Genetic Variants of CYP2D6 Gene and Cancer Risk: A HuGE Systematic Review and Meta-analysis

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Abstract

Objective: Genetic polymorphisms in metabolic enzymes are associated with numerous cancers. A large number of single nucleotide polymorphisms (SNPs) in the CYP2D6 gene have been reported to associate with cancer susceptibility. However, the results are controversial. The aim of this Human Genome Epidemiology (HuGE) review and meta-analysis was to summarize the evidence for associations. Methods: Studies focusing on the relationship between CYP2D6 gene polymorphisms and susceptibility to cancer were selected from the Pubmed, Cochrane library, Embase, Web of Science, Springerlink, CNKI and CBM databases. Data were extracted by two independent reviewers and the meta-analysis was performed with Review Manager Version 5.1.6 and STATA Version 12.0 software. Odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated. Results: According to the inclusion criteria, forty-three studies with a total of 7,089 cancer cases and 9,646 healthy controls, were included in the meta-analysis. The results showed that there was a positive association between heterozygote (GC) of rs1135840 and cancer risk (OR=1.92, 95% CI: 1.14-3.21, P=0.01). In addition, we found that homozygote (CC) of rs1135840 might be a protective factor for cancer (OR=0.58, 95% CI: 0.34-0.97, P=0.04). Similarly, the G allele and G carrier (AG + GG) of rs16947 and heterozygote (A/del) of rs35742686 had negative associations with cancer risk (OR=0.69, 95% CI: 0.48-0.99, P=0.04; OR=0.60, 95% CI: 0.38-0.94, P=0.03; OR=0.50, 95% CI: 0.26-0.95, P=0.03; respectively). Conclusion: This meta-analysis suggests that CYP2D6 gene polymorphisms are involved in the pathogenesis of various cancers. The heterozygote (GC) of rs1135840 in CYP2D6 gene might increase the risk while the homozygote (CC) of rs1135840, G allele and G carrier (AG + GG) of rs16947 and heterozygote (A/del) of rs35742686 might be protective factors.

Keywords: CYP2D6 - polymorphism - cancer - meta-analysis

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Introduction

Cytochrome P450 (CYP450) is a large and diverse group of metabolic enzymes containing heme, consisted by many isozyme, also known as P450 gene superfamily (Wexler et al., 2004). CYP450 is mainly in the endoplasmic reticulum of liver, involved in the endogenous and exogenous substances with biological transformation (Lewis et al., 2004). To date, it has been found 17 CYP450 gene families, 36 gene subgroups in mammals. The research work mainly focus on CYP1A, CYP2A6, CYP2D6, CYP2C9, CYP2C19 and CYP3A (Foster et al., 2003; Agundez et al., 2004). Cytochrome P450 2D6 (CYP2D6), a member of the cytochrome P450 mixed-function oxidase system, is one of the most important enzymes involved in the metabolism of xenobiotics in the body (Lewis et al., 2004). CYP2D6 is the first identified P450 enzymes controlled by single gene, the gene encoding this protein located on the long arm of chromosome 22q13 (Zhou et al., 2009). Although CYP2D6 only accounts for 2% of the total liver CYP450 protein, it is the most genetic polymorphism of metabolic enzymes so far, metabolizing nearly 20%-25% drugs in clinically with large individual differences (Kimura et al., 1989; Wilkinson et al., 2005; Sistonen et al., 2007).

CYP2D6 has a number of mutants which are the consequence of insertion or deletion or null of allele (Meyer et al., 1997; Singh et al., 2011). At present, the number of the identified CYP2D6 allelic variant is 80 and is still growing. The allelic variant distribution differs among different ethnic groups (Lewis et al., 2004). CYP2D6*2, *3, *4, *5, *6, *10 & *41 are more common in Caucasians, *2 and *17 are more frequently observed in Africans and *10 is more prevalent in Asians (Garcia-Barcelo et al., 2000; Ji et al., 2002; Roberts et al., 2006; ). CYP2D6 metabolic polymorphisms may have associations with some diseases susceptibility, such as cancers, Parkinson’s disease, Alzheimer’s disease, ankylosing
spondylitis and rheumatoid arthritis (Ouerhani et al., 2008). Metabolic activation of carcinogens might proceed via CYP2D6 which implies that a patient of extensive metabolism phenotype forms higher amounts of the active compounds. and therefore at a higher risk to develop cancer, such as bladder cancer, breast cancer, head cancer and neck cancer (Kroemer et al., 1995). Surekha et al have confirmed that that the CYP2D6*4 polymorphism plays an important role in breast cancer etiology (Surekha et al., 2010). However, the association between CYP2D6 alleles and cancer development is rather complicated. Abraham et al have found that common variants of CYP2D6 do not play a significant role in breast cancer susceptibility, but not including rare variants, such as CYP2D6* 6 which merit further investigation (Abraham et al., 2011). Besides, Morrow et al have demonstrated no significant effect of CYP2D6 genotype on risk of recurrence in breast cancer patients who received adjuvant tamoxifen therapy in a case-control study (Morrow et al., 2012). In addiction, a recent convey with 123 cases and 129 healthy controls has showed that no association was found between CYP2D6 and gastric cancer risk in Han ethnic population of Hunan Province (Luo et al., 2011). These studies reported a conflicting and inconclusive results. Given controversial results in those previous studies, we conducted a meta-analysis to explore the associations between CYP2D6 genetic polymorphisms and risk of cancer.

Materials and Methods

Literature search

We performed an electronic search of the Pubmed, Cochrane library, Embase, Web of science, Springerlink, CNKI and CBM databases extensively to identify relevant studies available up to May 20, 2012. The search terms were used, including (“Cytochrome P-450 CYP2D6” [Mesh] or “CYP2D6” or “CYP 2D6” or “Debrisoquine 4 Monooxygenase” or “Imipramine 2 Hydroxylase”) and (“SNPs” or “SNP” or “polymorphism, genetic” [Mesh]) and (“cancer” or “tumor” or “Neoplasms” [Mesh]). The references in the eligible studies or textbooks were also reviewed to check through manual searches to find other potentially eligible studies.

Inclusion and exclusion criteria

The included studies had to meet the following criteria: i) Case-control study focused on associations between CYP2D6 gene polymorphisms and cancer risk; ii) All patients with the diagnosis of malignant tumor confirmed by pathological examination of the surgical specimen; iii) The frequencies of alleles or genotypes in case and control groups could be extracted; iv) The publication was in English or Chinese. Studies were excluded when they were: i) Not case-control studies about CYP2D6 gene polymorphisms and cancer risk; ii) Based on incomplete data; iii) Useless or overlapping data were reported; iv) Meta-analyses, letters, reviews or editorial articles.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers to populate the necessary information. The following information was extracted from each of the articles included: first author, year of publication, country, language, ethnicity, study design, source of cases and controls, number of cases and controls, mean age, sample, cancer type, genotype method, allele and genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in controls. In case of conflicting evaluations, an agreement was reached following a discussion with a third reviewer.

Quality assessment of included studies

Two reviewers independently assessed the quality of papers according to modified STROBE quality score systems (von Elm et al., 2007; Zhang et al., 2011). Forty assessment items related with the quality appraisal were used in this meta-analysis, scores ranging from 0 to 40. Scores of 0-20, 20-30 and 30-40 were defined as low, moderate and high quality, respectively. Disagreement was resolved by discussion.

Statistical analysis

The odds ratio (OR) and 95% confidence interval (95%CI) were calculated using Review Manager Version 5.1.6 (provided by the Cochrane Collaboration, available at: http://ims.cochrane.org/revman/download) and STATA Version 12.0 (Stata Corp., College Station, TX) softwares. Between-study variations and heterogeneities were estimated using Cochran’s Q-statistic (Higgins et al., 2002; Zintzaras et al., 2005) (P≤0.05 was considered to be manifestation of statistically significant heterogeneity). We also quantified the effect of heterogeneity by using I2 test, which ranges from 0 to 100% and represents the proportion of inter-study variability that can be contributed to heterogeneity rather than by chance. When a significant Q-test (P≤0.05) or I2>50% indicated that heterogeneity among studies existed, the random effects model was conducted for meta-analysis. Otherwise, the fixed effects model was used. To establish the effect of heterogeneity on meta-analyses’ conclusions, subgroup analysis was operated. We tested whether genotype frequencies of controls were in HWE using the χ² test. Funnel plots are often used to detect publication bias. However, due to its limitations caused by varied sample sizes and subjective reviews, Egger’s linear regression test which measures funnel plot’s asymmetry using a natural logarithm scale of OR was used to evaluate the publication bias (Peters et al., 2006). When the P value is less than 0.1, publication bias is considered significant. All the P values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers populated the data in the statistical software programs independently and obtained the same results.

Results

Characteristics of included studies

We identified a total of 211 relevant publications after initial screening. According to the inclusion criteria, 43 studies (Agúndez et al., 1994; Wundrack et al., 1994; Agúndez et al., 1995; Agúndez et al., 1996; Ladona et al., 1996; Legrand et al., 1996; London et al., 1997; Agúndez et al., 1998; Febbo et al., 1998; González et al., 1998; Hu et
Table 1. Characteristics of Included Studies in this Meta-analysis

| First author             | Year | Country       | Number Case | Control | Sample Type | Genotype method   | Cancer Type       | Quality scores |
|--------------------------|------|---------------|-------------|---------|-------------|-------------------|------------------|----------------|
| Agúndez et al. 1994      | Spain| 89 Blood      | 98          |         | AS-PCR      | Lung cancer       | 24               |
| Wundrack et al. 1994     | Germany| 31 Blood/Tissue| 720 DNA sequencing | Menigioma | 20         |
| Agúndez et al. 1995      | Spain| 75 Blood      | 200         |         | PCR-RFLP    | Liver cancer      | 20               |
| Agúndez et al. 1996      | Spain| 100 Blood     | 258         |         | PCR-RFLP    | Liver cancer      | 20               |
| Ladoma et al. 1996       | Spain| 187 Blood     | 151         |         | AS-PCR      | Breast cancer     | 23               |
| Legrand et al. 1996      | France| 249 Blood    | 265         |         | PCR-SSCP    | Lung cancer       | 27               |
| London et al. 1997       | UK   | 158 Blood     | 246         |         | AS-PCR      | Lung cancer       | 20               |
| Agúndez et al. 1998      | Spain| 94 Blood      | 160         |         | PCR-RFLP/AS-PCR | Prostate cancer | 27               |
| Febbo et al. 1998        | USA  | 571 Blood     | 767         |         | PCR-RFLP    | Prostate cancer   | 25               |
| González et al. 1998     | Spain| 75 Blood      | 200         |         | PCR-RFLP    | Head and neck cancer | 22          |
| Hu et al. 1998           | China| 59 Blood      | 59          |         | PCR-RFLP    | Lung cancer        | 21               |
| Shaw et al. 1998         | USA  | 98 Blood      | 110         |         | DNA sequencing | Lung cancer      | 28               |
| Krajnovic et al. 1999    | Spain| 177 Blood     | 304         |         | PCR-RFLP    | Leukemia           | 28               |
| Lemos et al. 1999        | Portugal | 160 Blood | 128         |         | PCR-RFLP    | Neoplasias         | 27               |
| Topić et al. 2000        | Croatia| 76 Blood | 144         |         | PCRSSCP      | Breast cancer      | 21               |
| Butler et al. 2001       | Australia| 219 Blood | 200         |         | PCR-RFLP    | Colorectal cancer  | 21               |
| Liu et al. 2002          | China | 84 Blood/Tissue | 144 PCR-RFLP | Liver cancer | 20         |
| Sobti et al. 2003        | India | 100 Blood     | 76          |         | PCR-RFLP    | Lung cancer        | 22               |
| Chen et al. 2004         | China | 50 Blood      | 50          |         | PCR-RFLP    | Lung cancer        | 24               |
| Fukatsu et al. 2004      | Japan | 147 Blood/Tissue | 266 PCR-RFLP | Prostate cancer | 22          |
| Li et al. 2004           | China | 217 Blood     | 200         |         | PCR-RFLP    | Lung cancer        | 27               |
| Gajecka et al. 2005      | Poland| 289 Blood     | 316         |         | PCR-RFLP    | Laryngeal cancer   | 28               |
| Gomes et al. 2005        | Portugal | 235 Blood | 256         |         | PCR-RFLP    | Prostate tumor     | 25               |
| Guo et al. 2005          | China | 150 Blood     | 152         |         | PCR-RFLP    | Lung cancer        | 23               |
| Liang et al. 2005        | China | 227 Blood     | 227         |         | PCR-RFLP    | Lung cancer        | 27               |
| Mochizuki et al. 2005    | Japan  | 44 Blood      | 577         |         | PCR-RFLP    | Lung cancer        | 26               |
| Sobti et al. 2005        | India  | 100 Blood/Tissue | 76 PCR-RFLP | Bladder cancer | 25          |
| Aydin-Sayitoglu et al. 2006 | Turkey   | 250 Blood/Marrow | 140 PCR-RFLP | Leukemia | 28         |
| Bonanni et al. 2006      | Italy | 46 Blood      | 136         |         | TaqMan      | Breast cancer      | 25               |
| Li et al. 2006           | China | 286 Blood     | 305         |         | PCR-RFLP    | Breast cancer      | 26               |
| Lemos et al. 2007        | Portugal | 187 Blood | 256         |         | PCR-RFLP    | Thyroid cancer     | 27               |
| Chen et al. 2008         | China | 348 Blood     | 204         |         | PCR-RFLP    | Leukemia           | 26               |
| Khedhaier et al. 2008    | Tunisia| 314 Blood     | 246         |         | PCR-RFLP    | Breast cancer      | 30               |
| Majumdar et al. 2008     | India  | 110 Blood     | 144         |         | PCR-RFLP    | Leukemia           | 30               |
| Ouerhani et al. 2008     | Tunisia| 80 Blood      | 109         |         | PCR-RFLP    | Bladder cancer     | 26               |
| Torresan et al. 2008     | Brazil | 102 Blood     | 102         |         | PCR-RFLP    | Breast cancer      | 30               |
| Yan et al. 2008          | China | 118 Blood     | 118         |         | PCR-RFLP    | Lung cancer        | 27               |
| Altayli et al. 2009      | Turkey | 135 Blood     | 128         |         | PCR-RFLP    | Bladder cancer     | 28               |
| Gutman et al. 2009       | Israel | 43 Blood      | 123         |         | AS-PCR      | Cervical cancer    | 27               |
| Surekha et al. 2010      | India  | 230 Blood     | 250         |         | PCR-RFLP    | Breast cancer      | 25               |
| Lim et al. 2011          | Singapore | 165 Blood  | 228         |         | DNA sequencing | Breast cancer | 31               |
| Luo et al. 2011          | China | 123 Blood     | 129         |         | PCR-RFLP    | Gastric cancer     | 27               |
| Zhou et al. 2011         | China | 86 Blood      | 86          |         | PCR-RFLP    | Lung cancer        | 25               |

PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; AS, allele specific

Figure 1. Flow Chart Shows Study Selection Procedure
## Table 2. The Genotype Distribution of CYP2D6 Polymorphisms in Case and Control Groups

| First author          | SNP             | Total 1 | 1 | 2 | 1/1 2/1 1/2   | 1/1+2/1 2/2 | HWE test |
|-----------------------|-----------------|---------|---|---|-----|-----|-----|-----|-----|
| Agúndez et al         | rs3892097 (G/A) | 112     | 56 | 54 | 0   16 |   0   | 2   | 0   | 0.01|
| rs35742686 (A/-)      | 324             | 159     | 161| 34 | 17  | 54   | 2   | 0.00|
| Butler et al          | rs35742686 (A/-)| 146     | 42 | 104| 1   0  | 0    | 0   | 0.03|
| Gomes et al           | rs35742686 (A/-)| 345     | 221| 124| 1   0  | 0    | 0.00|
| Gao et al             | rs35742686 (A/-)| 225     | 40 | 185| 1   0  | 0    | 0.00|
| Li et al              | rs35742686 (A/-)| 288     | 162 |2   0  | 0    | 0.00|
| Moehl et al           | rs35742686 (A/-)| 207     | 40 | 167| 1   0  | 0    | 0.00|
| Moehl et al           | rs5030656 (ins/del)| 207     | 40 | 167| 1   0  | 0    | 0.00|
| Ouelhazi et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saavedra et al        | rs35742686 (A/-)| 37      | 3  | 34 | 0   1  | 0    | 0.00|
| Saaved...
Table 3. Meta-analysis of the Association between CYP2D6 Gene Polymorphisms and Cancer Susceptibility

| Polymorphisms       | Cancer    | Control   | OR [95%CI]       | P      | Heterogeneity | Effect model |
|---------------------|-----------|-----------|------------------|--------|---------------|--------------|
|                     | n/N       | n/N       |                  |        |               |              |
| rs3892097 (G>A)     | A allele  | 1629/10032| 2271/13948       | 1.00   | [0.93, 1.08]  | 0.92 <0.01   | 70% Random   |
|                     | A carrier | 1364/4822 | 1913/6774        | 1.01   | [0.84, 1.21]  | 0.94 <0.01   | 71%          |
|                     | AA        | 482/4822  | 253/6774         | 1.03   | [0.84, 1.26]  | 0.75 <0.06   | 32%          |
|                     | GA        | 1182/4822 | 1678/6774        | 1.01   | [0.84, 1.22]  | 0.93 <0.01   | 69%          |
| rs35742686 (A/del)  | del allele| 20/1352   | 38/1702          | 0.58   | [0.23, 1.47]  | 0.26 0.07    | 53% Fixed    |
|                     | del carrier| 14/766   | 31/851           | 0.55   | [0.29, 1.04]  | 0.06 0.15    | 44%          |
|                     | del/del  | 6/32     | 7/851            | 1.11   | [0.39, 3.15]  | 0.84 0.22    | 34%          |
|                     | A/del    | 14/766   | 32/851           | 0.50   | [0.26, 0.95]  | 0.03 0.57    | 0%           |
| rs5030656 (ins/del) | del allele| 40/2984  | 30/2478          | 1.90   | [0.62, 5.83]  | 0.26 0.02    | 74% Random   |
|                     | del carrier| 39/294   | 27/487           | 2.13   | [0.74, 6.17]  | 0.16 0.04    | 69%          |
|                     | del/del  | 3/394    | 4/487            | 0.54   | [0.12, 2.43]  | 0.42 0.39    | 0%           |
|                     | ins/del  | 38/294   | 23/487           | 2.33   | [0.92, 5.87]  | 0.07 0.1     | 57%          |
| rs1065852 (C/T)     | T allele  | 1851/3408| 2334/4452        | 0.86   | [0.73, 1.01]  | 0.07 <0.002  | 62% Fixed    |
|                     | T carrier | 1299/1704| 1608/2226        | 0.91   | [0.77, 1.07]  | 0.24 0.26    | 19%          |
|                     | CT       | 552/1704 | 726/2226         | 0.82   | [0.66, 1.01]  | 0.07 0.03    | 49%          |
|                     | I4001467 (C/T) | T allele | 31/168  | 41/288 | 1.36 | [0.82, 2.27] | 0.23 | - - | Fixed |
|                     | T carrier | 31/84   | 32/144           | 1.57   | [0.89, 2.80]  | 0.12 | - - | - |
|                     | TT       | 0/84    | 2/144            | 0.34   | [0.02, 7.11]  | 0.48 | - - | - |
|                     | CT       | 31/84   | 37/144           | 1.69   | [0.95, 3.02]  | 0.08 | - - | - |
| 2D6*5 (ins/del)     | del allele| 29/418  | 83/1608          | 1.27   | [0.77, 2.09]  | 0.35 0.2     | 38% Fixed    |
|                     | del carrier| 26/165  | 24/227           | 1.58   | [0.87, 2.87]  | 0.13 | - - | - |
|                     | del/del  | 0/165   | 0/227            | -      | - - | - - | - |
|                     | ins/del  | 26/165  | 24/227           | 1.58   | [0.87, 2.87]  | 0.13 | - - | - |
| Rs1135840 (G/C)     | C allele  | 164/236  | 177/236          | 0.76   | [0.51, 1.14]  | 0.18 | - - | Fixed |
|                     | C carrier | 117/118 | 114/118          | 4.11   | [0.45, 37.29] | 0.21 | - - | - |
|                     | CC       | 47/118  | 63/118           | 0.58   | [0.34, 0.97]  | 0.04 | - - | - |
|                     | GC       | 70/118  | 51/118           | 1.92   | [1.14, 3.21]  | 0.01 | - - | - |
| Rs16947 (A/G)       | G allele  | 57/278  | 108/396          | 0.69   | [0.48, 0.99]  | 0.04 | - - | Fixed |
|                     | G carrier | 47/139 | 91/198           | 0.60   | [0.38, 0.94]  | 0.03 | - - | - |
|                     | GG       | 10/139  | 17/198           | 0.83   | [0.37, 1.86]  | 0.64 | - - | - |
|                     | AG       | 37/139  | 74/198           | 0.61   | [0.38, 0.98]  | 0.04 | - - | - |
| Rs1080985 (C/G)     | G allele  | 40/278  | 76/406           | 0.73   | [0.48, 1.11]  | 0.14 | - - | Fixed |
|                     | G carrier | 34/139 | 67/203           | 0.66   | [0.40, 1.07]  | 0.09 | - - | - |
|                     | GG       | 6/139   | 9/203            | 0.97   | [0.34, 2.80]  | 0.96 | - - | - |
|                     | CG       | 28/139  | 58/203           | 0.63   | [0.38, 1.05]  | 0.08 | - - | - |
| 2D6*14 (G/A)        | A allele  | 4/204   | 2/364            | 3.62   | [0.66, 19.94] | 0.14 | - - | Fixed |
|                     | A carrier | 4/102  | 2/204            | 4.12   | [0.74, 22.89] | 0.11 | - - | - |
|                     | AA       | 0/204   | 0/204            | -      | - - | - - | - |
|                     | GA       | 4/102   | 2/204            | 4.12   | [0.74, 22.89] | 0.11 | - - | - |
| Rs28371725 (G/A)    | A allele  | 15/278  | 34/390           | 0.60   | [0.32, 1.12]  | 0.11 | - - | Fixed |
|                     | A carrier | 4/139  | 3/195            | 0.57   | [0.29, 1.11]  | 0.1 | - - | - |
|                     | AA       | 1/139   | 2/195            | 0.70   | [0.06, 7.79]  | 0.77 | - - | - |
|                     | GA       | 13/139  | 30/195           | 0.57   | [0.28, 1.13]  | 0.11 | - - | - |

OR, odds ratio; 95%CI, 95% confidence interval

Figure 3. Begger’s Funnel Plot of Publication Bias Based on rs3892097, rs5030656, rs1065852 and rs35742686 in CYP2D6 Gene

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Publication bias

Publication bias of the literatures was accessed based on rs3892097, rs5030656, rs1065852 and rs35742686 in CYP2D6 gene by Egger’s funnel plot and Egger’s linear regression test. Egger’s linear regression test was used to measure the asymmetry of the funnel plot. All graphical funnel plots of included studies appeared to be symmetrical (Figure 3). Egger’s test also showed that there was no statistical significance for all evaluations of publication bias (all P>0.05). Findings of Egger’s publication bias test are shown in Table 4.

Discussion

CYP450 is a enzymes superfamily of which function is to catalyze the oxidation of organic substances, and are the major enzymes involved in drug metabolism and bio-activation (Agundez et al., 2004). CYP2D6, located on chromosome 22, is one of the most important CYP450 enzymes involved in the metabolism of xenobiotics in the body (Jin et al., 2005; Singh et al., 2011). CYP2D6 gene polymorphisms are susceptibility factors to various diseases, including cancers, Parkinson’s disease, Systemic Lupus Erythematosus (SLE), nephropathy and ankylosing spondylitis (Surekha et al., 2010). According to the published studies, the association between CYP2D6 and cancer risk is not precise and very controversial. Agúndez et al have showed that individuals who were homozygous for functional CYP2D6 genes appear to be at higher risk of developing primary liver cancer (Agúndez et al., 1995). Gajecka et al have found that CYP2D6*4 allele and CYP2D6*4/*4 genotype might increase the risk of laryngeal cancer (Gajecka et al., 2005). However, Gutman et al have indicated that CYP2D6 mutations are not related to an increased risk for cervical cancer in the Jewish Israeli population (Gutman et al., 2009).

In this meta-analysis, we quantitatively assessed the association between CYP2D6 gene polymorphisms and cancer risk. Finally, 43 case-control studies were included with a total of 7009 cancer cases and 9646 healthy controls. We examined eleven polymorphisms of CYP2D6 gene, including rs3892097, rs5030656, rs1065852, rs35742686, i4001467, 2D6*5, rs1135840, rs16947, rs1080985, 2D6*14, rs28371725. The meta-analysis results showed a positive association between the heterozygote (GC) of rs1135840 and cancer risk, which indicated that heterozygote (GC) of rs1135840 might be a potential risk factor for cancer. In addiction, the G allele and G carrier (AG + GG) of rs16947 and heterozygote (A/del) of rs35742686 in CYP2D6 gene were found negative associations with cancer risk, which suggested that these SNPs of CYP2D6 gene might decrease the risk of cancer. Interestingly, we also found that the homozygote (CC) of rs1135840 in CYP2D6 gene might decrease the risk of cancer, suggesting rs1135840 might also be a protective factor for cancer. In the subgroup analysis by ethnicity, we found that the A carrier and heterozygote (GA) of rs3892097 might increase the risk of cancer in Asian population, but not in Caucasian and African populations. Sensitivity analysis was performed by omitting any single study and non-HWE studies, no influence was found.

Limitations in our meta-analysis should be acknowledged. Firstly, the control subjects in our study might not be representative of the general population, necessitating well-designed population-based studies with large sample sizes and detailed exposure information to validate our findings. Secondly, although the funnel plot and Egger’s test did not show any publication bias, selection bias could have occurred because only studies published in English or Chinese were included. Thirdly, some relevant studies could not be included in our analysis due to incomplete raw data. Fourthly, we were not able to address the sources of heterogeneity among all studies. In addiction, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results. Moreover, our meta-analysis was based on un-adjust ORs estimates because not all published presented adjusted ORs or when they did, the ORs were not adjusted by the same potential confounders.
such as ethnicity, gender, geographic distribution, etc. Given these results, additional investigation in these areas is needed, and our conclusions should be interpreted cautiously.

In conclusion, this meta-analysis of 43 case-control studies demonstrated that CYP2D6 gene polymorphisms are involved in the pathogenesis of variant cancer. The heterozygote (GC) of rs1135840 in CYP2D6 gene might increase the risk of cancer, while the homozygote (CC) of rs1135840, G allele and G carrier (AG + GG) of rs16947 and heterozygote (A/del) of rs35742686 might be protective factors for cancer.

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