A Polymorphism in the APE1 Gene Promoter is Associated with Lung Cancer Risk

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Abstract

Apurinic/apyrimidinic endonuclease 1 (APE1) is an essential enzyme in the base excision repair pathway, which is the primary mechanism for the repair of DNA damage caused by oxidation and alkylidy. We hypothesized that polymorphisms of APE1 are associated with risk for lung cancer. In the hospital-based matched case-control study, a total of 730 lung cancer cases and 730 cancer-free controls were genotyped for four APE1 haplotype-tagging polymorphisms (that is, -656 T>G, 400A>G, 630T>C, and 1350T>G). Among them, the single-nucleotide polymorphism -656 T>G located in the promoter region of APE1 was significantly associated with risk for lung cancer. We found that, compared with -656 TT homozygotes, the variant genotypes were associated with a significantly decreased risk [adjusted odds ratio, 0.51; 95% confidence interval (95% CI), 0.33-0.79 for -656 TG; adjusted odds ratio, 0.43; 95% CI, 0.25-0.76 for -656 GG, respectively]. Furthermore, we found a statistically significant reduced risk of -656 T>G variants among heavy smokers (adjusted odds ratio, 0.52; 95% CI, 0.30-0.93 for -656 TG; adjusted odds ratio, 0.27; 95% CI, 0.13-0.57 for -656 GG, respectively), with a significant gene-smoking interaction (P = 0.013). A similar gene-smoking interaction in the context of APE1 haplotypes was also observed. The in vitro promoter assay revealed that the -656 G allele had a significantly higher transcriptional activity than that of the -656 T allele. Together, our results suggest that polymorphisms of the APE1 gene possibly interact with smoking and may contribute to the development of lung cancer. (Cancer Epidemiol Biomarkers Prev 2009;18(1):223–9)

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide and in Taiwan (1) and is thus a major public health problem. Cigarette smoke contains many carcinogens and reactive oxygen species that can induce various types of DNA damage (2). Although cigarette smoking is a major risk factor in the development of lung cancer, only 10% to 15% of all smokers develop lung cancer, suggesting that variation in individual susceptibility to tumorigenesis of lung cancer (3-5). Susceptibility differences may be inherited in genes encoding for the metabolism of carcinogens or DNA repair molecules, which are essential in protecting the genomic integrity of the cells (6-8). One of the DNA repair pathways is the DNA base excision repair pathway, which repairs the DNA damage caused by oxidation and alkylidy and thus protects cells against the toxic effects of endogenous and exogenous agents (9, 10). Specifically, the damaged bases of purine and pyrimidine are recognized and excised by specific DNA glycosylases, leaving abasic sites. Apurinic/apyrimidinic endonuclease (APE) then incise the DNA 5’ to the abasic sites; further repair proceeds to short-patch (when the gap is only one nucleotide) or long-patch (when the gap is two or more nucleotides) subpathways of base excision repair (11). The major human APE, APE1 (also known as APE, APEX, HAP1, and REF-1), plays a central role in the base excision repair pathway. As a member of APE, it initiates repair of apurinic/apyrimidinic sites in DNA produced either spontaneously hydrolyzing the 5’-phosphodiester bond of the apurinic/apyrimidinic site or after enzymatic removal of damaged bases. The repair activity of APE1 serves to protect the cell from the apurinic/apyrimidinic sites that can accumulate in DNA via endogenous and exogenous sources. In addition to APE activity, it can also act as a 3’-phosphodiesterase, initiating repair of DNA strands breaks with 3’-blocking damage, which are produced either directly by reactive oxygen species or indirectly through the enzymatic removal of damaged bases (12, 13). As importantly, APE1 also functions as a reduction-oxidation activators of several transcription...
factors thought to be important in carcinogenesis, such as activator protein (Fos/Jun), hypoxia-inducible factor 1, cAMP-responsive element binding protein, and p53 (14, 15). Knockout mouse model showed that inactivation of APE1 protein induces embryonic lethality and highlights the importance of its function to the cells (16, 17).

Polymorphisms in the DNA repair genes may contribute to the DNA repair capacity variations in the general population. Therefore, it has been hypothesized that some of the APE1 polymorphisms and particularly their haplotypes may have an effect on APE1 expression and DNA repair capacity, and this can modulate individual susceptibility to lung cancer. The present hospital-based matched case-control study is aimed at evaluating the relationship between polymorphisms of APE1 and the risk for lung cancer. Among the identified single-nucleotide polymorphisms in the APE1 gene, we selected four tag single-nucleotide polymorphisms based on the International HapMap project (http://www.hapmap.org), one variant in promoter region (-656T>G, rs1760944), two amino acid substitution variants (400A>G, rs2307486, Ile64Val in exon 3; 1350T>G, rs1130409, Asp148Glu in exon 5), and one variant in intron (630T>C, rs3136817). Furthermore, because cigarette smoking may induce DNA damage and individual with a reduced DNA repair capacity is associated with an increased risk for lung cancer (2, 5), we hypothesized that the genetic association might be modulated by exposure to cigarette smoke. Therefore, we also investigated the gene-environment interaction between the APE1 genotypes and smoking habit in risk for lung cancer.

Materials and Methods

Study Population. Our case-control study is part of an ongoing cooperative study, the Genetic Epidemiological Study of Lung Adenocarcinoma, which is aimed at understanding the causes of lung cancer in Taiwan. The present study included 730 lung cancer patients and 730 cancer-free controls. Case patients were recruited between September 2002 and December 2005 at National Taiwan University Hospital, Taipei Veterans General Hospital, Chang-Gung Memorial Hospital, Taichung Veterans General Hospital, National Cheng-Kung University Hospital, and Kaohsiung Medical University Hospital. Eligible cases, including any person older than the age of 18 years with incident primary lung cancer confirmed by hospital pathologists, were enrolled with no limitations on age, gender, tumor histology, or stages. Cases with a history of cancer were excluded. These patients accounted for almost all (>95%) subjects with lung cancer attending our lung cancer clinics during the same period, the remaining patients being excluded because of a lack of suitable blood specimens. No significant differences in risk factors of lung cancer were found between the included and excluded subjects. Control subjects were cancer-free individuals randomly selected from the health examination clinics of the same hospitals during the same period of case recruitment. Controls with a history of cancer were excluded. The control subjects were frequency matched (1:1) to the cases on the basis of age, gender, and smoking status. The response rates were 87% for the controls and 94% for the cases. The study was done after approval by the institutional review board of each participating institute.

At recruitment, a trained research nurse was assigned to obtain informed consent for the collection of a blood sample and to administer a structured questionnaire. The questionnaire collected information about demographic characteristics, lifestyle factors (such as number of cigarettes smoked), medical history, and family history of cancer. For smoking status, a person who was then smoking at least once a day and had been doing so for more than 6 mos was regarded as a current smoker. A former smoker was defined as someone who had stopped smoking at least 6 mos before either the diagnosis in the cases or the date signed on the informed consent form in the controls. The cumulative cigarette dose (in pack-years) was calculated by multiplying the duration of smoking (in years) by smoking intensity (in cigarette packs).

Genotyping Analysis. Genomic DNA was extracted from blood samples of all subjects by the conventional phenol-chloroform extraction method. We used data from the International HapMap Project (http://www.hapmap.org) to select tag single-nucleotide polymorphisms. The options were done based on genotype data of the APE1 gene among Han Chinese, with the pairwise correlation coefficient ($r^2$) > 0.8 and minor allele frequency > 10%. Whenever possible, we tried to include single-nucleotide polymorphisms within coding regions (rs2307486) and the promoter (rs1760944). A total of four single-nucleotide polymorphisms [-656T>G (rs1760944), 400A>G (rs2307486, Ile64Val), 630T>C (rs3136817), and 1350T>G (rs1130409, Asp148Glu)] were selected for genotyping. All genotyping was done using the MassARRAY (SEQUENOM, Inc.) system at the National Genotyping Core of National Research Program for Genomic Medicine of Taiwan. To ensure that the observed polymorphisms were not due to the technical variation, we randomly selected 10% of total subjects for repeated assays, and no inconsistent results were found.

Construction of Expression Variants. The APE1 promoter region was PCR amplified from genomic DNA of either a TT or a GG homozygous subject of -656T>G (rs1760944) polymorphism and constructed into upstream of the luciferase reporter gene in the pGL3-Basic Vectors (Promega). PCR primers were designed based on the GenBank reference sequence (accession no. NT_026437). Briefly, the APE1 promoter region was amplified using the following primer sequences: the sense 5'-CCGCTCAGCCTAAGTCAGCGGCCGCA-3' (containing a XhoI site) and the antisense 5'-CCAGGTTTGAAGCATGGAAPCC-3' (containing a HindIII site) sequences. Then, the amplified APE1 promoter (422 bp) regions with T or G alleles of -656T>G were inserted into an XhoI-HindIII upstream site of the luciferase gene and generated the recombinant APE1-promoter plasmids, designated as -656G and -656T plasmids, respectively. The recombinant clones mentioned previously were all verified by DNA sequencing.

Cell Culture and Transient Transfection. Human lung adenocarcinoma cell lines (A549, H1355, CL1-0, H928) were cultured at 37°C with 5% CO₂ in RPMI 1640 (Gibco BRL) medium containing 10% fetal bovine serum (BioSource) and 1% penicillin-streptomycin (Gibco BRL). The cells were freshly inoculated at a density of 8 × 10⁴ to
Results

The selected demographic characteristics of study subjects are shown in Table 1. There were no statistical differences for the age, gender distribution, or smoking status between the cases and controls. However, the cumulative cigarette dose (pack-years) in ever smokers was significantly higher in the cases than in the controls (50.59 ± 36.39 versus 27.79 ± 25.36 pack-years of smoking; \( P < 0.001 \)).

The distributions of APE1 single-nucleotide polymorphism genotypes among the controls and cases, and the adjusted odds ratios associated with lung cancer are summarized in Table 2. All genotype frequencies in control population were in agreement with those predicted under Hardy-Weinberg equilibrium (\( P > 0.05 \)). For the APE1 -656T>G polymorphism, individuals with at least one variant -656 G allele were at a significantly decreased risk for lung cancer compared with those harboring the -656 TT genotype, assuming a dominant model (adjusted odds ratio, 0.49; 95% CI, 0.32-0.73; \( P = 0.001 \), and the risk for lung cancer decreased with an increase in the number of -656 G alleles (adjusted odds ratio, 0.51; 95% CI, 0.33-0.79; \( P = 0.002 \) for the -656 TG genotype; adjusted odds ratio, 0.43; 95% CI, 0.25-0.76; \( P = 0.003 \) for the -656 GG genotype, respectively; \( P_{\text{trend}} = 0.001 \)). A permutation for allele test (100,000 random assignments for case-control status) gave an empirical \( P \) value of 0.012, indicating that the value obtained for the -656T>G was unlikely to occur by chance. Other polymorphisms in the APE1 gene were not associated with the risk for lung cancer.

To further analyze the combined effect of these four tag single-nucleotide polymorphisms (-656T>G, 400A>G, 630T>C, and 1350T>G), we generated the haplotypes on the basis of the observed genotypes. Among the output APE1 haplotypes, six common (≥2%) haplotypes (TATT, GATT, GATG, TATG, GACG, TGTG) accounted for 96.8% of chromosomes obtained from the 1,460 subjects (97.1% for the cases and 96.5% for the controls). There was no overall association between APE1 haplotypes and risk for lung cancer (data not shown).

The risk for lung cancer related to APE1 genotypes and haplotypes was further examined with stratification by smoking habit based on the median pack-year value of cumulative cigarette dose of the control subjects. As

### Table 1. Distribution of selected characteristics among lung cancer cases and control subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n = 730)</th>
<th>Controls (n = 730)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean, y (SD)</td>
<td>60.77 (12.08)</td>
<td>60.80 (12.44)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>384 (52.60)</td>
<td>384 (52.60)</td>
</tr>
<tr>
<td>Female</td>
<td>346 (47.40)</td>
<td>346 (47.40)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>462 (63.29)</td>
<td>462 (63.29)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>170 (23.29)</td>
<td>159 (21.78)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>98 (13.42)</td>
<td>109 (14.93)</td>
</tr>
<tr>
<td>Pack-years (SD)*</td>
<td>50.59 (36.39)</td>
<td>27.79 (25.36)</td>
</tr>
<tr>
<td>ETS exposure, %</td>
<td>616 (84.38)</td>
<td>521 (71.37)</td>
</tr>
<tr>
<td>Histologic type (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>473 (64.79)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td>97 (13.29)</td>
<td>—</td>
</tr>
<tr>
<td>Others*</td>
<td>160 (21.92)</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviation: ETS, environmental tobacco smoking.

* In ever smokers.

Environmental tobacco smoking exposure was defined as having been around someone else’s cigarette smoking on a regular basis.

Others include large cell (n = 90) and small cell (n = 70) types.
shown in Table 3, a reduced risk of APE1 -656T>G variants among heavy smokers that were statistically significant (adjusted odds ratio, 0.52; 95% CI, 0.30-0.93; P = 0.023 for the TG genotype; adjusted odds ratio, 0.27; 95% CI, 0.13-0.57; P = 0.002 for the GG genotype, respectively; \( P_{\text{trend}} < 0.001 \)) with a significant gene-smoking interaction (P = 0.013).

Table 4 shows the haplotype distributions for the cases and controls by smoking habit, as well as the risk for lung cancer according to haplotypes. In the heavy smokers (>27.80 pack-years), the frequency distribution of haplotypes between lung cancer cases and controls was significant in the global test (\( \chi^2 \) test, \( P = 0.003 \)), showing a significant effect of haplotype on risk for lung cancer. Consistent with genotyping analysis (Table 3), individuals with the GATT haplotype, which carries the variant -656 G allele, showed a significantly decreased risk for lung cancer compared with those with the most common haplotype TATT (odds ratio, 0.45; 95% CI, 0.28-0.73).

Because all three haplotypes (GATT, GATG, and GACG) carry the variant -656 G allele were associated with a reduced risk for lung cancer, we further estimated the effect of the G(NNN) haplotype on development of lung cancer. As shown in Table 5, subjects were categorized into three groups by carrying none, one, or two G(NNN) haplotypes. Using the most common others/diplotypes as the reference, the risk for lung cancer decreased in a dose-dependent manner as the number of the G(NNN) haplotypes increased (adjusted odds ratio, 0.44; 95% CI, 0.25-0.78; P = 0.005 for the others/G(NNN)); adjusted odds ratio, 0.28; 95% CI, 0.13-0.57; P = 0.001 for the G(NNN)/G(NNN), respectively).

To examine whether the -656T>G polymorphism influences promoter activity of the APE1 gene, the APE1 promoter sequence connected to a luciferase reporter gene was transfected into human lung adenocarcinoma cell lines (A549, H1355, CL1-0, H928). The reporter activities were compared between two constructs containing either T or G allele at -656 bp in the APE1 gene promoter region (Fig. 1). Significantly higher luciferase reporter activity was detected for the -656G construct compared with the -656T construct (\( P < 0.05 \)). These results suggest that the -656 G allele may be associated with the increased transcriptional activity of the APE1 gene in lung cancer cells.

### Discussion

APE1 is an essential enzyme in the base excision repair pathway, which is the primary mechanism for the repair of endogenous DNA damage resulting from cellular metabolisms, including those resulting from reactive oxygen species, methylation, deamination, and hydrolysis (9). It is estimated that 2,000 to 10,000...
Table 4. Distribution of APE1 haplotypes between lung cancer cases and controls and association with risk for lung cancer stratified by smoking habit

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Controls, n (%)</th>
<th>Cases, n (%)</th>
<th>OR (95% CI)</th>
<th>Controls, n (%)</th>
<th>Cases, n (%)</th>
<th>OR (95% CI)</th>
<th>Controls, n (%)</th>
<th>Cases, n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TATT</td>
<td></td>
<td></td>
<td></td>
<td>116 (40.97)</td>
<td>60 (41.85)</td>
<td>1.00 (reference)</td>
<td>70 (34.93)</td>
<td>163 (44.97)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>GATT</td>
<td>158 (20.26)</td>
<td>171 (18.46)</td>
<td>0.86 (0.67-1.12)</td>
<td>33 (11.66)</td>
<td>21 (14.49)</td>
<td>1.23 (0.66-2.31)</td>
<td>51 (25.51)</td>
<td>54 (18.81)</td>
<td>0.45 (0.28-0.73)</td>
</tr>
<tr>
<td>TATG</td>
<td>145 (15.64)</td>
<td>145 (15.66)</td>
<td>0.95 (0.72-1.24)</td>
<td>31 (10.97)</td>
<td>22 (15.46)</td>
<td>1.37 (0.73-2.57)</td>
<td>21 (10.71)</td>
<td>62 (17.11)</td>
<td>1.27 (0.72-2.24)</td>
</tr>
<tr>
<td>GACG</td>
<td>61 (6.62)</td>
<td>66 (7.17)</td>
<td>1.02 (0.71-1.49)</td>
<td>25 (8.97)</td>
<td>13 (8.74)</td>
<td>1.01 (0.48-2.11)</td>
<td>14 (7.00)</td>
<td>24 (6.67)</td>
<td>0.74 (0.36-1.51)</td>
</tr>
<tr>
<td>TGTG</td>
<td>17 (1.86)</td>
<td>24 (2.61)</td>
<td>1.33 (0.71-2.53)</td>
<td>3 (1.17)</td>
<td>3 (1.84)</td>
<td>1.93 (0.38-9.87)</td>
<td>9 (4.43)</td>
<td>9 (2.35)</td>
<td>0.68 (0.14-1.13)</td>
</tr>
<tr>
<td>Global test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; 5df, 5 degree of freedom.

* Composed of four polymorphic sites: -656T>G, 400A>G, 630T>C, and 1350T>G polymorphisms. Haplotypes that had a frequency of <2% were excluded from analysis.

In this study, we found that the -656T>G variant in the APE1 promoter was associated with a significantly decreased risk for lung cancer (Table 2). We subsequently showed that the -656T>G polymorphism was associated with altered promoter activity in vitro (Fig. 1). Furthermore, APE1 variant genotypes or haplotypes were significantly associated with the risk for lung cancer for the heavy smokers, but not for the light or never smokers, which reflects a gene-environment interaction (Tables 3-5). This study is an important addition to previously published work investigating polymorphisms in the genes involved in the base excision repair pathway (7, 8, 23) and provides a new base excision repair marker for detecting genetic susceptibility to lung cancer.

The APE1 promoter polymorphism and their haplotypes interacted with cigarette smoking were also evaluated. We found that APE1 promoter variant genotypes or haplotypes were significantly associated with a decreased risk for lung cancer among heavy smokers (Tables 3-5), suggesting that the APE1 promoter polymorphism or haplotype in core base excision repair reaction had a great effect on the risk of heavy smokers only, not of light or never smokers. It is possible the variant protein is associated with increased repair activity and that this increase is influenced by gene-environment interaction. One example in support of such a model is that the XRCC1 Arg194Trp was associated with a decreased risk for lung cancer among heavy smokers (24, 25); it has been shown that individuals with wild-type XRCC1 Arg194Trp (Arg/Arg) exhibited more chromosomal breaks per cell in mutagen sensitivity assay

Table 5. Association between combined diplotypes of APE1 and risk for lung cancer stratified by smoking habit

<table>
<thead>
<tr>
<th>Haplotypes pairs</th>
<th>Never smokers</th>
<th>Light smokers</th>
<th>Heavy smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
<td>aOR (95% CI)</td>
</tr>
<tr>
<td>Others1/others2</td>
<td>186 (40.23)</td>
<td>181 (39.16)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Others/G(NNN)</td>
<td>200 (43.33)</td>
<td>211 (45.70)</td>
<td>1.05 (0.77-1.44)</td>
</tr>
<tr>
<td>G(NNN)/G(NNN)</td>
<td>76 (16.44)</td>
<td>70 (15.14)</td>
<td>1.01 (0.66-1.54)</td>
</tr>
</tbody>
</table>

Abbreviation: aOR, adjusted odds ratio.


1 Light and heavy were defined according to the median pack-year value of cumulative cigarette dose among the control population (light, pack-years ≤ 27.80; heavy, pack-years > 27.80).

2 Data were adjusted for age and gender.

3 Other than G(NNN) combination.
Figure 1. Transcription activity analysis of the -656T>G polymorphism of the APE1 promoter. The luciferase reporter construct having an APE1 promoter region with T or G allele of the -656T-G polymorphism designated as -656T and -656G plasmids, respectively. The relative transcriptional activities of the different reporter constructs were measured in the A549, H1355, CL1-0, and H928 cell lines. Luciferase activities are shown; values are based on the activity obtained with the pGL3-Basic Vector as 1. The constructs were tested in three independent experiments. Values are mean ± SD. The -656G construct significantly increased promoter activity compared with the -656T construct. *, Ps derived from Student’s t test.

than those with one or two variant (Typ) alleles (26). Likewise, lower levels of 8-hydroxyguanine in lymphocytes of smokers compared with nonsmokers have been reported in some studies (27, 28), which could be explained by the presence of efficient DNA repair processes for the oxidative damage induced by smoking.

The Ile64Val and Asp148Glu variants are the most common APE1 polymorphisms that result in single amino acid substitutions have been identified in the general population (23, 29, 30). These polymorphisms have been extensively studied in lung cancer, but the results are conflicting (25, 31-33). Thus far, only one epidemiologic study has reported a positive association between the APE1 Asp148Glu variant and risk for lung cancer for the current smokers in Japan (32) and the Ile64Val variants was associated with a decreased risk for smokers in Norway (34), whereas other studies have shown no association (33, 35, 36) or an inverse association (37) with risk for lung cancer. The discrepancy of these studies might be due to differences in the levels of cigarette smoking consumption and other potential effect modifiers (e.g., occupational exposures to lung carcinogens) that were not accounted for. About biological significance, although one study on Asp148Glu polymorphism has shown that the Glu variant was associated with increased mitotic delay after exposure to ionizing radiation (38), this variant had no impact on endonuclease or DNA-binding activities (30), suggesting that the polymorphism is unlikely to affect the DNA repair capacity of the protein. Consistent with this, when we conducted a logistic regression analysis of each polymorphism, we found that neither of the two polymorphisms (Asp148Glu and Ile64Val) was associated with the risk for lung cancer.

In this study, the frequencies of variant alleles of the APE1 -656T>G and Ile64Val polymorphisms among healthy controls (0.44 and 0.05, respectively) were consistent with the frequency (0.43 and 0.05, respectively) among Han Chinese reported in the NIH database (http://www.ncbi.nlm.nih.gov/SNP). However, that of APE1 -656T>G was much lower than those among Japanese (0.65-0.78) and Caucasians (0.61-0.79). Frequencies of the 630C and 148Glu alleles among healthy controls were 0.05 and 0.40, respectively, which were lower than those of healthy Caucasians (0.22 and 0.51-0.57, respectively). The differences in allele frequencies detected in these studies might be due to ethnic variation. Ethnic variation in the APE1 polymorphisms warrants additional study to clarify the association of the APE1 polymorphism with risk for lung cancer in diverse ethnic populations.

The possible selection bias was taken into consideration and reduced to a lowest level. Given that most lung cancer patients are diagnosed and treated at university or general hospitals in Taiwan, the demographics and clinical characteristics of the cancer patients included in the current study were compatible with those of lung cancer patients in Taiwan in general, and it is reasonable to assume that the case group is representative of the lung cancer patients in our community. In addition, all cases and controls were ethnically Taiwanese, and the Taiwanese population has a relatively homogenous genetic background (39). Therefore, the potential confounding effect of population stratification for genotype data is not a major concern.

To sum up, the APE1 -656T>G polymorphism has an influence on the APE1 promoter activity and is significantly associated with a reduced risk for lung cancer, which seemed to be modified by individual cigarette smoking status. These results strongly suggest that the APE1 gene may be involved in the development of lung cancer. Because cancer is a multifactorial disease that results from complex interactions between genetic and environmental factors, now we have provided an example of well-characterized metascale case-control study to comprehensively evaluate the gene-environment modification and address the important issue of the base excision repair pathway in lung cancer susceptibility and development.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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