Research Paper

Glutathione S-transferases genes variants and chemotherapy efficacy in gastrointestinal cancer patients: a meta-analysis based on 50 pharmacogenetic studies

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Abstract

Background: The role of glutathione s-transferase genes (*GSTP1*, *GSTM1* and *GSTT1*) variants and the GSTP1 expression level on chemotherapy efficacy of gastrointestinal cancer (GIC) patients were inconsistent.

Methods: A meta-analysis about *GSTP1*, *GSTM1* and *GSTT1* variants and the GSTP1 expression level on chemotherapy efficacy of GIC patients was performed using data from PubMed, PMC, EMBASE, Web of Science, and Wanfang database.

Results: Our meta-analysis enrolled 50 publications including 6518 patients. We found that patients with GIC harboring *GSTP1* (Ile105Val) Val locus had higher objective response rates (ORR) than the Ile/Ile genotypic patients (odds ratio (OR) = 1.580, 95% confidence interval (CI) = 1.159-2.154, *P* = 0.004). Significant associations were found between the Ile105Val variant and overall survival of Caucasian GIC patients (Ile/Val *vs.* Ile/Ile: OR = 0.797 (0.674-0.944), *P* = 0.009). Caucasian GIC patients and gastric cancer patients with *GSTT1* null genotype had worse response rates compared to *GSTT1* present patients (OR = 0.530 (0.356-0.789), *P* = 0.002; OR = 0.643 (0.463-0.895), *P* = 0.009, respectively).

Conclusion: This meta-analysis illustrates that *GSTP1* Ile105Val and *GSTT1* null/present variants could be useful predictors of chemotherapy efficacy in patients with gastrointestinal cancer.

Key words: gastrointestinal cancer, glutathione S-transferases genes, variants, chemotherapy, efficacy

Introduction

Esophagus, stomach, small and large intestine, and rectum constitute the digestive tract, which is one of the important parts of the body [1]. Gastrointestinal cancer (GIC), including esophageal cancer (EAC), gastric cancer (GC) and colorectal cancer (CRC) represent a major public health problem worldwide [2]. Chemotherapy is widely used in many patients with postoperative recurrence or distant metastasis.

[3, 4]. Platinum (oxaliplatin, cisplatin, carboplatin) combined with fluoropyrimidine (5-fluorouacil, capecitabine, S-1) is most commonly used in chemotherapy of GIC [3-7]. However, the effects of chemotherapy vary widely among GIC patients.

More evidence implied that the inter-individual variability of chemotherapy therapeutic efficacy in GIC patients was influenced by genetic factors including *GSTP1*, *GSTT1*, *GSTM1*, *ERCC2*, *ERCC2*, *ABCC2*, *ENOSF1* and *CD24* [8-13]. As a basic regiment to chemotherapy in GIC patients, platinum inhibits DNA synthesis and transcription [14].

Although resistance to chemotherapy is multifactorial, the metabolic enzymes of chemotherapeutic drugs play an important role in chemotherapy resistance. As a series of phase II metabolic enzymes, Glutathione S-transferases (GSTs) including GSTM1, GSTP1 and GSTT1 are involved in platinum detoxification [15, 16]. The effects of *GSTM1/GSTT1* (null/present) and *GSTP1* (rs1695, Ile105Val) genetic polymorphisms on chemotherapy efficacy in GIC patients were not consistent in previous research [9, 13, 17-26].

There were four meta-analyses for the efficacy of glutathione S-transferases (GSTs) variants and chemotherapy in patients with GC or CRC[27-30]. But updated publications were not analyzed in these meta-analyses, which may have biased conclusions. Moreover, there were no meta-analyses of the association between GSTP1 expression and the efficacy of chemotherapy in GC patients. There were no meta-analyses enrolled EAC patients and combined GC, CRC and EAC patients together in meta-analysis. Therefore, we have updated new literatures to investigate the associations between *GSTP1* (Ile105Val), *GSTM1* (null/present), *GSTT1* (null/present) variants and GSTP1 expression and clinical outcomes in GIC patients.

Materials and Methods

Studies selection

All literatures in PubMed, PMC, EMBASE, Web of Science, and Wanfang database until 14th July 2017 were reviewed. Searching key words were "glutathione S-transferase pi 1 or GSTP1", "glutathione S-transferase mu 1 or GSTM1", "glutathione S-transferase theta 1 or GSTT1", "gastrointestinal cancer or carcinoma or tumor", "colorectal cancer or carcinoma or tumor", "esophageal cancer or carcinoma or tumor", "gastric cancer or carcinoma or tumor", "SNPs or genetic polymorphisms or variations", "expression" and "chemotherapy". All literatures were reviewed by Dr. Jian Qu and Yuesheng Sun.

Inclusion and exclusion criteria

The inclusion criteria in our meta-analysis were as follows: (1) GIC patients including CRC, GC and EAC patients; (2) *GSTP1* IIe105Val variant, GSTP1 expression condition (high and low), and *GSTM1/GSTT1* (null /present) variants information; (3) at least having one clinical indicator (ORR, OS, TTP and PFS, ORs and HRs with corresponding to 95% CIs); (4) treatments with chemotherapy details. We excluded publications according: (1) duplicates and irrelevant studies; (2) no data for meta-analysis; (3) meta-analysis or basic research. All authors discussed literature selections that were enrolled in our meta-analysis.

Data processing and quality assessment

Two investigators extracted data independently. All authors discussed different opinions on data of each literature. Each literature data includes authors' names, the year of publication, the country, ethnicity, the number of patients, chemotherapy, median age (years), evaluation criteria, genotyping methods, quality score (QS), and outcomes (ORs or HRs and 95% CIs of ORR, OS, PFS, and TTP). The QS was evaluated independently by Dr. Qiang Qu and Jianghua Pan using previous methods [31]. Low quality publication was defined as QS ≤ 14 and high quality was QS >14.

Statistical analysis

Meta-analysis was analyzed by STATA version 12 (Stata Corp, College Station, TX, USA). Heterogeneity was analyzed by Cochrane's *Q*-statistic test and I^2 test. If $P < 0.05$ and $I^2 > 50\%$, we defined it as significant heterogeneity, then Mantel-Haenszel random effect model was used in pooling ORs and HRs [32]. Z-test was used to analyze the pooled ORs or HRs and statistical significance was accepted if $P < 0.05$. Egger's test and Begg's test were used in publication bias and statistical significance was accepted if $P < 0.05$.

Results

Studies' characteristics and selection

Figure 1 presents the process of research selection. We found 2374 publications after duplicate removal from 5527 publications. We excluded 2324 publications including 1340 irrelevant studies, 39 meta-analyses, 18 case reports, 898 basic studies and 29 studies having no data. Fifty studies including 6518 patients were enrolled for further review. Among them, there were four studies involving in the GSTP1 expression and the chemotherapy efficacy in 264 GIC patients; forty-six studies were enrolled in the

meta-analysis of glutathione S-transferase variants (*GSTP1* Ile105Val, *GSTM1*/ *GSTT1* null/present) and chemotherapy efficacy in 6254 GIC patients. Forty-six studies including 6254 patients were selected in investigation about *GSTP1* Ile105Val; 2408 patients in 17 studies were selected in meta-analysis about *GSTM1* null/present variant; and meta-analysis about *GSTT1* null/present variant has 17 studies, including 2414 patients.

The characteristics of author name, the year of publication, the country, the ethnicity, the number of patients, chemotherapy, median age (year), evaluation criterion, genotyping methods, and QS were present in **Table 1**. Seventeen literatures were conducted on GC patients; 28 literatures were related with CRC patients; 4 literatures were involved in EAC patients and one study was conducted on adenocarcinoma of gastroesophageal junction patients. The detail information of objective response rate (ORR), overall survival (OS), median time to progression (TTP) and median progression-free survival (PFS) in each study is shown in **Table S1** and **Table S2**.

## ORR of GIC patients harboring *GSTP1* Ile105Val variant

Thirty-one literatures with 3548 patients were selected for meta-analysis about ORR of GIC patients with *GSTP1* Ile105Val variant. ORR of GIC patients harboring *GSTP1* Ile105Val variants was different (Val carriers *vs.* IIe/IIe: OR=1.58(1.159-2.154), *P*=0.004). Tumor type-subgroup analyses found positive result in CRC patients (OR= 1.761(1.075-2.884), *P*=0.025). Subgroup analyses found association in Asian GIC patients (OR=1.567(1.058-2.319), *P*=0.025) (**Table 2, Figure 2a, 2b**). Subgroup analyses based on other index, such as evaluation criterion, chemotherapy, genotyping method, and quality score present in **Table S3**.

Compared with Asian GIC patients harboring *GSTP1* Val105Val genotypic patients, IIe105IIe genotype or IIe carriers have lower ORR (OR=3.400(1.521-7.599), *P*=0.003; OR=3.466 (1.610-7.463), *P*=0.001, separately, **Table 2**). Moreover, different ORRs in GIC patients harboring different IIe105Val genotype were found (Val/Val *vs.* IIe carriers: OR= 2.256(1.297-3.926), *P*=0.004). Tumor type-subgroup analyses found the association in GC patients (OR=2.279(1.169-4.443), *P*=0.016, **Figure 2c, 2d**).

OS of GIC patients harboring *GSTP1* Ile105Val variant

In order to pooling the HRs of the OS in GIC patients harboring different *GSTP1* Ile105Val genotypes, we selected 21 literatures including 3509 patients. OS of Caucasian GIC patients were different between *GSTP1* IIe/Val genotypic patients and IIe/IIe genotypic patients (HR=0.797(0.674-0.944), *P*=0.009, **Figure 3a, Table 3**).
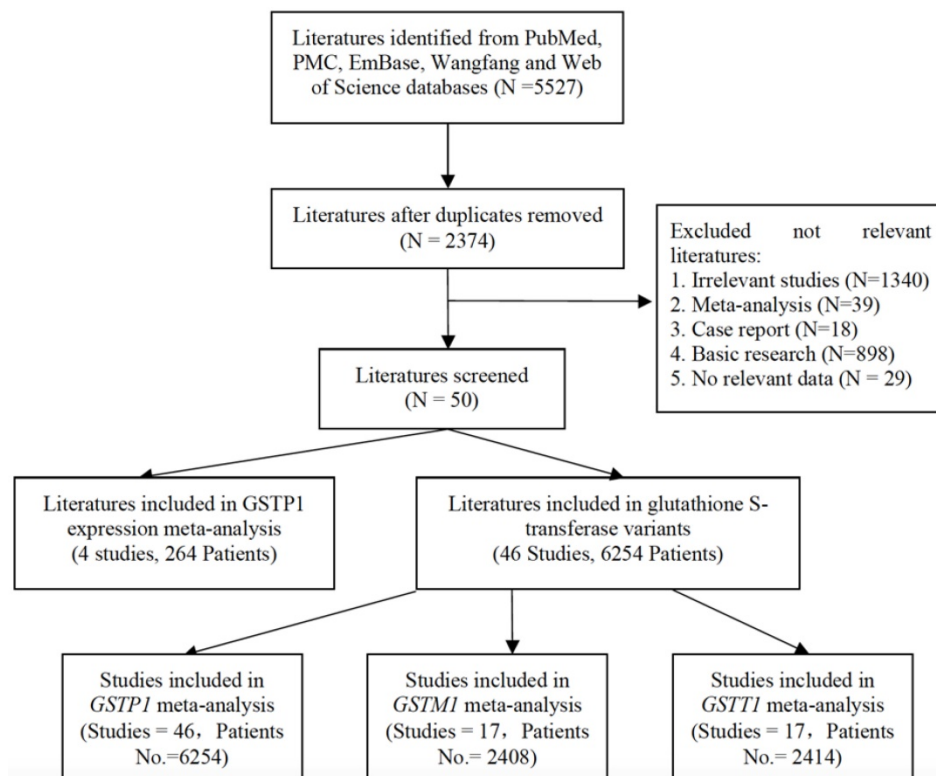
Figure 1. Procedure of literature selection. Figure 1 present the procedure of literature selection from PubMed, PMC, EMBASE, Web of Science, and Wanfang database.

Table 1. Basic information of publications enrolled in meta-analysis

| Author	Year	Country	Ethnicity	Tumor types	Study type	Patients No.	Chemotherapy	Median age (year)	Evaluation criterion	Outcomes	Genotyping method	Genes	QS
Meulendijks D[41]	2016	Mixed	Caucasian	GC	P	185	FU/platinum-based	59 (27–77)	RECIST	ORR, PFS, OS	TaqMan assay, PCR-RFLP	GSTP1	17
Liu R[17]	2016	China	Asian	GC	R	108	epirubicin/oxaliplatin/FU	-	RECIST	ORR,PFS, OS	TaqMan assay	GSTP1, GSTT1	19
Liang J[19]	2010	China	Asian	GC	R	85	FU/oxaliplatin	55(32-77)	NA	TTP,OS	TaqMan assay	GSTP1	10
Li QF[20]	2010	China	Asian	GC	R	89	FU/oxaliplatin	55(32-77)	NA	TTP,OS	TaqMan assay	GSTP1	10
Shim HJ[21]	2010	Korea	Asian	GC	R	200	taxane and cisplatin	58 (19–76)	RECIST	OS,PFS,ORR	TaqMan assay, HRM	GSTP1,GSTM1.GSTT1	21
Huang ZH[22]	2009	China	Asian	GC	R	102	FU/oxaliplatin	58 (34–76)	WHO	OS	PCR-LDR	GSTP1, GSTM1	16
Ott K[23]	2008	Germany	Caucasian	GC	R	139	cisplatin-based	57 (47-67)	NA	OS,TR	TaqMan assay	GSTP1,GSTM1.GSTT1	11
Goekkurt E[24]	2006	Germany	Caucasian	GC	R	52	FU/cisplatin/FA	56(27-82)	RECIST	OS,TR	PCR-RFLP	GSTP1,GSTM1.GSTT1	9
Seo BG[25]	2009	Korea	Asian	GC	R	75	FOLFOX	56 (29-84)	RECIST	ORR	PCR-RFLP	GSTP1,GSTM1.GSTT1	12
Goekkurt E[26]	2009	Germany	Caucasian	GC	P	134	platinum-based	64 (27-86)	NA	OS,ORR	PCR-RFLP	GSTP1,GSTM1.GSTT1	17
Ruzzo A[42]	2006	Italy	Caucasian	GC	R	175	fluorouracil/cisplatin	61(38–79)	RECIST	OS,ORR,PFS	PCR-RFLP	GSTP1,GSTM1.GSTT1	16
Keam B[43]	2008	Korea	Asian	GC	P	73	modified FOLFOX-6	59 (24–77)	WHO	OS,ORR	PCR-RFLP	GSTP1	15
Ji M[13]	2013	China	Asian	GC	R	59	docetaxel, cisplatin, and 5-FU	58.6(30-75)	NA	OS,ORR	PCR-LDR	GSTP1	10
JI YU-ZHI[44]	2011	China	Asian	GC	R	80	oxaliplatin–based	52 (25-69)	RECIST	ORR	TaqMan assay	GSTP1	13
Kap EJ[45]	2014	Germany	Caucasian	CRC	R	176	oxaliplatin	-	NA	OS	Fluorescence-based melting curve analysis	GSTP1,GSTM1.GSTT1	15
Kumamoto K[46]	2013	Japan	Asian	CRC	R	63	modified FOLFOX-6	65(32–84)	RECIST	ORR	PCR–RFLP	GSTP1,GSTM1.GSTT1	21
Lai CY[47]	2013	China	Asian	CRC	R	491	5-FU-Based	58.5±12.5	NA	OS	PCR–RFLP	GSTP1,GSTM1.GSTT1	16
Bohanes P[48]	2015	USA	Caucasian	CRC	R	746	5-FU	61(19–86)	NA	OS	DNA sequencing / PCR-RFLP	GSTP1	15
Nishina T[49]	2013	Japan	Asian	CRC	P	68	modified FOLFOX-6 + bevacizumab	63(28–81)	RECIST	ORR	TaqMan	GSTP1	16
Li HY[50]	2012	China	Asian	CRC		335	FOLFOX6	61.5±6.9	NA	OS	TaqMan	GSTP1	18
Fariña Sarasqueta A(1)[51]	2011	the Netherlands	Caucasian	CRC	R	50	fluorouracil/oxaliplatin	64(30–85)	NA	ORR	DNA sequencing/ PCR-RFLP	GSTP1,GSTM1.GSTT1	13
Fariña Sarasqueta A(2)[51]	2011	the Netherlands	Caucasian	CRC	R	42	fluorouracil/leucovorin	64(30–85)	NA	ORR	DNA sequencing/PCR-RFLP	GSTP1,GSTM1.GSTT1	13
Páez D[52]	2011	Spain	Caucasian	CRC	R	128	5-FU/capecitabine/oxaliplatin	65(32-83)	NA	ORR	DNA sequencing	GSTP1	16
Zarate R[53]	2010	Spain	Caucasian	CRC	R	87	oxaliplatin	58(37-75)	RECIST	ORR/PFS	PCR-RFLP	GSTP1,GSTM1.GSTT1	18
Jones BA[54]	2009	USA	Caucasian	CRC	R	47	5-FU, levamisole, leucovorin, methotrexate	-	NA	OS	PCR-RFLP	GSTP1	12
Le Morvan V(1)[55]	2007	France	Caucasian	CRC	R	48	TS inhibitor/irinotecan	65(45-85)	WHO	ORR	PCR–RFLP	GSTP1	18
Le Morvan V(2)[55]	2007	France	Caucasian	CRC	R	59	TS inhibitor/oxaliplatin	62(41-86)	WHO	ORR	PCR–RFLP	GSTP1	18
Stoehlmacher J[39]	2004	USA	Caucasian	CRC	R	106	5-FU/oxaliplatin	60 (24-84)	NA	TTP	PCR-RFLP	GSTP1,GSTM1.GSTT1	13
Stoehlmacher J[56]	2002	USA	mainly Caucasian	CRC	R	107	5-FU/oxaliplatin	60 (24-83)	NA	OS	PCR-RFLP	GSTP1,GSTM1.GSTT1	13
Chen Jian Guo[57]	2016	China	Asian	CRC	R	60	FOLFOX	-	WHO	ORR	PCR-RFLP	GSTP1	15
Dong Ning-ning[58]	2014	China	Asian	CRC	R	63	FOLFIRI	57 (29-75)	RECIST	ORR	Sequenom Mass ARRAY	GSTP1	16
Ying bei-bei[59]	2009	China	Asian	CRC	R	102	FOLFOX-4	-	RECIST	ORR/TTP	TaqMan-MGB	GSTP1	20
Han-lei[60]	2015	China	Asian	CRC	R	71	modified FOLFOX6	-	RECIST	ORR	Sequenom Mass Array	GSTP1	16
Dongya Shen[61]	2015	China	Asian	CRC	R	150	FOLFOX	-	RECIST	ORR	HRM-SNP	GSTP1	18
Ruzzo[62]	2007	Italy	Caucasian	CRC	R	167	FOLFOX-4	66(38-79)	NA	PFS	PCR-RFLP	GSTP1	15
Liang Jun[63]	2009	China	Asian	CRC	R	112	5-FU/oxaliplatin-based	58 (34–80)	RECIST	ORR	TaqMan	GSTP1	20
Joerger M[64]	2015	The Netherlands	Caucasian	CRC	P	64	capecitabine+oxaliplatin	58.4(31.7–72.8)	RECIST	ORR,PFS, OS	DNA sequencing	GSTP1	22
Boige V[65]	2010	France	Caucasian	CRC	P	346	LV5FU2/FOLFOX/FOLFIRI	68(34–83)	WHO	PFS	PCR/qPCR	GSTP1,GSTM1.GSTT1	20

Author	Year	Country	Ethnicity	Tumor types	Study type	Patients No.	Chemotherapy	Median age (year)	Evaluation criterion	Outcomes	Genotyping method	Genes	QS
Yen-Chung Chen[66]	2009	China	Asian	CRC	R	166	FOLFOX-4	-	RECIST	ORR	PCR–RFLP	GSTP1	17
Hong J[67]	2011	Korea	Asian	CRC	P	52	oxaliplatin + S-1	63 (37–76)	RECIST	ORR/PFS	PCR–RFLP	GSTP1	15
Huang MY[68]	2011	China	Asian	CRC	R	157	FOLFOX-4	62.5 ± 10.9	NA	PFS	PCR–RFLP/DNA sequencing	GSTP1	14
Lamas MJ[69]	2011	Spain	Caucasian	CRC	R	72	5-FU/oxaliplatin	66.5 (32–80)	RECIST	ORR	Snapshot	GSTP1	12
Rumiato E[70]	2013	Italy	Caucasian	EAC	R	63	cisplatin/5-FU-based	62(25-80)	RECIST	ORR	(ARMS)-PCR,PCR-RFLP	GSTP1,GSTM1.GSTT1	15
Wang Y[71]	2011	China	Asian	EAC	R	256	cisplatin-based	-	RECIST	ORR	DNA sequencing	GSTP1	16
Gui Yan[72]	2016	China	Asian	EAC	R	168	5-FU and cisplatin	-	RECIST	ORR,OS	DNA sequencing	GSTP1	17
Joerger M[64]	2015	The Netherlands	Caucasian	EAC	R	76	capecitabine+cisplatin+epirubicin	57.2(35–75.3)	RECIST	ORR,OS	DNA sequencing	GSTP1	22
Kwon HC[73]	2007	Korea	Asian	GC	R	64	5-FU/oxaliplatin	51(31–74)	RECIST	expression	immunohistochemistry	GSTP1	18
Boku N[74]	2007	Japan	Asian	GC	R	66	5-FU/cisplatin	63 (19–75)	WHO	expression	immunohistochemistry	GSTP1	20
In Sil Choi[75]	2011	Korea	Asian	GC	R	41	S-1 plus cisplatin	62 (33–73)	RECIST	expression	immunohistochemistry	GSTP1	16
Li S[76]	2017	China	Asian	AGEJ	R	93	oxaliplatin based	66.6(40–76)	RECIST	expression	immunohistochemistry	GSTP1	18

NR: not reported; QS, quality score; HR: hazard ratio; ORR: objective response rate; OS, overall survival; PFS, progression-free survival; MST, median survival time; TTP, time to progression; PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization; PCR-LDR, PCR-ligase detection reaction; PCR-CTPP, duplex PCR with the confronting-two-pair primer; HRM, high resolution melt; 5-FU, 5-fluorouracil; FOLFOX, leucovorin+5-fluorouracil+oxaliplatin; TS, thymidylate synthase; FOLFIRI, leucovorin+5-fluorouracil+irinotecan; LV5FU2, leucovorin+5-fluorouracil; EAC , esophageal cancer; GC, gastric cancer; CRC , colorectal cancer; AGEJ, Adenocarcinoma of Gastroesophageal Junction. P, prospective study; R, retrospective study.

Table 2. The pooling ORs of ORR in GIC patients with different *GSTP1* Ile105Val, *GSTM1/GSTT1* variants and GSTP1 expression levels.

Genetic comparisons	No. of studies	Study groups	Test of association				Test of heterogeneity			
			OR/HR (95% CI)	Z	P-value	Model	$\chi 2$	P-value	I² (%)	Tau-squared
GSTP1										
Val carriers *vs.* Ile/Ile	31	Overall	**1.580(1.159-2.154)**	2.9	**0.004**	R	102.39	<0.001	70.70%	0.5184
	11	GC	1.598(0.998-2.560)	1.95	0.051	R	31.75	<0.001	68.50%	0.4165
	16	CRC	**1.761(1.075-2.884)**	2.25	**0.025**	R	53.12	<0.001	71.80%	0.702
	4	EAC	1.080(0.482-2.418)	0.19	0.852	R	13.16	0.004	77.20%	0.5119
	20	Asian	**1.567(1.058-2.319)**	2.24	**0.025**	R	69.3	<0.001	72.60%	0.554
	11	Caucasian	1.607(0.944-2.736)	1.75	0.08	R	33.1	<0.001	69.80%	0.5374
Val/Val *vs.* Ile/Ile	14	Overall	2.265(0.937-5.475)	1.82	0.069	R	52.01	<0.001	75.00%	1.9912
	8	GC	1.982(0.599-6.563)	1.12	0.263	R	36.26	<0.001	80.70%	2.2709
	4	CRC	3.151(0.315-31.545)	0.98	0.329	R	13.75	0.003	78.20%	4.248
	2	EAC	2.480(0.784-7.842)	1.55	0.122	F	1.5	0.22	33.50%	-
	5	Asian	**3.400(1.521-7.599)**	2.98	**0.003**	F	8.11	0.088	50.70%	-
	9	Caucasian	2.059(0.661-6.412)	1.25	0.213	R	41.28	<0.001	80.60%	2.3382
Ile/Val *vs.* Ile/Ile	14	Overall	1.130(0.607-2.103)	0.38	0.701	R	69.89	<0.001	81.40%	1.0835
	8	GC	0.825(0.347-1.961)	0.44	0.663	R	48.96	<0.001	85.70%	1.2721
	4	CRC	2.780(0.710-10.892)	1.47	0.142	R	14.58	0.002	79.40%	1.51
	2	EAC	0.845(0.415-1.721)	0.46	0.642	F	2.44	0.118	59.10%	-
	5	Asian	1.270(0.836-1.929)	1.12	0.263	F	8.23	0.083	51.40%	-
	9	Caucasian	1.061(0.420-2.677)	0.12	0.901	R	61.01	<0.001	86.90%	1.6738
Val/Val *vs.* Ile carriers	15	Overall	**2.256(1.297-3.926)**	2.88	**0.004**	R	29.71	0.008	52.90%	0.5742
	8	GC	**2.279(1.169-4.443)**	2.42	**0.016**	R	18.72	0.016	57.30%	0.5481
	4	CRC	1.991(0.325-12.197)	0.74	0.457	R	10.1	0.018	70.30%	2.3401
	2	EAC	2.715(0.890-8.285)	1.76	0.079	F	0.68	0.409	0.00%	-
	5	Asian	**3.466(1.610-7.463)**	3.18	**0.001**	F	7.9	0.095	49.30%	-
	9	Caucasian	**2.011(1.324-3.052)**	3.28	**0.026**	R	19.65	0.02	54.20%	0.5014
GSTT1 Null vs. Present	10	Overall	**0.657(0.489-0.883)**	2.78	**0.005**	F	5.86	0.753	0.00%	-
	7	GC	**0.643(0.463-0.895)**	2.62	**0.009**	F	3.57	0.735	0.00%	-
	2	CRC	1.014(0.447-2.302)	0.03	0.973	F	0.17	0.68	0.00%	-
	3	Asian	0.873(0.557-1.368)	0.59	0.553	F	0.29	0.865	0.00%	-
	7	Caucasian	**0.530(0.356-0.789)**	3.13	**0.002**	F	2.96	0.814	0.00%	-
GSTM1 Null vs. Present	10	Overall	1.120(0.872-1.440)	0.89	0.375	F	6.29	0.71	0.00%	-
	7	GC	1.209(0.918-1.593)	1.35	0.177	F	3.07	0.8	0.00%	-
	2	CRC	0.772(0.351-1.701)	0.64	0.521	F	1.58	0.209	36.50%	-
	3	Asian	1.067(0.669-1.700)	0.27	0.786	F	0.07	0.966	0.00%	-
	7	Caucasian	1.143(0.849-1.540)	0.88	0.379	F	6.15	0.406	2.50%	-
GSTP1 expression	4	Overall	0.854(0.527-1.384)	0.64	0.521	F	7.5	5.70%	60.00%	-
	3	GC	0.671(0.369-1.221)	1.31	0.191	F	5.74	5.70%	65.20%	-

OR, odds ratio; HR: hazard ratio; CI, confidence interval; vs., versus; F, fixed effect model; R, random effect model.
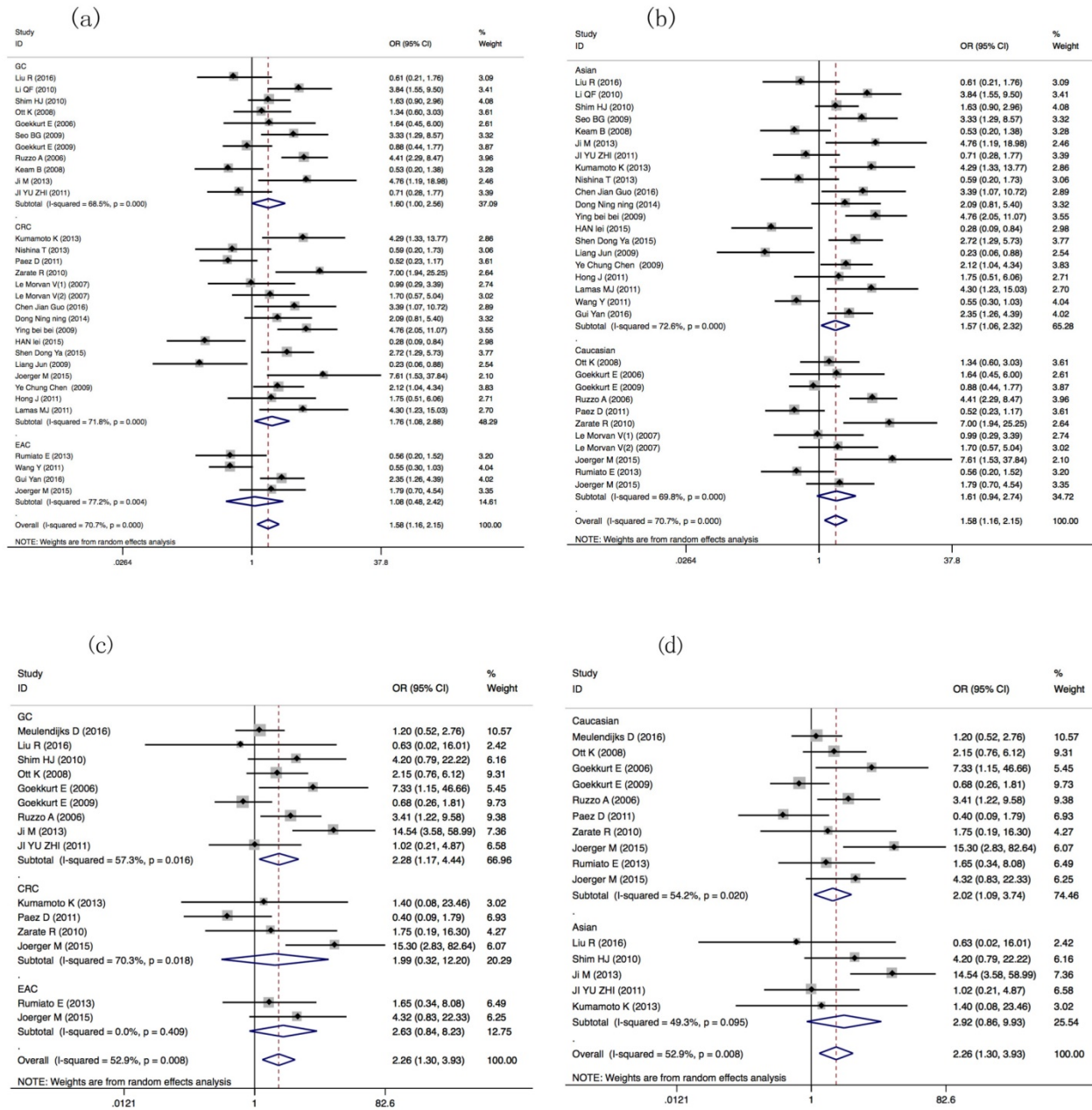
Figure 2. Forest plots of ORR in GIC patients with *GSTP1* Ile105Val variants (Val carriers *vs.* Ile/Ile, Val/Val *vs.* Ile carriers models). ORs and 95% CI of ORR stratified by (a) tumor types in Val carriers *vs.* Ile/Ile model; (b) ethnicity in Val carriers *vs.* Ile/Ile; (c) tumor types in Val/Val *vs.* Ile carriers model; (d) ethnicity in Val/Val *vs.* Ile carriers model.

Table 3. The pooling HRs of OS, PFS and TTP in GIC patients with different *GSTP1* Ile105Val and *GSTM1*/*GSTT1* variants.

Genetic comparisons	No. of studies	Study groups	Test of association				Test of heterogeneity			
			OR/HR(95% CI)	Z	P-value	Models	χ^2	P-value	I²(%)	Tau-squared
GSTP1-OS										
Val carriers *vs.* Ile/Ile	10	Overall	0.903(0.613-1.332)	0.51	0.608	R	48.2	<0.001	81.30%	0.3021
	5	GC	0.797(0.437-1.455)	0.74	0.461	R	24.64	<0.001	83.80%	0.3891
	4	CRC	0.967(0.515-1.819)	0.1	0.918	R	14.89	0.002	79.90%	0.3181
	7	Asian	0.975 (0.606-1.569)	0.11	0.916	R	41.13	<0.001	85.40%	0.3385
	3	Caucasian	0.738 (0.347-1.570)	0.79	0.43	R	6.56	0.038	69.50%	0.3093
Ile/Val *vs.* Ile/Ile	13	Overall	0.900(0.794-1.020)	1.65	0.098	F	18.31	0.107	34.50%	-
	11	CRC	0.878(0.763-1.010)	1.83	0.068	F	16.37	0.089	38.90%	-
	3	Asian	1.044(0.865-1.259)	0.45	0.655	F	1.34	0.512	0.00%	-
	10	Caucasian	**0.797(0.674-0.944)**	2.63	**0.009**	F	12.59	0.182	28.50%	-
Val/Val *vs.* Ile/Ile	13	Overall	0.646(0.398-1.046)	1.78	0.076	R	43.88	<0.001	72.70%	0.5021
	11	CRC	0.619 (0.342-1.120)	1.59	0.113	R	43.59	<0.001	77.10%	0.6777
	3	Asian	0.774 (0.495-1.210)	1.13	0.216	F	2.86	0.239	30%	-

Genetic comparisons	No. of studies	Study groups	Test of association				Test of heterogeneity			
			OR/HR(95% CI)	Z	P-value	Models	χ^2	P-value	I²(%)	Tau-squared
	10	Caucasian	0.605(0.315-1.164)	1.51	0.132	R	40.86	<0.001	78.00%	0.7601
GSTP1-PFS										
Val carriers *vs.* Ile/Ile	4	Overall	0.855(0.410-1.781)	0.42	0.675	R	17.22	0.001	82.60%	0.4565
	2	GC	**1.509(1.059-2.150)**	2.28	**0.023**	F	1.7	0.192	41.30%	-
	2	CRC	**0.420(0.247-0.715)**	3.19	**0.001**	F	0.13	0.714	0.00%	-
	3	Asian	1.115(0.552-2.253)	0.3	0.762	R	8.54	0.014	76.60%	0.2913
Ile/Val *vs.* Ile/Ile	5	Overall	0.990(0.827-1.185)	0.11	0.911	F	3.97	0.41	0.00%	-
	4	CRC	0.978(0.790-1.210)	0.21	0.835	F	3.92	0.27	23.50%	-
	2	Asian	0.996(0.719-1.379)	0.03	0.979	F	0.47	0.493	0.00%	-
	3	Caucasian	0.987(0.796-1.225)	0.12	0.907	F	3.49	0.174	42.80%	-
Val/Val *vs.* Ile/Ile	5	Overall	0.709(0.384-1.308)	1.1	0.27	R	16.5	0.002	75.80%	0.3262
	4	CRC	0.664(0.306-1.441)	1.04	0.3	R	16.49	0.001	81.80%	0.4454
	2	Asian	0.759(0.367-1.570)	0.74	0.457	F	0.55	0.459	0.00%	-
	3	Caucasian	0.707(0.306-1.638)	0.81	0.419	R	15.79	<0.001	87.30%	0.4745
GSTP1-TTP										
Val carriers *vs.* Ile/Ile	4	Overall	0.961(0.356-2.591)	0.08	0.937	R	43.02	<0.001	93.00%	0.9525
	3	GC	0.628(0.310-1.274)	1.29	0.198	R	10.03	0.007	80.10%	0.3121
	4	Asian	0.961(0.356-2.591)	0.08	0.937	R	43.02	<0.001	93.00%	0.9525
GSTT1-PFS	5	Overall	1.102(0.918-1.322)	1.04	0.299	F	1.42	0.841	0.00%	-
	3	GC	1.017(0.807-1.282)	0.14	0.885	F	0.2	0.904	0.00%	-
	2	CRC	1.257(0.934-1.692)	1.51	0.132	F	0	0.963	0.00%	-
	4	Caucasian	1.178(0.937-1.480)	1.4	0.161	F	0.52	0.915	0	-
GSTT1-OS	8	Overall	1.104(0.889-1.370)	0.89	0.371	R	15.36	0.032	54.40%	0.0482
	4	GC	1.136(0.689-1.872)	0.5	0.618	R	8.83	0.012	77.40%	0.1492
	4	CRC	0.998(0.844-1.180)	0.03	0.979	F	4.32	0.229	30.50%	-
GSTM1-PFS	5	Overall	0.957(0.823-1.114)	0.57	0.572	F	1.96	0.743	0.00%	-
	3	GC	1.034(0.838-1.275)	0.31	0.755	F	0.88	0.645	0.00%	-
	2	CRC	0.880(0.707-1.095)	1.14	0.253	F	0	1	0.00%	-
	2	Asian	1.054(0.810-1.371)	0.39	0.695	F	0.82	0.365	0.00%	-
	3	Caucasian	0.913(0.758-1.098)	0.97	0.333	F	0.37	0.83	0.00%	-
GSTM1-OS	7	Overall	1.001(0.862-1.163)	0.01	0.992	F	5.74	0.453	0.00%	-
	3	GC	1.103(0.889-1.368)	0.89	0.372	F	1.14	0.565	0.00%	-
	3	CRC	0.900(0.722-1.121)	0.94	0.346	F	2.89	0.236	30.80%	-
	2	Asian	1.174(0.891-1.545)	1.14	0.254	F	0.64	0.424	0.00%	-
	5	Caucasian	0.936(0.783-1.119)	0.73	0.466	F	3.27	0.514	0.00%	-

OR, odds ratio; HR: hazard ratio; CI, confidence interval; vs., versus; F, fixed effect model; R, random effect model.

PFS and TTP of GIC patients harboring *GSTP1* Ile105Val genotypes

For comparing the PFS, we selected 9 studies having 1378 patients in our meta-analysis. The HRs of PFS in GC or CRC patients harboring different Ile105Val genotypes was different (Val carriers *vs.* Ile/Ile: HR= 1.509(1.059-2.150), *P*=0.023; HR= 0.420(0.247-0.715), *P*=0.001, respectively, **Table 3, Figure 3b**).

In order to compare TTP in GIC patients with different *GSTP1* Ile105Val variants, four publications including 349 patients were enrolled and found no association between Val carriers and Ile/Ile patients (HR= 0.961(0.356-2.591), *P*=0.937). Tumor types or ethnicity subgroup analyses were also negative results (for GC patients: HR= 0.628(0.310-1.274), *P*=0.198; for Asian patients: HR= 0.961(0.356-2.591), *P*=0.937, **Table 3**).

## ORR of GIC patients harboring *GSTM1/GSTT1* (null/present) variants

For comparing ORR in *GSTT1* null/present patients, 10 publications including 1104 patients' data showed positive result between *GSTT1* null and present patients (OR= 0.657(0.489-0.883), *P*=0.005).

Ethnicity- and tumor type-subgroup analyses suggested that, for the Caucasian group, *GSTT1* null/present was associated with ORR (OR= 0.530(0.356-0.789), *P*=0.002); for GC patients, *GSTT1* null/present was associated with ORR (OR=0.643(0.463-0.895), *P*=0.009) (**Table 2, Figure 3c, 3d**).

Our meta-analysis about comparing the ORRs in *GSTM1* null/present patients included 10 literatures with 1102 patients. No association was found between patients harboring *GSTM1* null/present variant and ORRs in GIC patients (OR=1.120 (0.872-1.440), *P*= 0.375). Ethnicity-subgroup and tumor type-subgroup analyses also suggested the negative results (**Table 2**).

OS and PFS of GIC patients harboring *GSTM1/GSTT1* (null/present) variants

We compared the pooling OS in *GSTM1* null/present genotypic patients using 7 publications including 892 patients' data, no statistically significant associations were found in *GSTM1* null/present genotypic patients (HR= 1.001(0.862-1.163), *P*=0.992). No significant difference of OS was found between different *GSTM1* null/present variant patients (**Table 3**).
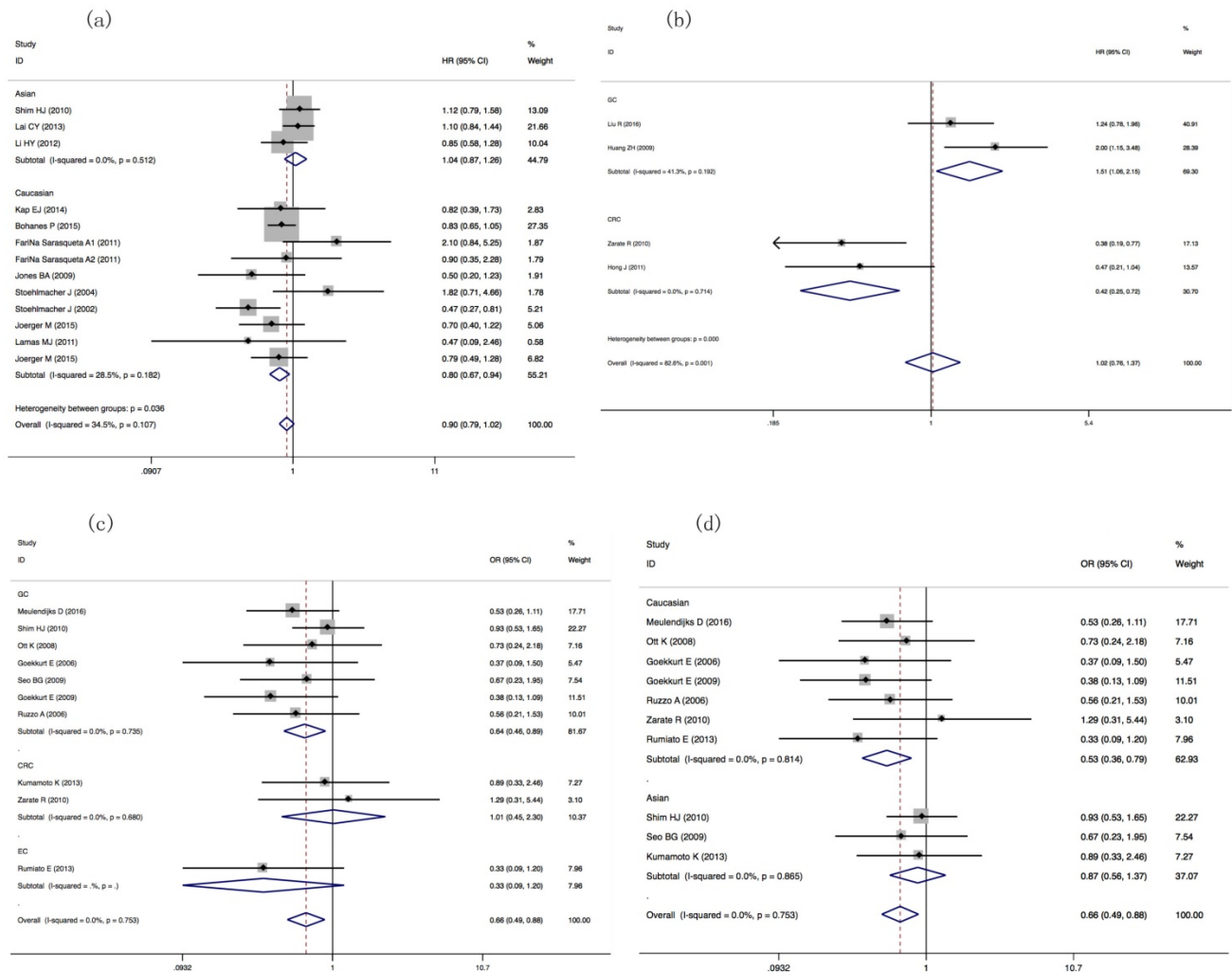
Figure 3. Forest plots of ORR, OS and PFS in GIC patients with *GSTP1* IIe105Val and *GSTT1* null/present variants. (a) HRs and 95%CI of OS stratified by ethnicity in *GSTP1* IIe105Val IIe/Val *vs.* IIe/IIe model; (b) HRs and 95%CI of PFS stratified by tumor types in *GSTP1* IIe105Val Val carriers *vs.* IIe/IIe model; (c) ORs and 95%CI of ORR stratified by tumor types in *GSTT1* null/present variant; (d) ORs and 95%CI of ORR stratified by ethnicity in *GSTT1* null/present variant.

We compared the pooling PFS in *GSTM1* null/present genotypic patients using five publications including 996 patients' data and found no significant association (HR= 0.957(0.823-1.114), *P*=0.572). Ethnicity- and tumor type-subgroup tests also showed negative results (**Table 3**).

We compared the pooled OS and PFS in *GSTT1* null/present genotypic patients using 8 publications including 1366 patients' data and found no significant associations (null *vs.* present: HR= 1.104(0.889-1.370), *P*=0.371; HR= 1.102(0.918-1.322), *P*=0.299, respectively). Ethnicity- and tumor type-subgroup tests also showed negative results (**Table 3**).

ORR and expression level of GSTP1 in GIC patients

No association was found between GSTP1 expression level and ORR after we pooling data from four publications including 264 patients (low expression *vs.* high expression: OR= 0.854

(0.527-1.384), *P*=0.64). After tumor type-subgroup analysis, GSTP1 expression level and ORR in GC patients were negative results (low expression *vs.* high expression: OR= 0.671 (0.369-1.221), *P*=0.191, **Table 2**).

Sensitivity analysis

Sensitivity analysis found that the OR and HR of every enrolled study didn't influence the final significant associations between *GSTP1, GSTM1* and *GSTT1* variants and chemotherapy efficacy in GIC patients (**Figure S1**), except the relationship between *GSTP1* (IIe105Val) Val carriers *vs.* IIe/IIe model and the pooled HRs of PFS, which was just two literatures enrolled in tumor type-subgroup analysis.

Moreover, changing the effect models could change the significant association to negative results about *GSTP1* Val/Val *vs.* IIe/IIe and Val/Val *vs.* IIe carriers models and the ORs of ORR in GIC Asian patients (**Figure S2**). It implies that the associations

between *GSTP1* Val/Val *vs.* IIe/IIe, Val/Val *vs.* IIe carriers and the ORR of GIC Asian patients were not robust.

Publication bias

Egger's test and Begg's test was used in Publication bias. As shown in **Figure S3**, Begg's and Egger's funnel plots found no publications bias under *GSTP1* (IIe105Val) any genetic models (all *P*>0.05, **Figure S4**), and under *GSTT1/GSTM1* (null/present) variants (*GSTT1*: *P*=0.788, *P*=0.247, *GSTM1*: P=0.421, *P*=0.272, respectively, **Figure S5**).

Begg's and Egger's tests showed no publication bias in pooling OS analysis among Caucasian genotypic GIC patients under *GSTP1* (IIe105Val) IIe/Val *vs.* IIe/IIe model (*P*=0.421, *P*=0.724, respectively, **Figure S6**) and in pooling PFS analysis among GC patients or CRC patients under Val carriers *vs.* IIe/IIe model (*P*=0.317, *P*=0.317, respectively, **Figure S6**).

Discussion

We performed a meta-analysis to investigate the association between glutathione S-transferase gene (*GSTP1* (IIe105Val), *GSTM1/GSTT1* (null/present) variants and GSTP1 expression and clinical outcomes in patients with GIC. The results showed that Asian GIC patients with *GSTP1* (IIe105Val) Val carriers had better anticancer efficacy than IIe/IIe patients. Caucasian GIC patients carrying the *GSTP1* Val/Val genotype, especially those with stomach disease, have better chemotherapy efficacy than patients with IIe carriers. Caucasian GIC patients bearing IIe/Val genotype have longer survival time than patients with IIe/IIe genotype. Caucasian GIC patients or gastric patients having *GSTT1* present genotype have higher ORR compared to *GSTT1* null genotypic patients. While *GSTM1* present/null variant and the expression level of GSTP1 were not associated with the chemotherapy efficacy to GIC patients. We found that *GSTP1* IIe105Val and *GSTT1* null/present polymorphisms could predict chemotherapy efficacy in GIC patients. Based on the individual genetic profile, the oncologists will have new possibilities to make treatment decisions for their patients, to predictive efficacy of chemotherapy and to redefine scheduling and dosage.

Platinum (oxaliplatin, cisplatin, carboplatin) combined with fluoropyrimidines (5-fluorouacil, capecitabine, S-1) was most commonly used in chemotherapy of gastrointestinal cancers[6, 33, 34]. However, the chemotherapy efficacy of GIC patients is different. Previous studies suggested that variants in *GSTP1*, *GSTM1*, *GSTT1*, *XPCC1*, *MTHFR*, *TYMS* and *ABCC2* influence the chemotherapy efficacy in

GC or/and CRC patients [5, 6, 12, 34-36]. *GSTP1*, *GSTM1* and *GSTT1* belong to human glutathione S-transferases super family members and are involved in the inactivation of chemotherapeutic drugs such as platinum through the glutathione metabolic pathway [9, 28, 37]. *GSTP1* IIe105Val and *GSTM1/GSTT1* (null/present) polymorphisms decrease enzyme activity, resulting in the lower intracellular concentration of drugs such as cisplatin [29, 38-40]. Therefore, patients harboring *GSTP1* IIe105Val mutant variants may reduce the ability to detoxify drug metabolites, and then have better chemotherapy efficacy.

Our meta-analysis showed that the *GSTP1* IIe105Val variant was associated with ORR of GIC patients (**Table 2**, **Figure 2a, 2b**). Heterogeneity is an important problem in meta-analysis. We also carried out heterogeneity analysis and we found significant heterogeneity when pooling the ORs of ORR in different *GSTP1* IIe105Val variant patients, so we used the Mantel-Haenszel random model to analyze the associations. Changing effect models (Mantel-Haenszel random model and fixed model) didn't change the final results. Moreover, sensitivity analysis results found that excluded any studies has no impact on the overall effective size in GIC patients (**Figure S1**). GIC is a series of complex cancer diseases. Tumor subtypes, patients' ethnicity, different chemotherapy regimens and clinical stage may affect the anti-cancer efficacy in GIC patients. Moreover, the evaluation criterion, genotyping method or quality assessment of literatures may also affect the heterogeneity of meta-analysis. Herein, we performed subgroup-analysis according to different evaluation criterion, genotyping methods and quality assessment of literatures. The subgroup-analysis also supported the significant association between *GSTP1* IIe105Val and chemotherapy efficacy in GC and EC patients, or Caucasian GIC patients under dominant genetic model (**Table 2, Table S3**). It implies that tumor type and ethnicity may contribute to the associations. The study-type subgroup analysis showed prospective study groups have no difference between *GSTP1* Val carriers vs. IIe/IIe and ORR of chemotherapy in GIC patients. But there were significant difference on *GSTP1* Val carriers vs. IIe/IIe and ORR of chemotherapy in GIC patients based on retrospective study.

Compared with Asian GIC patients harboring *GSTP1* IIe105IIe genotypes, Val105Val genotypic patients have better response rates to chemotherapy under the fixed model (OR=3.400(1.521-7.599), *P*=0.003, **Table 2**). However, the random model analysis showed no significant (**Figure S2a**), which

implied that the positive result was unstable and we could not draw a robust conclusion.

Compared with GIC patients harboring *GSTP1* IIe carriers, Val105Val genotypic patients have better chemotherapy efficacy (**Figure 2**). While changing the analytical models could change the significant association of *GSTP1* variants (Val/Val *vs.* IIe carriers) and ORR in Asian GIC patients (**Figure S2**). Sensitivity analysis confirmed the positive results (**Figure S1**). Tumor type-subgroup analysis showed that, compared with IIe carriers variants, GC patients harboring Val/Val variant, not CRC patients, have better chemotherapy efficacy (**Figure 2c, 2d**). Therefore, tumor types and ethnicity both influence the meta-analysis results about *GSTP1* variants (Val/Val *vs.* IIe carriers) and ORR of GIC patients.

We also found that *GSTP1* (Ile105Val) IIe/Val patients had longer survival time than wild-type patients. Exclusion studies did not influence the pooling HR of OS in Caucasian GIC patients. Although significant associations were found between *GSTP1* (Val carriers *vs.* IIe/IIe) and the HRs of PFS in GC or CRC patients, the enrolled studies were two, which could not draw the robust conclusion.

It is the first meta-analysis to investigate the relationship between GSTP1 expression level and anti-cancer efficacy in GIC patients. There were four literatures enrolled for this meta-analysis and we did not find any significant associations. Further updated meta-analysis should be done to confirm our negative results.

Our meta-analysis suggests that GIC patients harboring *GSTT1* present genotype have better chemotherapy efficacy compared to Caucasian patients harboring *GSTT1* null genotype, but not in Asian patients (**Table 2, Figure 3c, 3d**). Subgroup analysis with tumor types showed *GSTT1* null/present variant associated with ORR in GC patients (OR= 0.643(0.463-0.895), *P*=0.009, **Table 2, Figure 3c, 3d**). There was no significant association between *GSTM1* and chemotherapy efficacy. These varies results may be attributed to differences in the distribution of GST families and enzymatic activity of drug detoxification. Our results were consistent with previous meta-analyses, which was just enrolled seven literatures about the *GSTT1* null/present variant and the ORs of ORR in GC patients [28].

Heterogeneity and publication bias are important parts of meta-analysis. In order to draw a robust and confidential conclusion, heterogeneity analyzed by Q test and I² statistics; publication bias analyzed by Egger's test and Begg's test; sensitivity analysis and subgroup analysis were also performed. There were heterogeneities when we pooled ORs or HRs of ORR, OS, PFS and TTP in patients harboring *GSTP1* IIe105Val different variants (**Table 2, Table 3**). Therefore, we used fixed and random models to confirm the positive results. We also used subgroup analysis by other index to find the source of heterogeneity. However, there were still heterogeneities after subgroup-analysis (**Table S3**). Publication bias test also showed no publication bias (**Figure S3- S5**).

Previously, there were four meta-analyses involved in Glutathione S-transferases genes' variants and chemotherapy efficacy in CRC or GC patients [27, 28, 30, 36]. No meta-analysis is involved in the association between GSTP1 expression and chemotherapy efficacy in GC patients. No meta-analysis is enrolled with esophageal cancer patients and is combined GC, CRC and EC patients together in analysis. Moreover, previous meta-analyses' results are conflicting. Therefore, we systematically analyzed all available literatures related to GSTP1 expression levels and *GSTP1* IIe105Val, *GSTM1/GSTT1* deletion variants and chemotherapy efficacy in GIC patients.

There were several limitations about our meta-analysis. First, sample sizes and enrolled studies are still limited. Second, therapeutic indexes such as TTP or PFS were abandoned for analysis. Third, although subgroup analysis, sensitivity analysis, and publication bias were carried out to find the source of heterogeneity, there was still heterogeneity in pooled analysis for *GSTP1*. Fourth, among 50 publications enrolled in the meta-analysis, there were only seven prospective studies. After subgroup-analysis according to tumor type and genetic model, there were less prospective studies to carry out pooling ORs/HRs, or there were publication bias and heterogeneity.

Conclusion

In conclusion, we carried out the meta-analysis including 50 publications with 6518 gastrointestinal cancer patients. We found that *GSTP1* IIe105Val and *GSTT1* deletion variants were associated with chemotherapy efficacy in gastrointestinal cancer patients. A larger sample of further research is needed in different ethnic populations to confirm our conclusions.

Supplementary Material

Supplementary figures and tables.
http://www.jcancer.org/v10p2915s1.pdf

Acknowledgements

Author Contributions

J.Q. and Q.Q designed the study. Y.-S.S, J.Q. and Q.Q wrote the main manuscript text, J.-H.P., X.-C.T. and E.-D.C. performed figures and tables, W.-X.Y. and M.-P.W. analyzed data, all authors reviewed the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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