Polymorphisms in DNA Base Excision Repair Genes ADPRT and XRCC1 and Risk of Lung Cancer

Xuemei Zhang,1,5 Xiaoping Miao,1 Gang Liang,1 Bingtao Hao,3,4 Yonggang Wang,2 Wen Tan,1 Yi Li,1 Yongli Guo,1 Fuchu He,3,5 Qingyi Wei,1,6 and Dongxin Lin1

Abstract
Adenosine diphosphate ribosyl transferase (ADPRT) and X-ray repair cross-complementing 1 (XRCC1) are two major DNA base excision repair (BER) proteins and act interactively in stimulating and executing BER processes. Polymorphisms of ADPRT Val762Ala and XRCC1 Arg399Gln have been associated with altered protein function and BER activity. This case-control study examined the contribution of these two polymorphisms, alone and in combination, or in interaction with smoking, to the risk of developing lung cancer. We estimated the risk of lung cancer associated with these polymorphisms in 1,000 cases and 1,000 cancer-free controls using logistic regression models. Subjects having the ADPRT Ala/Ala genotype had an odds ratio (OR) of 1.68 [95% confidence interval (95% CI), 1.27-2.23] compared with those having the Val/Val genotype. A greater than multiplicative joint effect between the ADPRT polymorphism and smoking was observed. The ORs (95% CI) of the Ala/Ala genotype for nonsmokers and smokers who smoked ≤16, 16 to 28, or >28 pack-years were 1.13 (0.79-1.62), 1.35 (0.68-2.70), 2.46 (1.35-4.51) or 17.09 (8.15-35.83), respectively (P trend test < 0.001). Gene-gene interaction of ADPRT and XRCC1 polymorphisms increased risk of lung cancer in a supermultiplicative manner (OR for the presence of both ADPRT 762Ala/Ala and XRCC1 399Gln/Gln genotypes, 5.91; 95% CI, 2.09-16.72), although the XRCC1 polymorphism itself was not associated with the risk. In conclusion, the ADPRT Val762Ala polymorphism plays an important role in smoking-related lung cancer and the XRCC1 Arg399Gln polymorphism may serve as a risk modifier. (Cancer Res 2005; 65(3): 722-6)

Introduction
Human cancer can be initiated by DNA damage caused by UV, ionizing radiation, and environmental chemical agents. However, humans have developed a set of complex DNA repair systems to safeguard the integrity of genome by defending harmful consequences of DNA damage. Among the DNA repair systems, the base excision repair (BER) pathway is one important mechanism that repairs DNA damage resulting from chemical alterations of a single base, such as methylated, oxidized, or reduced bases, and rectifies single-strand interruptions in DNA (1, 2). BER includes two major processes (i.e., excision of damaged base residues and core BER reaction, including strand incision at the abasic site, one-nucleotide gap-filling reaction, and sealing of the remaining nick; ref. 2). It is well known that a number of proteins are involved in these steps, of which ADPRT and XRCC1 play key roles. In response to DNA damage generated by genotoxic agents, ADPRT specifically binds to DNA strand breaks where it is autoactivated and recruits XRCC1-Lig3 complex (1, 3). It has been shown that interactions of ADPRT with XRCC1 as well as other partner proteins such as Polβ are critical for stimulating and executing BER processes (3, 4).

Genetic polymorphisms have been identified in both ADPRT and XRCC1 genes. There are at least 38 reported variants in ADPRT (http://snp500cancer.nci.nih.gov), one of which is a T-to-C transition at codon 762 of ADPRT located in the sixth helix of catalytic domain that causes Val-to-Ala amino acid substitution. Although most of the functional relevance of these variants remains unknown, a recent study showed that the Val762Ala polymorphism is associated with altered ADPRT function, with the Ala allele contributing to significantly low poly(ADP-ribosyl)ation activities in an allele dosage-dependent manner (5). The low ADPRT activity due to the polymorphism is expected to reduce its ability to recruit XRCC1 and other related proteins. There are at least 17 XRCC1 variants identified to date (http://snp500cancer.nci.nih.gov), one of which is a G-to-A single nucleotide polymorphism (SNP) at codon 399 resulting in Arg-to-Gln amino acid change (6). Although biochemical and biological characteristics of these XRCC1 variants are not fully determined, the Arg399Gln variation is situated within the BRCT-1 region harboring the ADPRT binding domain (6) that is likely to affect functional interaction between XRCC1 and ADPRT. An altered DNA repair activity has been suggested to be associated with the XRCC1 polymorphism (7, 8).

Based on the interactive role that ADPRT and XRCC1 play at molecular level in BER activities and reported functional relevance of their variants, we hypothesized that the ADPRT Val762Ala and XRCC1 Arg399Gln polymorphisms may contribute to susceptibility to carcinogenesis. In this study, we specifically examined whether these two polymorphisms play an interactive role in the risk of lung cancer. We chose lung cancer as our disease model because the initiation of carcinogenesis by DNA damage caused by genotoxic compounds mostly found in cigarette smoke is well established in this cancer (9).

Materials and Methods
Study Population. This hospital-based, case-control study consisted of 1,000 patients with lung cancer and 1,000 cancer-free controls. All subjects were unrelated ethnic Han Chinese. The characteristics of the study subjects have been described previously (10). Briefly, the patients with newly diagnosed, histopathologically confirmed, and previously untreated...
(by radiotherapy or chemotherapy) primary lung cancer were recruited between January 1997 and June 2002 at Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China). There were no age, sex, stage, or histology restrictions; however, patients with previous cancer or metastasized cancer from other organs were excluded. The controls were randomly selected from a pool of cancer-free subjects recruited from a nutritional survey conducted in the same region during the same time period as the cases were collected. The selection criteria include no prior history of cancer, and controls were frequency matched to the cases by age (±5 years) and sex. At recruitment, informed consent was obtained from each subject who was then interviewed for detailed information on demographic characteristics and lifetime history of tobacco use. The study was approved by the institutional review board of the Cancer Institute and Hospital.

**Genotype Analysis.** Genotypes were analyzed using PCR-based RFLP methods done without knowledge of case/control status of the subjects. The PCR primers for amplifying DNA containing the **ADPRT** Val762Ala polymorphism site were ADPRTF5'-ttggtcctccagccaaag-3' and ADPRTR5'-catcgagtagcttctgtcgt-3', which produce a 110-bp fragment. To induce a restrict endonuclease site, we changed the 3’ end of primer ADPRTF from agg to acg which created a BstI cutting site. Amplification was accomplished with a 25-μL reaction mixture consisted of 50 ng template DNA, 0.2 μmol/L each primer, 0.2 μmol/L each deoxyribonucleotide triphosphate, 2.0 μmol/L MgCl2, and 1.0 unit Tag DNA polymerase with 1 × reaction buffer (Promega, Madison, WI). The reaction was carried out in the following conditions: an initial melting step of 5 minutes at 94°C, followed by 35 cycles of 30 seconds at 94°C, 30 seconds at 62°C, and 45 seconds at 72°C, and a final elongation step of 7 minutes at 72°C. The restriction enzyme BstFI (New England Biolabs, Inc., Beverly, MA) was used to distinguish **ADPRT** Val762Ala genotypes. The 762Val allele produces a single band representing the entire 110-bp fragments, and the variant 762Ala allele had 90- and 20-bp fragments because it gains a BstI site. The **Val762Ala** allele represents the entire 110-bp fragments, and the variant 762Ala allele had 90- and 20-bp fragments because it gains a BstI site. The Val762Ala polymorphism revealed by PCR-RFLP analysis was further confirmed by DNA sequencing. Genotyping analysis of the **XRCC1** Arg399Gln polymorphism was the same as described previously (11). A 15% of masked, random selected samples of the cases and controls were tested twice by different technical persons, and the results were concordant for all of the masked duplicate sets.

**Statistical Analysis.** The χ2 test was used to examine differences in demographic variables, smoking, and distribution of genotypes between cases and controls. The associations between genotype and risk of lung cancer were estimated by calculating odds ratio (OR) and their 95% confidence interval (95% CI) with unconditional logistic regression models. The ORs were adjusted for age, sex, and pack-years smoked. Light, moderate, and heavy smokers were categorized by using the 25th and 75th percentile pack-year [cigarettes per day/20] × (years smoked)] values of the controls as the cutoff points (i.e., ≤16, 16-28, and >28 pack-years). We tested the null hypotheses of multiplicative gene-gene and gene-smoking interactions by evaluating departures from multiplicative joint effect models (12). A more than multiplicative joint effect was suggested when OR11 > OR01 × OR00. Departures from these multiplicative models were assessed by including main effect variables and their product terms in the logistic regression model. The homogeneity test was done to compare the difference between smoking-related ORs among different genotypes or between the product of related ORs and the joint effect OR. All analyses were done with the computer programs of Statistical Analysis System (version 6.12; SAS Institute, Cary, NC).

**Results**

**Subject Characteristics.** The demographic information on study subjects is summarized in Table 1. No statistically significant differences were found between the cases and controls in terms of age and sex distributions. However, as expected, more smokers were represented in the cases compared with the controls (65.0% versus 51.1%; P < 0.0001). In addition, the cases had higher values of pack-years smoked than the controls; 65.1% of smokers among the cases smoked >28 pack-years, whereas this value was 33.5% among the controls (P < 0.0001). Among the cases, 44 (44.8%) were classified as squamous cell carcinoma, 297 (29.7%) as adenocarcinoma, and 255 (25.5%) as other type, including undifferentiated cancer (n = 90), bronchioalveolar carcinoma (n = 92), and mixed cell carcinoma (n = 73).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 1,000)</th>
<th>Controls (n = 1,000)</th>
<th>P&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>726 (72.6)</td>
<td>723 (72.3)</td>
<td>0.881</td>
</tr>
<tr>
<td>Female</td>
<td>274 (27.4)</td>
<td>277 (27.7)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>248 (24.8)</td>
<td>248 (24.8)</td>
<td>0.995</td>
</tr>
<tr>
<td>51-60</td>
<td>330 (33.0)</td>
<td>329 (32.9)</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>320 (32.0)</td>
<td>324 (32.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>102 (10.2)</td>
<td>99 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking status&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>350 (35.0)</td>
<td>489 (48.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>650 (65.0)</td>
<td>511 (51.1)</td>
<td></td>
</tr>
<tr>
<td>Pack-years smoked&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤16</td>
<td>106 (16.3)</td>
<td>179 (35.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>16-28</td>
<td>121 (18.6)</td>
<td>161 (31.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;28</td>
<td>423 (65.1)</td>
<td>171 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>448 (44.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>297 (29.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>255 (25.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>†</sup>Two-sided χ2 test.

<sup>‡</sup>Nonsmokers were defined as subjects smoked <10 cigarettes lifetime.

<sup>‡</sup>Other includes undifferentiated cancer (n = 90), bronchioalveolar carcinoma (n = 92), and mixed cell carcinoma (n = 73).
Gene-Gene Interaction. Because ADPRT functionally interacts with XRCCI in BER processes, we therefore evaluated the joint effect between the ADPRT Val762Ala polymorphism and smoking (Table 3). Among non-smokers, the ADPRT Ala/Ala genotype was not associated with increased lung cancer risk; however, among smokers, subjects carrying the Val/Val genotype had an OR of 4.32 (95% CI, 2.90-6.44) that was significantly higher than the OR among smokers carrying the Val/Ala genotype (OR, 2.22; 95% CI, 1.74-2.84; \( P < 0.001 \)) for homogeneity. Because the OR for the presence of adenocarcinoma (OR, 1.54; 95% CI, 1.06-2.30) but not other types (OR, 1.48; 95% CI, 0.95-2.31). However, the distributions of XRCCI Arg399Gln genotypes were not significantly different between the cases and controls and the XRCCI variant genotypes were not associated with increased risk of lung cancer (Table 2).

Gene-Smoking Interaction. We next analyzed the joint effect of the ADPRT Val762Ala or XRCCI Arg399Gln polymorphism and tobacco smoking. Because the Val/Ala heterozygous genotype was not associated with increased risk, this genotype was combined with the Val/Val genotype as reference group for analysis. A supermultiplicative joint effect was found between the ADPRT Val762Ala polymorphism and smoking (Table 3). Among non-smokers, the ADPRT Ala/Ala genotype was not associated with increased lung cancer risk; however, among smokers, subjects carrying the Val/Val genotype had an OR of 4.32 (95% CI, 2.90-6.44) that was significantly higher than the OR among smokers carrying the Val/Ala genotype (OR, 2.22; 95% CI, 1.74-2.84; \( P < 0.001 \), test for homogeneity). Because the OR for the presence of both smoking and Ala/Ala genotype was greater than the product of OR for smoking and OR for the genotype (\( P < 0.001 \)), these data clearly suggested a supermultiplicative joint effect between smoking and the ADPRT polymorphism. Moreover, when the risk associated with the ADPRT polymorphism were further evaluated within strata of \( \leq 16 \), 16-28, and >28 pack-years smoked, a supermultiplicative joint effect between the susceptible genotype and categories of pack-years smoked was observed; the ORs were 1.02, 1.27, and 4.49, respectively, for the Val/Val or Val/Ala genotype, but 1.35, 2.46, and 17.09, respectively, for the Ala/Ala genotype (\( P \) for trend < 0.001). However, there was no such an effect between the XRCCI Arg399Gln polymorphism and smoking (either smoking status or number of pack-years; data not shown).

## Table 2. Genotype frequencies of ADPRT and XRCCI among cases and controls and their association with lung cancers

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls (n = 1,000)</th>
<th>Overall cases (n = 1,000)</th>
<th>Cases with squamous cell carcinoma (n = 448)</th>
<th>Cases with adenocarcinoma (n = 297)</th>
<th>Cases with other* (n = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>ADPRT Val762Ala</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val/Val</td>
<td>339 (35.9)</td>
<td>307 (30.7)</td>
<td>144 (32.1)</td>
<td>84 (28.3)</td>
<td>79 (31.0)</td>
</tr>
<tr>
<td>Val/Ala</td>
<td>504 (50.4)</td>
<td>509 (50.9)</td>
<td>215 (48.0)</td>
<td>159 (53.5)</td>
<td>135 (52.9)</td>
</tr>
<tr>
<td>Ala/Ala</td>
<td>137 (13.7)</td>
<td>184 (18.4)</td>
<td>89 (19.9)</td>
<td>54 (18.2)</td>
<td>41 (16.1)</td>
</tr>
<tr>
<td>One Ala, OR (95% CI)( \dagger )</td>
<td>1.17 (0.95-1.43)</td>
<td>1.01 (0.76-1.32)</td>
<td>1.36 (0.91-1.93)</td>
<td>1.21 (0.89-1.68)</td>
<td></td>
</tr>
<tr>
<td>Two Ala, OR (95% CI)( \dagger )</td>
<td>1.68 (1.27-2.23)</td>
<td>2.17 (1.49-3.14)</td>
<td>1.54 (1.06-2.30)</td>
<td>1.48 (0.95-2.31)</td>
<td></td>
</tr>
<tr>
<td>XRCCI Arg/Gln</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>531 (53.1)</td>
<td>535 (53.5)</td>
<td>239 (53.3)</td>
<td>161 (54.2)</td>
<td>135 (52.9)</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>380 (38.0)</td>
<td>363 (36.3)</td>
<td>163 (36.4)</td>
<td>108 (36.4)</td>
<td>92 (36.1)</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>89 (8.9)</td>
<td>102 (10.2)</td>
<td>46 (10.3)</td>
<td>28 (9.4)</td>
<td>28 (11.0)</td>
</tr>
<tr>
<td>One Gln, OR (95% CI)( \dagger )</td>
<td>0.93 (0.77-1.13)</td>
<td>0.97 (0.75-1.26)</td>
<td>0.74 (0.71-1.24)</td>
<td>0.93 (0.69-1.27)</td>
<td></td>
</tr>
<tr>
<td>Two Gln, OR (95% CI)( \dagger )</td>
<td>1.17 (0.85-1.61)</td>
<td>1.16 (0.76-1.78)</td>
<td>1.01 (0.63-1.59)</td>
<td>1.27 (0.79-2.04)</td>
<td></td>
</tr>
</tbody>
</table>

*Other includes undifferentiated cancer (n = 90), bronchioalveolar carcinoma (n = 92), and mixed cell carcinoma (n = 73).

†Data were calculated by unconditional logistic regression and adjusted for age, sex, smoking status, and pack-years.

## Table 3. Risk of lung cancer associated with ADPRT genotypes by smoking status

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>ADPRT genotype</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Val/Val + Val/Ala*</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
<td>1.13 (0.79-1.62)</td>
<td>0.491</td>
</tr>
<tr>
<td></td>
<td>Val/Val + Val/Ala*</td>
<td>2.22 (1.74-2.84)</td>
<td>&lt;0.001</td>
<td>115/52</td>
<td>4.32 (2.90-6.44)</td>
</tr>
<tr>
<td></td>
<td>Val/Val + Val/Ala*</td>
<td>1.02 (0.73-1.42)</td>
<td>0.092</td>
<td>16/21</td>
<td>1.35 (0.68-2.70)</td>
</tr>
<tr>
<td></td>
<td>Val/Val + Val/Ala*</td>
<td>1.27 (0.90-1.80)</td>
<td>0.180</td>
<td>29/22</td>
<td>2.46 (1.35-4.51)</td>
</tr>
<tr>
<td></td>
<td>Val/Val + Val/Ala*</td>
<td>4.49 (3.34-6.05)</td>
<td>&lt;0.001</td>
<td>70/9</td>
<td>17.09 (8.15-35.83)</td>
</tr>
</tbody>
</table>

*No. cases/no. controls.

†Data were calculated by logistic regression, with the Val/Val or Val/Ala genotype as reference group and adjusted for age and sex.

\( P < 0.001 \), test for homogeneity between smoking-related ORs among Val/Val + Val/Ala and Ala/Ala genotypes.

\( P = 0.026 \), test for homogeneity between smoking-related ORs among Val/Val + Val/Ala and Ala/Ala genotypes.
has shown that ADPRT activities of lung cancer patients were
BER by detecting DNA strand breaks and poly(ADP-ribosyl)ating
ability to tobacco-induced lung cancer. Moreover, a supermultiplicative joint effect between
gene-environment interaction that may have played
catalytic domain, increases susceptibil-
ADPRT Ala/Ala genotype and smoking in a dose-response
The supermultiplicative joint effect between these two SNPs
lower than those of cancer-free individuals (15). Upon binding to
DNA, ADPRT becomes auto-poly(ADP-ribosyl)ated, allowing itself
to interact with other proteins involved in BER. Because the
762Val-to-Ala substitution located within the COOH-terminal
catalytic domain is associated with deficient poly(ADP-ribosyl)ation activity (5), this amino acid change may reduce the BER
capacity and therefore cause genome instability. Our result
showing an association between the 762Ala/Ala genotype and
increased risk of lung cancer is consistent with this functional
relevance. Our findings are also consistent with previously
published studies, in which the ADPRT Val762Ala polymorphism
has been reported to be associated with increased risk of other
cancers, including esophageal cancer (16) and prostate cancer (5).
To date, there is only one published lung cancer study reporting
that the ADPRT haplotypes of three SNPs (codons 81, 284, and 762)
were not associated with increased risk in a Korean population
(17). The discrepancy between this study and ours might reflect the
differences in genetic background, carcinogen exposure in different
populations or just simply sample sizes (only 352 cases and 352
controls in the Korean study). Tobacco smoke contains various
carcinogens that can cause DNA damage (9). Theoretically, if the
ADPRT 762Ala variant actually diminishes BER capacity, smokers
carrying the ADPRT 762Ala/Ala homozygous variant genotype will
be at higher risk for lung cancer than those carrying the wild-type
allele. Indeed, we found a supermultiplicative joint effect of the
ADPRT 762Ala/Ala genotype and smoking in a dose-response
manner, with the risk being the highest among heavy smokers who
carried the ADPRT 762Ala/Ala genotype. Therefore, our findings
are biologically plausible.
The XRCC1 Arg399Gln polymorphism has been extensively
studied in many cancer sites including lung cancer, but the results
are conflicting (reviewed in ref. 18). In 1,000 cases and 1,000
controls of a Han Chinese population, we failed to observe any
association between the XRCC1 Arg399Gln polymorphism (alone or in combination with smoking) and risk of lung cancer. These
results are generally consistent with previous findings in a
relatively large lung cancer study (19). However, it is interesting
that our data suggest that the XRCC1 399Gln variant modified lung
cancer risk associated with the ADPRT Val762Ala polymorphism.
The supermultiplicative joint effect between these two SNPs
genotype than the controls (2.0% versus 0.5%; \(P = 0.017\)). Evidence
for a supermultiplicative joint effect of the SNPs in ADPRT and
XRCC1 comes from the fact that the OR for subjects with the
ADPRT Ala/Ala and XRCC1 Gln/Gln genotypes versus subjects with
the ADPRT Val/Val and XRCC1 Arg/Arg genotypes; that is, 5.91
(Table 4), is larger than the product of the OR for subjects with the
ADPRT Ala/Ala genotype versus the ADPRT Val/Val genotype and the
OR for subject with the XRCC1 Gln/Gln genotype versus XRCC1
Arg/Arg genotype (i.e., 1.68 \(\times\) 1.17 = 1.97; Table 2; \(P = 0.018\)). These results clearly indicate that a more than multiplicative joint effect
between the ADPRT Ala/Ala and XRCC1 Arg/Gln genotype exists in the
risk of developing lung cancer (12).

**Table 4. Risk of lung cancer associated with ADPRT genotypes by XRCC1 genotype among 1,000 patients and 1,000 controls**

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Cases, (n) (%)</th>
<th>Controls, (n) (%)</th>
<th>OR (95% Cl)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPRT Val762Ala</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val/Val Arg/Arg</td>
<td>157 (15.7)</td>
<td>186 (18.6)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Val/Val Arg/Gln</td>
<td>124 (12.4)</td>
<td>142 (14.2)</td>
<td>1.02 (0.73-1.42)</td>
</tr>
<tr>
<td>Val/Val Gln/Gln</td>
<td>26 (2.6)</td>
<td>31 (3.1)</td>
<td>0.95 (0.53-1.71)</td>
</tr>
<tr>
<td>Val/Ala Arg/Arg</td>
<td>273 (27.3)</td>
<td>286 (28.6)</td>
<td>1.20 (0.90-1.59)</td>
</tr>
<tr>
<td>Val/Ala Arg/Gln</td>
<td>180 (18.0)</td>
<td>183 (18.3)</td>
<td>1.11 (0.82-1.52)</td>
</tr>
<tr>
<td>Val/Ala Gln/Gln</td>
<td>56 (5.6)</td>
<td>53 (5.3)</td>
<td>1.26 (0.81-1.97)</td>
</tr>
<tr>
<td>Ala/Ala Arg/Arg</td>
<td>105 (10.5)</td>
<td>77 (7.7)</td>
<td>1.66 (1.13-2.42)</td>
</tr>
<tr>
<td>Ala/Ala Arg/Gln</td>
<td>59 (5.9)</td>
<td>55 (5.5)</td>
<td>1.38 (0.89-2.15)</td>
</tr>
<tr>
<td>Ala/Ala Gln/Gln</td>
<td>20 (2.0)</td>
<td>5 (0.5)</td>
<td>5.91 (2.09-16.72)</td>
</tr>
</tbody>
</table>

*Data were calculated by unconditional logistic regression, adjusting for sex, age, and smoking status.

**Discussion**

DNA repair systems play a key role in protecting against
carcinogenesis and genetic defect in DNA repair can cause human cancer (1). Accumulating evidence shows that reduced DNA repair capacity resulting from genetic polymorphism is associated with increased risk of lung cancer (13). Our previous study has shown that SNPs in XPD, a gene that plays important role in nucleotide excision repair pathway; increases susceptibility to lung cancer in this Chinese population (10). The present study extends our findings to SNPs in BER genes, showing that the functional polymorphism in the ADPRT catalytic domain may have a great impact on risk for the development of lung cancer. A 4.32-fold increased lung cancer risk associated with the variant ADPRT 762Ala/Ala genotype among smokers, in which a supermultiplicative joint effect between the ADPRT polymorphism and cigarette smoking was evident, is an excellent example for gene-environment interaction that may have played an important role in the etiology of lung cancer in this Chinese population. Moreover, a supermultiplicative joint effect between two functional polymorphisms of the ADPRT and XRCC1 genes provides the rationale of studying underlying genetic susceptibility to tobacco-induced lung cancer.

ADPRT is a DNA-binding protein involved in the regulation of BER by detecting DNA strand breaks and poly(ADP-ribosyl)ating nuclear acceptor proteins (including itself) that relate to DNA repair programs and/or apoptosis decision (2, 14). Previous study has shown that ADPRT activities of lung cancer patients were
suggestions that they are likely to act in the same causal pathway (12). This observation is also in agreement with the functional interaction of ADPRT and XRCC1 in BER, in which ADPRT directly interacts with XRCC1 through the ADPRT binding domain in the BRCT-1 region of XRCC1 (4), whereas XRCC1 interacts preferentially with autoribosylated ADPRT, distinguished by a degenerate consensus motif for interaction with poly(ADP-ribose) located in the BRCT-1 domain (4). If a cell carries functional polymorphisms in both of the genes that affect ADPRT autoactivation and physical connection between ADPRT and XRCC1, then a multiplicative joint effect is to be expected. Whether these genetic polymorphisms actually affect the interaction between ADPRT and XRCC1 proteins and the overall BER activity warrant further investigations.

Genetic polymorphisms often vary in ethnicity. With this study, we evaluated the ADPRT 762Ala allele frequency was 0.389 and that Ala/Ala homozygotes accounted for 13.7% of the Han Chinese population studied, compared with 0.145 and 2% among U.S. Caucasians and 0.045 and 0% among African Americans (5). The ADPRT 762Ala allele frequency was shown to be 0.443 in a Korean population but the genotype frequency is unavailable in this study (17). Distribution of XRCC1 Arg399Gln polymorphism also displays an ethnic difference. In the present study, we observed frequencies of 0.279 for the XRCC1 399Gln allele and 8.9% for the Gln/Gln genotype.

In summary, our study shows a significant association between a functional polymorphism in ADPRT and increased risk of developing lung cancer in a Han Chinese population. The increase in risk of lung cancer associated with this ADPRT polymorphism was more pronounced among smokers, displaying a super-multiplicative gene-environment joint effect. Furthermore, we observed a more than multiplicative interaction between the ADPRT and XRCC1 polymorphisms. Our findings suggest that deficient BER may play an important role in the development of lung cancer.

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Xuemei Zhang, Xiaoping Miao, Gang Liang, et al.


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