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CYP1A1 and *GSTM1* polymorphisms and lung cancer risk in Chinese populations: A meta-analysis

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Summary Genetic polymorphisms of cytochrome p450 (*CYP1A1*) and glutathione *S*-transferase M1 (*GSTM1*) genes are thought to have significant effects on the metabolism of environmental carcinogens and thus on cancer risk, but the reported results are not always consistent. In this meta-analysis, we assessed reported studies of associations between polymorphisms of these two genes and risk of lung cancer in Chinese populations. Through a systematic literature search for publications between 1989 and 2006, we summarized the data from 46 studies on polymorphisms of MspI and exon7-Val of *CYP1A1* and *GSTM1* and lung cancer risk in Chinese populations, and found that compared with the wild-type homozygous genotype (type A), lung cancer risk for the combined variant genotypes (types B and C) was 1.34-fold (95% confidence interval [CI] = 1.08—1.67) ($Z = 2.64$, $P = 0.008$); the risk for the combined variant genotypes (Ile/Val and Val/Val) of *CYP1A1* exon7 was 1.61-fold (95% CI = 1.24—2.08) ($Z = 3.62$, $P < 0.001$), compared with the Ile/Ile genotype; and that the risk for the *GSTM1* null genotype was 1.54-fold (95% CI = 1.31—1.80) ($Z = 5.32$, $P < 0.001$), compared with the *GSTM1* present genotype. Therefore, in 46 published studies in Chinese populations, we found evidence of an association between the *CYP1A1* variant and *GSTM1* null genotypes and increased risk of lung cancer.

1. Introduction

Environmental chemical pollutants (ECPs) are increasingly present in our living environment as a result of the development of the modern industry and urbanization. Many ECPs are widely spread and difficult to be degradated in the environment. Therefore, ECPs could have a long-term effect on

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human health. Among the ECPs are the most-studied pollutants, polycyclic aromatic hydrocarbons (PAHs), which have been found in cigarette smoke and in polluted indoor and outdoor air and shown to be associated with risk of many diseases including cancer.

Lung cancer is a serious threat to public health, ranking number 1 in cancer-related deaths. Human cancers can be initiated by DNA damage caused by environmental chemical agents, such as PAHs, and some adverse habits including tobacco smoking and alcohol use [1]. Studies have shown that exposures to environmental and occupational PAHs are risk factors for lung cancer [2—4]. However, not all of those who have been exposed to the risk factors will develop lung cancer, suggesting that there is individual variation in cancer susceptibility in the general population [1]. For example, phase I and phase II enzymes, such as *CYP1A1* and *GSTM1*, respectively, that can metabolize xenobiotics in humans are polymorphic [5—8]. Both biological and biochemical evidence indicates that genetic polymorphisms of these genes can influence the balance between metabolic activation and detoxication of some toxicants, such as benzo[*a*] pyrene, and thus they are relevant to individual susceptibility to lung cancer. *CYP1A1* and *GSTM1* are good candidate genes, because they are modifiers of risk of lung cancer due to their allelic variants that alter the inducibility of the enzyme by the inducers. The effect of metabolic polymorphisms on lung cancer risk has been shown to depend on the level of exposure to xenobiotics in some subgroups of individuals. For example, it is suggested that the effect of the *CYP1A1* polymorphism is greater in non-smokers than in smokers and in women than in men [9,10]. It is conceivable that individuals who have inherited specific variants in these genes, such as *CYP1A1* and/or *GSTM1*, may become susceptible to chemical carcinogens and thus at a high risk of developing lung cancer.

In this report, we tested the hypothesis by performing a meta-analysis that the inter-individual susceptibility to lung cancer is associated with genetic variation in metabolic enzymes. We summarized reported case—control studies on three most-studied polymorphisms (i.e., MspI-restriction fragment length polymorphism and exon7-Val polymorphism of *CYP1A1* and *GSTM1*) in Chinese populations. Because a single study may have been underpowered in detecting the effect of low penetrance genes, particularly in assessing dose—response relationships, a quantitative synthesis of accumulated data from published studies may enhance statistical power to detect the association between genetic polymorphisms and lung cancer risk. Meta-analyses of studies on these two genes in other ethnic groups have been reported elsewhere (Raimondi et al. [6]; Houlston [11]; Ye et al. [12]; Vineis et al. [13]).

2. Materials and methods

2.1. Literature search strategy for identification of the studies

We carried out a search in the Medline and Chinese National Knowledge Infrastructure (CNKI), covering all papers published between 1989 and 2006, with a combination of the following keywords: lung cancer and *GSTM1* and China/Chinese; lung cancer and *CYP1A1* and China/Chinese; lung cancer and *P4501A1* and China/Chinese. We evaluated potentially relevant publications by examining their titles and abstracts and then procured the most relevant publications for a closer examination. Besides the database search, the references lists of the selected papers were also screened for other potential articles that may have been missed in the initial search. The search and evaluation were conducted from January to March 2007.

The following criteria were used for the literature selection for the meta-analysis:

(1) the articles should be published in either English or Chinese between January 1989 and December 2006;
(2) the articles should describe studies only in Chinese populations;
(3) only the case—control studies and cohort studies were considered;
(4) the paper should clearly describe lung cancer diagnoses and the sources of cases and controls;
(5) the authors must offer the size of the sample, odds ratios (ORs) and their 95% confidence intervals (CIs) or the information that can help infer the results in the papers;
(6) the definition of the exposure/risk genotypes was similar in all papers;
(7) the methods of data collection and analysis should be statistically acceptable;
(8) those publications that presented data allowing such outcomes to be derived were also included.

Accordingly, the following exclusion criteria were also used:

(1) the articles had studied ethnic populations other than Chinese;
(2) the design and the definition of the exposure were obviously different from those of the selected papers;
(3) not offering the source of cases and controls and other essential information;
(4) reviews and repeated literatures were also excluded.

After the searching, we selected 49 published papers dealing with case—control and cohort studies of the polymorphisms. We reviewed all papers in accordance with the criteria defined above, and we then excluded 14 papers because their study designs were different from others or they did not list data clearly enough for further analysis or repeated literatures. For the included studies, we used Jadad scale to appraise their qualities of study designs (hospital versus population-based study, response rates, lack of bias, control of confounding, etc.) and gave a matched score to each paper, in the final the weighted score was 3.65 for Jadad score, and thus, the qualities of the included studies were acceptable. Among the 35 qualified literatures, 15 studies focused on the *CYP1A1* MspI polymorphism, 11 studies focused on the *CYP1A1* exon7 polymorphism, and 20 papers reported on the polymorphism of *GSTM1*. Apparently, there were 11 articles that had reported two kinds of polymorphisms.