RESEARCH ARTICLE

Meta-analysis of the CYP1A2 -163C>A Polymorphism and Lung Cancer Risk

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Abstract

　　Many published studies have concerned associations between the CYP1A2 -163 C>A polymorphism and risk of lung cancer, but the results have been inconsistent. Therefore, we performed a meta-analysis to obtain a more precise estimate. We searched the PubMed database up to March 1, 2013 for relevant cohort and case-control studies. Supplementary search was conducted manually by searching the references of the included studies and relevant meta-analyses. A meta-analysis was performed using RevMan 5.2 software for calculation of pooled odds ratios (ORs) and relevant 95% confidence intervals (CIs) after data extraction. Finally, seven case-control studies and one nested case-control study involving 1,675 lung cancer patients and 2,393 controls were included. The meta-analysis showed that there was no association of CYP1A2 -163 C>A polymorphism with risk of lung cancer overall [(OR=0.89, 95% CI= 0.74-1.07) for C vs. A; (OR=0.73, 95% CI= 0.50-1.07) for AA vs. CC ; (OR=0.82, 95% CI= 0.62-1.09) for AC vs. CC; (OR=0.79, 95% CI= 0.58-1.07) for (AC+AA) vs. CC; and (OR=0.87, 95% CI= 0.67-1.13) for AA vs. (CC+AC)]. Subgroup analysis indicated that there was an association between CYP1A2 -163C>A polymorphism and lung cancer risk for population-based controls, a trend risk for SCCL (squamous cell carcinoma of lung) and Caucasians. These results suggested that -163 C>A polymorphism is likely to be associated with risk of lung cancer compared with population-based controls.

Keywords: CYP1A2 rs762551 polymorphism - lung cancer - meta-analysis

Introduction

　　The cytochromes P450 (CYPs) gene polymorphisms played an important role in the development of various cancers (Jin et al., 2011; Leng et al., 2012; Niu et al., 2012). Cytochrome P450 1A2 (CYP1A2) is one enzyme of the CYPs and it is a key enzyme in the activation of major classes of indirect carcinogens (Boobis et al., 1994). CYP1A2 gene has been mapped on chromosome 15q24.1 and is highly polymorphic (Zhou et al., 2009). According to NCBI dbSNP database, there are more than 200 polymorphisms existed in CYP1A2 gene region. CYP1A2 -163 C>A polymorphism (CYP1A2*1F; rs762551) is located in the intron1 of CYP1A2 (Sachse et al., 1999), there are many studies focused on this polymorphism and risk of cancer have been published (Wang et al., 2012). In 2012, a meta-analysis by Wang et al (Wang et al., 2012) identified 19 eligible case - control studies on the association between CYP1A2 -163 C>A polymorphism and risk of cancer, which suggested that CYP1A2 -163 C>A polymorphism is likely to be associated with susceptibility to cancer in Caucasians. Lung cancer is one of the six different cancers in this meta-analysis; however, there are histopathological types of lung cancer

and different cancer site of body has its histological properties. In addition, there are three studies (Zienolddiny et al., 2008; Pavanello et al., 2012; Gervasini et al., 2013) investigate CYP1A2 -163 C>A polymorphism and risk of lung cancer have been searched since the meta-analysis (Wang et al., 2012).

　　Thus, we performed this meta-analysis to address the association between CYP1A2 -163 C>A polymorphism and overall and subgroups risk in the development of lung cancer.

Materials and Methods

Search strategy

　　The PubMed database was searched up to March 1, 2013 using the following search strategy: ("CYP1A2" OR "Cytochrome P450 1A2") AND "polymorphism" AND "lung cancer". In addition, the reference lists of the included articles and relevant meta-analyses were manually searched.

Inclusion Criteria

　　The inclusion criteria were as following: (1) the topic was evaluated the association of CYP1A2 -163 C>A

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Table 1. Characteristics of Included Studies

Reference	Country (Ethnicity)	Study design	Cancer type	Case Total	CC	AC	AA	Source of control	Control Total	CC	AC	AA	Genotype method	HWE
Gemignani 2007	Six European countries (Caucasian)	CC	Mixed	297	120	151	26	HB	310	149	130	31	PCR	0.74
Osawa 2007	Japan (Asian)	CC	Mixed	113	18	40	45	HB	121	17	52	42	PCR-RFLP	0.89
Zienolddiny 2008	Norway (Caucasian)	CC	SCCL	335	40	149	146	PB	393	34	159	200	PCR	0.76
Aldrich 2009	USA (Latino)	CC	Mixed	113	16	51	46	PB	299	14	114	171	PCR	0.36
B'chir 2009	Tunisia (Tunisian)	CC	Mixed	101	24	44	33	HB	98	26	57	15	PCR–RFLP	0.08
Singh 2010/2011	India (Asian)	CC	SCCL	200	73	94	33	PB	200	61	90	49	PCR–RFLP	0.17
Pavanello 2012	Denmark (Caucasian)	NCC	Mixed	421	45	174	202	PB	776	53	311	412	PCR–RFLP	0.58
Gervasini 2013	Spain (Caucasian)	CC	Mixed	95	13	55	27	HB	196	22	119	55	PCR–RFLP	<0.05

CC, case-control study; NCC, nested case-control study; SCCL, squamonus cell carcinoma of lung; HB, hospital-based; PB, population-based

Table 2. Overall and Subgroups Meta-analysis of CYP1A2 -163 C>A Polymorphism and Lung Cancer Risk

Overall and Subgroups	N	A vs. C OR(95%CI)	I^2(%)	AA vs. CC OR(95%CI)	I^2(%)	AC vs. CC OR(95%CI)	I^2(%)	(AC+AA) vs. CC OR(95%CI)	I^2(%)	AA vs. (CC+AC) OR(95%CI)	I^2(%)
Overall	8	0.89(0.74-1.07)	72	0.73(0.50-1.07)	65	0.82(0.62-1.09)	52	0.79(0.58-1.07)	65	0.87(0.67-1.13)	66
Ethnicity											
Caucasian	4	0.90(0.75-1.09)	58	0.70(0.53-0.92)*	0	0.91(0.59-1.38)	67	0.84(0.54-1.31)	72	0.81(0.69-0.96)*	0
Asian	2	0.87(0.63-1.21)	52	0.69(0.44-1.08)	30	0.83(0.57-1.23)	0	0.80(0.57-1.12)	0	0.86(0.43-1.74)	73
Other	2	0.89(0.33-2.44)	93	0.75(0.08-7.26)	94	0.59(0.28-1.24)	51	0.60(0.16-2.26)	86	1.15(0.23-5.81)	94
Source of control											
HB	4	1.14(0.97-1.34)	0	1.17(0.81-1.67)	21	1.14(0.88-1.49)	39	1.17(0.91-1.49)	0	1.26(0.81-1.96)	57
PB	4	0.75(0.67-0.84)*	36	0.53(0.41-0.70)*	36	0.72(0.56-0.92)*	9	0.64(0.50-0.81)*	38	0.72(0.62-0.85)*	21
Cancer type											
Mixed	6	0.94(0.73-1.22)	78	0.80(0.47-1.37)	74	0.79(0.53-1.19)	65	0.91(0.75-1.12)	73	0.98(0.68-1.40)	72
SCCL	2	0.77(0.65-0.92)*	0	0.59(0.41-0.86)*	0	0.84(0.60-1.17)	0	0.74(0.54-1.01)	0	0.71(0.55-0.91)*	0
Study design											
CC	7	0.91(0.72-1.14)	75	0.77(0.49-1.21)	69	0.85(0.63-1.16)	51	0.82(0.59-1.15)	65	0.90(0.64-1.26)	71
NCC	1	0.80(0.67-0.97)*	/	0.58(0.38-0.89)*	/	0.66(0.43-1.02)	/	0.61(0.40-0.93)*	/	0.81(0.64-1.03)	/
HWE for control											
>0.05	7	0.88(0.72-1.09)	76	0.72(0.47-1.10)	70	0.82(0.60-1.12)	58	0.78(0.56-1.10)	70	0.86(0.64-1.15)	70
<0.05	1	0.96(0.67-1.36)	/	0.83(0.36-1.90)	/	0.78(0.37-1.67)	/	0.80(0.38-1.66)	/	1.02(0.59-1.75)	/

CC, case-control study; NCC, nested case-control study; SCCL, squamonus cell carcinoma of lung; HB, hospital-based; PB, population-based; HWE, Hardy Weinberg Equilibrium

polymorphism with lung cancer risk; (2) the study design was cohort or case-control, the cases were diagnosed by histology, pathology, or cytology; the controls were healthy or cancer-free; (3) providing the number of individual genotypes in both case and control group respectively, or the data can calculate them; (4) the published language was English or Chinese.

Data extraction

Two authors (Deng S.Q. and Wang Y.) independently select the studies and extract the data according to the pre-specified selection criteria, disagreements were resolved by discussion. Finally seven case-control studies and one nested case-control study were identified. The following data were extracted: the surname of first author, year of publication, country of origin and ethnicity, study design, cancer type, source of control, number and genotyping distribution of cases and controls, genotyping method, HWE (Hardy Weinberg Equilibrium) for controls.

Statistical analysis

The odds ratio (OR) and relevant 95% confidence interval (CI) was used to present the strength of associations between CYP1A2 -163 C>A polymorphism and risk of lung cancer by using five genetic models: A vs. C, AA vs. CC, AC vs. CC, (AC+AA) vs. CC, and AA vs. (CC+AC). The heterogeneity among included studies was detected firstly using I^2 statistics (Huedo-Medina et al., 2006). The value of $I^2 \leq 50\%$ indicated there was no substantive heterogeneity existed and the fixed effect

model was used; otherwise the random-effects model was used. We also performed subgroups analysis based on the ethnicity, source of controls, cancer types, study design, and HWE for controls. The sensitive analysis was conducted by omitting any single included study each tern, and the publication bias was detected by funnel plot analysis. All the analysis was performed using the RevMan 5.2 software.

Results

Study section and characteristics

The electronic searching yielded 19 studies and the hand searching yielded 11 studies initially. After deleted duplicate and non-relevant studies, finally seven case-control studies (Gemignani et al., 2007; Osawa et al., 2007; Zienolddiny et al., 2008; Aldrich et al., 2009; B'Chir et al., 2009; Singh et al., 2010; Gervasini et al., 2013) and one nested case-control study (Pavanello et al., 2012) involving 1675 lung cancer patients and 2393 controls were included.

The main characteristics and genotype distribution and frequency of the eight studies are shown in Table 1. Of these, one is a multicenter study focus on Caucasians contained six European countries (Gemignani et al., 2007), the others are single center study.

Overall and subgroups analyses

Table 2 presented the overall and subgroups results of CYP1A2 -163 C>A polymorphism and lung cancer
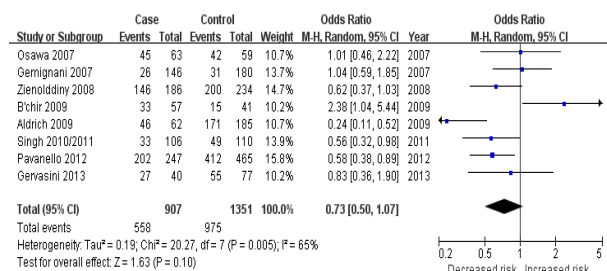
Figure 1. Forest Plot of Cancer Risk Associated with CYP1A2 -163 C>A Polymorphism and Lung Cancer Risk for AA vs. CC Genetic Model
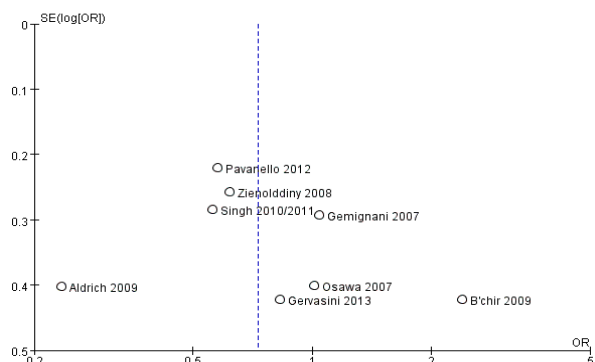

Figure 2. Funnel Plot for Publication bias Test Based on AA vs. CC Genetic Model

risk. Overall, the meta-analysis showed that there was no association of CYP1A2 -163 C>A polymorphism with risk of lung cancer [(OR=0.89, 95%CI= 0.74-1.07) for A vs. C; (OR=0.73, 95%CI= 0.50-1.07) for AA vs. CC, Figure 1; (OR=0.82, 95%CI= 0.62-1.09) for AC vs. CC; (OR=0.79, 95%CI= 0.58-1.07) for (AC+AA) vs. CC; and (OR=0.87, 95%CI= 0.67-1.13) for AA vs. (CC+AC)]. Subgroups analysis showed that there is an associations between CYP1A2 -163 C>A polymorphism and lung cancer risk for population-based controls, a trend risk for SCCL (squamonus cell carcinoma of lung) and Caucasians.

Sensitivity analysis and publication bias

We conducted a leave-one-out sensitivity analysis and found a significant association in the comparisons of C vs. A (OR = 0.84, 95% CI=0.71-0.99; I^2=65%), as well as AA vs. CC (OR = 0.64, 95% CI: 0.52-0.80; I^2=46%) and AA vs. (CC+AC) (OR = 0.78, 95% CI=0.68-0.90; I^2=31%) in the overall analysis when omitting the study by B'Chir et al. (2009).

The funnel plot showed a relatively symmetric distribution, which means there may be no publication bias existed (Figure 2).

Discussion

Our meta-analysis based on eight studies shows that there is no association between CYP1A2 -163 C>A polymorphism and lung cancer risk, this is similar with the study by Wang et al. (2012). However, our meta-analysis conducted more subgroups analysis and the results are unlike their study. The previously meta-analysis (Wang et al., 2012) indicated that CYP1A2 -163 C>A polymorphism is likely to be associated with susceptibility to cancer in Caucasians, but our meta-analysis do not support this. In addition, our result indicates the CYP1A2

-163 C>A polymorphism is associated with risk of lung cancer when the controls are population-based and the histopathological type is squamonus cell carcinoma. The reason why the results of subgroups analysis are different may because of our analysis only focuses on the lung cancer and included more studies.

Sensitivity analysis indicated the overall result was influenced by the study of B'Chir et al. (2009), we found the sample size was the fewest of all included studies. As we know, single study often failed to provide convincing evidence of linkage and have resulted in contradicting findings, especially the small sample size studies (Lohmueller et al., 2003). Meta-analysis provided a popular method for combining worldwide literatures across studies to resolve the statistical power and discrepancy problem in of genetic association studies (Munafo et al., 2004). In addition, we found the source of controls were hospital-based of B'Chir et al. (2009) and this study failed to identify a significant association between CYP1A2 -163 C>A polymorphism and lung cancer risk of overall population (*p*>0.5); however, when they divided the cases into SCC and adenocarcinoma, a significant association was found of SCC (*p*<0.01) but remain no significant of adenocarcinoma (*p*>0.1). The result is similar with our subgroup analysis according to source of control and cancer type.

To we knowledge, this meta-analysis is firstly available for comprehensively evaluating the associations between CYP1A2 -163 C>A polymorphism and lung cancer risk. However, there are also some limitations should demonstrate. First, although the no obviously publication bias was detected, our meta-analysis only included published studies, publication bias may have occurred. At the same time, we try our best to search but the number of included studies is not enough, for the limiting of the languages and permission of databases to use. Second, our meta-analysis could not escape from the inherent vice of meta-analysis. For it is a type of secondary and retrospective study, it is limited by the quality of primary studies and different populations, measurement tools, or researchers. Third, for lacking of detailed genotype information stratified by main confounding variables, such as gender, age, smoking, and alcohol in original studies, this meta-analysis was based on unadjusted data. Therefore, we could not obtain a more precise analysis that based on the adjusted other factors currently.

In conclusion, our meta-analysis indicated that there is no association between CYP1A2 -163 C>A polymorphism and lung cancer risk of overall population; there is an association between CYP1A2 -163 C>A polymorphism and population-based controls; there is a tendency of SCCL, nested case-control study, and Caucasians. However, due to the limitations of our meta-analysis, the results should be explained with caution and need to further identify by high quality studies.

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