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Association between CYP1A2 and CYP1B1 Polymorphisms and Colorectal Cancer Risk: A Meta-Analysis

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Abstract

Background: The previous published data on the association between CYP1A2*F (rs762551), CYP1B1 Leu432Val (rs1056836), Asn453Ser (rs180040), and Arg48Gly (rs10012) polymorphisms and colorectal cancer risk remained controversial.

Methodology/Principal Findings: The purpose of this study is to evaluate the role of CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly genotypes in colorectal cancer susceptibility. We performed a meta-analysis on all the eligible studies that provided 5,817 cases and 6,544 controls for CYP1A2*F (from 13 studies), 9219 cases and 10406 controls for CYP1B1 Leu432Val (from 12 studies), 6840 cases and 7761 controls for CYP1B1 Asn453Ser (from 8 studies), and 4302 cases and 4791 controls for CYP1B1Arg48Gly (from 6 studies). Overall, no significant association was found between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly and colorectal cancer risk when all the eligible studies were pooled into the meta-analysis. And in the subgroup by ethnicity and source of controls, no evidence of significant association was observed in any subgroup analysis.

Conclusions/Significance: In summary, this meta-analysis indicates that CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms do not support an association with colorectal cancer, and further studies are needed to investigate the association. In addition, our work also points out the importance of new studies for CYP1A2*F polymorphism in Asians, because high heterogeneity was found (dominant model: $I^2 = 81.3\%$; heterozygote model: $I^2 = 79.0$).

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Introduction

Sporadic colorectal cancer (CRC) is considered to be a multifactorial disease, in which multiple exposures to endogenous factors and dietary carcinogens interact with individual genetic background in a complex manner resulting in modulation of the risk [1]. In 2010, an estimated 142,570 new cases will be diagnosed and 51,370 deaths will occur in the whole world [2]. Epidemiologic studies on Western populations have emphasized the large contribution of food and lifestyle to sporadic CRC risk [3–7]. High-fat and low-fiber diets, as well as alcohol, tobacco, and red or processed meat consumption, have been shown to produce high levels of polycyclic aromatic hydrocarbons and heterocyclic aromatic amines. These procarcinogenic agents are potentially very harmful and may play a key role in the malignant transformation of cells by interacting with DNA [8]. It has been proposed that this risk may be due to carcinogenic polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines produced when meat is cooked at high temperatures [9].

CYP1B1 gene is located on chr2p22-p21, which is involved in the metabolic activation of polycyclic aromatic hydrocarbons (PAHs) including benzo(a)pyrene and dimethylbenz(a)anthracene (DMBA), but with a product distribution that is distinct from CYP1A1 [10,11]. Several lines of evidence suggest that CYP1B1 plays a role in carcinogenesis. CYP1B1 is commonly over-expressed inhumanmalignancies [12] and activates a variety of carcinogens. For example, CYP1B1 catalyzes both the formation of dihydrodiols of specific PAHs and their subsequent oxidation to carcinogenic dihydrodiol epoxides [13]. In humans, CYP1B1 is genetically polymorphic and more than 50 single nucleotide polymorphisms (SNPs) have been reported so far, of which certain deleterious mutations are associated with primary congenital glaucoma [14]. Of the most common SNPs of CYP1B1 gene, four

have been reported to result in amino acid substitutions including Arg by Gly at codon 48 (rs10012), Leu by Val at codon 432 (rs1056836) and Asn by Ser at codon 453 (rs1800440). CYP 1A2 is an important gene in catalyzing 2- and 4-hydroxylations of estrogens [40–42] and metabolism of carcinogens [43–45]. CYP1A2*1C, located in the 5′-non-coding promoter region of CYP1A2, was reported to be associated with decreased enzyme inducibility in Japanese smokers but seems to be very rare [46].

To date, a number of molecular epidemiological studies have been done to evaluate the association between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and colorectal cancer risk in diverse populations [15–29,31,32,34–39]. However, the results were inconsistent or even contradictory. Therefore, we performed a comprehensive meta-analysis by including the most recent and relevant articles to identify statistical evidence of the association between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and risk of colorectal cancer that have been investigated. Meta-analysis is a powerful tool for summarizing the different studies. It can not only overcome the problem of small size and inadequate statistical power of genetic studies of complex traits, but also provide more reliable results than a single case–control study.

Materials and Methods

Identification and eligibility of relevant studies

A comprehensive literature search was performed using the PubMed, CNKI, and Medline database for relevant articles published (the last search update was Sep 10, 2013) with the following key words "CYP1A2", "CYP1B1", "polymorphism", "Variant", or "Mutation", and "Colorectal". 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*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and colorectal 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*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and the risk of colorectal cancer; (3) the genotype distribution of the polymorphism in cases and controls were described in details 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; (3) duplicate of previous publication (When the same patient population was used in several publications, only the most recent, largest or complete study was included following careful examination).

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), and numbers of cases and controls in the CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly genotypes whenever possible. Ethnicity was categorized as "Caucasian" and "Asian". When one study did not state which ethnic groups was included or if it was impossible to separate participants according to phenotype, the sample was termed as "mixed population". We did not define any minimum number of patients to include in this meta-analysis. Articles that reported different ethnic groups and different countries or locations, we considered them different study samples for each category cited above.

Statistical analysis

Crude odds ratios (ORs) together with their corresponding 95% confidence intervals (95% CIs) were used to assess the strength of association between the CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and colorectal cancer risk. The pooled ORs were performed for dominant model (CYP1A2*F: CY + YY vs. CC; CYP1B1 Leu432Val: Leu/Val + Val/Val vs. Leu/Leu; CYP1B1 Asn453Ser: Asn/Ser + Ser/Ser vs. Asn/Asn; CYP1B1 Arg48Gly: Arg/Gly + Gly/Gly vs. Arg/Arg), recessive model (CYP1A2*F: YY vs. CC + CY; CYP1B1 Leu432Val: Val/Val vs. Leu/Leu + Leu/Val; CYP1B1 Asn453Ser: Ser/Ser vs. Asn/Asn + Asn/Ser; CYP1B1 Arg48Gly: Gly/Gly vs. Arg/Arg + Arg/Gly), co-dominant model (CYP1A2*F: YY vs. CC and CY vs. CC; CYP1B1 Leu432Val: Val/Val vs. Leu/Leu and Leu/Val vs. Leu/Leu; CYP1B1 Asn453Ser: Ser/Ser vs. Asn/Asn and Asn/Ser vs. Asn/Asn; CYP1B1 Arg48Gly: Gly/Gly vs. Arg/Arg and Arg/Gly vs. Arg/Arg), and additive model (CYP1A2*F: Y vs. C; CYP1B1 Asn453Ser: Ser/Asn; CYP1B1 Asn453Ser: Ser vs. Asn; CYP1B1 Arg48Gly: Gly vs. Arg), respectively. Between-study heterogeneity was assessed by calculating Q-statistic (Heterogeneity was considered statistically significant if $P<0.10$) [47] and quantified using the I^2 value, Venice criteria [48] for the I^2 test included: "$I^2<25\%$ represents no heterogeneity, $I^2=25$–50% represents moderate heterogeneity, $I^2=50$–75% represents large heterogeneity, and $I^2>75\%$ represents extreme heterogeneity". 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) [49]. Otherwise, a random effect model was used (when the heterogeneity between-studies were significant) [50]. We also performed subgroup analysis by ethnicity and source of controls were conducted. 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 [51]. HWE was calculated by using the goodness-of-fit test, and deviation was considered when $P<0.05$. Begg's funnel plots [52] and Egger's linear regression test [53] were used to assess publication bias. We opted for using ethnicity, source of controls, menopausal status, and sample size as possible different 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

Relevant publications were retrieved and preliminarily screened. As shown in **Fig. 1**, 43 publications were identified, among which 6 irrelevant papers were excluded. Thus, 37 publications were eligible. Among these publications, 14 articles were excluded because they were review articles, case reports, and other polymorphisms of CYP1A2 and CYP1B1. As summarized in **Table 1**, 23 articles with 39 studies were selected in this meta-analysis, including 5,817 cases and 6,544 controls for CYP1A2*F (from 13 studies), 9,219 cases and 10,406 controls for CYP1B1

Leu432Val (from 12 studies), 6,840 cases and 7,761 controls for CYP1B1 Asn453Ser (from 8 studies), and 4,302 cases and 4,791 controls for CYP1B1 Arg48Gly (from 6 studies). Among these studies, eight were Caucasians, four were Asians, and 1 mixed populations for CYP1A2*F. All studies were Caucasians except for one study was mixed population for CYP1B1 polymorphisms. The distribution of genotypes in the controls was consistent with Hardy–Weinberg equilibrium in all studies. All of the cases were pathologically confirmed.

Meta-analysis results

Table 2 lists the main results of the meta-analysis of CYP1A2*F polymorphism and colorectal cancer risk. Overall, no significant association was found between CYP1A2*F polymorphism and colorectal cancer risk (dominant model: OR = 1.05, 95% CI = 0.94–1.18, $P_h = 0.010$, $I^2 = 54.1\%$; recessive model: OR = 1.01, 95% CI = 0.90–1.13, $P_h = 0.426$, $I^2 = 2.0\%$; homozygote model: OR = 1.04, 95% CI = 0.93–1.17, $P_h = 0.144$, $I^2 = 30.0\%$; heterozygote model: OR = 1.05, 95% CI = 0.94–1.17, $P_h = 0.023$, $I^2 = 49.2\%$; additive model: OR = 1.03, 95% CI = 0.95–1.11, $P_h = 0.026$, $I^2 = 48.2\%$, **Fig. 2**). Significant between-study heterogeneity was detected. Hence, we performed the stratified analyses according to ethnicity and source of controls. In the stratified analysis by ethnicity, no significant association was found among Caucasians (dominant model: OR = 1.02, 95% CI = 0.95–1.10, $P_h = 0.233$, $I^2 = 24.6\%$; recessive model: OR = 1.06, 95% CI = 0.94–1.20, $P_h = 0.387$, $I^2 = 5.6\%$; homozygote model: OR = 1.07, 95% CI = 0.94–1.21, $P_h = 0.224$, $I^2 = 25.6\%$; heterozygote model: OR = 1.01, 95% CI = 0.94–1.09, $P_h = 0.403$, $I^2 = 3.5\%$; additive model: OR = 1.03, 95% CI = 0.97–1.08, $P_h = 0.157$, $I^2 = 34.0\%$, **Fig. 3**) and Asians (recessive model: OR = 0.78, 95% CI = 0.57–1.05, $P_h = 0.681$, $I^2 = 0.0\%$; homozygote model: OR = 0.91, 95% CI = 0.49–1.68, $P_h = 0.076$, $I^2 = 56.5\%$; additive model: OR = 0.98, 95% CI = 0.69–1.42, $P_h = 0.009$, $I^2 = 74.3\%$, **Fig. 4**). In addition, high heterogeneity was found among Asians (dominant model: $I^2 = 81.3\%$; heterozygote model: $I^2 = 79.0$). When grouped by source of control, there was still no evidence of significant association.

Table 2 also lists the main results of the meta-analysis of CYP1B1 Leu432Val polymorphism and colorectal cancer risk. Overall, no significant association was found between CYP1B1 Leu432Val polymorphism and colorectal cancer susceptibility (dominant model: OR = 1.00, 95% CI = 0.94–1.06, $P_h = 0.770$, $I^2 = 0.0\%$; recessive model: OR = 1.05, 95% CI = 0.98–1.13, $P_h = 0.251$, $I^2 = 20.3\%$; homozygote model: OR = 1.04, 95% CI = 0.96–1.13, $P_h = 0.383$, $I^2 = 6.3\%$; heterozygote model: OR = 0.98, 95% CI = 0.91–1.04, $P_h = 0.687$, $I^2 = 0.0\%$; additive model: OR = 1.02, 95% CI = 0.98–1.06, $P_h = 0.498$, $I^2 = 0.0\%$).

Table 2 also lists the main results of the meta-analysis of CYP1B1 Asn453Ser polymorphism and colorectal cancer risk. Overall, no significant association was found between CYP1B1 Asn453Ser polymorphism and colorectal cancer susceptibility (dominant model: OR = 0.97, 95% CI = 0.87–1.08, $P_h = 0.053$, $I^2 = 49.6\%$; recessive model: OR = 0.92, 95% CI = 0.76–1.11, $P_h = 0.617$, $I^2 = 0.0\%$; homozygote model: OR = 0.92, 95% CI = 0.76–1.11, $P_h = 0.685$, $I^2 = 0.0\%$; heterozygote model: OR = 0.97, 95% CI = 0.86–1.11, $P_h = 0.016$, $I^2 = 61.8\%$; additive model: OR = 0.97, 95% CI = 0.91–1.03, $P_h = 0.135$, $I^2 = 38.6\%$). Significant between-study heterogeneity was detected. Hence, we performed the stratified analysis according to source of controls. And in the subgroup analysis by source of controls, there was still no significant association detected in any genetic model.

Table 2 also lists the main results of the meta-analysis of CYP1B1 Arg48Gly polymorphism and colorectal cancer risk. Overall, no significant association was found between CYP1B1 Arg48Gly polymorphism and colorectal cancer susceptibility (dominant model: OR = 0.99, 95% CI = 0.91–1.08, $P_h = 0.780$, $I^2 = 0.0\%$; recessive model: OR = 1.00, 95% CI = 0.86–1.16, $P_h = 0.138$, $I^2 = 40.1\%$; homozygote model: OR = 1.00, 95% CI = 0.86–1.16, $P_h = 0.124$, $I^2 = 42.1\%$; heterozygote model:

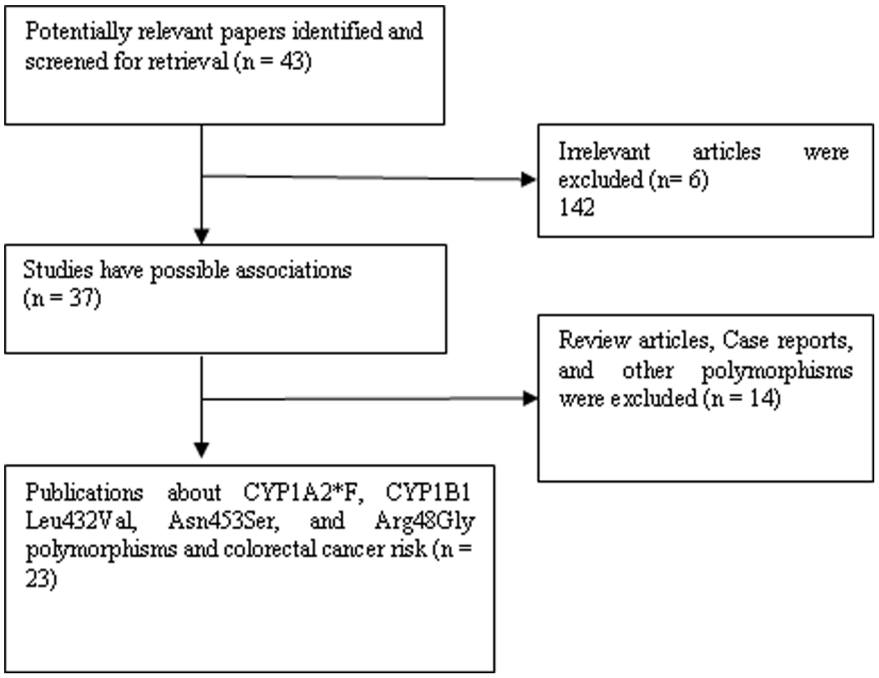

Figure 1. Study flow chart explaining the selection of the 23 eligible articles included in the meta-analysis.
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Table 1. Main characteristics of all studies included in the meta-analysis.

First author/Year	Country	Ethnicity	SC	Genotype distribution						HWE	No. of case/control
				Cases			Controls				
				CC	CY	YY	CC	CY	YY		
CYP1A2*F											
Wang [15] 2012	USA	Mixed	FB	164	117	24	184	144	29	Y	305/357
Rudolph [16] 2011	German	Caucasian	PB	354	261	63	353	280	47	Y	678/680
Sainz [17] 2011	German	Caucasian	PB	872	735	157	887	732	167	Y	1764/1786
Cleary [18] 2010	Canada	Caucasian	PB	598	461	106	648	517	125	Y	1165/1290
Kobayashi [19] 2009	Japan	Asian	HB	53	40	11	96	94	35	Y	104/225
Saebø [20] 2008	Norway	Caucasian	HB	97	87	14	122	84	16	Y	198/222
Sachse [21] 2002	UK	Caucasian	PB	264	193	33	325	233	35	Y	490/593
Yoshida [22] 2007	Japan	Asian	HB	26	32	6	42	52	17	Y	64/111
Kiss [23] 2007	Hungary	Caucasian	HB	219	212	69	228	207	65	Y	500/500
Küry [24] 2007	France	Caucasian	HB	514	420	79	553	480	85	Y	1013/1118
Bae [25] 2006	Korea	Asian	HB	24	71	16	44	37	12	Y	111/93
Chen [26] 2005	China	Asian	PB	19	62	57	47	133	160	Y	138/340
Landi [27] 2005	Spain	Caucasian	HB	141	172	48	158	137	26	Y	361/321
CYP1B1 Leu432Val (rs1056836)											
First author/Year	**Country**	**Ethnicity**	**SC**	**Genotype distribution**						**HWE**	**No. of case/control**
				Cases			**Controls**				
				Leu/Leu	**Leu/Val**	**Val/Val**	**Leu/Leu**	**Leu/Val**	**Val/Val**		
Wang [39] 2012	USA	Mixed	FB	86	139	75	118	151	81	Y	300/350
Rudolph et al. [28] 2011	German	Caucasian	PB	220	320	128	224	339	106	Y	668/669
Sainz et al. [29] 2011	German	Caucasian	PB	237	339	143	245	358	110	Y	719/713
Cleary et al. [18] 2010	Canada	Caucasian	PB	391	547	224	424	617	250	Y	1162/1291
Hlavata et al. [31] 2010	Czech	Caucasian	HB	174	237	84	155	262	78	Y	495/495
Trubicka et al. [32] 2010	Poland	Caucasian	PB	214	275	108	206	265	127	Y	597/598
Sachse et al. [21] 2002	UK	Caucasian	PB	141	258	91	187	283	123	Y	490/593
Cotterchio et al. [34] 2008	Canada	Caucasian	PB	283	382	166	407	604	237	Y	831/1248
Küry et al. [35] 2007	France	Caucasian	PB	317	507	189	368	576	174	Y	1013/1118
Bethke et al. [36] 2007	UK	Caucasian	HB	519	1277	763	538	1365	792	Y	2559/2695
Huber [37] 2005	Australia	Caucasian	HB	14	28		112	225		Y	42/337

Table 1. Cont.

First author/Year	Country	Ethnicity	SC	Genotype distribution						HWE	No. of case/control
				Cases			Controls				
				Leu/Leu	Leu/Val	Val/Val	Leu/Leu	Leu/Val	Val/Val		
Landi [38] 2005	Spain	Caucasian	HB	128	151	64	101	139	59	Y	343/299
Asn453Ser (rs1800440)											
First author/ Year	**Country**	**Ethnicity**	**SC**	**Genotype distribution**						**HWE**	**No. of case/control**
				Cases			**Controls**				
				Asn/Asn	**Asn/Ser**	**Ser/Ser**	**Asn/Asn**	**Asn/Ser**	**Ser/Ser**		
Rudolph [28] 2011	German	Caucasian	PB	467	187	22	452	202	26	Y	676/680
Sainz [29] 2011	German	Caucasian	PB	505	203	23	473	222	27	Y	731/722
Cleary [18] 2010	Canada	Caucasian	PB	775	354	34	897	349	46	Y	1163/1292
Hlavata [31] 2010	Czech	Caucasian	HB	353	134	8	320	163	12	Y	495/495
Cotterchio [34] 2008	Canada	Caucasian	PB	549	262	21	867	340	42	Y	832/1249
Bethke [36] 2007	UK	Caucasian	HB	1734	739	86	1,790	828	76	Y	2559/2694
Huber [37] 2005	Australia	Caucasian	HB	26	16		219	113		Y	42/332
Landi [38] 2005	Spain	Caucasian	HB	219	107	16	190	90	17	Y	342/297
Arg48Gly (rs10012)											
First author/Year	**Country**	**Ethnicity**	**SC**	**Genotype distribution**						**HWE**	**No. of case/control**
				Cases			**Controls**				
				Arg/Arg	**Arg/Gly**	**Gly/Gly**	**Arg/Arg**	**Arg/Gly**	**Gly/Gly**		
Rudolph [28] 2011	German	Caucasian	PB	329	295	55	322	299	54	Y	679/675
Sainz [29] 2011	German	Caucasian	PB	354	318	60	342	321	57	Y	732/720
Cleary [18] 2010	Canada	Caucasian	PB	593	478	92	651	529	112	Y	1163/1292
Trubicka [32] 2010	Poland	Caucasian	PB	261	266	70	265	265	67	Y	597/597
Cotterchio [34] 2008	Canada	Caucasian	PB	424	347	61	624	518	107	Y	832/1249
Landi [38] 2005	Spain	Caucasian	HB	169	101	29	161	87	10	Y	299/258

PB population-based studies, HB hospital-based studies, FB family-based studies, Y yes, N no, SC source of control, HWE Hardy–Weinberg equilibrium.

doi:10.1371/journal.pone.0100487.t001

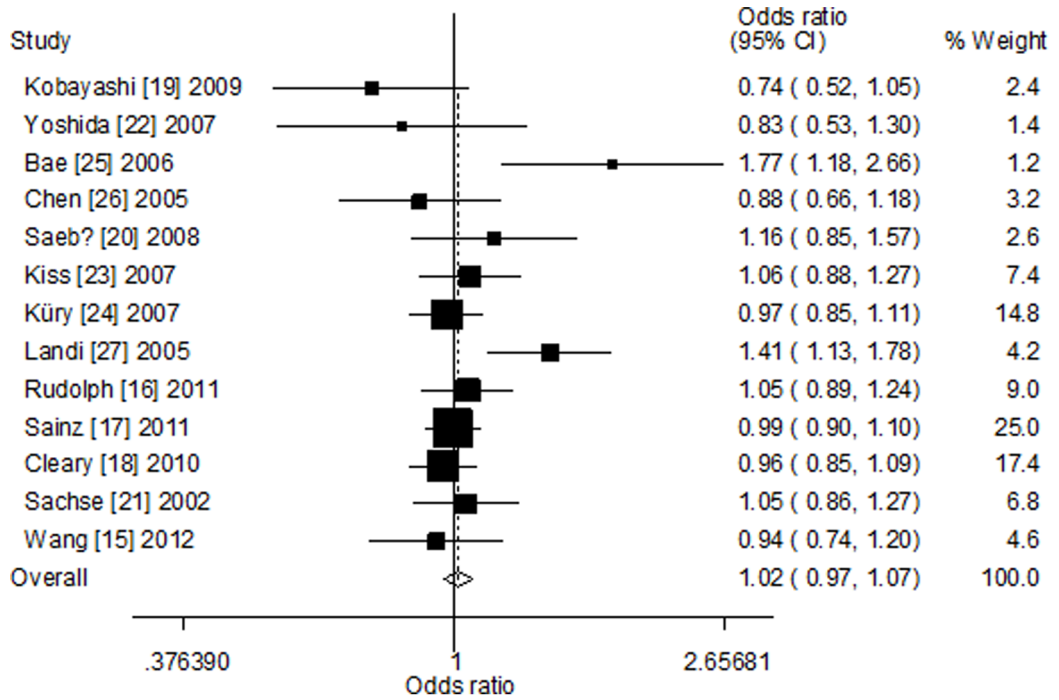

Figure 2. Forest plot of CYP1A2*F polymorphism and colorectal cancer risk among overall analysis (additive model).
doi:10.1371/journal.pone.0100487.g002

OR = 0.99, 95% CI = 0.91–1.08, $P_h = 0.989$, $I^2 = 0.0\%$; additive model: OR = 0.97, 95% CI = 0.91–1.03, $P_h = 0.135$, $I^2 = 38.6\%$).

Test of heterogeneity and sensitivity

There was significant heterogeneity among these studies for dominant model comparison ($P_h = 0.008$ for CYP1A2*F and $P_h = 0.053$ for CYP1B1 Asn453Ser), heterozygote model comparison ($P_h = 0.020$ for CYP1A2*F and $P_h = 0.016$ for CYP1B1 Asn453Ser) and additive model comparison ($P_h = 0.022$ for CYP1A2*F). Then, we assessed the source of heterogeneity by ethnicity and source of controls. We found that ethnicity and source of controls (*data not shown*) did not contribute to substantial heterogeneity. Sensitivity analysis was conducted to determine whether modification of the inclusion criteria of this meta-analysis affected the results. Although the sample size for cases and controls in all eligible studies ranged from 175 to 2,455, the corresponding pooled ORs were not qualitatively altered with or without the study of small sample. In addition, a single study involved in the

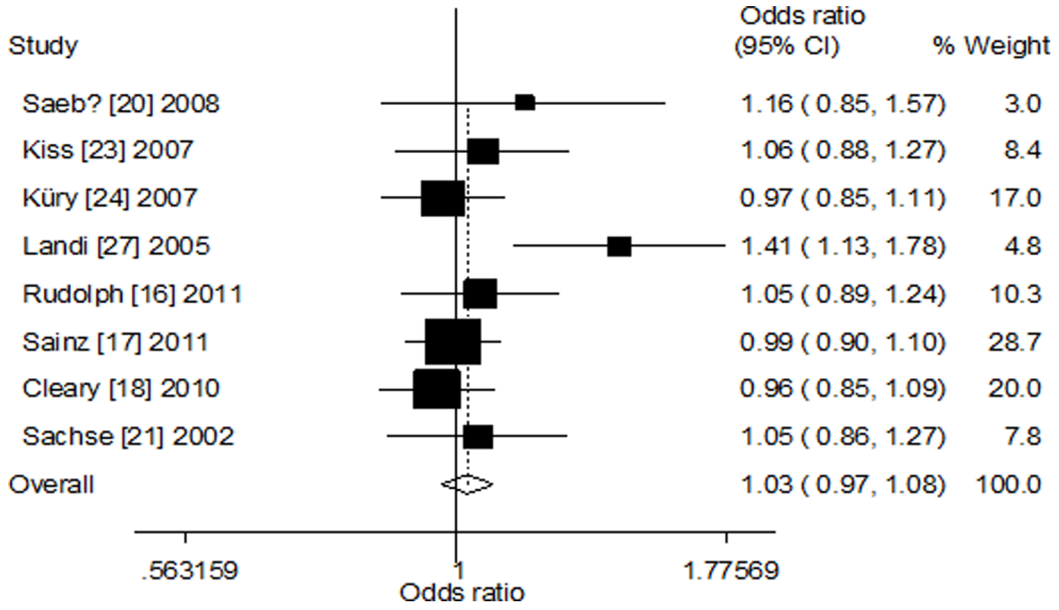

Figure 3. Forest plot of CYP1A2*F polymorphism and colorectal cancer risk among Caucasians (additive model).
doi:10.1371/journal.pone.0100487.g003

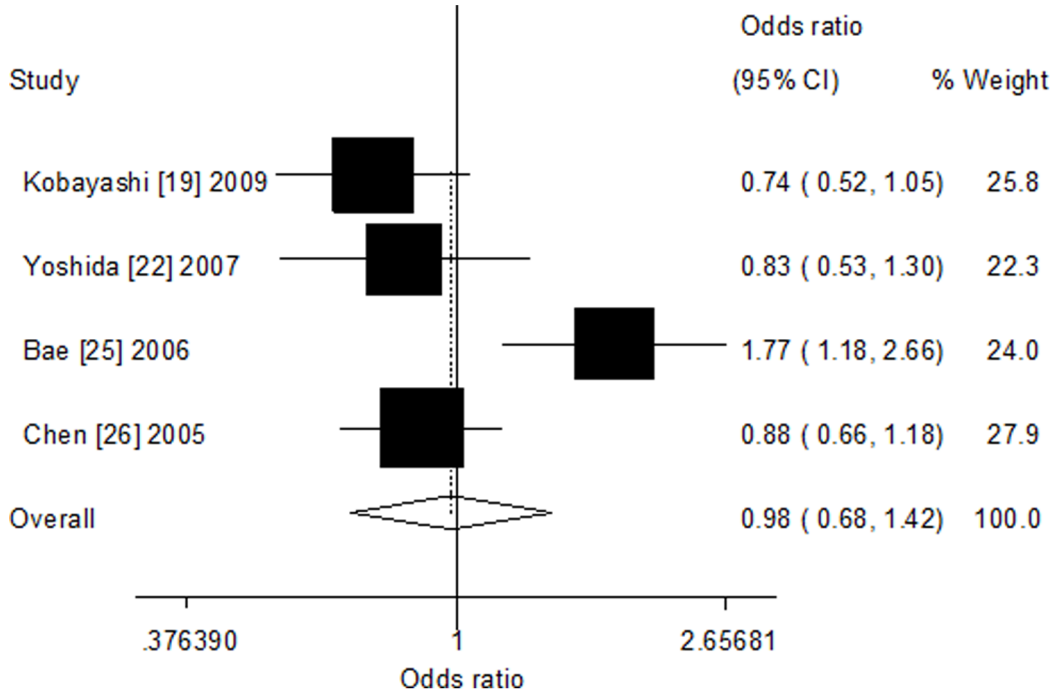

Figure 4. Forest plot of CYP1A2*F polymorphism and colorectal cancer risk among Asians (additive model).
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meta–analysis was deleted each time to reflect the influence of individual data set to the pooled ORs. The results were also not qualitatively altered.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The Egger's test results and Begg's funnel plot (**Fig. 5, 6**) suggested no evidence of publication bias in the meta-analysis of CYP1A2*F ($P = 0.160$ for dominant model, $P = 0.714$ for recessive model, $P = 0.862$ for homozygote model; $P = 0.248$ for heterozygote model; $P = 0.462$ for additive model) and Leu432Val ($P = 0.749$ for dominant model, $P = 0.864$ for recessive model, $P = 0.991$ for homozygote model; $P = 0.721$ for heterozygote model; $P = 0.689$ for additive model), although possible publication bias was suggested for Asn453Ser polymorphism with colorectal cancer risk in additive model and recessive model and for Arg48Gly with colorectal cancer risk in any genetic model. This might be a limitation for meta-analysis of Arg48Gly and Asn453Ser polymorphisms, especially those with small sample size, are less likely to be published. **Figure 7, 8** lists the Duval and Tweedie nonparametric "trim and fill" methods funnel plot in additive model and recessive model. Adjusting for possible publication bias using the Duval and Tweedie nonparametric "trim and fill" method for overall studies, the results did not change between Arg48Gly and Asn453Ser polymorphism with colorectal cancer risk.

Discussion

CYP1B1 is commonly over-expressed inhumanmalignancies and activates a variety of carcinogens. For example, CYP1B1 catalyzes both the formation of dihydrodiols of specific PAHs and their subsequent oxidation to carcinogenic dihydrodiol epoxides. The importance of CYP1B1 in chemical carcinogens is well illustrated in animal models in which metabolites of CYP1B1 were shown to induce Prostate cancer risk [54,55]. CYP 1A2 is an important gene in catalyzing 2- and 4-hydroxylations of estrogens and metabolism of carcinogens. A major reason for the limited number of studies of heterocyclic amine (HCA) and cancer risk is the difficulty of 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 [56]. 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 epidemiological studies have evaluated the association between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and colorectal cancer risk, but the results remain inconclusive. In order to resolve this conflict, this meta-analysis of 39 eligible studies including 5,817 cases and 6,544 controls for CYP1A2*F (from 13 studies), 9,219 cases and 10,406 controls for CYP1B1 Leu432Val (from 12 studies), 6,840 cases and 7,761 controls for CYP1B1 Asn453Ser (from 8 studies), and 4,302 cases and 4,791 controls for CYP1B1 Arg48Gly (from 6 studies) was performed to derive a more precise estimation of the association between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and risk of colorectal cancer.

Overall, no significant association was found between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly when

Table 2. Results of meta-analysis for CYP1A2 and CYP1B1 polymorphisms on colorectal cancer risk.[1]

Generic model		Recessive model			Dominant model			Homozygote			Heterozygote			Additive model		
CYP1A2*F	**N (case/control)**	**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 (%)
Overall	13 (6891/7636)	1.01 (0.90–1.13)	0.426	2.0	1.05 (0.94–1.18)*	0.010	54.1	1.09 (0.93–1.17)	0.144	30.0	1.05 (0.94–1.17)*	0.023	49.2	1.03 (0.95–1.11)*	0.026	48.2
Ethnicity																
Caucasian	8 (6169/6510)	1.06 (0.94–1.20)	0.387	5.6	1.02 (0.95–1.10)	0.233	24.6	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
Asian	4 (417/769)	0.78 (0.57–1.05)	0.681	0.0	[2]	0.001	81.3	0.91 (0.49–1.68)*	0.076	56.5	[2]	0.003	79.0	0.98 (0.69–1.42)*	0.009	74.3
Source of controls																
PB	5 (4235/4689)	0.98 (0.85–1.13)	0.329	13.3	0.99 (0.91–1.08)	0.982	0.0	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
HB	7 (2351/2590)	1.06 (0.88–1.28)	0.303	16.6	1.18 (0.91–1.53)*	0.001	74.5	1.14 (0.82–1.59)*	0.040	54.5	1.20 (0.93–1.55)*	0.002	71.1	1.09 (0.92–1.30)*	0.004	69.1
Leu432Val	**N (case/control)**	**Recessive model**			**Dominant 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 (%)
Overall	12 (9219/10406)	1.05 (0.98–1.13)	0.251	20.3	1.00 (0.94–1.06)	0.770	0.0	1.04 (0.96–1.13)	0.383	6.3	0.98 (0.91–1.04)	0.687	0.0	1.02 (0.98–1.06)	0.498	0.0
Asn453Ser	**N (case/control)**	**Recessive model**			**Dominant 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 (%)
Overall	8 (6840/7761)	0.92 (0.76–1.11)	0.617	0.0	0.97 (0.87–1.08)*	0.053	49.6	0.92 (0.76–1.11)	0.685	0.0	0.97 (0.86–1.11)*	0.016	61.8	0.97 (0.91–1.03)	0.135	38.6
Source of controls																
PB	4 (3402/3943)	0.81 (0.62–1.05)	0.988	0.0	1.01 (0.86–1.19)*	0.054	60.8	0.82 (0.63–1.07)	0.996	0.0	0.90 (0.81–1.01)	0.275	22.5	0.94 (0.86–1.03)	0.183	41.1
HB	4 (3438/3818)	1.07 (0.81–1.40)	0.332	9.2	0.92 (0.83–1.02)	0.300	18.1	1.04 (0.79–1.37)	0.310	14.6	1.04 (0.87–1.23)*	0.036	64.9	1.00 (0.92–1.09)	0.143	44.8
Arg48Gly	**N (case/control)**	**Recessive model**			**Dominant 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 (%)
Overall	6 (4302/4791)	1.00 (0.86–1.16)	0.138	40.1	0.99 (0.91–1.08)	0.780	0.0	1.00 (0.86–1.16)	0.124	42.1	0.99 (0.91–1.08)	0.989	0.0	1.00 (0.93–1.06)	0.286	19.6

[1]All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models.
[2]The results were excluded due to high heterogeneity.
doi:10.1371/journal.pone.0100487.t002

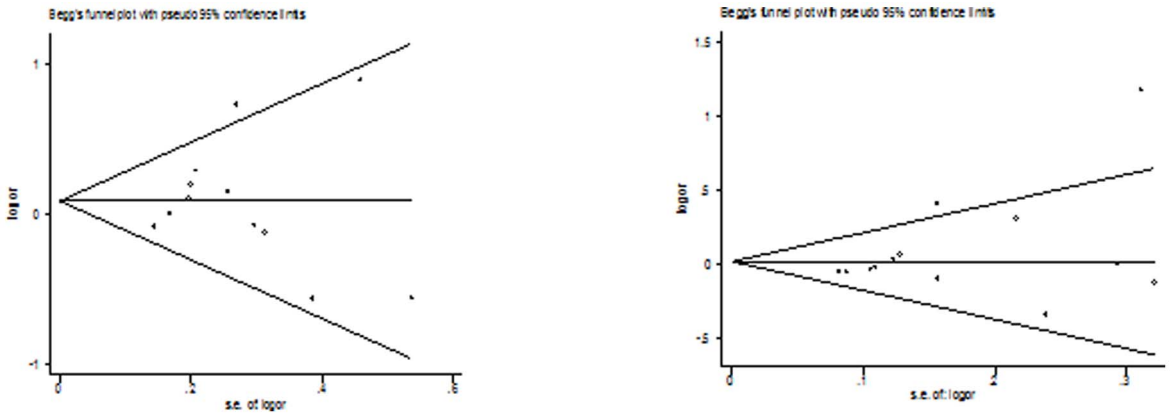

Figure 5. Begg's funnel plot of the meta-analysis of colorectal cancer risk and CYP1A2*F polymorphism (homozygote model and dominant model).
doi:10.1371/journal.pone.0100487.g005

all the eligible studies were pooled into the meta-analysis. And in the subgroup, no evidence of significant association was also observed in any subgroup. Sachse et al. [33] in 2002 and Küry et al. [24] in 2007 reported that CYP1B1 Leu432Val was not associated with increased the risk of colorectal cancer. Landi et al. [27] and Huber et al. [37] in 2005 reported that CYP1B1 Leu432Val and Asn453Ser polymorphisms were also not associated with increased the risk of colorectal cancer. Cleary et al. [18] in 2010 found that CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly were not associated with increased the risk of colorectal cancer. Sachse et al. [21] in 2002, Yoshida et al. [22] in 2007, Kiss et al. [23] in 2007, and Cleary et al. [18] reported that CYP1A2*F, was not associated with increased the risk of colorectal cancer. The results of our meta-analysis supported the negative association between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and colorectal cancer risk. However, a careful matching should be considered in future larger genetic association studies including multiple ethnic groups.

We noticed that 3 previous meta-analysis [33,57,58] had been reported on the colorectal cancer risk with CYP1A2*F, CYP1B1 Leu432Val, and Asn453Ser polymorphisms. We have read with great interest the meta-analysis by Mei et al. [57] and Xie et al. [58]. Mei et al. [35] had 7 studies including 6,375 cases and 7,003 controls. The pooled analysis suggested that no significant association was found between the CYP1B1 Asn453Ser polymorphism and the risk of colorectal cancer among Caucasians. Xie et al. [58] had 10 studies including 8,466 cases and 9,301 for Leu432Val. Their meta-analyses suggested that CYP1B1 Leu432Val were not associated with colorectal cancer risk. However, the study of Northwood et al. [30] should be excluded in the meta-analyses of Mei et al. [57] and Xie et al. [58] because they performed CYP1B1 Leu432Val with colorectal adenoma risk but not colorectal cancer. Adopting the same search strategy as Mei et al. [57] and Xie et al. [58], we identified 4 additional eligible studies, which have not been included in the meta-analysis of Xie et al. [36]. Worthy of note, these 4 studies included 3,638 samples. Zhao et al. [33] included 11 studies. Their meta-analysis suggests that the CYP1A2*F polymorphism is a protective factor against CRC among Asians. The OR (95% CI) reported by Zhao et al. [33] for the study by Bae et al. [25] do not seem in line with the OR (95% CI) provided by Bae et al. [25] in their original publication. The OR (95% CI) reported by Zhao et al. [33] in

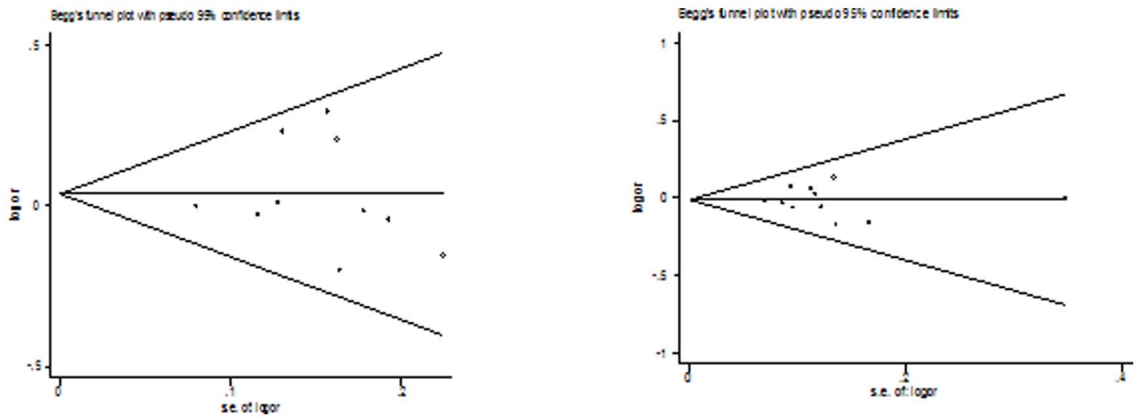

Figure 6. Begg's funnel plot of the meta-analysis of colorectal cancer risk and CYP1B1 Leu432Val polymorphism (homozygote model and dominant model).
doi:10.1371/journal.pone.0100487.g006

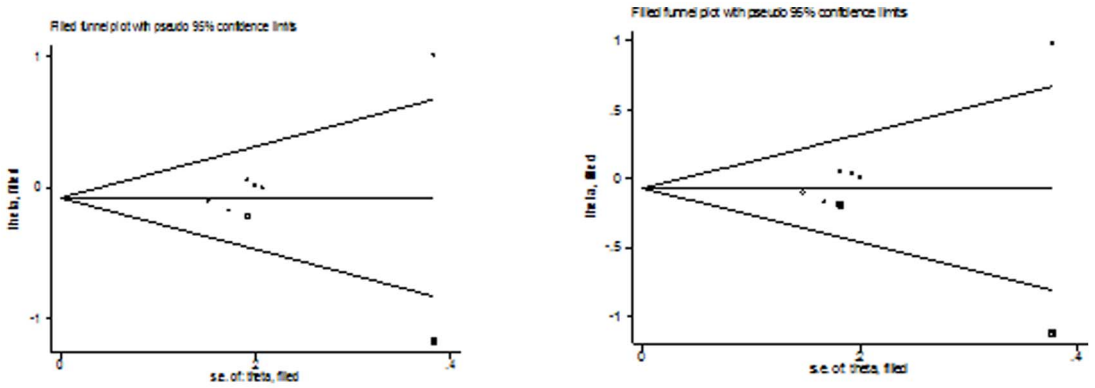

Figure 7. The Duval and Tweedie nonparametric ''trim and fill'' method's funnel plot funnel plot of the meta-analysis of colorectal cancer risk and CYP1B1 Arg48Gly polymorphism (additive model and dominant model).
doi:10.1371/journal.pone.0100487.g007

additive model are 0.56 (0.38–0.84). Interestingly enough, after carefully studying the OR (95% CI) presented by Bae et al. [25], The OR (95% CI) were 1.77 (1.18–2.66). In addition, the study of Wang et al. [59] should be excluded in the meta-analysis of Zhao et al. [33] because the data on CYP1A2*F polymorphism with colorectal cancer risk did not be found in the study of Wang et al. [59]. Adopting the same search strategy as Zhao et al. [33], we identified 3 additional eligible studies, which have not been included in the meta-analysis of Zhao et al. [33]. Worthy of note, these 3 studies included 2687 samples. Having analyzed an almost twofold larger number of studies than the previous meta-analysis [33,57,58], our results seem to confirm and establish the trend in the meta-analysis of CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms that the data by the previous meta-analysis [33,57,58] had indicated. The results of the present meta-analysis are not in accordance with those reported by Zhao et al. [33]. Our meta-analysis indicates that CYP1A2*F are not associated with colorectal cancer risk.

There are several limitations in this meta-analysis. First, the controls were not uniformly defined. Although most of them were common populations, some controls were population-based; other controls were hospital-based. Hence, non–differential misclassification bias is possible. Second, in the subgroup analysis may have had insufficient statistical power to check an association, Third, we were also unable to examine the interactions among gene-environment, lacking of the original data of the included studies limited our further evaluation of potential interactions, which may be an important component of the association between CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and environment and colorectal cancer risk. Last, our results were based on unadjusted published estimates. Because of data limitations, we were unable to adjust them such as age and alcohol consumption et al.

In summary, this meta-analysis indicates that CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly are not associated with colorectal cancer. However, it is necessary to conduct large sample studies using standardized unbiased genotyping methods, homogeneous cancer patients and well-matched controls. Moreover, further studies estimating the effect of gene–gene and gene–environment interactions may eventually lead to our better, comprehensive understanding of the association between

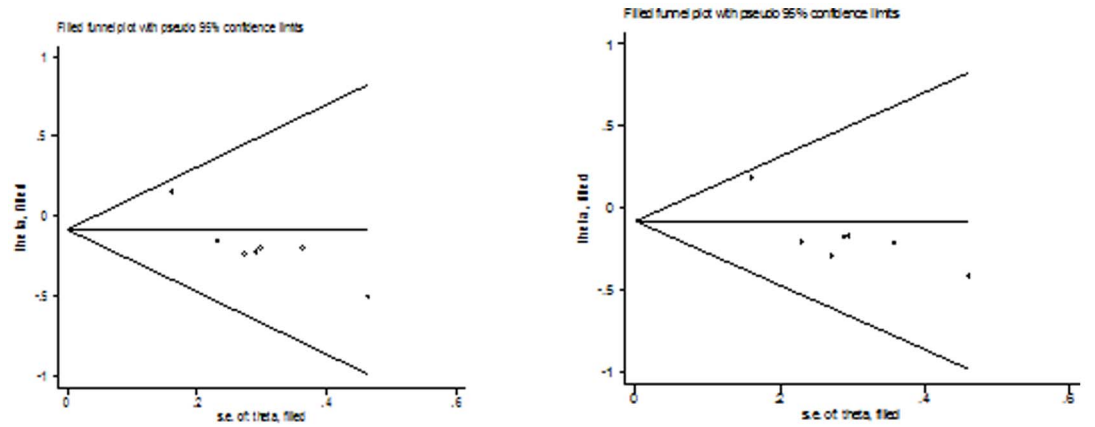

Figure 8. The Duval and Tweedie nonparametric ''trim and fill'' method's funnel plot funnel plot of the meta-analysis of colorectal cancer risk and CYP1B1 Asn453Ser polymorphism (additive model and dominant model).
doi:10.1371/journal.pone.0100487.g008

the CYP1A2*F, CYP1B1 Leu432Val, Asn453Ser, and Arg48Gly polymorphisms and colorectal cancer risk.

Supporting Information

Checklist S1 PRISMA Checklist.
(DOC)

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Author Contributions

Conceived and designed the experiments: XFH. Performed the experiments: XFH JW. Analyzed the data: XFH. Contributed reagents/materials/analysis tools: XFH JW ZZL JJX W. Wang YPD YC HQS QL LXW W. Wei. Wrote the paper: XFH.

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