

Point/CounterpointPoint: Myeloperoxidase  $^{-463}G \rightarrow A$  Polymorphism and Lung Cancer Risk<sup>1</sup>

Anne Feyler, Anu Voho, Christine Bouchardy,  
Katja Kuokkanen, Pierre Dayer, Ari Hirvonen, and  
Simone Benhamou<sup>2</sup>

Unit of Cancer Epidemiology (INSERM U521), Gustave-Roussy Institute, 94805 Villejuif, France [A. F., S. B.]; Department of Industrial Hygiene and Toxicology, Finnish Institute of Occupational Health, 00250 Helsinki, Finland [A. V., K. K., A. H.]; Geneva Cancer Registry, 1205 Geneva, Switzerland [C. B.]; and Division of Clinical Pharmacology, University Hospital, 1211 Geneva, Switzerland [P. D.]

**Abstract**

Myeloperoxidase (MPO) is released from neutrophils in lung tissue in response to exposure to various pulmonary insults, including tobacco smoking. This enzyme is involved in the activation of an intermediate metabolite of benzo(a)pyrene to the highly reactive benzo(a)pyrene diol epoxide. A  $^{-463}G \rightarrow A$  polymorphism in the promoter region of the *MPO* gene has been identified. The *A* allele is associated with a decreased transcriptional activity attributable to the disruption of a SP1-binding site. We therefore examined whether carriers of the *A* allele may be at reduced risk of lung cancer in a case-control study of 150 cases and 172 control individuals, all Caucasian smokers. Relative to subjects with the *MPO* *G/G* genotype, a significant decreased risk of lung cancer was found for carriers of the *G/A* genotype [odds ratio (OR) = 0.5, 95% confidence interval (CI): 0.29–0.88]. A reduction in risk, although not statistically significant, was also observed for subjects with the *A/A* genotype (OR = 0.84, 95% CI: 0.31–2.32). The lung cancer risk for carriers of one or two copies of the *A* allele was 0.55 (95% CI: 0.33–0.93). Because of the low prevalence of the *A/A* genotype, we also performed a meta-analysis of 2686 lung cancer cases and 3325 controls. The summary OR suggested a slight protective effect of the *A/A* genotype (OR = 0.86, 95% CI: 0.67–1.1), but this finding was strongly influenced by the results of a single large study. The meta-analysis restricted to studies comprising a homogeneous set yielded an OR of 0.68 (95% CI: 0.5–0.93). However, because of the heterogeneity in individual study results, additional large case-control studies are warranted to provide a more definitive conclusion.

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<sup>2</sup> To whom requests for reprints should be addressed, at INSERM U521, Institut Gustave-Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France. Phone: (33) 1 42 11 41 39; Fax: (33) 1 42 11 53 15; E-mail: simone.benhamou@igr.fr.

**Introduction**

Several tobacco carcinogens are metabolized via complex enzymatic mechanisms involving both activation and detoxication reactions. Differences in these metabolism pathways are potentially important sources of interindividual susceptibility to cancer development. The MPO<sup>3</sup> enzyme is found in primary granules of neutrophils and monocytes and functions as an oxidative antimicrobial agent by catalyzing the generation of genotoxic hypochlorous acid and other reactive oxygen species (1). MPO is released from neutrophils in lung tissue in response to exposure to various pulmonary insults, including tobacco smoke (2, 3). MPO has been shown to activate an intermediate metabolite of B(a)P, the 7,8 diol B(a)P, to the highly reactive and carcinogenic B(a)P diol epoxide (4) and to enhance the binding of B(a)P diol to lung DNA *in vitro* (5). A  $^{-463}G \rightarrow A$  polymorphism in the promoter region of the *MPO* gene has been identified, and the *A* allele has been associated with a decreased transcriptional activity attributable to the disruption of a SP1-binding site (6). It is therefore conceivable that carriers of the *A* allele may be at reduced risk of lung cancer because of reduced ability to convert B(a)P to carcinogenic B(a)P diol epoxide. To our knowledge, five case-control studies of lung cancer were published previously (7–11), and a protective effect of the *A* allele was suggested in all studies, except one (11).

We have conducted a hospital-based, case-control study in France to investigate the role of several xenobiotic-metabolizing enzymes, including cytochrome P4501A1 (CYP1A1; Ref. 12) and GSTM1 (13), on smoking-related cancers among Caucasian smokers. In this study, we examined whether polymorphism in the *MPO* gene is associated with lung cancer. Because CYP1A1 and GSTM1 are also involved in B(a)P metabolism, we also examined their potential modifying effect on the relationship between *MPO* gene polymorphism and lung cancer.

We also present a meta-analysis to summarize our results along with those from other case-control studies, including >6000 individuals.

**Materials and Methods**

**Study Subjects.** Details of the study population have been published previously (12). In brief, French Caucasian individuals were recruited between 1988 and 1992 in 10 hospitals, of which 9 were located in Paris. Peripheral blood samples were available for 150 lung cancer cases and 172 controls who fulfilled the criteria described below. Cases were all consecutive patients with histologically confirmed incident squamous or small cell lung cancer. The control group, frequency matched on age, sex, and hospital, consisted of all consecutive Caucasian patients without previous or current malignant diseases. The main medical diagnoses in the control population were rheumatological (33%), mainly lumbago and sciatica (71%), infectious and parasitic (10%), respiratory (9%), cardiovascular

<sup>3</sup> The abbreviations used are: MPO, myeloperoxidase; B(a)P, benzo(a)pyrene; OR, odds ratio; CI, confidence interval; GSTM1, glutathione *S*-transferase M1.

(8%), digestive (6%), and traumatologic diseases (6%). The main admission motives were related to general symptoms (7%) for the other categories. All cases and controls had to be regular smokers, defined as individuals having smoked five cigarettes or more (or cigars or pipe) per day for  $\geq 5$  years. They were recruited by seven trained interviewers who enrolled both cases and controls. Subjects completed a questionnaire during a personal interview to collect detailed information on demographic factors, medical history, lifetime tobacco and alcohol use, and occupational exposures. The daily consumption of each type of tobacco smoked was expressed in g/day (1 g for cigarette, 2 g for cigar, and 3 g for pipe; Ref. 14). The average number of grams of tobacco smoked per day was calculated by dividing the cumulative lifetime tobacco consumption by the overall duration of smoking. Lifetime smoking exposure was also expressed in pack-years of smoking (years smoked times the packs of cigarettes per day).

Of the 150 cases, 98 (65%) had squamous cell carcinoma, and 52 (35%) had small cell carcinoma. Individuals were almost all men (93% of cases and 95% of controls). The mean age was slightly higher for cases than for controls (58.4 years versus 55 years;  $P < 0.01$ ). The average daily consumption of tobacco was similar in cases (26.3 g/day) and controls (25.1 g/day), but patients had smoked longer than controls (38 years versus 32.2 years;  $P < 0.0001$ ), and the mean number of pack-years was higher in cases than in controls (48.3 versus 39.7;  $P < 0.01$ ). Cases reported greater occupational exposure to asbestos than controls (19% versus 7%;  $P < 0.001$ ). For arsenic exposure, the figures were 5% for cases and 1% for controls ( $P = 0.12$ ).

**Genotyping Analyses.** Peripheral blood samples were collected in EDTA tubes and stored at  $-20^{\circ}\text{C}$ . Total WBC DNA extraction was performed using standard techniques. Analyses were conducted blindly to case-control status.

The *CYP1A1* and *GSTM1* genotype data have been published earlier (12, 13). The *MPO* genotype was determined essentially as described in Ref. 7. Briefly, a 350-bp PCR product was amplified using forward primer MPOF (5'-CGG TAT AGG CAC ACA ATG GTG AG-3') and reverse primer MPOR (5'-GCA ATG GTT CAA GCG ATT CTT C-3'). Subsequent to PCR, an aliquot was digested with *AclI* restriction enzyme (New England BioLabs, Beverly, MA). The presence of a 289-bp band in gel picture revealed the variant A allele, whereas in the PCR product from the wild-type G allele, this fragment was cut into 169- and 120-bp fragments. In addition to the above fragments, a 61-bp digestion fragment was seen in both cases serving as an internal control for successful enzymatic digestion.

Positive and negative controls were used within each batch of PCR amplification performed unaware of the case-control status. Two independent readers interpreted gel pictures. All samples with ambiguous results, and a random selection of 10% of all samples, were repeated to ensure laboratory quality control.

**Statistical Analyses.** Hardy-Weinberg equilibrium was tested by a goodness of fit  $\chi^2$  test to compare the observed frequencies of G/G, G/A, and A/A genotypes with the expected frequencies in controls.

ORs of lung cancer and 95% CIs in relation to *MPO* genotype were estimated by unconditional logistic regression models (15). All risk estimates were adjusted for age (<50, 50–59, 60–69, and  $\geq 70$  years), sex, and hospital. Multivariate analyses included additional terms for the subject's status (ex-smoker/current smokers), inhalation of tobacco smoke (never-

ever), pack-years of smoking ( $\leq 25$ , 26–45, and  $> 45$ ), and occupational exposures to asbestos (never-/ever) or arsenic (never-/ever), as potential confounders.

Interactions between *MPO* genotypes and smoking-related variables were studied to test the equality of the effect of genotypes across levels of smoking exposure. Because of small numbers of homozygotes for the A allele, the G/A and A/A genotypes were combined in these analyses. The interactive effects were assessed by the likelihood ratio tests to compare the goodness of fit of the models with and without the interaction term, taking into account the above-mentioned adjusting factors. For that purpose, average daily consumption, duration of smoking, and pack-years of smoking were expressed as categorical variables dichotomized at the median in the control population. Similar analyses were conducted to test interactions between *MPO* genotype and the *GSTM1* genotype (homozygous null versus others), the *CYP1A1 MspI* genotype (\*1/\*1 versus others), and the *CYP1A1 Ile-Val* genotype (\*1/\*1 versus others).

**Meta-Analysis.** A search using MEDLINE was conducted to identify studies published before July 2001, using combinations of the key words: lung cancer and MPO. For a given study, we retained the most recent results in the case of more than one publication. When results of a study were stratified by ethnicity, we treated data of each ethnic group as separate studies. A total of 10 case-control studies (Refs. 7–9, 11, and 16; the present study and the study by Xu *et al.*, this issue) were included in a meta-analysis, with a total of 2686 lung cancer cases and 3325 controls.

Crude ORs and their 95% CIs associated with *MPO* genotypes were estimated for each individual study. Meta-analytic techniques that weight the logarithm of the OR of each study by a function of its variance were used to calculate a summary estimate. Both fixed- and random-effects models were used. Results of the latter are presented in case of heterogeneity between studies, defined as Q statistics with  $P < 0.05$  (17).

Meta-analysis based on only published reports will yield biased results if publication bias (tendency for authors to submit or of journals to accept preferentially papers reporting an association over papers reporting no association) is present (18). This bias was assessed using the Egger's test (19).

All analyses were performed using STATA package (version 6.0). Results were considered significant at the two-sided  $P$  of 0.05.

## Results

The distributions of *MPO* genotypes are displayed in Table 1. Genotype frequencies among the controls were in agreement with those predicted under the conditions of Hardy-Weinberg equilibrium ( $P = 0.56$ ). These distributions were similar across the main medical diagnoses (data not shown).

The A allele was relatively common both in cases (allele frequency = 0.21, 95% CI: 0.16–0.25) and controls (allele frequency = 0.26, 95% CI: 0.21–0.31). The frequency of subjects with at least one A allele was lower in cases than in controls (34.7 and 44.2%, respectively,  $P = 0.08$ ).

Relative to subjects with the G/G genotype, a significant decreased risk of lung cancer was found for carriers of the G/A genotype (OR = 0.5, 95% CI: 0.29–0.88; Table 1). A reduction in risk, although not statistically significant, was also observed for subjects with the A/A genotype (OR = 0.84, 95% CI: 0.31–2.32). The lung cancer risk was halved for carriers of one or two A alleles (OR = 0.55, 95% CI: 0.33–0.93); stratification by histology yielded an OR of 0.49 (95% CI: 0.27–0.88) for

Table 1 Distribution of MPO genotype among lung cancer patients and controls and ORs (95% CI) of lung cancer

MPO genotype	Cases		Controls		OR <sup>a</sup>	(95% CI)
	n	(%)	n	(%)		
G/G	98	(65.3)	96	(55.8)	1 <sup>b</sup>	
G/A	42	(28.0)	63	(36.6)	0.50	(0.29–0.88)
A/A	10	(6.7)	13	(7.6)	0.84	(0.31–2.32)
G/A or A/A	52	(34.7)	76	(44.2)	0.55	(0.33–0.93)

<sup>a</sup> Adjusted for sex, age, hospital, smoking, and occupational exposures. Data on smoking are missing for four cases and three controls.

<sup>b</sup> Reference category.

Table 2 ORs (95% CI) of lung cancer in relation to MPO genotype by pack-years of smoking, GSTM1 genotype, and CYP1A1 MspI genotype

	MPO genotype	
	G/G	G/A or A/A
Pack-years of smoking < 35		
OR <sup>a</sup> (95% CI)	1 <sup>b</sup>	0.49 (0.22–1.07)
Cases/controls	33/46	18/40
Pack-years of smoking ≥ 35		
OR <sup>a</sup> (95% CI)	1 <sup>b</sup>	0.57 (0.26–1.12)
Cases/controls	61/47	34/36
GSTM1 positive		
OR <sup>a</sup> (95% CI)	1 <sup>b</sup>	0.46 (0.21–0.99)
Cases/controls	42/46	24/35
GSTM1 null		
OR <sup>a</sup> (95% CI)	1 <sup>b</sup>	0.57 (0.28–1.16)
Cases/controls	52/48	28/41
CYP1A1*1/*1		
OR <sup>a</sup> (95% CI)	1 <sup>b</sup>	0.56 (0.31–1.00)
Cases/controls	79/78	39/58
CYP1A1*1/*2A or *2A/*2A		
OR <sup>a</sup> (95% CI)	1 <sup>b</sup>	0.34 (0.10–1.11)
Cases/controls	15/15	13/18

<sup>a</sup> Adjusted for sex, age, smoking, and occupational exposures. Data on smoking are missing for four cases and three controls.

<sup>b</sup> Reference category.

squamous cell carcinomas and 0.66 (95% CI: 0.28–1.52) for small cell carcinomas (data not shown).

We found no evidence of interaction between MPO genotype and pack-years of smoking dichotomized at the median of 35 in the control population (Table 2), duration of smoking, or daily tobacco consumption (data not shown). Relative to the G/G genotype, the OR was 0.49 (95% CI: 0.22–1.07) for the combined (G/A and A/A) genotypes among individuals with a history of <35 pack-years and 0.57 (95% CI: 0.26–1.12) among those with a history of ≥35 pack-years. Likewise, no differences in risks associated with MPO genotypes were found according to GSTM1, CYP1A1 MspI (Table 2), or Ile-Val genotype (data not shown).

## Discussion

Our results suggest that MPO genotype influences the risk of smoking-related lung cancer; individuals with one or two A alleles were at 45% reduced risk of lung cancer compared with those without any A alleles. No gene-environment or gene-gene interactions were observed. The statistical power to detect them was, however, limited.

A potential limitation of our study is the use of hospital controls, especially if there are any associations between MPO genotype and the diseases diagnosed. Nevertheless, the distributions of genotypes were not significantly different across the

disease groups, although the power to detect such differences is low. Moreover, the frequency of the A allele in our control population was consistent with those reported in Caucasian populations (Refs. 7–9, 11, and 16; Xu *et al.*, this issue).

Consistent with our findings, a significant reduction in risk among carriers of the A allele (A/A and A/G genotypes) was recently demonstrated in two studies among Caucasians (8, 16). A reduced risk of lung cancer was also found among carriers of the A/A genotype among Caucasian (7, 9), African-American (7), and Japanese (9) populations. These results contrast with the two remaining studies, reporting a lack of association (Ref. 11; Xu *et al.*, this issue).

The statistical power to detect a decreased risk of lung cancer associated with the MPO A/A genotype of the individual studies is generally limited because of its low prevalence. Therefore, we combined the data of 10 case-control studies in a meta-analysis totalling 2686 lung cancer cases and 3325 controls. Selected characteristics of the studies and individual study results of lung cancer associated with MPO <sup>-463</sup>G → A polymorphism are displayed in Table 3. The majority of subjects of the pooled data set were Caucasians (86%). More than one-third of cases and controls were included in the study by Xu *et al.* (this issue). Although control selection procedures differed between studies, the frequencies of the A allele among Caucasians were very comparable in studies with healthy controls (range: 0.2–0.26) or hospital controls (range: 0.21–0.26). An OR suggesting a protective effect for A allele containing genotypes (A/A and G/A) was found in six studies, but the decrease in risk was statistically significant in only two of them (Table 3).

The summary OR of all of the 10 studies (Table 4) suggested a slight protective effect for the MPO A/A genotype (OR = 0.86, 95% CI: 0.67–1.1). However, the large study by Xu *et al.* (this issue) had a strong influence on the results of the meta-analysis; in this study, the OR associated with the A/A genotype was 1.34 (95% CI: 0.87–2.06). The other nine studies constituted a homogeneous set (homogeneity test, *P* = 0.55), which yielded a significantly reduced summary OR for the A/A genotype (OR = 0.68, 95% CI: 0.5–0.93). This pooled OR was significantly different (*P* = 0.007) from the OR of 1.34 observed in the study by Xu *et al.* (this issue).

Restriction to studies with Caucasian individuals (seven studies) did not materially alter these results (Table 4). The OR generated by all studies was 0.86 (95% CI: 0.66–1.13) for carriers of the A/A genotype, but the estimates lacked homogeneity (*P* = 0.08). Again, exclusion of the study by Xu *et al.* (this issue) provided a more homogeneous set (*P* = 0.46), and a protective effect of the A/A genotype on lung cancer risk was found (summary OR = 0.65, 95% CI: 0.45–0.92).

In our analyses, the Egger's test, although not very powerful, suggests an absence of substantial publication bias.

In conclusion, the results of our study support the biolog-

Table 3 Summary of case-control studies of lung cancer and MPO genotype

Study	Cases			Controls			Crude OR <sup>a</sup> (95% CI)				
	Total	% of G/A	% of A/A	Source	Total	% of G/A	% of A/A	For G/A genotype	For A/A genotype	For (G/A + A/A) genotypes	
London <i>et al.</i> <sup>b</sup> (7)	USA	182	32.4	2.2	Healthy	459	31.2	7.8	0.97 (0.67–1.41)	0.26 (0.09–0.75)	0.83 (0.58–1.19)
London <i>et al.</i> <sup>c</sup> (7)	USA	157	47.1	7.6	Healthy	244	41.0	9.4	1.26 (0.83–1.92)	0.89 (0.42–1.90)	1.19 (0.77–1.78)
Cascorbi <i>et al.</i> <sup>b</sup> (8)	Germany	196	25.0	3.1	Hospital	196	38.3	2.0	0.54 (0.35–0.84)	1.25 (0.34–4.52)	0.58 (0.38–0.88)
Le Marchand <i>et al.</i> <sup>b</sup> (9)	USA	135	28.2	5.2	Healthy	171	33.9	8.8	0.71 (0.43–1.17)	0.51 (0.20–1.30)	0.67 (0.42–1.07)
Le Marchand <i>et al.</i> <sup>d</sup> (9)	USA	108	21.3	0.9	Healthy	163	25.1	4.3	0.77 (0.43–1.38)	0.20 (0.02–1.62)	0.68 (0.39–1.20)
Le Marchand <i>et al.</i> <sup>e</sup> (9)	USA	80	20.0	5.0	Healthy	103	16.5	4.8	1.27 (0.59–2.72)	1.08 (0.28–4.19)	1.23 (0.62–2.45)
Misra <i>et al.</i> <sup>b</sup> (11)	Finland	315	34.3	5.1	Healthy	311	39.8	6.8	1.39 (0.98–1.96)	0.82 (0.42–1.62)	1.27 (0.92–1.76)
Schabath <i>et al.</i> <sup>b</sup> (16)	USA	375	33.6	3.7	Healthy	378	41.5	5.1	0.69 (0.51–0.93)	0.63 (0.31–1.29)	0.68 (0.51–0.91)
Xu <i>et al.</i> <sup>b</sup> (this issue)	USA	988	34.7	4.8	Healthy	1128	34.6	3.6	1.03 (0.85–1.23)	1.34 (0.87–2.06)	1.05 (0.89–1.26)
Present study <sup>b</sup>	France	150	28.0	6.7	Hospital	172	36.6	7.6	0.65 (0.40–1.06)	0.75 (0.32–1.80)	0.67 (0.43–1.05)

<sup>a</sup> G/G genotype as reference category, 95% CI of ORs computed by Woolf's method.

<sup>b</sup> Caucasians.

<sup>c</sup> African-Americans.

<sup>d</sup> Japanese.

<sup>e</sup> Hawaiians.

Table 4 Results of meta-analyses of lung cancer risk associated with MPO genotype

Subjects	Total	MPO genotype			
		G/G	G/A	A/A	G/A or A/A
All (10 studies)					
Cases/controls	2686/3325	1687/2013	878/1128	121/184	999/1312
Meta-OR (95% CI)		1 (Reference)	0.89 (0.73–1.08)	0.86 (0.67–1.10)	0.86 (0.71–1.03)
P			0.24	0.22	0.10
All but those from the study by Xu <i>et al.</i>					
Cases/controls	1698/2197	1089/1316	535/738	74/143	609/881
Meta-OR (95% CI)		1 (Reference)	0.87 (0.69–1.09)	0.68 (0.50–0.93)	0.83 (0.67–1.01)
P			0.22	0.02	0.07
All Caucasians (7 studies)					
Cases/controls	2341/2815	1472/1696	765/970	104/149	869/1119
Meta-OR (95% CI)		1 (Reference)	0.84 (0.67–1.06)	0.86 (0.66–1.13)	0.82 (0.66–1.02)
P			0.15	0.29	0.07
Caucasians, except those from the study by Xu <i>et al.</i>					
Cases/controls	1353/1687	874/999	422/580	57/108	479/688
Meta-OR (95% CI)		1 (Reference)	0.80 (0.60–1.06)	0.65 (0.45–0.92)	0.77 (0.60–0.98)
P			0.12	0.02	0.03

ically plausible hypothesis that individuals with MPO A/A genotype are at reduced risk of lung cancer, because of their reduced ability to activate an intermediate metabolite of the major carcinogen B(a)P found in tobacco smoke. A protective effect of the A/A genotype was also suggested in our meta-analysis. However, the findings were hampered by the heterogeneity in individual study results. Therefore, additional large case-control studies are warranted to provide a more definitive conclusion. Additional studies are also needed to clarify the functional significance of MPO polymorphism *in vivo*.

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## Point: Myeloperoxidase –463G → A Polymorphism and Lung Cancer Risk

Anne Feyler, Anu Voho, Christine Bouchardy, et al.

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