Tumor Biol. (2013) 34:3449–3455
DOI 10.1007/s13277-013-0921-x

RESEARCH ARTICLE

Association between MPO 463G>A polymorphism and risk of lung cancer: a meta-analysis

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Received: 10 May 2013 / Accepted: 11 June 2013 / Published online: 14 August 2013

Abstract There is a possible association between myeloperoxidase (MPO) 463G>A polymorphism and risk of lung cancer, but previous studies report conflicting results. We performed a meta-analysis of available molecular epidemiologic studies to comprehensively assess the association between MPO 463G>A polymorphism and risk of lung cancer. A systemic literature search was performed in Pubmed, Embase, and Wanfang databases for molecular epidemiologic studies on the association MPO 463G>A polymorphism and risk of lung cancer on March 16, 2013. The pooled odds ratios (ORs) with their 95 % confidence interval (95 % CI) were calculated to assess the strength of the association. Twenty-six individual case–control studies with a total of 18,433 subjects (7,752 cases and 10,681 controls) were finally included into the meta-analysis. Overall, MPO 463G>A polymorphism was significantly associated with decreased risk of lung cancer under two main genetic comparison models (for A versus G, OR=0.91, 95 % CI 0.83–0.99, *P*=0.035; for AG/AA versus GG, OR=0.90, 95 % CI 0.81–0.99, *P*=0.029). Meta-analysis of studies with high quality also showed that MPO 463G>A polymorphism was significantly associated with decreased risk of lung cancer under two main genetic comparison models (for A versus G, OR=0.91, 95 % CI 0.83–0.99, *P*=0.035; for AG/AA versus GG, OR=0.90, 95 % CI 0.80–0.99, *P*=0.048). Subgroup analysis by ethnicity further showed that there was a significant association between MPO 463G>A polymorphism and decreased risk of lung cancer in Caucasians but not in Asians. The meta-analysis suggests that MPO 463G>A polymorphism is associated with decreased risk of lung cancer, especially in Caucasians.

Keywords Myeloperoxidase · Lung cancer · Polymorphism · Meta-analysis

Introduction

Lung cancer is the second most common malignancy and has the highest cancer mortality rate worldwide [1, 2]. Currently, lung cancer accounts for about 15 % of all new cancer cases and nearly 30 % of all cancer-related deaths in the USA [3]. Previous studies have suggested that risk of developing lung cancer can be modified by the interactions between genetic and environmental factors such as smoking [4, 5]. Besides, tobacco smoking is accepted as the dominant causal factor of lung cancer, but fewer than 20 % of cigarette smokers develop lung cancer, suggesting that the genetic factors also play important roles in the development of lung cancer [5]. Myeloperoxidase (MPO) is an oxidative lysosomal enzyme, and it is linked to both inflammation and oxidative stress by its role in catalyzing the formation of oxidizing agents [6, 7]. The MPO gene is located on chromosome 17q23.1 and consists of 11 introns and 12 exons [8]. MPO 463G>A polymorphism (rs2333227) is a common single nucleotide polymorphism within the 5′ untranslated region of the MPO gene [8–10]. Previous studies suggested that the -463A allele could result in a decreased MPO expression, and individuals with the -463A allele may be afforded protection due to the decreased transcriptional activity of MPO and subsequent decreased metabolic activation of procarcinogens [8–10]. Therefore, there was a possible association between MPO

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463G>A polymorphism and risk of lung cancer, and many studies were case–control studies performed to assess the association [11–25]. However, results from previous studies reported conflicting findings [11–25]. These inconclusive results may be due to the low sample size of single study or the different characteristics among studies, such as ethnicity and sources of controls [11–25]. We performed a meta-analysis of available molecular epidemiologic studies to comprehensively assess the association between MPO 463G>A polymorphism and risk of lung cancer.

Methods

Search strategy

An electronic search in the Pubmed, Embase, Web of Science, and Wanfang databases was performed to identify the eligible studies assessing the association between MPO 463G>A polymorphism and risk of lung cancer. There were no language restrictions, and the last search time was March 16, 2013. We used the keywords and subject terms: ("lung carcinoma" or "lung cancer"), ("polymorphism" or "variant" or "genotype" or "mutation") and ("Myeloperoxidase" or "MPO" or "rs2333227"). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications.

Inclusion criteria and exclusion criteria

To be eligible for the inclusion criteria in the meta-analysis, the following criteria were used: (1) case–control studies comparing lung cancer cases with healthy or non-cancer controls; (2) studies evaluating the association between MPO 463G>A polymorphism and risk of lung cancer; (3) sufficient genotype data of MPO 463G>A polymorphism were reported; and (4) studies was excluded if they were the following: (a) case-only studies; (b) case reports, letters, or reviews; (c) incomplete data or no usable data were reported; (d) studies containing overlapping data; and (e) family-based design or related cases and controls were contained.

Data extraction and quality assessment

The data extraction was performed independently by two reviewers, and the conflicting data extracted were settled by discussion. A standardized form was used in the data extraction from the published studies, and the following data were extracted: first author, year of publication, country, ethnicity, study design, diagnostic criteria, source of cases and controls, number of cases and controls, genotyping methods, frequencies of MPO 463G>A genotypes, and the confirmation of Hardy–Weinberg equilibrium (HWE) in controls. The quality of included studies was assessed by the confirmation of HWE in controls, and studies without the confirmation of HWE in controls were defined as low-quality studies, while studies with the confirmation of HWE in controls were defined as high-quality studies.

Statistical analysis

We firstly tested whether the genotype frequencies of MPO 463G>A genotypes in the controls were confirmed with HWE using the χ^2 test. The strength of the associations between the MPO 463G>A polymorphism and risk of lung cancer was estimated using odds ratios (ORs) and their 95 % confidence interval (95 % CI). The following contrasts for the associations between the MPO 463G>A polymorphism and lung cancer were evaluated: comparison of the variant allele with ancestral allele (A versus G), comparison of the variant homozygote with the ancestral homozygote (AA versus GG), comparison of the variant homozygote combined with the heterozygote versus ancestral homozygote (AA/GA versus GG), and comparison of the variant homozygote versus ancestral homozygote combined with the heterozygote (AA versus GA/GG). The I^2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated, and an I^2 value of more than 50 % was interpreted as significant heterogeneity among studies [26]. When the effects were assumed to be homogenous, the fixed-effects model was used (Mantel–Haenszel method) [27]. If obvious heterogeneity was present, the random-effects model was used (DerSimonian–Laird method) [28]. Subgroup analysis based on ethnicity was used to explore the possible race-specific effect in the association. Potential publication bias was assessed by visual inspection of the funnel plots, in which the standard error of logOR of each study was plotted against its logOR, and an asymmetric plot suggested possible publication bias. In addition, we also performed the Egger linear regression test at the $P<0.05$ level of significance to assess the funnel plot asymmetry [29]. All analyses were conducted using STATA (Version 11, StataCorp, College Station, TX, USA). All P values in the meta-analysis were two-sided, and statistical significance was considered when the P value was less than 0.05.

Results

Study selection and description of included studies

A total of 123 potentially individual abstracts were found from the Pubmed, Embase, Web of Science, and Wanfang databases. After checking the abstracts and reviewing the full texts of possible studies, 26 individual case–control studies from 25 publications were finally included into the meta-analysis [9, 11–25, 30–38]. There were a total of 18,433 subjects (7,752 cases and 10,681 controls) from those 26

studies. There were 17 studies from Caucasians [9, 11, 13, 15–18, 20, 22, 25, 30–34, 37, 38], and 7 studies from Asians [14, 19, 21, 23, 24, 35, 36]. In addition, 19 studies from those 26 studies had the confirmation of HWE in controls and were defined as high-quality studies [13–16, 18, 19, 21–23, 25, 30, 32–38]. There were seven studies without the confirmation of HWE in controls and were defined as low-quality studies [9, 11, 12, 17, 20, 24, 31].

Meta-analysis

Overall, MPO 463G>A polymorphism was significantly associated with decreased risk of lung cancer under two main genetic comparison models (for A versus G, OR=0.91, 95 % CI 0.83−0.99, *P*=0.035; for AG/AA versus GG, OR=0.90, 95 % CI 0.81−0.99, *P*=0.029) (Table 1, Fig. 1).

Meta-analysis of studies with high quality also showed that MPO 463G>A polymorphism was significantly associated with decreased risk of lung cancer under two main genetic comparison models (for A versus G, OR=0.91, 95 % CI 0.83−0.99, *P*=0.035; for AG/AA versus GG, OR=0.90, 95 % CI 0.80−0.99, *P*=0.048) (Table 1). Subgroup analysis by ethnicity further showed that there was a significant association between MPO 463G>A polymorphism and decreased risk of lung cancer in Caucasians but not in Asians (Table 1).

Publication bias

Publication bias was investigated by funnel plot, and funnel plot asymmetry was further assessed by Egger's test. There was a low possibility of asymmetry in the comparison model (AA/GA versus GG) of this meta-analysis (Fig. 2). The Egger's test also suggested that there was no evidence for the funnel plot asymmetry (*P*=0.204). Therefore, there was no obvious risk of publication bias in this meta-analysis.

Discussion

There is a possible association between MPO 463G>A polymorphism and risk of lung cancer, but previous studies report conflicting results. We performed a meta-analysis of

Table 1 Meta-analysis of the association between MPO 463G>A polymorphism and lung cancer

Groups	Studies	Subjects (Cases/Controls)	OR (95 % CI)	*P* value	I^2 value
Total studies					
A vs. G	26	7,752/10,681	0.91 (0.83–0.99)	0.035	60.4 %
AA vs. GG	26	7,752/10,681	0.87 (0.67–1.12)	0.273	54.3 %
AG/AA vs. GG	26	7,752/10,681	0.90 (0.81–0.99)	0.029	51.7 %
AA vs. AG/GG	26	7,752/10,681	0.89 (0.70–1.15)	0.380	53.0 %
Studies with high quality					
A vs. G	19	6,395/8,845	0.91 (0.82–1.02)	0.097	65.7 %
AA vs. GG	19	6,395/8,845	0.90 (0.66–1.22)	0.491	58.0 %
AG/AA vs. GG	19	6,395/8,845	0.90 (0.80–0.99)	0.048	55.3 %
AA vs. AG/GG	19	6,395/8,845	0.94 (0.70–1.25)	0.667	54.6 %
Studies with low quality					
A vs. G	7	1,357/1,836	0.88 (0.77–0.99)	0.039	34.1 %
AA vs. GG	7	1,357/1,836	0.70 (0.50–0.98)	0.040	34.0 %
AG/AA vs. GG	7	1,357/1,836	0.89 (0.77–1.03)	0.130	46.2 %
AA vs. AG/GG	7	1,357/1,836	0.70 (0.50–0.98)	0.038	41.7 %
Caucasians					
A vs. G	17	5,701/8,287	0.91 (0.82–1.01)	0.072	62.5 %
AA vs. GG	17	5,701/8,287	0.90 (0.67–1.22)	0.500	62.7 %
AG/AA vs. GG	17	5,701/8,287	0.89 (0.80–0.99)	0.039	50.0 %
AA vs. AG/GG	17	5,701/8,287	0.94 (0.70–1.26)	0.687	62.1 %
Asians					
A vs. G	7	1,571/1,713	0.87[0.68–1.22]	0.282	61.7 %
AA vs. GG	7	1,571/1,713	0.64[0.39–1.07]	0.091	15.1 %
AG/AA vs. GG	7	1,571/1,713	0.89[0.67–1.17]	0.389	61.6 %
AA vs. AG/GG	7	1,571/1,713	0.66[0.39–1.09]	0.104	0.0 %

OR odds ratio, *95%CI* 95 % confidence interval

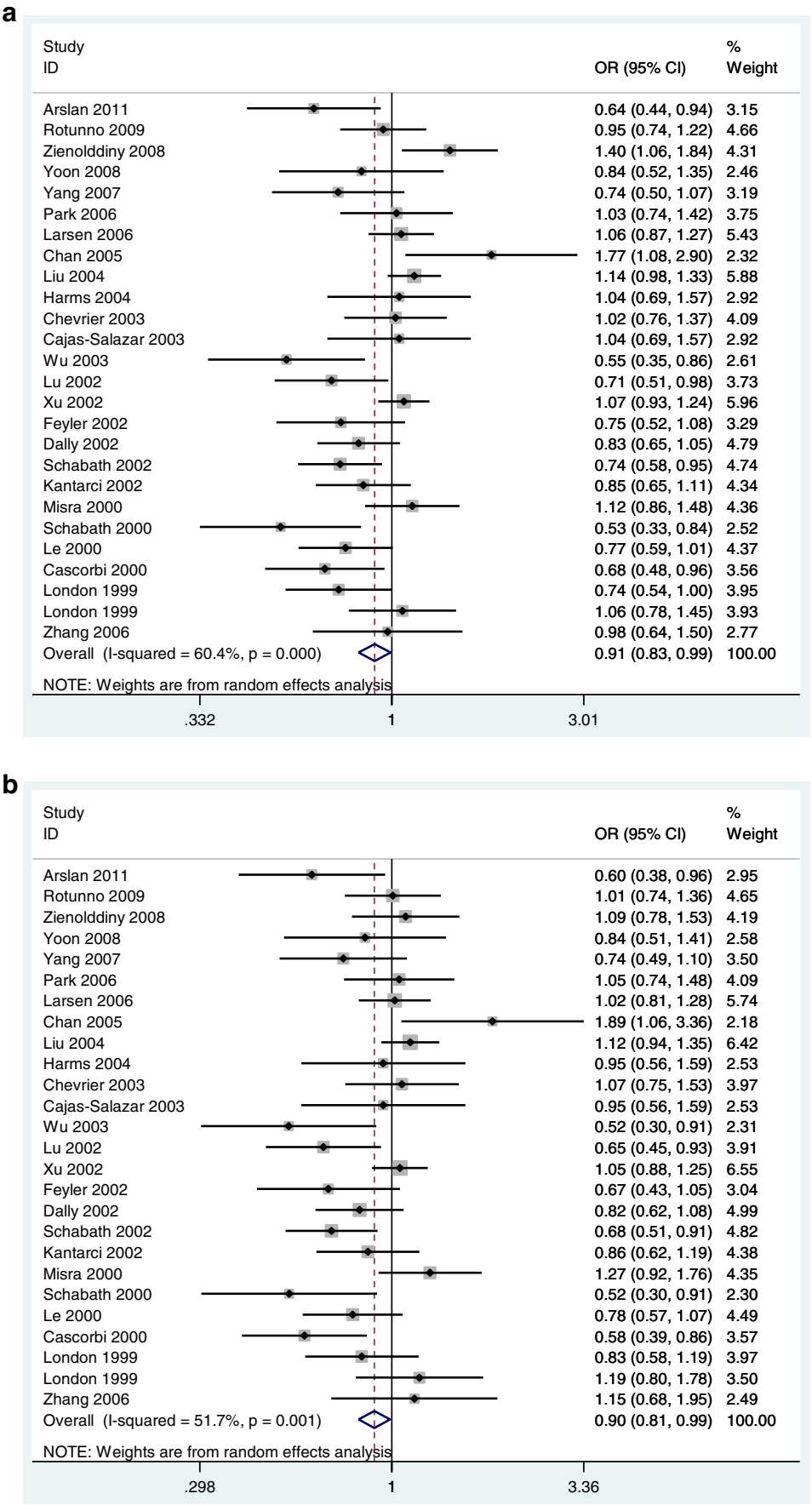

Fig. 1 Forest plot describing the association between MPO 463G>A polymorphism and lung cancer (each study is shown by the point estimate of the OR and 95 % CI, and the size of the square is proportional to the weight of each study). **a** A versus G. **b** AA/GA versus GG

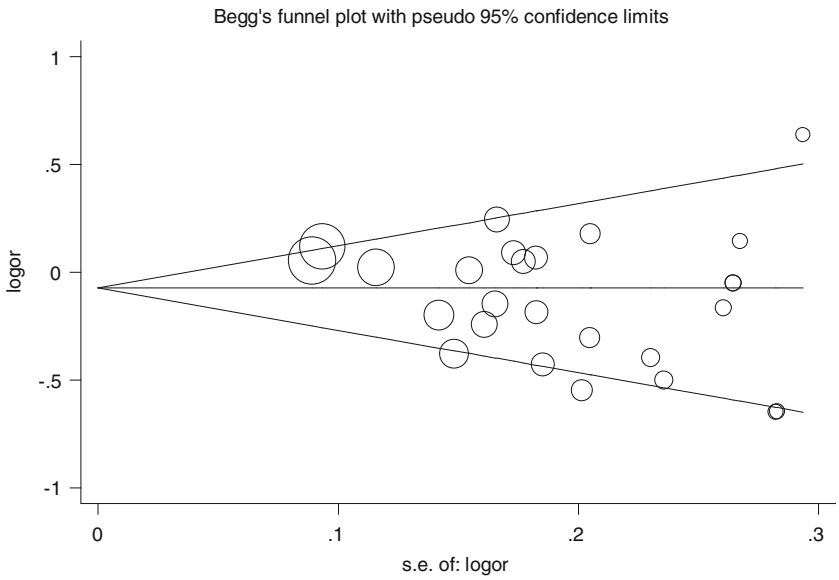

Fig. 2 Funnel plot for the detection of the publication bias in this meta-analysis

available molecular epidemiologic studies to comprehensively assess the association between MPO 463G>A polymorphism and risk of lung cancer. However, results from previous studies reported conflicting findings [11–25]. These inconclusive results may due to the low sample size of single study or the different characteristics among studies, such as ethnicity and sources of controls [11–25]. We performed a meta-analysis of available molecular epidemiologic studies to comprehensively assess the association between MPO 463G>A polymorphism and risk of lung cancer. Therefore, we performed a systemic literature search in Pubmed, Embase, and Wanfang databases and carried out a meta-analysis of 26 individual case–control studies with a total of 18,433 subjects (7,752 cases and 10,681 controls). Overall, MPO 463G>A polymorphism was significantly associated with decreased risk of lung cancer under two main genetic comparison models (Table 1, Fig. 1). Meta-analysis of studies with high quality also showed that MPO 463G>A polymorphism was significantly associated with decreased risk of lung cancer under two main genetic comparison models (Table 1). Subgroup analysis by ethnicity further showed that there was a significant association between MPO 463G>A polymorphism and decreased risk of lung cancer in Caucasians but not in Asians. Therefore, the meta-analysis suggests that MPO 463G>A polymorphism is associated with decreased risk of lung cancer, especially in Caucasians.

Previous studies have suggested that risk of developing lung cancer can be modified by the interactions between genetic and environmental factors such as smoking, and the genetic factors also play important roles in the development of lung cancer [4, 5]. MPO is an oxidative lysosomal enzyme, and it is linked to both inflammation and oxidative stress by its role in catalyzing the formation of oxidizing agents [6, 7]. MPO 463G>A polymorphism is a common single nucleotide polymorphism within the 5′ untranslated region of the MPO gene, and the -463A allele could result in decreased MPO expression [8–10]. Individuals with the -463A allele may be afforded protection due to the decreased transcriptional activity of MPO and subsequent decreased metabolic activation of procarcinogens [8–10]. Previous studies have shown that individuals with lower transcriptional activity AA genotype of MPO 463G>A polymorphism may have significantly reduced risk of cancer, such as breast cancer [39]. Therefore, there is biochemical evidence for the association between MPO 463G>A polymorphism and risk of lung cancer.

The previous study by Taioli et al. included 10 studies (3,688 cases and 3,874 controls) [40], while this present meta-analysis included 26 individual case–control studies with a total of 18,433 subjects (7,752 cases and 10,681 controls), which had obviously larger size and could provide a more precise assessment of the association between MPO 463G>A polymorphism and lung cancer. Besides, subgroup analysis by ethnicity further showed that there was a significant association between MPO 463G>A polymorphism and decreased risk of lung cancer in Caucasians but not in Asians (Table 1). These results may indicate that there is a race-specific effect in the association between MPO 463G>A polymorphism and lung cancer.

There were some limitations in our meta-analysis. Firstly, there was a limited number of eligible studies in the subgroup analysis of the association between MPO 463G>A polymorphism and lung cancer in Asians. The limited sample size in the subgroup analysis of Asians may fail to provide enough statistical power to detect a possible or weak effect of MPO 463G>A polymorphism on lung cancer in Asians. Therefore, more studies with large sample are needed to give a more precise estimation of the association between MPO 463G>A polymorphism and lung cancer in

Asians. Secondly, this meta-analysis was based on unadjusted data, as the ORs adjusted for the main confounding variables were not available from those studies. To provide a more reliable estimation of the association, more studies with well-designed and large sample size are needed to further identify the association. Finally, gene–gene interactions were not fully addressed in the meta-analysis for the lack of relevant data. Future studies may further assess the possible gene–gene interactions in the association between MPO 463G>A polymorphism and lung cancer risk.

In summary, the meta-analysis suggests that MPO 463G>A polymorphism is associated with decreased risk of lung cancer, especially in Caucasians. Besides, more studies with large sample are needed to give a more precise estimation of the association between MPO 463G>A polymorphism and lung cancer in Asians.

Conflicts of interest None

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