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Association between the CYP1A1 T3801C polymorphism and risk of cancer: Evidence from 268 case–control studies

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ABSTRACT

T3801C is a common polymorphism in CYP1A1, showing differences in its biological functions. Case–control studies have been performed to elucidate the role of T3801C in cancer, although the results are conflicting and heterogeneous. Hence, we performed a meta-analysis to investigate the association between cancer susceptibility and T3801C (55,963 cases and 76,631 controls from 268 studies) polymorphism in different inheritance models. We used odds ratios with 95% confidence intervals to assess the strength of the association. Overall, significantly increased cancer risk was observed in any genetic model (dominant model: odds ratio [OR] = 1.14, 95% confidence interval [CI] = 1.09–1.19; recessive model: OR = 1.23, 95% CI = 1.12–1.34; CC vs. TT: OR = 1.31, 95% CI = 1.19–1.45; TC vs. TT: OR = 1.12, 95% CI = 1.07–1.18; additive model: OR = 1.14, 95% CI = 1.09–1.19) when all eligible studies were pooled into the meta-analysis. In further stratified and sensitivity analyses, the elevated risk remained for subgroups of cervical cancer, head and neck cancer, hepatocellular cancer, leukemia, lung cancer, prostate cancer and breast cancer. In addition, significantly decreased colorectal cancer risk was also observed. In summary, this meta-analysis suggests that the participation of CYP1A1 T3801C is a genetic susceptibility for some cancer types. Moreover, our work also points out the importance of new studies for T3801C association in some cancer types, such as gallbladder cancer, Asians of acute myeloid leukemia, and thyroid cancer, where at least some of the covariates responsible for heterogeneity could be controlled, to obtain a more conclusive understanding about the function of the CYP1A1 T3801C polymorphism in cancer development.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are environmental compounds ubiquitously distributed in smoked, foods, tobacco smoke and the urban outdoor environment in large cities (Shimada, 2006). PAHs acquire carcinogenicity following activation by xenobiotic-metabolizing enzymes to highly reactive metabolites (Elovaara et al., 2007). Cytochrome P450 (CYP) enzymes are pivotal to the metabolic activation of PAHs to epoxide intermediates. These intermediates are converted into the ultimate carcinogens, diol-epoxides, via epoxide hydrolase. CYP1A1 was believed to be the most important enzyme catalyzing activation of these pro-carcinogenic PAHs (Quiñones and Gil, 1995). Cytochrome P450 (CYP) enzyme catalyze phase I metabolism reaction. Cytochrome P450 1A1 (CYP1A1) is a member of the CYP family that participates in the metabolism of xenobiotics and endogenous compounds, particularly polycyclic aromatic hydrocarbons such as benzo[a]pyrene (Guengerich and Shimada, 1998). A commonly studied single nucleotide polymorphism (SNP) in the CYP1A1 gene has been indicated to associate with cancer risk, which was localized on chromosome 15q22 (Crofts et al., 1993). The commonly studied is the 3801T>C polymorphism (also referred to as 2A, m1, or rs4646903), which is characterized by the T to C mutation at nucleotide 3801 in the 30 flanking region of the CYP1A1 gene. The 3801T>C polymorphism can alter the level of gene expression or messenger RNA stability, resulting in a highly inducible activity of the enzyme (Shah et al., 2009). Hence, certain variant genotypes of the CYP1A1 gene which may cause enhanced enzymatic activity appear to play a role in susceptibility to adduct formation and presumably cancer risk (Rojas et al., 2000).

Abbreviations: PAHs, polycyclic aromatic hydrocarbons; CYP, cytochrome P450; CYP1A1, cytochrome P450 1A1; SNP, single nucleotide polymorphism; OR, odds ratios; HWE, Hardy–Weinberg equilibrium; NSCLC, non-small cells lung cancer; AC, adenocarcinoma; SCC, squamous cell carcinomas; SCLC, small cell lung cancer; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CALL, acute lymphoblastic leukemia; SZ, sample size; HNC, head and neck cancer; SC, source of controls; PB, population-based studies; HB, hospital-based studies.

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Table 1
Scale for quality assessment criterion.

Criterion	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens used for determining genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy–Weinberg equilibrium in controls	
Hardy–Weinberg equilibrium	3
Hardy–Weinberg disequilibrium	0
Total sample size	
>1000	3
>500 and < 1000	2
>200 and <500	1
<200	0

In the past decade, a number of molecular epidemiological studies have been done to evaluate the association between CYP1A1 T3801C polymorphism and different types of cancer risk in diverse populations. However, the results were inconsistent or even contradictory. Partially because of the possible small effect of the polymorphism on cancer risk and the relatively small sample size in each of published studies. In addition, some recent meta-analyses analyzed such an association only for single cancer such as prostate cancer, leukemia, oral cancer, ovarian cancer, lung cancer, and so on (Ding et al., 2013; Ji et al., 2012; Sergentanis et al., 2012; Zhuo et al., 2012a, 2012b). Therefore, we performed a comprehensive meta-analysis by including the most recent and relevant articles to identify statistical evidence of the association between CYP1A1 T3801C polymorphism and risk of all cancers that have been investigated. Meta-analysis is a powerful tool for summarizing the different studies. It cannot only overcome the problem of small size and inadequate statistical power of genetic studies of complex traits, but also can provide more reliable results than a single case–control study.

2. Materials and methods

2.1. Identification and eligibility of relevant studies

A comprehensive literature search was performed using the PubMed, ISI, and EMBASE database for relevant articles published (the last search update was Apr. 15, 2013) with the following key words "CYP1A1," "polymorphism," and "cancer" or "carcinoma." The search was not limited to language. Additional studies were identified by hand searching references in original articles and review articles. Authors were contacted directly regarding crucial data not reported in

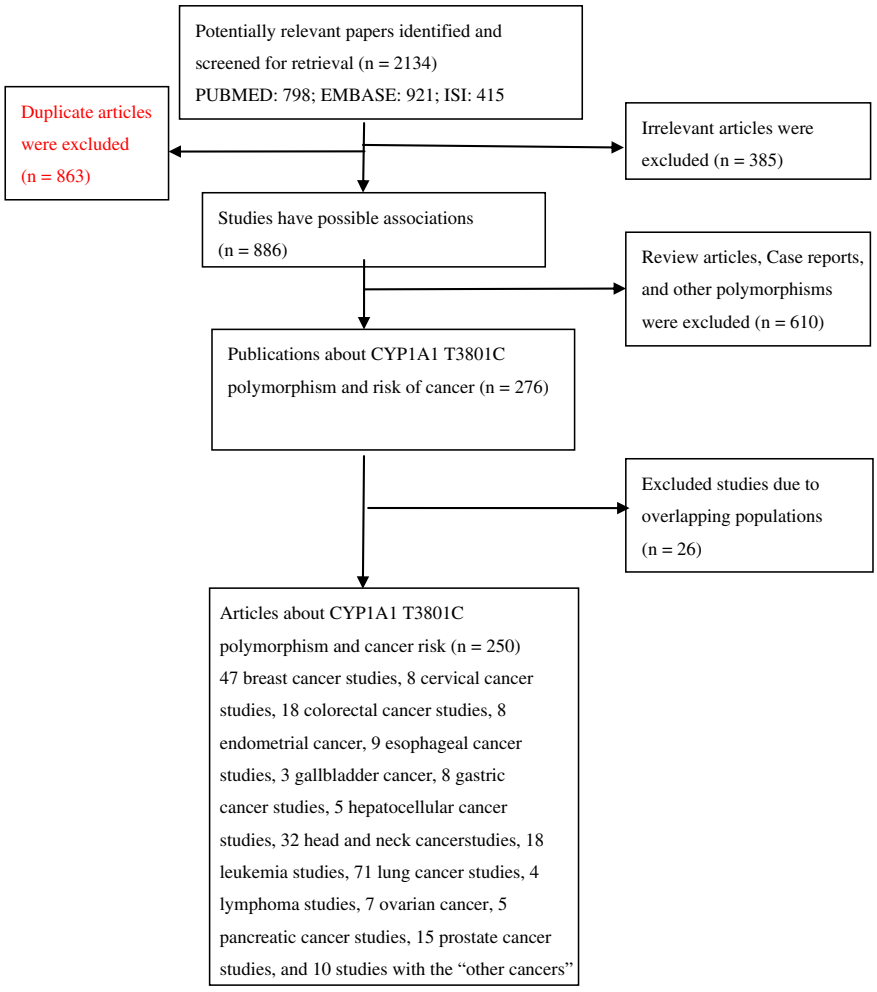

Fig. 1. Study flow chart explaining the selection of the 250 publications included in the meta-analysis.