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Review

The Use of Predictive or Prognostic Genetic Biomarkers in Endometrial and Other Hormone-Related Cancers: Justification for Extensive Candidate Gene Single Nucleotide Polymorphism Studies of the Matrix Metalloproteinase Family and their Inhibitors

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Abstract

Genome-wide association studies have accelerated the discovery of single nucleotide polymorphisms (SNP) associated with susceptibility to complex diseases, including many malignancies. The matrix metalloproteinase (MMP) family of proteases are involved in many cell processes, most notably the degradation of the extracellular matrix, and differences in gene and protein expression have been reported to be associated with many cancers. Surprisingly, none of the SNPs located within these genes have been identified to be associated with cancer in the genome-wide association studies published to date. This may be in part due to the proportion and the tagging efficiency of *MMP* SNPs covered by high-throughput genotyping chips. This review will provide an overview of current evidence for *MMPs* and associated SNPs in endometrial and other hormone-related cancers, to provide justification for the further detailed studies of *MMP* SNPs as cancer markers. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2352–65)

Introduction

For cancer cells to metastasize, invasion and destruction of the extracellular matrix (ECM) and proliferation at the metastatic site are necessary. The matrix metalloproteinases (MMP) are a family of 23 zinc-dependent endopeptidases that collectively participate in the degradation of essentially all protein components of the ECM as well as in other biological processes such as angiogenesis and cytokine activation (reviewed in ref. 1). Under normal physiologic conditions, the MMPs are expressed in low levels in adult tissue, except in those that undergo tissue remodeling, such as the cycling endometrium (reviewed in ref. 2). The invasion of endometrial cancer cells through the myometrium and to nearby lymph nodes is a key factor related to poor prognosis and involves the action of proteases to facilitate escape of tumor cells from their site of origin, their penetration of blood or lymph vessel walls, and the subsequent growth at a new site. Given the physiologic and pathologic roles of the MMPs in the endometrium, it is thus not surprising that both *MMP* gene expression and MMP protein expression have been reported to be associated with endometrial cancer (as detailed in tabular format below; Table 3).

It has been hypothesized that complex diseases like cancer, including endometrial cancer, are due to the effect of many low-risk gene variants that collectively increase disease risk (3). Single nucleotide polymorphisms (SNP) are the most common sequence variation in the human genome and can affect coding sequences, splicing, or transcription regulation, and may thus be associated with increased susceptibility to or progression of cancer (4). The relatively new genome-wide association study (GWAS) approach has investigated hundreds of thousands of genetic variants across the whole human genome for association with cancer. Results from GWAS have shown that cancer risks associated with common variation are very low and large studies are required to confirm associations (5). This suggests that conflicting results for previous numerous candidate gene studies were at least partly due to paucity of power to detect such low risks.

It is surprising that from all GWAS in cancer done to date, SNPs located within the *MMP* gene family have not been identified. Whereas it is acknowledged that virtually all GWAS designs to date have been underpowered

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Note: The literature review presented covers all relevant articles relating to MMP and TIMP expression and SNP studies of endometrial, breast, ovarian, and prostate cancer to December 2008.

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to detect the effect sizes that were subsequently confirmed by replication studies (6), and thus many cancer-associated SNPs remain to be identified, another possible explanation is poor coverage of *MMP* genes by current methodologies. At present, there are more than 10 million SNPs known in the human genome, and a typical GWAS currently investigates 500,000 to 1 million SNPs. The majority of these SNPs have been selected using the International HapMap Project, a catalogue used as a reference to choose tagSNPs for association studies. The tagSNP approach uses linkage disequilibrium to evaluate associations between SNPs and choose a subset of SNPs to best "tag" or capture common haplotypes within genes or genomic regions. The coverage of *MMP* SNPs by the HapMap database has been reported to be as low as 30% (7), which may partly explain their failure to be identified by published GWAS. Also, by definition, the SNPs included in GWAS designs have a minimum frequency of 5%, and thus risk-associated SNPs occurring at lower frequencies would not be detected using current scans. Moreover, considering the role of MMPs in the degradation of the ECM, it is possible that these genes are likely to be involved in cancer progression. Hence, *MMP* SNPs may be more strongly associated with prognosis rather than predisposition. However, current published GWAS have not directly examined associations of SNPs with cancer progression, and investigation of surrogates of prognosis such as grade have been limited by relatively poor availability of detailed clinical information from the cohorts studied. This suggests that despite the emergence of GWAS, there is still a need for *MMP* candidate gene studies of cancer predisposition and prognosis to be done. In this article, we review current evidence for the role of MMPs in endometrial and other hormone-related cancers and discuss results from SNP studies done to date.

Matrix Metalloproteinases

The MMPs contain four well-defined domains: a signal peptide, a propeptide with a conserved cysteine residue, a catalytic domain with a Zn-binding site, and a hemopexin-like domain at the COOH-terminal region, and are frequently subgrouped based on substrate specificities and sequence characteristics (Table 1). The MMPs are regulated by endogenous tissue inhibitors of MMPs (TIMP). Four TIMPs have been identified (named TIMP1-4), which form high-affinity 1:1 noncovalent complexes with all active MMPs, thereby inhibiting their action (8). The balance between the levels of activated MMPs and free TIMPs determines in part the net MMP activity (reviewed in ref. 9). In addition to regulating the MMPs, TIMPs have also been shown to have angiogenic and growth factor–like activity (9).

The MMPs play a key role in the process of ECM degradation, an essential element of angiogenesis, cellular invasion, and tumor metastasis. Indeed, MMP activity was first reported to be correlated with metastatic potential of cancer cells from investigations of MMP2 (10). However, more recent studies suggest an expanded role of MMPs in tumor initiation and progression, with evidence for the involvement of certain MMPs in the regulation of bioactive molecules acting in these processes. MMPs play an important role in ectodomain shedding of cell surface molecules, such as tumor necrosis factor-α and Fas ligand, heparin-binding epidermal growth factor and E-cadherin, resulting in various facets of cancer cell progression, including apoptosis, proliferation, invasion, and angiogenesis. MMP9 has been shown to activate transforming growth factor-β to facilitate angiogenesis and tumor invasion. Many of the MMPs have been shown to degrade insulin-like growth factor binding protein, which in turn releases insulin-like growth factor and results in increased proliferation of tumor cells (reviewed in ref. 11). MMP2 and MMP14 play a critical role in the formation of vasculogenic-like networks and matrix remodeling by aggressive ovarian cancer cells (12). MMP1 has been shown to act as a protease agonist for protease activator receptor 1, which has been proposed to be involved in the invasive and metastatic processes of various cancers (13). Hormonal regulation of MMPs and TIMPs has been observed in a variety of cells (14, 15). Differential expression patterns of the MMPs and TIMPs have been observed in many cancers, most notably lung, head and neck, and colorectal cancers, as well as the hormone-related cancers of the prostate, breast, ovary, and endometrium. We chose to focus this review on hormone-related cancers specifically because that would allow us to draw parallels between endometrial cancer, for which there is strong epidemiologic evidence for hormone-driven etiology, and other hormone-related cancers.

MMPs and TIMPs and Endometrial Cancer

Endometrial cancer (cancer of the uterine corpus) is the most common malignancy of the female genital tract. Each year, it is estimated there are almost 200,000 cases diagnosed worldwide, and an estimated 50,000 women will die from this disease. Although several different histologic subtypes of endometrial cancer are recognized (16), these are commonly explained by a dualistic model that categorizes cancers into two major types, type I and type II carcinomas (17). The major features discriminating these etiologic types are detailed in Table 2. Type I tumors (endometrioid epithelial carcinoma) comprise ~80% of all new cases of endometrial cancer and are histologically well or moderately differentiated, estrogen-dependent, and typically have a favorable prognosis. Type II tumors (nonendometrioid) include other subtypes, often with serous papillary or clear cell histology. These tend to be poorly differentiated and are associated with a much more aggressive phenotype. Although type II tumors make up only 10% to 15% of all endometrial cancer cases, they are responsible for ~50% of all relapses (18).

MMPs are known to play a role in cyclic repair mechanisms of normal endometrium (19) and thus might be expected to play a very important role in the development and prognosis of this cancer. Current evidence for their role in endometrial cancer is summarized below.

MMP and TIMP Expression in Endometrial Cancer. Expression studies done in endometrial cancer have observed an increase of MMP production in cancerous tissues and association with poor prognostic parameters for all but one MMP investigated to date (Table 3). The mRNA or protein levels of MMP1 (20), MMP2 (21-28), MMP7 (26, 29-31), MMP9 (21, 22, 26-28, 32-34), and MMP12 (29, 35) were reported to be increased in endometrial cancer and/or associated with poor prognostic features. Increased expression of MMP14 in endometrial cancer has been correlated with increased myometrial and lymphatic invasion (28), which is concordant with studies describing MMP14 to be a key

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Table 1. MMP synonyms and subgroups

MMP	Other name/s	Subgroup
MMP1	Collagenase 1, interstitial collagenase	Collagenases
MMP2	Gelatinase A, 72-kDa type IV collagenase	Gelatinases
MMP3	Stomelysin 1	Stromeolysins
MMP7	Matrilysin, PUMP1	Matrilysins
MMP8	Collagenase 2, neutrophil collagenase	Collagenases
MMP9	Gelatinase B, 92-kDa type IV collagenase	Gelatinases
MMP10	Stromelyin 2, STMY2	Stromeolysins
MMP11	Stromelysin 3, ST-3	Stromeolysins
MMP12	Macrophage metalloelastase, MME	Metalloelastase
MMP13	Collagenase 3	Collagenases
MMP14	MT1-MMP	Membrane-type MMPs
MMP15	MT2-MMP	Membrane-type MMPs
MMP16	MT3-MMP	Membrane-type MMPs
MMP17	MT4-MMP	Membrane-type MMPs
MMP19	MMP18	Others
MMP20	Enamelysin	Others
MMP21		Others
MMP23A	MMP21	Others
MMP23B	MMP22	Others
MMP24	MT5-MMP	Membrane-type MMPs
MMP25	MT6-MMP, leukolysin, MMP20A	Membrane-type MMPs
MMP26	Endometase, matrilysin 2	Matrilysins
MMP28	Epilysin	Others

enzyme in tumor invasion and metastasis (36, 37). It is somewhat surprising, therefore, that the levels of MMP14 mRNA have been reported to be decreased in endometrial cancer compared with normal endometrial tissue (38). Although the relatively small size of this study suggests that investigation in a larger cohort would be optimal to confirm this result, it has been hypothesized that reduced expression of MMP14 in cancers may make malignant cells less likely to be shed during menses, thereby augmenting persistence of lesions (28, 38).

Conflicting results for MMP expression have only been reported for two studies assessing MMP26 gene and protein expression. Increased MMP26 protein expression was reported in endometrial tumor tissue compared with noncarcinoma tissue from postmenopausal but not premenopausal women, with this increased expression in postmenopausal women associated with increased grade, stage, and invasiveness of tumors (39). Decreased MMP26 mRNA and protein was observed in endometrial cancer compared with normal endometrial tissue, with menopausal status of subjects not reported (40). Thus, the conflicting results between these two studies may possibly be due to the differences in menopausal status of subjects analyzed.

Research into the differences of MMP expression by endometrial cancer subtypes has been limited. However, tissue microarray immunohistochemical data have provided evidence of increased MMP2 and MMP9 protein levels in less aggressive type I endometrial cancers compared with more aggressive type II subtypes (25, 41), and gene expression microarray studies have reported increased MMP11 mRNA expression in type I endometrial cancers compared with type II subtypes (42, 43). Gene microarray analysis is invaluable for the identification of molecular signatures of cancers and cancer subtypes, and results such as those reported in endometrial tissues for MMP7 (29), MMP11 (42, 43), MMP12 (29), and MMP14 (38) have provided evidence of MMP expression in these signatures. Further detailed analysis of the raw expression data from these studies would be required to investigate exactly which members of the *MMP* family have been successfully interrogated on the microarray chips used, and what additional study is required to comprehensively assess the role of *MMP* gene expression in endometrial tumor subtypes.

Whereas the expression of MMPs in endometrial cancer is generally consistent across the vast majority of studies, the mRNA and protein levels between endometrial cancer and normal endometrial tissue are more variable for the four TIMPs (Table 3). TIMP1 (21, 31) and TIMP3 (39) mRNA and protein have been reported to be increased in endometrial cancer compared with normal tissue. However, both TIMP2 and TIMP4 have conflicting reports. TIMP4 mRNA expression was reported to be decreased in endometrial cancer (44), and protein levels were reported to be elevated in tumor compared with normal tissue (39). TIMP2 protein expression was reported to be similar between tumor tissues and noncarcinoma tissue remote from the tumor site (45), whereas another study reported an increase in TIMP2 protein expression in tumor tissue compared with normal tissue (21). Findings for predisposition and prognosis may not be concordant as TIMP2 mRNA expression was decreased in high-grade cancers (46), and TIMP2 expression was inversely correlated with grade, invasion, and lymph node involvement in patients (25, 26). Similarly, analyses by histologic subtype have revealed that TIMP2 protein expression is decreased in high-grade type II cancers compared with type I endometrial cancers (25).

These observations need to be interpreted in light of the role of TIMPs as agonists to MMPs, which are elevated in cancer. That is, the increased production of TIMPs at the mRNA or protein level in five of seven studies comparing expression in endometrial cancer versus normal tissue is consistent with the possibility that TIMP expression may be up-regulated in tumor tissue in response to increased MMP levels during cancer development and progression. Moreover, the ratio of MMPs to TIMPs is likely to be most clinically relevant. Indeed, the MMP-to-TIMP ratio is increased in endometrial cancer compared with normal tissue, despite the increased production of TIMP protein (31). Although endometrial studies to date have largely not reported MMP-to-TIMP ratios, the clinical relevance of the MMP-to-TIMP ratio is supported by the observation

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Table 2. Endometrial cancer subtype differences

	Type I	Type II
Age	Premenopausal and perimenopausal	Postmenopausal
Hyperestrogenism	High	Low
Endometrial background	Hyperplasia	Atrophic
Grade	Low	High
Myometrial invasion	Minimal	Deep
Histologic type	Endometrioid epithelial	Nonendometrioid epithelial
Behavior	Stable	Progressive
Genetic alterations	Microsatellite instability, *PTEN, PIK3CA, K-Ras, CTNNB1*	*p53* mutations, Her-2/*neu* amplification, loss of heterozygosity

NOTE: Adapted from ref. 17.

that studies assessing prognostic features of cancer patients show an inverse relationship between TIMP levels and poor prognostic features, in opposition to the direct correlation between MMP levels and poor prognostic features. Moreover, it is important to note that TIMPs also have other functions distinct from MMP inhibition, including angiogenic and growth factor–like activity (reviewed in ref. 47).

SNP Studies in Endometrial Cancer. Only two very small association studies investigating SNPs in *MMPs* have been done in endometrial cancer. The *MMP1 −16071G/2G* (rs1799750) was shown to result in the creation of an Ets binding site (48), and the *2G* allele had significantly higher transcriptional activity in normal and melanoma cells than the *1G* allele (48). The *2G* allele was observed to be more frequently present in a study of 100 Japanese endometrial cancer cases compared with 150 controls (91% versus 80%, χ^2 $P = 0.019$; ref. 49). This study also reported that endometrial tumors with the *2G* allele expressed MMP1 protein more frequently than tumors with a *1G1G* genotype, suggesting that the *2G* allele affected the MMP1 protein expression level. Another Japanese study (endometrial cancer cases $n = 107$, controls $n = 213$) reported a nonsignificant decreased allele frequency in cases versus controls (64% versus 70%, χ^2 $P = 0.13$; ref. 50). This same study (50) investigated another SNP *MMP9 −1562C > T* (rs3918242), which is predicted to result in a loss of a repressor protein binding site. The *T*-allele was significantly less frequent in endometrial cancer cases (10.7%) than controls (16.7%), particularly endometrioid cases [10.2%; odds ratio (OR), 1.76; 95% confidence interval (95% CI), 1.02-3.03, $P = 0.043$]. There are no studies of *TIMP* SNPs in endometrial cancer to date.

MMP and TIMP Expression in Other Hormone-Related Cancers

Similar to that of endometrial cancer, much of the research on MMPs in breast, ovarian, and prostate cancers has focused on the expression levels of MMP2, MMP9, MMP11, and MMP14, detailed in Table 4, and salient features are discussed below. Increased MMP expression is generally observed in hormone-related cancers, although differences can sometimes be seen according to whether expression was studied at the transcription or translational level or according to expression location (e.g., serum or tissue). An increase in MMP mRNA or protein expression is almost invariably accompanied by an association with poor prognosis parameters.

Expression studies in prostate cancer have yielded variable results. For example, MMP1 protein expression was found to be increased in the sera of prostate cancer patients compared with hospital controls, and increased production was associated with metastasis in patients (51). However, expression studies done using immunohistochemistry and *in situ* hybridization on prostate cancer tissue have shown a decreasing gradient of MMP1 protein from normal adjacent prostate, prostate intraepithelial neoplasia, to prostate cancer tissue (52). Similarly, down-regulation of MMP2 mRNA was observed in prostate cancer compared with normal tissue in two studies (53, 54), whereas increased expression of MMP2 protein has been reported in five studies (55-59). This suggests a discrepancy between MMP2 RNA and protein levels in prostate tumors. This discrepancy is also observed for MMP14, with a decrease in mRNA expression observed in prostate cancer compared with normal tissue by one study (54) but an increase in immunohistochemically detected protein expression reported by another (52).

Both MMP mRNA and protein expression have been uniformly reported to be increased in breast cancer in tissue and serum samples (Table 4). As with prostate cancer, increased MMP production in breast cancer is generally associated with poor prognostic factors, with some exceptions. Numerous studies done in breast cancer reported increased total MMP2 or MMP9 protein expression to be associated with poor prognostic factors (60-66). However, two studies have reported evidence for an inverse association with poor prognosis: One study found lower levels of active MMP2 protein to confer a decreased recurrence-free survival in breast cancer patients and an inverse relationship between increasing total pro-MMP2 protein in breast cancer serum with nodal status, grade, and stage (67); the second reported a negative association between tumor grade and pro-MMP2 and pro-MMP9 protein expression in breast cancer patient serum (68). Like prostate cancer, TIMP protein and mRNA expression is variable in breast cancer. TIMP1 mRNA and protein expression is reported be increased in all studies of breast cancer to date (Table 4). However, high expression of TIMP1 mRNA and a TIMP1 variant lacking exon 2 were reported to be associated with good prognosis (69), and high TIMP1 protein expression was associated with poor prognosis in three other studies (66, 70, 71). This differential association of mRNA and protein with prognosis suggests that posttranscriptional regulatory mechanisms affecting protein concentration, activity, and stability may be at work.

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Table 3. Clinical significance of MMP and TIMP expression in endometrial cancer

	Protein/mRNA	Endometrial cancer		Samples	
		Expression	Clinical relevance	Cancer	Normal
MMP1	Protein-conditioned media	↑ (20)			
MMP2	Protein-tissue	↑ **(28)**	↑**Grade (28)**	29 Tumor tissues	None
	Protein-tissue	↑ **(27)**	↑**Grade (27)**	88 Tumor tissues	
	Protein-tissue	↑ **(25)**	↑**Grade, lymph node, invasion (25)**	50 Tumor tissues	
	Protein-tissue	↑ **(26)**	↑**Grade (26)**	38 Tumor tissues	20 Normal tissues, 39 hyperplastic tissues
	Protein-tissue	↑ **(24)**	↓**OS (24)**	112 Tumor tissues	
	Protein-tissue	↑ **(23)**	↓**RFS, DSS (23)**	266 Tumor tissues	
	Protein-tissue	↑ **(22)**	↑**Invasion (22)**	42 Tumor tissues	
	Protein-tissue	↑ **(21)**	↑**Grade, invasion (21)**	37 Tumor tissues	7 Normal tissues
MMP7	Protein-tissue	↑ **(31)**	↑**Stage, metastasis (31)**	53 Tumor tissues	30 Noncarcinoma, remote from tumor
	Protein-tissue	↑ **(30)**	↑**Grade, ↓DF-interval (30)**	196 Tumor tissues	
	Protein-tissue	↑ **(26)**	↑**Lymph node (26)**	38 Tumor tissues	20 Normal tissues, 39 hyperplastic tissues
	cDNA microarray	↑ (29)	16 Nonendometrioid, 19 endometrioid	7 Normal tissues	
MMP8	Protein-tissue	↑ (31)	53 Tumor tissues	30 Noncarcinoma, remote from tumor	
MMP9	Protein-tissue	↑ (31)	3 Tumor tissues	30 Noncarcinoma, remote from tumor	
	Protein-tissue	↑ **(28)**	↑**Grade, invasion (28)**	29 Tumor tissues	
	Protein-tissue	↑ **(27)**	↑**Grade, stage (27)**	88 Tumor tissues	
	Protein-tissue	↑ (26)	38 Tumor tissues	20 Normal tissues, 39 hyperplastic tissues	
	Protein-endometrial flushings	↑ (34)	11 Endometrial cancer flushings	32 Noncarcinoma flushings	
	mRNA-tissue	↑ (33)	9 Tumor tissues	20 Noncarcinoma and hyperplasia	
	Protein-tissue	↑ (32)	28 Tumor tissues	15 Normal tissues	
	Protein-tissue	↑ **(22)**	↑**Invasion (22)**	42 Tumor tissues	
	Protein-tissue	↑ **(21)**	↑**Grade, invasion (21)**	37 Tumor tissues	7 Normal tissues
MMP11	cDNA microarray	↑ (43)	↑Type 1 vs type 2 (43)	10 Type 1, 11 type 2	
		↑ (42)	↑Type 1 vs type 2 (42)	24 Type 1, 11 type 2	
MMP12	mRNA-tissue	↑ **(35)**	↑**Stage (35)**	61 Tumor tissues	38 Noncarcinoma from patients with benign disease
	Protein-tissue	↑ **(35)**	↑**Grade (35)**	61 Tumor tissues	38 Noncarcinoma from patients with benign disease
	cDNA microarray	↑ (29)	16 Nonendometrioid, 19 endometrioid	7 Normal tissues	
MMP14	Protein-tissue	↑ **(28)**	↑**Invasion (28)**	29 Tumor tissues	
	cDNA microarray	↓ (38)	10 Tumor tissues	4 Noncarcinoma	
MMP26	Protein-tissue	↑ **(39)**	↑**Grade, stage, invasion (39)**	86 Tumor tissues	50 Noncarcinoma from patients with benign disease
	mRNA-tissue	↓ (40)	24 Tumor tissues	36 Normal and 3 hyperplasia	
	Protein-tissue	↓ (40)	24 Tumor tissues	36 Normal and 3 hyperplasia	
TIMP1	Protein-tissue	↑ (31)	53 Tumor tissues	30 Noncarcinoma, remote from tumor	
	Protein-tissue	↑ **(21)**	↑**Grade (21)**	37 Tumor tissues	7 Normal tissues
TIMP2	Protein-tissue	No change (31)	53 Tumor tissues	30 Noncarcinoma, remote from tumor	
	Protein-tissue	↑ (25)	↓Grade, lymph node, invasion (25)	50 Tumor tissues	
	Protein-tissue	↑ (26)	↓Grade, invasion, lymph node (26)	38 Tumor tissues	20 Normal tissues, 39 hyperplastic tissues
	Protein-tissue	↑ (21)	37 Tumor tissues	7 Normal tissues	
TIMP3	Protein-tissue	↑ **(39)**	↑**Grade, stage, invasion (39)**	86 Tumor tissues	50 Noncarcinoma from patients with benign disease
TIMP4	Protein-tissue	↑ **(39)**	↑**Stage, invasion (39)**	86 Tumor tissues	50 Noncarcinoma from patients with benign disease
	mRNA-tissue	↓ (44)		20 Tumor tissues	43 Noncarcinoma from patients with benign disease and hyperplasia

NOTE: Studies that have examined prognostic indicators have been noted in bold if associated with unfavorable outcomes.
Abbreviations: OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; MFS, metastasis-free survival; DSS, disease-free survival; DF, disease-free.

In all reported MMP and TIMP expression studies done in ovarian cancer, an increase in MMP and TIMP mRNA or protein level and an association with poor prognostic factors has generally been observed. The only exception to this is the MMP7 protein, with increased expression reported to be associated with favorable prognostic characteristics in a single study (72). These results are similar to those reported for breast cancer (73) but not for prostate cancer (52, 74).

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Table 4. MMP and TIMP expression in hormone-related cancers and their clinical significance

	Prostate cancer			Breast cancer			Ovarian cancer		
	Protein/mRNA	Expression	Clinical relevance	Protein/mRNA	Expression	Clinical relevance	Protein/mRNA	Expression	Clinical relevance
MMP1	Protein-serum	↑ **(51)**	↑**Metastasis (51)**	Protein-tissue	↑ **(65)**	↑**Node (65)**	Protein-cyst	↑ (121)	
	Protein-tissue	↓ (52)							
MMP2	mRNA-tissue	↓ (54)		mRNA-tissue	↑ (134)		Protein-tissue	↑ **(120)**	↓**DSS (120)**
	mRNA-tissue	↓ (53)		Protein-serum	↑ **(64)**	↑**Tumor size (64)**			
	Protein-tissue	↑ (59)		Protein-serum	↑ (76)				
	Protein-tissue	↑ **(58)**	↑**Grade (58)**	Protein-serum	↑ (67)	↓Node, grade, stage, ↑RFS (67)			
	Protein-tissue	↑ **(57)**	↑**Metastasis (57)**	Protein-serum	↑ **(63)**	↓**DFS and OS (63)**			
	Protein-tissue	↑ **(56)**	↓**DFS (56)**	Protein-serum	↑ **(62)**	↑**Node, stage (62)**			
	Protein-plasma	↑ (55)		Protein-serum	↑ (68)	↓Grade (68)			
				Protein-tissue	↑ **(61)**	↑**Recurrence (61)**			
				Protein-tissue	↑ **(64)**	↑**Tumor size, metastasis, grade (64)**			
MMP3	Protein-plasma	↑ (136)							
	Protein-plasma	↑ (135)							
MMP7	mRNA-tissue	↑ **(74)**	↑**Stage, metastasis, invasion, PSA (74)**	Protein-tissue	↑ (73)	↓Grade (73)	mRNA-tissue	↑ (119)	
	Protein-tissue	↑ **(52)**	↑**Gleason (52)**				Protein-tissue	↑ (72)	↑DRS, RFS, ↓stage, grade (72)
MMP8				Protein-tissue	↑ **(110)**	↓**OS (110)**	Protein-tissue	↑ **(109)**	↑**Grade, stage, poor prognosis (109)**
							Protein-cyst	↑ (121)	
MMP9	mRNA-tissue	↑ (57)		Tissue-mRNA	↑ (133)		Protein-tissue	↑ **(120)**	↓**DSS (120)**
	mRNA-tissue	↑ (54)		Protein-serum	↑ **(66)**	↑**Grade, stage ↓ RFS and OS (66)**			
	Protein-serum	↑ **(58)**	↑**Grade (58)**	Protein-serum	↑ (76)				
	Protein-tissue	↑ **(52)**	↑**Gleason (52)**	Protein-serum	↑ (68)	↓Grade (68)			
	Protein-plasma	↑ (55)		Protein-tissue	↑ **(66)**	↑**Metastasis, grade (66)**			
				Protein-tissue	↑ **(65)**	↑**Tumor size (65)**			
				Protein-tissue	↑ (64)				
				Protein-tissue	↑ (75)				
				Protein-tissue	↑ **(60)**	↓**RFS (60)**			
MMP10	mRNA-tissue	↑ (53)							
MMP11	mRNA-tissue	↓ (54)		mRNA-tissue	↑ **(132)**	↑**Invasion, metastasis, fatality (132)**	mRNA-tissue	↑ **(118)**	↑**Grade, stage (118)**
				mRNA-tissue	↑ **(134)**	↑**Node, grade, ↓RFS (134)**			
				mRNA-tissue	↑ (133)				
				Protein-tissue	↑ **(131)**	↑**Grade, ↓DFS and OS (131)**			
				Protein-tissue	↑ **(130)**	↓**DFS (130)**			
				Protein-tissue	↑ **(129)**	↑**Lymph node, grade ↓survival (129)**			

(*Continued on the following page*)

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Table 4. MMP and TIMP expression in hormone-related cancers and their clinical significance (Cont'd)

	Prostate cancer			Breast cancer			Ovarian cancer		
	Protein/mRNA	Expression	Clinical relevance	Protein/mRNA	Expression	Clinical relevance	Protein/mRNA	Expression	Clinical relevance
MMP13	Protein-plasma	↑ (55)		Protein-tissue	↑ **(128)**	↓**RFS and OS (128)**	Protein-cyst	↑ (121)	
							Protein-ascites	↑ **(117)**	↓**OS (117)**
MMP14	mRNA-tissue	↓ (54)		mRNA-tissue	↑ **(77)**	↓**DFS, OS (77)**	Protein-tissue	↑ **(120)**	↓**DSS (120)**
	Protein-tissue	↑ **(52)**	↑**Gleason (52)**	mRNA-tissue	↑ **(127)**	↑**Stage, grade, metastasis (127)**			
				mRNA-tissue	↑ **(126)**	↓**OS (126)**			
				mRNA-tissue	↑ **(125)**	↑**Metastasis (125)**			
				mRNA-tissue	↑ **(124)**	↑**Stage, grade, metastasis, size (124)**			
				Protein-tissue	↑ **(61)**	↑**Recurrence (61)**			
				Protein-tissue	↑ **(127)**	↑**Stage, grade, metastasis (127)**			
MMP15	mRNA-tissue	↑ **(53)**	↑**Gleason (53)**						
MMP17				Protein-tissue	↑ **(123)**	↑**Metastasis (123)**			
MMP23	mRNA-tissue	↓ (53)							
MMP24	mRNA-tissue	↑ (53)							
MMP25	mRNA-tissue	↑ (53)							
MMP26	mRNA-tissue	↑ **(53)**	↑**Gleason score (53)**				Protein-tissue	↑ **(116)**	↑**Stage (116)**
TIMP1	Protein-serum	↑ (51)		mRNA-tissue	↑ (133)		Protein-serum	↑ (115)	
	Protein-plasma	↑ (136)	↑Stage (136)	mRNA-tissue	↑ (69)	↑MFS and OS (69)	Protein-tissue	↑ (117)	
	Protein-plasma	↑ (135)	↑Stage (135)	Protein-serum	↑ (66)	↓OS (66)			
				Protein-serum	↑ (70)	↓OS (70)			
				Protein-plasma	↑ (71)	↓DFS (71)			
TIMP2	mRNA-tissue	↓ (54)		Protein-serum	↓ (85)		Protein-tissue	↑ (125)	
	Protein-serum	↓ (51)		Protein-tissue	↑ (84)	↑Size, recurrence (84)			
	Protein-tissue	↑ (59)	↑Stage (59)						
TIMP3	mRNA-tissue	↓ (53)	↓Gleason score (53)	Protein-tissue	↓ (122)	↑Grade, ↓DFS (122)	Protein-tissue	↑ (116)	↑Stage (116)
	mRNA-tissue	↓ (54)							
TIMP4	mRNA-tissue	↓ (53)	↓Gleason score (53)				Protein-tissue	↑ (116)	

NOTE: Studies of MMPs that have examined prognostic indicators have been noted in bold if associated with unfavorable outcomes.

Studies investigating the ratio and coexpression of various MMPs to TIMPs have been done in both prostate and breast cancer. As expected, all studies have reported an increase in the MMP-to-TIMP ratio in cancer samples and an association with unfavorable prognostic parameters (54, 74, 75). Regarding enzymatic activity, increased activity of MMP2, MMP7, and MMP9 proteins have been observed in hormone-related cancers and increased activity associated with a more aggressive phenotype (55, 58, 64, 74, 76), consistent with the hypothesized role of these enzymes in cancer progression and invasion. Functional studies using MMP-overexpressing or knockdown cell lines derived from breast (77-80), ovarian (81), and prostate cancer (82, 83) have shown the ability of the MMPs to increase the proliferative and invasive properties of cancer cells and support the suggested role of MMPs in cancer progression.

Overall, 62 of 69 studies assessing MMP expression in relation to prognosis showed increased expression of MMPs associated with poor prognostic features (Tables 3 and 4), and there are actually relatively few instances of inconsistencies in reported expression levels for a given gene/protein:

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Table 5. Summary of MMP and TIMP association studies done in hormone-related cancers

SNP	Disease	Cases	Controls	Association?	Risk estimates (95% CI)	Reference
rs1799750	PrCa	55	43	No	No significant difference	114
MMP1-1607 1G/2G	BrCa	959	952	No	No significant difference	93
	BrCa	**221**	**—**	**Yes, with metastasis and poor prognosis**	**2G2G: HR, 3.1 (1.1-8.7)**	**87**
	BrCa	**270**	**300**	**Yes**	**1G2G/2G2G: OR, 2.58 (1.38-4.91)**	**65**
	BrCa	**135**	**—**	**Yes, with metastasis**	**2G allele frequency higher metastasis patients ($P < 0.001$)**	**89**
	BrCa	86	110	No	No significant difference	97
	OvCa	122	151	No	No significant difference	100
	OvCa	**151**	**—**	**Yes, with poor prognosis**	**2G2G: DFS, 2.1 (1.2-3.8); OS, 1.9 (1.1-3.4)**	**88**
	OvCa	311	387	No	No significant difference	113
	OvCa	**163**	**150**	**Yes**	**2G allele: OvCa 89%, Co 80%, $P = 0.028$**	**86**
rs243865	**BrCa**	**90**	**96**	**Yes**	**CC: OR, 2.15 (1.1-4.1)**	**92**
MMP2 −1306 C/T					**<50 y at diagnosis vs controls CC: OR, 2.66 (1.04-6.96)**	
	BrCa	959	952	No	No significant difference	93
	BrCa	**462**	**509**	**Yes**	**CT/TT: OR, 0.46 (0.34-0.63)**	**91**
	BrCa	**251**	**—**	**Yes, with tumor size in ER− patients**	**TT: smaller tumors ($P = 0.006$)**	**95**
				Yes, with OS in ER− patients	**For ER− tumors, poor survival ($P < 0.001$)**	
	OvCa	246	342	No	No significant difference	94
rs2285053	**OvCa**	**246**	**342**	**Yes**	**TT/CT: 1.0 (reference)**	**94**
MMP2 −735 C/T					**CC: OR, 1.58 (1.12-2.23) Endometrioid OvCa vs other subtypes CC: OR,1.69 (1.03-2.79) >50 y at diagnosis vs controls CC: OR, 1.71 (1.14-2.57)**	
rs3025058	BrCa	959	952	No	No significant difference	93
MMP3 5A/6A	BrCa	500	500	No	No significant difference	102
	BrCa	246	182	No	No significant difference	99
	BrCa	**86**	**110**	**Yes**	**5A5A/5A6A: OR, 1.53 (1.02-2.29, $P = 0.035$)**	**97**
				Yes, with metastatic patients	**5A5A/5A6A: OR, 1.96 (1.16-3.30)** Not metastasized vs controls: no significant difference	
	OvCa	122	151	No	No significant difference	100
	OvCa	118	118	No	No significant difference	101
	OvCa	100	—	No	No significant difference	98
rs11568818	BrCa	1079	1082	No	No significant difference	104

(*Continued on the following page*)

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Table 5. Summary of MMP and TIMP association studies done in hormone-related cancers (Cont'd)

SNP	Disease	Cases	Controls	Association?	Risk estimates (95% CI)	Reference
MMP7 −181 A/G	BrCa	76	320	No	No significant difference	112
	OvCa	**138**	**160**	**Yes**	**AG/GG: OR, 3.53 (1.58-7.89)**	**100**
rs12184413 MMP7	**BrCa**	**2,963**	**2,877**	**Yes**	**TT (CC/CT ref): OR, 0.7 (0.6-0.9) Effect greatest in postmenopausal women: OR, 0.6 (0.4-0.8)**	**104**
rs880197 MMP7	BrCa	2,963	2,877	No	No significant difference	104
rs17098318 MMP7	BrCa	1,079	1,082	No	No significant difference	104
rs11568819 MMP7	BrCa	1,079	1,082	No	No significant difference	104
rs11225307 MMP7	BrCa	1,079	1,082	No	No significant difference	104
rs17352054 MMP7	BrCa	1,079	1,082	No	No significant difference	104
rs495041 MMP7	BrCa	1,079	1,082	No	No significant difference	104
rs10895304 MMP7	BrCa	2,963	2,877	No	No significant difference	104
rs7935378 MMP7	BrCa	1,079	1,082	No	No significant difference	104
rs11225297 MMP7	BrCa	1,079	1,082	No	No significant difference	104
rs11225395 MMP8 −894 C/T	**BrCa**	**140**	**—**	**Yes, improved DFS**	**CT/TT: HR, 0.7 (0.5-0.9, P = 0.02)**	**108**
rs3918242 MMP9 −1562 C/T	**PrCa**	**101**	**106**	**Yes**	**CT/TT: OR, 2.86; P = 0.004**	**106**
				Yes, with high grade patients	**CT/TT: OR, 3.21; P = 0.004**	
				Yes, with advanced diseased patients	**CT/TT: OR, 2.47, P = 0.026**	
	BrCa	959	952	No	No significant difference	93
	BrCa	**270**	**300**	**Yes**	**CT/TT: OR, 2.61 (1.33-4.87)**	**65**
	BrCa	251	—	No	No significant difference	95
	OvCa	138	160	No	No significant difference	100
rs2276109 MMP12 −82 A/G	BrCa	1,129	1,229	No	No significant difference	107
rs652438 MMP12 1082 A/G	**BrCa**	**1,129**	**1,229**	**Yes, with poor prognosis**	**AG/GG: HR, 1.36 (0.92-2.0)**	**107**
rs2252070 MMP13 −105 A/G	BrCa	221	—	No	No significant difference	87
	BrCa	959	952	No	No significant difference	93
rs28381275 MMP21 572 C/T	BrCa	959	952	No	No significant difference	93
TIMP2 −418 G/C	**BrCa**	**462**	**509**	**Yes**	**CC/GC: OR, 0.76 (0.58-0.99)**	**91**
	OvCa	**246**	**342**	No	No significant difference	94
				Suggested association, with endometrioid subtype	**GG: OR, 1.62 (0.94-2.78)**	
rs9619311 TIMP3 −1296 T/C	**BrCa**	**959**	**952**	**Yes**	**CC/TC: OR, 1.25 (1.05-1.50)**	**93**

NOTE: Studies of SNPs that are associated with increased risk or poor prognosis factors are noted in bold. Results from studies with sample sizes larger than 500 subjects are underlined. Unless otherwise stated, the reference is the common homozygote genotype.
Abbreviations: HR, hazard ratio; RR, relative risk.

Differences in direction of expression for transcription versus translational level include MMP2 (53-59) and MMP14 (52, 54) for prostate cancer, and MMP14 (28, 38) and TIMP4 (39, 44) for endometrial cancer; differences observed for levels in serum versus tumor tissue include TIMP2 for prostate cancer (51, 59) and breast cancer (84, 85).

Taken together, the differential expression patterns of MMPs and TIMPs in cancer tissue, their association with

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prognostic factors, and their strong association with functionalpathophysiologic roles in this disease highlight the likelihood that genetic variation in *MMP* genes will be associated with cancer susceptibility and/or progression.

MMP and TIMP SNPs and Other Hormone-Related Cancers

Investigations of polymorphisms in the *MMP* family have primarily focused on those found within the promoters of these genes, which may affect transcription activity through their ability to affect transcription factor binding. A summary of SNP association studies of *MMPs* in breast, prostate, and ovarian cancer is provided in Table 5. We defined small SNP association studies as those with <500 samples, and larger studies as those with >900 samples, to consider the study sample size when interpreting SNP association study results. Results from larger studies (underlined), are considered more reliable. SNPs significantly associated with risk are noted in bold. Significant associations are reported for several SNPs, sometimes in multiple studies across different cancers, with larger studies reporting significant associations for a subset of SNPs. Moreover, most studies assessing prognostic features showed an association with *MMP* SNPs.

MMP1. One of the highly researched SNPs from the *MMP* family is the *MMP1 −16071G/2G* SNP (rs1799750), which results in the creation of an Ets binding site and increases *MMP1* expression (48). The *2G* allele has been reported to be associated with increased expression of the MMP1 protein in a number of cancers, including breast ($P < 0.01$; ref. 65) and ovarian cancer ($P = 0.0038$; ref. 86). Considering that increased MMP1 protein expression has been shown to be correlated with unfavorable prognosis, the *2G* allele or *2G2G* genotype association with poor prognosis among hormone-related cancer patients is consistent (87-89). However, only one small case-control association study for the *−16071G/2G* SNP (86) identified significant differences in allele or genotype frequencies according to cancer status. Taken together, these study results suggest that the *MMP1 −16071/2G* SNP is likely to be associated with cancer progression but may not be associated with predisposition to cancer.

MMP2. The *MMP2 −1306C > T* SNP (rs243865) SNP abolishes an Sp-1 binding site and has been shown to reduce transcriptional activity (90) and result in decreased expression of the MMP2 protein. Accordingly, the *T* allele should be associated with decreased risk of cancer and/or favorable cancer prognosis. Indeed, a strong inverse association with breast cancer predisposition was observed for the *CT* and *TT* genotype (OR, 0.46; 95% CI, 0.34-0.63; ref. 91), supported by results from another very small study (OR, 0.47; 95% CI, 0.24-0.88; ref. 92). However, a large breast cancer case-control study (93) and a small ovarian cancer case-control study (94) of Chinese cases and controls reported no associations. Regarding cancer progression, a small study reported patients homozygous for the *T*-allele to have significantly smaller breast tumors compared with *CT* or *CC* patients, in concordance with previous results (95). After stratification by ER status, a nonsignificant trend for favorable survival for *TT* patients with ER-positive tumors was shown, but poorer survival was observed among the subgroup of ER-negative *TT* patients compared with *CT* or *CC* patients ($P = 0.002$; ref. 95). Another *MMP2* promoter SNP (rs2285053, *MMP2 −735C > T*), which disrupts an Sp-1 binding site to decrease expression of the MMP2 protein (90), was investigated in a small study (94). As expected, the *CT* and *TT* genotypes were reported to be associated with decreased ovarian cancer risk (OR, 0.63; 95% CI, 0.45-0.89; ref. 90).

MMP3. Another widely investigated SNP is the *MMP3 −11715A/6A* SNP (rs3025058). The insertion of an A residue allows for binding of a transcription repressor, thereby reducing MMP3 protein expression (96). A small pilot case-control study of breast cancer patients is consistent with the functional effects of this SNP, reporting the *5A* allele associated with risk (OR, 1.53; 95% CI, 1.02-2.29, $P = 0.035$), particularly among patients with breast cancer metastasis (OR, 1.96; 95% CI, 1.16-3.30; ref. 97). Although other studies of ovarian cancer (98) and breast cancer (99-101) were null, an association with increased lymph node metastases in breast cancer patients was observed among carriers of the *5A5A* genotype, compared with the *5A6A* or *6A6A* genotype ($P = 0.010$; refs. 93, 94, 102). As for *MMP1*, these results suggest that the MMP3 protein may be involved in tumor invasion rather than predisposition.

MMP7. A functional SNP in the *MMP7* promoter, *MMP7 −181A > G* (rs11568818), affects interaction of nuclear binding proteins, with the minor allele associated with an increase in MMP7 protein expression (103). An increased risk of ovarian cancer was reported for patients carrying the *G* allele ($P = 0.002$; ref. 94). A large two-stage study evaluating 11 *MMP7* SNPs in breast cancer did not find a significant association for this SNP, although increased risk was suggested among premenopausal women (OR, 2.4; 95% CI, 0.5-12.5, $P = 0.61$; ref. 104). Of the remaining SNPs investigated in this study, only a single SNP was associated with risk in the final pooled analysis, a decreased risk of breast cancer associated with the *TT* genotype of the rs12184413 SNP located 3′ downstream of *MMP7*. This result is supported by functional studies showing decreased protein binding for the T allele using luciferase and electrophoretic mobility shift assays (104). Interestingly, the rs112184413 SNP is flanked by a highly conserved region, indicating that these novel findings should be investigated further. No association studies to date have examined the relationship of *MMP7* SNPs with cancer prognosis, despite previously reported associations between MMP7 production and prognosis of both ovarian and breast cancers (72, 73).

MMP9. A polymorphism in the promoter of *MMP9 −1562C > T* (rs3918242) has been reported to result in a loss of binding of a nuclear protein and an increase in transcriptional activity (105). Accordingly, the *T* allele was found to be associated with prostate cancer development and the poor prognostic characteristics high-grade tumor and advanced disease (106). Similarly, the *T* allele was significantly associated with 2.6-fold increased risk of breast cancer (65), and the *TT* genotype was associated with a nonsignificant 1.9-fold risk of breast cancer in a larger study (93).

Other MMP SNPs. Regarding the remaining *MMP* SNPs, large association studies done in breast cancer for

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MMP12 (rs2276109, *–82A > G*) and *MMP21* (rs28381275, *572C > T*) were null (93, 107) as were association studies of both risk and prognosis in breast cancer for an *MMP13* SNP (rs2252070, *–105A > G*; refs. 87, 93). A small study of an *MMP8* promoter SNP (*C > T*, rs11225395) found to alter MMP8 transcription, with the *T*-allele associated with increased promoter activity, found the *T*-allele to confer a reduced risk of breast cancer metastasis (108). Considering that increased expression of the MMP8 protein in breast and ovarian cancer has been associated with poor prognostic parameters (109, 110), the SNP association results is surprising and may reflect the small size of the SNP study. A nonsignificant poorer overall survival (hazard ratio, 1.36; 95% CI, 0.92-2.00), but not disease risk, was observed with the *MMP12 1082A > G* SNP (rs652438) in a large breast cancer study (107). This SNP is located within the coding region of the hemopexin domain responsible for MMP12 activity and results in an amino acid change from asparagine to serine, although its functional importance remains unknown.

TIMPs. There have been limited studies of SNPs harbored by *TIMPs* for hormone-related cancers. The variant allele of the *TIMP2 –418G > C* SNP, which abolishes Sp-1 binding (111), was found in a moderate-sized study to be associated with a decrease in breast cancer risk (91), which is surprising given the *C* allele would be expected to result in decreased TIMP2 expression. However, as previously discussed, it is difficult to make conclusions from TIMP expression given that it is the MMP-to-TIMP ratio that is of most importance. A nonsignificant association of the *GG* genotype was reported for endometrioid ovarian cancer (OR, 1.62; 95% CI, 0.94-2.78; ref. 94), an effect in the same direction as previously reported for breast cancer. Finally, a single *TIMP3* SNP (rs9619311, *–1296T > C*) has also been found to be associated with increased risk in breast cancer (93). This SNP is predicted using *in silico* methods to change transcription factor binding sites, although the sites that were affected were not reported and the function of this SNP has not been tested experimentally (93).

In summary, *MMP* and *TIMP* SNP analyses in cancer fall short of conclusive, and, for the most part, studies involved small sample numbers and single SNPs. At least some large studies of proven functional SNPs report associations with cancer predisposition and numerous studies report associations with cancer prognosis.

Conclusion

Proteases are important factors in the etiology and progression of many cancers. There is substantial evidence associating *MMP* gene expression with hormone-related cancers, including endometrial cancer. The functions of this protease family have been implicated in cancer processes, most notably ECM degradation, and the aberrant expression of many members have been correlated to patient clinical parameters and disease outcomes in many studies. Expression levels of the MMPs at both the mRNA and protein levels are affected by the introduction or loss of transcription binding sites by SNPs. A role for such SNPs in disease predisposition, and particularly in disease prognosis, is also indicated by significant associations reported for some studies of hormone-dependent cancers. It seems likely that such SNPs would be associated with susceptibility and/or prognosis of endometrial cancer; however, only two association studies have investigated *MMP* SNPs in this disease. Investigation of SNPs in the *TIMP* genes would be a necessary complement for any study of *MMP* SNPs, given the evidence that the MMP-to-TIMP ratio plays a role in defining overall MMP activity. In addition, such a pathway-based approach would also open avenues for downstream analysis of gene-gene interactions. A more comprehensive analysis of *MMP* and *TIMP* SNPs is thus required, and given the coverage by existing GWAS platforms, a candidate gene approach is justified.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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The Use of Predictive or Prognostic Genetic Biomarkers in Endometrial and Other Hormone-Related Cancers: Justification for Extensive Candidate Gene Single Nucleotide Polymorphism Studies of the Matrix Metalloproteinase Family and their Inhibitors

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