Matrix Metalloproteinase-1 Promoter Polymorphism and Lung Cancer Risk

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Abstract

Extracellular matrix-degrading matrix metalloproteinase-1 (MMP-1) is an interstitial collagenase that degrades the interstitial types I, II, and III collagens, and overexpression of MMP-1 is associated with cancer development and cellular invasion. The *2G* allele of the *MMP-1 −1607 1G/2G* polymorphism is associated with enhanced transcriptional activity. We investigated the association between the *MMP-1 1G/2G* polymorphism and lung cancer risk in 1,752 Caucasian lung cancer patients and 1,363 healthy controls. There were no overall associations between the *MMP-1* genotypes and risk of lung cancer, with the adjusted odds ratios of 1.15 [95% confidence interval (CI), 0.94-1.40] for the *1G/2G* genotype and 1.14 (95% CI, 0.90-1.45) for the *2G/2G* genotype, when versus the *1G/1G* genotype. Stratified analyses suggested higher lung cancer risk for the *2G* allele in never-smokers and males, with the adjusted odds ratios of 1.67 (95% CI, 1.02-2.76; *1G/2G*) and 1.50 (95% CI, 0.86-2.62; *2G/2G*) in never-smokers; and 1.30 (95% CI, 1.00-1.75; *1G/2G*) and 1.23 (95% CI, 0.88-1.73; *2G/2G*) in males, respectively. In conclusion, genotypes containing the *2G* allele of the *MMP-1* polymorphism are associated with higher risk of lung cancer in never-smokers and in males. (Cancer Epidemiol Biomarkers Prev 2005;14(3):567–70)

Introduction

The matrix metalloproteases (MMP) are a family of secreted zinc metalloproteases that degrade the extracellular matrix collagens. MMP-1 (collagenase) may degrade the interstitial types I, II, and III collagens (1) and contribute to tumor initiation and development by altering the cellular microenvironment that facilitates tumor formation (2-4). There is a single nucleotide polymorphism at −1,607 bp in the *MMP-1* promoter, with the *2G* allele associated with higher expression levels (5, 6). Cells expressing the *2G* allele may provide a mechanism for more aggressive matrix degradation, thereby facilitating cancer progression. The *MMP-1 2G/2G* genotype has been associated with significantly higher risk of lung cancer in one previous study, specifically for males, current smokers, and heavy smokers (3). We hypothesized that the *2G* allele of the *MMP-1 1G/2G* polymorphism is associated with higher risk of lung cancer in our large case-control population.

Materials and Methods

Study Population and Genotyping. The study was approved by the Human Subjects Committees of Massachusetts General Hospital and the Harvard School of Public Health, Boston, MA. Details of this case-control population have been described previously (7, 8). In brief, all eligible histologically confirmed lung cancers were recruited at Massachusetts General Hospital between December 1992 and April 2003. Unmatched controls were recruited among healthy friends and non–blood-related family members (usually spouses) of cancer patients or patients with a cardiothoracic condition undergoing surgery. Over 85% of eligible cases and >90% of controls participated in this study and provided blood samples. Interviewer-administered questionnaires collected information on demographic and detailed smoking histories from each subject. The *MMP1 −1607 1G/2G* polymorphism was genotyped by the 5′ nuclease assay (TaqMan) using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA).

Statistical Analysis. Although individuals of all races were recruited for this study, we restricted our analyses to Caucasians (97%) in order to minimize confounding due to allele frequency variation by ethnicity. Logistic regression models were fit to examine the relationship between the log odds of lung cancer and each covariate, after adjusting for possible confounding factors such as age, gender, smoking status, pack-years of smoking, and years since smoking cessation (if ex-smoker, defined as those who quit smoking more than a year before recruitment). As suggested before, square root transformed pack-years of smoking were used in the analyses instead of the original untransformed variable (7). In addition to the overall association analysis, we did a stratified analysis by gender, age, smoking status, histology, and clinical stages, to further explore the association between *MMP-1* polymorphism and the risk of lung cancer in each stratum. Case-only analyses were done to investigate the effect of *MMP-1* polymorphism on different histologic subtypes or clinical stages among lung cancer patients. Statistical analyses were undertaken using SAS statistical packages (SAS Institute, Cary, NC).

Results

Population Characteristics. A total of 3,413 (99.6%) of 3,426 enrolled subjects were genotyped successfully for the *MMP-1* polymorphism. Complete information on race, age, gender, and detailed smoking variables was available for 3,219 subjects (94%). Of these, there were 1,752 Caucasian lung

Received 6/29/04; revised 9/9/04; accepted 10/27/04.

Grant support: NIH grants CA74386, CA90578, ES/CA 06409, Flight Attendants Medical Research Institute Young Clinical Scientist Award, and a Doris Duke Clinician Scientist Award.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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Table 1. Demographic information by case status

Characteristic	Cases (n = 1,752)	Controls (n = 1,363)	P
Age*	67 (26-91)	60 (27-100)	<0.001
Gender†			
Male	919 (52%)	603 (44%)	
Female	833 (48%)	760 (56%)	<0.001
Smoking status†			
Never	135 (8%)	480 (35%)	
Ex-smoker	924 (53%)	623 (46%)	
Current smoker	693 (39%)	260 (19%)	<0.001
Pack-years*,‡	51 (0.1-231)	25 (0.1-210)	<0.001
Cigarettes per day*,‡	30 (0.1-120)	20 (0.1-100)	<0.001
Smoking duration*,‡	40 (0.5-73)	26 (0.5-65)	<0.001
Years since quitting smoking*,§	12 (1-59)	18 (1-65)	<0.001
Histology cell type (available for 1,688 cases)			
Adenocarcinoma	857 (51%)		
Squamous	375 (22%)		
Large cell	141 (8%)		
Small cell	143 (8%)		
Others	172 (11%)		
Clinical stage (available for 1,675 cases)			
Early (I and II)	896 (53%)		
Late (III and IV)	779 (47%)		
MMP1 genotype			
1G/1G	455 (26%)	372 (27%)	
1G/2G	898 (51%)	667 (49%)	
2G/2G	399 (23%)	324 (24%)	0.44

*For age, pack-years, number of cigarettes per day, and years since smoking cessation, the data is reported as median (range), and tested by nonparametric Wilcoxon rank sum test.
†Cases and controls were compared using χ^2 tests.
‡Excludes individuals who have never smoked.
§Ex-smokers only.

cancer cases and 1,363 Caucasian controls. The distributions of demographic characteristics for cases and controls are summarized in Table 1. Compared to the controls, cases were older, had a higher proportion of males, were more likely to be current smokers or heavy smokers, and had a shorter time since smoking cessation (if an ex-smoker) and larger pack-years of cigarette smoking.

Distribution of *MMP-1* Polymorphisms among Cases and Controls. The *MMP-1* polymorphism in this control population was consistent with Hardy-Weinberg Equilibrium ($P = 0.46$ by χ^2 goodness of fit). *MMP-1* genotype frequencies were very similar between cases and controls, with the frequencies of *1G/1G*, *1G/2G*, and *2G/2G* genotypes of 26%, 51%, and 23% in cases, and 27%, 49% and 24% in controls, respectively. There is no statistical difference in genotype distributions between cases and controls for different strata of age, gender, smoking status, pack-years of smoking, and clinical stage subgroups ($P > 0.10$; Table 2).

Association Between *MMP-1* Genotypes and Lung Cancer Risk in Different Age, Gender, and Smoking Groups. There was no overall association between *MMP-1* polymorphism and lung cancer risk, with the crude and adjusted odds ratios (OR) of 1.08 [95% confidence interval (CI), 0.91-1.28] and 1.14 (95% CI, 0.94-1.39) for the *1G/2G* genotype, and 0.99 (95% CI, 0.81-1.21) and 1.13 (95% CI, 0.89-1.42) for the *2G/2G* genotypes, respectively, when compared with the *1G/1G* genotype.

No statistically significant association was found between *MMP-1* polymorphism and lung cancer risk in younger or older subjects (Table 2). Statistically significant higher lung cancer risk (only for the *1G/2G* genotype) was found in males but not in females, with the adjusted ORs for *1G/2G* and *2G/2G* genotypes (when using the *1G/1G* genotype as reference) of 1.30 (95% CI, 1.00-1.75) and 1.23 (95% CI, 0.88-1.73) in males, and 0.99 (95% CI, 0.74-1.32) and 1.05 (95% CI, 0.75-1.46) in females, respectively. For different smoking categories, statistically higher lung cancer risk (only for the *1G/2G* genotype) was found in never-smokers, with the adjusted ORs for *1G/2G* and *2G/2G* genotypes (when versus the *1G/1G* genotype) of 1.67 (95% CI, 1.02-2.76) and 1.50 (95% CI, 0.86-2.62), respectively. No associations were found in ex-smokers or current smokers, or in different pack-years of smoking (Table 2).

Association Between *MMP-1* Genotypes and Lung Cancer Risk in Different Histologic and Disease Stages. For different histologic subtypes of lung cancer, higher lung cancer risk of *MMP-1* polymorphism was found for patients with adenocarcinoma than for patients with squamous cell carcinoma (when each was compared with all controls), with the adjusted ORs for *1G/2G* and *2G/2G* genotypes (when versus the *1G/1G* genotype) of 1.20 (95% CI, 0.95-1.52) and 1.21 (95% CI, 0.92-1.59), respectively, for patients with adenocarcinoma; and 0.93 (95% CI, 0.66-1.31), and 0.72 (95% CI, 0.47-1.11), respectively, for squamous cell carcinoma patients (Table 3). In case-only analysis, the adjusted ORs of adenocarcinoma versus squamous cell carcinoma for *1G/2G* and *2G/2G* genotypes were 1.12 (95% CI, 0.83-1.51) and 1.51 (95% CI, 1.04-2.20), respectively. By gender, the histologic difference of *MMP-1* polymorphism was found in males only, and not in females, with the case-only adjusted ORs (adenocarcinoma versus squamous cell carcinoma) for the *1G/2G* and *2G/2G* genotypes were 1.25 (95% CI, 0.85-1.85) and 1.88 (95% CI, 1.16-3.07) in males; and 0.90 (95% CI, 0.55-1.48) and 1.05 (95% CI, 0.58-1.91) in females.

Table 2. Genotype frequencies and adjusted ORs of the *MMP-1* polymorphism in different age, gender, and smoking groups

	Cases (n = 1,752)				Controls (n = 1,363)				Adjusted ORs*	
	n	*1G/1G*	*1G/2G*	*2G/2G*	n	*1G/1G*	*1G/2G*	*2G/2G*	*1G/2G*	*2G/2G*
Age <55	304	26%	49%	25%	519	25%	52%	23%	0.99 (0.67-1.47)	1.48 (0.92-2.36)
Age ≥55	1,448	26%	52%	22%	844	29%	47%	24%	1.22 (0.97-1.55)	1.05 (0.79-1.38)
Female	833	26%	50%	24%	760	25%	50%	25%	0.99 (0.74-1.32)	1.05 (0.75-1.46)
Male	919	26%	52%	22%	603	30%	47%	23%	1.30 (1.00-1.75)	1.23 (0.88-1.73)
Never-smokers	135	22%	51%	27%	480	29%	45%	26%	1.67 (1.02-2.76)	1.50 (0.86-2.62)
Ex-smokers	924	27%	52%	21%	623	28%	49%	23%	1.18 (0.90-1.54)	1.08 (0.77-1.50)
Current smokers	693	26%	50%	24%	260	23%	55%	22%	0.90 (0.61-1.33)	1.07 (0.67-1.70)
Mild smokers	136	26%	46%	28%	291	22%	51%	27%	0.86 (0.51-1.43)	1.35 (0.77-2.45)
Moderate smokers	324	22%	53%	25%	285	23%	53%	24%	1.05 (0.70-1.58)	0.93 (0.57-1.52)
Heavy smokers	1,157	22%	51%	27%	307	22%	49%	29%	1.17 (0.86-1.59)	1.05 (0.72-1.53)

NOTE: Mild, moderate, and heavy smokers correspond to the three tertiles of pack-years in ever-smokers for controls. The tertiles were divided at 15.5 and 36 pack-years.
*Adjusted for age, gender, smoking status, square-root of pack-years, and years since smoking cessation. In all of the logistic regression models, the *MMP-1 1G/2G* and *2G/2G* genotypes were treated as dummy variables, with the *1G/1G* genotype as the reference group.

Table 3. Genotype frequencies and adjusted ORs of the *MMP-1* polymorphism in different histology and clinical stage groups

	MMP-1 polymorphism				Adjusted ORs*	
	n	*1G/1G*	*1G/2G*	*2G/2G*	*1G/2G*	*2G/2G*
Early stage patients	896	26%	52%	22%	1.30 (1.01-1.66)	1.13 (0.84-1.52)
Male	471	25%	53%	22%	1.50 (1.07-2.12)	1.24 (0.82-1.88)
Female	425	26%	51%	23%	1.10 (0.77-1.58)	1.01 (0.66-1.54)
Late stage patients	779	26%	50%	24%	0.99 (0.78-1.27)	1.08 (0.81-1.44)
Male	413	26%	52%	22%	1.15 (0.83-1.60)	1.13 (0.76-1.69)
Female	366	27%	48%	25%	0.87 (0.61-1.23)	1.02 (0.68-1.54)
Patients with adenocarcinoma	857	25%	51%	24%	1.20 (0.95-1.52)	1.21 (0.92-1.59)
Male	402	25%	51%	24%	1.34 (0.96-1.87)	1.31 (0.88-1.94)
Female	455	25%	51%	24%	1.10 (0.79-1.53)	1.14 (0.78-1.66)
Patients with squamous cell carcinoma	375	29%	52%	19%	0.93 (0.66-1.31)	0.72 (0.47-1.11)
Male	246	31%	51%	18%	0.87 (0.57-1.33)	0.58 (0.34-1.01)
Female	129	25%	52%	22%	1.05 (0.59-1.87)	0.96 (0.48-1.93)

*Adjusted for age, gender, smoking status, square-root of pack-years, and years since smoking cessation, where different histology or clinical stage patients were compared with all controls (or males or female controls). In all of the logistic regression models, the *MMP-1 1G/2G* and *2G/2G* genotypes were treated as dummy variables, with the *1G/1G* genotype as the reference group.

The associations between *MMP-1* polymorphism and lung cancer risk for different disease stages (early or late) are also shown in Table 3. Although we observed a slightly higher lung cancer risk associated with *MMP-1* genotypes in early stage patients [adjusted ORs, 1.30 (95% CI, 1.01-1.66) for the *1G/2G* genotype and 1.13 (95% CI, 0.84-1.52) for the *2G/2G* genotype, respectively] than for late stage patients [adjusted ORs, 0.99 (95% CI, 0.78-1.27) for the *1G/2G* genotype and 1.08 (95% CI, 0.81-1.44) for the *2G/2G* genotype, respectively], these differences were not statistically significant in the case-only analysis, overall or stratified by gender ($P > 0.30$, early stage versus late stage).

Discussion

Carcinogenesis is a multicellular and multistage process in which the destruction of the microenvironment is required for the conversion of normal tissue to tumor. MMPs may alter cell cycle checkpoint controls, conceivably promote genomic instability by affecting cell adhesion (9), and alter the microenvironment that can influence tumor formation and play an important role in several steps of cancer development (3). MMP-1 is the most highly expressed interstitial collagenase degrading fibrillar collagens. Overexpression of MMP-1 has been associated with higher risks of lung cancer (10, 11).

In this study, the *MMP-1 2G* allele was associated with higher lung cancer risk in never-smokers, but not in ex- or current smokers, nor in any of the smoking subgroups. One possible explanation is that although cigarette smoking may increase *MMP-1* mRNA levels and MMP-1 activity (12, 13), smoking may also increase the mRNA levels of tissue inhibitors of metalloprotease (14, 15). Therefore, the effect of *MMP-1* polymorphism in smokers may depend on the balances between MMPs and tissue inhibitors of metalloprotease. The results are inconsistent with a previous study where the *2G/2G* genotype was found to be associated with higher lung cancer risk in current smokers and heavy smokers, and not in never-smokers (3). However, the genotype distribution of this polymorphism was out of Hardy-Weinberg equilibrium in the control population for the previous study, and the *1G/2G* genotype was combined with the *1G/1G* genotype in all analyses. Further studies are needed to investigate the effect of cigarette smoking on the expression levels of different genotypes of *MMP-1*.

Consistent with the previous study (3), we found that lung cancer risk conferred by the *2G* allele was higher in males than females. Similar gender differences in risk for the *MMP-1* polymorphism were also found for renal cell and gastric cancer patients (16, 17). Sex hormones including progesterone, estradiol, and ovarian steroids levels may decrease the MMP-1 expression levels and increase the tissue inhibitor levels of MMP-1 proteins (18-20). Therefore, females may have lower MMP-1 levels than males, and estrogen levels may be more important in the influence on the expression levels of MMP-1 than the polymorphism (16).

For different histologic subtypes of patients, we observed a higher risk of the *2G* allele for patients with adenocarcinoma when compared with patients with squamous cell carcinoma, specifically for males. This finding is echoed in a study that reported adenocarcinoma overexpressed MMP-1 more frequently than squamous cell carcinoma in non–small cell lung cancer tissues (21). The mechanism for this histologic difference is still under investigation, but there are two distinct theories. The *MMP-1 −1607 1G/2G* polymorphism is adjacent to an activating protein-1 site at −1,602 bp, which may cooperate with the *2G* allele (Ets site) to induce higher levels of transcription (5), and the activator protein-1 site is inhibitory in the context of the *1G* allele, but activating the *2G* allele (6). If this activator protein-1 site is mutated, it could lead to a substantial increase in expression of the *1G* allele where the difference in transcription between *1G* and *2G* alleles is abolished and the MMP-1 expression is similar between the two alleles (6). It is possible that activator protein-1 mutant frequencies are different between different histologic subtypes of lung cancer, which may induce the differential association between *MMP-1* polymorphism and lung cancer risk by histologic subtypes. An alternative explanation is that squamous cell carcinoma tumor tissues have been found to have higher rates of p53 mutations than adenocarcinoma tissues (22). *MMP-1* is a target of the p53 protein, and wild-type p53 can exert a strong inhibitory effect on the human MMP-1 promoter by disrupting communications between the transactivator −72AP-1 and the basal transcriptional complex, whereas p53 mutants lose such repressive activity (23, 24). The down-regulation of the human MMP1 promoter by p53 was abolished after the proximal −72AP-1 site was deleted or mutated (24). Therefore, mutated p53 may lose the ability of regulating MMP-1 transcription.

There are several limitations to this study. Firstly, this is a hospital-based case-control study, where a subset of the controls included healthy spouses and friends of patients with

lung cancer. Secondly, we only evaluated the *MMP-1 −1607 1G/2G* polymorphism that has been suggested to be associated with MMP-1 expression levels, which may result in some misclassification in *MMP-1* action. It is possible that other polymorphisms might also be associated with MMP-1 expression levels, which may be one reason why we observed a stronger association for the *1G/2G* genotype than the *2G/2G* genotype in most of the comparisons. Thirdly, although we adjusted for various smoking variables in all of the analyses, secondhand smoke exposure, alcohol consumption, diet, and environmental and occupational exposure data were not adjusted in our logistic regression models because of missing or incomplete information. Lastly, we did multiple comparisons through subgroup analyses. It is possible that the borderline significant results could be due to multiple comparisons. Given our sample size, we have tried as much as possible to avoid the bias by careful *a priori* specification of our primary hypotheses.

In conclusion, the *2G* allele of the *MMP-1 −1607 1G/2G* polymorphism is associated with higher lung cancer risk in never-smokers and males, where the risk is mostly attributable to patients with adenocarcinoma.

Acknowledgments

We thank the following staff members of the Lung Cancer Susceptibility Group: Barbara Bean, Jessica Shin, Andrea Solomon, Andrea Shafer, Thomas Van Geel, Lucy Ann Principe, Salvatore Mucci, Richard Rivera-Massa, David P. Miller, Steven Su, and the generous support of Dr. Panos Fidias and the physicians and surgeons of the Massachusetts General Hospital Cancer Center.

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Cancer Epidemiol Biomarkers Prev 2005;14:567-570.