Short Communication

Combined Effects of the *p53* and *p73* Polymorphisms on Lung Cancer Risk

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Abstract

Lung cancer is a multigenic disease where one variant single nucleotide polymorphism may have only a modest independent effect on the disease phenotype, yet in aggregate, multiple biologically relevant single nucleotide polymorphisms may provide a more accurate representation of risk. Polymorphisms in members of the p53 family, such as p53 and p73, that have a functional relevance would be predicted to contribute to the disease phenotype. In this analysis, we used genotype data from 863 lung cancer cases and 852 healthy controls to test for multigenetic effects of polymorphisms at *p53* exon 4, introns 3 and 6, and at *p73* exon 2. All individuals in this analysis were self-reported non–Hispanic Caucasians. When the *p73* and *p53* variant alleles were combined and analyzed as a continuous variable, there was a 13% increase [odds ratios (OR), 1.13; 95% confidence intervals (CI), 1.05-1.21] in lung cancer risk for each additional variant allele. Furthermore, when the number of variant alleles was categorized into three groups (zero, one to three, and four or more variants), there was evidence of a gene-dosage effect with increased risks for individuals with one to three variants (OR, 1.30; 95% CI, 1.05-1.61) and four or more variants (OR, 1.78; 95% CI, 1.23-2.56). When the data were stratified by smoking status, an increased risk for lung cancer was evident only in current (OR, 2.32; 95% CI, 1.25-4.33) and former smokers (OR, 1.73; 95% CI, 1.02-2.94) with four or more variants. Younger individuals with four or more variants were also at a significantly increased risk for lung cancer (OR, 3.15; 95% CI, 1.62-6.12). This study provides support for the multigenetic effects of variant alleles from *p53* exon 4, and introns 3 and 6, and *p73*, and their interplay with smoking, resulting in a significantly increased risk for lung cancer in this Caucasian population. (Cancer Epidemiol Biomarkers Prev 2006;15(1):158–61)

Introduction

Lung cancer is a multigenic disease. Although one variant single nucleotide polymorphism (SNP) may have only a modest independent effect on the disease phenotype, in aggregate, multiple biologically relevant SNPs in the same pathway may provide a more accurate representation of lung cancer risk. This concept may be illustrated by evaluating the individual and joint effects of variants in two genes in the p53 family. This pathway encompasses widely diverse biological effects ranging from development to oncogenesis (1, 2).

The *p53* gene encodes for a tumor suppressor protein that is associated with many cellular functions, including cell cycle regulation, DNA repair, inhibition of spontaneous mutations, cellular differentiation, and apoptosis (1, 2). Furthermore, p53 is a major determinant of cell survival and is a safeguard against genetic instability (2). The p53 mutational spectrum provides molecular evidence of the role of tobacco smoke in the causation of this disease (3). p73, a member of the p53 family, has structural and functional homology with p53. The *p73* gene is predicted to encode a protein with significant amino acid sequence similarity to p53 (4), and its DNA-binding domain shows 63% identity with that of p53. p73 activates several *p53*-responsive genes participating in cell cycle control, DNA repair, and apoptosis. Furthermore, p73 inhibits cell growth in a p53-like manner by inducing apoptosis or G_1 cell cycle arrest (1).

Both the *p53* and *p73* genes are highly polymorphic. To date, there are at least 13 different polymorphisms identified in the human *p53* gene (5, 6), of which 5 are found in exons and 8 in introns, and there are at least 19 polymorphisms in *p73* (4, 7, 8), of which 10 are found in exons, 8 found in introns, and 1 found in the promoter region. At present, the functional effect for many of these polymorphisms is not known. We have previously reported an elevated risk for lung cancer among non–Hispanic Caucasians (n = 517 cases) associated with the *p53* polymorphisms in codon 72 of exon 4 (G/C transversion), intron 3 (16 bp duplication), and intron 6 (G/A transition; ref. 5). Similarly, in a separate analysis from the same population of cases and controls, we reported that two linked polymorphisms at positions 4 and 14 of exon 2 (G4C14-to-A4T14) of the *p73* gene were also associated with an elevated risk for lung cancer among non–Hispanic Caucasians (n = 1,054 cases; ref. 7).

In this analysis, we used existing and additional genotype data on 863 lung cancer cases and 852 healthy controls to test the interactive effects of polymorphisms associated with *p53* exon 4, and introns 3 and 6, and *p73* exon 2. We genotyped an additional 346 lung cancer cases and 308 healthy controls since the study by Wu et al. (5) for the *p53* genotypes and combined them with existing *p73* genotype data from Li et al. (7). The hypothesis was that individuals who possess a higher number of variant *p53* and *p73* alleles would be at higher risk for lung cancer, and that combining the variant alleles would improve the precision of the risk estimates.

Materials and Methods

Study population. Details and response rates for this ongoing case-control study have been previously published (5, 7). For this specific analysis, the subgroup of cases and controls were

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recruited from February 1996 to November 2002. This research was approved by the M.D. Anderson Cancer Center Institutional Review Board.

Epidemiologic data. All study participants signed an informed consent and completed a 45-minute personal interview to obtain information on demographics and smoking history. Ever smokers were defined as individuals who had smoked at least 100 cigarettes in their lifetime. A former smoker had quit smoking at least 1 year before diagnosis (cases) or before interview (controls). Pack-years were estimated from the product of the number of cigarette packs smoked per day and the number of years smoked.

Genotyping. Details of the assays used to genotype the polymorphic regions of *p53* (5) and *p73* (7) have been previously described.

Statistical analysis. All analyses were done using the Intercooled Stata 8.2 statistical software package (Stata Corporation, College Station, TX). Pearson's χ^2 test was used to test for differences between the cases and controls in terms of gender and smoking status. Student's *t* test was used to test differences in mean age and cigarette pack-years smoked. Odds ratios (OR) and 95% confidence intervals (CI) were calculated as an estimate of the relative risk. Unconditional multivariable logistic regression analysis was used to control for confounding by age, gender, smoking status, and cigarette pack-years, where appropriate. Trend tests were done by creating a categorical variable that assigned the score *n* to the *n*th quartile of intake. The categorical variable was treated as an interval predictor in the multivariable logistic models. Interaction was tesFed on the multiplicative scale by entering product terms in the main effects multivariable models.

Results

For this analysis, complete *p53* and *p73* genotype data were available on 863 lung cancer patients and 852 healthy controls. For brevity and because they have been published elsewhere (5, 7), we did not include tables for the study population demographics. All individuals were self-reported non–Hispanic Caucasians, 53% of the cases and 52% of the controls were men ($P = 0.690$). There was no statistically significant difference in mean age between the cases (61.5 years ± 10.1 SD) and controls (61.6 years ± 10.1 SD; $P < 0.890$). Current smokers were overrepresented (42%) among cases compared with controls (33%; $P < 0.001$). Cases were also self-reported heavier smokers compared with controls for both current smokers (59.9 pack-years ± 33.2 SD versus 46.8 pack-years ± 27.8 SD; $P = 0.006$) and former smokers (47.1 pack-years ± 30.1 SD versus 42.1 pack-years ± 30.6 SD; $P = 0.021$).

As previously published (7), the *p73* variant genotypes (i.e., GC/AT + AT/AT) versus the wild-type genotype (i.e., GC/GC) were associated with statistically significantly increased risk (OR, 1.37; 95% CI, 1.13-1.67) after adjusting for age, gender, smoking status, and pack-years (Table 1). The *p53* variant genotypes (i.e., WM + MM) versus the wild-type (i.e., WW) were also associated with statistically significantly increased risks for intron 3 (OR, 1.38; 95% CI, 1.10-1.74) and intron 6 (OR, 1.36; 95% CI, 1.09-1.70), and borderline statistically significant for exon 4 (OR, 1.15; 95% CI, 0.94-1.40), confirming our previous findings (5) in a smaller subset of cases and controls. When the *p73* and *p53* variant alleles were combined and analyzed as a continuous variable, there was a 13% increase (OR, 1.13; 95% CI, 1.05-1.21) in lung cancer risk for each additional variant allele. Furthermore, there was evidence of a gene-dosage effect. The risk for individuals with one to three variants was 1.30 (95% CI, 1.05-1.61) and 1.78 (95% CI, 1.23-2.56) for four or more variants.

Current (OR, 2.32; 95% CI, 1.25-4.33) and former smokers (OR, 1.73; 1.02-2.94) with four or more *p73* and *p53* variant alleles exhibited increased risks, but there was no similar pattern in never smokers with four or more variants (OR, 0.98; 95% CI, 0.38-2.57; Table 2). A similar trend, but with attenuated ORs, was observed for individuals with one to three variant alleles. In the joint effects analysis, current smokers with one to three variants (OR, 1.39; 95% CI, 0.85-2.25) and four or more variants (OR, 2.45; 95% CI, 1.20-5.02) were at the highest risk (P for interaction = 0.285). None of the other joint effects were statistically significant.

When age was categorized by tertiles (Table 3), younger individuals (≤58 years) with four or more variants exhibited the highest risk (OR, 3.15; 95% CI, 1.62-6.12). The risk was also elevated for older individuals (≥67 years; OR, 1.89; 95% CI, 1.01-3.51; P for interaction = 0.978). There were no elevations in risk in the intermediate age group (59-66 years).

Gender-specific risks were also evident (Table 3). For the same number of variant alleles, men exhibited higher risks compared with women; for four or more variants, there was a 1.96-fold increased risk (95% CI, 1.19-3.24), compared with a 1.55-fold increased risk (95% CI, 0.90-2.66) in women with four or more variants (P for interaction = 0.212).

Table 1. *p73* and *p53* variant alleles and lung cancer risk

Genotypes and no. of variant alleles	Cases, % (n = 863)	Controls, % (n = 852)	Univariate OR (95% CI)	Multivariate OR (95% CI)*
Main effects of the genotypes				
p73				
GC/GC	486 (56.3)	540 (63.4)	1.0	1.0
GC/AT + AT/AT	377 (43.7)	312 (36.6)	1.34 (1.10-1.64)	1.37 (1.13-1.67)
p53 exon 4				
WW	552 (63.9)	571 (67.0)	1.0	1.0
WM + MM	311 (36.1)	281 (33.0)	1.14 (0.93-1.40)	1.15 (0.94-1.40)
p53 intron 3				
WW	642 (74.4)	678 (79.6)	1.0	1.0
WM + MM	221 (25.6)	174 (20.4)	1.34 (1.06-1.69)	1.38 (1.10-1.74)
p53 intron 6				
WW	626 (72.5)	664 (77.9)	1.0	1.0
WM + MM	237 (27.5)	188 (22.1)	1.34 (1.07-1.68)	1.36 (1.09-1.70)
Number of variant alleles				
Continuous	863	852	1.12 (1.05-1.20)	1.13 (1.05-1.21)
Categorical†				
0	253 (29.3)	302 (35.5)	1.0	1.0
1-3	518 (60.0)	487 (57.2)	1.27 (1.03-1.57)	1.30 (1.05-1.61)
≥4	92 (10.7)	63 (7.3)	1.74 (1.20-2.55)	1.78 (1.23-2.56)

*Adjusted by age, sex, smoking status, and pack-years smoked.
† P for trend < 0.001.

Table 2. Number of *p73* and *p53* variant alleles, smoking, and lung cancer risk

No. of variant alleles and smoking status		Cases, % (n = 863)	Controls, % (n = 852)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Stratified by smoking status					
Never smokers					
0		41 (32.5)	45 (34.1)	1.0	1.0
1-3		75 (59.5)	76 (57.6)	1.08 (0.62-1.91)	1.05 (0.62-1.80)*
≥4		10 (8.0)	11 (8.3)	1.00 (0.34-2.89)	0.98 (0.38-2.57)*
Former smokers					
0		98 (26.0)	147 (33.7)	1.0	1.0
1-3		239 (63.4)	255 (58.5)	1.41 (1.02-1.94)	1.38 (1.01-1.89)†
≥4		40 (10.6)	34 (7.8)	1.76 (1.01-3.09)	1.73 (1.02-2.94)†
Current smokers					
0		114 (31.7)	110 (38.7)	1.0	1.0
1-3		204 (56.7)	156 (55.0)	1.26 (0.89-1.79)	1.25 (0.89-1.76)†
≥4		42 (11.6)	18 (6.3)	2.25 (1.18-4.41)	2.32 (1.25-4.33)†
Joint effects with smoking status ‡					
0	never	41 (4.7)	45 (5.3)	1.0	1.0
0	former smoker	98 (11.4)	147 (17.3)	0.73 (0.43-1.24)	0.76 (0.45-1.28)§
0	current smoker	114 (13.2)	110 (12.9)	1.14 (0.67-1.93)	1.14 (0.68-1.89)§
1-3	never	75 (8.7)	76 (8.9)	1.08 (0.62-1.91)	1.05 (0.62-1.79)§
1-3	former smoker	239 (27.7)	255 (29.9)	1.03 (0.63-1.67)	1.01 (0.63-1.62)§
1-3	current smoker	204 (23.6)	156 (18.3)	1.44 (0.87-2.37)	1.39 (0.85-2.25)§
≥4	never	10 (1.2)	11 (1.3)	1.00 (0.34-2.89)	0.98 (0.38-2.57)§
≥4	former smoker	40 (4.6)	34 (4.0)	1.29 (0.66-2.54)	1.31 (0.68-2.53)§
≥4	current smoker	42 (4.9)	18 (2.1)	2.56 (1.21-5.47)	2.45 (1.20-5.02)§

*Adjusted by age and sex.
†Adjusted by age, sex, smoking status, and pack-years smoked.
‡P for interaction = 0.285.
§Adjusted by age, sex, and smoking status.

Histology-specific analyses yielded no appreciable differences in the ORs, and there was no effect on the mean age at onset of lung cancer or on survival in the cases by genotype status (data not shown). When the joint effects of the variant genotypes were examined, it was evident that most of the effect was driven by the *p73* variant genotypes (data not shown).

Discussion

The main findings in this brief report are that combined analysis of *p53* and *p73* variant alleles showed evidence of gene-dosage effects, that the effects were restricted to current and former smokers, and were most evident in younger individuals.

Although the functional spectrum of the p53 family encompasses diverse biological events (1-3), there are biological interactions between members of the p53 family (1). For example, higher levels of p73 expression in lung tumor tissues compared with adjacent normal tissues are associated with p53 mutations (9, 10), which suggests that p73 compensates for the loss of p53 function (9). Also, p53 is completely inactive in multiple knockout mice in which p73 and p63 are absent (11). Additionally, the p53 and p73 proteins have similar domain structure, very high amino acid identity in the DNA-binding domain, and they activate transcription of many of the same genes, such as *p21* and *Bax* (1). Hence, there is substantial justification to analyze the combined effects of these two genes.

Thus far, few epidemiologic studies (12-17) have simultaneously studied SNPs from multiple members of the p53 family for cancer risk. The only study on lung cancer failed to detect a gene-gene interaction by a case-only analysis (13) and did not test for multigenetic effects in a case-control analysis. Previous studies suffered from small sample sizes (<350 cases) and only evaluated one SNP from *p53* and one SNP from *p73*. By comparison, the present study includes four different SNPs and a relatively large sample size, and we were able detect a statistically significant 13% increase in lung cancer risk for each additional variant allele.

Previous studies have provided substantial evidence for interplay between p53, smoking, and lung cancer (3, 18-20). For example, mutations in the *p53* gene are present in ~40% of all human lung cancers, and are more common in smokers than in nonsmokers (18, 19) and the p53 mutational spectrum in lung cancer is different from that of other cancers (20). In the present analysis, the interaction term for the joint effects analysis was not statistically significant; however, there was evidence nonetheless of a possible effect modification for current smokers but no effect in never smokers. Furthermore, in the stratified analysis, elevated risks were only evident in current and former smokers. Multigenetic effects may be relatively modest or nonexistent in lung cancer without the relevant tobacco exposure.

Previous studies have also provided evidence of interplay between p53, age, and cancer (21, 22). Specifically, p53 suppresses the onset of malignancy and thereby extends life span, and at the same time, it promotes cellular senescence and apoptosis in response to DNA damage (21). Therefore, if *p53* functions as a pleiotropic antagonistic gene (22), genetic variants in the p53 family could result in higher cancer risks in younger individuals, as we observed in this analysis. In support of this hypothesis, we previously showed that the variant *p53* genotype of exon 4 was associated with risk of early age onset of lung cancer in African-Americans (23). Although lung cancer risk was also elevated in the oldest individuals (≥67 years) in the present analysis, this observation would be expected as reflecting longer cumulative exposure to smoking and other deleterious exposures.

Although controversy exists as to whether lung cancer risks differ between men and women, there have been relatively consistent gender-specific differences associated with the SNPs in the *CYP1A1* and *GSTM1* genes (reviewed in ref. 24) and gender-specific differences exist in the p53 mutational spectrum (25). In the present study, the risk tended to be higher in men. However, it is not apparent if these SNPs represent gender-specific susceptibility alleles because the interaction term was not statistically significant and various biases can affect gender-specific risks such as under reported smoking habits, confounding effects of passive smoking (24), occupational, and hormonal exposures.

In conclusion, this study provides support for the multigenetic effects of the variant alleles from *p53* exon 4, and

Table 3. Number of *p73* and *p53* variant alleles and lung cancer risk stratified by age and gender

No. of variant alleles	Cases, % (n = 863)	Controls, % (n = 852)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age*,†				
≤58				
0	93 (29.4)	109 (36.5)	1.0	1.0
1-3	183 (57.9)	175 (58.5)	1.23 (0.85-1.76)	1.19 (0.83-1.69)‡
≥4	40 (12.7)	15 (5.0)	3.13 (1.56-6.47)	3.15 (1.62-6.12)‡
59-66				
0	83 (32.6)	82 (31.6)	1.0	1.0
1-3	150 (58.8)	153 (59.1)	0.97 (0.65-1.44)	0.92 (0.63-1.36)‡
≥4	22 (8.6)	24 (9.3)	0.91 (0.46-1.83)	0.82 (0.41-1.63)‡
≥67				
0	77 (26.4)	111 (37.8)	1.0	1.0
1-3	185 (63.3)	159 (54.1)	1.68 (1.15-2.44)	1.77 (1.22-2.57)‡
≥4	30 (10.3)	24 (8.1)	1.80 (0.94-3.48)	1.89 (1.01-3.51)‡
Gender§				
Men				
0	129 (28.3)	169 (38.2)	1.0	1.0
1-3	277 (60.8)	239 (54.1)	1.52 (1.13-2.05)	1.54 (1.15-2.07)‖
≥4	50 (10.9)	34 (7.7)	1.63 (1.15-3.26)	1.96 (1.19-3.24)‖
Women				
0	124 (30.5)	133 (32.4)	1.0	1.0
1-3	241 (59.2)	248 (60.5)	1.04 (0.77-1.43)	1.07 (0.79-1.45)‖
≥4	42 (10.3)	29 (7.1)	1.55 (0.88-2.76)	1.55 (0.90-2.66)‖

*Age categorized by the tertile values in the controls.
†P for interaction = 0.978.
‡Adjusted by age, sex, smoking status, and pack-years smoked.
§P for interaction = 0.212.
‖Adjusted by age, smoking status, and pack-years smoked.

introns 3 and 6, and *p73*, resulting in a significantly increased risk for lung cancer in a non–Hispanic Caucasian population. We also noted that the multigenetic effects were most evident in smokers, younger individuals, and men. To the best of our knowledge, this is the largest study to examine multiple SNPs from two different genes in the p53 family. This approach highlights the value of examining multiple polymorphisms in genes in common pathways to improve the precision of risk estimates.

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