The Contribution of Matrix Metalloproteinase-1 Genotypes to Hepatocellular Carcinoma Susceptibility in Taiwan

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Abstract. Background/Aim: Metalloproteinases (MMPs) are a family of proteases which have been shown to be overexpressed in various types of cancers. However, the contribution of MMP1 genotype to hepatocellular carcinoma (HCC) has not been well studied. This study aimed to evaluate the contribution of MMP1 promoter 1607 genotype to the risk of HCC in Taiwan, where HCC incidence is relatively high in the world. Materials and Methods: In this case–control study, MMP1 genotype and its interaction with consumption of cigarettes and alcohol in determining HCC risk was investigated among 298 HCC patients and 889 age- and gender-matched healthy controls. Results: The percentages of ever smokers and ever alcohol drinkers were much higher in the case group than in the control group. The percentages of 2G/2G, 1G/2G and 1G/1G for MMP1 promoter 1607 genotype were 37.2%, 38.3% and 24.5% in the HCC group and 34.8%, 44.0% and 21.2% in the control group, respectively (p for trend=0.2048). The allelic frequency distribution analysis showed the variant 1G allele of MMP1 promoter 1607 conferred similar HCC susceptibility as the wild-type 2G allele (odds ratio (OR)=1.01, 95% confidence interval (CI)=0.84-1.22, p=0.8735). As for the gene–lifestyle interaction, there was an obvious protective effect of MMP1 promoter 1607 1G allele on the risk of HCC among non-smokers, but not non-smokers, even alcohol drinkers or non-drinkers. Conclusion: The 1G allele of MMP1 promoter 1607 may have a protective effect on HCC risk for non-smokers in Taiwan and further validations are needed in other population groups.

Statistically, hepatocellular carcinoma (HCC) is diagnosed in more than 500,000 people worldwide annually and is one of the leading causes of cancer-related deaths (1). Geographically, HCC incidence is of relatively high density in Taiwan, China and other Asia-Pacific regions but has a low incidence in the United States and Europe (2), and has been reported to be closely associated with chronic infection with hepatitis B (HBV) or C virus (HCV), aflatoxin exposure, cigarette smoking, alcohol consumption, cirrhosis, male gender and family history of HCC (3, 4). In addition to these environmental factors, the genetic factors may contribute to the initiation and progression of HCC. In Taiwan, although specific biomarkers for HCC have been reported in recent years (5-9), the genomic susceptibility of HCC and the interactions among the genetic and environmental risk factors are largely unrevealed.

Extracellular matrix (ECM) components, which are composed of glycosaminoglycans and fibrous proteins, may contribute to the regulation and progression of morphogenesis, angiogenesis, inflammation, would healing and tumorigenesis (10). The matrix metalloproteinases (MMPs), also known as matrixins, are a family of calcium-dependent endopeptidases that play a key role in cell recruitment, migration (adhesion and dispersion), differentiation, angiogenesis, cell death...
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Table I. Summary of selected characteristic data of the 298 patients with hepatocellular carcinoma and the 889 matched healthy controls.

| Characteristic                  | Controls (n=889) | Cases (n=298) | p-Valuea |
|--------------------------------|-----------------|---------------|----------|
|                                | n    | %    | Mean (SD) | n    | %    | Mean (SD) |          |
| Age (years)                    | 55.4 (4.9)     | 52.3 (4.5)    | 0.7418   |
| Gender                         |       |      |           |       |      |           |          |
| Male                           | 636   | 71.5% |           | 213   | 71.5% |           | 0.9830   |
| Female                         | 253   | 28.5% |           | 85    | 28.5% |           |          |
| Personal habits                |       |      |           |       |      |           |          |
| Ever smokers                   | 579   | 65.1% |           | 224   | 75.2% |           | 0.0017*  |
| Ever drinkers                  | 518   | 41.7% |           | 206   | 69.1% |           | 0.0011*  |

SD: Standard deviation; a based on Student’s t-test and Chi-square test. *Statistically significant, p<0.05.

Materials and Methods

Investigated population. Two hundred and ninety-eight patients diagnosed with HCC by Dr. Jeng were recruited at the Department of General Surgery at the China Medical University Hospital, Taiwan, in 2004-2010. Each patient and non-cancerous healthy person completed a self-administered questionnaire and provided their peripheral blood samples. Originally, three times as many non-cancer healthy volunteers as controls were selected by matching for age and gender after initial random sampling from the Health Examination Cohort of our hospital. The exclusion criteria of the controls included previous malignancy, metastasized cancer from other or unknown origin, and any genetic or familial diseases. The included control population was 898. Our study was approved by the Institutional Review Board of the China Medical University Hospital (DMR103-IRB-094), and written informed consent was obtained from all participants. The selected characteristic information extracted from personal questionales is summarized in Table I.

Genotyping conditions. The genomic DNA from the peripheral blood leukocytes of each investigated subject was prepared applying the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and stored at −80°C until processed as per our recent publications (25-28). The sequences of primers and the restriction enzymes for MMP1 promoter 1607 genotyping are the same as our previous publication (29-31). Briefly, the sequences for forward and reverse primer pairs were 5’-TGACTTTTTAAACATAGTCTTATG-3’ and 5’-GATTG ATTTGAGATAAAGTCATAGC-3’, respectively. The polymerase chain reaction (PCR) cycling conditions were set as: one cycle at 94°C for 5 min; 35 cycles of 94°C for 30 s, 58°C for 30 s, and 72°C for 30 s; and a final extension step at 72°C for 10 min. After PCR amplification, the PCR products were subject to the digestion by Alul restriction endonuclease for 2 h at 37°C and separation via 3% agarose gel electrophoresis for 25 min. The genotypes were identified as homozygous 2G/2G with 269-bp product, heterozygous 1G/2G with 269-, 241- and 28-bp products, and homozygous 1G/1G with 241- and 28-bp products, respectively. All the genotypic processing was repeated by two researchers independently and blindly, and all the genotyping results were 100% concordant.

Statistical analyses. Student’s t-test was applied for the comparison of ages between the HCC case and the control groups, Pearson’s Chi-square test was applied to compare the distribution of the MMP1 promoter 1607 genotypes among the subgroups. The associations between the MMP1 promoter 1607 genotypes and HCC risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. Statistically, any difference at p<0.05 was taken as significant between the two groups compared.

(apoptosis and autophagy), and control degradation of the components of connective tissue matrices (10-14). Homeostasis statuses of MMPs is under the control of a complex network (15), and the imbalance of MMPs, include MMP-1, was a common feature for HCC etiology (16-19). MMP1, also known as collagenase-1, is the most abundant MMP in ECM and under the control of activator protein-1 (AP1) that binds to the promoter region of mitogen-activated kinase through polymavirus-enhancing activity-3 (20, 21). A polymorphic site was found in the MMP1 promoter region at upstream position of 1607 bp, which was reported to control the transcriptional activity of the MMP1 gene and was also correlated with the incidence and progression of several cancer types (22).

The genomic contribution of MMP1 to cancer has not been well elucidated and few scientific reports have investigated its role in HCC. In 2005, Okamoto and his colleagues reported that the 2G allele of MMP1 promoter 1607 polymorphism was not associated with risk of HCC, compared with the 1G allele in a Japanese population with only 92 HCC cases and 83 controls (16). In 2010, the same group further proposed that IL-1β -31 T allele and MMP-3 5A allele, but not MMP-1 allele, are cooperative risk factors for poor prognosis in HCC patients (23). Zhai and colleagues reported that MMP1 promoter 1607 polymorphism was not associated with risk of HCC in 434 cases and 480 controls in south China (24). In the current study, we aimed to firstly reveal the contribution of MMP1 genotype at the promoter 1607 site to the risk of HCC in Taiwanese.
Results

The frequency distributions of selected characters including age, gender and personal lifestyles for the 298 HCC patients in the case group and 889 non-cancer healthy subjects in the control group are summarized and compared in Table I. Since we applied frequency matching to recruit the non-cancer healthy subjects as the controls, it is granted that there was no difference in the distributions of age and gender between the control and case groups (Table I). For these investigated individuals, it was found that the percentages of ever smokers and ever alcohol drinkers were much higher in the case group than in the control one (Table I). These findings fit the previous reports that smoking and alcohol drinking are risk factors for HCC in Taiwan.

The distributions of the MMP1 promoter 1607 genotype among the 889 non-cancer controls and the 298 HCC patients are presented and statistically analyzed in Table II. The results showed that the genotypes of MMP1 promoter 1607 were not differently distributed between case and control groups (p for trend=0.2048) (Table II). In detail, the MMP1 promoter 1607 heterozygous 1G/2G and homozygous 1G/1G were not associated with HCC risk, compared to wild-type 2G/2G genotype (OR=0.82 and 1.08, 95%CI=0.60-1.10 and 0.76-1.52, p=0.1737 and 0.6815, respectively; Table II). In the recessive and dominant models, there was still no association between the genotype of MMP1 promoter 1607 and HCC risk (OR=1.20 and 0.90, 95%CI=0.88-1.64 and 0.68-1.18, p=0.2436 and 0.4366, respectively; Table II).

To confirm the results in Table II, the analysis of allelic frequency distribution for the MMP1 promoter 1607 polymorphism was further conducted and the results are presented in Table III. Supporting the findings that neither heterozygous 1G/2G nor homozygous 1G/1G genotype of MMP1 promoter 1607 was associated with HCC risk, the variant allele 1G was found at 43.6% in the case group, non-significantly different from that of 43.2% in the control group (OR=1.01, 95% CI=0.84-1.22, p=0.8735). To sum-up, there was no significant difference in the allelic frequencies of MMP1 promoter 1607 between the case and control groups (Table III).

Since we found that smoking and alcohol drinking are risk factors for HCC in Taiwan, we were interested in investigating the interactions between the genotype of MMP1...
In the literature, MMP-1, together with MMP-2, -9, -13 and their regulators TIMP-1 and -2 are involved in the liver fibrosis processions (32-36), but few has studied the genomic contribution of MMP-1 to the carcinogenesis of HCC. In the current hospital–based case–control study, the contribution of MMP1 promoter 1607 to HCC risk and its interaction with alcohol drinking and cigarette smoking were firstly examined among Taiwanese. The results showed that although neither the genotypic (Table II) nor the allelic frequencies (Table III) of MMP1 promoter 1607 were differentially distributed among the HCC patients and non-cancer healthy controls, the 1G allele was a protective determinant for risk of HCC among the non-smokers (Table IV).

This is the first study to reveal an interaction between MMP1 1607 genotype and cigarette smoking on the susceptibility to HCC. Previously, long-term tobacco smoking has been shown to contribute to the etiology of HCC development (37-40) but little was known about the contributions of genomic factors to HCC development. Recently, others and our team have reported that specific genotypes may be combined with cigarette smoking habits and contribute to increased HCC risk, such as the polymorphisms on CYP1A1 (41), N-acetyltransferase 2 (42) and tumor necrosis factor-alpha (9). Several genomic markers did not have joint effects with cigarette smoking habit on HCC risk (5, 8). However, the overall mechanisms are very complex and need more investigations. In Table I, it can be found that a higher proportion of individuals had consumed cigarettes and alcohol in the group of patients with HCC than the controls. However, the incomplete records of other factors, such as infection status with hepatitis B (HBV) or C virus (HCV), limited us to observe the interactions of genotypes of MMP1 1607 with these environmental factors of HCC in Taiwan.

### Discussion

In the literature, matrix metalloproteinase-1 (MMP1) promoter 1607 and personal cigarette smoking and alcohol drinking habits. Among the non-smokers, those with genotype of 1G/2G or 1G/1G at MMP1 promoter 1607 were at 0.52- and 0.47-fold odds of having HCC (95% CI=0.30-0.92 and 0.23-0.97, \( p=0.0222 \) and 0.0371, respectively), seemingly conferring a protective effect, but this was not the case among those smokers (Table IV). After the adjusting of age, gender and alcohol drinking status, the significance were still existing at the similar level (OR=0.54 and 0.44, 95% CI=0.33-0.90 and 0.25-0.95, respectively, Table IV). There was no such close interaction of MMP1 promoter 1607 genotype with personal alcohol drinking habits (Table V).
MMP1 has been reported to be in charge of the degradation of the interstitial collagens, hence it is called collagenase-1. In normal conditions, MMP1 is under the suppression of TIMP1 (43, 44) and elevated MMP1 has been reported to play an important role in invasive and migration capacity of tumor cells (45). Mounting evidence indicates that elevated MMP1 expression was observed in the borders of solid tumors, such as breast and oral cancer (46-48). Mechanically, MMP1 is thought to promote invasion and metastasis through the degradation of the ECM as the main component of connective tissue, like to relieve the reims for the horses (49-51). In 2012, Liu and his colleagues performed a meta-analysis exploring the association between MMP1 promoter 1607 1G/2G polymorphism and risk of several types of cancer, and the results showed that an elevated cancer risk was found regarding breast, colorectal, genitourinary neoplasm but not HCC (52). The dynamic balance between MMPs and TIMPs play a pivotal role in the maintenance of normal physiological conditions for cells, but it seems that the closely regulation of MMP1 by TIMP1 in HCC tissues is not as simple as a 'see-saw' relationship. In 2009, Al tadill and his colleagues reported that overexpressed MMP-1 by fibroblast cells is correlated with poor prognosis (19), supported by the findings that overexpressed MMP-1 was associated with an elevated metastasis capacity of the HCC cells (53, 54). Al tadill and his colleagues also reported that overexpressed TIMP1 by stromal cells is correlated with shortened overall survival period (19), and accordingly TIMP-1 overexpression was reported to be associated increased invasive and metastatic capacity of the HCC cells (55, 56). In the near future, further analysis of TIMP1 genotype/phenotype may provide further evidence for evaluating the contribution of combined genotypes of MMP-1 and TIMP1 to the carcinogenesis of HCC. In addition, the promoter assay with the different genotypes of MMP-1 1607 and possible TIMP1 promoter polymorphic site, may add more evidence for the functional differences between the different genotypes or haplotypes. Moreover, the involvement of smoking in etiology of HCC, especially the initial step of unbalanced DNA damage, was accessible with the treatment of cigarette components to the cells with different MMP-1 and/or TIMP1 genotypes. Of course, the genetic-environmental interactions could also be approached with the treatments of increasing doses of cigarette components to the cells with different MMP-1 and/or TIMP1 genotypes, and investigating their genomic instability. It is very possibly that the cells with 2G/2G genotypes at MMP-1 1607 with highest dose of BPDE, an ultimate carcinogenic metabolite of tobacco smoke carcinogen benz(a)pyrene, was of the highest instable genomic integrity, which is most prone to carcinogenesis.

In conclusion, the study provides evidence that the 1G allele at MMP1 promoter 1607 may interact with personal smoking status to determine the personal susceptibility to HCC, and more investigations should be conducted to reveal the detail alteration of ECM components with HCC risk and prognosis.

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
2. Yang JD and Roberts LR: Hepatocellular carcinoma: a global view. Nat Rev Gastroenterol Hepatol 7: 448-458, 2010.
3. Beasley RP: Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 61: 1942-1956, 1988.
4. Yu MW and Chen CJ: Hepatitis B and C viruses in the development of hepatocellular carcinoma. Crit Rev Oncol Hematol 17: 71-91, 1994.
5. Chang WS, Yang MD, Tsai CW, Cheng LH, Jeng LB, Lo WC, Lin CH, Huang CY and Bau DT: Association of cyclooxygenase 2 single-nucleotide polymorphisms and hepatocellular carcinoma in Taiwan. Chin J Physiol 55: 1-7, 2012.
6. Hsu CM, Yang MD, Chang WS, Jeng LB, Lee MH, Lu MC, Chang SC, Tsai CW, Tsai Y, Tsai FJ and Bau DT: The contribution of XRCC6/Ku70 to hepatocellular carcinoma in Taiwan. Anticancer Res 33: 529-535, 2013.
7. Hsu CM, Yang MD, Tsai CW, Ho CY, Chang WS, Chang SC, Jeng LB, Tsai Y, Tsai FJ and Bau DT: The contribution of caveolin-1 genotype and phenotype to hepatocellular carcinoma. Anticancer Res 33: 671-677, 2013.
8. Hsieh YH, Chang WS, Tsai CW, Tsai JP, Hsu CM, Jeng LB and Bau DT: DNA double-strand break repair gene XRC6C7 genotypes were associated with hepatocellular carcinoma risk in Taiwanese males and alcohol drinkers. Tumour Biol 36: 4101-4106, 2015.
9. Yang MD, Hsu CM, Chang WS, Yueh TC, Lai YL, Chuang CL, Wang SC, Jeng LB, Ji PX, Hsiao CL, Wu CN, Tsai CW, Chung JG and Bau DT: Tumor necrosis factor-alpha genotypes are associated with hepatocellular carcinoma risk in Taiwanese males, smokers and alcohol drinkers. Anticancer Res 35: 5417-5423, 2015.
10. Woessner JF Jr.: Matrix metalloproteinases and their inhibitors in connective tissue remodeling. Faseb J 5: 2145-2154, 1991.
11. Mannello F, Luchetti F, Falcieri E and Papa S: Multiple roles of matrix metalloproteinases during apoptosis. Apoptosis 10: 19-24, 2005.
12. Augustin S, Berard M, Kellaf S, Peyri N, Fauvel-Lafeve F, Legrand C, He L and Crepin M: Matrix metalloproteinases are involved in both type I (apoptosis) and type II (autophagy) cell death induced by sodium phenylacetate in MDA-MB-231 breast tumour cells. Anticancer Res 29: 1335-1343, 2009.
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13 Mannello F: Multipotent mesenchymal stromal cell recruitment, migration, and differentiation: what have matrix metalloproteinases got to do with it? Stem Cells 24: 1904-1907, 2006.
14 Rundhaug JE: Matrix metalloproteinases and angiogenesis. J Cell Mol Med 9: 267-285, 2005.
15 Murphy G and Docherty AJ: The matrix metalloproteinases and their inhibitors. Am J Respir Cell Mol Biol 7: 120-125, 1992.
16 Okamoto K, Mandai M, Mimura K, Murawaki Y and Yuasa I: The association of MMP-1, -3 and -9 genotypes with the prognosis of HCV-related hepatocellular carcinoma patients. Res Commun Mol Pathol Pharmacol 117:118: 77-89, 2005.
17 Sakamoto Y, Mafune K, Mori M, Shiraishi T, Imamura H, Mori M, Takayama T and Makuuchi M: Overexpression of MMP-9 correlates with growth of small hepatocellular carcinoma. Int J Oncol 17: 237-243, 2000.
18 Kim JH, Kim TH, Jang JW, Jang YJ, Lee KH and Lee ST: Analysis of matrix metalloproteinase mRNAs expressed in hepatocellular carcinoma cell lines. Mol Cells 12: 32-40, 2001.
19 Altadill A, Rodriguez M, Gonzalez LO, Junquera S, Corté M, Gonzalez-Dieuguez ML, Linares A, Barbon E, Fresno-Forcelledo M, Rodrigo L and Vizoso FJ: Liver expression of matrix metalloproteases and their inhibitors in hepatocellular carcinoma. Dig Liver Dis 41: 740-748, 2009.
20 Sharrocks AD, Brown AL, Ling Y and Yates PR: The ETS-domain transcription factor family. Int J Biochem Cell Biol 29: 1371-1387, 1997.
21 Westermarck J, Seth A and Kahari VM: Differential regulation of interstitial collagenase (MMP-1) gene expression by ETS transcription factors. Oncogene 14: 2651-2660, 1997.
22 Rutter JL, Mitchell TI, Batteux G, Meyers J, Gusella JF, Ozelius LJ and Brinckerhoff CE: A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an Ets binding site and augments transcription. Cancer Res 58: 5321-5325, 1998.
23 Okamoto K, Ishida C, Ikebuchi Y, Mandai M, Mimura K, Murawaki Y and Yuasa I: The genotypes of IL-1 beta and MMP-3 are associated with the prognosis of HCV-related hepatocellular carcinoma. Intern Med 49: 887-895, 2010.
24 Zhai Y, Qiu W, Dong XJ, Zhang XM, Xie WM, Zhang HX, Yuan XY, Zhou GQ and He FC: Functional polymorphisms in the promoters of MMP-1, MMP-2, MMP-3, MMP-9, MMP-12 and MMP-13 are not associated with hepatocellular carcinoma risk. Gut 56: 445-447, 2007.
25 Chang WS, Liao CH, Tsai CW, Hu PS, Wu HC, Hsu SW, Hsiao CL, Hsu CH, Hung YW and Bau DT: Association of enhancer of Zeste 2 (EZH2) genotypes with bladder cancer risk in Taiwan. Anticancer Res 36: 4509-4514, 2016.
26 Chang WS, Liao CH, Tsai CW, Hu PS, Wu HC, Hsu SW, Ji HY, Hsiao CL and Bau DT: The role of IL-10 promoter polymorphisms in renal cell carcinoma. Anticancer Res 36: 2205-2209, 2016.
27 Chang WS, Yueh TC, Tsai CW, Ji HY, Wu CN, Wang SC, Lai YL, Hsu SW, Hsieh MH, Hsiao CL, Hung YW, Shih TC and Bau DT: Contribution of DNA repair xeroderma pigmentosum group D genotypes to colorectal cancer risk in Taiwan. Anticancer Res 36: 1657-1663, 2016.
28 Pei JS, Chang WS, Hsu PC, Tsai CW, Hsu CM, Ji HY, Hsiao CL, Hsu YN and Bau DT: The Association of Flap Endonuclease 1 Genotypes with the Risk of Childhood Leukemia. Cancer Genomics Proteomics 13: 69-74, 2016.
29 Pei JS, Hsu PC, Chou AK, Tsai CW, Chang WS, Hsiao CL, Hsu YN, Cheng SP and Bau DT: Matrix metalloproteinase-1 genotype contributes to the risk of non-solid tumor in childhood leukemia. Anticancer Res 36: 5127-5132, 2016.
30 Su CH, Lane HY, Hsiao CL, Liu LC, Ji HY, Li HT, Yen ST, Su CH, Hsia TC, Chang WS, Tsai CW and Bau DT: Matrix metalloproteinase-1 genetic polymorphism in breast cancer in Taiwanese. Anticancer Res 36: 3341-3345, 2016.
31 Tsai CW, Chang WS, Gong GL, Shih LC, Chen LY, Lin EY, Li HT, Yen ST, Wu CN and Bau DT: Contribution of matrix metalloproteinase-1 genotypes, smoking, alcohol drinking and areca chewing to nasopharyngeal carcinoma susceptibility. Anticancer Res 36: 3335-3340, 2016.
32 Sawada S, Murakami K, Murata J, Tsukada K and Saiki I: Accumulation of extracellular matrix in the liver induces high metastatic potential of hepatocellular carcinoma to the lung. Int J Oncol 19: 65-70, 2001.
33 Milani S, Herbst H, Schuppans D, Grapponne C, Pellegrini G, Pinzani M, Casini A, Calabro A, Ciancio G, Stefanini F et al: Differential expression of matrix-metalloproteinase-1 and -2 genes in normal and fibrotic human liver. Am J Pathol 144: 528-537, 1994.
34 Benyon RC, Iredale JP, Goddard S, Winwood PJ and Arthur MJ: Expression of tissue inhibitor of metalloproteinases 1 and 2 is increased in fibrotic human liver. Gastroenterology 110: 821-831, 1996.
35 Kapranos N, Karaiosifidis H, Kouri E and Vasilarios S: Nm23 expression in breast ductal carcinomas: a ten year follow-up study in a uniform group of node-negative breast cancer patients. Anticancer Res 16: 3987-3990, 1996.
36 Takahara T, Furui K, Yata Y, Jin B, Zhang LP, Nambu S, Sato H, Seiki M and Watanabe A: Dual expression of matrix metalloproteinase-2 and membrane-type 1-matrix metalloproteinase in fibrotic human livers. Hepatology 26: 1521-1529, 1997.
37 Austin H, Delzell E, Grufferman S, Levine R, Morrison AS, Stolley PD and Cole P: A case-control study of hepatocellular carcinoma and the hepatitis B virus, cigarette smoking, and alcohol consumption. Cancer Res 46: 962-966, 1986.
38 Yu MW, Chen CJ, Luo JC, Brandt-Rauf PW, Carney WP and Santella RM: Correlations of chronic hepatitis B virus infection and cigarette smoking with elevated expression of neocentropin A in the development of hepatocellular carcinoma. Cancer Res 54: 1059-1063, 2000.
39 Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, Trichopoulos D and Suver SO: Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. Int J Cancer 85: 498-502, 2000.
40 Koh WP, Robien K, Wang R, Govindarajan S, Yuan JM and Yu MC: Smoking as an independent risk factor for hepatocellular carcinoma: the Singapore Chinese Health Study. Br J Cancer 105: 1430-1435, 2011.
41 Yu L, Sun L, Jiang YF, Lu BL, Sun DR and Zhu LY: Interactions between CYP1A1 polymorphisms and cigarette smoking are associated with the risk of hepatocellular carcinoma: evidence from epidemiological studies. Mol Biol Rep 39: 6641-6646, 2012.
42 Zhang J, Xu F and Ouyang C: Joint effect of polymorphism in the N-acetyltransferase 2 gene and smoking on hepatocellular carcinoma. Tumour Biol 33: 1059-1063, 2012.
43 Nagase H and Woessner JF Jr.: Matrix metalloproteinases. J Biol Chem 274: 21491-21494, 1999.
44 Surlin V, Ioana M and Plesea IE: Genetic patterns of metalloproteinases and their tissue inhibitors – clinicopathologic and prognostic significance in colorectal cancer. Rom J Morphol Embryol 52: 231-236, 2011.
45 Kessenbrock K, Plaks V and Werb Z: Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 141: 52-67, 2010.
46 Boire A, Covic L, Agarwal A, Jacques S, Sherif S and Kulopoulos A: PAR1 is a matrix metalloprotease-1 receptor that promotes invasion and tumorigenesis of breast cancer cells. Cell 120: 303-313, 2005.
47 George A, Ranganathan K and Rao UK: Expression of MMP-1 in histopathological different grades of oral squamous cell carcinoma and in normal buccal mucosa – an immunohistochemical study. Cancer Biomark 7: 275-283, 2010.
48 Zhou J, Brinckerhoff C, Lubert S, Yang K, Saini J, Hooke J, Mural R, Shriver C and Somiari S: Analysis of matrix metalloproteinase-1 gene polymorphisms and expression in benign and malignant breast tumors. Cancer Invest 29: 599-607, 2011.
49 Uhmann ME, Georgieva M, Sill M, Linnemann U and Berger MR: Prognostic value of tumor progression-related gene expression in colorectal cancer patients. J Cancer Res Clin Oncol 138: 1631-1640, 2012.
50 Zhang M, Teng XD, Guo XX, Li ZG, Han JG and Yao L: Expression of tissue levels of matrix metalloproteinases and their inhibitors in breast cancer. Breast 22: 330-334, 2013.
51 Kurahara S, Shinohara M, Ikebe T, Nakamura S, Beppu M, Hiraki A, Takeuchi H and Shirasuna K: Expression of MMPS, MT-MMP, and TIMPs in squamous cell carcinoma of the oral cavity: correlations with tumor invasion and metastasis. Head Neck 21: 627-638, 1999.
52 Liu D, Guo H, Li Y, Xu X, Yang K and Bai Y: Association between polymorphisms in the promoter regions of matrix metalloproteinases (MMPs) and risk of cancer metastasis: a meta-analysis. PLoS One 7: e31251, 2012.
53 Kang Y, Siegel PM, Shu W, Drobnjak M, Kakonen SM, Cordon-Cardo C, Guise TA and Massague J: A multigenic program mediating breast cancer metastasis to bone. Cancer Cell 3: 537-549, 2003.
54 Przybylowska K, Kluczna A, Zadrozny M, Krawczyk T, Kulig A, Rykala J, Kolacinska A, Morawiec Z, Drzewoski J and Blasiak J: Polymorphisms of the promoter regions of matrix metalloproteinases genes MMP-1 and MMP-9 in breast cancer. Breast Cancer Res Treat 95: 65-72, 2006.
55 Roeb E, Bosserhoff AK, Hamacher S, Jansen B, Dahmen J, Wagner S and Matern S: Enhanced migration of tissue inhibitor of metalloproteinase overexpressing hepatoma cells is attributed to gelatinases: relevance to intracellular signaling pathways. World J Gastroenterol 11: 1096-1104, 2005.
56 Nakatsukasa H, Ashida K, Higashi T, Ohguchi S, Tsuboi S, Hino N, Nours K, Urabe Y, Kinugasa N, Yoshida K, Uematsu S, Ishizaki M, Kobayashi Y and Tsui T: Cellular distribution of transcripts for tissue inhibitor of metalloproteinases 1 and 2 in human hepatocellular carcinomas. Hepatology 24: 82-88, 1996.

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