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ORIGINAL ARTICLE

Matrix Metalloproteinase-2 Single Nucleotide Polymorphism in Egyptian Non-Hodgkin Lymphoma Patients: Correlation with Clinicopathological Characteristics and Outcome

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Abstract Non-Hodgkin's lymphoma (NHL) is an exceedingly diversified group of lymphoproliferative neoplasms emerging from B-, T- or natural killer -lymphocytes. This study was done to detect Matrix metalloproteinase-2 (MMP2)-735C/T gene polymorphism in patients with NHL and its relation to the clinicopathological characteristics of the studied patients in addition to detection the association between it and NHL disease susceptibility and progression. Clinico-hematological profiles were done on 50 NHL patients. The genotypes and allelic frequencies of MMP-2 polymorphisms were recognized utilizing Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR–RFLP). PCR products after adding restriction endonuclease were analyzed using QIAxcel advanced (automated) instrument. The CT + TT genotypes and T allele of MMP2 735C/T were statistically significant in patients having advanced clinical stages III/IV compared to patients with stages I/II. Another significance was observed in patients with intermediate high/high IPI score and BM infiltration. Interestingly, patients with MMP2-735C/T genotype exhibit lower rate of survival. Our results demonstrated that MMP2-735C/T polymorphism may potentially affect the progression of NHL. Further larger scale studies are needed.

Keywords Non hodjkin lymphoma · Matrix metalloproteinase-2 · Polymorphism

Introduction

Non-Hodgkin's lymphoma (NHL) is an extremely diversified group of lymphoproliferative neoplasms of either lymphocytes or natural killer (NK) cells and is also considered the fastest growing malignant tumor in the world currently. It constitutes approximately 3% of all malignancies. The course of the disease relies upon different biological and clinical parameters as well as therapeutic choices at the start of the treatment regimen [1]. Immunesuppression, genetics, and exposure to chemical agents have contributed to increase the incidence of NHL [2]. According to Ferlay et al. [3], the estimated incidence of NHL is 5/100,000, and a mortality rate of 2.5/100,000 worldwide. In light of 2013 appraisals from the American Cancer Society, NHL is considered the fifth utmost widespread human neoplasm and the sixth most elevated cause of cancer-related mortality [4]. In Egypt lymphoma, essentially NHL, has high incidence rates and considered as one of the highest frequency rates in the world, even higher than the lymphoma incidence in the United States [5] and the other developed countries where hematopoietic malignancies are more common. NHL is the second common adults' cancer in Egyptian and the most widely recognized cancer in children [6]. The overall 5-year relative survival rate for NHL patients is 69% and with 58% 10-year relative survival rate [7].

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Matrix metalloproteinase (MMPs) "zinc-dependent endopeptidases" are one of the tumor-related biomarkers that have lately a remarkable consideration capable of extracellular matrix degradation [8]. MMPs have twenty three recognized types [9], many functional single nucleotide polymorphisms (SNPs) in the MMP2 promoter have been depicated [10]. The MMP2-735C/T polymorphism is located in the promoter region of the MMP2 gene, and exhibits a substantial influence on transcriptional activity. MMP2-735C/T destroys the Sp1-binding element, with T allele characterized by decreased promoter activity [11]. MMP2 is the keystone part controlling the tumor invasion, growth and metastasis [12]. Numerous researches reported that MMP-2 has poor prognostic effects in cancers especially in stomach [13], breast [14], lung [15], colorectal [16] and even ovarian cancers [17]. MMP-2 has an essential role in development of some hematologic malignancies [11] like myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) where abnormal expression of MMP2 and even MMP9 were found [18]. Serum MMP9 levels may be useful in predicting prognosis and clinical outcomes of CLL patients in early periods [19]. Clear distinction in expression of MMP2 and MMP9 of adult and pediatric acute lymphoblastic leukemia (ALL) patients was seen [20]. MMP2 expression was found to be related with extramedullary disease pattern in adult ALL patients.

The aim of the present study was to detect MMP2-735C/T gene polymorphismin patients with NHL using PCR–RFLP technique and correlation with the clinicopathological attributes of our studied patients to realize an association with NHL disease susceptibility and progression.

Patients and Methods

Patients and Controls

A prospective randomized study was carried on 50 Egyptian patients from 2015 to 2017. They were 27 males versus 23 females and their ages ranged from 28 to 80 years old with mean age of (55.20 ± 13.05). The patients were presented at the Clinical Pathology Department, the outpatient clinic of Medical Oncology Department at South Egypt Cancer Institute, Assiut University and the Department of Internal Medicine, Faculty of Medicine, Assiut University after approval of the medical ethics committee of faculty of medicine, Assiut University with IRP number (17100381). All participants gave informed consent. In addition, 50 individuals (healthy blood donors) of both sexes served as controls. Their ages were ranged from 25 to 50 years old. They were 32 males and 18 females.

Patients were diagnosed as NHL on the basis of lymph node excisional biopsy, bone marrow aspirate/biopsy and immunohistochemical studies. The stage of the disease was determined according to An Arbor staging and the Eastern Cooperative was used to evaluate the performance status. All studied patients were submitted to full history taking, clinical examination and laboratory investigations. For patient's characteristics, (Table 1).

Genotyping of MMP2-735C/T gene polymorphism-polymerase chain reaction restriction fragment length polymorphism (PCR–RFLP) assay

DNA was extracted from the peripheral whole blood taken on EDTA using the Qiagen DNA isolation kit (QiAmp Blood Kit, Qiagen GmbH, Hilden, Germany, Lot No: 148026863) following the recommendations of manufacturer. The following primer pair was used for MMP2-735C/T gene to get 391-bp long fragment: 5′-ATA GGG TAA ACC TCC CCA CAT T-3′ (forward) and 5′-GGT AAA ATG ACC CTG AGA CCT G-3′ (reverse). The total volume of the PCR reaction was 25 µl containing the following: 12.5 µl My Taq Red Mix, 0.3 µl forward primer, 0.3 µl reverse primer and 1 µl genomic extracted DNA. The PCR cycling conditions as per the following: 95 °C for 5 min pursued by 35 cycles of 95 °C for 15 s, 57 °C for 15 s and 72 °C for 10 s, with a last elongation step at 72 °C for 10 min. PCR products analysis was done using Electrophoresis in a 2% agarose gel with ethidium bromide and visualized under a UV-transilluminator and the results were recorded by Photography Fig. 1.

The PCR products of MMP2 were digested with Hinf I (New England Biolabs, Beverly, MA, Lot: 0401505) restriction endonucleases and analyzed using QIAxcel advanced instrument (QIAGEN, Hilden, Germany) using QX Alignment Marker (15–3 kb) and QX DNA Size Marker (100–2.5 kb) Figs. 2, 3 and 4. The 391 bp fragment of MMP2 polymorphism remained uncut in individuals homozygous for the C allele, three fragments of 391, 338 and 53 bp were observed in heterozygous individuals or two fragments of 338 and 53 bp were detected in individuals homozygous for the T variant.

Statistical Analysis

Data entry and data analysis were done using computer program SPSS version 19 (Statistical Package for Social Science). Data were presented as number, percentage, mean ± SD. For statistical evaluation, Chi square test was used to compare between qualitative variables, Independent sample t test was used to compare quantitative variables and Mann–whitney test was used to determine significance for numerical variables that were non

Table 1 Clinical and pathological characteristics of the studied NHL patients

	No. (n = 50)	%
Smoking status		
Smokers	13	26
No smokers	37	74
BMI		
Under wt < 18.5	35	70
Normal 18.5–25	10	20
Over wt 25–30	5	10
Blood_pressure		
Normal	20	40
Elevated	30	60
Ann Arbor staging		
Grade I	20	40.0
Grade II	7	14.0
Grade III	8	16.0
Grade IV	15	30.0
Performance status		
< 2	39	78.0
≥ 2	11	22.0
IPI risk group		
Low risk	26	52.0
Intermediate low	8	16.0
Intermediate high	12	24.0
High risk	4	8.0
Extra-nodal sites		
Yes	17	34.0
No	33	66.0
Histological aggressiveness		
Indolent	29	58.0
FL	5	10.0
SLL	4	8.0
MZL	3	6.0
Other B-cell lymphoma	17	34.0
Aggressive	21	42.0
DLBCL	20	40.0
Peripheral T-cell lymphoma	1	2.0
BM		
No infiltration	38	76.0
Infiltration	12	24.0

N number, *BMI* Body mass index, *IPI* International prognostic index, *FL* Follicular lymphoma, *SLL* Small lymphocytic lymphoma, *MZL* Marginal zone lymphoma, *DLBCl* Diffuse large Bcell lymphoma and *BM* BoneMarrow

parametric. Hardy–Weinberg equation was applied for determination of allelic frequencies from genotypic frequencies.

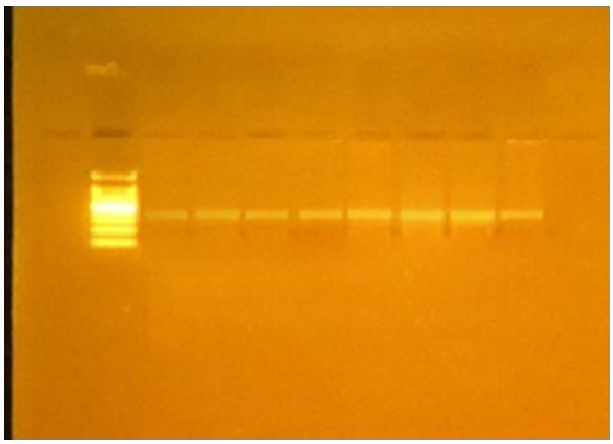

Fig. 1 PCR products of our studied patients were analyzed on 2% agarose gel electrophoresis showing 391 bp long fragment of the MMP-2 gene in the promoter region

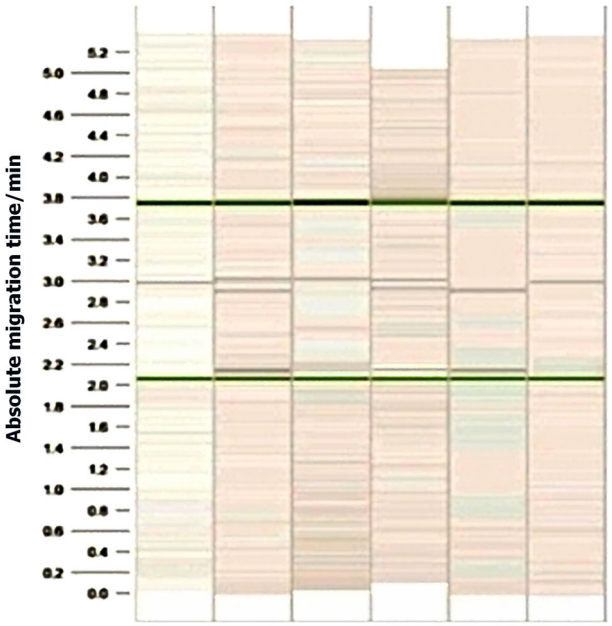

Fig. 2 Analysis by QIAxcel instrument after digestion of PCR products with HinfI RE, the 1st, 3rd and last columns show one band at 391 bp (homozygous wild type, CC) while the 2nd and 4th columns from the left side shows 3 bands at 391,338,53 bp (heterozygous genotype, CT). The 5th column shows 2 bands at 338,53 bp (homozygous mutant genotype)

Probability value < 0.05 was considered significant. Survival analysis was performed employing Kaplan–Meier analysis and log rank test.

Results

Genotypes and allelic frequencies of the studied polymorphism are presented in (Table 2). Also, statistical analysis revealed that the MMP2-735 T variant was more frequent

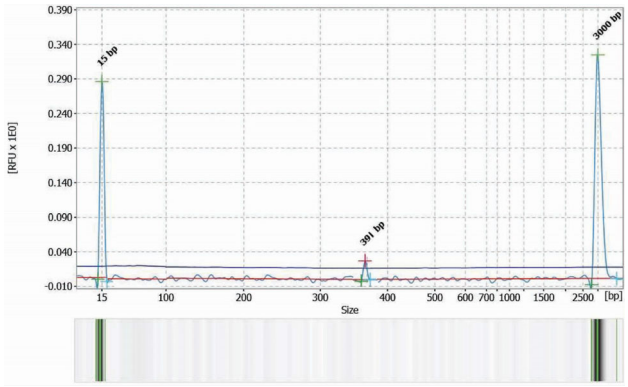

Fig. 3 Analysis by QIAxcel instrument showing one band at 391 bp (homozygous genotype, CC) using QX Alignment Marker (15–3 kb) and QX DNA Size Marker (100–2.5 kb)

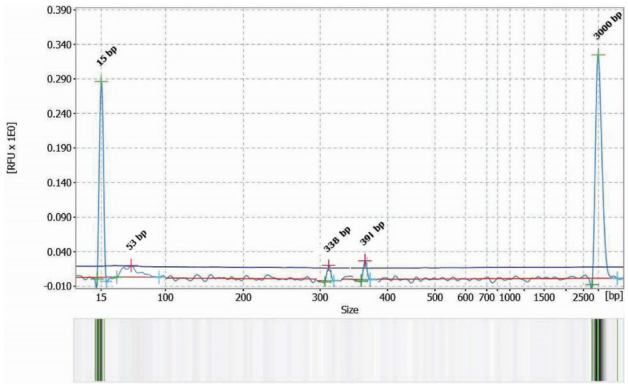

Fig. 4 Analysis by QIAxcel instrument showing 3 bands at 391,338,53 bp (heterozygous genotype, CT) using QX Alignment Marker (15–3 kb) and QX DNA Size Marker (100–2.5 kb)

among patients (20%) than controls (4%) with *P* value 0.014, OR = 6 and 95%Cl = (1.42–28.99) (Table 2).

Analysis of the impact of the MMP2-735C/T genetic polymorphism on the clinicopathological highlights of the disease demonstrated that the polymorphic variants of MMP-2 were significantly associated with patients having advanced clinical stages III/IV compared to patients with stages I/II with *P* value 0.030. Also, MMP-2 CT + TT genotypes and IPI were statistically significant in patients with intermediate high/high IPI score as compared to patients with low/intermediate low IPI and statistically frequent in patients with BM infiltration with *P* value 0.007 and 0.001 respectively (Table 3). No statistical significance was observed as regard age, gender, smoking status, body mass index and blood pressure.

As regards the treatment regimen applied in our study, patients with late stages received chemotherapy, while those with early stages received chemotherapy as well as radiotherapy and patients who couldn't tolerate chemotherapy or had localized disease received radiotherapy. They were followed up for length of 24 months to examine the ailment result outcome and treatment response. It was found that 27 patients (54%) were in complete remission, 15 patients (30%) were in partial remission while 8 patients (16%) showed no response. Analysis of the impact of the MMP2-735C/T genetic polymorphism on the disease outcome revealed that there was a trend of significance between MMP2 CT + TT genotypes and response to treatment including complete, partial remission or no response as almost half of the patients with no response or partial remission showed the polymorphic genotypes (CT + TT) while most of the patients with complete remission showed the wild type CC with *P* value 0.053 (Table 3).

The effect of MMP-2 gene polymorphism on NHL patients' overall survival was considered utilizing Kaplan–Meier analysis and Log rank test Fig. 5. In this study the follow- up length was 24 months. The median months of follow up in patients without polymorphism (CC) were 21 months and were 15 months in patients with polymorphism (CT + TT) (Table 4). There were 3 deaths among patients who were included in the genotype of the study.

Table 2 The frequency of MMP2 genotypes and alleles in NHL patients and controls group

	Patients (n = 50)		Controls (n = 50)		OR (95% CI)	*P* value
	No.	%	No.	%		
MMP-2					6.00 (1.42–28.99)	0.014*
CC	40	80.0	48	96.0		
CT	7	14.0	2	4.0		
TT	3	6.0	0	0.0		
CT + TT	10	20.0	2	4.0		
C allele	0.87	–	0.98	–	–	–
T allele	0.13	–	0.02	–	–	–

Chi square test for calculation of genotypic frequencies between the study groups

Hardy–Weinberg equation for calculation of allelic frequencies between the study groups

MMP-2 Matrix metalloproteinase-2, *N* number, *CI* Confidence interval and *OR* Odds ratio

*Significant *P* value < 0.05

Table 3 The relation between MMP-2 gene polymorphism and the clinical and pathological data of the studied patients

Clinical and pathological data	MMP-2				*P* value
	CC (n = 40)		CT + TT (n = 10)		
	No.	%	No.	%	
Response to treatment					
Complete remission	25	62.5	2	20.0	0.053
Partial remission	10	25.0	5	50.0	
No response	5	12.5	3	30.0	
An arbor staging					
Grade I/Grade II	25	62.5	2	20.0	0.030*
Grade III/Grade IV	15	37.5	8	80.0	
IPI risk groups					
Low/intermediate low	31	77.5	3	30.0	0.007*
Intermediate high/high	9	22.5	7	70.0	
Histological aggressiveness					
Indolent	23	58.0	6	60.0	0.943
Aggressive	17	42.0	4	40.0	
BM					
No infiltration	35	87.5	3	30.0	0.001*
Infiltration	5	12.5	7	70.0	

Chi square test

MMP-2 Matrix metalloproteinase-2, *IPI* International prognostic index and *BM* Bone marrow

*Significant *P* value < 0.05

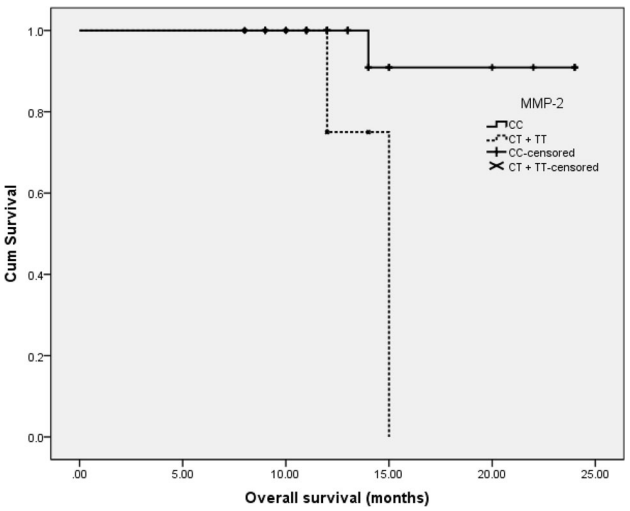

Fig. 5 Cox regression overall survival curve for patients with NHL according to MMP2 (735 C–T) polymorphisms

Table 4 The relation between MMP-2 gene polymorphism and NHL patients' overall survival

	Mean ± SE	Median	*P* value
CC	23.09 ± 0.87	21.0	0.006*
CT + TT	14.25 ± 0.92	15.0	

Independent samples t test

MMP-2 Matrix metalloproteinase-2

*Significant *P* value < 0.05

The CT + TT genotypes of 735 C–T polymorphism demonstrated a statistically significant association with lower two-year overall survival with *P* value 0.006 (Table 4).

Discussion

The incidence of NHL expanded altogether amid the most recent years everywhere throughout the world and considered as one of the most well-known malignancies.

MMPs are ECM degrading enzymes that assume a critical role in the inflammatory processes and angiogenesis [12]. Furthermore, expanding proof shows that tumor progression and also the aggressive nature of the disease all are related to MMPs, which considered as prognostic indicators in specific kinds of malignancies like lymphoma [21]. Here in our NHL patients, 80% of patients were homozygous wild genotype (CC), 14% of them were heterozygous genotype (CT), while 6% had the homozygous mutated genotype (TT). These results are close to what reported by Gouda et al. [22] who found that 23% of cases had the heterozygous genotype (CT), while 7% had the homozygous mutated genotype (TT). In another study of Diao et al. on Chinese, it was reported that 30% were heterozygous, and 5.9% were homozygous mutated. The higher frequency of the heterozygous genotype (CT) in the study of Diao et al. might be clarified by quite low number

of our studied patients and distinctive ethnicity of the examined populations.

As regards the frequency of MMP2-735C/T polymorphism in controls, the heterozygous genotype (CT) was 4%, while none of our controls had the homozygous mutated genotype (TT) and most of them were homozygous wild genotype (CC). Our results are near that already revealed by other studies in Sub-Saharan Africans population and African Americans' which was around 4.4%. While, MMP2-735C/T heterozygosity in European was 25% and not detected in Asians [23]. This could be ascribed to the ethnic diversity between the considered populations.

Examination of the impact of the MMP2-735C/T genetic polymorphism on the clinicopathological highlights of NHL uncovered that the polymorphic variants were more eminent in patients with advanced clinical stages III and IV with *P* value 0.030. This was in agreement with the study of Diao et al. [21] as in his study the polymorphic variants were significantly associated with greater tumor cell invasion (stages III and IV). Another former study reported similar results where the polymorphic variants of MMP-2 were more frequent in patients with advanced clinical stages (III, IV) (22].On the other hand Zhou et al. [24] noted that genotype CC of − 735C/T was associated with increased MMP-2 expression and greater risk of invasion and metastasis of esophageal and lung cancer. On the other hand, Rollin et al. [25] exhibited that in cancer lung MMP-2 gene expression was less in the CC genotype compared to other genotypes (CT/TT).

Moreover, in the present analysis study, it was discovered that conveying the T variant of MMP2-735C/T was associated with a diminished overall survival rate. This was in agreement with Diao et al. [21] who reported that overall survival time was lower in patients with the MMP-2-735T allele. On the other hand Rollin et al. demonstrated that the survival time was longer in lung cancer patients who exhibited the MMP-2-735T allele compared to those with the CC genotype. The relative risk of death in his study increased 2.6-fold in the − 735CC genotype. The discrepancy between previous research works might be clarified by various roles for the MMP-2-735C/T polymorphism in different diseases [26]. Besides, the hereditary genetic polymorphism in the some region notably that in MMP-1 promoter region (1G/2G) or even in MMP-3 (5A/6A), which likewise affects the genes transcriptional activity, may influence the occurrence of some cancer types or its inhibition [27].

As regard the influence of the MMP-2-735C/T on the disease outcome in the current study, it was noted that there was a borderline significance between MMP2 CT + TT genotypes and treatment response including complete or partial remission or those had no response to treatment with *P* value 0.053. In contrast to Gouda et al. [22] who found no statistical significance regarding the disease outcome which may be explained in the previous study by the relatively high percentage (34%) of inaccessible information's during the follow up period.

In the present study, a significant relation between patients carrying the variant genotypes (CT/TT) of MMP2-735C/T and BM infiltration was observed with *P* value 0.001. On the other hand this correlation between MMP-2 and BM infiltration was not observed by Diao et al. [21]. In another study concerning multiple myelomas, increased activity of MMPs can cause the excessive bone marrow resorption and result in spreading the myeloma cells [28].

Another significant relation in our study was found where the 735-T allele was more frequent in patients with IPI score 3 or 4 with *P* value 0.007, but the study of Gouda et al. [22] showed no relation between MMP2-735C/T variant genotypes and IPI score. The diverse results between our study and other studies concerning this polymorphism could be clarified as SNPs can alter or adjust the transcription factor binding motifs, also change the adequacy of either enhancer or repressor components [29] and can likewise modify the structure of translation initiation codons which may prompt wild-type transcript down regulation [30].

In conclusion, MMP2-735C/T variant genotypes may increase risk and impute to aggressive course of NHL with decreased overall survival. Additionally, it could be profitable prognostic biomarker and its function may turn out to be more vital with the improvement of new treatment alternatives, for example immunotherapy and also targeted therapy.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

References

1. Wróbel T, Mazur G, Dzietczenia J, Gębura K, Kuliczkowski K (2013) Bogunia-Kubik K (2013) VEGF and bFGF gene polymorphisms in patients with non-Hodgkin's lymphoma. Biomed Res Int 2013:159813. https://doi.org/10.1155/2013/159813
2. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, (2002). CA Cancer J Clin 55:74–108
3. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F GLOBOCAN (2012) v1.0. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, IARC, 2013
4. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics. CA Cancer J Clin 63(1):11–30
5. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al. (eds) (2007) Cancer incidence in five continents, vol IX. IARC Scientific Publication No. 160. http://gco.iarc.fr

6. Herzog CM, Dey S, Hablas A, Khaled HM, Seifeldin IA, Ramadan M, El-Hamzawy H, Wilson ML, Soliman AS (2012) Geographic distribution of hematopoietic cancers in the Nile delta of Egypt. Ann Oncol 23:2748–2755
7. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, Alteri R, Robbins AS, Jemal A (2014) Cancer treatment and survivorship statistics, 2014: Cancer Treatment and Survivorship Statistics, 2014. CA A Cancer J Clin 64:252–271
8. Hadler-Olsen E, Winberg JO, Uhlin-Hansen L (2013) Matrix metalloproteinases in cancer: their value as diagnostic and prognostic markers and therapeutic targets. TumourBiol 34:2041–2051
9. Butler GS, Overall CM (2009) Proteomic identification of multitasking proteins in unexpected locations complicates drug targeting. Nat Rev Drug Discov 8:935–948
10. Yu C, Zhou Y, Miao X et al (2004) Functional haplotypes in the promoter of matrix metalloproteinase-2 predict risk of the occurrence and metastasis of esophageal cancer. Cancer Res 64:7622–7628
11. Sag SO, Gorukmez O, Ture M, Gorukmez O, Topak A, Sahinturk S, Ocakoglu G, Gulten T, Ali R, Yakut T (2015) MMP2 gene-735 C/T and MMP9 gene -1562 C/T polymorphisms in JAK2V617F positive myeloproliferative disorders. Asian Pac J Cancer Prev 16:443–449
12. Cauwe B, Van den Steen PE, Opdenakker G (2007) The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases. Crit Rev Biochem Mol Biol 42:113–185
13. Shen W, Xi H, Wei B, Chen L (2014) The prognostic role of matrix metalloproteinase 2 in gastric cancer: a systematic review with meta-analysis. J Cancer Res Clin Oncol 140:1003–1009
14. Jezierska A, Motyl T (2009) Matrix metalloproteinase-2 involvement in breast cancer progression: a mini-review. Med Sci Monit 15:Ra32–Ra40
15. Qian Q, Wang Q, Zhan P, Peng L, Wei SZ, Shi Y et al (2010) The role of matrix metalloproteinase 2 on the survival of patients with non-small cell lung cancer: a systematic review with meta-analysis. Cancer Invest 28:661–669
16. Van der Jagt MF, Wobbes T, Strobbe LJ, Sweep FC, Span PN (2010) Metalloproteinases and their regulators in colorectal cancer. J Surg Oncol 101:259–269
17. Gadducci A, Cosio S, Tana R, Genazzani AR (2009) Serum and tissue biomarkers as predictive and prognostic variables in epithelial ovarian cancer. Crit Rev Oncol Hematol 69:12–27
18. Travaglino E, Benatti C, Malcovati L et al (2008) Biological and clinical relevance of matrix metalloproteinases 2 and 9 in acute myeloid leukaemias and myelodysplastic syndromes. Eur J Haematol 80:216–226
19. Buggins AG, Levi A, Gohil S et al (2011) Evidence for a macromolecular complex in poor prognosis CLL that contains CD38, CD49d, CD44 and MMP-9. Br J Haematol 154:216–222
20. Kuittinen O, Savolainen ER, Koistinen P, Möttönen M, Turpeenniemi-Hujanen T (2001) MMP-2 and MMP-9 expression in adult and childhood acute lymphatic leukemia (ALL). Leuk Res 25:125–131
21. Diao LP, Ma H, Wei GC, Li T, Liu HS, Liu LH, Wu LL, Zhao GM, Gao YH (2012) Matrix metalloproteinase-2 promoter and tissue inhibitor of metalloproteinase-2 gene polymorphisms in non-Hodgkin's lymphoma. Int J Cancer 131(5):1095–1103
22. Gouda HM, Khorshied MM, El Sissy MH, Shaheen IAM, Mohsen MMA (2014) Association between matrix metalloproteinase 2 (MMP2) promoter polymorphisms and the susceptibility to non-Hodgkin's lymphoma in Egyptians. Ann Hematol 93:1313–1318
23. Vasku A, Vasku JB, Necas M, Vasku V (2010) Matrix Metalloproteinase-2 promoter genotype as a marker of cutaneous T-cell lymphoma early stage. J Biomed Biotechnol 2010:805907
24. Zhou Y, Yu C, Miao X, Wang Y, Tan W, Sun T, Zhang X, Xiong P, Lin D (2005) Functional haplotypes in the promoter of matrix metalloproteinase-2 and lung cancersusceptibility. Carcinogenesis 26:1117–1121
25. Rollin J, Régina S, Vourc'h P, Iochmann S, Bléchet C, Reverdiau P, Gruel Y (2007) Influence of MMP-2 and MMP-9 promoter polymorphisms on gene expression and clinical outcome of non-small cell lung cancer. Lung Cancer 56:273–280
26. Miao X, Yu C, Tan W, Xiong P, Liang G, Lu W, Lin D (2003) A functional polymorphism in the matrix metalloproteinase-2 gene promoter (− 1306C/T) is associated with risk of development but not metastasis of gastric cardia adenocarcinoma. Cancer Res 63:3987–3990
27. Ghilardi G, Biondi ML, Caputo M, Leviti S, DeMonti M, Guagnellini E, Scorza R (2002) A single nucleotide polymorphism in the matrix metalloproteinase-3 promoter enhances breast cancer susceptibility. Clin Cancer Res 8:3820–3823
28. Kelly T, Borset M, Abe E et al (2000) Matrix metalloproteinases in multiple myeloma. Leuk Lymphoma 37(3–4):273–281
29. Thomas KH, Myen P, Suttorp N (2006) Single nucleotide polymorphismin 5′-flankingregion reduces transcription of surfactant protein B gene in H441 cells. Am J Physiol Lung Cell Mol Physiol 291(3):L386–L390
30. Zysow BR, Lindahl GE, Wade DP, Knight BL, Lawn RM (1995) C/T polymorphism in the 5′ untranslated region of the apolipoprotein(a) gene introduces an upstream ATG and reduces in vitro translation. Arterioscler Thromb Vasc Biol 15(1):58–64