Matrix Metalloproteinase Polymorphisms and Survival in Stage I Non–Small Cell Lung Cancer

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Abstract

Purpose: The matrix metalloproteinases (MMP) are a family of enzymes that can degrade extracellular matrix and facilitate invasion through the basement membrane. Several polymorphisms in *MMP-1, MMP-2, MMP-3*, and *MMP-12* have been described, some of which lead to differential transcription. We hypothesized that polymorphisms in these *MMP* genes may be associated with survival outcomes in early-stage non–small cell lung cancer (NSCLC).

Experimental Design: We evaluated the relationship between *MMP-1, MMP-2, MMP-3*, and *MMP-12* polymorphisms and both recurrence-free survival (RFS) and overall survival (OS) among 382 patients with stage I NSCLC. Analyses of genotype associations with survival outcomes were done using Cox proportional hazards models and Kaplan-Meier methods and the log-rank test.

Results: Patients carrying the variant *G* allele of the *MMP-12 1082A/G* polymorphism had significantly worse outcomes [crude hazard ratio (HR) for OS 1.74; 95% confidence interval (95% CI), 1.18-2.58, $P = 0.006$; crude HR for RFS, 1.53; 95% CI, 1.05-2.23, $P = 0.03$]. After adjusting for age, sex, stage, pack-years of smoking, and histologic subtype, the *MMP-12 1082A/G* polymorphism remained significantly associated with survival outcomes [adjusted HR (AHR) for OS, 1.94; 95% CI, 1.28-2.97, $P = 0.002$; AHR for RFS, 1.61; 95% CI, 1.07-2.41, $P = 0.02$]. None of the other *MMP* polymorphisms was significantly associated with survival.

Conclusions: Our results show that patients with stage I NSCLC carrying the variant *G* allele of the *MMP-12 1082A/G* polymorphism have worse survival.

Survival in lung cancer remains poor and even among patients in the earliest stage, a substantial proportion will have recurrence and ultimately die from their disease. Recent studies have suggested that adjuvant chemotherapy can improve survival (1–3), but exactly which patients to treat among those with stage I non–small cell lung cancer (NSCLC) remains to be fully defined. Identifying molecular prognostic factors in stage I disease may be helpful to further risk stratify these patients.

The matrix metalloproteinases (MMP) are a family of over 20 proteolytic enzymes that can degrade extracellular matrix and facilitate invasion through the basement membrane (4, 5). The ability of MMPs to remodel the extracellular environment has led to extensive study of their role in carcinogenesis, particularly with respect to risk, invasion, and metastasis. MMPs are generally up-regulated in cancers compared with normal tissues and in many cases have been associated with worse survival (6). In NSCLC, MMPs have been associated with tumor invasion and metastasis, via their ability to remodel and degrade extracellular matrix and mediate cell-cell adhesions (7, 8). In addition to disruption of the basement membrane, MMPs have been shown to influence the cellular microenvironment via complex cell-cell and cell-matrix interactions, by altering cellular signals and regulating cytokines, growth factors, and angiogenic factors (9).

Although dozens of MMPs have been identified, MMP-1, MMP-2, MMP-3, and MMP-12 are some of the most extensively studied in relation to cancer. MMP-1 is a collagenase that primarily degrades structural collagens types I, II, and III. MMP-2 is a gelatinase that degrades type IV collagen. MMP-3, a stromelysin, has broad substrate specificity, including degradation of proteoglycans, laminin, and fibronectin, and can contribute to the activation of other MMP family members. MMP-12 is a macrophage metalloelastase and participates in elastin degradation. Each of these MMPs has a broad range of substrates as identified *in vitro* (10).

Functional polymorphisms in these *MMP* genes have been described that seem to alter transcriptional levels (11). The *2G* allele of the *MMP-1 2G/1G* polymorphism (rs1799750) is associated with higher transcription and protein expression (12). Similarly, the *5A* allele of the *MMP-3 6A/5A* polymorphism (rs3025058) has greater transcriptional activity (13).

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A functional polymorphism in *MMP-2*, a *C→T* change at position −1306 (rs243865), has been shown to lead to decreased promoter activity with the *T* allele (14). In *MMP-12*, the *A* allele of the *−82A/G* polymorphism (rs2276109) is associated with higher transcriptional activity (15). The function of the *MMP-12 1082A/G* polymorphism (*357Asn/Ser*, rs652438) remains unknown, although its location in the coding region of the hemopexin domain has raised the possibility of function.

Although several studies have investigated the role of *MMP* polymorphisms and lung cancer risk (16–18), there is considerably less information on lung cancer outcomes. Because the MMP family of enzymes plays an important role in tissue invasion and remodeling, we hypothesized that polymorphisms of the *MMP* genes described above would be important for aggressiveness or spread of disease, and therefore may be associated with survival outcomes in early-stage lung cancer.

Materials and Methods

Study population. Since 1992, patients with histologically confirmed NSCLC have been recruited prospectively into a molecular epidemiology study at Massachusetts General Hospital. These patients were part of a large ongoing case-control study being conducted to evaluate genetic polymorphisms and lung cancer risk. Blood samples for genotyping and patient and demographic information (including age, sex, and smoking status) were collected at the time of recruitment, and informed consent was obtained to collect follow-up data. More than 85% of eligible patients were recruited in this cohort.

We limited our analysis to all patients with incident cases of stage I NSCLC, enrolled between December 1992 and September 2001, who had their surgical resection done at Massachusetts General Hospital. By limiting our set to stage I cancers, we were able to study a homogenous population where issues of tissue invasion and spread would be critical to progression of disease.

The study was approved by the Institutional Review Boards of Massachusetts General Hospital and the Harvard School of Public Health.

Genotyping. Blood samples were collected from all study subjects at the time of recruitment. DNA was extracted from peripheral blood samples using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN). The *MMP-1 2G/1G*, *MMP-2 -1306C/T*, *MMP-3 6A/5A*, *MMP-12 −82A/G*, and *MMP−12 1082A/G* polymorphisms were genotyped by the 5′-nuclease assay (TaqMan) using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Genotyping was done by laboratory personnel blinded to case status, and a random 5% of the samples were repeated to validate genotyping procedures. Hardy-Weinberg equilibrium was tested using the χ^2 test.

Outcomes collection. Overall survival (OS) was the primary end point and was calculated from date of surgery to date of death, or last known date alive. For OS, data were collected from at least one of the following sources: (*a*) Massachusetts General Hospital inpatient and outpatient records, (*b*) Massachusetts General Hospital tumor registry, (*c*) Social Security Death Index, (*d*) primary physician's office, and (*e*) patient or family contact. Permission to contact patients and their families to obtain follow-up information was included in our original consent form. We were able to collect OS data on all the patients in this case series using one of the five sources described above. Therefore, there are no missing data for our OS end point.

Recurrence-free survival (RFS) was a secondary end point in this analysis. RFS was calculated from the date of surgery to date of first recurrence or death from any cause. Data on recurrence were obtained by reviewing the hospital and outpatient records of all patients. This included physicians' notes, surgeons' notes, radiographic reports, and biopsy results if a biopsy was done. For those patients who had their primary follow-up outside of the Massachusetts General Hospital system, we contacted the primary physician or the patient to obtain follow-up information on recurrence. Copies of the original signed consent were forwarded to the local physician's office and data regarding frequency of clinic and radiographic follow-up and date of recurrence was collected. Data regarding recurrence (date of first recurrence, or last known date without recurrence) were collected for all patients in this study. However, there were 18 patients (<5%) for whom we were not able to obtain medical records beyond 1 year after surgery, who are known to have longer-term survival beyond this. This likely reflects inadequate follow-up data among these patients. As our RFS data is less clear-cut than our OS data, we analyzed this as a secondary end point only.

Statistical analyses. Demographic and clinical information was compared across genotype using Pearson χ^2 tests (for categorical variables) and Kruskal-Wallis tests (for continuous variables), where appropriate. The associations between polymorphism status and survival outcomes were estimated using the method of Kaplan and

Table 1. Patient characteristics

Characteristic	*N* = 382
Median age (range)	69 (31-89)
Male	190 (50%)
Female	192 (50%)
Stage IA	244 (64%)
Stage IB	138 (36%)
Adenocarcinoma	185 (49%)
Squamous cell	104 (27%)
Bronchioalveolar	51 (13%)
Large cell	20 (5%)
NSCLC not otherwise specified	22 (6%)
Never smoker	28 (7%)
Former smoker	210 (55%)
Current smoker	144 (38%)
Pack-years (median, range)	50 (0-204)
Wedge/segmentectomy	115 (30%)
Lobectomy	246 (64%)
Bilobectomy	3 (1%)
Sleeve lobectomy	9 (2%)
Pneumonectomy	6 (2%)
Other	2 (1%)
Adjuvant chemotherapy	0
Adjuvant radiation	8 (2%)
Complete resection with negative margins	373 (98%)
MMP-12 1082A/G	
A/A	336 (88%)
A/G	44 (11%)
G/G	2 (1%)
MMP-12 −82A/G	
A/A	298 (78%)
A/G	74 (19%)
G/G	10 (3%)
MMP-1 2G/1G	
1G/1G	109 (29%)
1G/2G	188 (49%)
2G/2G	85 (22%)
MMP-3 6A/5A	
6A/6A	100 (26%)
6A/5A	189 (50%)
5A/5A	93 (24%)
MMP-2 C/T	
C/C	223 (59%)
C/T	134 (35%)
T/T	24 (6%)

Meier and assessed using the log-rank test. Median follow-up time was computed among censored observations only. Cox regression models were used to adjust for potential confounders. All statistical testing was done at the two-sided 0.05 level, and SAS software version 9.1 (SAS Institute, Cary, NC) was used. As we were testing five different single-nucleotide polymorphisms for association with survival, we also did a correction for multiple comparisons using the false discovery rate as proposed by Benjamini and Hochberg (19).

Results

Patient characteristics, treatment, and genotype information. There were 382 patients (see Table 1). The median age was 69 years (range 31-89 years), 50% were female, 64% were stage IA and 36% stage IB, and 38% were current smokers. Adenocarcinoma, squamous cell, bronchioalveolar, and large-cell carcinomas represented 49%, 27%, 13%, and 5%, respectively, of the histologic subtypes.

All patients had surgical resection as their primary treatment, with 64% having lobectomy, 30% wedge resection or segmentectomy, and 6% a larger resection. The type of surgery done was at the discretion of the treating surgeon. As all surgeries were done at Massachusetts General Hospital, there was a stable group of thoracic surgeons who did the operations. The practice at the Massachusetts General Hospital thoracic surgery group has been to consider a variety of factors in the decision regarding type of surgery, including tumor size, the anatomy, and location of the tumor, as well as the patient's functional lung capacity and comorbidities. As expected, the type of surgery was significantly associated with stage, with patients receiving a segmentectomy or wedge resection being more likely to have earlier stage disease than those receiving lobectomies or other more extensive surgeries. No patients received adjuvant chemotherapy and eight (2%) received adjuvant radiation. The eight patients who received radiation all had positive margins after resection.

All *MMP* polymorphisms were in Hardy-Weinberg equilibrium ($P > 0.05$, χ^2 goodness of fit). Genotype was not significantly associated with age, sex, stage, histologic subtype, or smoking. In addition, genotype was not significantly associated with type of surgery.

There were 187 deaths and 120 recurrences, including 100 deaths that occurred in the absence of reported recurrence, and 33 recurrences without death. The median follow-up time for the 195 patients still alive was 4.5 years (range 0.2-11.4 years).

Individual single-nucleotide polymorphisms and overall and RFS. On univariate analysis, age, sex, stage, histologic subtype, pack-years of smoking, and the *MMP-12 1082A/G* polymorphism were all significantly associated with overall and RFS (see Table 2). Patients carrying the variant *G* allele of the *MMP-12 1082A/G* polymorphism had significantly worse outcomes [crude hazard ratio (HR) for OS, 1.74; 95% confidence interval, (95% CI), 1.18-2.58, $P = 0.006$; crude

Table 2. Univariate analysis for OS and RFS

	OS		RFS	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age	1.04 (1.02-1.05)	<0.0001	1.02 (1.004-1.03)	0.01
Sex	1.62 (1.21-2.17)	0.001	1.37 (1.05-1.79)	0.02
Squamous cell	Reference		Reference	
Adenocarcinoma	0.52 (0.38-0.73)	0.0001	0.68 (0.50-0.92)	0.01
Bronchioloalveolar	0.36 (0.20-0.66)	0.0009	0.46 (0.27-0.78)	0.004
Other	0.65 (0.34-1.24)	0.19	0.92 (0.53-1.61)	0.77
Stage				
IA	Reference		Reference	
IB	1.44 (1.07-1.95)	0.02	1.68 (1.27-2.21)	0.0002
Smoking				
Never	Reference		Reference	
Former	1.39 (0.74-2.59)	0.31	1.25 (0.72-2.18)	0.43
Current	1.61 (0.86-3.03)	0.14	1.49 (0.84-2.61)	0.17
Pack-years	1.007 (1.003-1.01)	<0.0001	1.005 (1.002-1.008)	0.002
Type of surgery				
Lobectomy/other	Reference		Reference	
Wedge/segmentectomy	0.98 (0.72-1.33)	0.88	0.85 (0.64-1.14)	0.27
MMP-12 1082A/G				
A/A	Reference		Reference	
A/G + G/G	1.74 (1.18-2.58)	0.006	1.53 (1.05-2.23)	0.03
MMP-12 −82A/G				
A/A	Reference		Reference	
A/G + G/G	1.08 (0.76-1.53)	0.68	1.03 (0.75-1.44)	0.84
MMP-1				
1G/1G	Reference		Reference	
2G/1G	0.78 (0.56-1.09)	0.15	0.70 (0.52-0.96)	0.03
2G/2G	0.94 (0.64-1.39)	0.76	0.85 (0.59-1.22)	0.39
MMP-3 6A/5A				
6A/6A	Reference		Reference	
6A/5A	1.02 (0.72-1.44)	0.91	1.22 (0.88-1.69)	0.24
5A/5A	0.85 (0.56-1.30)	0.46	1.21 (0.83-1.78)	0.32
MMP-2 −1306 C/T				
C/C	Reference		Reference	
C/T + T/T	1.14 (0.85-1.53)	0.37	1.15 (0.88 0 1.51)	0.31

Table 3. Five-year OS by genotype

	Events/total	5-y OS (95% CI); *P*	Corrected *P**	AHR† (95% CI); *P*	Corrected *P**
MMP-12 1082A/G					
A/A	157/336	62% (56-68)		Reference	
A/G + G/G	30/46	47% (31-61); *P* = 0.005	0.02	1.94 (1.28-2.97); *P* = 0.002	0.01
MMP-12 −82A/G					
A/A	147/298	61% (55-67)		Reference	
A/G + G/G	40/84	56% (42-67); *P* = 0.68	0.68	1.16 (0.79-1.69); *P* = 0.45	0.80
MMP-1					
1G/1G	57/109	57% (46-67)		Reference	
2G/1G	84/188	63% (55-70)		1.03 (0.72-1.49); *P* = 0.86	0.99
2G/2G	46/85	57% (45-68); *P* = 0.31	0.62	1.27 (0.82-1.96); *P* = 0.29	0.68
MMP-3 6A/5A					
6A/6A	50/100	60% (48-70)		Reference	
6A/5A	98/189	60% (52-67)		1.00 (0.69-1.47); *P* = 0.99	0.99
5A/5A	39/93	61% (48-71); *P* = 0.64	0.68	0.69 (0.44-1.10); *P* = 0.12	0.41
MMP-2 −1306 C/T					
C/C	108/223	62% (55-69)		Reference	
C/T + T/T	78/158	57% (48-66); *P* = 0.37	0.62	1.03 (0.75-1.41); *P* = 0.85	0.99

*Adjusted ***P*** value for multiple comparisons.
†Adjusted for age, sex, stage, pack-years, and histology.

HR for RFS, 1.53; 95% CI, 1.05-2.23, *P* = 0.03]. None of the other *MMP* polymorphisms (*MMP-1 2G/1G, MMP-2 −1306C/T, MMP-3 6A/5A, MMP-12 −82A/G*) was significantly associated with survival. After adjusting for age, sex, stage, pack-years of smoking, and histologic subtype, the *MMP-12 1082A/G* polymorphism remained significantly associated with survival outcomes [adjusted HR (AHR) for OS, 1.94; 95% CI; 1.28-2.97, *P* = 0.002; AHR for RFS; 1.61; 95% CI, 1.07-2.41, *P* = 0.02; see Tables 3 and 4. Results remained the same when type of surgery was added into the model. Because type of surgery was not associated with survival outcomes on univariate analysis (see Table 2) and did not affect the multivariate model, we left it out of the final adjusted model.

Five-year OS for patients carrying a variant *G* allele of the *MMP-12 1082A/G* polymorphism was 47% (95% CI, 31-61%) versus 62% (95% CI, 56-68%) for patients who were wild type (*P* = 0.005; see Table 3; Fig. 1A). Similarly, 5-year RFS for patients carrying a variant *G* allele was 37% (95% CI, 22-51%) versus 51% (95% CI, 45-57%) for wild type (*P* = 0.03; see Table 4; Fig. 1B).

Discussion

The MMPs have been studied extensively in cancer due to their tissue-invasive and metastatic capabilities. Our results show that among patients with stage I NSCLC, those carrying the variant *G* allele of the *MMP-12 1082A/G* polymorphism have worse survival. Finding prognostic markers in stage I lung cancer is important for better risk stratification. Recent studies have suggested a benefit for adjuvant chemotherapy, but the

Table 4. Five-year RFS by genotype

	Events/total	5-y RFS (95% CI); *P*	Corrected *P**	AHR† (95% CI); *P*	Corrected *P**
MMP-12 1082A/G					
A/A	188/336	51% (45-57)		Reference	
A/G + G/G	32/46	37% (22-51); *P* = 0.03	0.13	1.61 (1.07-2.41); *P* = 0.02	0.16
MMP-12 −82A/G					
A/A	175/298	51% (45-57)		Reference	
A/G + G/G	45/84	41% (45-84); *P* = 0.85	0.85	1.11 (0.78-1.59); *P* = 0.56	0.94
MMP-1					
1G/1G	70/109	44% (33-54)		Reference	
2G/1G	98/188	54% (46-61)		0.83 (0.60-1.16); *P* = 0.28	0.75
2G/2G	52/85	46% (34-57); *P* = 0.08	0.20	1.00 (0.67-1.49); *P* = 0.99	0.99
MMP-36A/5A					
6A/6A	53/100	54% (43-65)		Reference	
6A/5A	113/189	48% (40-55)		1.20 (0.84-1.71); *P* = 0.32	0.75
5A/5A	54/93	46% (35-57); *P* = 0.47	0.58	1.04 (0.69-1.57); *P* = 0.87	0.99
MMP-2 −1306 C/T					
C/C	128/223	52% (45-59)		Reference	
C/T + T/T	91/158	45% (36-53); *P* = 0.31	0.52	1.06 (0.80-1.42); *P* = 0.67	0.94

*Adjusted ***P*** value for multiple comparisons.
†Adjusted for age, sex, stage, pack-years, and cell type.

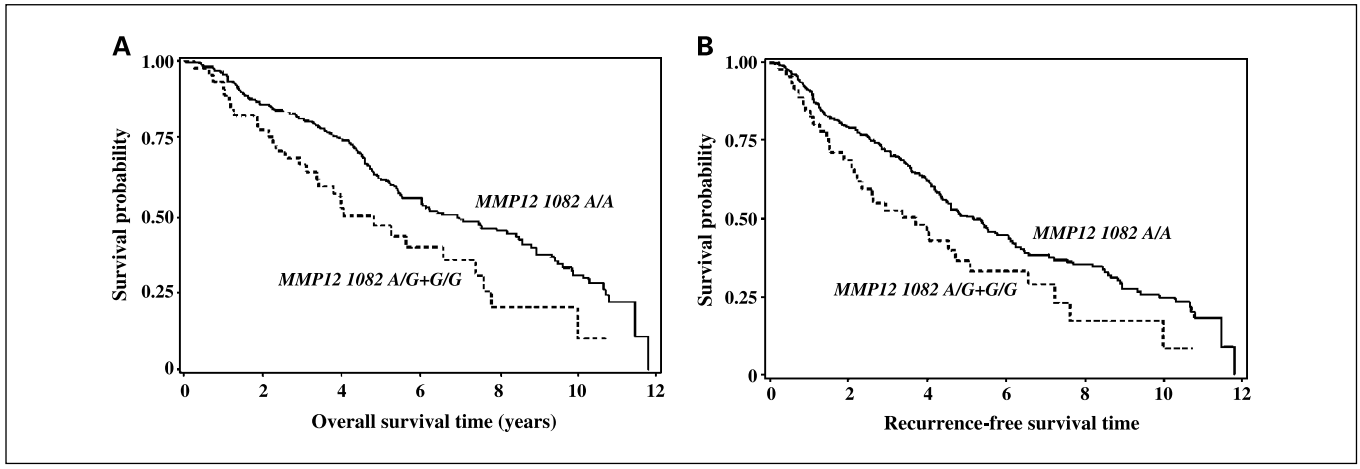

Fig. 1. Kaplan-Meier curves of the *MMP12 1082 A/G* polymorphism for OS (*A*; $P = 0.005$, by log-rank test) and RFS (*B*; $P = 0.03$, by log rank test).

best treatment for stage I is still being defined as the magnitude of benefit may be less compared with later stages. Stratifying patients into high risk versus low risk of aggressive disease can play a critical role in determining which patients should receive adjuvant chemotherapy.

Although *MMP* polymorphisms have been studied extensively with regard to risk of lung cancer (16, 18, 20, 21), much less is known about survival outcomes. Studies in other cancers are provocative and suggest that various *MMP* polymorphisms may have a prognostic role. In breast cancer, patients carrying the variant *G* allele of the *MMP-12 1082A/G* polymorphism have been reported to have worse survival compared with patients with the wild-type *A/A* genotype (22). The *2G* allele of the *MMP-1 2G/1G* polymorphism was found to be associated with worse survival among patients with colorectal cancer (23), ovarian cancer (24), and breast cancer (25).

There is reason to think that MMP-12 expression may have a role in prognosis. Cho et al. (26) compared expression profiles of recurred versus nonrecurred stage IB NSCLC cases and found that MMP-12 expression was up-regulated in those patients whose cancers recurred. Hofmann et al. (27) reported a significantly worse relapse-free survival among surgically resected NSCLC patients who had high MMP-12 expression. Others have shown worse survival with overexpression of other MMPs, including MMP-1, MMP-2, and MMP-9 (28–33).

One caveat to our findings is the disjunction between the expected function of specific polymorphisms and the effect observed. We did not find significant associations with survival among the polymorphisms that have clearly defined function. However, although the exact function of the *MMP-12 1082A/G* polymorphism is unknown, it has been hypothesized to have functional significance based on its location in the coding region of the hemopexin domain. Interestingly, the *MMP-12 1082G* allele is linked to the *MMP-12 82A* allele, which is associated with higher transcription. Whether the association between the *1082G* allele and worse prognosis is a function of higher transcription, via linkage with neighboring polymorphisms, or of thus far uncharacterized enzymatic function changes, remains unclear.

We tested several different polymorphisms in this study, raising the question of whether our findings were due to chance alone from multiple comparisons. However, the *P* values for the effect of *MMP-12 1082A/G* on OS are in the range of 0.002 to 0.006, raising our confidence in these findings. When corrected for the multiple comparisons, these *P* values remain significant (see Tables 3 and 4). However, it should be noted that the numbers of patients with the variant allele of the *MMP-12 1082A/G* polymorphism were relatively small (46 of 382). Therefore, our analysis is based on relatively small numbers and there remains a possibility that these findings were due to chance alone.

Another limitation of this study is that we were able to collect data on OS and not cancer-specific survival. The sources of survival data that we used did not reliably denote cause of death, although this would be helpful to know particularly in the early-stage setting, where a significant proportion of patients ultimately die of non–cancer-related causes. We analyzed RFS as a potential surrogate for cancer-related death, as we thought that this might identify those patients who were more likely to ultimately die from their lung cancer. However, there are limitations to collecting recurrence data retrospectively, as patients were not on a predefined surveillance schedule and therefore there was heterogeneity in the frequency and intensity of follow-up.

In conclusion, we report that among patients with stage I NSCLC, carrying the *G* allele of the *MMP-12 1082A/G* polymorphism is associated with worse recurrence-free and OS. More studies are needed to confirm these findings.

References

1. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in Stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. J Clin Orthod 2004;22:7019.
2. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. New Engl J Med 2004;350:351–60.
3. Winton T, Livingston R, Johnson D, et al. Vinorelbine

plus cisplatin versus observation in resected non-small cell lung cancer. New Engl J Med 2005;352:2589–97.
4. Lee MH, Murphy G. Matrix metalloproteinases at a glance. J Cell Sci 2004;117:4015–6.
5. De Souza AP, Line SRP. The biology of matrix metalloproteinases. Rev FOB 2002;10:1–6.
6. Sternlicht MD, Bergers G. Matrix metalloproteinases as emerging targets in anti-cancer therapy: status and prospects. Emerg Ther Targets 2000;4:609–33.
7. Stetler-Stevenson WG. Progelatinase A activation during tumor cell invasion. Invasion Metastasis 1994;14:259–68.
8. Kleiner DE, Stetler-Stevenson WG. Matrix metalloproteinases and metastasis. Cancer Chemother Pharmacol 1999;43:S42–51.
9. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. Annu Rev Cell Dev Biol 2001;17:463–516.
10. Brinckerhoff CE, Rutter JL, Benbow U. Interstitial collagenases as markers of tumor progression. Clinical Cancer Res 2000;6:4823–30.
11. Ye S. Polymorphism in matrix metalloproteinase gene promoters: implication in regulation of gene expression and susceptibility of various diseases. Matrix Biol 2000;19:623–9.
12. Rutter JL, Mitchell TI, Buttice G, et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an Ets binding site and augments transcription. Cancer Res 1998;58:5321–5.
13. Ye S, Ericksson P, Hamsten A, et al. Progression of coronary atherosclerosis is associated with a common genetic variant of the human stromelysin-1 promoter which results in reduced gene expression. J Biol Chem 1996;271:13055–60.
14. Price SJ, Greaves DR, Watkins H. Identification of novel, functional genetic variants in the human metalloproteinase-2 gene: role of Sp1 in allele specific transcriptional regulation. J Biol Chem 2001;276:7549–58.
15. Jormsjo SYS, Ye S, Moritz J, et al. Allele-specific regulation of matrix metalloproteinase-12 gene activity is associated with coronary artery luminal dimensions in diabetic patients with manifest coronary artery disease. Circ Res 2000;86:998–1003.
16. Su L, Zhou W, Park S, et al. Matrix metalloproteinase-1 promoter polymorphism and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2005;14:567–70.
17. Zhou Y, Yu C, Miao X, et al. Functional haplotypes in the promoter of matrix metalloproteinase-2 and lung cancer susceptibility. Carcinogenesis 2005;26:1117–21.
18. Fang S, Jin X, Wang R, et al. Polymorphisms in the MMP1 and MMP3 promoter and non-small cell lung carcinoma in North China. Carcinogenesis 2005;26:481–6.
19. Benjamini Y, Hochberg Y. Controlling the false discover rate: a practical and powerful approach to multiple testing. J R Stat Soc 1995;57:290–300.
20. Su L, Zhou W, Asomaning K, et al. Genotypes and haplotypes of matrix metalloproteinase 1, 3 and 12 genes and the risk of lung cancer. Carcinogenesis 2006;27:1024–9.
21. Zhu Y, Spitz MR, Lei L, et al. A single nucleotide polymorphism in the matrix metalloproteinase 1 promoter enhances lung cancer susceptibility. Cancer Res 2001;61:7825–9.
22. Shin A, Cai Q, Shu X, et al. Genetic polymorphisms in the matrix metalloproteinase 12 gene and breast cancer risk and survival: the Shanghai Breast Cancer Study. Breast Cancer Res 2005;7:R506–12.
23. Zinzindohoue F, Lecomte T, Ferraz JM, et al. Prognostic significance of MMP-1 and MMP-3 functional promoter polymorphisms in colorectal cancer. Clin Cancer Res 2005;11:594–9.
24. Six L, Grimm C, Leodolter S, et al. A polymorphism in the matrix metalloproteinase-1 gene promoter is associated with the prognosis of patients with ovarian cancer. Gynecol Oncol 2006;100:506–10.
25. Przybylowska K, Kluczna A, Zadronzny M, et al. Polymorphisms of the promoter regions of matrix metalloproteinases genes MMP-1 and MMP-9 in breast cancer. Breast Cancer Res Treat 2006;95:65–72.
26. Cho NH, Hong KP, Hong SH, et al. MMP expression profiling in recurred stage IB lung cancer. Oncogene 2004;23:845–51.
27. Hofmann HS, Hansen G, Richter G, et al. Matrix metalloproteinase-12 expression correlates with local recurrence and metastatic disease in non-small cell lung cancer. Clin Cancer Res 2005;11:1086–92.
28. Lin TS, Chiou SH, Wang LS, et al. Expression spectra of matrix metalloproteinases in metastatic non-small cell lung cancer. Oncol Rep 2004;12:717–23.
29. Passlick B, Sienel W, Seen-Hibler R, et al. Overexpression of matrix metalloproteinase 2 predicts unfavorable outcome in early-stage non-small cell lung cancer. Clin Cancer Res 2000;6:3944–8.
30. Cox G, Jones JL, O'Byrne KJ. Matrix metalloproteinase 9 and the epidermal growth factor signal pathway in operable non-small cell lung cancer. Clin Cancer Res 2000;6:2349–55.
31. Yamaguchi NH, Lichtenfels AJ, Demarchi LMM, et al. Cox-2, MMP-9, and Noguchi classification provide additional prognostic information about adenocarcinoma of the lung. Anat Pathol 2004;121:78–86.
32. Pinto CA, de Oliveira Carvalho PE, Antonangelo L, et al. Morphometric evaluation of tumor matrix metalloproteinase 9 predicts survival after surgical resection of adenocarcinoma of the lung. Clin Cancer Res 2003;9:3098–104.
33. Sienel W, Hellers J, Morresi-Hauf A, et al. Prognostic impact of matrix metalloproteinase-9 in operable non-small cell lung cancer. Int J Cancer 2003;103:647–51.

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