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Original article

The associations between CYP24A1 polymorphisms and cancer susceptibility: A meta-analysis and trial sequential analysis

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ABSTRACT

Purpose: Published data have shown that vitamin D may have a protective effect on cancer development. CYP24A1, the main enzyme responsible for the degradation of active vitamin D, plays an important role in many cancer related cellular processes. Up to now, relationships between CYP24A1 polymorphisms and cancer susceptibility have been widely investigated, whereas the results are inconsistent. The aim of present meta-analysis was to explore the associations between CYP24A1 polymorphisms and cancer susceptibility.

Methods: We searched on EMBASE, Web of Science, PubMed and China National Knowledge Infrastructure (CNKI) electronic databases (up to July 1, 2017) for relevant studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to make the evaluation clear.

Results: Twenty-nine studies published in eight publications involving 20,593 cases and 25,458 controls were included. Five CYP24A1 gene polymorphisms were evaluated: rs2181874, rs2585428, rs4809960, rs6022999, and rs6068816. Our analyses suggested that rs2585428 and rs4809960 polymorphisms were significantly associated with overall cancer risk. Stratification analyses of ethnicity indicated that rs2585428 and rs4809960 polymorphisms decreased the risk of cancer among Caucasians. When studies were stratified by cancer type, our results indicated that rs2585428 significantly decreased the risk of pancreas cancer, while rs4809960 significantly decreased the risk of breast cancer. There were no associations of rs2181874, rs6022999, or rs6068816 with overall cancer risks.

Conclusion: Associations between CYP24A1 polymorphisms and cancer risks were examined, and additional multi-center studies with large samples are necessary to validate our results.

1. Introduction

Cancer is still a major public health problem. It was estimated that there were approximately 14 million new cancer cases and 8 million deaths occurred in 2012 worldwide [1]. As a multifactorial disease, various etiologies involving multiple environmental and genetic factors contribute to cancer's development. In addition, genetic factors play important roles in carcinogenesis, and many genes have been described as cancer-susceptible genes [2], although the exact mechanism of carcinogenesis has not been fully understood.

Vitamin D, from sun exposure (accounting for up to 90%) and diet, was found to be associated with reduced risk of several cancers, including colorectal cancer, prostate cancer and breast cancer. It has become increasingly clear that vitamin D not only has a function in bone metabolism, but it also has a protective effect against malignant neoplasms due to its role in regulating cell differentiation, proliferation and apoptosis [3,4]. These biological functions demonstrated that vitamin D might be treated as an ideal therapeutic agent to resist the development of malignancy. The serum 25-hydroxyvitamin D (25(OH)D) is a widely accepted biomarker of vitamin D status. Up to now, a number of studies have been published and implied a possible association between serum 25(OH)D and cancer risk. Unfortunately, some studies have presented contradictory results. For instance, Stolzenberg et al. [5] indicated that high levels of circulating 25(OH)D was significantly associated with a high risk for pancreas cancer. However, Wolpin et al. [6] found an inverse association between 25(OH)D and

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; 25(OH)D, 25-hydroxyvitamin D; GWAS, genome-wide association study; CNKI, China National Knowledge infrastructure; HWE, Hardy-Weinberg Equilibrium; TSA, trial sequential analysis; ER, estrogen receptor

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pancreas cancer. Besides, such contradictions also existed in some other studies [7–9]. The possible reason is that serum 25(OH)D levels may not correspond to vitamin D exposure levels.

Several genes are involved in vitamin D metabolism. 1α-hydroxylase (encoded by CYP27B1 gene) converts 25(OH)D to $1,25(OH)_2D_3$ in the kidney, then it will be released into the blood circulation. $1,25(OH)_2D_3$ plays an important role in the regulation of cell functions and metabolic pathway. Finally, circulating 25(OH)D and $1,25(OH)_2D_3$ are degraded by 25-hydroxyvitamin D 24-hydrolase (encoded by CYP24A1 gene). It is evident that CYP24A1 is the main enzyme responsible for the degradation of vitamin D. Of note, the relationship between the mRNA expression levels of CYP24A1 and cancer risk has been investigated by some researchers in depth. Zhalehjoo et al. [10] demonstrated that the expression of CYP24A1 was significantly up-regulated in breast cancer. Moreover, Bokhari et al. [11] found that endometrial cancer expressed higher levels of CYP24A1 than normal tissues. Therefore, we believe that CYP24A1 may possess potential clinical value in cancer.

Recently, genome-wide association studies (GWASs) have identified CYP24A1 polymorphisms significantly associated with 25(OH)D concentrations. Up to now, five common CYP24A1 SNPs, rs2181874, rs2585428, rs4809960, rs6022999 and rs6068816, were found to be associated with cancer risks, including prostate cancer, breast cancer, colon cancer and pancreas cancer. However, the results are inconsistent, possibly because of limited sample sizes. To better explore the precise relationship, we performed a meta-analysis using currently published data to characterize the associations of rs2181874, rs2585428, rs4809960, rs6022999 and rs6068816 in CYP24A1 with cancer risks.

2. Material and methods

2.1. Literature search

We systematically searched on EMBASE, Web of Science, PubMed and China National Knowledge Infrastructure (CNKI) electronic databases (up to July 1, 2017) for relevant studies exploring the relationships between CYP24A1 polymorphisms and cancer risks. The detailed search strategy is described in Supplementary Table 1. The literature covered was limited to human. Three independent authors (Shili Qiu, Xianwei Zhang and Xue Wen) conducted the search. Finally, we also searched the references lists of all retrieved articles for potential studies manually.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) case-control/cohort studies; (2) investigating the associations between CYP24A1 polymorphisms (at least one of the five polymorphisms) and cancer risks; (3) providing sufficient data to calculate the OR and 95% CI, and *P* value; (4) genotype frequencies in controls were in agreement with Hardy-Weinberg Equilibrium (HWE). In addition, the exclusion criteria were: (1) non-human research; (2) not concerned with cancer risk; (3) did not study CYP24A1 polymorphisms (rs2181874, rs2585428, rs4809960, rs6022999 or rs6068816); (4) only a case population.

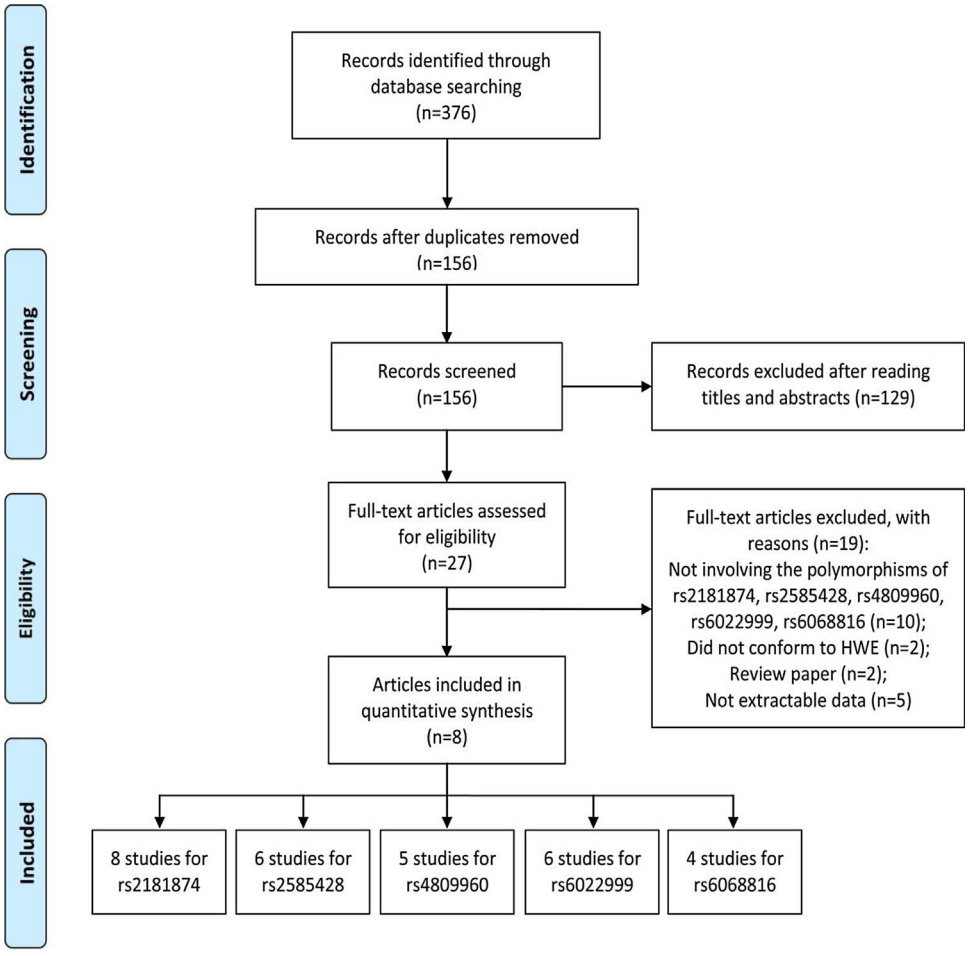

Fig. 1. Flow chart of the process for study identification and selection.