Molecular Human Reproduction Vol.10, No.10 pp. 713–717, 2004
Advance Access publication August 6, 2004 doi:10.1093/molehr/gah095

Glutathione S-transferase M1*null genotype but not myeloperoxidase promoter G–463A polymorphism is associated with higher susceptibility to endometriosis

Yao-Yuan Hsieh[1,4], Chi-Chen Chang[1], Fuu-Jen Tsai[2], Cheng-Chieh Lin[3], Jiun-Ming Chen[2] and Chang-Hai Tsai[2,5]

[1]Department of Obstetrics and Gynecology, [2]Department of Pediatrics and Medical Genetics, [3]Department of Family Medicine, China Medical University Hospital, Taichung, and [4]Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan

[5]To whom correspondence should be addressed at: Department of Pediatrics and Medical Genetics, China Medical University Hospital, No.2 Yuh-Der Road, Taichung, Taiwan. E-mail: d0704@www.cmuh.org.tw

Glutathione S-transferase M1 (GSTM1), one member of the GST family, is responsible for metabolism of xenobiotics and carcinogens. Myeloperoxidase (MPO) plays an important role in the oxidation and activation of carcinogens and nitric oxide. Allelic variants of GSTM1 and MPO gene polymorphisms might impair detoxification function and increase the susceptibility to endometriosis. We aimed to investigate if these polymorphisms are useful markers for predicting endometriosis susceptibility. Women were divided into two groups: (i) endometriosis (n = 150); (ii) non-endometriosis (n = 159). Polymorphisms for GSTM1 and MPO were amplified by polymerase chain reaction and detected by electrophoresis after restriction digestion. The relative frequencies of the GSTM1*wild (+/+, +/0)/null (0/0) genotypes and MPO–463*G/A gene polymorphisms between both groups were compared. The distribution of GSTM1 polymorphisms was significantly different between the two groups. Proportions of GSTM1*wild/null alleles in both groups were: (i) 36.7/63.3%; (ii) 95/5% (P = 0.001). In contrast, MPO–463 genotypes were not significantly different between the two groups. Proportions of MPO*A homozygote/heterozygote/G homozygote in both groups were: (i) 2.7/17.4/79.9% and (ii) 1.9/17/81.1% ($P >$ 0.05). We conclude that the GSTM1*null genotype is associated with a higher risk of endometriosis development. MPO–463*G/A gene polymorphism is not related to the susceptibility of endometriosis.

Key words: endometriosis/gene polymorphism/glutathione S-transferase (GSTM1)/myeloperoxidase (MPO)

Introduction

Endometriosis, a common polygenic/multifactorial disease, might be caused by an interaction between multiple genes as well as the environment (Bischoff and Simpson, 2000). Endometriosis displays features similar to malignancy, including local invasion and aggressive spread to distant organs. Tumor suppressor genes play a role in the regulation of cell growth and prevention of carcinogenesis. The altered tumor suppressor genes might be related to the development of endometriosis. Genetic alterations have been identified in endometriotic lesions, which might contribute to their initiation and progression (Jiang *et al.*, 1998). It is logical to suspect that somatic genetic factors might contribute to the development of endometriosis (Treloar *et al.*, 1999).

The glutathione S-transferases (GSTs) are a family of enzymes responsible for the metabolism of xenobiotics and carcinogens. GSTM1, one member of the GST family, was formerly termed GST1 or GST class 'mu' (Mannervik *et al.*, 1992). GSTM1 is critical in the detoxification of the oxidative stress product during ovulation (Baxter *et al.*, 2001). Failure to detoxify these products may result in rapid accumulation of genetic damage and increase susceptibility to epithelial ovarian cancer (Baxter *et al.*, 2001). Endometriosis is characterized by cyclical degeneration and chronic inflammation, which will result in the production of reactive oxygen species and other toxins. Because of the detoxification properties of the GST enzymes, it is logical to suspect the role of GSTM1-related gene in endometriosis patients.

Many gene polymorphisms have been reported to be associated with endometriosis, including GSTM1 gene polymorphism (Baranova *et al.*, 1997, 1999; Arvanitis *et al.*, 2003). The GSTM1 gene is located on chromosome 1p13 (Zhong *et al.*, 1992). GSTM1 gene deletions might influence an individual's enzymatic function, impair their detoxification system and further increase the risk when exposed to carcinogens and toxic chemicals (Seidegard *et al.*, 1990). An elevated frequency of the inactive GSTM1 gene has been reported in endometriosis patients (Baranova *et al.*, 1997, 1999). Baranova *et al.* (1999) observed a significant excess of the GSTM null genotype among women with endometriosis.

Myeloperoxidase (MPO), a 150 kDa hemoprotein secreted by activated macrophages, is involved in many pathological processes (Rutgers *et al.*, 2003). MPO plays an important role in the oxidative pathway of neutrophils and monocytes by producing hypochlorous acid (HOCl). MPO functions not only antimicrobiotically, but also acts as a metabolic enzyme with many other substrates, which produces some reactive intermediates and consumes hydrogen peroxide (Schabath *et al.*, 2000). Moreover, the MPO–HOCl system has been shown to oxidize low-density lipoprotein (LDL) (Winterbourn *et al.*,

Table I. The primer sequences and PCR conditions for GSTM1 and MPO−463 G/A gene polymorphisms

Polymorphisms	Primer sequences (5′ → 3′)*	PCR conditions (°C/s)			Restriction enzyme digestion	Allele	DNA fragment size (bp)
		Denaturing	Annealing	Extension			
GSTM1	F-AGCTGCCCTACTTGATTGATGG R-CTGGGGACACTCACAAATTCTG	93/30	62/30	72/20	–	Wild-type[a] Null type	271 –
CYP1A1[b]	F-GCATTGAGCTTGCATGCTTG R-TAGGAGTCTTGTCTCATGCCT	93/30	62/30	72/20	–	Wild-type	583
MPO−463	F-CGGTATAGGCACACAATGGTGA R-GCAATGGTTCAAGCGATTCTTC	95/30	60/30	72/45	*Aci* I (37°C/30 min)	A allele G allele	289 + 61 169 + 120 + 61

* F and R indicate forward and reverse primers.
[a]Homozygotes or heterozygotes could not be specified.
[b]Concomitant PCR with GSTM1 gene for internal controls.

2000), activate carcinogens (Schabath *et al.*, 2000) and reduce nitric oxide (NO) bioavailability (Eiserich *et al.*, 1998). A functional MPO promoter polymorphism, −463G/A, has been associated with incidence or severity of inflammatory diseases, including atherosclerosis, Alzheimer's disease, and some cancers (Kumar *et al.*, 2004). MPO−463G/A polymorphism could modify the binding site for the SP1 transcription factor and significantly decrease the expression of MPO as well as the severity of leukemia (Piedrafita *et al.*, 1996).

It is generally accepted that heritable genetic factors might contribute to the development of endometriosis. Unlike mutations, polymorphisms are not directly linked to a certain disease. However, they are useful tools in the study of multifactorial disorders (Anderson *et al.*, 1994). In our previous surveys, we observed the correlation of endometriosis and some gene polymorphisms, including p53 (Chang *et al.*, 2002) and androgen receptor (Hsieh *et al.*, 2001). Based on these surveys, we tried to assess the risk of endometriosis associated with GSTM1 and MPO gene polymorphism. We aimed to evaluate whether these polymorphisms are attractive markers for endometriosis susceptibility. To our knowledge, this report is the largest survey for GSTM1 polymorphisms in endometriosis. Furthermore, it is the first report about the MPO polymorphism in endometriosis.

Materials and methods

Pre-menopausal Taiwanese women with surgically diagnosed endometriosis and non-endometriosis were included. All patients were divided into two groups: (i) endometriosis stage III/IV ($n = 150$); (ii) non-endometriosis ($n = 159$). All individuals with endometriosis accepted laparoscopy or laparotomy management and were confirmed pathologically. All patients had normal blood pressure without obvious cardiovascular diseases. There were non-significant differences between both groups in age, weight and height. All women had consented to peripheral blood sampling for genotype analyses. The studies were approved by the ethical committee and institutional review board of the China Medical University Hospital. Informed consents were signed by all women who donated their blood.

The GSTM1*wild/null and MPO−463*G/A gene polymorphisms were determined according to previously described methods (Baxter *et al.*, 2001;

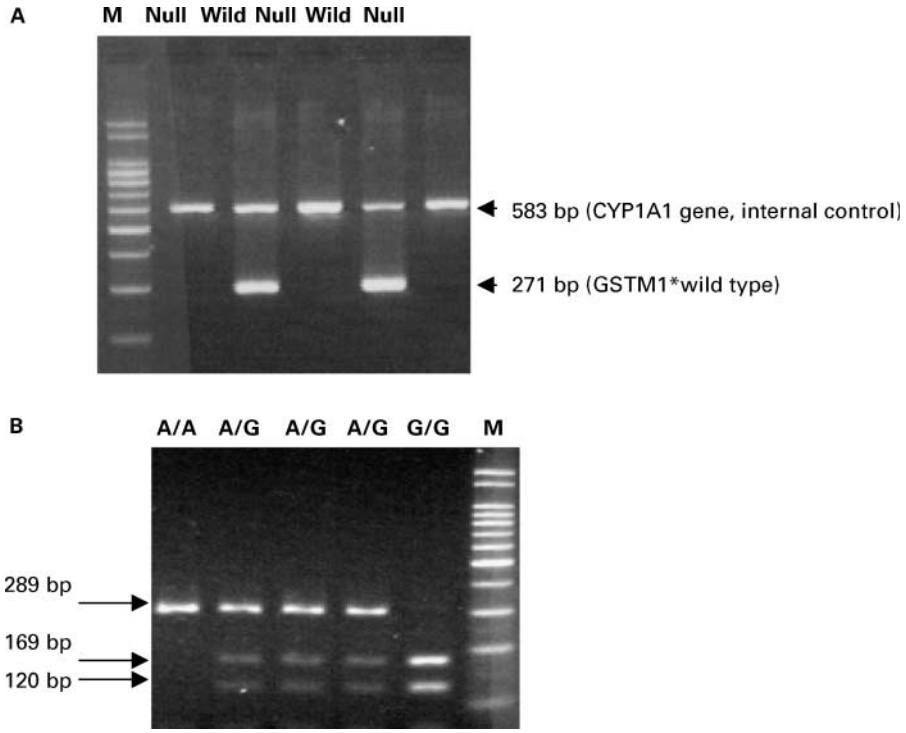

Figure 1. Genotyping of (**A**) GSTM1*wild/null and (**B**) MPO−463*G/A gene polymorphisms (M: Marker).

Table II. Distributions of GSTM1 genotypes in women with and without endometriosis

GSTM1 genotype	Endometriosis Group (i) $n = 150$ (%)	Non-endometriosis Group (ii) $n = 159$ (%)	*P*-value
Wild-type (+/+ homozygote; + /0 heterozygote)	55 (36.7)	151 (95)	0.001
Null type (0/0 homozygote)	95 (63.3)	8 (5)	

Reynolds *et al.*, 2002). The genomic DNA was prepared from peripheral blood leukocytes by use of a genomic DNA isolation kit (Blossom, Taipei, Taiwan). A total of 50 ng genomic DNA was mixed with 20 pmol of each polymerase chain reaction (PCR) primer in a total volume of 25 μl containing 10 mM Tris–HCL pH 8.3, 50 mM potassium chloride, 2.0 mM magnesium chloride, 0.2 mM each deoxyribonucleotide triphosphate and 1 U DNA polymerase (Amplitag; Perkin-Elmer, Foster City, CA). A total of two gene polymorphisms were surveyed, including GSTM1*wild/null and MPO–463*G/A. The SNP information for the genes involved was obtained via the NCBI website (http://www.ncbi.nlm.nih.gov/LocusLink/).

The PCR primer sequences and condition of each primer are listed in Table I. To confirm the successful amplification, an internal control was included in the PCR reaction of GSTM1. It consisted of a 583 bp amplicon from the CYP1A1 gene (Nicholl *et al.*, 1999). The PCR amplification was performed in a programmable thermal cycler GenAmp PCR system 2400 (Perkin Elmer Applied Biosystems, Foster City, CA). After PCR amplification, the individual gene polymorphisms were analyzed after restriction digestion (New England Biolabs Inc., Beverly, MA). The base pairs for their wild-type, null type and SNP type are listed in Table I.

The PCR products were mixed together and 10 μl of this solution was loaded into 3% agarose gel containing ethidium bromide for electrophoresis. Each allele was recognized according to its size (Figure 1). Genotypes and allelic frequencies for GSTM1 and MPO gene polymorphisms in both groups were compared. Correlation of the GSTM1 and MPO genotype and endometriosis was evaluated. Allelic frequencies are expressed as a percentage of the total number of alleles. The SAS system with χ^2 and Fisher's exact tests were utilized for statistical analyses. A *P*-value of <0.05 was considered statistically significant.

Results

Proportions of the GSTM1 genotype in both groups were significantly different. The GSTM1 null genotype frequency was strikingly high among the individuals with endometriosis. Most normal individuals appear to have the wild genotype of GSTM1 (Table II). Proportions of the wild/null alleles of the GSTM1 gene in the two groups were: group (i) 36.7/63.3% and group (ii) 95/5%, respectively (Table II, $P = 0.001$). Null type (0/0 homozygote) of GSTM1 gene is associated with higher susceptibility of endometriosis. Wild-type (+/ + homozygote or + /− heterozygote) of GSTM1 gene is associated with lower risk of endometriosis development.

In contrast, genotype proportions of different MPO polymorphisms in both groups were not significantly different (Table III). Most individuals in both groups appear to have the G-related genotype and G allele. Proportions of MPO*A homozygote/heterozygote/G homozygote in the two groups were: group (i) 2.7/17.4/79.9% and group (ii) 1.9/17/81.1%, respectively (Table III). Furthermore, A and G allele frequencies in the two groups were: (i) 11.4/88.6% and (ii) 10.4/89.6%, respectively (Table III).

Table III. Genotypes and allelic frequencies for MPO*–463 gene polymorphism in women with and without endometriosis

Genotype	Endometriosis Group (i) $n = 150$ (%)	Non-endometriosis Group (ii) $n = 159$ (%)	*P*-value*
A/A	4 (2.7)	3 (1.9)	NS
A/G	26 (17.4)	27 (17)	
G/G	119 (79.9)	129 (81.1)	
Allele frequencies			
A	34 (11.4)	33 (10.4)	NS
G	264 (88.6)	285 (89.6)	

NS, not significant.
**P*-value was calculated by χ^2 tests.

Discussion

Numerous chronic disorders, such as endometriosis, osteoporosis, hypertension, diabetes and asthma, have been attributed to genetic susceptibility. Endometriosis, a multifactorial disease, involves complex interactions between hormones and cytokines activation, immunoinflammatory processes and genetic factors (Vigano *et al.*, 1998). Recent experimental studies indicated that dioxin may be involved in the pathogenesis of endometriosis (Gibbons, 1993). Dioxin is widely present in the environment; most people absorb traces of dioxin by exposure to pesticides in their diet. These toxins might also contribute to an imbalance of sex hormones or alter growth factors and the immune response (Mayani *et al.*, 1997).

GSTM1 functions both as a detoxification enzyme and an intracellular drug- and hormone-binding protein (Chasseaud, 1979). GSTM1 catalyzes the detoxification of genotoxic chemicals, including the products of chronic oxidative stress such as cytotoxic lipid and DNA species (Hayes *et al.*, 1995). GSTM1 enhances the conjugation of glutathione with several alkylating agents (Dulik *et al.*, 1990). The GSTM1 gene is specific for certain carcinogens, including trans-stilbene oxide and a metabolite of benzopyrene contained in smoke fumes (Seidegard *et al.*, 1990). The GSTM1 gene might influence the related isoenzyme expression as well as the host susceptibility to lung cancer among smokers (Seidegard *et al.*, 1990). Impaired GSTM1 function might result in increased risk to DNA damage and malignant transformation. The null condition of GSTM1 gene (0/0 genotype) represented an expanded deletion (~ 10 kb) of the gene, which might impair the further production of mRNA and protein (Seidegard *et al.*, 1988).

GSTM1 gene deletion (0/0 genotype) is a useful marker for the early detection of many diseases, including endometriosis, ovarian cancer (Baxter *et al.*, 2001), cystic fibrosis (Baranov *et al.*, 1996), bladder (Brockmoller *et al.*, 1984), lung (Nakachi *et al.*, 1993) and stomach cancers (Harada *et al.*, 1992). Baranova *et al.* (1999) reported a highly significant excess of the GSTM1 null genotype in women with endometriosis versus controls (76.9 versus 45.8%). Recently, Arvanitis *et al.* (2003) also demonstrated that the GSTM1 null deletion adds to this risk of endometriosis. In contrast, Baxter *et al.* (2001) demonstrated that the GSTM1 null allele is not an endometriosis susceptibility allele; however, it may predispose endometriotic lesions to malignant transformation to endometrioid and clear cell ovarian cancer. Some investigators demonstrated the non-association between the individual diseases with GSTM1, including cancers of the ovary (Cehisselbauer *et al.*, 1992), bladder (Brockmoller *et al.*, 1994), lung (Brockmoller *et al.*, 1993) and stomach (Harada *et al.*, 1992). These discrepancies might be due to different illness classification, racial and disease variation.

In this study, we observed that the genotype distribution for GSTM1 gene polymorphism was significantly different between the individuals with and without endometriosis. The null genotype is related with higher susceptibility of endometriosis; whereas the wild-type is related with lower risk of endometriosis development. Our data strongly suggest that the lack of GSTM1 gene products might substantially contribute to the pathogenesis of endometriosis. However, our finding only suggested their connection as well as possibility. The related scientific proof for the underlying mechanisms is still warranted.

In this survey, the GSTM1 null genotype frequency (63.3%) in individuals with endometriosis was significantly lower than that observed by Baranova *et al.* (1997, 1999; 75–86%) and higher than that observed by Arvanitis *et al.* (2003; 58.5%). The discrepancies between Baranova *et al.* (1997, 1999) and Arvanitis *et al.* (2003) suggested racial differences within the French and Greek populations, even though they are both Caucasian populations. However, the conclusions of Baranova *et al.* (1997, 1999) were based on fewer case numbers (<100). Our study of 150 endometriosis cases and 159 controls provides the stronger support for the claim that the GSTM1 null allele is a predisposing factor for endometriosis. Furthermore, our finding is the first indication that GSTM1 gene deficiency predisposes to endometriosis in an Asian population.

However, we also observed a different distribution of null GSTM1 genotype between normal Asians and Caucasians (Board, 1990; Groppi *et al.*, 1991; Harada *et al.*, 1992). The fluctuation of GSTM1 deficiency found in most Caucasians is in the range of 40–52% (Baranov *et al.*, 1996; Arvanitis *et al.*, 2003). In contrast, in our study we found the null genotype in 5% of the normal controls. The discrepancy might be mainly due to the ethnic differences between Asians and Caucasians. Furthermore, whether the GSTM1 0/0 genotype in different populations results from identical deletion or from other alterations of the GSTM1 gene remains unknown.

MPO is a 150 kDa hemoprotein stored exclusively in the azurophilic granules of monocytes and neutrophils (PMNs). MPO produces not only the strong oxidant bleach (hypochlorous acid) from hydrogen peroxide and chloride ions but also oxidizes LDL into a macrophage high-uptake form, inactivates protease inhibitors, and consumes nitric oxide (Rutgers *et al.*, 2003). These may contribute to endothelial dysfunction and damage (Rutgers *et al.*, 2003). Additionally, MPO produces a strong oxidant and procarcinogens such as benzo(a)pyrene and aromatic amine intermediates (Hazen *et al.*, 1996). MPO may act as a cocarcinogen by generating free radicals and activating aromatic amines and carcinogens (Josephy, 1996).

The combination of genetic factors involved in oxidative stress response with environmental carcinogens may play an important role in carcinogenesis (Hung *et al.*, 2004). MPO*–463G/A gene polymorphism may be related to numerous diseases, including lung cancer (Chevrier *et al.*, 2003), atherosclerosis (Makela *et al.*, 2003), coronary artery disease (Makela *et al.*, 2004), bladder carcinogenesis (Hung *et al.*, 2004), sarcoidosis (Rothkrantz-Kos *et al.*, 2003), Alzheimer's disease (Leininger-Muller *et al.*, 2003), hepatoblastoma (Pakakasama *et al.*, 2003), among others. MPO–463**A genotype/allele are related to lower MPO expression (Chevrier *et al.*, 2003) as well as reduced risk of individual cancers (London *et al.*, 1993). The 'A' allele is a protective factor with regard to the risk of hepatoblastoma (Pakakasama *et al.*, 2003). Furthermore, the MPO expression might be regulated by an estrogen-dependent mechanism involving the −463G/A promoter polymorphism (Kumar *et al.*, 2004). The effects of hormone replacement therapy (HRT) on atherosclerosis progression in subjects with the GG genotype seem to be especially beneficial compared with controls with the same genotype but without HRT (Makela *et al.*, 2003).

However, some investigators indicated the non-association between MPO–463G/A polymorphism with individual diseases, including lung cancer (Dally *et al.*, 2003), vasculitis (Fiebeler *et al.*, 2004), sarcoidosis (Rothkrantz-Kos *et al.*, 2003), and others. The functional MPO promoter polymorphism is not related to the disease severity in the sarcoidosis population (Rothkrantz-Kos *et al.*, 2003). In this study, we observed the non-association between the MPO promoter −463 gene polymorphisms and the susceptibility to endometriosis. We also observed the frequency of the A allele (10–11%) in our population was significantly lower than the reported frequencies in Caucasian populations [23.4% (London *et al.*, 1997), 25.7% (Le Marchand *et al.*, 2000), 21.2% (Cascorbi *et al.*, 2000), 29.8% (Schabath *et al.*, 2000) and 30.6% (Misra *et al.*, 2001)]. These discrepancies might be due to racial variation.

In conclusion, an association between endometriosis and GSTM1 gene polymorphism exists. The GSTM1 null genotype is related to an increased susceptibility to endometriosis. The GSTM1 gene polymorphism likely contributes to the pathogenesis of endometriosis. It also suggests the defects in carcinogen detoxification may be involved in the pathogenesis of endometriosis. In contrast, the MPO*–463G/A gene polymorphisms are not related to the susceptibility of endometriosis. Although the real roles of GSTM1 and MPO gene polymorphism have not yet been clarified, these polymorphisms deserve more attention to realize their roles upon endometriosis development. This study could be extended to investigate whether and how the detoxification affects the endometriosis formation. Furthermore, after the clarification of these issues, GSTM1 gene polymorphism may become a useful marker to predict the future development of endometriosis and to permit early therapeutic intervention in women at high risk for endometriosis.

References

Anderson TI, Heimdal KR, Skrede M, Tveit K, Berg K and Borresen AL (1994) Oestrogen receptore (ESR) polymorphisms and breast cancer susceptibility. Hum Genet 94,665–670.

Arvanitis DA, Koumantakis GE, Goumenou AG, Matalliotakis IM, Koumantakis EE and Spandidos DA (2003) CYP1A1, CYP19, and GSTM1 polymorphisms increase the risk of endometriosis. Fertil Steril 79,702–709.

Baranov VS, Ivaschenko T, Bakay B et al. (1996) Proportion of the GSTM1 0/0 genotype in some Slavic populations and its correlation with cystic fibrosis and some multifactorial diseases. Hum Genet 97,516–520.

Baranova H, Bothorishvilli R, Canis M, Albuisson E, Perriot S, Glowaczower E, Bruhat MA, Baranov V and Malet P (1997) Glutathione S-transferase M1 gene polymorphism and susceptibility to endometriosis in a French population. Mol Hum Reprod 3,775–780.

Baranova H, Canis M, Ivaschenko T, Albuisson E, Bothorishvilli R, Baranov V, Malet P and Bruhat MA (1999) Possible involvement of arylamine N-acetyltransferase 2, glutathione S-transferases M1 and T1 genes in the development of endometriosis. Mol Hum Reprod 5,636–641.

Baxter SW, Thomas EJ and Campbell IG (2001) GSTM1 null polymorphism and susceptibility to endometriosis and ovarian cancer. Carcinogenesis 22, 63–65.

Bischoff FZ and Simpson JL (2000) Heritability and molecular genetic studies of endometriosis. Hum Reprod Update 6,37–44.

Board PG (1990) Biochemical genetics of glutathione S-transferase in man. Am J Hum genet 33,36–43.

Brockmoller J, Kerb R, Drakoulis N, Niz M and Webb G (1993) genotype and phenotype of glutathione S-transferase class mu and kappa in lung cancer patients and controls. Cancer Res 53,1004–1009.

Brockmoller J, Kerb R, Drakoulis N, Staffeldt B and Roots I (1994) Glutathione S-transferase M1 and its variants A and B as host factors of bladder cancer susceptibility, a case-control study. Cancer Res 54, 4103–4111.

Cascorbi I, Henning S, Brockmoller J, Gephart J, Meisel C, Muller JM, Loddenkemper R and Roots I (2000) Substantially reduced risk of cancer

of the aerodigestive tract in subjects with variant −463A of the myeloperoxidase gene. Cancer Res 60,644–649.

Cehisselbauer JC, Hogan WM, Buctow KH and Twe KD (1992) Heterogeneity of glutathione S-transferase enzyme and gene expression in ovarian carcinoma. Pharmacogenetics 2,63–72.

Chang CC, Hsieh YY, Tsai FJ, Tsai CH, Tsai HD and Lin CC (2002) The proline form of p53 codon 72 polymorphism is associated with endometriosis. Fertil Steril 77,43–45.

Chasseaud LF (1979) The role of glutathione S-transferase in the metabolism of chemical carcinogenes and other electrophilic agents. Adv Cancer Res 29,175–274.

Chevrier I, Stucker I, Houllier AM, Cenee S, Beaune P, Laurent-Puig P and Loriot MA (2003) Myeloperoxidase, new polymorphisms and relation with lung cancer risk. Pharmacogenetics 13,729–739.

Dally H, Bartsch H and Risch A (2003) The myeloperoxidase (−463)G → A polymorphism does not decrease lung cancer susceptibility in Caucasians. Cancer Epidemiol Biomarkers Prev 12,683.

Dulik DM, Colvin OM and Fenselau C (1990) Characterization of glutathione conjugates of chlorambucil by fast atom bombardment and thermospray liquid chromatography/mass spectrometry. Biomed Environ Mass Spectrom 19,248–252.

Eiserich JP, Hristova M, Cross CE, Jones AD, Freeman BA, Halliwell B and van der Vliet A (1998) Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. Nature 391, 393–397.

Fiebeler A, Borgmann S, Woywodt A, Haller H and Haubitz M (2004) No association of G-463A myeloperoxidase gene polymorphism with MPO-ANCA-associated vasculitis. Nephrol Dial Transplant 19,969–971.

Gibbons A (1993) Dioxin tied to endometriosis. Science 362,1373.

Groppi A, Coutelle CH, Fleury B, Iron A, Begueret J and Couzigou P (1991) Glutathione S-transferase class mu in French alcoholic cirrhotic patients. Hum Genet 87,628–630.

Harada S, Misawa S, Nakamura T, Tanaka N, Ueno E and Nozoe M (1992) Detection of GST1 gene deletion by the polymerase chain reaction and its possible correlation with stomach cancer in Japanese. Hum Genet 90, 62–64.

Hayes JD and Strange RC (1995) Potential contribution of the glutathione S-transferase supergene family to resistance to oxidative stress. Free Radic Res 22,193–207.

Hazen SL, Hsu FF, Duffin K and Heinecke JW (1996) Molecular chlorine generated by the myeloperoxidase hydrogen peroxide chloride system of phagocytes converts low density lipoprotein cholesterol into a family of chlorinated sterols. J Biol Chem 271,23080–23088.

Hsieh YY, Chang CC, Tsai FJ, Wu JY, Tsai CC and Tsai HD (2001) Androgen receptor trinucleotide polymorphism in endometriosis. Fertil Steril 76,412–413.

Hung RJ, Boffetta P, Brennan P, Malaveille C, Gelatti U, Placidi D, Carta A, Hautefeuille A and Porru S (2004) Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental exposures and bladder cancer risk. Carcinogenesis.

Jiang X, Morland SJ, Hitchocock A, Thomas EJ and Campbell IG (1998) Allelotyping of endometriosis with adjacent ovarian carcinoma reveals evidence of a common lineage. Cancer Res 58,1707–1712.

Josephy PD (1996) The role of peroxidase-catalyzed activation of aromatic amines in breast cancer. Mutagenesis 11,3–7.

Kumar AP, Piedrafita FJ and Reynolds WF (2004) Peroxisome proliferator-activated receptor gamma ligands regulate myeloperoxidase expression in macrophages by an estrogen-dependent mechanism involving the −463GA promoter polymorphism. J Biol Chem 279,8300–8315.

Le Marchand L, Seifried A, Lum A and Wilkens LR (2000) Association of the myeloperoxidase −463G → A polymorphism with lung cancer risk. Cancer Epidemiol Biomarkers Prev 9,181–184.

Leininger-Muller B, Hoy A, Herbeth B, Pfister M, Serot JM, Stavljenic-Rukavina M, Massana L, Passmore P, Siest G and Visvikis S (2003) Myeloperoxidase G–463A polymorphism and Alzheimer's disease in the ApoEurope study. Neurosci Lett 349,95–98.

London SJ, Lehman TA and Taylor JA (1997) Myeloperoxidase genetic polymorphism and lung cancer risk. Cancer Res 57,5001–5003.

Makela R, Dastidar P, Jokela H, Saarela M, Punnonen R and Lehtimaki T (2003) Effect of long-term hormone replacement therapy on atherosclerosis progression in postmenopausal women relates to myeloperoxidase promoter polymorphism. J Clin Endocrinol Metab 88,3823–3828.

Makela R, Laaksonen R, Janatuinen T, Vesalainen R, Nuutila P, Jaakkola O, Knuuti J and Lehtimaki T (2004) Myeloperoxidase gene variation and coronary flow reserve in young healthy men. J Biomed Sci 11,59–64.

Mannervik B, Awasthi YC, Board PG, Hayes JD, Di Ilio C, Ketterer B, Listowsky I, Morgenstern R, Muramatsu M, Pearson WR et al. (1992) Nomenclature for human glutathione transferases. Biochem J 282,305–306.

Mayani A, Barel S, Soback S and Almagor M (1997) Dioxin concentrations in women with endometriosis. Hum Reprod 12,373–375.

Misra RR, Tangrea JA, Virtamo J, Ratnasinghe D, Andersen MR, Barrett M, Taylor PR and Albanes D (2001) Variation in the promoter region of the myeloperoxidase gene is not directly related to lung cancer risk among male smokers in Finland. Cancer Lett 164,161–167.

Nakachi K, Imai K, Hayashi S and Kwasjiri K (1993) Polymorphism of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Res 53,2994–2999.

Nicholl DJ, Bennett P, Hiller L, Bonifati V, Vanacore N, Fabbrini G, Marconi R, Colosimo C, Lamberti P, Stocchi F et al. (1999) A study of five candidate genes in Parkinson's disease and related neurodegenerative disorders. European Study Group on Atypical Parkinsonism. Neurology 53,1415–1421.

Pakakasama S, Chen TT, Frawley W, Muller C, Douglass EC and Tomlinson GE (2003) Myeloperoxidase promotor polymorphism and risk of hepatoblastoma. Int J Cancer 106,205–207.

Piedrafita FJ, Molander RB, Vansant G, Orlova EA, Pfahl M and Reynolds WF (1996) An Alu element in the myeloperoxidase promoter contains a composite SP1-thyroid hormone-retinoic acid response element. J Biol Chem 271,14412–14420.

Reynolds WF, Stegeman CA and Tervaert JW (2002) –463 G/A myeloperoxidase promoter polymorphism is associated with clinical manifestations and the course of disease in MPO-ANCA-associated vasculitis. Clin Immunol 103,154–160.

Rothkrantz-Kos S, Drent M, Rutgers A, Heeringa P, De Vries J, van Dieijen-Visser MP and Cohen Tervaert JW (2003) Relationship between myeloperoxidase promotor polymorphism and disease severity in sarcoidosis. Eur J Intern Med 14,296–301.

Rutgers A, Heeringa P, Giesen JE, Theunissen RT, Jacobs H and Tervaert JW (2003) Neutrophil myeloperoxidase activity and the influence of two single-nucleotide promoter polymorphisms. Br J Haematol 123,536–538.

Rutgers A, Heeringa P and Tervaert JW (2003) The role of myeloperoxidase in the pathogenesis of systemic vasculitis. Clin Exp Rheumatol 21, S55–S63.

Schabath MB, Spitz MR, Zhang X, Delclos GL and Wu X (2000) Genetic variants of myeloperoxidase and lung cancer risk. Carcinogenesis 21, 1163–1166.

Seidegard J, Pero RW, Markowits MM, Roush G, Miller DG and Beatti EJ (1990) Isozyme of glutathione transferase (class Mu) as a marker for the susceptibility to lung cancer, a follow up study. Carcinogenesis 11,33–36.

Seidegard J, Vorachek WR, Pero RW and Pearson WR (1988) Hereditary differences in the expression of the human glutathione transferase active on trans-stilbene oxide are due to a gene deletion. Proc Natl Acad Sci USA 85,7293–7297.

Treloar SA, O'Connor DT, O'Connor VM and Martin NG (1999) Genetic influences on endometriosis in an Australian twin sample. Fertil Steril 71, 701–710.

Vigano P, Gaffuri B, Somigliana E, Busacca M, Di Blasio AM and Vignali M (1998) Expression of intercellular adhesion molecule (ICAM)-1 mRNA and protein is enhanced in endometriosis versus endometrial stromal cells in culture. Mol Hum Reprod 4,1150–1156.

Winterbourn CC, Vissers MC and Kettle AJ (2000) Myeloperoxidase. Current Opinion in Hematology 7,53–58.

Zhong S, Wolf CR and Spurr NK (1992) Chromosomal assignment and linkage analysis of the human glutathione S-transferase mu gene (GSTM1) using intron specific polymerase chain reaciton. Hum Genet 90,435–439.

Submitted on March 27, 2004; revised on June 2, 2004; accepted on July 11, 2004