Myeloperoxidase (MPO) \(-463G\rightarrow A\) Reduces MPO Activity and DNA Adduct Levels in Bronchoalveolar Lavages of Smokers

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Abstract

The myeloperoxidase (MPO) \(-463G\rightarrow A\) genetic polymorphism is associated with a reduced risk for lung cancer, but the underlying mechanism is not yet elucidated. Therefore, the impact of this polymorphism on MPO activity and lipophilic DNA adducts was studied in respectively bronchoalveolar lavage (BAL) fluid and cells, from 106 smoking Caucasian lung patients. MPO activity was determined spectrophotometrically, aromatic DNA adducts by \(^{32}\)P-postlabeling and MPO genotypes by RFLP analysis. Frequencies of MPO \(-463AA\) (13%), MPO \(-463AG\) (36%), and MPO \(-463GG\) (51%) were in line with earlier observations. MPO activity/neutrophil was lower in MPO \(-463AA\) (median 0.04 pU/cell) than in MPO \(-463AG\) (median 0.07 pU/cell) and MPO \(-463GG\) (median 0.14 pU/cell); \(P = 0.059\) individuals. DNA adducts in BAL cells were measured in 11 MPO \(-463AA\) subjects and equal numbers of MPO \(-463AG\) and MPO \(-463GG\) subjects matched for smoking, age, gender, and clinical diagnosis. DNA adduct levels in MPO \(-463AA\) individuals (median 0.62 adducts/\(10^8\) nucleotides) were lower than in MPO \(-463AG\) (median 1.51 adducts/\(10^8\) nucleotides) and MPO \(-463GG\) (median 3.26 adducts/\(10^8\) nucleotides; \(P = 0.003\)) subjects. Overall, no significant correlation was observed between amount of inhaled tar/day and DNA adduct levels. However, correlations improved considerably on grouping according to the MPO genotype; MPO \(-463AA\) subjects were the least responsive (\(R^2 = 0.73\), slope = 0.4, \(P = 0.01\)) followed by MPO \(-463AG\) subjects (\(R^2 = 0.70\), slope = 1.3, \(P = 0.01\)) and MPO \(-463GG\) patients (\(R^2 = 0.67\), slope = 2.8, \(P = 0.02\)). These data demonstrate that MPO \(-463AA/AG\) genotypes are associated with (a) reduced MPO activity in BAL fluid and (b) reduced smoking-related DNA adduct levels in BAL cells in a gene-dose manner. These data provide a plausible biological explanation for the reduced risk for lung cancer as observed in MPO \(-463AA/AG\) compared with MPO \(-463GG\) subjects. (Cancer Epidemiol Biomarkers Prev 2004; 13(5):828–33)

Introduction

Cancer is a multifactorial disease, which is the result of an interaction between inherited genetic factors and genetic changes induced by environmental exposures. A clear example of this is the relation between the exposure to carcinogenic compounds through tobacco smoking and the development of lung cancer. In the United States, up to 90% of all lung cancer deaths are caused by smoking. Although long-term smokers are at a considerable higher risk of getting lung cancer, it is still not clear why certain smokers are more susceptible than others. One possible explanation could be found in the genetic variation in carcinogen-metabolizing enzymes that may cause individual differences in the ultimate biological effective dose of tobacco carcinogens.

Tobacco smoke contains a large number of chemical compounds including carcinogenic substances like polycyclic aromatic hydrocarbons (PAHs; Ref. 1). PAHs exert their carcinogenic activity after metabolic activation to form reactive metabolites that can bind covalently to DNA (DNA adducts). If not repaired, these DNA adducts may lead to mutations in oncogenes (e.g., \(ras\)) and tumor suppressor genes (e.g., \(p53\)), causing transformation of a normal cell into a cancer cell. Direct evidence for the relevance of PAH-DNA adducts comes from the observation that benzo(a)pyrene (BaP)-derived DNA adducts in vitro are directly related to \(p53\) mutational hotspots found in human lung cancer tissue (2). Furthermore, recently, a prospective molecular epidemiological study showed that levels of aromatic DNA adducts were strongly associated with lung cancer outcome (3). As such, measurements of DNA adduct levels are generally accepted as relevant intermediate end points in the carcinogenic process.

Smoking causes a local inflammatory response in the lung that is accompanied by the influx of...
polymorphonuclear neutrophils (PMN; Ref. 4). Activated neutrophils release myeloperoxidase (MPO), which catalyzes the conversion of $H_2O_2$ into the bactericidal compound hypochlorous acid (5). However, in addition to the direct damaging effects of the oxidants generated by MPO, the enzyme is involved in the activation of PAHs, such as BaP, into their reactive metabolites (e.g., BaP-diol-epoxide; Refs. 6, 7). This process may be especially relevant for tissues and/or organs, including the lung, where the levels of cytochrome P450 are relatively low. Previously, we showed that BaP-diol-epoxide DNA adduct levels were significantly increased in lung epithelial cells after coinubation with BaP and stimulated PMN, implicating a role for neutrophil-derived MPO (8). A frequently occurring polymorphism in the promoter region of MPO in the Caucasian population is a $-463G\rightarrow A$ transition that is associated with reduced gene expression (9). The distribution of this $-463G\rightarrow A$ polymorphism among healthy Caucasians shows that 2–10% of the population is associated with lung cancer; persons carrying the $A$ allele, 31–43% heterozygous for $G$, and 49–64% is homozygous for the wild-type $G$ allele (10, 11). Several case-control studies showed that this MPO polymorphism is closely associated with lung cancer; persons carrying the mutant AA genotype have a 40–70% reduced risk for lung cancer (10–18). Although not all studies could confirm these results (19, 20), the protective effect was predominantly observed in Caucasian smokers. Interestingly, in a recent study, the protective effect was strongest for small cell lung cancer, which is a type of lung cancer strongly associated with cigarette smoking (11).

Although it is obvious to speculate on a role of the MPO polymorphism in PAH-mediated lung carcinogenesis, the underlying mechanisms are still not clear. Previously, we observed a strong relationship between MPO polymorphism and PAH-DNA adducts in skin of atopic dermatitis patients (21). Because PAH-DNA adducts are closely associated with lung carcinogenesis and MPO is implicated in the activation of PAHs, the present study has aimed to further investigate the relation among MPO genotype, MPO activity, and DNA adduct levels in bronchoalveolar lavage (BAL) cells derived from smokers.

Materials and Methods

Study Design. A population of 106 Caucasian smokers with nonmalignant lung disease consisting of 69 males and 37 females, aged 25–65 years, mean 48.9 ± 13.1 years, was recruited from the Department of Respiratory Medicine at the University Hospital Maastricht. For diagnostic reasons, BAL on the suspicion of either pneumonia or interstitial lung disease (such as sarcoidosis, idiopathic pulmonary fibrosis, and extrinsic allergic alveolitis) was performed. Informed consent was obtained from all patients. Bronchoscopy with BAL and the subsequent laboratory workup were as described previously (22). Differential cell counts were made on May-Grünewald Giemsa-stained cytocentrifuged preparations. After centrifugation, the cellular fraction and the cell-free BAL fluid were stored at −70°C. DNA was extracted for subsequent MPO genotyping and aromatic DNA adduct analysis. The cell-free BAL fluid was used to determine MPO activity. To study the effect of MPO genotypes on DNA adduct levels, 11 MPO-AA individuals from the study population were matched with 11 MPO-AG and 11 MPO-GG individuals regarding age, smoking, gender, and diagnosis. These 33 participants were interviewed about their smoking behavior including the number of cigarettes smoked/day, types of cigarettes consumed, and period they had been smoking. Based on these data, total cigarette consumption was expressed in smoking years and pack years. Tar exposure was calculated from the tar content of the specific brand and the number of cigarettes smoked.

MPO Activity in BAL Fluid. MPO packaged in neutrophils will have no effect on PAH metabolism because MPO must be released extracellularly during the oxidative burst of neutrophils (6–8). Therefore, extracellular MPO activity was measured to assess the role of MPO in PAH metabolism and DNA adduct formation. MPO activity in cell-free BAL fluid was measured as described by Klebanoff (23). The assay solution was prepared freshly by mixing 107.6 ml $H_2O_2$, 12 ml 0.1 M sodium phosphate buffer, 0.192 ml Guaiacol, and 0.4 ml 0.1 M $H_2O_2$. Cell-free BAL fluid (100 μl) was added to a 1 cm light path cuvette containing 400 μl of the assay solution and mixed rapidly. The generation of tetraguaiacol was measured spectrophotometrically at 470 nm (Beckman DU-64) and the change of absorbance/min was calculated. The activity of MPO in units (1 unit is the amount of enzyme that consumes 1 μmol $H_2O_2$/min) was calculated with the formula: $U/ml = (\Delta A \times V_t \times 4) / (E \times t \times V_s)$ in which $V_t$ = total volume (ml), $V_s$ = sample volume (ml), $A$ = delta absorption, and $t$ = measuring time.

MPO Genotyping. The detection of the MPO $-463G\rightarrow A$ polymorphism was performed by RFLP after PCR as described by London et al. (12). A 350-bp DNA fragment was amplified using forward primer MPOF ($5’$-CGG TAT AGG CAC ACA ATG GTG AG) and reverse primer MPOR ($5’$-CGA ATG CAA CGG ATT CT C). PCR was performed and 10 μl of the PCR product were digested with the restriction enzyme AcI. After electrophoresis, the digested products resulted in banding patterns indicative for the genotypes: 169, 120, and 289 bp fragments for the heterozygous type ($463GG$); 289 and 61 bp fragments for the homozygous wild-type ($463GG$); 289, 169, 120, and 61 bp fragments for the heterozygous type ($463AG$); and 289 and 61 bp fragments for the homozygous mutant type ($463AA$). GSTM1 genotypes were determined as described by Brockmöller et al. (24).

$^{32}$P-Postlabeling of Aromatic DNA Adducts. DNA was isolated with the QIAamp DNA blood midi kits according to the instructions of the manufacturer (Qiagen, Inc., Hilden, Germany). The DNA was dissolved in 2 mM Tris (pH 7.4) and concentration and purity of the DNA were determined spectrophotometrically at 230, 260, and 280 nm. DNA concentrations were adjusted to 2 μg/μl. The $^{32}$P-postlabeling assay for lipophilic DNA adducts was performed as described earlier (25). Briefly, DNA (10 μg) was digested into deoxyribonucleoside 3’-monophosphates by incubation with micrococal endonuclease and spleen phosphodiesterase for 3 h at

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37°C. Half of the digest was treated with nuclease P1 for 40 min at 37°C and the reaction was terminated by adding 0.5 M Tris. The other half of the digest was used for determination of the amount of normal nucleotides in the analysis. Labeling was performed using [γ-32P]-ATP (50 μCi) in the presence of T4 polynucleotide kinase for 30 min at 37°C, and subsequently, TLC was performed using polyethyleneimine cellulose sheets (Macherey Nagel, Düren, Germany) using the following solvent systems: D1 1 M NaH2PO4 (pH 6.5); D2 8.5 M urea, 5.3 M Nagel, Düren, Germany) using polyethyleneimine cellulose sheets (Macherey Nagel, Düren, Germany) using the following solvent systems: D1 1 M NaH2PO4 (pH 6.5); D2 8.5 M urea, 5.3 M lithium formate (pH 3.5); D3 1.2 M lithium chloride, 0.5 M Tris, 8.5 M urea (pH 8.0); D4 1.7 M NaH2PO4 (pH 6.0). Nucleotide quantification was performed by diluting 1 μl aliquot of the DNA digest 1200 times. Normal nucleotides were labeled under the same conditions as the modified nucleotides mentioned above and subsequently one-dimensionally chromatographed on polyethyleneimine cellulose sheet (Merck, Darmstadt, Germany) using a solvent system of 0.12 M NaH2PO4 (pH 6.8). For calibration, two standards of [3H]BaP-diol-epoxide modified DNA with known modification levels (1 per 107 and 108 nucleotides) were run in parallel in each experiment. Quantification was performed using a PhosphorImager (Molecular Dynamics, Sunnyvale, CA) with a detection limit of 1 adduct/108 nucleotides.

Statistics. Data were not normally distributed and therefore presented as median and range. The nonparametric Jonckheere-Terpstra test was applied to assess statistical significance among the subjects carrying the wild-type (MPO-463AA), -463AG, and -463GG genotypes. Linear regression was used to investigate the relationship between DNA adduct levels and the amount of inhaled tar/day for the entire study population and for individuals grouped according to the MPO genetic polymorphism. Multiple linear regression was used to assess the additional impact of other factors (age, gender, diagnosed disease, genotypes, or cigarette consumption). P < 0.05 was considered statistically significant.

Results

MPO Genotypes and MPO Activity. Among the 106 Caucasian smokers with pulmonary diseases, 54 (51%) of the subjects carried the wild-type (MPO-463GG), 38 (36%) of the subjects carried one A allele (MPO-463AG), and 14 (13%) were homozygote mutant (MPO-463AA). The observed MPO genotype distribution was in Hardy-Weinberg equilibrium (P > 0.05, tested by χ2). The MPO activity was measured in duplicate in BAL fluid samples from 95 subjects. Duplicate measurements showed a mean difference of 7%. The median MPO activity in BAL fluid samples of individuals with the MPO-463AA genotype (0.19 mU/ml, range 0–52.26; n = 13) did not significantly differ from the median activity found in BAL fluid of subjects with the MPO-463AG genotype (0.41 mU/ml, range 0–137.09; n = 35) or subjects with the MPO-463GG genotype (0.34 mU/ml, range 0–257.60; n = 47; P = 0.86; Table 1). However, the MPO activity is mainly determined by the number of neutrophils (PMN) as evidenced by the positive correlation between MPO activity and number of PMN in the BAL fluid samples ($R^2 = 0.303, P = 0.01$). Therefore, we adjusted the MPO activity for the number of PMN to see whether genotype-related differences could be found. MPO-463AA displayed the lowest median MPO activity/neutrophil (median 0.04 pU/cell, range 0–0.17) compared with MPO-463AG (0.07, range 0–10.66) and MPO-463GG (0.14, range 0–80.47), reaching borderline significance (P = 0.059; Table 1).

MPO Genotype and DNA Adducts in BAL Cells. To study the effect of MPO genotypes on DNA adduct levels, 11 MPO-AA individuals were matched with 11 MPO-AG and 11 MPO-GG individuals regarding age, smoking, gender, and diagnosis. An overview of the characteristics of the study population is presented in Table 2.

The chromatograms of postlabeled DNA adducts showed a diagonal radioactive zone, which is typical for smoking-induced DNA damage. Diagonal radioactive zones were quantitated giving total aromatic DNA adduct levels. However, this correlation was not significant ($P < 0.05$).

Table 1. MPO activities (median and range) measured in BAL fluid samples according to MPO–463 genotypes

<table>
<thead>
<tr>
<th>MPO activity</th>
<th>MPO–463AA (n = 13)</th>
<th>MPO–463AG (n = 35)</th>
<th>MPO–463GG (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mU/ml BAL fluid supernatants</td>
<td>0.19 (0–52.26)*</td>
<td>0.41 (0–137.09)*</td>
<td>0.34 (0–257.60)*</td>
</tr>
<tr>
<td>pU/PMN</td>
<td>0.04 (0–0.17)</td>
<td>0.07 (0–10.66)</td>
<td>0.14 (0–80.47)</td>
</tr>
</tbody>
</table>

* Zero means lower than detection limit (~0.05 mU/ml). Numbers of samples with MPO activity lower than the detection limit were 2, 11, and 7 for AA, AG, and GG, respectively.

$P = 0.059$. 

Cancer Epidemiol Biomarkers Prev 2004;13(5). May 2004
according to their MPO genotypes, the correlations became very strong and statistically significant. For patients carrying the MPO/C0 463AA genotype, a $R^2 = 0.727$ was observed ($P = 0.011$); for MPO/C0 463AG, $R^2 = 0.697$ ($P = 0.017$); and for MPO/C0 463GG, $R^2 = 0.671$ ($P = 0.024$; Fig. 2). The dose response was clearly modulated by the genotypes in which the GG group was the most responsive group having a slope of 2.8 followed by AG with a slope of 1.3 and then by the least responsive group (MPO/C0 463AA) having the lowest slope of 0.4. No significant association was found between MPO activity/PMN in BAL fluid from homozygous mutant individuals (MPO/C0 463AA) was more than three times lower than in homozygous wild-type subjects (MPO/C0 463GG). Similarly, DNA adduct levels were even 5-fold lower in MPO/C0 463AA subjects than in homozygous wild-type subjects, providing a possible biological explanation for the epidemiological studies showing a relation between MPO/C0 463 genotype and lung cancer risk.

Because DNA adduct levels represent the net effect of PAH exposure, absorption, activation, detoxification, and DNA repair, they can be seen as an integrative measurement of the biological effective PAH dose, which is closely linked with lung carcinogenesis (1, 2). Although DNA adducts were not determined in target cells for lung carcinogenesis, we and others have demonstrated that similar smoking-related DNA adduct types can be found in both whole lung tissue samples and BAL cells, including BaP DNA adducts (26–30). Moreover, previous studies in smokers showed that BAL cells contained about 4-fold more lipophilic DNA adducts than circulating blood lymphocytes and that DNA adduct levels

Table 2. Characteristics of the study population in which DNA adducts were studied

<table>
<thead>
<tr>
<th>MPO/C0 463AA</th>
<th>MPO/C0 463AG</th>
<th>MPO/C0 463GG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Male/female</td>
<td>5/6</td>
<td>5/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.9 ± 12.2</td>
<td>45.6 ± 9.3</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>21.3 ± 12.3</td>
<td>19.8 ± 5.8</td>
</tr>
<tr>
<td>Tar (mg)/day</td>
<td>314.2 ± 191.5</td>
<td>291.8 ± 148.2</td>
</tr>
<tr>
<td>Smoking years</td>
<td>23.2 ± 12.0</td>
<td>21.3 ± 13.2</td>
</tr>
<tr>
<td>Package years</td>
<td>23.4 ± 14.5</td>
<td>21.5 ± 15.4</td>
</tr>
<tr>
<td>BAL fluid differential cell counts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Neutrophils</td>
<td>33.1 ± 34.6</td>
<td>33.1 ± 40.9</td>
</tr>
<tr>
<td>% Lymphocytes</td>
<td>10.1 ± 13.3</td>
<td>8.7 ± 14.2</td>
</tr>
<tr>
<td>% Alveolar macrophages</td>
<td>54.6 ± 35.2</td>
<td>53.5 ± 38.2</td>
</tr>
<tr>
<td>% Eosinophils</td>
<td>1.5 ± 1.9</td>
<td>4.3 ± 9.4</td>
</tr>
<tr>
<td>% Mast cells</td>
<td>0.3 ± 0.6</td>
<td>0.1 ± 0.2</td>
</tr>
</tbody>
</table>

Discussion

In the present study, we showed that the MPO/C0 463GA and −463AA polymorphisms were associated with reduced MPO activities and with lower aromatic DNA adduct formations in cells obtained by BAL from smokers with lung diseases. We have found that MPO activity/PMN in BAL fluid from homozygous mutant individuals (MPO/C0 463AA) was more than three times lower than in homozygous wild-type subjects (MPO/C0 463GG). Similarly, DNA adduct levels were even 5-fold lower in MPO/C0 463AA subjects than in homozygous wild-type subjects, providing a possible biological explanation for the epidemiological studies showing a relation between MPO/C0 463 genotype and lung cancer risk.

Figure 1. DNA adduct levels in BAL cells according to the MPO/C0 463G−A genetic polymorphism ($P = 0.003$). Smoking behavior did not differ between the groups (see Table 2).

Figure 2. Correlations between dose (tar inhaled/day) and DNA adduct levels in cells obtained by BAL. Subgroups were composed according to the MPO genotype: (■) MPO/C0 463GG, (●) MPO/C0 463AG, and (○) MPO/C0 463AA.
in BAL cells were closely related to smoking behavior (31–33). As such, the sensitivity of BAL cells toward adduct inducing agents in cigarette smoke and their easy accessibility make them a very suitable source of DNA to determine the biologically effective dose of carcinogens in lung tissue.

Genetic polymorphisms in carcinogen-metabolizing enzymes may at least partly explain the observed large interindividual differences in DNA adduct formation. Indeed, currently, there is accumulating evidence that genetic polymorphisms in carcinogen activating and detoxifying enzymes are associated with the formation of PAH-DNA adducts (reviewed in Ref. 34). BaP activation mainly occurs through the sequential oxidation into BaP-7,8-oxide, BaP-7,8-diol, and, ultimately, BaP-diol-epoxide, a process in which various genes are involved, including an array of CYP450 genes (35). However, the epoxidation of BaP-7,8-diol to BaP-diol-epoxide is also mediated through the action of MPO (7). This MPO-mediated activation of PAHs may be especially relevant in organs such as the lung that contain relatively low levels of CYP450. As a result, a polymorphism in the MPO gene could have deleterious effects on the ultimate DNA adduct level in lung tissue, especially in case of inflammatory diseases that are characterized by a high PMN influx into the lung. In the present study, we hypothesized that a reduced MPO activity in mutant (MPO-463AA/AG) subjects would decrease the formation of reactive metabolites on exposure to PAH. As a result, DNA adduct levels were expected to be lower in these individuals as compared with those with the wild-type (MPO-463GG) genotype. Indeed, we showed that the mutant subjects (MPO-463AA/AG) had 5-fold lower DNA adduct levels than the carriers of the wild-type gene. This is in line with previous studies in which we determined adduct formation in skin biopsies from patients suffering from atopic dermatitis, who were therapeutically treated with PAH-containing coal-tar ointments (21). DNA adduct levels in the skin of coal-tar treated patients were similarly reduced (5–6-fold) in MPO-463AA/AG individuals as compared with the MPO-463GG genotype. Importantly, in the present study, we have additionally investigated phenotypical effects of the MPO polymorphism, as we assessed MPO activity in the cell-free BAL fluid. Because MPO activity in BAL fluid is derived from activated neutrophils, MPO activity was expressed per neutrophil to correct for interindividual differences in BAL cellularity. We found that MPO activity/neutrophil in the mutant subjects (MPO-463AA/AG) was lower as compared with the wild-type carriers, albeit of borderline significance.

Other important genetically polymorphic enzymes involved in the detoxification of PAH metabolites are the μ and π class glutathione S-transferases. However, a recent study showed that GSTM1 and GSTP1 genotypes were no significant determinants of aromatic DNA adduct levels in BAL fluid samples from active smokers (33). In the present study, we also investigated the GSTM1 polymorphism and found that persons lacking the GSTM1 had higher levels of DNA adducts than those carrying the gene. However, this effect was completely lost when the MPO genotype was taken into account. Recent in vitro studies showed that GSTP1 activity could potently be inhibited by the MPO product hypochlorous acid (36). Apart from its role in the activation of BaP, these observations indicate that MPO may also modulate DNA adduct formation by inhibition of detoxification processes.

The overall lipophilic DNA adduct levels in the present study were positively associated with the number of cigarettes smoked/day and the amount of tar daily consumed, although correlation coefficients were low and of borderline significance. These correlations improved substantially within the groups carrying the respective MPO genotypes, indicating that the MPO genotype is an important modulator of the dose-response relationship (Fig. 2). Most of the studies investigating gene and xenobiotic-dose interactions are dealing with acute exposures to (single) compounds in relative high doses in medical settings. In addition, the study by Rojas et al. (21) involved short-term treatment of dermatitis patients with therapeutic coal-tar containing extremely high doses of PAH. The present study, however, is an illustration of how genetic polymorphisms may modulate the metabolism and adverse reactions of a chronic and rather low-dose exposure to a complex mixture of compounds.

In conclusion, this study provides an example of a gene-environment interaction in which DNA adduct formation at a given dose of environmental carcinogens (e.g., PAHs in cigarette smoke) is profoundly affected by the individual genetic background. Specifically, the results showed that, in comparison with wild-type MPO-463GG genotypes, the mutant MPO-463AA/AG genotypes are associated with (a) reduced MPO activity in BAL fluid and (b) reduced smoking-related DNA adduct levels in human lung-derived cells. Moreover, because DNA adduct formation is closely linked to carcinogenesis, these data provide a plausible biological explanation for the association between the MPO-463AA/AG genotypes and the decreased risk for lung cancer.

References


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