RESEARCH ARTICLE

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 7,009 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

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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) ($P \leq 0.05$ 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 ($P \leq 0.05$) or $I^2 > 50\%$ 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 χ^2 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		Sample	Genotype method	Cancer type	Quality scores
			Case	Control				
Agúndez et al	1994	Spain	89	98	Blood	AS-PCR	Lung cancer	24
Wundrack et al	1994	Germany	31	720	Blood/Tissue	DNA sequencing	Meningioma	20
Agúndez et al	1995	Spain	75	200	Blood	PCR-RFLP	Liver cancer	20
Agúndez et al	1996	Spain	100	258	Blood	PCR-RFLP	Liver cancer	28
Ladona et al	1996	Spain	187	151	Blood	AS-PCR	Breast cancer	23
Legrand et al	1996	France	249	265	Blood	PCR-SSCP	Lung cancer	21
London et al	1997	UK	158	246	Blood	AS-PCR	Lung cancer	30
Agúndez et al	1998	Spain	94	160	Blood	PCR-RFLP/AS-PCR	Prostate cancer	27
Febbo et al	1998	USA	571	767	Blood	PCR-RFLP	Prostate cancer	25
González et al	1998	Spain	75	200	Blood	PCR-RFLP	Head and neck cancer	22
Hu et al	1998	China	59	59	Blood	PCR-RFLP	Lung cancer	21
Shaw et al	1998	USA	98	110	Blood	DNA sequencing	Lung cancer	28
Krajinovic et al	1999	Canada	177	304	Blood	PCR-RFLP	Leukemia	28
Lemos et al	1999	Portugal	160	128	Blood	PCR-RFLP	Neoplasias	27
			64	128	Blood	PCR-RFLP	Leukemia	
Topić et al	2000	Croatia	76	144	Blood	PCR-SSCP	Breast cancer	21
			56	144	Blood	PCR-SSCP	Head and neck cancer	
Butler et al	2001	Australia	219	200	Blood	PCR-RFLP	Colorectal cancer	21
Liu et al	2002	China	84	144	Blood/Tissue	PCR-RFLP	Liver cancer	20
Sobti et al	2003	India	100	76	Blood	PCR-RFLP	Lung cancer	22
Chen et al	2004	China	50	50	Blood	PCR-RFLP	Lung cancer	24
Fukatsu et al	2004	Japan	147	266	Blood/Tissue	PCR-RFLP	Prostate cancer	22
Li et al	2004	China	217	200	Blood	PCR-RFLP	Lung cancer	27
Gajecka et al	2005	Poland	289	316	Blood	PCR-RFLP	Laryngeal cancer	28
Gomes et al	2005	Portugal	235	256	Blood	PCR-RFLP	Pituitary tumor	25
Guo et al	2005	China	150	152	Blood	PCR-RFLP	Lung cancer	23
Liang et al	2005	China	227	227	Blood	PCR-RFLP	Lung cancer	27
Mochizuki et al	2005	Japan	44	577	Blood	PCR-RFLP	Liver cancer	26
Sobti et al	2005	India	100	76	Blood/Tissue	PCR-RFLP	Bladder cancer	25
Aydin-Sayitoglu et al	2006	Turkey	250	140	Blood/Marrow	PCR-RFLP	Leukemia	28
Bonanni et al	2006	Italy	46	136	Blood	TaqMan	Breast cancer	25
Li et al	2006	China	286	305	Blood	PCR-RFLP	Breast cancer	26
Lemos et al	2007	Portugal	187	256	Blood	PCR-RFLP	Thyroid cancer	27
Chen et al	2008	China	348	204	Blood	PCR-RFLP	Leukemia	26
Khedhaier et al	2008	Tunisia	314	246	Blood	PCR-RFLP	Breast cancer	30
Majumdar et al	2008	India	110	144	Blood	PCR-RFLP	Leukemia	30
Ouerhani et al	2008	Tunisia	80	109	Blood	PCR-RFLP	Bladder cancer	26
Torresan et al	2008	Brazil	102	102	Blood	PCR-RFLP	Breast cancer	30
Yan et al	2008	China	118	118	Blood	PCR-RFLP	Lung cancer	27
Altayli et al	2009	Turkey	135	128	Blood	PCR-RFLP	Bladder cancer	28
Gutman et al	2009	Israel	43	123	Blood	AS-PCR	Cervical cancer	27
Surekha et al	2010	India	250	250	Blood	PCR-RFLP	Breast cancer	25
Lim et al	2011	Singapore	165	228	Blood	DNA sequencing	Breast cancer	31
Luo et al	2011	China	123	129	Blood	PCR-RFLP	Gastric cancer	27
Zhou et al	2011	China	86	86	Blood	PCR-RFLP	Lung cancer	25

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

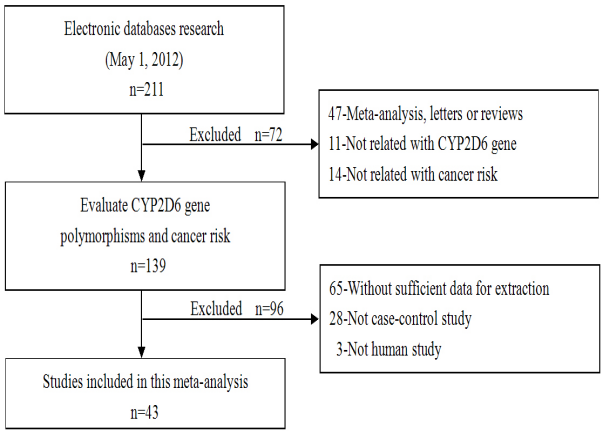

Figure 1. Flow Chart Shows Study Selection Procedure

al., 1998; Shaw et al., 1998; Krajinovic et al., 1999; Lemos et al., 1999; Topić et al., 2000; Butler et al., 2001; Liu et al., 2002; Sobti et al., 2003; Chen et al., 2004; Fukatsu et al., 2004; Li et al., 2004; Gajecka et al., 2005; Gomes et al., 2005; Guo et al., 2005; Liang et al., 2005; Mochizuki et al., 2005; Sobti et al., 2005; Aydin-Sayitoglu et al., 2006; Bonanni et al., 2006; Li et al., 2006; Lemos et al., 2007; Chen et al., 2008; Khedhaier et al., 2008; Majumdar et al., 2008; Ouerhani et al., 2008 ; Torresan et al., 2008; Yan et al., 2008; Altayli et al., 2009; Gutman et al., 2009; Surekha et al., 2010; Lim et al., 2011; Luo et al., 2011; Zhou et al., 2011) appeared to have met the inclusion criteria and were subjected to further examination. The flow chart of study selection is shown in Figure 1. In total, 7009 cancer cases and 9646 healthy controls from 43 studies were included

Table 2. The Genotype Distribution of CYP2D6 Polymorphisms in Case and Control Groups

First author	SNP	Case							Control							HWE test	
		Total	1	2	1/1	1/2	2/1	1/2+2/2	Total	1	2	1/1	1/2	2/11/2+2/2		χ^2	P
Agúndez et al	rs3892097 (G/A)	70	124	16	54	16	0	16	92	152	32	67	18	7	25	9.37	<0.01
	rs5030656 (ins/del)	70	123	17	54	15	1	16	69	136	2	67	2	0	2	0.01	0.90
Wundrack et al	rs3892097 (G/A)	31	47	15	18	11	2	13	720	1165	275	476	213	31	244	1.31	0.25
Agúndez et al	rs3892097 (G/A)	62	122	2	60	2	0	2	167	289	45	127	35	5	40	1.71	0.19
Agúndez et al	rs3892097 (G/A)	81	157	5	77	3	1	4	213	367	59	160	47	6	53	1.21	0.27
	rs5030656 (ins/del)	85	162	8	77	8	0	8	172	331	13	160	11	1	12	2.50	0.11
Ladona et al	rs3892097 (G/A)	171	280	62	115	50	6	56	143	252	34	113	26	4	30	2.50	0.11
Legrand et al	rs5030656 (ins/del)	239	463	15	224	15	0	15	246	476	16	233	10	3	13	30.83	<0.01
London et al	rs3892097 (G/A)	158	284	32	130	24	4	28	246	418	74	180	58	8	66	1.48	0.22
	rs3892097 (G/A)	185	289	81	115	59	11	70	464	720	208	283	154	27	181	0.97	0.32
Agúndez et al	rs3892097 (G/A)	76	131	21	59	13	4	17	132	229	35	101	27	4	31	1.62	0.20
Febbo et al	rs3892097 (G/A)	571	889	253	355	179	37	216	767	1239	295	511	217	39	256	6.11	0.01
González et al	rs3892097 (G/A)	75	133	17	61	11	3	14	200	346	54	153	40	7	47	4.13	0.04
Hu et al	rs1065852 (C/T)	59	57	61	19	19	21	40	59	44	74	13	18	28	46	7.13	0.01
Shaw et al	rs3892097 (G/A)	93	139	47	53	33	7	40	100	162	38	63	36	1	37	2.88	0.09
	rs35742686 (A/-)	54	107	1	53	1	0	1	64	127	1	63	1	0	1	0.00	0.95
Krajinovic et al	rs35742686 (A/-)	167	323	11	159	5	3	8	302	590	14	289	12	1	13	4.53	0.03
	rs3892097 (G/A)	176	281	71	113	55	8	63	302	500	104	207	86	9	95	0.00	0.99
Lemos et al	rs3892097 (G/A)	160	265	55	114	37	9	46	128	193	63	73	47	8	55	0.01	0.91
	rs3892097 (G/A)	64	109	19	49	11	4	15	128	193	63	73	47	8	55	0.01	0.91
Topić et al	rs35742686 (-/A)	76	151	1	75	1	0	1	144	284	4	140	4	0	4	0.03	0.87
	rs3892097 (G/A)	76	124	28	52	20	4	24	144	255	33	114	27	3	30	0.83	0.36
	rs35742686 (-/A)	56	110	2	54	2	0	2	144	284	4	140	4	0	4	0.03	0.87
	rs3892097 (G/A)	56	96	16	41	14	1	15	144	255	33	114	27	3	30	0.83	0.36
Butler et al	rs3892097 (G/A)	194	305	83				0	200	313	87	122	69	9	78	0.04	0.85
Liu et al	rs1065852 (C/T)	84	79	89	20	39	25	64	144	115	173	25	65	54	119	0.50	0.48
	i4001467 (C/T)	84	137	31	53	31	0	31	144	247	41	105	37	2	39	0.39	0.53
Sobti et al	rs3892097 (G/A)	100	175	25	75	25	0	25	76	138	14	62	14	0	14	0.78	0.38
Chen et al	rs1065852 (C/T)	50	49	51	17	15	18	33	50	37	63	12	13	25	38	9.78	<0.01
Fukatsu et al	rs3892097 (G/A)	136	269	3	133	3	0	3	232	463	1	231	1	0	1	0.00	0.97
Li et al	rs1065852 (C/T)	217	190	244	63	64	90	154	200	148	252	48	52	100	152	39.13	<0.01
Gajecka et al	rs35742686 (A/-)	164	326	2	162	2	0	2	201	390	12	191	8	2	10	19.67	<0.01
	rs3892097 (G/A)	283	427	139	162	103	18	121	305	487	123	191	105	9	114	1.46	0.23
Gomes et al	rs3892097 (G/A)	235	394	76	165	64	6	70	256	401	111	159	83	14	97	0.52	0.47
Guo et al	rs1065852 (C/T)	150	139	161	34	71	45	116	152	120	184	28	64	60	124	2.15	0.14
Liang et al	rs3892097 (G/A)	227	447	7	221	5	1	6	227	452	2	225	2	0	2	0.00	0.95
Mochizuki et al	2D6*5 (ins/del)	44	85	3				0	577	1095	59	520	55	2	57	0.18	0.67
	rs1065852 (C/T)	44	57	31	20	17	7	24	577	706	448	247	212	118	330	29.60	<0.01
Sobti et al	rs3892097 (G/A)	100	178	22	80	18	2	20	76	138	14	62	14	0	14	0.78	0.38
Aydin-Sayitoglu et al	rs35742686 (A/-)	249	495	3	246	3	0	3	140	273	7	133	7	0	7	0.09	0.76
	rs3892097 (G/A)	247	409	85	171	67	9	76	140	241	39	103	35	2	37	0.25	0.61
Bonanni et al	rs3892097 (G/A)	46	72	20	30	12	4	16	136	232	40	97	38	1	39	1.76	0.18
Li et al	rs1065852 (C/T)	286	201	371	56	89	141	230	305	243	367	73	97	135	232	34.54	0.00
Lemos et al	rs3892097 (G/A)	187	324	50	140	44	3	47	256	401	111	159	83	14	97	0.52	0.47
Chen et al	rs1065852 (C/T)	348	337	359	59	219	70	289	204	189	219	30	129	45	174	15.05	0.00
Khedhaier et al	rs3892097 (G/A)	300	528	72	235	58	7	65	230	390	70	167	56	7	63	0.73	0.39
Majumdar et al	rs3892097 (G/A)	110	185	35	78	29	3	32	143	261	25	120	21	2	23	0.90	0.34
Ouerhani et al	rs3892097 (G/A)	80	143	17	63	17	0	17	109	200	18	94	12	3	15	8.14	0.00
Torresan et al	rs3892097 (G/A)	102	163	41	66	31	5	36	102	165	39	70	25	7	32	4.39	0.04
Yan et al	rs1065852 (C/T)	118	110	126	27	56	35	91	118	90	146	22	46	50	96	3.57	0.06
	rs1135840 (G/C)	118	72	164	1	70	47	117	118	59	177	4	51	63	114	2.75	0.10
Altayli et al	rs3892097 (G/A)	135	182	88	65	52	18	70	128	167	89	52	63	13	76	0.93	0.34
Gutman et al	rs3892097 (G/A)	43	71	15	29	13	1	14	121	200	42	85	30	6	36	2.23	0.14
Surekha et al	rs3892097 (G/A)	250	390	110	144	102	4	106	250	419	81	181	57	12	69	6.42	0.01
Lim et al	rs16947 (A/G)	139	221	57	92	37	10	47	198	288	108	107	74	17	91	0.66	0.42
	rs1080985 (C/G)	139	238	40	105	28	6	34	203	330	76	136	58	9	67	0.76	0.38
	rs3892097 (G/A)	136	271	1	135	1	0	1	169	322	16	157	8	4	12	38.16	0.00
	2D6*5 (ins/del)	165	304	26	139	26	0	26	227	430	24	203	24	0	24	0.71	0.40
	2D6*14 (G/A)	102	200	4	98	4	0	4	182	362	2	180	2	0	2	0.01	0.94
	rs1065852 (C/T)	139	138	140	42	54	43	97	202	244	160	82	80	40	120	5.99	0.01
	rs28371725 (G/A)	139	263	15	125	13	1	14	195	356	34	163	30	2	32	0.22	0.64
Luo et al	rs1065852 (C/T)	123	115	131	22	71	30	101	129	115	143	19	77	33	110	5.58	0.02
Zhou et al	rs1065852 (C/T)	86	85	87	26	33	27	60	86	67	105	19	29	38	67	7.28	0.01

SNP, single nucleotide polymorphism; 1, wild allele; 2, variant allele; 1/1, wild homozygote; 1/2, heterozygote; 2/2, variant homozygote; HWE, Hardy-Weinberg equilibrium

in the pooled analysis. The publication year of involved studies ranged from 1994~2011. Overall, there were 12 lung cancer studies, 8 breast cancer studies, 5 leukemia cancer studies, 4 liver cancer studies, 3 bladder cancer studies, 3 prostate cancer studies, 2 head and neck cancer studies and others studies including colorectal cancer, meningioma, laryngeal squamous cell carcinoma, pituitary tumor, thyroid cancer, cervical cancer study, gastric cancer. The characteristics and methodological quality of the included studies are summarized in Table 1. The genotype distribution of CYP2D6 gene polymorphisms in case and control groups were presented in Table 2.

Main results and subgroup analysis

A summary of the meta-analysis findings of the association between CYP2D6 gene polymorphisms and cancer risk is provided in Table 3. The meta-analysis results showed that the homozygote (CC) of rs1135840, G allele and G carrier (AG + GG) of rs16947 and heterozygote (A/del) of rs35742686 in CYP2D6 gene had negative associations with cancer risk (OR=0.58, 95%CI: 0.34-0.97, P=0.04; OR=0.69, 95%CI: 0.48-0.99,

Table 3. Meta-analysis of the Association between CYP2D6 Gene Polymorphisms and Cancer Susceptibility

Polymorphisms		Cancer n/N	Control n/N	OR [95%CI]	P	Heterogeneity P	Heterogeneity I^2	Effect model
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	20/1532	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	6/766	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	40/788	31/974	1.90 [0.62, 5.83]	0.26	0.02	74%	Random
	del carrier	39/394	27/487	2.13 [0.74, 6.17]	0.16	0.04	69%	
	del/del	1/394	4/487	0.54 [0.12, 2.43]	0.42	0.39	0%	
	ins/del	38/394	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%	
	TT	552/1704	726/2226	0.82 [0.66, 1.01]	0.07	0.03	49%	
	CT	747/1704	882/2226	1.08 [0.94, 1.24]	0.31	0.99	0%	
I4001467 (C/T)	T allele	31/168	41/288	1.36 [0.82, 2.27]	0.23	-	-	Fixed
	T carrier	31/84	39/144	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	31/195	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

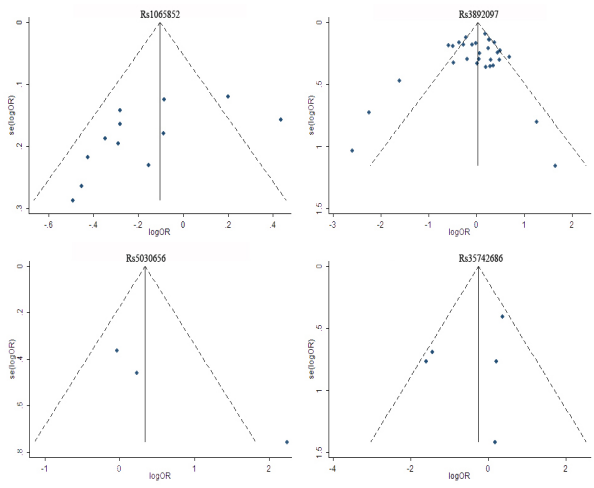

Figure 3. Begger's Funnel Plot of Publication Bias Based on rs3892097, rs5030656, rs1065852 and rs35742686 in CYP2D6 Gene

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). Interestingly, we found that heterozygote (GC) of rs1135840 was the only only risk factor for cancer (OR=1.92, 95%CI: 1.14-3.21, P=0.01) (Figure 2). However there were no association among rs3892097, rs503065, rs1065852, i4001467, 2D6*5, rs1080985, 2D6*14 and rs28371725 and cancer risk (all P>0.05). In the subgroup analysis by ethnicity, associations were found in both the A carrier and heterozygote (GA) of rs3892097 with susceptibility to cancer in Asian population, which suggested that the A carrier and heterozygote (GA) of rs3892097 might increase the risk of cancer (OR=1.53, 95%CI: 1.03-2.27, P=0.03; OR=1.62, 95%CI: 1.10-2.38, P=0.02; respectively), but not in Caucasian and African populations (all p>0.05). Unfortunately, we also found no association among rs503065, rs1065852, i4001467, 2D6*5, rs1080985, 2D6*14 and rs28371725with cancer risk in Asian, Caucasian and African populations (all P>0.05).

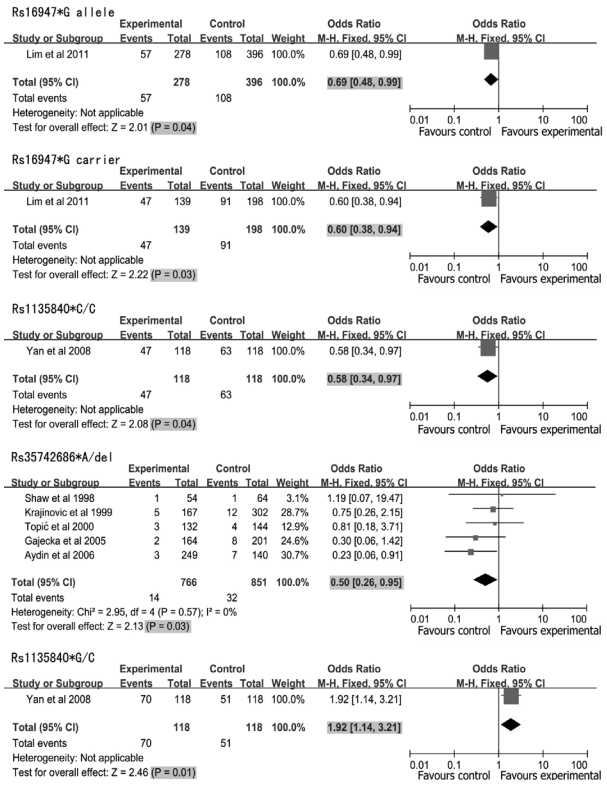

Figure 2. Associations between CYP2D6 Gene Polymorphism and Cancer Risk

Table 4. Evaluation of Publication Bias Based on rs3892097, rs5030656, rs1065852 and rs35742686 in CYP2D6 Gene by Egger's Linear Regression Test

SNP	Coefficient	SE	t	P	95%CI
rs3892097	-0.483	0.743	-0.65	0.521	[-2.005, 1.040]
rs5030656	5.72	1.058	5.41	0.116	[-7.722, 19.163]
rs1065852	-3.509	1.59	-2.21	0.052	[-7.051, 0.033]
rs35742686	-1.529	1.9	-0.8	0.48	[-7.575, 4.517]

SE, standard error; 95%CI, 95% confidence interval

Publication bias

Publication bias of the literatures was accessed based on rs3892097, rs5030656, rs1065852 and rs35742686 in CYP2D6 gene by Begger'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 erthematosus (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, rs503065, 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, which was just the opposite to heterozygote (GC) of rs1135840. Unfortunately, we found no significant association among rs3892097, rs503065, rs1065852, i4001467, 2D6*5, rs1080985, 2D6*14, rs28371725 with cancer risk (all P > 0.05). 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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References

Abraham JE, Maranian MJ, Driver KE, et al (2011). CYP2D6 gene variants and their association with breast cancer susceptibility. *Cancer Epidemiol Biomarkers Prev*, **20**, 1255-8.

Agundez JA (2004). Cytochrome P450 gene polymorphism and cancer. *Curr Drug Metab*, **5**, 211-24.

Agúndez JA, Jiménez-Jiménez FJ, Luengo A, et al (1995). Association between the oxidation polymorphism and early onset of Paekinson's disease. *Clin Pharmacol Ther*, **57**, 291-8.

Agúndez JA, Ledesma MC, Benítez J, et al (1995). CYP2D6 genes and risk of liver cancer. *Lancet*, **345**, 830-1.

Agúndez JA, Martínez C, Ladero JM, et al (1994). Debrisoquin oxidation genotype and susceptibility to lung cancer. *Clin Pharmacol Ther*, **55**, 10-4.

Agúndez JA, Martínez C, Olivera M, et al (1998). Expression in human prostate of drug- and carcinogen-metabolizing enzymes: association with prostate cancer risk. *Br J Cancer*, **78**, 1361-7.

Agúndez JA, Olivera M, Ladero JM, et al (1996). Increased risk for hepatacellular carcinoma in NAT2-slow acetylators and CYP2D6-rapid metabolizers. *Pharmacogenetics*, **6**, 501-12.

Altayli E, Gunes S, Yilmaz AF, et al (2009). CYP1A2, CYP2D6, GSTM1, GSTP1, and GSTT1 gene polymorphisms in patients with bladder cancer in a Turkish population. *Int Urol Nephrol*, **41**, 259-66.

Aydin-Sayitoglu M, Hatirnaz O, Erensoy N, et al (2006). Role of CYP2D6, CYP1A1, CYP2E1, GSTT1, and GSTM1 genes in the susceptibility to acute leukemias. *Am J Hematol*, **81**, 162-70.

Bonanni B, Macis D, Maisonneuve P, et al (2006). Polymorphism in the CYP2D6 tamoxifen-metabolizing gene influences clinical effect but not hot flashes: data from the Italian Tamoxifen Trial. *J Clin Oncol*, **24**, 3708-9.

Butler WJ, Ryan P, Roberts-Thomson IC (2001). Metabolic genotypes and risk for colorectal cancer. *J Gastroenterol Hepatol*, **16**, 631-5.

Chen HC, Hu WX, Liu QX, et al (2008). Genetic polymorphisms of metabolic enzymes CYP1A1, CYP2D6, GSTM1 and GSTT1 and leukemia susceptibility. *Eur J Cancer Prev*, **17**, 251-8.

Chen SQ, Xu L, Ma GJ, Xue KX (2004). Genetic polymorphism of CYP2D6 and its relation to lung cancer susceptibility. *Tumor Mar*, **24**, 96-98.

Febbo PG, Kantoff PW, Giovannucci E, et al (1998). Debrisoquine hydroxylase (CYP2D6) and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **7**, 1075-8.

Foster BC, Vandenhoek S, Hana J, et al (2003). In vitro inhibition of human cytochrome P450-mediated metabolism of marker substrates by natural products. *Phytomedicine*, **10**, 334-42.

Fukatsu T, Hirokawa Y, Araki T, et al (2004). Genetic polymorphisms of hormone-related genes and prostate cancer risk in the Japanese population. *Anticancer Res*, **24**, 2431-7.

Gajecka M, Rydzanicz M, Jaskula-Sztul R, et al (2005). CYP1A1, CYP2D6, CYP2E1, NAT2, GSTM1 and GSTT1 polymorphisms or their combinations are associated with the increased risk of the laryngeal squamous cell carcinoma. *Mutat Res*, **574**, 112-23.

Garcia-Barcelo M, Chow LY, Chiu HF, et al (2000). Genetic analysis of the CYP2D6 locus in a Hong Kong Chinese population. *Clin Chem*, **46**, 18-23.

Gomes L, Lemos MC, Paiva I, et al (2005). CYP2D6 genetic polymorphisms are associated with susceptibility to pituitary tumors. *Acta Med Port*, **18**, 339-43.

González MV, Alvarez V, Pello MF, et al (1998). Genetic polymorphism of N-acetyltransferase-2, glutathione S-transferase-M1, and cytochromes P450IIE1 and P450IID6 in the susceptibility to head and neck cancer. *J Clin Pathol*, **51**, 294-8.

Guo Z, Zhou Q, Zhu W, et al (2005). A case-control study on the association between genetic polymorphisms of metabolizing enzymes CYP2D6 and susceptibility to lung cancer. *Zhongguo Fei Ai Za Zhi*, **8**, 89-94.

Gutman G, Morad T, Peleg B, et al (2009). CYP1A1 and CYP2D6 gene polymorphisms in Israeli Jewish women with cervical cancer. *Int J Gynecol Cancer*, **19**, 1300-2.

Higgins JP and Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, **21**, 1539-58.

Hu YL, Gao Y, Zhang Q (1998). Genetic polymorphisms of CYP1A1, 2D6 and GSTM1 related with susceptibility to lung cancer. *Tumor*, **18**, 269-71.

Ji L, Pan S, Marti-Jaun J, et al (2002). Single-step assays to analyze CYP2D6 gene polymorphisms in Asians: allele frequencies and a novel *14B allele in mainland Chinese. *Clin Chem*, **48**, 983-88.

Jin Y, Desta Z, Stearns V, et al (2005). CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*, **97**, 30-9.

Khedhaier A, Hassen E, Bouaouina N, et al (2008). Implication of Xenobiotic Metabolizing Enzyme gene (CYP2E1, CYP2C19, CYP2D6, mEH and NAT2) polymorphisms in breast carcinoma. *BMC Cancer*, **8**, 109.

Kimura S, Umeno M, Skoda RC, et al (1989). The human debrisoquine 4-hydroxylase (CYP2D) locus: sequence and identification of the polymorphic CYP2D6 gene, a related gene, and a pseudogene. *Am J Hum Genet*, **45**, 889-904.

Krajinovic M, Labuda D, Richer C, et al (1999). Susceptibility to childhood acute lymphoblastic leukemia: influence of CYP1A1, CYP2D6, GSTM1, and GSTT1 genetic polymorphisms. *Blood*, **93**, 1496-501.

Kroemer HK, Eichelbaum M (1995). "It's the genes, stupid". Molecular bases and clinical consequences of genetic cytochrome P450 2D6 polymorphism. *Life Sciences*, **56**, 2285-98.

Ladona MG, Abildúa RE, Ladero JM, et al (1996). CYP2D6 genotypes in Spanish women with breast cancer. *Cancer Lett*, **99**, 23-8.

Legrand M, Stucker I, Marez D, et al (1996). Influence of a mutation reducing the catalytic activity of the cytochrome P450 CYP2D6 on lung cancer susceptibility. *Carcinogenesis*,

17, 2267-9.
Lemos MC, Carrilho F, Rodrigues F, et al (2007). Genetic polymorphism of CYP2D6 influences susceptibility to papillary thyroid cancer. *Clin Endocrinol (Oxf)*, **67**, 180-3.
Lemos MC, Cabrita FJ, Silva HA, et al (1999). Genetic polymorphism of CYP2D6, GSTM1 and NAT2 and susceptibility to haematological neoplasias. *Carcinogenesis*, **20**, 1225-9.
Lewis DF (2004). Varieties: the human cytochromes P450. *Pharmacogenomics*, **5**, 305-18.
Li H, Feng L, Xu Y, et al (2006). The association of CYP2D6 *10 polymorphism with breast cancer risk and clinico-pathologic characteristics in Chinese women. *Acta Oncol*, **45**, 597-601.
Li WY, Lai BT, Zhan XP (2004). The relationship between genetic polymorphism of mebabolizing enzymes and the genetic susceptibility to lung cancer. *Chin J Epidemiol*, **25**, 1042-45.
Liang GY (2005). Studies on susceptibility genes of lung cancer in Chinese Han population and rapid detection techniques of single nucleotides polymorphisms. *Southeast University*, 1-108.
Lim JS, Chen XA, Singh O, et al (2011). Impact of CYP2D6, CYP3A5, CYP2C9 and CYP2C19 polymorphisms on tamoxifen pharmacokinetics in Asian breast cancer patients. *Br J Clin Pharmacol*, **71**, 737-50.
Liu CZ, Jiang F, Bian JC, et al (2002). Cytochrome P450 2D6 gene polymorphism and susceptibility to hepatocellular carcinoma research. *Chinese Journal of Cancer*, **21**, 1016-17.
London SJ, Daly AK, Leathart JB, et al (1997). Genetic polymorphism of CYP2D6 and lung cancer risk in African-Americans and Caucasians in Los Angeles County. *Carcinogenesis*, **18**, 1203-14.
Luo YP, Chen HC, Khan MA, et al (2011). Genetic polymorphisms of metabolic enzymes-CYP1A1, CYP2D6, GSTM1, and GSTT1, and gastric carcinoma susceptibility. *Tumour Biol*, **32**, 215-22.
Majumdar S, Mondal BC, Ghosh M, et al (2008). Association of cytochrome P450, glutathione S-transferase and N-acetyl transferase 2 gene polymorphisms with incidence of acute myeloid leukemia. *Eur J Cancer Prev*, **17**, 125-32.
Meyer UA, Zanger UM (1997). Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol*, **37**, 269-96.
Mochizuki J, Murakami S, Sanjo A, et al (2005). Genetic polymorphisms of cytochrome P450 in patients with hepatitis C virus-associated hepatocellular carcinoma. *J Gastroenterol Hepatol*, **20**, 1191-7.
Morrow PK, Serna R, Broglio K, et al (2012). Effect of CYP2D6 polymorphisms on breast cancer recurrence. *Cancer*, **118**, 1221-7.
Ouerhani S, Marrakchi R, Bouhaha R, et al (2008). The role of CYP2D6*4 variant in bladder cancer susceptibility in Tunisian patients. *Bull Cancer*, **95**, E1-4.
Peters JL, Sutton AJ, Jones DR, et al (2006). Comparison of two methods to detect publication bias in meta-analysis. *JAMA*, **295**, 676-80.
RobertsRL, KennedyMA (2006). Rapiddetection of common cytochrome P450 2D6 alleles in Caucasians. *Clin Chmi Acta*, **366**, 348-51.
Shaw GL, Falk RT, Frame JN, et al (1998). Genetic polymorphism of CYP2D6 and lung cancer risk. *Cancer Epidemiol Biomarkers Prev*, **7**, 215-9.
Singh D, Kashyap A, Pandey RV, Saini KS (2011). Novel advances in cytochrome P450 research. *Drug Discov Today*, **16**, 793-9.
Singh MS, Francis PA, Michael M. (2011). Tamoxifen, cytochrome P450 genes and breast cancer clinical outcomes. *Breast*, **20**, 111-8.
Sistonen J, Sajantila A, Lao O, et al (2007). CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenet Genomics*, **17**, 93-101.
Sobti RC, Al-Badran AI, Sharma S, et al (2005). Genetic polymorphisms of CYP2D6, GSTM1, and GSTT1 genes and bladder cancer risk in North India. *Cancer Genet Cytogenet*, **156**, 68-73.
Sobti RC, Sharma S, Joshi A, et al (2003). CYP1A1 and CYP2D6 polymorphism and risk of lung cancer in a North Indian population. *Biomarkers*, **8**, 415-28.
Surekha D, Sailaja K, Rao DN, et al (2010). Association of a CYP17 gene polymorphism with development of breast cancer in India. *Asian Pac J Cancer Prev*, **11**, 1653-7.
Surekha D, Sailaja K, Rao DN, et al (2010). CYP2D6*4 polymorphisms and breast cancer risk. *Biology and Medicine*, **2**, 49-55.
Topić E, Stefanović M, Ivanisević AM, et al (2000). The cytochrome P450 2D6 (CYP2D6) gene polymorphism among breast and head and neck cancer patients. *Clin Chim Acta*, **296**, 101-9.
Torresan C, Oliveira MM, Torrezan GT, et al (2008). Genetic polymorphisms in oestrogen metabolic pathway and breast cancer: a positive association with combined CYP/GST genotypes. *Clin Exp Med*, **8**, 65-71.
von Elm E, Altman DG, Egger M, et al (2007). STROBE Initiative: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*, **18**, 800-804.
Wexler D, Courtney R, Richards W, et al (2004). Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. *Eur J Pharm Sci*, **21**, 645-53.
Wilkinson GR (2005). Drug metabolism and variability among patients in drug response. *N Engl J Med*, **352**, 2211-21.
Wundrack I, Meese E, Müllenbach R, Blin N (1994). Debrisoquine hydroxylase gene polymorphism in meningioma. *Acta Neuropathol*, **88**, 472-74.
Yan Z, Wu YM, Wu YJ (2008). CYP2D6*10 polymorphisms and lung cancer susceptibility. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*, **30**, 564-8.
Zhang L, Liu JL, Zhang YJ, Wang H (2011). Association between HLA-B*27 polymorphisms and ankylosing spondylitis in Han populations: a meta-analysis. *Clin Exp Rheumatol*, **29**, 285-92.
Zhou SF (2009). Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. *Clin Pharmacokinet*, **48**, 689-723.
Zhou JL, Yao ZJ, Zeng ZP, Zhao XR (2011). Case-control study for the relationship of CYP1A1 and CYP2D6 polymorphisms with the genetic susceptibility to lung cancer. *J Guangdong Phar*, **27**, 528-31.
Zintzaras E, Ioannidis JP (2005). Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol*, **28**, 123-37.