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 lung 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 polymorphism and lung cancer risk; (2) the study was a cohort study, case-control study or nested case-control study; (3) the study population included lung cancer patients and healthy controls; (4) the study reported odds ratio (OR) and 95% confidence interval (CI) for the association of CYP1A2 -163 C>A polymorphism and lung cancer risk; (5) the study was published in English or Chinese. After excluding studies that did not meet the inclusion criteria, seven case-control studies and one nested case-control study involving 1,675 lung cancer patients and 2,393 controls were included.

Meta-analysis

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. 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. AA; (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 -163 C>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

Asian Pacific J Cancer Prev, 14 (5), 3155-3158
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
were included.

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)

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).

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

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>N</th>
<th>A vs. C</th>
<th>AA vs. CC</th>
<th>AC vs. CC</th>
<th>(AC+AA) vs. CC</th>
<th>AA vs. (CC+AC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8</td>
<td>0.80(0.74-1.07)</td>
<td>0.73(0.50-1.07)</td>
<td>0.82(0.62-1.09)</td>
<td>0.79(0.58-1.07)</td>
<td>0.87(0.67-1.13)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>4</td>
<td>0.90(0.75-1.09)</td>
<td>0.70(0.53-0.92)*</td>
<td>0.91(0.59-1.38)</td>
<td>0.84(0.54-1.31)</td>
<td>0.81(0.69-0.96)*</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>0.87(0.63-1.21)</td>
<td>0.69(0.44-1.10)</td>
<td>0.83(0.57-1.23)</td>
<td>0.80(0.57-1.12)</td>
<td>0.86(0.43-1.74)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0.89(0.33-2.44)</td>
<td>0.75(0.08-7.26)</td>
<td>0.59(0.28-1.24)</td>
<td>0.60(0.16-2.26)</td>
<td>0.86(0.43-1.74)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>6</td>
<td>0.94(0.73-1.22)</td>
<td>0.80(0.47-1.37)</td>
<td>0.79(0.53-1.39)</td>
<td>0.91(0.75-1.12)</td>
<td>0.90(0.68-1.40)</td>
</tr>
<tr>
<td>SCCL</td>
<td>2</td>
<td>0.77(0.50-0.92)*</td>
<td>0.59(0.41-0.86)*</td>
<td>0.84(0.60-1.17)</td>
<td>0.74(0.54-1.01)</td>
<td>0.71(0.55-0.91)*</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>7</td>
<td>0.91(0.72-1.14)</td>
<td>0.75(0.49-1.21)</td>
<td>0.85(0.63-1.16)</td>
<td>0.82(0.59-1.15)</td>
<td>0.90(0.64-1.26)</td>
</tr>
<tr>
<td>NCC</td>
<td>1</td>
<td>0.80(0.67-0.97)*</td>
<td>0.58(0.38-0.89)*</td>
<td>0.66(0.43-1.02)</td>
<td>0.63(0.40-0.93)</td>
<td>0.81(0.64-1.03)</td>
</tr>
<tr>
<td>HWE for control</td>
<td>&gt;0.05</td>
<td>7</td>
<td>0.88(0.72-1.09)</td>
<td>0.72(0.47-1.10)</td>
<td>0.82(0.60-1.12)</td>
<td>0.78(0.56-1.10)</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>1</td>
<td>0.80(0.67-1.36)</td>
<td>0.83(0.36-1.90)</td>
<td>0.78(0.37-1.67)</td>
<td>0.80(0.38-1.66)</td>
<td>1.02(0.59-1.75)</td>
</tr>
</tbody>
</table>

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

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; Osaka 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)
including 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country (Ethnicity)</th>
<th>Study design</th>
<th>Cancer type</th>
<th>Case</th>
<th>Source of control</th>
<th>Control</th>
<th>Genotype method</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemignani 2007</td>
<td>Six European countries (Caucasian)</td>
<td>CC</td>
<td>Mixed</td>
<td>297 120 151</td>
<td>26</td>
<td>HB 130 149 310</td>
<td>30</td>
<td>PCR</td>
</tr>
<tr>
<td>Osaka 2007</td>
<td>Japan (Asian)</td>
<td>CC</td>
<td>Mixed</td>
<td>113 18 40</td>
<td>45</td>
<td>HB 121 17</td>
<td>52</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Zienolddiny 2008</td>
<td>Norway (Caucasian)</td>
<td>CC</td>
<td>SCCL</td>
<td>335 40 149</td>
<td>146</td>
<td>PB 393 34</td>
<td>159</td>
<td>200</td>
</tr>
<tr>
<td>Aldrich 2009</td>
<td>USA (Latino)</td>
<td>CC</td>
<td>Mixed</td>
<td>113 16 51</td>
<td>46</td>
<td>PB 299 14</td>
<td>114</td>
<td>171</td>
</tr>
<tr>
<td>B’Chir 2009</td>
<td>Tunisia (Tunisian)</td>
<td>CC</td>
<td>Mixed</td>
<td>101 24 44</td>
<td>33</td>
<td>HB 98 26</td>
<td>57</td>
<td>15</td>
</tr>
<tr>
<td>Singh 2010/2011</td>
<td>India (Asian)</td>
<td>CC</td>
<td>SCCL</td>
<td>200 73</td>
<td>94</td>
<td>PB 200 61</td>
<td>90</td>
<td>49</td>
</tr>
<tr>
<td>Pavanello 2012</td>
<td>Denmark (Caucasian)</td>
<td>NCC</td>
<td>Mixed</td>
<td>421 45 174</td>
<td>202</td>
<td>PB 776 53</td>
<td>311</td>
<td>412</td>
</tr>
<tr>
<td>Gervasini 2013</td>
<td>Spain (Caucasian)</td>
<td>CC</td>
<td>Mixed</td>
<td>95 13 55</td>
<td>27</td>
<td>HB 196 22</td>
<td>119</td>
<td>55</td>
</tr>
</tbody>
</table>

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

Support this. In addition, our result indicates the CYP1A2 polymorphism is likely to be associated with susceptibility to cancer in Caucasians, but our meta-analysis do not. The previously 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 squamous 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 our 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 be explained with caution and need to be further identify by high quality studies. 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 source of control and cancer type.

In conclusion, our meta-analysis indicated that there is 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 (squamous 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; F=65%), as well as AA vs. CC (OR = 0.64, 95% CI= 0.52-0.80; F=46%) and AA vs. (CC+AC) (OR = 0.78, 95% CI=0.68-0.90; F=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 squamous 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.

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To our 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 be explained with caution and need to be further identify by high quality studies.

Acknowledgements

This research was supported (in part) by the Natural Science Foundation of Hubei Ministry of Education (Q20122405), the Science Planning Project of Shiyan City
(068s), and the Intramural Research Program of the Hubei University of Medicine (2011CZX01), without commercial or not-for-profit sectors. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study. The author(s) declare that they have no competing interests.

References


