Polymorphism of the DNA Repair Gene *XRCC1* and Risk of Primary Lung Cancer[1]

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Abstract

DNA repair plays a critical role in protecting the genome of the cell from insults of cancer-causing agents, such as those found in tobacco smoke. Reduced DNA repair capacity, therefore, can increase the susceptibility to smoking-related cancers. Recently, three coding polymorphisms in X-ray cross-complementing group 1 (XRCC1) DNA repair gene have been identified, and it is possible that these polymorphisms may affect DNA repair capacity and thus modulate cancer susceptibility. We investigated the relationship between the codon 399 polymorphism in *XRCC1* gene and lung cancer risk in male smokers. The study population consisted of 192 lung cancer patients and 135 healthy controls. The distribution of XRCC1 genotypes was not significantly different between cases and controls. When the cases were categorized by histological type, however, the presence of at least one Gln allele was associated with a significant increased risk for squamous cell carcinoma [crude odds ratio (OR) = 1.77, 95% confidence interval (CI) = 1.06–2.93 and adjusted OR = 1.66, 95% CI = 0.99–2.79]. The risk for the disease increased as the number of Gln alleles increased (Arg/Gln genotype: adjusted OR = 1.45, 95% CI = 0.84–2.5; Gln/Gln genotype: adjusted OR = 3.26, 95% CI = 1.17–9.15). When the subjects dichotomized by cigarette consumption into two pack-year groups (≤40 pack-years, >40 pack-years), the Gln allele was associated with an increased risk for squamous cell carcinoma only in the group of individuals having ≤40 pack-years of smoking (Arg/Gln genotype: adjusted OR = 1.48, 95% CI = 0.78–2.8; Gln/Gln genotype: adjusted OR = 5.75, 95% CI = 1.46–22.69). These results suggest that XRCC1 codon 399 polymorphism may be an important genetic determinant of squamous cell carcinoma of the lung in persons with lower degrees of cigarette use.

Introduction

Lung cancer has been considered as a disease determined solely by exposure to environmental carcinogens. However, there is a growing realization that genetic constitution is of importance in determining individual's susceptibility to lung cancer (1, 2). This genetic susceptibility may result from inherited polymorphisms in genes controlling carcinogen metabolism and repair of DNA damage (3, 4).

DNA repair systems are fundamental to the maintenance of genomic integrity in the face of replication errors, environmental insults, and the cumulative effects of age, and their inactivation can dramatically increase individual susceptibility to cancer (5, 6). In humans, >70 genes are involved in the five major DNA repair pathways: direct repair, BER[3], NER, mismatch repair, and double-strand break repair (7, 8). NER targets bulky, helix-distorting adducts, such as benzo(*a*)pyrene-guanine adduct, whereas BER removes small base adducts produced by oxidation, methylation, and radiation (7–9).

XRCC1 acts as a facilitator or coordinator in BER, through its interaction with poly(ADP-ribose) polymerase, DNA polymerase β, and DNA ligase III (9–12). Shen *et al.* (13) identified three coding polymorphisms in the *XRCC1* gene at the codons 194 (Arg to Trp), 280 (Arg to His), and 399 (Arg to Gln). Whereas the functional effects of these polymorphisms in XRCC1 has not been well known, amino acid changes at evolutionary conserved regions may alter its function. In particular, the 399Gln polymorphism resulting from a guanine to adenine nucleotide occurs in the poly(ADP-ribose) polymerase binding domain and may affect complex assembly or repair efficiency. Lunn *et al.* (14) reported that the *399Gln* allele was significantly associated with higher levels of aflatoxin B_1-DNA adducts and glycophorin A somatic mutations. Duell *et al.* (15) reported that sister chromatid exchange frequencies were higher in carriers of the *399Gln* allele than in homozygous carriers of the *399Arg* allele. These studies (14, 15) suggest that individuals with the *399Gln* allele are less able to repair DNA damage.

Epidemiological characteristics of lung cancer in Korea are remarkably different from those of Western countries. In Korea, lung cancer occurs predominantly in male smokers, and squamous cell carcinoma is the most frequent histological type, which may be because of a very high smoking rate among

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[3] The abbreviations used are: BER, base excision repair; NER, nucleotide excision repair; XRCC1, X-ray repair cross-complementing group 1; OR, odds ratio; CI, confidence interval; PAH, polyaromatic hydrocarbon.

Table 1 Characteristics of nonparticipated and participated patients and controls

	Nonparticipated patients (n = 614)	Participated patients[a] (n = 192)	Controls (n = 135)
Age (years)	61.9 ± 9.7	61.2 ± 8.4	60.7 ± 8.4
Smoking status			
Current	576 (93.8)[b]	184 (95.8)	95 (70.4)[c]
Former	28 (4.6)	6 (3.1)	37 (27.4)
Never	10 (1.6)	2 (1.1)	3 (2.2)
Pack-yr[d]	39.2 ± 17.4	38.7 ± 18.1	31.0 ± 22.2[c]
Histologic types			
Squamous cell ca.	358 (58.3)	111 (57.8)	
Adenocarcinoma	141 (23.0)	47 (24.5)	
Small cell ca.	106 (17.3)	34 (17.7)	
Large cell ca.	9 (1.4)	0 (0.0)	

[a] All differences between nonparticipated and participated patients are not significant.
[b] Numbers in parenthesis, percentage.
[c] $P < 0.05$, controls *versus* cases or nonparticipated patients.
[d] In eversmokers.

Table 2 XRCC1 genotypes and allele frequency among controls and cases

	Genotype			Gln allele frequency (%)
	Arg/Arg	Arg/Gln	Gln/Gln	
Control	81 (60.0)[a]	48 (35.6)	6 (4.4)	22.2
Case	100 (52.1)	75 (39.1)	17 (8.8)	28.4
SQ[b]	51 (46.0)	46 (41.4)	14 (12.6)[c]	33.3
AD[d]	28 (59.6)	17 (36.2)	2 (4.2)	22.3
SM[e]	21 (61.8)	12 (35.3)	1 (2.9)	20.6

[a] Numbers in parenthesis, percentage.
[b] Squamous cell carcinoma.
[c] $P = 0.02$, control *versus* squamous cell carcinoma.
[d] Adenocarcinoma.
[e] Small cell carcinoma.

males (68.3%) and a contrastingly low smoking rate among females (6%; Refs. 16 and 17). To determine whether the XRCC1 *399Gln* allele is a risk factor for lung cancer in Korea, we performed RFLP analysis of the codon 399 polymorphism of *XRCC1* gene in a hospital-based case control study of lung cancer.

Materials and Methods

Study Population. Cases were 192 male patients who agreed to this study among 806 male patients diagnosed with lung cancer between January 1997 and June 2000 in Kyungpook National University Hospital, Taegu, Korea. The histological types of cancer were as follows: 111 squamous cell carcinoma, 47 adenocarcinoma, and 34 small cell carcinoma. Despite the low participation rate, the demographics and clinical characteristics of participated cases were similar to those of nonparticipated patients (Table 1) and also compatible to those of the nationwide lung cancer survey conducted by the Korean Association of Tuberculosis and Respiratory Disease in 1998 (17). Controls were randomly selected from a pool of healthy volunteers that visited the general health check-up center of Kyungpook National University Hospital during the same period. It was difficult to collect enough controls >65 years of age because younger-aged persons mainly visited the health check-up center. Therefore, these controls were frequency (2:3) matched to cases on age (±5 years). All cases and controls were residents of Taegu City and surrounding regions. Information concerning gender, age, tobacco consumption, and past history was obtained for each case and control by a trained interviewer. For smoking status, a person who had smoked at least once a day for >1 year in his lifetime was regarded as a smoker. A former smoker was defined as one who had stopped smoking at least 1 year before diagnosis in the case of patients and 1 year before the study began in the case of controls. Cumulative cigarette dose (pack-years) was calculated by the following formula: pack-years = [(pack per day) × (years smoked)].

XRCC1 Genotyping. Genomic DNA was extracted from peripheral blood lymphocytes by proteinase K digestion and phenol/chloroform extraction. XRCC1 genotype was determined by a PCR-RFLP assay. PCR primers (GenBank accession no. L34079) were 5′-GCCCCGTCCCAGGTAAG-3′ (bases 27775–27794 of XRCC1) and 5′-AGCCCCAAGACCCTTTCACT-3′ (bases 28370–28389 of XRCC1), which generate a 615-bp fragment. PCR reaction mixture (20 μl) consisted of 100 ng of genomic DNA, 25 pmol of each primer, 4 mM deoxynucleotide triphosphate, 1 × PCR buffer [50 mM KCl and 10 mM Tris-HCl (pH 8.3)], 1.5 mM $MgCl_2$, and 1 unit of Taq polymerase (Takara Shuzo Co., Otsu, Shiga, Japan). PCR program initiated by a 5-min denaturation step at 94°C, followed by 35 cycles of 94°C for 30 s, 60°C for 20 s, 72°C for 30 s, and a final elongation step of 72°C for 10 min. The PCR products were digested overnight with 10 units of *Msp*I (New England BioLabs, Inc., Beverly, MA) at 37°C. The digestion product was then resolved on 1.5% agarose gel (Life Technologies, Inc., Grand Island, NY). The homozygous Arg allele is determined by the presence of two bands at 377 and 238 bp, the homozygous Gln allele is determined by the presence of the uncut 615-bp band (indicative of absence of the *Msp*I cutting site), and the heterozygous Arg/Gln allele is determined by the presence of three bands at 615, 377, and 238 bp. Genotyping analysis was repeated twice for all subjects, and selected PCR-amplified DNA samples (n = 2 respectively for Arg/Arg, Arg/Gln, and Gln/Gln genotypes) were examined by DNA sequencing to confirm genotyping results.

Statistical Analysis. The comparison of age and pack-years of smoking was performed by Student's t test and the comparison of smoking status (current/former/never) by χ^2 test. The statistical significance of the differences in the frequencies of XRCC1 codon 399 genotypes between groups was calculated by χ^2 test. Hardy-Weinberg equilibrium was tested by a goodness-of-fit χ^2 test to compare the observed genotype frequencies with the expected genotype frequencies among the cases and controls. The ORs and 95% CIs were obtained using unconditional logistic regression analysis. Crude ORs and ORs adjusted for age and pack-years as continuous variables were calculated. To analyze the association between genotype and lung cancer risk after stratification into cigarette consumption (≤40 pack-years and >40 pack-years), multiple logistic regression analysis was performed after adjusting age. Trends test for the number of polymorphic alleles on lung cancer risk was conducted by a Mantel-Haenszel χ^2 test. All analyses were performed using Statistical Analysis Software for Windows, version 6.12 (SAS institute, Cary, NC).

Results

The details of cases and controls enrolled in this study are shown in Table 1. All of the subjects were Korean males. The mean age was similar between cases (61.2 ± 8.4 years, range 38–85) and controls (60.7 ± 8.9 years, range 38–86). Cases showed a higher prevalence of current smokers compared with

Table 3 Logistic regression analysis of XRCC1 codon 399 polymorphism in lung cancer

Genotype	All cases		Squamous cell carcinoma cases	
	Crude OR (CI)	Adjusted[a] OR (CI)	Crude OR (CI)	Adjusted OR (CI)
Arg/Arg	1.00	1.00	1.00	1.00
Arg/Gln	1.27 (0.81–2.04)	1.28 (0.80–2.05)	1.52 (0.89–2.60)	1.45 (0.84–2.50)
Gln/Gln	2.30 (0.87–6.09)	2.02 (0.75–5.43)	3.71 (1.34–10.26)[b]	3.26 (1.17–9.15)
Arg/Gln + Gln/Gln	1.40 (0.89–2.18)	1.36 (0.87–2.15)	1.77 (1.06–2.93)	1.66 (0.99–2.79)

[a] Adjusted for age and pack-years of smoking.
[b] Linear association by Mantel-Haenszel χ^2 test, $\chi^2 = 7.3$; $P = 0.007$.

Table 4 Association between XRCC1 genotypes and squamous cell carcinoma according to pack-years of smoking

Genotype	≤40 pack-years			>40 pack-years		
	Control (%)	Case (%)	Adjusted[a] OR (CI)	Control (%)	Case (%)	Adjusted OR (CI)
Arg/Arg	67 (62.0)	34 (47.2)	1.00	14 (51.9)	17 (43.6)	1.00
Arg/Gln	38 (35.2)	29 (40.3)	1.48 (0.78–2.80)	10 (37.0)	17 (43.6)	1.44 (0.50–4.17)
Gln/Gln	3 (2.8)	9 (12.5)	5.75 (1.46–22.69)	3 (11.1)	5 (12.8)	1.38 (0.28–6.83)
Arg/Gln + Gln/Gln	41 (38.0)	38 (52.8)	1.79 (0.98–3.28)[b]	13 (48.1)	22 (56.4)	1.43 (0.53–3.85)

[a] Adjusted for age.
[b] $P = 0.06$.

controls ($P < 0.05$). The pack-years of smoking were significantly higher in cases than in controls (38.7 ± 18.1 *versus* 31.0 ± 22.2 pack-years, $P < 0.05$).

The distributions of XRCC1 genotypes and *399Gln* allele frequencies among controls and cases are shown in Table 2. The distribution of genotypes was in Hardy-Weinberg equilibrium. No significant deviation was observed for the distribution of genotypes between cases and controls. When the cases were categorized by histological type, however, the frequencies of Arg/Arg, Arg/Gln, and Gln/Gln genotypes in the squamous cell carcinoma group (46, 41.4, and 12.6%, respectively) were significantly different from those among controls (60, 35.6, and 4.4%, respectively, $P < 0.05$). The frequencies of genotypes in the groups of adenocarcinoma and small cell carcinoma were similar to those of controls.

Table 3 shows the crude and adjusted ORs for all lung cancer and squamous cell carcinoma by XRCC1 genotypes. When the Arg/Arg genotype was used as the reference group, the Arg/Gln and Gln/Gln genotypes were associated with elevated but not statistically significant risk for all lung cancer (adjusted OR =1.28, 95% CI = 0.80–2.05 and adjusted OR = 2.02, 95% CI = 0.75–5.43, respectively). When analyses were stratified by tumor histology, the presence of at least one Gln allele was associated with a borderline significant increased risk for squamous cell carcinoma (adjusted OR = 1.66, 95% CI = 0.99–2.79). The risk for the disease increased as the number of Gln alleles increased (Arg/Gln genotype: adjusted OR = 1.45, 95% CI = 0.84–2.5; Gln/Gln genotype: adjusted OR = 3.26, 95% CI = 1.17–9.15).

The association between XRCC1 genotypes and squamous cell carcinoma according to the extent of tobacco smoke exposure (≤40 pack-years and >40 pack-years) is shown in Table 4. In the group of individuals having ≤40 pack-years of smoking, the *399Gln* allele was associated with a borderline significantly increased risk for squamous cell carcinoma (adjusted OR = 1.79, 95% CI = 0.98–3.28), and the risk for the disease was increased as the number of Gln alleles increased (Arg/Gln genotype: adjusted OR = 1.48, 95% CI = 0.78–2.8; Gln/Gln genotype: adjusted OR = 5.75, 95% CI = 1.46–22.69). In the group of individuals with >40 pack-years of smoking, however, the distribution of XRCC1 genotypes was not significantly different between squamous cell carcinoma cases and controls.

Discussion

This is the first study showing that the XRCC1 codon *399Gln* allele is associated with an increased risk for squamous cell carcinoma of the lung in persons with lower degrees of cigarette smoking. These findings suggest that the *399Gln* allele could be used as a biomarker for genetic susceptibility to lung cancer in smokers.

Three coding polymorphisms at conserved sites have been reported in the *XRCC1* gene (13). In this study, we focused on the codon 399 polymorphism because two other polymorphisms (codons 194 and 280) reside in functionally insignificant regions (9, 13). The frequency of the *399Gln* allele among the healthy Koreans in this study was 0.22, which was lower than those in Chinese, Taiwanese (both 0.26; Refs. 14 and 18), and Caucasians (0.32–0.37; Refs. 14 and 19–21).

We demonstrated that the *399Gln* allele was associated with an increased risk for squamous cell carcinoma of the lung. These results are consistent with previous studies that the Gln/Gln genotype is the risk genotype for various smoking-related cancers (18, 20, 21). A characteristic finding in this study is that there was a gene-dosage effect with the *399Gln* allele (test for linear association, $\chi^2 = 7.3$, $P = 0.007$). In previous studies (18, 20, 21), the Arg/Gln genotype was classified in the same group with the Arg/Arg or Gln/Gln genotype according to the distribution of genotypes in controls and cases. Therefore, it has not been determined if individuals carrying one Gln allele have an increased risk for cancer. In the current study, however, individuals heterozygous for the *399Gln* allele had an intermediate risk for the cancer. This finding confirms the study of Lunn *et al.* (14), in which the levels of aflatoxin B_1-DNA adducts and glycophorin A somatic mutations were highest in individuals with two Gln alleles, intermediate with one allele, and lowest with no Gln allele.

A few studies have investigated the potential role of XRCC1 codon 399 polymorphism on lung cancer risk, but the

results were inconsistent (21, 22). Butkiewicz *et al.* (22) found no association of lung cancer with this polymorphism in the Polish population. Divine *et al.* (21) reported that the Gln/Gln genotype was associated with an increased risk of adenocarcinoma; the risk estimates for the risk genotype were much higher in non-Hispanic Whites than in Hispanics. In our study, this polymorphism was associated with squamous cell carcinoma. The different results in different populations may be because of genetic and environmental differences (23).

Genetic susceptibility to lung cancer may depend on the level of exposure to tobacco smoke (24, 25). Therefore, we examined further association between tobacco smoke exposure and the distribution of XRCC1 genotypes. When the subjects dichotomized by cigarette consumption into two pack-year groups ($\leq$40 pack-years and $>$40 pack-years), the Gln allele was associated with an increased risk for squamous cell carcinoma only in the group of low level of exposure. This might be explained by the fact that at high levels of exposure, the DNA repair capacity may be saturated even in individuals having higher repair capacity (24–26). It is possible that such a finding is attributable to chance because of the relatively small numbers in the subgroups. Additional studies with more patients will be needed to confirm this finding.

This study implicates that BER, including XRCC1, may be the major pathway for removing the mutagenic DNA damages arising from procarcinogens in cigarette smoke. Although it is difficult to attribute the carcinogenicity of tobacco to any particular compound, most important causative agents for squamous cell carcinoma are PAHs, such as benzo[a]pyrene (27, 28). PAH-induced bulky DNA adducts, such as benzo[a]pyrene diol epoxide-DNA adducts, which are the most potent premutagenic adducts, are mainly repaired by NER (28, 29). However, the metabolic activation pathway resulting in the formation of a diol epoxide ultimate carcinogen is a quantitatively minor one (30, 31). A variety of reactive oxygen species, such as hydroxyl radical and hydrogen peroxide, are generated during enzymatic oxidation of PAHs (32, 33). These reactive oxygen species can lead to DNA damages, which may be quantitatively a predominant PAH-induced DNA damage. Oxidative DNA damages are primarily removed via BER, including XRCC1. Moreover, BER also targets depurinating DNA adducts, such as N7-methylguanine and N3-methyladenine, derived from radical cations formed by one-electron oxidation of PAHs (34). Another explanation for the association between squamous cell carcinomas and XRCC1 polymorphism may be that interactions with other procarcinogens induced DNA damage (35, 36). This is especially likely for exposure to cigarette smoke, where there are many potent procarcinogens producing various DNA damages.

In conclusion, we found that the codon *399Gln* allele of *XRCC1* gene was associated with an increased risk of squamous cell carcinoma of the lung in smokers, especially when the cigarette dose is low. These results suggest that genotyping analysis of *XRCC1* gene could be used to identify individuals susceptible to lung cancer in smokers.

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