lung cancer risk in combination with smoking, smokers without the C-T/C-T diplotype showed a significantly increased risk of lung cancer compared with nonsmokers without the C-T/C-T diplotype (adjusted OR, 2.2; 95% CI, 1.67-3.02), and smokers with the C-T/C-T diplotype showed the highest OR of lung cancer (adjusted OR, 2.7; 95% CI, 1.78-4.21). Moreover, a trend test showed an additive interaction between smoking and the *NQO1* C-T/C-T diplotype ($P_{trend} < 0.01$). The additive effect of smoking and the *NQO1* C-T/C-T diplotype was more apparent in squamous cell carcinoma, although this effect was statistically significant in all lung cancer cell types (all cell types, $P_{trend} < 0.05$). This result suggests that haplotypes of the *NQO1* gene play an important role in the development of lung cancer by interaction with smoking.

Keywords: Smoking; *NQO1* Polymorphism; Lung Cancer Risk; Interaction

INTRODUCTION

Global statistics estimate that approximately 25% of lung cancers are not directly attributable to smoking although cigarette smoking has been known to be the major cause of lung cancer (1). Moreover, only 10% of smokers develop lung cancer (2). These observations suggest that genetic variations related to the individual metabolism may determine susceptibility to lung cancer.

NAD(P)H:quinone oxidoreductase 1 (NQO1, previously called DT-diaphorase), a protein related to carcinogen metabolism, functions as a cytosolic flavoenzyme that catalyzes the electron reduction of substrate, to reduce oxidative stress (3). NQO1 catalyzes highly toxic quinones derived from tobacco smoking to less toxic hydroquinone analogues as a two-electron reductase (3-5). Moreover, cellular oxidation-reduction events controlled by this enzyme regulate the level of p53, a tumor suppressor (6). Because of their major role in cytoprotection and the inhibition of reactive oxygen generation in human tissue (7-9), the expression or mutation of the *NQO1* gene has been considered to be potentially associated with the risk of cancer in the lung or other sites (10-16).

One point mutation in exon 6 of the *NQO1* gene involves a C-to-T base pair substitution at position 609 of *NQO1* cDNA, which codes for a proline-to-serine change at position 187 in the amino acid sequence of NQO1 protein. This *NQO1* pro187ser polymorphism has been reported to be associated with greatly diminished levels of protein due to its accelerated degradation via the ubiquitin proteasomal pathway (17, 18). Moreover, in genotype-phenotype studies, cell lines and tissues obtained from persons with the homozygous mutant *NQO1* genotype were reported to show deficient NQO1 activity (19-22). Although several studies have reported a relation between the *NQO1* pro187ser polymorphism and lung cancer risk, their results were found to be inconsistent probably due to small sample sizes, mixed populations, or disregard of polymorphisms in other sites of the *NQO1* gene (10-15, 23-27).

Therefore, in this study we estimated the effects of *NQO1* gene polymorphisms on lung cancer risk using a haplotype-based approach in a relatively large sample.

MATERIALS AND METHODS

Study populations

A total of 616 Korean patients that were newly diagnosed with lung cancer at Chungbuk National University Hospital in Cheongju, Dankook University Hospital in Cheonan, and Inha Univer-

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sity Hospital in Incheon between 2001 and 2003, and 616 controls without lung cancer that were individually matched to cases by age and sex were recruited. The exclusion and inclusion criteria applied were reported in a previous study (2, 28). Detailed information on diet, smoking habits, lifestyle, weight, height, medical treatment, and other socio-economic characteristics were collected by trained interviewers using a structured questionnaire. Venous blood samples of all subjects were collected into heparinized tubes and stored at -70°C until used for DNA extraction.

Genotyping

In studies of single nucleotide polymorphism (SNP) based on limited numbers of subjects, low minor allele frequencies of SNPs may lead to null results, despite meaningful relationships between these SNPs and target diseases. Therefore, we first selected four *NQO1* SNPs (rs689452, rs689453, rs1800566, and rs10517) which have more than 10% minor allele frequencies based on the SNP500Cancer database (http://snp500cancer.nci.nih.gov/home.cfm). Dan Stram's haplotype-tagging SNP program (*tagSNPsv2.exe*) was then used to determine the best set of haplotype-tagging SNPs. Based on this tagging SNP program, three SNPs (rs689452, rs689453 and rs1800566; min RSQ = 0.9507) were selected from the above four and genotyped in 43 controls preferentially. One (rs689453) of these SNPs (rs689452, rs689453, and rs1800566) was excluded for further genotyping because it showed the same genotype (GG) in all of the 43 controls. Finally, two sites (rs689452, IVS1-27C>G; and rs1800566, Ex6+40C>T) were genotyped in all samples. Genotypings were performed completely blind of case-control status, and repeatability testing was conducted on 5% of the subjects, which resulted in a 99.6% concordance rate.

DNA was extracted from whole blood samples using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). SNP genotyping was performed using a single base primer extension assay (for rs689452) with the SNaPShot assay kit (ABI, Foster City, CA, USA) and using SNP-IT™ assays (for rs1800566) with the SNPstream 25K® System (Orchid Biosciences, Princeton, NJ, USA), as previously described (29). The designed primers were as follows: rs689452-forward, 5′-TCCTTTACAGACTGCAACTCC-3′, rs689452-reverse, 5′-TCTGAGTGAGCCAGTACGATC-3′, rs689452-SNP, 5′-TTTGCTGGTTGGTAATGGGTTTTCC-3′; rs1800566-forward, 5′-TGTGCTTTCTGTATCCTCAGAGT-3′, rs1800566-reverse, 5′-ATTTGAATTCGGGCGTCT-3′, rs1800566-SNP, 5′- TGCCCAATGCTATATGTCAGTTGAG-3′.

Statistical analyses

To identify whether each SNP site was on the Hardy-Weinberg equilibrium (HWE), the distributions of observed and expected genotype frequencies were compared using the chi-square test. When genotype data was not available for at least one of the two SNPs, the subjects with missing genotype were excluded in haplotype estimation. Individual haplotypes composed of two polymorphisms, IVS1-27C>G and Ex6+40C>T, were estimated from genotype data using the PHASE program (ver. 2.0.2). Linkage disequilibrium between two polymorphic sites was estimated as the relative disequilibrium (*D′*) (30). Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the *NQO1* polymorphisms in the lung cancer patients and control subjects. A probability level of 0.05 was used as the criterion for statistical significance, and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis.

Ethics statement

The study protocol was approved by institutional review board at the Seoul National University Hospital (IRB No., C-0602-083-169). Written informed consent was provided by all study participants.

RESULTS

The characteristics of the lung cancer cases and control subjects are shown in Table 1. Body mass index (BMI) and smoking were found to affect the OR of lung cancer (BMI, OR, 1.1; 95% CI, 1.06-1.14; and smoking, OR, 2.4; 95% CI, 1.86-3.09) while age, sex, and family history of cancer were not significantly different between cases and controls.

Table 1. Comparison of the baseline characteristics of lung cancer cases and controls

Characteristics	Case (n = 616)	Control (n = 616)	Crude OR (95% CI)
Age (mean ± SD [yr])	65.3 ± 10.2	65.3 ± 10.2	1.0 (0.99-1.01)
Sex (number of male [%])	483 (78.4)	483 (78.4)	1.0 (0.76-1.31)
Body mass index (mean ± SD [kg/m^2])	22.0 ± 3.3	22.9 ± 3.1	1.1 (1.06-1.14)
Cigarette smoking (number of smokers [%])	490 (79.6)	381 (61.9)	2.4 (1.86-3.09)
Family history of cancer (% present)	118 (22.7)	105 (20.9)	1.1 (0.82-1.49)
Cell type of lung cancer (number [%])			
AC	168 (27.3)		
SCC	240 (39.0)		
Other NSCLCs	112 (18.1)		
SCLC	96 (15.6)		

AC, adenocarcinoma; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; OR, odds ratio; CI, confidence interval.

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In the evaluation of the effect of the *NQO1* genotypes (Table 2), we did not find any significant association with lung cancer risk after adjusting for BMI and smoking status, although the CC genotype of Ex6+40C>T showed a preventive effect for lung cancer risk as shown by its crude OR (crude OR, 0.7; 95% CI, 0.50-0.97).

When we tested HWE of each *NQO1* site, both cases and controls were found to be on the HWE (both IVS1-27C>G and Ex6+40C>T, $P > 0.05$). In addition, the two sites were found to be strongly linked ($D' = 1$, $P < 0.01$). Therefore, we evaluated the effect of the *NQO1* diplotypes for lung cancer risk and did not find any significant association with lung cancer risk after adjusting for BMI and smoking status (Table 3). Because smoking is a major risk factor of lung cancer and the *NQO1* is related to the metabolism of tobacco carcinogens, we evaluated the effects of smoking in combination with the various *NQO1* diplotypes. When smoking status and diplotypes were analyzed as categorical variables (Table 4), both smokers with the C-T/C-T diplotype and smokers without the C-T/C-T diplotype showed significantly higher risks of lung cancer than nonsmokers without the C-T/C-T diplotype (adjusted OR, 2.7; 95% CI, 1.78-4.21 and adjusted OR, 2.2; 95% CI, 1.67-3.02, respectively). In addition, the trend test showed an additive interaction of smoking with the *NQO1* diplotype ($P_{trend} < 0.01$). Furthermore, when we estimated the combined effect of smoking and the *NQO1* diplotypes on non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) separately (Table 4), the additive effect of smoking and the *NQO1* diplotype was found in both NSCLC and SCLC although the OR of lung cancer was greater in SCLC than in NSCLC. In the analyses of each NSCLC cell type (Table 5), the additive effect of smoking and *NQO1* diplotype was found to be more apparent in squamous cell carcinoma (SCC) than in adenocarcinoma (AC) or in other NSCLCs, although all types showed similar trends in terms of the combined effect of smoking and *NQO1* diplotypes on lung cancer risk.

Table 2. Distribution of *NQO1* genotypes and lung cancer risks

Genotypes (rs number)	Case, No. (%)	Control, No. (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
IVS1-27C>G (rs689452)				
CC	247 (40.6)	228 (37.2)	1.1 (0.77-1.56)	1.0 (0.70-1.47)
CG	277 (45.6)	299 (48.9)	0.9 (0.67-1.32)	0.8 (0.58-1.21)
CC+CG	524 (86.2)	527 (86.1)	1.0 (0.73-1.39)	0.9 (0.65-1.29)
GG	84 (13.8)	85 (13.9)	1.0 (ref.)	1.0 (ref.)
Ex6+40C>T (rs1800566)				
CC	189 (30.8)	213 (34.6)	0.7 (0.50-0.97)	0.7 (0.51-1.04)
CT	306 (49.8)	309 (50.3)	0.8 (0.57-1.06)	0.8 (0.54-1.06)
CC+CT	495 (80.6)	522 (84.9)	0.7 (0.55-1.00)	0.7 (0.54-1.03)
TT	119 (19.4)	93 (15.1)	1.0 (ref.)	1.0 (ref.)

*OR obtained after adjusted for BMI and smoking status. OR, odds ratio; CI, confidence interval.

DISCUSSION

NQO1 has been reported to be an important factor for carcinogen metabolism and cancer patient survival (3). However, previous studies have produced inconsistent results on the associations between lung cancer risk and *NQO1* gene polymorphisms (10-15, 26, 27). Because these inconsistencies may have been due to small sample sizes or disregard for other polymorphisms

Table 3. *NQO1* diplotypes and lung cancer risk

Diplotypes*	Case, No. (%)	Control, No. (%)	Crude OR (95% CI)	Adjusted OR† (95% CI)
C-T/G-C	189 (31.2)	191 (31.3)	1.0 (ref.)	1.0 (ref.)
C-T/C-C	113 (18.7)	115 (18.8)	1.0 (0.72-1.38)	1.1 (0.74-1.49)
C-T/C-T	115 (19.0)	92 (15.1)	1.3 (0.90-1.78)	1.3 (0.92-1.90)
C-C/G-C	88 (14.5)	107 (17.5)	0.8 (0.59-1.18)	0.9 (0.61-1.27)
G-C/G-C	82 (13.5)	85 (13.9)	1.0 (0.68-1.40)	1.1 (0.77-1.65)
C-C/C-C	19 (3.1)	21 (3.4)	0.9 (0.48-1.76)	0.9 (0.47-1.87)
Total	606 (100)	611 (100)		

*A pair of haplotypes composed of two polymorphic sites, IVS1-27C>G and Ex6+40C>T. †OR obtained after adjusted for BMI and smoking status. OR, odds ratio; CI, confidence interval.

Table 4. The effects of smoking and *NQO1* diplotypes on the risk of NSCLC or SCLC

Subgroup of lung cancer	Smoking status	Diplotypes*	Case, No. (%)	Control, No. (%)	Crude OR (95% CI)	Adjusted OR‡ (95% CI)	P_{trend}§
All	Nonsmoker	Others†/Others or C-T/Others	98 (16.2)	201 (32.9)	1.0 (ref.)	1.0 (ref.)	< 0.01
		C-T/C-T	27 (4.5)	33 (5.4)	1.7 (0.96-2.95)	1.6 (0.87-2.94)	
	Smoker	Others/Others or C-T/Others	393 (64.8)	318 (52.0)	2.5 (1.91-3.36)	2.2 (1.67-3.02)	
		C-T/C-T	88 (14.5)	59 (9.7)	3.1 (2.03-4.60)	2.7 (1.78-4.21)	
NSCLC	Nonsmoker	Others/Others or C-T/Others	88 (17.2)	169 (32.7)	1.0 (ref.)	1.0 (ref.)	< 0.01
		C-T/C-T	24 (4.7)	31 (6.0)	1.5 (0.82-2.69)	1.4 (0.76-2.69)	
	Smoker	Others/Others or C-T/Others	328 (63.9)	265 (51.3)	2.4 (1.75-3.22)	2.1 (1.51-2.87)	
		C-T/C-T	73 (14.2)	52 (10.0)	2.7 (1.74-4.18)	2.5 (1.56-3.95)	
SCLC	Nonsmoker	Others/Others or C-T/Others	10 (10.8)	32 (34.0)	1.0 (ref.)	1.0 (ref.)	< 0.01
		C-T/C-T	3 (3.2)	2 (2.1)	4.8 (0.70-32.90)	5.0 (0.39-63.04)	
	Smoker	Others/Others or C-T/Others	65 (69.9)	53 (56.4)	3.9 (1.77-8.71)	3.8 (1.69-8.71)	
		C-T/C-T	15 (16.1)	7 (7.5)	6.9 (2.18-21.53)	5.0 (1.55-16.33)	

*A pair of haplotypes composed of two polymorphic sites, IVS1-27C>G and Ex6+40C>T. †Other haplotypes except C-T. ‡OR obtained after adjusted for BMI. §*P* value obtained from the Cochran-Armitage trend test. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; OR, odds ratio; CI, confidence interval.

Table 5. The effects of smoking and *NQO1* diplotypes on lung cancer risk in each NSCLC cell type

Cell type	Smoking status	Diplotypes*	Case, No. (%)	Control, No. (%)	Crude OR (95% CI)	Adjusted OR‡ (95% CI)	P_{trend}§
AC	Nonsmoker	Others†/Others or C-T/Others	45 (27.1)	65 (38.9)	1.0 (ref.)	1.0 (ref.)	0.02
		C-T/C-T	11 (6.6)	11 (6.6)	1.4 (0.58-3.62)	1.4 (0.55-3.38)	
	Smoker	Others/Others or C-T/Others	93 (56.0)	78 (46.7)	1.7 (1.06-2.80)	1.7 (1.04-2.87)	
		C-T/C-T	17 (10.3)	13 (7.8)	1.9 (0.84-4.27)	1.7 (0.76-4.04)	
SCC	Nonsmoker	Others/Others or C-T/Others	17 (7.3)	60 (25.2)	1.0 (ref.)	1.0 (ref.)	< 0.01
		C-T/C-T	5 (2.1)	11 (4.6)	1.6 (0.49-5.25)	2.1 (0.55-8.16)	
	Smoker	Others/Others or C-T/Others	169 (71.9)	136 (57.2)	4.4 (2.45-7.86)	3.1 (1.69-5.86)	
		C-T/C-T	44 (18.7)	31 (13.0)	5.0 (2.47-10.17)	4.1 (1.94-8.78)	
Other NSCLCs	Nonsmoker	Others/Others or C-T/Others	26 (23.2)	44 (39.3)	1.0 (ref.)	1.0 (ref.)	< 0.01
		C-T/C-T	8 (7.2)	9 (8.0)	1.5 (0.52-4.38)	1.3 (0.43-4.07)	
	Smoker	Others/Others or C-T/Others	66 (58.9)	51 (45.6)	2.2 (1.19-4.02)	2.2 (1.13-4.16)	
		C-T/C-T	12 (10.7)	8 (7.1)	2.5 (0.92-7.02)	2.7 (0.90-7.91)	

*A pair of haplotypes composed of two polymorphic sites, IVS1-27C > G and Ex6+40C > T. †Other haplotypes except C-T. ‡OR obtained after adjusted for BMI. §*P* value obtained from the Cochran-Armitage trend test. AC, adenocarcinoma; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval.

in the *NQO1* gene, we used a haplotype-based approach in a relatively large number of subjects to increase statistical sensitivity. The two sites investigated in this study (IVS1-27C > G and Ex6+40C > T) were found to be linked strongly to each other. In connection with the strong linkage in our study, HapMap showed that these two loci exist as a haplotype block in the Asian population [http://www.hapmap.org/cgi-perl/gbrowse/gbrowse/], showing the reliability of our data and the importance of considering both of these loci.

In the present study, we evaluated the combined effect of smoking and *NQO1* diplotype on lung cancer risk because smoking is the major factor in the development of lung cancer. Our study results showed that diplotypes of the *NQO1* gene as well as smoking play an important role in the development of lung cancer and there is an additive interaction between smoking and *NQO1* diplotype. These study results support the hypothesis that NQO1 has a shorter protein half-life in individuals with the T allele at Ex6+40C > T compared to individuals with the wild type C allele, and thus confers a higher risk of lung cancer development (17-22). Moreover, in the present study, we used a web-based tool (Improbizer, http://www.cse.ucsc.edu/%7Ekent/improbizer/improbizer.html#NumMotifs) to identify whether or not the IVS1-27G > C polymorphism is located in a protein binding motif that has a potential to modulate NQO1 functionally although it is located in an intron. In the analysis using the web-based tool, this site was found to be located in the protein binding motif of *NQO1* intron1, indicating the potential for the functional regulation of NQO1 protein activity.

In the present study, we also conducted subgroup analyses according to lung cancer cell type, because subtypes of lung cancer differ in many respects in terms of cellular origin, genetic and molecular changes, and clinical features. Trend analyses showed that the combined effect of smoking and *NQO1* diplotype on lung cancer risk was statistically significant for all lung cancer cell types. However, our data also showed that this trend was more apparent in SCC. This more apparent relation with SCC is biologically plausible, because NQO1 protein may function as an oxidative stress inhibitor and SCC is more likely to be affected by tobacco smoke containing oxidative stress inducers than the other cell types of lung cancer (3, 31-35). Although SCLC showed the largest OR of lung cancer in terms of *NQO1* diplotype effect, the small number of nonsmokers with the C-T/C-T diplotype in SCLC patients and controls caused the confidence interval to broaden. Therefore, further studies are needed on a larger number of subjects to estimate the effects of the *NQO1* diplotype on lung cancer risk in various types of lung cancer.

One of the weaknesses of the present study is that the control population was a heterogeneous mixture of healthy people and patients with a variety of different conditions that could be associated with *NQO1* polymorphisms. This may possibly weaken our results even though we did not find any significant relationship between *NQO1* polymorphisms and the development of diseases of the controls by our literature search (36, 37).

The present study suggests that diplotypes of the *NQO1* gene play an important role in the development of lung cancer, and there is an additive interaction between smoking and polymorphisms in the *NQO1* gene for the risk of developing lung cancer. However, we need to clearly understand the function of the *NQO1* C-T haplotype in the development of lung cancer through further laboratory research.

DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHER CONTRIBUTION

Conception and coordination of the study, statistical analysis, and manuscript preparation: Kim JH, Hong YC.

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