The Role of $P_53$ and $MDM2$ Polymorphisms in the Risk of Esophageal Squamous Cell Carcinoma

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Abstract

The tumor suppressor $P_53$ pathway plays a crucial role in preventing carcinogenesis and genetic variations of this pathway may be associated with cancer susceptibility. We tested this hypothesis by examining the contribution of functional polymorphisms in $P_53$ and $MDM2$ to risk of esophageal squamous cell carcinoma (ESCC). DNA from 758 ESCC patients and 1,420 controls were genotyped for $P_53$ codon 72Arg>Pro and $MDM2$ 309T>G polymorphisms. Odds ratios (OR) and 95% confidence intervals (CI) of ESCC were estimated by logistic regression. We observed an increased risk of ESCC associated with the $P_53$ Pro/Pro (OR, 1.83; 95% CI, 1.69-2.07) and $MDM2$ GG (OR, 1.49; 95% CI, 1.16-1.91; $P = 0.002$) genotype, compared with the $P_53$ Arg/Arg or $MDM2$ TT genotype, respectively. Interaction between these $P_53$ and $MDM2$ polymorphisms increased risk of ESCC in a multiplicative manner, with the OR being 3.10 (95% CI, 2.07-4.69) for subjects carrying both $P_53$ Pro/Pro and $MDM2$ GG genotypes. Significant interactions were observed between these polymorphisms and smoking, with risk being the highest (OR, 5.29; 95% CI, 2.91-9.61) in smokers having both $P_53$ Pro/Pro and $MDM2$ GG genotypes. The $MDM2$ GG genotype was also associated with risk of developing poorly differentiated and advanced ESCC compared with the GT or TT genotype (OR for high-grade and stages III-IV versus low-grade and stages I-II = 1.60; 95% CI, 1.00-2.64; $P = 0.049$). The $P_53$ and $MDM2$ polymorphisms may be genetic determinants for the development of ESCC. (Cancer Res 2005; 65(20): 9582-7)

Introduction

The $P_53$ tumor suppressor pathway is well-known to be crucial in maintaining genomic integrity and preventing cells from oncogenic transformation. When a cell is exposed to genotoxic stress such as DNA damage and oncogene activation, the $P_53$ protein accumulates rapidly through posttranscriptional mechanisms and is also activated as a transcriptional factor, which leads to cell cycle arrest for DNA repair or apoptotic cell death (1, 2). $MDM2$ plays a key role in regulating $P_53$ pathway by directly binding to $P_53$ protein, inhibiting its activity and mediating its location and degradation via the ubiquitination system; $P_53$ also positively regulates $MDM2$ expression, which forms a negative feedback loop (3). In most physiologic conditions, $MDM2$ maintains $P_53$ at low levels to enable normal cell growth and development; however, overexpression of $MDM2$ may inhibit $P_53$ function, thus making damaged cells to escape the cell cycle checkpoint control and become carcinogenic (4, 5). It is now clear that disruption of $P_53$ pathway, either through inactivating $P_53$ mutations or through overexpression of $MDM2$, is associated with the formation and progression of malignancies. For example, it has been shown that >50% of human tumors have inactivating $P_53$ mutations (6). Both mice and humans harboring germ line inactivating mutations in one $P_53$ allele are highly susceptible to cancer: they develop cancer very early in life and at very high frequencies (7, 8). In humans, overexpression of $MDM2$ is common in a variety of tumor types and, in some cases, overexpression of $MDM2$ but not $P_53$ mutation is observed (9–11), suggesting that it can take the place of inactivating $P_53$ mutations.

Because $P_53$ and $MDM2$ and their interaction play central roles in cancer formation and progression, one may reason that functional single nucleotide polymorphisms in these two genes might render the carrier susceptible to cancer. Recently, a single nucleotide polymorphism at nucleotide 309 (T>G) in the promoter region of $MDM2$ has been reported and cells carrying the 309G genotype, due to enhanced affinity to bind stimulatory protein (Sp) 1, show a heightened $MDM2$ expression and significant attenuation of $P_53$ pathway compared with those carrying the 309TT genotype (12). Furthermore, this functional single nucleotide polymorphism has been shown to be associated with earlier age of onset of certain hereditary and sporadic cancers in the human. The $P_53$ gene is also polymorphic and among its single nucleotide polymorphisms, a G>C change at codon 72 results in Arg>Pro amino acid substitution. The functional impact of this $P_53$ polymorphism has been reported and the Arg/Arg genotype seems to induce apoptosis with faster kinetics and to suppress transformation more efficiently than the Pro/Pro genotype (13).

Esophageal squamous cell carcinoma (ESCC) is one of the most common and fatal malignancies in the world, particularly in northern China (14, 15). Although the integrated etiology of ESCC remains to be elucidated, cumulative evidence suggests that tobacco smoking, heavy alcohol drinking, micronutrient deficiency, and dietary carcinogen exposure may cause the disease (16–19). All these factors can induce or enhance DNA damage mediated by either oxidative stress or DNA-binding electrophiles. However, even in the at-risk population, only a portion of exposed individuals develop the cancer in their life span, indicating that there may be important genetic basis rendering such individuals susceptible to the disease. In view of the crucial role that $P_53$-$MDM2$ interaction plays in the cell cycle checkpoint, DNA repair, apoptotic cell death, and the reported functional significance of their variants, we hypothesized that genetic variations in $P_53$ and $MDM2$ might underlie phenotypic variation in susceptibility to ESCC. Here, we
report a large case-control study aimed at examining this hypothesis, showing that the P53 and MDM2 polymorphisms, alone and in combination, had significant impact on the occurrence and development of ESCC.

Materials and Methods

Study subjects. This study consisted of 758 incident patients with ESCC and 1,420 healthy controls. All subjects were unrelated ethnic Han Chinese and residents in Beijing and the surrounding regions. Patients with ESCC were newly diagnosed and histologically confirmed, which were consecutively recruited from January 1997 to July 2003, at the Cancer Hospital, Chinese Academy of Medical Sciences (Beijing). All patients underwent esophagectomy which had detailed metastatic data. Most patients (n = 656) were enrolled in our previous study, which is reported elsewhere (20). In the present study, we added 102 cases, which were further consecutively recruited after the previous study was terminated, to extend the sample sizes of patients to 758. Patients that received chemotherapy or radiotherapy prior to surgery or had no detailed metastatic data were excluded from this study. The pathologic stage of ESCC at the time of diagnosis was classified into stage I (T1N0M0), stage II (T2-3N0M0 or T1-2N1M0), stage III (T3N1M0 or T4NanyM0), and stage IV (TanyNanyM1) according to the tumor-node-metastasis classification (21). Tumor grade was classified into low grade (well-differentiated), intermediate grade (moderately differentiated), and high grade (poorly differentiated) according to the WHO grade classification (22). All histopathologic classifications were determined by senior pathologists of the hospital on the basis of the postoperative histopathologic examination. The controls were cancer-free individuals based on a physical examination, randomly selected from a pool of 2,800 subjects which were recruited from a community cancer screening program for early detection of cancer in the same region during the same time period as the patient data was collected. The selection criteria include no individual history of cancer, and the controls were frequency-matched to ESCC patients on the basis of age (±5 years) and sex. At recruitment, informed consent was obtained from each subject, and each participant was then interviewed to collect detailed information on demographic characteristics and lifetime history of tobacco use. This study was approved by the Institutional Review Board of the Chinese Academy of Medical Sciences Cancer Institute.

Polymorphism analysis. P53 72Arg-Pro genotypes were determined by PCR-RFLP assay as described previously (23), whereas MDM2 309T>G genotypes were analyzed using the tetra-amplification refractory mutation system–PCR method (24). The primers for amplification refractory mutation system–PCR amplification of DNA fragment containing the MDM2 309T allele were MDM2F1 (5'-GGGGGGCCGGGGGCTGCGGGGCCGTTT-3') and MDM2R1 (5'-TGCCCTAGTGAACGGCCTCCCGCCGAG-3'), and for the MDM2 309G allele were MDM2F2 (5'-GGGGGGCCGGGGGCTGCGGGGCCGTTT-3') and MDM2R2 (5'-ACCTGGCATACGGGCTGACGAGGG-3') and MDM2R2 (5'-ACCTGGCATACGGGCTGACGAGGG-3'). The amplification was accomplished with a 10 μL reaction mixture containing 10 ng of template DNA, 0.8 μmol/L of each primer from MDM2F1 and MDM2R1, 4.8 μmol/L of primers MDM2F2 and MDM2R2, 0.2 mmol/L of deoxynucleotide triphosphates, 1.5 mmol/L of MgCl2, 0.4 units of HotStar Taq with 1× buffer and 1× Q-solution (Qiagen, Chatsworth, CA). The reaction was carried out with an initial melting step of 15 minutes at 95°C; followed by 35 cycles of 45 seconds at 95°C, 45 seconds at 64°C, and 1 minute at 72°C; and a final elongation step of 7 minutes at 72°C. The amplified DNA was visualized on 3.0% agarose gel containing ethidium bromide. The MDM2 309T allele generated a 158-bp band, although they had a common 224-bp band which is amplified by primers MDM2F2 and MDM2R1. The genotypes revealed by amplification refractory mutation system–PCR were further confirmed by DNA sequencing. Genotyping was done without knowledge of case/control status of the study subjects. For quality control, a 10% masked random sample of DNA from cases and controls was genotyped twice by different investigators (Y. Hong and X. Miao), and the results were concordant for all of the masked duplicate sets.

Real-time analysis of MDM2 mRNA. Forty-two normal esophageal tissues adjacent to the tumors were obtained from surgically removed specimens of individual patients (25). The normal tissues sampled at least 5 cm away from the margin of the tumor were immediately placed in liquid nitrogen and then stored at −80°C before analysis. Total RNA was isolated from tissues using the Trizol reagent (Molecular Research Center, Inc., Cincinnati, OH) and converted to cDNA using a oligo (dT)25 primer and SuperScript II (Invitrogen, Carlsbad, CA). Relative gene expression quantification for MDM2, with β-actin as an internal reference gene, was carried out using the ABI Prism 7000 sequence detection system (Applied Biosystems, Foster City, CA) in triplicates, based on the SYBR-Green method. The primers used for MDM2 were 5'-TGTAAGTGAACATTCAGGTG-3' and 5'-TTCCAAATATCGCTAAGGA-3'; and for β-actin were 5'-GGCCGCCACCCACATGTACCTCT-3' and 5'-AGGGGCCGGACTCTGCTCATCACT-3'. The PCR reaction mixture consisted of 0.1 μmol/L of each primer, 1× SYBR Premix EX Taq (Perfect Real Time) premix reagent (TakaRa, Dalian, China), and 50 ng cDNA to a final volume of 20 μL. Cycling conditions were 95°C for 10 minutes, followed by 40 cycles at 95°C of 15 seconds and 62°C for 1 minute. PCR specificity was confirmed by dissociation curve analysis and gel electrophoresis. All analysis were done in a blinded fashion with the laboratory persons unaware of genotyping data. The expression of individual MDM2 measurements was calculated relative to expression of β-actin using a modification of the method described by Lehmann et al. (26).

Statistical analysis. χ² test was used to evaluate differences in demographic variables, smoking, and genotype distribution of P53 and MDM2 polymorphisms between cases and controls and between metastatic and nonmetastatic cases. The associations between the polymorphisms and risk of development and metastasis of ESCC were estimated by odds ratios (OR) and their 95% confidence intervals (CI) calculated by unconditional univariate and multivariate logistic regression models. Smokers were considered current smokers if they smoked up to 1 year before the date of diagnosis for cases or up to the date of the interview for controls. Because only 40 patients and 32 controls were ex-smokers, they were combined with current smokers for analysis. Light and heavy smokers were categorized by median pack-year value [pack-years = (cigarettes/d/20) × years of smoking] of the controls—that is, ≤24 pack-years and >24 pack-years. The ORs were all adjusted for age, sex, and smoking status or pack-years where it was appropriate. The probability level of <0.05 was used as the criterion of significance and all tests were two-sided tests. We tested the null hypotheses of additivity and multiplicativity gene-gene joint effects and evaluated departures from additivity and multiplicative joint effects models by including main effect variables and their product terms in the logistic regression model (27). Student's t test and ANOVA were used to assess differences in MDM2 transcript abundance with different genotypes. All analyses were done using Statistical Analysis System (version 6.12, SAS Institute, Cary, NC).

Results

Characteristics of study subjects. The frequency distributions of selected characteristics of the patients and controls are presented in Table 1. The cases and controls seemed to be adequately matched in terms of sex and age. The median age was 59.3 years (range, 28-89 years) for the patients and 58.6 years (range, 26-94 years) for the controls (P = 0.194). There was no significant difference between patients and controls in sex distribution (74.8% among controls (59.1% versus 52.3%; OR, 1.37; 95% CI, 1.10-1.68; P = 0.240). However, significantly more smokers were presented among cases than among controls (59.1% versus 52.3%; OR, 1.37; 95% CI, 1.10-1.68; P = 0.003). In addition, heavy smokers had a higher OR of ESCC than light smokers [1.63 (95% CI, 1.28-2.08) versus 1.25 (95% CI, 1.00-1.55); P = 0.034]. These results indicate that smoking is a risk factor for ESCC in our study population. Of the 758 patients, 107 (14.1%) had stage I ESCC, 285 (37.6%) had stage II ESCC, and 343 (45.3%) had stage III ESCC, whereas only 23 (3.0%) patients had
Table 1. Distributions of select characteristics in patients and controls

| Characteristics       | Cases, no. (%) | Controls, no. (%) | P*  
|-----------------------|----------------|-------------------|-----
| Total no.             | 758 (100)      | 1,420 (100)       | 0.240  
| Sex                   |                |                   | 0.003  
| Male                  | 567 (74.8)     | 1,029 (72.5)      | 0.194  
| Female                | 191 (25.2)     | 391 (27.5)        | 0.194  
| Age (year)            |                |                   | 0.002  
| ≤50                   | 163 (21.5)     | 335 (23.6)        | 0.002  
| 51-60                 | 268 (35.3)     | 493 (34.7)        | 0.002  
| 61-70                 | 247 (32.6)     | 478 (33.7)        | 0.002  
| >70                   | 80 (10.6)      | 114 (8.0)         | 0.002  
| Smoking status        |                |                   | 0.002  
| Nonsmoker             | 310 (40.9)     | 677 (47.7)        | 0.002  
| Smoker                | 448 (59.1)     | 743 (52.3)        | 0.002  
| Tumor grade           |                |                   | 0.002  
| Low                   | 199 (26.3)     |                   | 0.002  
| Intermediate          | 426 (56.2)     |                   | 0.002  
| High                  | 133 (17.5)     |                   | 0.002  
| Tumor grade at diagnosis |         |                   | 0.002  
| I                     | 107 (14.1)     |                   | 0.002  
| II                    | 285 (37.6)     |                   | 0.002  
| III                   | 343 (45.3)     |                   | 0.002  
| IV                    | 23 (3.0)       |                   | 0.002  

*Two-sided χ² test.

Table 2. Genotype and allele frequencies of P53 and MDM2 among cases and controls and their association with the risk of esophageal squamous cell carcinoma

| Genotype   | Cases (n = 758) | Controls (n = 1,420) | OR* (95% CI)  
|------------|-----------------|----------------------|---------------
|            | no. (%)         | no. (%)              |               
| P53 72Arg-Pro |                 |                      |               
| Arg/Arg     | 340 (44.9)      | 731 (51.5)           | 1.00 (0.81-1.24)  
| Arg/Pro     | 219 (28.9)      | 264 (18.6)           | 1.83 (1.43-2.35)  
| Pro allele frequency | 0.513 | 0.443               |               
| MDM2 309T>G  |                 |                      |               
| TT          | 203 (27.3)      | 418 (29.4)           | 1.00           
| TG          | 348 (46.0)      | 711 (50.1)           | 1.01 (0.82-1.25)  
| GG          | 207 (26.7)      | 291 (20.5)           | 1.49 (1.16-1.91)  
| G allele frequency | 0.503 | 0.455               |               

*Data were calculated by unconditional logistic regression and adjusted for sex, age, and smoking status, and other genotype where appropriate.
ESCC. Because of this observation, and the correlation between genotype and MDM2 mRNA level (Fig. 1), we combined the P53 Arg/Pro and Arg/Arg or MDM2 TT and TG into one group for subsequent analysis. In the stratification analysis, age and sex had no effect on the risk of ESCC related to these two polymorphisms. However, the increased risk associated with the P53 Pro/Pro or MDM2 GG genotype was more pronounced in smokers (OR, 2.16; 95% CI, 1.63-2.86 for P53 and OR, 1.60; 95% CI, 1.21-2.12 for MDM2) than in nonsmokers (OR, 1.43; 95% CI, 1.04-1.97 for P53 and OR, 1.37; 95% CI, 0.99-1.86 for MDM2).

Gene-gene and gene-gene-smoking interactions. We next examined whether there was a statistical joint effect between the P53 and MDM2 polymorphisms (Table 3). We found that patients carrying the P53 Pro/Pro genotype were also more likely to carry the MDM2 GG genotype than the controls (7.9% versus 3.2%; \( P < 0.001 \)). The presence of one risk genotype (MDM2 GG or P53 Pro/Pro) was associated with a moderate increase in risk of developing ESCC (OR, 1.43; 95% CI, 1.08-1.78 or OR, 1.21-2.12 for MDM2) than in nonsmokers (OR, 1.43; 95% CI, 1.04-1.97 for P53 and OR, 1.37; 95% CI, 0.99-1.86 for MDM2).

Discussion

This molecular epidemiologic study examined whether genetic polymorphisms in P53 and MDM2 were associated with risk of developing ESCC. On the basis of analyzing 758 patients and 1,420 frequency-matched controls, we showed that both P53 72Arg-Pro and MDM2 309T>G polymorphisms were associated with increased risk for the development of ESCC. Furthermore, increased multiplicative interactions between P53 Pro/Pro and MDM2 GG

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Cases (n = 758)</th>
<th>Controls (n = 1,420)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P53 72Arg-Pro</td>
<td>MDM2 309T&gt;G</td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Arg/Arg + Arg/Pro</td>
<td>TT + TG</td>
<td>392 (51.7)</td>
<td>910 (64.1)</td>
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<tr>
<td>Arg/Arg + Arg/Pro</td>
<td>GG</td>
<td>147 (19.4)</td>
<td>246 (17.3)</td>
</tr>
<tr>
<td>Pro/Pro</td>
<td>TT + TG</td>
<td>159 (21.0)</td>
<td>219 (15.4)</td>
</tr>
<tr>
<td>Pro/Pro</td>
<td>GG</td>
<td>60 (7.9)</td>
<td>45 (3.2)</td>
</tr>
</tbody>
</table>

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

\( P < 0.001 \), test for homogeneity between Pro/Pro-GG and Arg/Arg + Arg/Pro-GG or Pro/Pro-TT + GG.
significantly higher. Our real-time PCR data showed that the GG genotype carriers had significance (12, 13, 28). Consistent with the previous report (12), we also observed that patients carrying the MDM2 polymorphism showed an increased multiplicative gene-gene interaction between smoking and the Pro/Pro genotype. This is also biologically plausible. Firstly, the P53 pathway plays a key role in maintaining genomic integrity and preventing against oncogenic transformation of cells. It has been shown that loss of P53 activity due to mutations or overexpression of MDM2 is a common feature of malignant transformation and early event of carcinogenesis (6–11). Secondly, the investigated polymorphisms in the P53 and MDM2 genes have been shown to be of functional significance (12, 13, 28). Consistent with the previous report (12), our real-time PCR data showed that the GG genotype carriers had significantly higher P53 expression in the target tissue than the TT or TG genotype carriers, suggesting that the variant MDM2 genotype may cause attenuated P53 function. Given the important role of P53 pathway in cancer development and the effects of these polymorphisms on P53 and MDM2 function, one may expect that individuals with the P53 72Pro/Pro and/or MDM2 309GG genotypes are more susceptible to cancer. Moreover, the P53 and MDM2 polymorphisms have been linked to susceptibility to other cancers (12, 13, 28). Together, these data strongly support our observations that P53 72Arg>Pro and MDM2 309T>G polymorphisms are genetic risk factors for ESCC. In addition, our results showed an increased multiplicative gene-gene interaction between the MDM2 and P53 polymorphism. This is also biologically reasonable and consistent with the notion that MDM2 acts in carcinogenesis through eliminating P53 (4, 5). It has been suggested that if two risk factors act in the same causal pathway, a multiplicative interaction is to be expected (27).

Another interesting finding in our study is that both P53 and MDM2 polymorphisms seemed to interact with tobacco smoking. As shown in Table 4, the interaction between smoking and the mutual presence of MDM2 GG and P53 Pro/Pro genotypes conferred an OR of >5 for developing ESCC. Smoking is an established etiologic factor for ESCC (17, 31), and exposure to smoke causes genotoxic stress including DNA damage (32). When cells are exposed to smoke, an adaptive response of the genome-protection machinery including the P53 pathway occurs to prevent the cells from DNA damage. A higher risk of ESCC associated with smoking and mutual presence of MDM2 GG and P53 Pro/Pro genotypes may be attributed to attenuated P53 pathway resulting from the polymorphisms, which increases the possibility of damaged cells, caused by tobacco carcinogens, to escape cell cycle check-point control and apoptosis triggered by P53 and become malignant. This hypothesis is supported by several previous studies. For example, it has been shown that the P53-72Pro variant induces apoptosis and suppresses transformation less efficiently than the P53-72Arg counterpart (13). For the MDM2 polymorphism, Bond et al. (12) showed that after treatment with etoposide to induce DNA damage, which activates the P53 pathway, leading to DNA repair, cell cycle arrest, and apoptosis, significant death was observed in cells with the MDM2 TT genotype but not in cells with the MDM2 GG genotype. In this regard, smokers with both MDM2 GG and P53 Pro/Pro genotypes are therefore expected to have the highest risk of ESCC.

To the best of our knowledge, thus far, there have been no published reports on MDM2 polymorphism and risk of ESCC and our present study remains the first one. However, several case-control studies have examined the association between the P53 72Arg>Pro polymorphism and risk of ESCC. In a pilot study including 91 patients and 204 controls, Zhang et al. (33) showed that subjects carrying the P53 72Pro/Pro genotype had a >2-fold increased risk for developing ESCC in a Chinese population. Lee et al. (34) reported a similar result showing that the P53 72Pro allele was more frequently found in ESCC patients than in controls and the Pro/Pro genotype conferred a 2.5-fold increased risk in a Chinese population in Taiwan. Recently, Zhang et al. (35) analyzed 173 ESCC patients and 136 controls in an at-risk population in northern China and also found that the P53 72Pro/Pro genotype was associated with 2-fold increased risk of the cancer. These results are consistent with our present larger study in Chinese population. However, in contrast with our and other’s studies showing that the P53 72Pro/Pro genotype is an at-risk genotype, three additional studies in Chinese and Japanese populations reported that the P53 72Arg>Arg genotype is an at-risk genotype for human papillomavirus–associated ESCC (36–38). The hypothesis of these studies was based on a report showing that the P53-72Arg is more susceptible to degradation by human papillomavirus E6 protein than is the P53-72Pro and is associated with increased risk of cervical cancer (39). However, unlike tobacco smoking, the role of human papillomavirus infection in the etiology of ESCC has not been established (40). In addition, even in cervical cancer, where human papillomavirus infection as an etiologic factor is well-established, research on this topic has produced controversial results (41).

### Table 4. Risk of esophageal squamous cell carcinoma associated with MDM2 and P53 genotypes by smoking status

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Non-smoker</th>
<th>Smoker</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/controls</td>
<td>OR* (95% CI)</td>
<td>Cases/controls</td>
</tr>
<tr>
<td><strong>P53 72Arg&gt;Pro</strong></td>
<td>MDM2 309T&gt;G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg/Arg + Arg/Pro</td>
<td>TT + TG</td>
<td>163/416</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Arg/Arg + Arg/Pro</td>
<td>GG</td>
<td>66/125</td>
<td>1.36 (0.96-1.93)</td>
</tr>
<tr>
<td>Pro/Pro</td>
<td>TT + TG</td>
<td>60/111</td>
<td>1.40 (0.98-2.02)</td>
</tr>
<tr>
<td>Pro/Pro</td>
<td>GG</td>
<td>21/25</td>
<td>2.18 (1.18-4.01)</td>
</tr>
</tbody>
</table>

*Data were calculated by unconditional logistic regression and adjusted for sex and age.  
† P < 0.05, test for homogeneity between smoking-related ORs among different genotypes.
Overexpression of MDM2 has been associated with poor prognosis of ESCC (42–44). We were therefore interested in examining whether there was an association between the MDM2 polymorphism and ESCC disease status at the time of diagnosis. Logistic regression analysis showed a significant association between increased risk for poorly differentiated and advanced ESCC and the MDM2 GG genotype, suggesting that heightened expression of MDM2 might have an effect on tumor progression. These results could be explained by the attenuated P53 pathway function resulting from the MDM2 polymorphism, which facilitates cancer cell proliferation and accumulates mutations that favor invasion and metastasis and poor differentiation of the cancer cells. However, no such associations with the P53 tumor suppressor pathway plays an important role in the development of esophageal cancer.

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