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ORIGINAL PAPER

Association between the CYP1A2 polymorphisms and risk of cancer: a meta-analysis

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Abstract The previously published data on the association between CYP1A2*1C (rs2069514) and CYP1A2*1F (rs762551) polymorphisms and cancer risk have remained controversial. Hence, we performed a meta-analysis to investigate the association between CYP1A2*1F and CYP1A2*1C polymorphisms and cancer risk under different inheritance models. Overall, significant association was observed between CYP1A2*1F and cancer risk when all the eligible studies were pooled into the meta-analysis (dominant model: OR 1.08, 95 % CI 1.02–1.15; heterozygous model: OR 1.06, 95 % CI 1.01–1.12; additive model: OR 1.07, 95 % CI 1.02–1.13). In the further stratified and sensitivity analyses, for CYP1A2*1F polymorphism, significantly increased lung cancer risk and significantly decreased bladder cancer risk were observed in Caucasians. For CYP1A2*1C polymorphism, no significant association was found in overall and all subgroup analyses. In summary, this meta-analysis suggests that CYP1A2*1F polymorphism is associated with lung cancer and bladder cancer risk in Caucasians.

Keywords CYP1A2 · Polymorphism · Cancer · Susceptibility · Meta-analysis

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Introduction

As the preservation of genomic integrity is essential in the prevention of tumor initiation and progression, mutations and variations, may play a role in the genetic predisposition to cancer, especially in genes of enzymes in carcinogen metabolism. Phase I enzymes catalyze the activation and detoxification of xenobiotics, drugs, and endogenous compounds. The phase I system is mainly composed of cytochrome P450 (CYP) enzymes, which introduce a reactive group to the exogenous or endogenous compound (Guengerich 2001). The metabolism of xenobiotics and drugs is mainly a detoxification process; however, phase I metabolism has the risk of formation of highly reactive electrophiles that can bind to macromolecules, for example, proteins and DNA, potentially inducing carcinogenesis (Smith et al. 1994; Windmill et al. 1997). Therefore, genetic polymorphisms leading to alteration of activity in phase I enzymes may cause variations in the levels of DNA damage and cancer susceptibility (Brockstedt et al. 2002). CYP1A2 is located on chromosome 15q in opposite orientation and separated by 23.3 kb, a major drug-metabolizing

enzyme, with a wide range of substrates (Eaton et al. 1995). CYP1A2 is a key phase I enzyme required for the activation of the major recognized carcinogens [polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HAs)] (Landi et al. 1999). Since both PAHs and HAs are present in food, the activity of the CYP1A2 enzyme may affect the formation of their activated forms after absorption from the large bowel, and thus influencing the risk of cancer. In humans, CYP1A2 is highly polymorphic and several single nucleotide polymorphisms (SNPs) including two common SNPs represented as CYP1A2*1C (rs2069514) and CYP1A2*1F (rs762551) alleles have been identified in different ethnic populations worldwide (Chida et al. 1999). The CYP1A2*1C allele was first reported to be associated with decreased CYP1A2 activity and inducibility in smokers of Japanese ancestry (Nakajima et al. 1999). CYP1A2*1F was reported to influence the inducibility of the enzyme, leading to a higher enzyme activity in the presence of an inducer, such as smoking (Pilgrim et al. 2012, Sachse et al. 1999), omeprazole treatment (Han et al. 2002) or heavy coffee consumption (Djordjevic et al. 2010a, b). However, there is some controversy as to the impact of CYP1A2*1C and CYP1A2*1F polymorphisms on theophylline metabolism in different ethnic populations. Obase et al. (2003) observed that CYP1A2*1C polymorphism was associated with reduced theophylline clearance in asthmatic patients of Japanese ancestry. However, the study of Wang et al. (2013) thought that CYP1A2*1F (rs762551) polymorphism can result in two- to threefold increase in activity/protein and has been associated with increased enzyme inducibility in non-smoking healthy volunteers in male Chinese population. Moreover, another study in Japanese patients reported that there was no influence of CYP1A2*1C and CYP1A2*1F on the theophylline metabolic ratio (2006). As a result, the effect of CYP1A2*1C and CYP1A2*1F polymorphisms on theophylline metabolism remains unconfirmed.

To date, a number of molecular epidemiological studies have been performed to evaluate the association between CYP1A2*1C and CYP1A2*1F polymorphisms and different types of cancer risk in diverse populations (Gervasini et al. 2013; Cui et al. 2013; Pavanello et al. 2012; Wei et al. 2011; Barbieri et al. 2012; Khvostova et al. 2012; Wang et al. 2012a; Rudolph et al. 2011; Jang et al. 2012; Sainz et al. 2011; Goodman et al. 2003; Cleary et al. 2010; Pavanello et al. 2010; Kobayashi et al. 2009a, b; Singh et al. 2010–2011; Zienolddiny et al. 2008; Imaizumi et al. 2009; MARIE-GENICA et al. 2010; Sangrajrang et al. 2009; B'chir et al. 2009; Aldrich et al. 2009; Yeh et al. 2009; Shimada et al. 2009; Kotsopoulos et al. 2009; Saebø et al. 2008; Sachse et al. 2002; Figueroa et al. 2008; Suzuki et al. 2008; Gulyaeva et al. 2008; Hirata et al. 2008; Yoshida et al. 2007; Kiss et al. 2007; Küry et al. 2007; Kotsopoulos et al. 2007; Osawa et al. 2007; Takata et al. 2007; Gemignani et al. 2007; Yeh et al. 2007; Agudo et al. 2006; De Roos et al. 2006; Bae et al. 2006; Long et al. 2006; Chen et al. 2005, 2006; Mikhailova et al. 2006; Le Marchand et al. 2005; Landi et al. 2005; Li et al. 2006; Prawan et al. 2005; Doherty et al. 2005; Tsukino et al. 2004; Goodman et al. 2001; Altayli et al. 2009; Villanueva et al. 2009; Rebbeck et al. 2006; Mochizuki et al. 2005; Chiou et al. 2005; Barbieri et al. 2013; Ghoshal et al. 2014; Lowcock et al. 2013; Lee et al. 2013; Ayari et al. 2013). However, the results were inconsistent or even contradictory. In addition, three recent meta-analyses have confirmed the association between CYP1A2*1C and CYP1A2*1F polymorphisms and risk of cancer. However, some published studies were not included in the three recent meta-analyses (Tian et al. 2013; Zhenzhen et al. 2013; Wang et al. 2012a, b). Therefore, we performed a comprehensive meta-analysis by including the most recent and relevant articles to identify statistical evidence of the association between CYP1A2*1C and CYP1A2*1F polymorphisms and risk of all cancers that have been investigated.

Materials and methods

Identification and eligibility of relevant studies

A comprehensive literature search was performed using the PubMed, ISI, CNKI, and WanFang database for relevant articles published (the last search update was April 15, 2014) with the following keywords: "CYP1A2'', ''cytochrome P-450 1A2'', ''cytochrome P450 1A2'', ''polymorphism'' and "Cancer" or Carcinoma". MeSH term: ["Cytochrome P-450 CYP1A2" (mesh) AND "Neoplasms" (mesh)] AND "Polymorphism, Genetic" (mesh). In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. We included all the case–control studies and cohort studies that investigated the association between CYP1A2*1C and CYP1A2*1F polymorphisms and cancer risk with genotyping data. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications.

Inclusion criteria

The included studies have to meet the following criteria: (1) only the case–control studies or cohort studies were considered, (2) evaluated the CYP1A2*1C and CYP1A2*1F polymorphisms and the risk of cancer, and (3) the genotype distribution of the CYP1A2*1C and CYP1A2*1F polymorphisms in cases and controls were described in detail and the results were expressed as odds ratio (OR) and corresponding 95 % confidence interval (95 % CI). Major reasons for exclusion of

studies were as follows: (1) not for cancer research, (2) only case population, and (3) duplicate of previous publication.

Data extraction

Information was carefully extracted from all eligible studies independently by two investigators according to the inclusion criteria listed above. The following data were collected from each study: first author's name, year of publication, country of origin, ethnicity, source of controls (population-based controls, hospital-based controls, and family-based controls), source of cases, genotype method, sample size, and numbers of cases and controls in the CYP1A2*1C and CYP1A2*1F genotypes whenever possible. Ethnicity was categorized as ''Caucasian'', ''Asian'', and "African". When one study did not state which ethnic group was included or if it was impossible to separate participants according to phenotype, the sample was termed as ''mixed population''. Meanwhile, studies investigating more than one kind of cancer were counted as individual data set only in subgroup analyses by cancer type. We did not define any minimum number of patients to include in this meta-analysis. Articles that reported different ethnic groups and countries or locations, we considered them different study samples in this meta-analysis.

Statistical analysis

Crude odds ratios (ORs) together with their corresponding 95 % CIs were used to assess the strength of association between the CYP1A2*1C and CYP1A2*1F polymorphisms and risk of cancer. The pooled ORs were calculated for co-dominant model (AG versus AA or GG versus AA), dominant model (AG + GG versus AA), recessive model (GG versus AA + AG), and additive model (G versus A), respectively. Between-study heterogeneity was assessed by calculating Q-statistic (heterogeneity was considered statistically significant if $P < 0.10$.) (Davey and Egger 1997) and quantified using the I^2 value, a value that describes the percentage of variation across studies that are due to heterogeneity rather than chance, where $I^2 = 0$ % indicates no observed heterogeneity, with 25 % regarded as low, 50 % as moderate, and 75 % as high (Higgins et al. 2003). If results were not heterogeneous, the pooled ORs were calculated by the fixed-effect model (we used the Q-statistic, which represents the magnitude of heterogeneity between studies) (Mantel and Haenszel 1959). Otherwise, a random-effect model was used when the heterogeneity between studies was significant (DerSimonian and Laird 1986). Moreover, sensitivity analysis was performed by excluding a single study each time. We also ranked studies according to sample size, and then repeated this meta-analysis. Sample size was classified according to a minimum of 200 participants and those with fewer than 200 participants. The cite criteria were previously described (Klug et al. 2009). HWE was calculated using the goodness-of-fit test, and deviation was considered when $P < 0.05$. Begg's funnel plots (Begg and Mazumdar 1994) and Egger's linear regression test (Egger et al. 1997) were used to assess publication bias. A meta-regression analysis was carried out to identify the major sources of between-studies variation in the results, using the log of the ORs from each study as dependent variables, and cancer type, ethnicity, sample size, and source of controls as the possible sources of heterogeneity. All of the calculations were performed using STATA version 10.0 (STATA Corporation, College Station, TX).

Results

Literature search and meta-analysis databases

Figure 1 provides a flow chart for this meta-analysis. A total of 64 articles examined the association of CYP1A2*1C and CYP1A2*1F polymorphisms with cancer risk. Of these published articles, 2 (Yeh et al. 2007; Goodman et al. 2001) were excluded because their populations overlapped with another 2 included studies. As summarized in Table 1, 62 publications with 78 case–control studies were included in the meta-analysis, including 27,301 cases and 33,885 controls for CYP1A2*1C polymorphism (57 studies from 54 publications) and 4,722 cases and 6,555 controls for CYP1A2*1F polymorphism (21 studies from 21 publications). Among these studies, 4 were included in the dominant model only because they provided the genotypes of AG + GG ver. AA as a whole and two studies were included in the recessive model only because they provided the genotypes of GG ver. AA + AG. In addition, for CYP1A2*1C polymorphism, there were 4 bladder cancer studies, 13 breast cancer studies, 13 colorectal cancer studies, 4 endometrial cancer studies, 3 gastric cancer studies, 8 lung cancer studies, 3 pancreatic cancer studies, and 9 studies with the "other cancers". There were 5 colorectal cancer studies, 3 liver cancer studies, 8 lung cancer studies, and 5 studies with the "other cancers" for CYP1A2*1F polymorphism. All of the cases were pathologically confirmed.

Meta-analysis results

*CYP1A2*1F*

Table 2 lists the main results of the meta-analysis of CYP1A2*1 F polymorphism and cancer risk. Overall, significantly increased cancer risk was observed in any genetic model (dominant model: OR 1.08, 95 % CI 1.02–1.15, $P_h < 0.001$, $I^2 = 61.4$ %; heterozygous model: OR

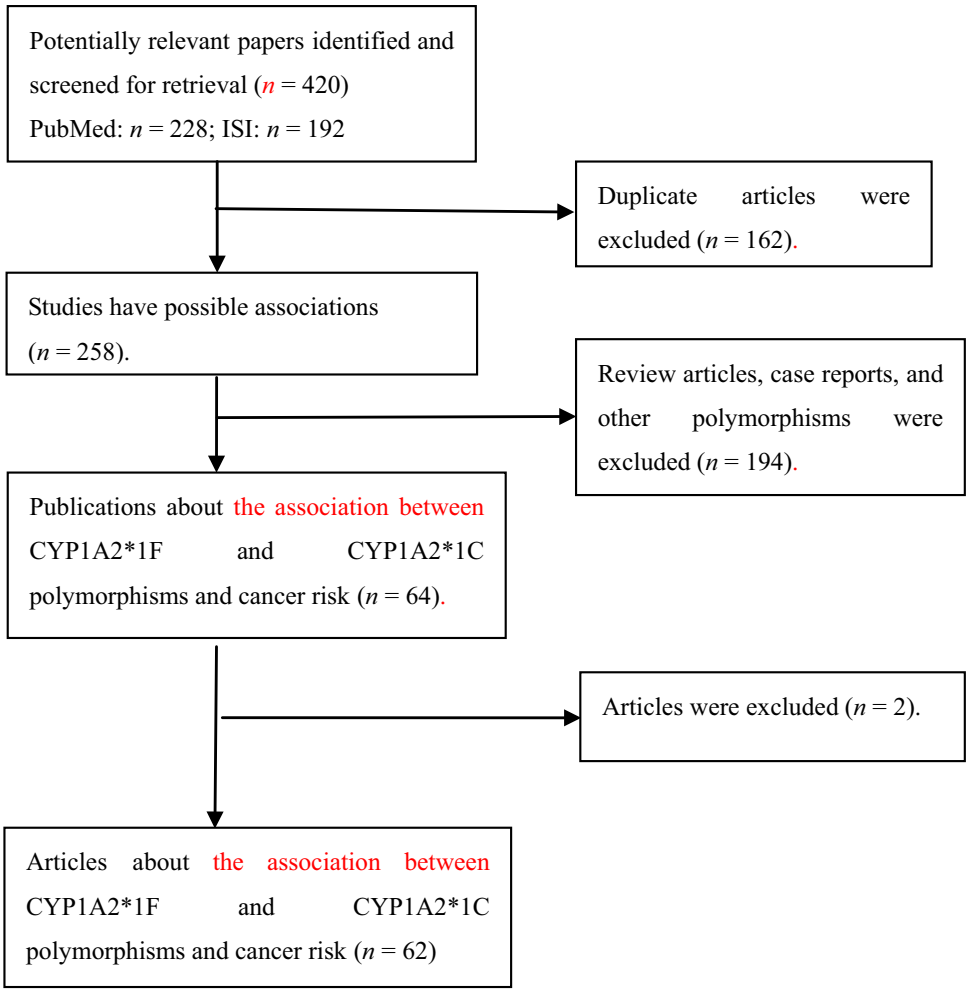

Fig. 1 Flow chart explaining the selection of the 62 eligible articles included in the meta-analysis

1.06, 95 % CI 1.01–1.12, $P_h < 0.001$, $I^2 = 50.8$ %; additive model: OR 1.07, 95 % CI 1.02–1.13, $P_h < 0.001$, $I^2 = 71.4$ %) when all the eligible studies were pooled into meta-analysis. Then we performed subgroup analysis by cancer type. Significant association was observed between lung cancer (dominant model: OR 1.21, 95 % CI 1.00–1.46, $P_h = 0.083$, $I^2 = 44.3$ %; heterozygous model: OR 1.18, 95 % CI 1.02–1.36, $P_h = 0.157$, $I^2 = 35.5$ %) and bladder cancer (dominant model: OR 0.88, 95 % CI 0.78–0.99, $P_h = 0.563$, $I^2 = 0.0$ %; recessive model: OR 0.79, 95 % CI 0.66–0.94, $P_h = 0.849$, $I^2 = 0.0$ %; homozygous model: OR 0.76, 95 % CI 0.63–0.93, $P_h = 0.702$, $I^2 = 0.0$ %; additive model: OR 0.89, 95 % CI 0.81–0.97, $P_h = 0.622$, $I^2 = 0.0$ %). We further examined the association between the CYP1A2*1F polymorphism and cancer risk according to cancer type and ethnicity (Table 3). For samples of Caucasians, significant association was observed between CYP1A2*1F polymorphism and bladder cancer (dominant model: OR 0.88, 95 % CI 0.78–0.99, $P_h = 0.563$, $I^2 = 0.0$ %; recessive model: OR 0.79, 95 % CI 0.66–0.94, $P_h = 0.849$, $I^2 = 0.0$ %; homozygous model: OR 0.76, 95 % CI 0.63–0.93, $P_h = 0.702$, $I^2 = 0.0$ %; additive model: OR 0.89, 95 % CI 0.81–0.97, $P_h = 0.622$, $I^2 = 0.0$ %) and lung cancer risk (dominant model: OR 1.29, 95 % CI 1.11–1.51, $P_h = 0.948$, $I^2 = 0.0$ %; recessive model: OR 1.33, 95 % CI 1.01–1.75, $P_h = 0.181$, $I^2 = 41.4$ %; homozygous model: OR 1.49, 95 % CI 1.12–1.98, $P_h = 0.358$, $I^2 = 2.7$ %; heterozygous model: OR 1.25, 95 % CI 1.06–1.48, $P_h = 0.540$, $I^2 = 0.0$ %; additive model: OR 1.23, 95 % CI 1.09–1.39, $P_h = 0.828$, $I^2 = 0.0$ %). For samples of Asians, no significant association was observed between any cancer types. We also examined the association of the CYP1A2*1F polymorphism with cancer risk according to cancer type and source of controls (Table 4). For the population-based studies, no significant association was observed between CYP1A2*1F polymorphism and cancer risk in any cancer type. For the hospital-based studies, significant association was observed only between CYP1A2*1F polymorphism and bladder cancer risk (dominant model: OR 0.88, 95 % CI 0.78–0.99, $P_h = 0.563$, $I^2 = 0.0$ %; recessive model: OR 0.79, 95 % CI 0.66–0.94, $P_h = 0.849$, $I^2 = 0.0$ %; homozygous model: OR 0.76, 95 % CI 0.63–0.93, $P_h = 0.702$,

Table 1 Main characteristics of all studies included in the meta-analysis

References	Country	Ethnicity	Source of cases	Case–control	SC	Genotype method	HWE
*CYP1A2*1F*							
Gervasini et al. (2013)	Spain	Caucasian	Patients were Caucasian lung cancer patients diagnosed at the hospital, based on histological analyses of endoscopic biopsies and/or surgical resection specimens	95–196	HB	PCR–RFLP	Y
Ayari et al. (2013)	Tunisia	Caucasian	Study subjects included 125 women with histologically confirmed breast cancer	117–42	HB	TaqMan	Y
Lee et al. (2013)	Korea	Asian	Study investigators confirmed breast cancer cases through review of medical records and pathology reports	579–981	PB	Not reported	Y
Lowcock et al. (2013)	Canada	Mixed	Patients were identified from the Ontario Cancer Registry and women aged 25 to 74 yr diagnosed with a first pathologically confirmed breast cancer in 2002 or 2003	1,693–1,761	PB	MassARRAY	Y
Ghoshal et al. (2014)	India	Asian	88 Patients with histology-confirmed non-cardia gastric cancer	88–299	HB	PCR–RFLP	Y
Barbieri et al. (2013)	Brazil	Mixed	Medullary thyroid carcinoma was confirmed by cytology and/or by elevated serum calcitonin levels	123–339	HB	TaqMan	Y
Pavanello et al. (2012)	Italy	Caucasian	428 Cases of lung cancer, diagnosed between 1994 and 2003, were identified in the files of the nationwide Danish Cancer Registry	421–776	PB	TaqMan	Y
Barbieri et al. (2012)	Brazil	Mixed	47 Patients with pathologically confirmed thyroid cancer	47–339	HB	TaqMan	Y
Khvostova et al. (2012)	Russia	Caucasian	335 Patients with different stages of breast cancer	323–526	HB	PCR–RFLP	Y
Wang et al. (2012a, b)	USA	Mixed	577 Incident cases of colorectal cancer	305–357	FB	PCR–RFLP	Y
Jang et al. (2012)	Canada	Caucasian	Patients had a primary pathology-confirmed adenocarcinoma of the pancreas or adenocarcinoma metastasis, confirmed as pancreatic cancer by treating physicians, diagnosed between April 2003 and July 2009 and initially identified through the population-based Ontario Cancer Registry	447–880	PB	MassARRAY	Y
Catsburg et al. (2012)	USA	Mixed	Prostate cancer was classified as advanced disease if the tumor extended beyond the prostatic capsule or into the adjacent tissue, involved regional lymph nodes or metastasized to distant locations (Surveillance, Epidemiology, and End Result 1995 clinical and pathologic extent of disease codes 41–85)	1,405–750	PB	TaqMan	Y
Rudolph et al. (2011)	German	Caucasian	811 Cases with a first diagnosis of colorectal cancer receiving in-patient treatment	678–680	PB	KASPar assays	Y
Sainz et al. (2011)	German	Caucasian	Colorectal cancer cases were recruited from patients who received in-patient treatment in a hospital of the Rhein-Neckar-Odenwald region	1,764/1786	PB	KASPar assays	Y
Singh et al. (2010–2011)	India	Asian	200 Male patients with pathologically confirmed lung cancer	200–200	HB	PCR–RFLP	Y
Cleary et al. (2010)	Canada	Caucasian	All 1174 incident, pathology-confirmed colorectal cancer patients	1,165–1,290	PB	TaqMan	Y
Pavanello et al. (2010)	Italy	Caucasian	216 Incident patients with pathologically confirmed bladder cancer	155–148	HB	PCR–RFLP	Y
MARIE-GENICA et al. (2010)	German	Caucasian	3,155 Patients with histologically confirmed primary breast cancer	3,147–5,485	PB	PCR–RFLP	Y
Kobayashi et al. (2009a, b)	Japan	Asian	A total of 153 consecutive patients newly diagnosed with stomach cancer	141–286	HB	MassARRAY	Y
Kobayashi et al. (2009a, b)	Japan	Asian	A total of 121 consecutive patients newly diagnosed with colorectal cancer	104–225	HB	MassARRAY	Y
Sangrajrang et al. (2009)	Thailand	Asian	570 Patients with histopathologically confirmed breast cancer	552–483	HB	TaqMan	Y
B'chir et al. (2009)	Tunisia	African	101 Patients with pathologically confirmed lung cancer	101–98	HB	PCR–RFLP	Y
Aldrich et al. (2009)	USA	Mixed	197 Patients diagnosed with pathologically confirmed lung cancer	113–299	HB	Not reported	Y
Shimada et al. (2009)	Japan	Asian	483 Diagnosed and histologically confirmed breast cancer patients	483–484	HB	PCR–RFLP	Y
Shimada et al. (2009)	Brazil	Mixed	389 Diagnosed and histologically confirmed breast cancer patients	389–389	HB	PCR–RFLP	Y

Table 1 continued

References	Country	Ethnicity	Source of cases	Case–control	SC	Genotype method	HWE
Altayli et al. (2009)	Turkey	Caucasian	135 Patients with histological confirmation of bladder cancer	135–128	HB	PCR–RFLP	Y
Villanueva et al. (2009)	Spain	Caucasian	1,107 Patients with newly diagnosed histologically confirmed bladder cancer	1,034–911	HB	TaqMan	Y
Saebø et al. (2008)	Norway	Caucasian	198 Patients with histological confirmation of CRC diagnosis	198–222	HB	PCR–RFLP	Y
Figueroa et al. (2008)	Spain	Caucasian	patients with a new diagnosis of histologically confirmed bladder cancer	1,091–1,021	HB	GoldenGate	Y
Suzuki et al. (2008)	USA	Mixed	755 Patients with pathologically confirmed pancreatic adenocarcinoma	649–585	HB	PCR–RFLP	Y
Gulyaeva et al. (2008)	Russia	Caucasian	96 Patients with histologically confirmed breast cancer	96–180	HB	PCR–RFLP	Y
Gulyaeva et al. (2008)	Russia	Caucasian	96 Patients with histologically confirmed ovarian cancer	93–180	HB	PCR–RFLP	Y
Gulyaeva et al. (2008)	Russia	Caucasian	166 Patients with histologically confirmed endometrial cancer	166–180	HB	PCR–RFLP	Y
Hirata et al. (2008)	USA	Caucasian	A total of 150 patients confirmed by pathology to have endometrial cancer	150–165	HB	PCR–RFLP	Y
Zienolddiny et al. (2008)	Norway	Caucasian	Diagnosis of lung cancer was confirmed by two pathologists	335–393	PB	TaqMan	Y
Yoshida et al. (2007)	Japan	Asian	A total of 66 histologically confirmed colorectal cancer	64–111	HB	PCR–RFLP	Y
Kiss et al. (2007)	Hungary	Caucasian	500 Patients who were diagnosed with histologically confirmed colorectal cancer	500–500	HB	PCR–RFLP	Y
Küry et al. (2007)	France	Caucasian	1,023 Patients with histologically confirmed colorectal cancer	1,013–1,118	HB	TaqMan	Y
Kotsopoulos et al. (2007)	Multiple	Mixed	170 Patients with pathologically confirmed breast cancer	170–241	HB	PCR–RFLP	Y
Osawa et al. (2007)	Japan	Asian	113 Patients with histologically diagnosed lung cancer	103–111	HB	PCR–RFLP	Y
Gemignani et al. (2007)	Multiple	Caucasian	299 Patients with newly histologically diagnosed lung cancer	297–310	HB	PCR–RFLP	Y
Takata et al. (2007)	USA	Mixed	607 Patients with pathologically confirmed breast cancer	325-250	PB	PCR–RFLP	Y
Agudo et al. (2006)	Multiple	Caucasian	290 Patients with histologically diagnosed gastric cancer	242–943	PB	PCR	Y
De Roos et al. (2006)	USA	Mixed	All non-Hodgkin's lymphoma cases were histologically confirmed.	745–640	PB	TaqMan	Y
Bae et al. (2006)	Korea	Asian	111 Patients with pathologically confirmed colorectal cancer	111–93	HB	PCR–RFLP	Y
Long et al. (2006)	China	Asian	1,459 Patients with pathologically confirmed breast cancer	1,082–1,139	PB	PCR–RFLP	Y
Mikhailova et al. (2006)	Russia	Caucasian	Clinical diagnosis of multiple cancers was performed by board-certified gynecologic-oncologists from the Regional	166–170	HB	PCR–RFLP	Y
Rebbeck et al. (2006)	USA	Mixed	The endometrial cancer patients were identified through active surveillance at 61 hospitals that were open during this period	475–1233	PB	TaqMan	Y
Li et al. (2006)	USA	Mixed	365 Patients with pathologically confirmed pancreatic cancer	307–333	HB	PCR–RFLP	Y
Le Marchand et al. (2005)	USA	Mixed	1,339 Patients with diagnosed and pathologically confirmed breast cancer	1,339–1,369	PB	PCR–RFLP	Y
Landi et al. (2005)	Spain	Caucasian	Patients with a new diagnosis of colorectal adenocarcinoma attending a University Hospital in Barcelona, Spain, between January 1996 and December 1998	361–321	HB	APEX	Y
Prawan et al. (2005)	Thailand	Asian	216 Patients diagnosed with histopathologically confirmed CCA	216–233	HB	PCR–RFLP	Y
Doherty et al. (2005)	USA	Caucasian	371 Participants from a population-based case–control study of endometrial cancer	371–420	PB	PCR–RFLP	Y
Chen et al. (2005)	China	Asian	140 patients with pathologically conformed colorectal cancer	138–340	PB	PCR–RFLP	Y
Mochizuki et al. (2005)	Japan	Asian	Hepatocellular cancer patients were diagnosed by liver biopsy or computed tomography and ultrasonography	44–159	PB	PCR	Y
Goodman et al. (2003)	USA	Mixed	160 Patients with histologically confirmed primary epithelial ovarian cancer	160–194	PB	PCR–RFLP	Y
Sachse et al. (2002)	UK	Caucasian	A total of 490 patients with colorectal cancer were recruited in the period August 1997–February 2001 at either Ninewells Hospital, Dundee, Perth Royal Infirmary, Leeds General Infirmary, St James's Hospital, Leeds or York District Hospital	490–593	PB	PCR–RFLP	Y

Table 1 continued

References	Country	Ethnicity	Source of cases	Case–control	SC	Genotype method	HWE
*CYP1A2*1C*							
Gervasini et al. (2013)	Spain	Caucasian	95 Patients with histologically diagnosed lung cancer	95–196	HB	PCR–RFLP	Y
Ayari et al. (2013)	Tunisia	Caucasian	Study subjects included 125 women with histologically confirmed breast cancer	109–41	HB	TaqMan	Y
Cui et al. (2013)	Japan	Asian	282 Consecutive patients histologically diagnosed with bladder cancer	282–257	HB	PCR	Y
Pavanello et al. (2012)	Italy	Caucasian	428 Patients with histologically diagnosed lung cancer	423–777	PB	PCR–RFLP	Y
Wei et al. (2011)	China	Asian	206 Patients with histologically diagnosed prostate cancer	206–253	HB	PCR	Y
Singh et al. (2010–2011)	India	Asian	200 Male patients with pathologically confirmed lung cancer	200–200	HB	PCR–RFLP	Y
Imaizumi et al. (2009)	Japan	Asain	226 Incident cases with pathologically confirmed hepatocellular cancer	209–637	HB	PCR–RFLP	Y
B'chir et al. (2009)	Tunisia	African	101 Patients with pathologically confirmed lung cancer	101–98	HB	PCR–RFLP	Y
Yeh et al. (2009)	China	Asian	776 Newly diagnosed and histologically confirmed colorectal adenocarcinoma	718–731	HB	PCR–RFLP	Y
Zienolddiny et al. (2008)	Norway	Caucasian	Diagnosis of lung cancer was confirmed by two pathologists	243–214	PB	TaqMan	Y
Yoshida et al. (2007)	Japan	Asian	A total of 66 histologically confirmed colorectal cancer	66–113	HB	PCR–RFLP	Y
Osawa et al. (2007)	Japan	Asian	113 Patients with histologically diagnosed lung cancer	106–113	HB	PCR–RFLP	Y
Gemignani et al. (2007)	European	Caucasian	299 Patients with newly histologically diagnosed lung cancer	288–194	HB	PCR–RFLP	Y
Agudo et al. (2006)	Multiple	Caucasian	243 Cases with of pathologically confirmed gastric cancer	243–945	PB	PCR	Y
Bae et al. (2006)	Korea	Asian	111 Patients of pathologically confirmed colorectal cancer	111–93	HB	PCR–RFLP	Y
Chen et al. (2006)	China	Asian	431 Patients with histologically diagnosed with hepatocellular cancer	430–546	HB	PCR–RFLP	Y
Landi et al. (2005)	Spain	Caucasian	Patients with a new diagnosis of colorectal adenocarcinoma attending a University Hospital in Barcelona, Spain, between January 1996 and December 1998	328–295	HB	APEX	Y
Mochizuki et al. (2005)	Japan	Asian	Hepatocellular cancer patients were diagnosed by liver biopsy or computed tomography and ultrasonography	44–159	PB	PCR	Y
Chiou et al. (2005)	China	Asian	162 Patients with pathologically diagnosed primary lung cancer	162–208	HB	PCR–RFLP	Y
Tsukino et al. (2004)	Japan	Asian	306 Patients histologically diagnosed for urothelial transitional cell carcinoma	306–306	HB	PCR	Y
Sachse et al. (2002)	UK	Caucasian	A total of 490 patients with colorectal cancer were recruited in the period August 1997-February 2001 at either Ninewells Hospital, Dundee, Perth Royal Infirmary, Leeds General Infirmary, St James's Hospital, Leeds or York District Hospital	60–73	PB	PCR–RFLP	Y

CCA cholangiocarcinoma, *TGCC* testicular germ cell cancer, *PB* population-based study, *HB* hospital-based study, *Y* yes, *N* no, *SC* source of controls, *FB* family-based study

$I^2 = 0.0$ %; additive model: OR 0.89, 95 % CI 0.81–0.97, $P_h = 0.622$, $I^2 = 0.0$ %).

There was significant heterogeneity in any genetic model ($P_h < 0.001$). We assessed the source of heterogeneity by ethnicity, cancer type, source of cases, genotype method, source of controls, and sample size. The results indicated that source of controls (dominant model: $P = 0.048$; heterozygous model: $P = 0.013$) and cancer type (dominant model: $P = 0.024$; additive model: $P = 0.030$; heterozygous model: $P = 0.005$) but not ethnicity (dominant model: $P = 0.089$; recessive model: $P = 0.522$; homozygous model: $P = 0.336$; heterozygous model: $P = 0.091$; additive model: $P = 0.133$), sample size (dominant model: $P = 0.874$; recessive model: $P = 0.259$; homozygous model: $P = 0.543$; heterozygous model: $P = 0.643$; additive model: $P = 0.748$), source of cases (dominant model: $P = 0.367$; recessive model: $P = 0.396$; homozygous model: $P = 0.839$; heterozygous model: $P = 0.291$; additive model: $P = 0.686$), and genotype method (dominant model: $P = 0.777$; recessive model: $P = 0.155$; homozygous model: $P = 0.208$; heterozygous model: $P = 0.881$; additive model: $P = 0.543$) contributed to substantial heterogeneity in the meta-analysis. High between-studies heterogeneity was observed in breast cancer (recessive model: $I^2 = 75.1$; homozygous model: $I^2 = 76.6$; heterozygous model: $I^2 = 77.0$) and other cancer (dominant model: $I^2 = 80.0$; recessive model: $I^2 = 77.2$; homozygous model: $I^2 = 81.2$; additive model: $I^2 = 87.9$). When we performed subgroup analysis by source of controls and cancer type, high between-studies heterogeneity was also observed in breast cancer (recessive model: $I^2 = 54.6$; homozygous model: $I^2 = 45.5$; heterozygous model: $I^2 = 0.0$) and other cancer (dominant model: $I^2 = 0.0$; recessive model: $I^2 = 0.0$; homozygous model: $I^2 = 0.0$; additive model: $I^2 = 0.0$) for the population-based studies.

When the meta-analysis was performed excluding studies with small sample sizes, there was no difference in results between overall analysis and subgroup analysis. In addition, a single study involved in the meta-analysis was deleted each time to reflect the influence of individual data set on the pooled ORs, and the corresponding pooled ORs were not essentially altered (data not shown). We performed Begg's funnel plot and Egger's test to assess the publication bias of literatures. Begg's funnel plots and Egger's test suggested that there was publication bias in any genetic model (dominant model: $P = 0.001$; heterozygous model: $P = 0.001$; recessive model: $P = 0.025$; additive model: $P = 0.001$; homozygous model: $P = 0.004$). This might be a limitation for the meta-analysis because studies with null findings, especially those with small sample size, are less likely to be published. Adjusting for possible publication bias using the Duval and Tweedie nonparametric "trim and fill" method for overall studies, the results did not change between CYP1A2*1F polymorphism with cancer risk. Figure 2 lists the Duval and Tweedie nonparametric "trim and fill" methods funnel plot.

*CYP1A2*1C*

Table 2 also lists the main results of the meta-analysis of CYP1A2*1C polymorphism and cancer risk. Overall, no significant association was observed in any genetic model (dominant model: OR 1.02, 95 % CI 0.85–1.23, $P_h < 0.001$, $I^2 = 59.9$ %; recessive model: OR 1.05, 95 % CI 0.86–1.29, $P_h = 0.262$, $I^2 = 18.0$ %; homozygous model: OR 1.06, 95 % CI 0.86–1.30, $P_h = 0.252$, $I^2 = 18.9$ %; heterozygous model: OR 1.01, 95 % CI 0.84–1.22, $P_h = 0.002$, $I^2 = 56.1$ %; additive model: OR 1.05, 95 % CI 0.88–1.25, $P_h < 0.001$, $I^2 = 67.0$ %) when all the eligible studies were pooled into meta-analysis. No significant association was observed between CYP1A2*1C polymorphism and any subgroup analysis (Tables 3 and 4).

There was significant heterogeneity in dominant model ($P_h < 0.001$), heterozygous model ($P_h = 0.002$), and additive model ($P_h < 0.001$). Then, we assessed the source of heterogeneity by ethnicity, cancer type, source of cases, genotype method, source of controls, and sample size. The results indicated that ethnicity (dominant model: $P = 0.026$; additive model: $P = 0.004$) contributed to substantial heterogeneity in the meta-analysis. High between-studies heterogeneity was also observed in lung cancer (dominant model: $I^2 = 76.3$; recessive model: $I^2 = 88.6$; homozygous model: $I^2 = 90.6$; additive model: $I^2 = 85.9$). However, when the study of B'chir [36] was excluded, the high between-studies heterogeneity was deleted in lung cancer (dominant model: $I^2 = 0.0$; heterozygous model: $I^2 = 0.0$; additive model: $I^2 = 0.0$).

When the meta-analysis was performed excluding studies with small sample sizes, there was no difference in results between overall analysis and subgroup analysis. In addition, a single study involved in the meta-analysis was deleted each time to reflect the influence of individual data set on the pooled ORs, and the corresponding pooled ORs were not essentially altered (data not shown). Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The Egger's test results (dominant model: $P = 0.463$; recessive model: $P = 0.216$; additive model: $P = 0.406$; homozygous model: $P = 0.326$; heterozygous model: $P = 0.677$) and Begg's funnel plot (Fig. 3) suggested no evidence of publication bias in the meta-analysis.

Discussion

CYP1A2 is an important gene for catalyzing 2- and 4-hydroxylations of estrogens and metabolism of

Table 2 Stratified analysis of CYP1A2*1F (rs762551) and CYP1A2*1C (rs2069514) polymorphisms on cancer risk

Genetic model	*N* (case/control)	Dominant model		Recessive model		Homozygous model		Heterozygous model		Additive model	
		OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
CYP1A2*1F (rs762551)											
Overall	57 (27301/33885)	**1.08 (1.02–1.15)**[a]	<0.001/61.4	1.06 (0.96–1.18)[a]	<0.001/60.7	1.11 (0.99–1.25)[a]	<0.001/64.8	**1.06 (1.01–1.12)**[a]	<0.001/50.8	**1.07 (1.02–1.13)**[a]	<0.001/71.4
Cancer type											
Bladder cancer	4 (2415/2208)	**0.88 (0.78–0.99)**	0.563/0.0	**0.79 (0.66–0.94)**	0.849/0.0	**0.76 (0.63–0.93)**	0.702/0.0	0.91 (0.80–1.04)	0.658/0.0	**0.89 (0.81–0.97)**	0.622/0.0
Breast cancer	13 (10295/13330)	1.07 (0.96–1.20)	<0.001/69.6	[b]	<0.001/75.1	[b]	<0.001/76.6	1.05 (0.94–1.16)[a]	0.002/60.9	[b]	<0.001/77.0
Colorectal cancer	13 (6891/7636)	1.05 (0.94–1.18)[a]	0.010/54.1	1.01 (0.90–1.13)	0.426/2.0	1.09 (0.93–1.17)	0.144/30.0	1.05 (0.94–1.17)[a]	0.023/49.2	1.03 (0.95–1.11)[a]	0.026/48.2
Endometrial cancer	4 (1162/1998)	1.06 (0.88–1.27)	0.609/0.0	1.14 (0.79–1.63)	0.545/0.0	1.15 (0.78–1.70)	0.557/0.0	1.04 (0.84–1.30)	0.403/0.0	1.07 (0.91–1.26)	0.432/0.0
Gastric cancer	3 (471/1528)	1.04 (0.73–1.47)[a]	0.083/59.7	0.88 (0.62–1.24)	0.309/14.8	0.89 (0.62–1.29)	0.844/0.0	1.05 (0.66–1.67)[a]	0.020/74.4	1.02 (0.87–1.19)	0.559/0.0
Lung cancer	8 (1665/2383)	**1.21 (1.00–1.46)**[a]	0.083/44.3	1.39 (0.92–2.11)[a]	0.001/73.9	1.45 (0.93–2.26)[a]	0.001/73.4	**1.18 (1.02–1.36)**	0.157/35.5	1.19 (0.98–1.45)[a]	0.002/71.4
Pancreatic cancer	3 (1403/1798)	1.07 (0.93–1.23)	0.350/4.7	1.04 (0.80–1.35)	0.874/0.0	1.08 (0.82–1.42)	0.733/0.0	1.06 (0.92–1.24)	0.358/2.8	1.05 (0.94–1.17)	0.473/0.0
Other cancer	9 (2999/3004)	[b]	<0.001/80.0	[b]	<0.001/77.2	[b]	<0.001/81.2	1.17 (0.95–1.45)[a]	0.009/62.5	[b]	<0.001/87.9
CYP1A2*1C (rs2069514)											
Overall	21 (4722/6555)	1.02 (0.85–1.23)[a]	<0.001/59.9	1.05 (0.86–1.29)	0.262/18.0	1.06 (0.86–1.30)	0.252/18.9	1.01 (0.84–1.22)[a]	0.002/56.1	1.05 (0.88–1.25)[a]	<0.001/67.0
Cancer type											
Colorectal cancer	5 (1283/1305)	0.96 (0.65–1.43)	0.074/53.2	0.98 (0.69-–1.39)	0.535/0.0	0.99 (0.69–1.41)	0.730/0.0	0.93 (0.58–1.48)[a]	0.034/61.5	1.02 (0.88–1.17)	0.162/38.9
Liver cancer	3 (685/1348)	0.93 (0.77–1.13)	0.743/0.0	0.90 (0.65–1.26)	0.659/0.0	0.88 (0.62–1.24)	0.618/0.0	0.95 (0.77–1.15)	0.870/0.0	0.94 (0.81–1.09)	0.604/0.0
Lung cancer	8 (1608/2100)	[b]	<0.001/76.3	[b]	0.003/88.6	[b]	<0.001/90.6	1.22 (0.64–2.30)[a]	0.003/72.7	[b]	<0.001/85.9
Other cancer	5 (1146/1802)	1.00 (0.72–1.39)[a]	0.045/58.9	1.16 (0.76–1.77)	0.274/22.8	1.16 (0.75–1.79)	0.375/3.6	1.00 (0.82–1.22)[a]	0.029/63.0	1.01 (0.78–1.31)[a]	0.080/52.0

In the article ORs were calculated using fixed-effects models

The bold values indicate that the results are statistically significant

[a] In the case of significant heterogeneity, ORs were calculated using random-effects models

[b] The results were excluded due to high heterogeneity

Table 3 Summary ORs (95 % CI) categorized by ethnicity for the CYP1A2*1F (rs762551) and CYP1A2*1C (rs2069514) polymorphisms under different genetic models and cancer type

Ethnicity	Cancer type	*N*	Dominant model		Recessive model		Homozygote		Heterozygote		Additive model	
			OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
*CYP1A2*1F (rs762551)*												
Caucasian	Bladder cancer	4 (2415/2208)	**0.88 (0.78–0.99)**	0.563/0.0	**0.79 (0.66–0.94)**	0.849/0.0	**0.76 (0.63–0.93)**	0.702/0.0	0.91 (0.80–1.04)	0.658/0.0	**0.89 (0.81–0.97)**	0.622/0.0
	Breast cancer	4 (3683/6233)	[b]	<0.001/91.3	[b]	0.006/76.0	[b]	<0.001/84.7	[b]	<0.001/88.7	[b]	<0.001/91.9
	Colorectal cancer	8 (6169/6510)	1.02 (0.95–1.10)	0.233/24.6	1.06 (0.94–1.20)	0.387/5.6	1.07 (0.94–1.21)	0.224/25.6	1.01 (0.94–1.09)	0.403/3.5	1.03 (0.97–1.08)	0.157/34.0
	Endometrial cancer	3 (687/765)	1.07 (0.86–1.32)	0.406/0.0	1.14 (0.79–1.63)	0.545/0.0	1.15 (0.78–1.70)	0.557/0.0	1.04 (0.84–1.30)	0.403/0.0	1.07 (0.91–1.26)	0.432/0.0
	Lung cancer	4 (1148/1675)	**1.29 (1.11–1.51)**	0.948/0.0	**1.33 (1.01–1.75)**	0.181/41.4	**1.49 (1.12–1.98)**	0.358/2.7	**1.25 (1.06–1.48)**	0.540/0.0	**1.23 (1.09–1.39)**	0.828/0.0
Asian	Breast cancer	4 (2696/3087)	1.06 (0.95–1.17)	0.764/0.0	[b]	0.005/76.6	1.26 (0.87–1.82)	0.011/73.2	1.03 (0.92–1.15)	0.817/0.0	1.05 (0.97–1.14)	0.177/39.1
	Colorectal cancer	4 (417/769)	[b]	0.001/81.3	0.78 (0.57–1.05)	0.681/0.0	0.91 (0.49–1.68)[a]	0.076/56.5	[b]	0.003/79.0	0.98 (0.69–1.42)[a]	0.009/74.3
*CYP1A2*1C (rs2069514)*												
Caucasian	Lung cancer	4 (1039/1481)	0.86 (0.49–1.50)	0.301/17.9	–	–	–	–	0.95 (0.50–1.81)	0.194/39.0	0.95 (0.50–1.80)	0.199/38.1
Asian	Colorectal cancer	3 (895/937)	1.00 (0.83–1.20)	0.246/28.8	0.97 (0.68–1.37)	0.408/0.0	0.97 (0.68–1.39)	0.633/0.0	1.00 (0.83–1.22)	0.105/55.6	0.99 (0.86–1.15)	0.570/0.0
	Liver cancer	3 (685/1348)	0.93 (0.77–1.13)	0.743/0.0	0.90 (0.65–1.26)	0.659/0.0	0.88 (0.62–1.24)	0.618/0.0	0.95 (0.77–1.15)	0.870/0.0	0.94 (0.81–1.09)	0.604/0.0
	Lung cancer	3 (468/521)	0.92 (0.69–1.22)	0.701/0.0	0.65 (0.21–2.05)	–	0.61 (0.19–1.95)	–	0.84 (0.56–1.25)	0.973/0.0	0.82 (0.58–1.16)	0.867/0.0
	Other cancer	3 (794/816)	1.04 (0.85–1.27)	0.176/42.4	1.22 (0.79–1.88)	0.373/0.0	1.23 (0.79–1.91)	0.622/0.0	1.03 (0.72–1.47)	0.058/64.9	1.05 (0.89–1.24)	0.603/0.0

In the article ORs were calculated using fixed-effects models

The bold values indicate that the results are statistically significant

[a] In the case of significant heterogeneity, ORs were calculated using random-effects models

[b] The results were excluded due to high heterogeneity

Table 4 Summary ORs (95 % CI) and value of the heterogeneity of CYP1A2*1F (rs762551) and CYP1A2*1C (rs2069514) polymorphisms for studies according to source of controls and cancer type

SC	Cancer type	*N*	Dominant model		Recessive model		Homozygote		Heterozygote		Additive model	
			OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
*CYP1A2*1F (rs762551)*												
HB	Bladder cancer	4 (2415/2208)	**0.88 (0.78–0.99)**	0.563/0.0	**0.79 (0.66–0.94)**	0.849/0.0	**0.76 (0.63–0.93)**	0.702/0.0	0.91 (0.80–1.04)	0.658/0.0	**0.89 (0.81–0.97)**	0.622/0.0
	Breast cancer	7 (2130/2345)	[b]	<0.001/75.4	[b]	<0.001/81.9	[b]	<0.001/82.7	1.24 (0.98–1.58)[a]	0.004/68.4	[b]	<0.001/82.2
	Colorectal cancer	7 (2351/2590)	1.18 (0.91–1.53)[a]	0.001/74.5	1.06 (0.88–1.28)	0.303/16.6	1.14 (0.82–1.59)[a]	0.040/54.5	1.20 (0.93–1.55)[a]	0.002/71.1	1.09 (0.92–1.30)[a]	0.004/69.1
	Lung cancer	6 (909/1214)	1.16 (0.85–1.58)[a]	0.033/58.8	[b]	<0.001/81.0	[b]	<0.001/80.1	1.10 (0.80–1.52)[a]	0.063/55.2	[b]	0.001/80.0
	Other cancer	5 (645/1261)	[b]	<0.001/83.8	[b]	<0.001/84.7	[b]	<0.001/86.6	1.36 (0.91–2.03)[a]	0.008/70.8	[b]	<0.001/89.9
PB	Breast cancer	6 (8165/10985)	0.95 (0.90–1.01)	0.906/0.0	0.99 (0.84–1.16)[a]	0.051/54.6	0.98 (0.88–1.09)	0.102/45.5	0.94 (0.89–1.01)	0.830/0.0	0.97 (0.93–1.01)	0.622/0.0
	Colorectal cancer	5 (4235/4689)	0.99 (0.91–1.08)	0.982/0.0	0.98 (0.85–1.13)	0.329/13.3	1.00 (0.86–1.17)	0.566/0.0	0.99 (0.91–1.09)	0.929/0.0	0.99 (0.93–1.06)	0.795/0.0
	Other cancer	4 (2354/1743)	0.98 (0.86–1.12)	0.966/0.0	0.88 (0.71–1.08)	0.810/0.0	0.90 (0.72–1.13)	0.912/0.0	1.00 (0.87–1.15)	0.924/0.0	0.97 (0.88–1.07)	0.979/0.0
*CYP1A2*1C (rs2069514)*												
HB	Colorectal cancer	3 (895/937)	1.00 (0.83–1.20)	0.246/28.8	0.97 (0.68–1.37)	0.408/0.0	0.97 (0.68–1.39)	0.633/0.0	1.00 (0.83–1.22)	0.105/55.6	0.99 (0.86–1.15)	0.570/0.0
	Lung cancer	6 (942/1109)	[b]	<0.001/82.1	[b]	0.003/88.6	[b]	0.001/90.6	[b]	0.001/77.6	[b]	<0.001/88.5
	Other cancer	4 (903/857)	0.94 (0.66–1.33)[a]	0.039/64.1	1.16 (0.76–1.77)	0.274/22.8	1.16 (0.75–1.79)	0.375/3.6	0.92 (0.62–1.36)[a]	0.026/67.7	0.97 (0.74–1.27)[a]	0.069/57.7

In the article ORs were calculated using fixed-effects models

PB population-based studies, *HB* hospital-based studies

The bold values indicate that the results are statistically significant

[a] In the case of significant, ORs were calculated using random-effects models

[b] The results were excluded due to high heterogeneity

carcinogens. A major reason for the limited number of studies of heterocyclic amine (HCA) and cancer risk is the difficulty in assessing human exposure to HCAs. HCA concentrations depend on cooking methods and the "doneness" level of the meat or fish, hampering the development of a complete and standardized database of concentrations; any estimation of dietary intake from food-frequency questionnaires (FFQs) is thus likely to result in misclassification. Like other environmental chemical carcinogens, HCAs require metabolic activation by host enzymes to become genotoxic. Phase I enzymes, including cytochrome P450 1A2, can metabolically activate carcinogens to form genotoxic electrophilic intermediates (McManus et al. 1990). The relative activity of these metabolizing enzymes, which is in large part genetically determined, is thought to be an important host determinant of cancer incidence. A number of molecular epidemiological studies have been performed to evaluate the association between CYP1A2*1C and CYP1A2*1F polymorphisms and different types of cancer risk in diverse populations. However, the results were inconsistent or even contradictory. In addition, three recent meta-analyses have studied the association between CYP1A2*1C and CYP1A2*1F and risk of cancer. However, some published studies were not included in the three recent meta-analyses (Tian et al. 2013; Zhenzhen et al. 2013; Wang et al. 2012a, b). Hence, we performed a meta-analysis to explore the association between CYP1A2*1C and CYP1A2*1F polymorphisms and cancer risk.

This meta-analysis suggests that CYP1A2*1F polymorphism is associated with increased lung cancer risk and CYP1A2*1F polymorphism is associated with decreased bladder cancer risk, while results from other subgroups remain negative. A possible explanation may be that the biological effect of the genetic mutation is influenced by the variable environmental conditions at different tumor sites, leading to unpredictable physiological characteristics. It may also be attributed to the uncertainty of CYP1A2*1F polymorphism's function at different tumor positions. Aldrich et al. (2009) reported that CYP1A2 rs762551 polymorphism was associated with an increased risk of lung cancer. Gemignani et al. (2007) reported that CYP1A2 rs762551 was associated with an increased risk of lung cancer in heterozygote carriers ($P < 0.05$), although not in homozygote. Singh et al. (2010–2011) found that variant genotype of CYP1A2*1F was significantly associated with increased susceptibility to squamous cell carcinoma (SCC) of lung. Pavanello et al. (2012) identified not only increased CYP1A2 metabolic activity but also increased urine mutagenicity in Italian heavy smokers having an ancestral allele of this variant. These findings are consistent with our meta-analysis results being associated with risk of lung cancer. However, at any case, the association between CYP1A2*1F polymorphism and bladder cancer risk remains an open field, as the number of studies ($n = 4$ for CYP1A2*1F) is considerably smaller than that needed for the achievement of robust conclusions (Higgins and Green 2008).

In the subgroup analysis by ethnicity and cancer type, significantly increased lung cancer risk was found in Caucasians and significantly decreased bladder cancer risk was also found in Caucasians, but not Africans or Asians. The results suggested a possible role of ethnic difference in genetic background and the environment they lived in. The same polymorphisms play different roles in cancer susceptibility in different ethnic populations, because cancer is a complicated multigenetic disease, and different genetic backgrounds may contribute to the discrepancy (Hirschhorn et al. 2002). In the present meta-analysis, between-studies heterogeneity was observed between CYP1A2*1C and CYP1A2*1F polymorphisms and cancer of risk. Meta-regression analysis indicated that source of control and cancer type contributed to substantial heterogeneity between the meta-analyses for CYP1A2*1F polymorphism and ethnicity contributed to substantial heterogeneity between the meta-analyses for CYP1A2*1C. The hospital-based studies may have certain biases for such controls and may only represent a sample of an ill-defined reference population, and may not be representative of the general population or it may be that numerous subjects in the population-based controls were susceptible individuals. The small number of studies hinders the ability to draw more definite conclusions. Therefore, the use of proper and representative population-based control subjects is important to reduce biases in such genetic studies. And this indicates that it may not be appropriate to use an overall estimation of the relationship between CYP1A2*1C and CYP1A2*1F polymorphism and risk of cancer.

We noticed with great interest that 3 previous meta-analyses had been reported on the overall cancer risk with CYP1A2*1C and CYP1A2*1F polymorphisms (Tian et al. 2013; Zhenzhen et al. 2013; Wang et al. 2012a, b). Tian et al. (2013) had 46 case–control studies for CYP1A2*1F polymorphism, in which a total of 22,993 cases and 28,420 controls were included. Their meta-analysis suggested that the allele of CYP1A2*1F polymorphism may be associated with breast and ovarian cancer risk, especially in Caucasian populations. However, two articles (Cui et al. 2013; Tsukino et al. 2004) should be excluded from their meta-analyses, because the two articles explored the CYP1A2*1C polymorphism and cancer risk. In addition, the study subjects should be mixed population, but not Caucasians in the study of Rebbeck et al. (2006). Zhenzhen et al. (2013) included 37 case–control studies for CYP1A2*1F (16,825 cases and 21,513 controls) and 15 studies for CYP1A2*1C (3,677 cases and 5,127 controls). Their meta-analyses suggested that the rs762551 polymorphism of the CYP1A2 gene might be a potential biomarker for the risk of cancer in Caucasians. Wang et al. (2012a, b) had 19 eligible case–control studies for CYP1A2*1F, in which a total of

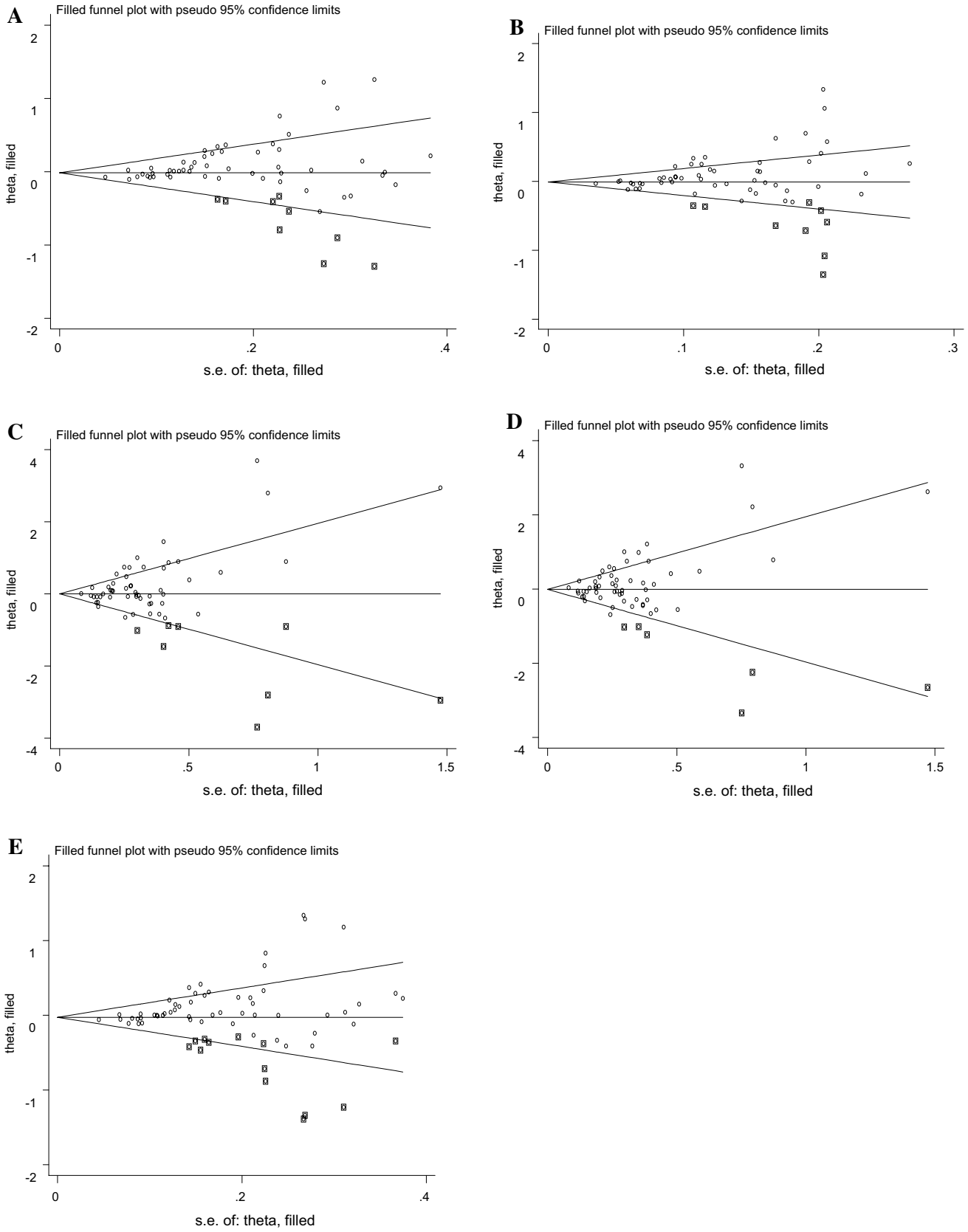

Fig. 2 The Duval and Tweedie nonparametric "trim and fill" method's funnel plot of the meta-analysis of cancer risk and CYP1A2*1F polymorphism [heterozygous model: (**a**), additive model: (**b**), homozygous model: (**c**), recessive model: (**d**), and dominant model: (**e**)]

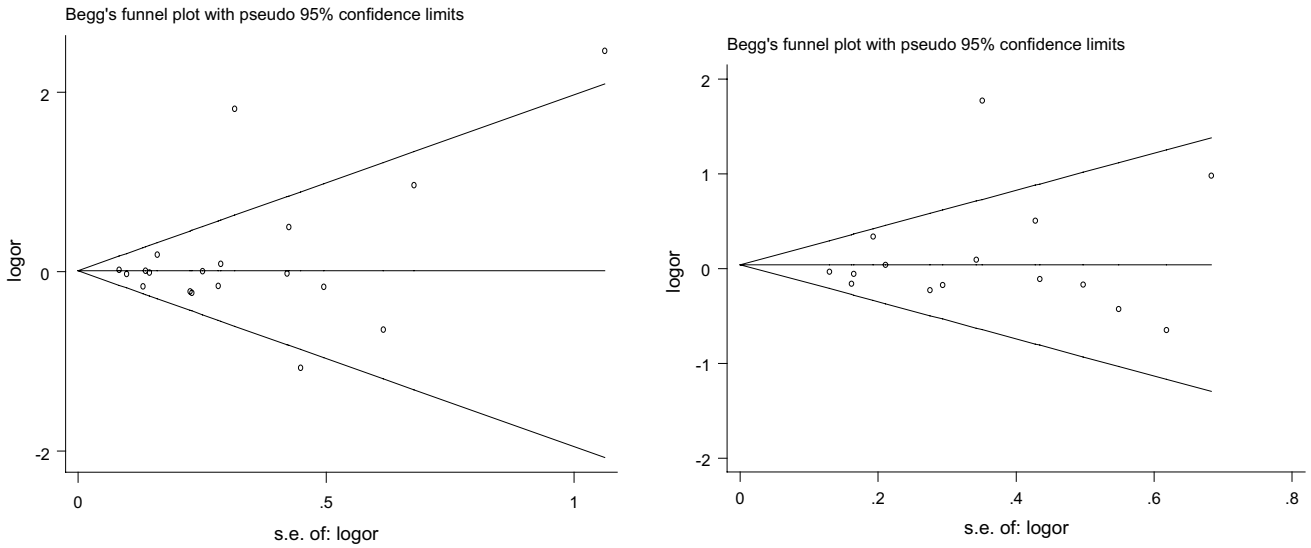

Fig. 3 Begg's funnel plot of association between CYP1A2*1C polymorphism and cancer risk (additive model and dominant model)

8,128 cases and 11,165 controls were included. Their meta-analysis suggested that the CYP1A2 rs762551 polymorphism is likely to be associated with susceptibility to cancer in Caucasians. However, some published studies were not included in their meta-analyses (Tian et al. 2013; Zhenzhen et al. 2013; Wang et al. 2012a, b). By analyzing a larger number of studies than the previous meta-analysis (Tian et al. 2013; Zhenzhen et al. 2013; Wang et al. 2012a, b), our meta-analysis included 27,301 cases and 33,885 controls (from 57 studies) for CYP1A2 rs762551 and 4,722 cases and 6,555 controls (from 21 studies) for CYP1A2*1C to perform the two gene polymorphisms and cancer risk. Our meta-analysis suggests that CYP1A2*1F polymorphism is associated with increased lung cancer risk and CYP1A2*1F polymorphism is associated with decreased bladder cancer risk in Caucasians. Our results seem to confirm and establish the trend in the meta-analysis of the CYP1A2*1C and CYP1A2*1F polymorphisms according to the previous meta-analysis (Tian et al. 2013; Zhenzhen et al. 2013; Wang et al. 2012a, b).

There are still some limitations inherited from the published studies. First, our results were based on single-factor estimations without adjustment for other risk factors including alcohol usage, environmental factors and other lifestyles. Second, in the subgroup analysis there may exist insufficient statistical power to check an association. Third, the controls were not uniformly defined. Therefore, non-differential misclassification bias is possible because these studies may have included the control groups who have different risks for developing cancer in the various organs. However, this meta-analysis has also several strengths. First, a systematic review of the association of CYP1A2*1C and CYP1A2*1F polymorphisms with cancer risk is statistically more powerful than any single study. Second, the quality of eligible studies included in current meta-analysis was satisfactory and met our inclusion criteria. Third, we included more published studies than previously published meta-analysis.

In conclusion, this meta-analysis suggests that CYP1A2*1F polymorphism is associated with increased lung cancer risk and CYP1A2*1F polymorphism is associated with decreased bladder cancer risk in Caucasians. However, further studies are still needed to validate the associations between genetic polymorphisms in the CYP1A2 gene and cancer risks.

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Conflict of interest None.

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