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ORIGINAL RESEARCH

Can *GSTM1* and *GSTT1* polymorphisms predict clinical outcomes of chemotherapy in gastric and colorectal cancers? A result based on the previous reports

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Background: Gastric and colorectal cancers remain the major causes of cancer-related death. Although chemotherapy improves the prognosis of the patients with gastrointestinal cancers, some patients do not benefit from therapy and are exposed to the adverse effects. The polymorphisms in genes including *GSTM1* and *GSTT1* have been explored to predict therapeutic efficacy; however, the results were inconsistent and inconclusive.

Materials and methods: A systematic review and meta-analysis was performed by searching relevant studies about the association between the *GSTM1* and *GSTT1* polymorphisms and chemotherapy efficacy in gastrointestinal cancers in databases such as PubMed, EMBASE, Web of Science, Chinese National Knowledge Infrastructure, and Wanfang database up to January 10, 2016. Subgroup analyses were also performed according to ethnicity, cancer type, evaluation criteria, study type, chemotherapy type, and age.

Results: A total of 19 articles containing 3,217 cases were finally included. Overall analysis suggested that no significance was found between overall toxicity, neurotoxicity, neutropenia, gastrointestinal toxicity, tumor response, and progression-free survival, and the polymorphisms in *GSTM1* and *GSTT1*, while *GSTM1* polymorphism associated with overall survival (OS; hazard ratio =1.213, 95% confidence interval =1.060–1.388, P=0.005). Subgroup analyses suggested that neurotoxicity was associated with *GSTM1* polymorphism in the Asian population, neutropenia was associated with *GSTM1* polymorphism in palliative chemotherapy and older patients (mean age >60 years), and tumor response was associated with *GSTT1* polymorphism in gastric cancer and responders defined by complete and partial responses. Meanwhile, *GSTM1* was associated with OS in Caucasians, Asians, those with colorectal cancer, and patients with mean age <60 years. *GSTT1* polymorphism was also associated with OS in Caucasians and patients with mean age >60 years.

Conclusion: The polymorphisms in *GSTM1* and *GSTT1* did not associate with the chemotherapy-related toxicity in gastrointestinal cancers, while *GSTT1* polymorphism associated with OS, and further well-designed, larger-scale epidemiological studies are needed to validate our results.

Keywords: meta-analysis, polymorphism, gastrointestinal cancer, chemotherapy, *GSTT1*, *GSTM1*

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Introduction

Gastric and colorectal cancers remain the major causes of cancer-related death and have bad prognosis to date.[1–3] Surgery has been the common choice for managing early-stage and advanced gastrointestinal malignancies. Unfortunately, many patients

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relapse with local recurrence or distant metastasis after surgery.[4] On the other hand, about 20%–30% patients were diagnosed as having inoperable disease initially. Hence, a systemic therapy is needed for the majority of patients at some point during the course of the disease. Palliative, neoadjuvant, and adjuvant chemotherapy have been widely used for gastrointestinal cancers.[5]

Up to now, 5-fluropyrimidines, oxaliplatin, irinotecan, and monoclonal antibodies such as cetuximab, panitumumab, and bevacizumab are the most common drugs for gastrointestinal cancers in chemotherapy.[6] Although chemotherapy improves prognosis of the patients with gastrointestinal cancers, some patients do not benefit from the therapy and are exposed to the adverse effects.[7,8] One major cause of different efficacy resulting from a homologous regimen may be the individual genetic variation in genes associated with detoxification, metabolism, DNA repair, excretion, or transport.[9]

GSTM1 and *GSTT1* are members of the glutathione *S*-transferase (GST) family and are involved in the detoxification pathway of a wide variety of electrophiles, including chemotherapeutic agents. A null polymorphism or total gene deletion of the two genes will block the gene activity.

In recent years, a series of studies have been conducted to investigate the associations of *GSTM1* and *GSTT1* polymorphisms with clinical outcomes of chemotherapy, including toxicities, tumor response, and progression-free survival/overall survival (PFS/OS) in gastric or colorectal cancer; however, the results were inconsistent and inconclusive. Here, a systematic review and meta-analysis was performed, for the first time, to explore these associations.

Materials and methods

Publication search

A systematic search was performed for published articles on the relationship between glutathione *S*-transferases M1 or T1 polymorphisms and chemotherapy in gastrointestinal cancers using the following search terms: "gastric or stomach or colorectal or colon or rectal," "cancer or tumor or carcinoma," "polymorphism or polymorphisms or variant" "glutathione S-transferase M1 or glutathione S-transferase T1 or *GSTM1* or *GSTT1*," and "chemotherapy" in English databases (PubMed, EMBASE, and Web of Science) with the last search update on January 10, 2016. Two independent authors screened and selected the retrieved articles according to the inclusion and exclusion criteria. The review articles and the references of selected articles were also screened to identify additional eligible studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) studies evaluating the relationship between glutathione *S*-transferases M1 or T1 polymorphisms and chemotherapy efficacy including toxicities, tumor response, and/or PFS/OS; 2) studies performed in gastric cancer or colorectal cancer; and 3) studies in which genotype frequency data was specific to clinical features and/or prognosis and could be obtained. Exclusion criteria were as follows: 1) studies including patients with carcinoma other than gastric or colorectal cancers; 2) studies with insufficient or duplicate data; and 3) studies that were not original research articles, such as abstracts, letters, or review articles.

Data extraction

Two independent authors collected data from all eligible studies in duplicate. A predefined table containing the following terms was used: name of first author, year of publication, country of origin, study type, cancer type, ethnicity cases number, sex, mean age, Eastern Cooperative Oncology Group (ECOG) score, Karnofsky scale, metastatic sites number, disease stage/grade, pre-/postsurgery data, prechemotherapy/-radiotherapy details, responder definition, genotyping method, chemotherapy strategy, chemotherapy type, toxicity type, evaluation criteria, and genotype data. Inconsistency was resolved by discussion.

Statistical analysis

The crude odds ratios (ORs) and hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were calculated to assess the strength of association between *GSTM1* or *GSTT1* polymorphism and chemotherapy outcomes in gastric and colorectal cancers. The statistical significant level was determined by *Z*-test, with *P*-value less than 0.05. The heterogeneity was assessed by the chi-square test based on *Q*-statistic test, with a *P*-value <0.1 or $I^2>50\%$. If $P>0.1$and $I^2<50\%$, the pooled OR and 95% CIs were calculated by the fixed effects model (Mantel–Haenszel method); otherwise, the random-effects model (DerSimonian–Laird method) was used.[10] Sensitivity analysis was also conducted to evaluate the effect of each study on the combined ORs and HRs by omitting each study in each turn. Besides, subgroup analyses according caner type, ethnicity, chemotherapy type, study type, evaluation criteria, mean age, and responder definition were also performed. Potential publication bias was checked by Begg's funnel plots and Egger's test.[11,12] Stata 12.0 software (StataCorp, College Station, TX, USA) was used to perform all the analyses.

Results

Study characteristics

According to the searching strategy and the criteria of inclusion and exclusion, the literature was collected. As shown in Figure 1, a total of 95 documents were initially retrieved, of which 25 were from PubMed, 33 were from EMBASE, and 37 were from Web of Science. After excluding 48 duplicated papers, 12 reviews or meeting abstracts, and 11 irrelevant papers, 24 articles were left for further evaluation. Then, a further 5 papers were excluded because they did not have sufficient data or had overlapping data. Finally, 19 eligible articles containing 3,217 cases were included in the meta-analysis.[9,13–30] The characteristics of each included study are listed in the Tables 1 and S1. These 19 articles were published from 2006 to 2014. Of these, 13 studies were performed in Caucasians and six were done in Asians. Eighteen articles reported *GSTM1* polymorphism–related data, while 13 articles reported *GSTT1* polymorphism.

Meta-analysis results

Associations of *GSTM1* and *GSTT1* polymorphisms with chemotherapy-related toxicities

Overall, no significance was found between overall toxicity, neurotoxicity, neutropenia, or gastrointestinal toxicity and the polymorphisms in *GSTM1* and *GSTT1* (Table 1). Then, subgroup analyses stratified by ethnicity, cancer type, evaluation criteria, study type, chemotherapy type, and mean age were performed to investigate the association of the toxicity with polymorphisms. Unfortunately, there was still no significant association identified between the toxicities and the polymorphisms, except for the neurotoxicity associated with *GSTM1* polymorphism in the Asian subgroup (OR =3.361, 95% CI =1.324–8.532, *P*=0.011); however, the number of included studies was less (n=2). Neutropenia associated with *GSTM1* polymorphism in palliative chemotherapy (OR =1.503, 95% CI =1.024–2.208, *P*=0.038) and elder patients with mean age >60 years (OR =1.613, 95% CI =1.064–2.445, *P*=0.024; Figure 2 and Table 2).

Associations of *GSTM1* and *GSTT1* polymorphisms with tumor response

No significant association was identified between polymorphisms in *GSTM1* and *GSTT1* and tumor response after chemotherapy in gastric and colorectal cancers in overall analysis; however, we observed that patients with *GSTT1* null genotype had a trend of lower response rate (OR =0.760, 95% CI =0.568–1.016, *P*=0.064; Figure 2 and Table 3). We also performed subgroup analysis according to ethnicity, cancer type, evaluation criteria, chemotherapy type, mean age, and responder definition, and the results revealed that *GSTT1* null genotype was associated with a lower tumor response in patients with gastric cancer (OR =0.674, 95% CI =0.466–0.974, *P*=0.036) and in responders, as defined by complete and partial response (CR + PR; OR =0.730, 95% CI =0.535–0.994, *P*=0.046; Figure 2 and Table 3).

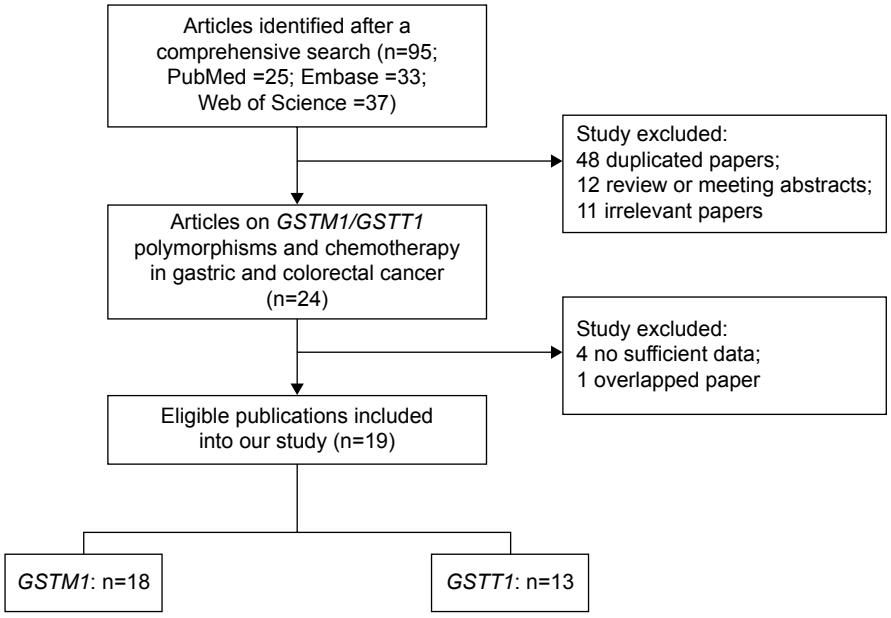

Figure 1 Flowchart of study selection.

Table 1 Characteristics of the included studies

Reference	Country	Ethnicity	Cases (M/F)	Age	Cancer type	Genotyping method	Chemotherapy regimen	Chemotherapy type	Clinical parameters	Criteria	Genes
Goekkurt et al[21]	Germany	Caucasian	52 (34/18)	56 (27–83)	AGC	PCR-RFLP	6-FU/cisplatin/FA	Palliative	Response	RECIST	*GSTM1* and *GSTT1*
Lecomte et al[17]	France	Caucasian	64 (35/32)	64 (24–87)	Gastrointestinal (colon and gastric cancer)	PCR	FOLFOX4/FOLFOX7/ FOLFOX9/ GEMOX/TOMOX	Palliative	Neurotoxicity	OSS	*GSTM1* and *GSTT1*
Romero et al[19]	Spain	Caucasian	51 (38/13)	63 (41–77)	IV CRC	PCR-RFLP	5-Fu/CPT-11/Lv	Palliative	Gastrointestinal and hematological toxicity	NCI-CTC	*GSTM1* and *GSTT1*
Ruzzo et al[22]	Japan	Asian	175 (99/76)	61 (38–79)	AGC	PCR-RFLP	Fluorouracil/cisplatin	Palliative	Response	RECIST	*GSTM1* and *GSTT1*
Ruzzo et al[23]	Italy		167 (87/79)	66	mCRC	PCR-RFLP	FOLFOX-4	Palliative	PFS		*GSTM1* and *GSTT1*
Ott et al[24]	Germany	Caucasian	139 (101/38)	57±10	GC	Multiplex PCR	Cisplatin	Neoadjuvant	OS, response		*GSTM1* and *GSTT1*
Goekkurt et al[15]	Germany	Caucasian	134 (92/42)	64 (27–86)	AGC	PCR	FU and platinum	Palliative	Neurotoxicity, neutropenia, and anemia, response	OSS and NCI-CTC	*GSTM1* and *GSTT1*
Huang et al[25]	People's Republic of China	Asian	102 (73/29)	58 (34–74)	GC	PCR-LDR	Oxa-based FOLFOX	Adjuvant	OS		*GSTM1*
Seo et al[20]	Korea	Asian	75 (44/31)	56 (29–84)	AGC	PCR-RFLP	mFOLFOX	Palliative	Neurotoxicity, neutropenia, and response	NCI-CTC	*GSTM1* and *GSTT1*
Boige et al[13]	France	Caucasian	346 (214/132)	67–68 (34–83)	mCRC	PCR	LV5FU2/FOLFOX/ FOLFIRI	Palliative	Overall toxicity, neurotoxicity, neutropenia, OS, PFS, and response	WHO and NCI-CTC	*GSTM1* and *GSTT1*
Funke et al[26]	Germany	Caucasian	338 (201/137)	64.8	CRC	Fluorescence-based melting curve/PCR	Chemotherapy	Adjuvant/ palliative	OS	RECIST	*GSTM1*
McLeod et al[18]	Canada	Caucasian	520 (306/214)	61 (26–85)	aCRC	Pyrosequencing	IFL/FOLFOX/IROX	Palliative	Neutropenia	NCI-CTC	*GSTM1*
Shim et al[27]	Korea	Asian	200 (150/50)	58 (19–76)	GC	TaqMan/HRM	Taxane + cisplatin as first line	Neoadjuvant/ adjuvant	OS, PFS, and response	RECIST	*GSTM1* and *GSTT1*
Zarate et al[28]	Spain	Caucasian	60 (45/15)	58 (37–75)	mCRC	PCR-RFLP	Oxaliplatin, irinotecan, and capecitabine	Palliative	Response	RECIST	*GSTM1* and *GSTT1*
Cecchin et al[14]	Italy	Caucasian	144 (82/62)	59 (25–82)	II–III CRC	Pyrosequencing/ TaqMan	FOLFOX4	Adjuvant	Neutropenia	NCI-CTC	*GSTM1*
Cortejoso et al[9]	Spain	Caucasian	162 (95/67)	64 (38–85)	CRC	PCR/TaqMan/ Snapshot	Irinotecan/oxaliplatin-based treatment	Palliative	Overall toxicity	CTCAE	*GSTT1*
Kumamoto et al[16]	Japan	Asian	63 (41/22)	65 (32–86)	CRC	PCR-RFLP	mFOLFOX8	Palliative	Neurotoxicity and response	CTCAE and RECIST	*GSTM1* and *GSTT1*
Lai et al[29]	People's Republic of China	Asian	491 (260/231)	58.5±12.5	CRC	PCR-RFLP	5-FU based	Adjuvant	OS		*GSTM1*
Kap et al[30]	Germany	Caucasian	431 (268/163)	66	CRC	Fluorescence-based melting curve analysis	5-FU/Cap/Oxa	Adjuvant/ palliative	OS		*GSTM1*

Abbreviations: PFS, progression-free survival; OS, overall survival; AGC, advanced gastric cancer; CRC, colorectal cancer; GC, gastric cancer; mCRC, metastatic colorectal cancer; RECIST, response evaluation criteria in solid tumors; WHO, Word Health Organization; CTCAE, common terminology criteria for adverse events; PCR, polymerase chain reaction; PCR-LDR, polymerase chain reaction-ligase detection reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; aCRC, advanced colorectal cancer; NCI-CTC, National Cancer Institute Common Toxicity Criteria; OSS, Oxaliplatin specified scale.

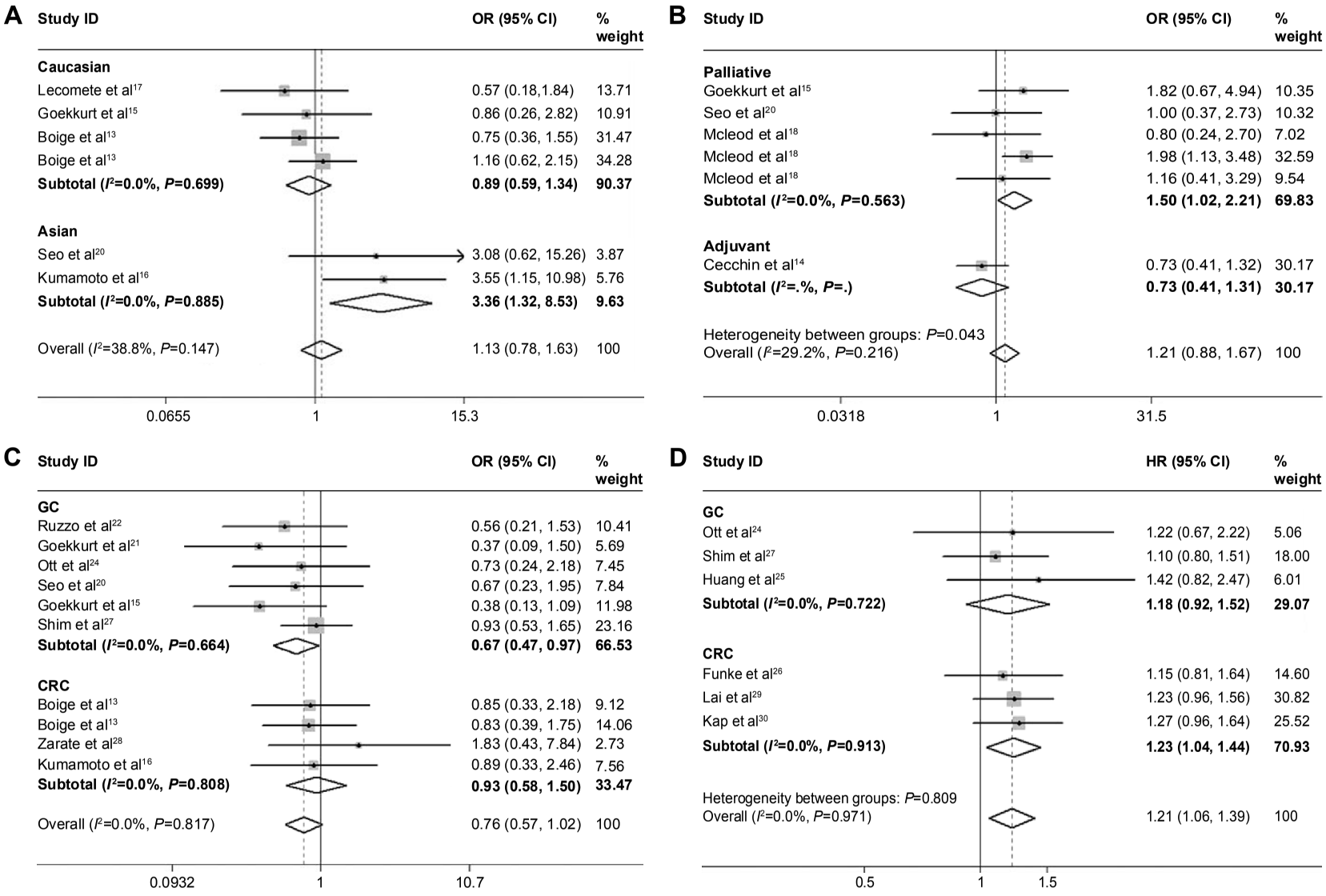

Figure 2 Forest plots for the associations of *GSTM1* and *GSTT1* polymorphisms with toxicity, tumor response, and OS.

Notes: (**A**) Association of *GSTM1* polymorphism with neurotoxicity stratified by ethnicity. (**B**) Association of *GSTM1* polymorphism with neutropenia stratified by chemotherapy. (**C**) Association of GSTT1 polymorphism with tumor response stratified by cancer type. (**D**) Association of *GSTM1* polymorphism with OS stratified by cancer type. The heterogeneity was assessed by the chi-square based on Q statistic test. Bold values show subgroup information.

Abbreviations: OR, odds ratio; OS, overall survival; CI, confidence interval; GC, gastric cancer; CRC, colorectal cancer; HR, hazard ratio.

Table 2 Associations of GSTM1 and GSTT1 polymorphisms with toxicities

Toxicity	Polymorphism	Subgroup analysis	N	OR (95% CI)	P_{OR}	M	I^2 (%)	P_{Heter}	P_{Begg}	P_{Egger}
Overall toxicity	GSTM1 (– vs +)	Overall	2	1.109 (0.634–1.940)	0.716	F	0.0	0.534		
	GSTT1 (– vs +)	NCI-CTC	2	1.432 (0.718–2.853)	0.308	F	1.8	0.313		
		Overall	3	2.101 (0.458–9.646)	0.340	F	51.9	0.125	1.000	0.900
Neurotoxicity	GSTM1 (– vs +)	Caucasian	4	0.891 (0.592–1.342)	0.582	F	0.0	0.699		
		Asian	2	**3.361 (1.324–8.532)**	**0.011**	F	0.0	0.885		
		GC	2	1.442 (0.579–3.586)	0.432	F	36.9	0.208		
		CRC	3	1.298 (0.621–2.714)	0.485	R	61.1	0.076		
		OSS	2	0.701 (0.306–1.608)	0.402	F	0.0	0.632		
		NCI-CTC	3	1.080 (0.692–1.685)	0.734	F	24.3	0.267		
		Retrospective	2	1.436 (0.240–8.581)	0.691	R	79.4	0.028		
		Prospective	4	1.051 (0.693–1.593)	0.816	F	0.0	0.433		
		Age (>60)	5	1.051 (0.718–1.538)	0.798	F	38.7	0.163		
		Overall	6	1.129 (0.782–1.630)	0.516	F	38.8	0.147	0.707	0.480
	GSTT1 (– vs +)	Caucasian	4	1.252 (0.757–2.069)	0.381	F	0.0	0.708		
		Asian	2	1.105 (0.549–2.225)	0.780	F	0.0	0.706		
		GC	2	1.160 (0.523–2.575)	0.715	F	0.0	0.779		
		CRC	3	1.197 (0.713–2.010)	0.496	F	0.0	0.469		
		OSS	2	1.118 (0.406–3.077)	0.829	F	0.0	0.793		
		NCI-CTC	3	1.281 (0.783–2.094)	0.324	F	0.0	0.529		
		Retrospective	2	1.055 (0.455–2.445)	0.900	F	0.0	0.742		
		Prospective	4	1.248 (0.782–1.992)	0.353	F	0.0	0.708		
		Age (>60)	5	1.190 (0.755–1.876)	0.454	F	0.0	0.810		
		Overall	6	1.200 (0.798–1.804)	0.382	F	0.0	0.901	0.707	0.480
Neutropenia	GSTM1 (– vs +)	Caucasian	5	1.235 (0.880–1.734)	0.222	F	42.2	0.140		
		GC	2	1.352 (0.667–2.740)	0.408	F	0.0	0.408		
		CRC	4	1.130 (0.642–1.989)	0.673	R	52.1	0.100		
		Palliative	5	**1.503 (1.024–2.208)**	**0.038**	F	0.0	0.563		
		Age (<60)	2	0.792 (0.478–1.311)	0.364	F	0.0	0.526		
		Age (>60)	4	**1.613 (1.064–2.445)**	**0.024**	F	0.0	0.590		
		Overall	6	1.209 (0.877–1.667)	0.247	F	29.2	0.216	0.452	0.801
	GSTT1 (– vs +)	Overall	2	1.167 (0.544–2.500)	0.692	F	0.0	0.505		
Gastrointestinal toxicity	GSTM1 (– vs +)	Overall	2	2.378 (0.868–6.511)	0.092	F	0.0	0.322		
	GSTT1 (– vs +)	Overall	2	1.192 (0.512–2.777)	0.684	F	0.0	0.771		

Notes: The heterogeneity was assessed by the chi-square based on Q statistic test. Potential publication bias was checked by Begg's funnel plots and Egger's test. Bold values represent a significant association or presence of the trend.

Abbreviations: CI, confidence interval; GC, gastric cancer; CRC, colorectal cancer; NCI-CTC, NCI common toxicity criteria; OSS, Oxaliplatin specified scale; M, model; F, fixed model; R, random model.

Associations of *GSTM1* and *GSTT1* polymorphisms with PFS and OS

There was no significant association between polymorphisms of *GSTM1* and *GSTT1* with PFS. For OS, data of six studies were available to analyze its association with *GSTM1*and *GSTT1* polymorphisms. After pooling analysis and subgroup analysis stratified by ethnicity, cancer type, and mean age, we found that *GSTM1* null type associated with a shorter OS in overall analysis (HR =1.213, 95% CI =1.060–1.388, *P*=0.005) and with subgroups of Caucasian (HR =1.222, 95% CI =1.000–1.493, *P*=0.050), Asian (HR =1.205, 95% CI =1.004–1.446, *P*=0.045), colorectal cancer (HR =1.226, 95% CI =1.044–1.438, *P*=0.013), and patients with mean age <60 years (HR =1.206, 95% CI=1.013–1.435, *P*=0.035). *GSTT1* polymorphism was associated only with OS in the Caucasian subgroup (HR =1.299, 95% CI =1.046–1.613, *P*=0.018) and patients with mean age >60 years (HR =1.370, 95% CI =1.063–1.765, *P*=0.015; Figure 2 and Table 4).

Sensitivity analysis and publication bias

Sensitivity analysis was performed to examine the influence of individual studies on the pooled ORs by deleting each study once, and similar results were identified for all analyses. Begg's funnel plot and Egger's test were carried out to assess the publication bias among the included studies for chemotherapy efficacy and polymorphisms in *GSTM1* and *GSTT1* in gastric and colorectal cancers. Symmetrical funnel plots were obtained (Figure 3). The results showed no evidence of publication bias (Tables 2–4). Sensitivity and publication bias analyses were not performed when the number of included original studies was less than three.

Table 3 Associations of GSTM1 and GSTT1 polymorphisms with tumor response

Polymorphism	Subgroup analysis	N	OR	95% CI	P_{OR}	M	I^2 (%)	P_{Heter}	P_{Begg}	P_{Egger}
GSTM1 – vs +	Caucasian	7	1.123	0.842–1.498	0.429	F	0.0	0.451		
	Asian	3	1.067	0.669–1.700	0.786	F	0.0	0.966		
	GC	6	1.162	0.853–1.585	0.341	F	0.0	0.734		
	CRC	5	1.021	0.684–1.524	0.920	F	0.0	0.411		
	RECIST	6	1.141	0.811–1.604	0.448	F	0.0	0.590		
	WHO	2	1.126	0.706–1.795	0.618	F	0.0	0.391		
	Others	2	1.005	0.586–1.721	0.987	F	19.1	0.266		
	Palliative	8	1.094	0.823–1.453	0.536	F	0.0	0.613		
	Neoadjuvant/adjuvant	2	1.148	0.707–1.863	0.578	F	0.0	0.499		
	<60	5	1.039	0.669–1.545	0.851	F	0.0	0.603		
	>60	5	1.152	0.844–1.572	0.374	F	0.0	0.558		
	Responder (CR + PR)	8	1.129	0.869–1.467	0.366	F	0.0	0.865		
	Overall	10	1.107	0.867–1.415	0.415	F	0.0	0.753	0.474	0.448
GSTT1 – vs +	Caucasian	7	0.689	0.470–1.009	**0.056**	F	0.0	0.635		
	Asian	3	0.873	0.557–1.368	0.553	F	0.0	0.865		
	GC	6	0.674	**0.466–0.974**	**0.036**	F	0.0	0.664		
	CRC	4	0.931	0.568–1.016	0.064	F	0.0	0.808		
	RECIST	6	0.813	0.558–1.183	0.279	F	0.0	0.651		
	WHO	2	0.836	0.465–1.505	0.551	F	0.0	0.962		
	Others	2	0.513	0.240–1.095	0.085	F	0.0	0.399		
	Palliative	8	0.705	0.494–1.006	**0.054**	F	0.0	0.716		
	Neoadjuvant/adjuvant	2	0.884	0.534–1.463	0.631	F	0.0	0.695		
	<60	5	0.842	0.558–1.270	0.412	F	0.0	0.594		
	>60	5	0.688	0.456–1.037	0.074	F	0.0	0.724		
	Responder (CR + PR)	8	0.730	**0.535–0.994**	**0.046**	F	0.0	0.809		
	Overall	10	0.760	0.568–1.016	**0.064**	F	0.0	0.817	0.592	0.383

Notes: The heterogeneity was assessed by the chi-square based on Q statistic test. Potential publication bias was checked by Begg's funnel plots and Egger's test. Bold values represent significant association or presence of the trend.

Abbreviations: RECIST, response evaluation criteria in solid tumors; WHO, response evaluation according to Word Health Organization criteria; OR, odds ratio; CI, confidence interval; GC, gastric cancer; CRC, colorectal cancer; CR, complete response; PR, partial response; Others: did not report the response evaluation criteria; M, model; F, fixed model; R, random model.

Table 4 Associations of GSTM1 and GSTT1 polymorphisms with PFS and OS

PFS/OS	Comparison model	Subgroup analysis	N	HR	95% CI	P_{HR}	M	I^2 (%)	P_{Heter}	P_{Begg}	P_{Egger}
PFS	GSTM1 – vs +	Overall	2	0.980	0.738–1.301	0.889	F	0.0	1.000		
PFS	GSTT1 – vs +	GC	2	1.119	0.860–1.457	0.402	R	67.0	0.082		
		Palliative	2	1.474	0.960–2.263	0.076	F	0.0	0.400		
		>60	2	1.474	0.960–2.263	0.076	F	0.0	0.400		
		Overall	3	1.123	0.877–1.438	0.359	F	34.0	0.220	1.000	0.545
OS	GSTM1 – vs +	Caucasian	3	**1.222**	**1.000–1.493**	**0.050**	F	0.0	0.914		
		Asian	3	**1.205**	**1.004–1.446**	**0.045**	F	0.0	0.704		
		GC	3	1.182	0.920–1.517	0.191	F	0.0	0.722		
		CRC	3	**1.226**	**1.044–1.438**	**0.013**	F	0.0	0.913		
		<60	4	**1.206**	**1.013–1.435**	**0.035**	F	0	0.876		
		>60	2	**1.225**	**0.990–1.515**	**0.062**	F	0	0.660		
		Overall	6	**1.213**	**1.060–1.388**	**0.005**	F	0.0	0.971	1.000	0.728
OS	GSTT1 – vs +	Caucasian	4	**1.299**	**1.046–1.613**	**0.018**	F	0.0	0.419		
		Asian	2	0.953	0.643–1.410	0.808	R	75.0	0.046		
		GC	3	1.135	0.677–1.904	0.631	R	77.2	0.012		
		CRC	3	1.189	0.991–1.427	0.062	F	0.0	0.916		
		Palliative/ adjuvant	2	1.243	0.942–1.640	0.099	F	0.0	0.957		
		<60	3	0.988	0.755–1.293	0.930	R	51.8	0.126		
		>60	3	**1.370**	**1.063–1.765**	**0.015**	F	4.8	0.350		
		Overall	6	1.144	0.920–1.421	0.226	R	51.3	0.068	0.260	0.385

Notes: The heterogeneity was assessed by the chi-square based on Q statistic test. Potential publication bias was checked by Begg's funnel plots and Egger's test. Bold values represent significant association or presence of the trend.

Abbreviations: PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; GC, gastric cancer; CRC, colorectal cancer; M, model; F, fixed model; R, random model.

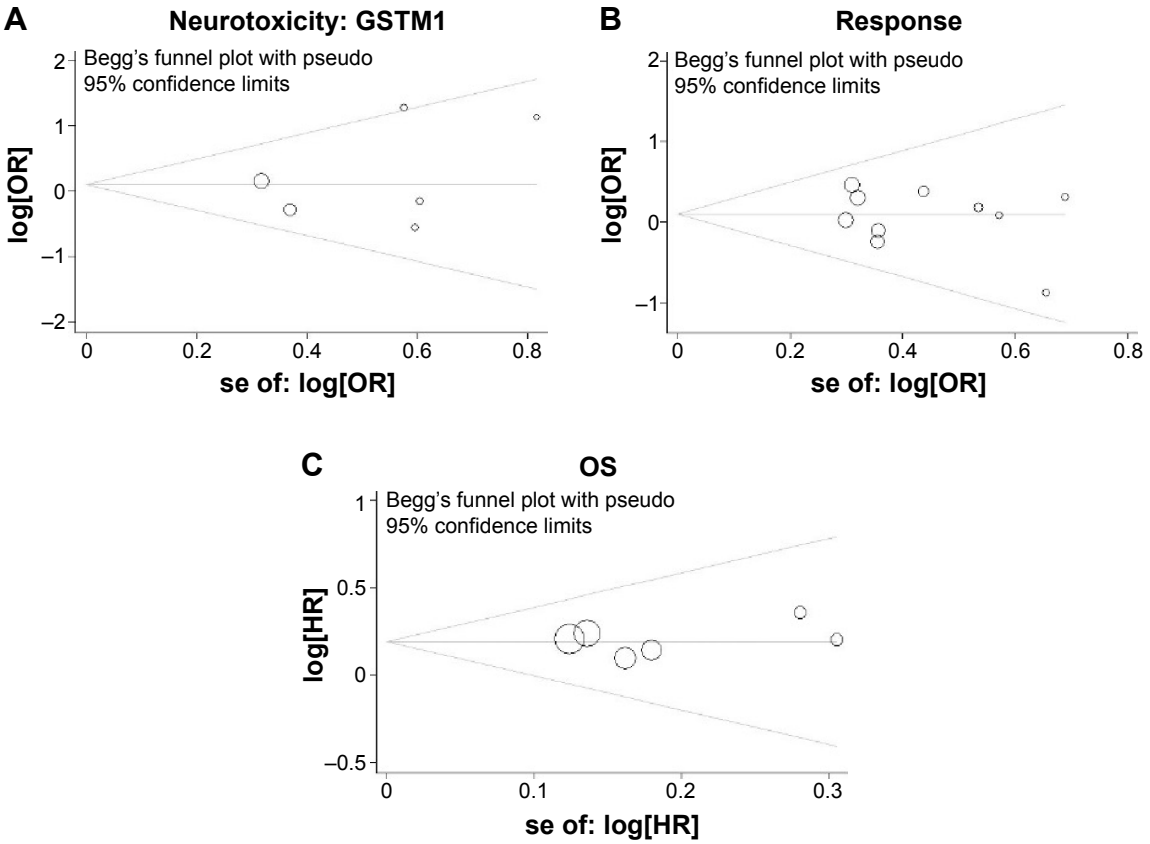

Figure 3 Begg's funnel plot for publication bias analysis for associations of *GSTM1* polymorphism with neurotoxicity (**A**), tumor response (**B**), and OS (**C**).
Abbreviations: OS, overall survival, se, standard error; OR, odds ratio; HR, hazard ratio.

Discussion

In this meta-analysis study, we pooled 19 publications to explore the associations between *GSTM1* and *GSTT1* polymorphisms and chemotherapy efficacy in gastric and colorectal cancers.

Chemotherapy has been widely used in the treatment of gastrointestinal malignancies, especially for metastatic or advanced cancers. The most common chemotherapeutic regimens involve the combination of oxaliplatin and irinotecan with fluoropyrimidines. However, the toxicity profile, tumor response, and prognosis of chemotherapy are very heterogeneous, even in a homologous regimen. It is well known that the individual genetic background may be a major cause for the variability of clinical outcomes. In recent years, a series of studies have tried to investigate the predictive value of the polymorphisms in genes involved in detoxification, metabolism, DNA repair, excretion, or transport on chemotherapy of gastrointestinal cancers.[22,23] For example, polymorphisms in thymidylate synthase have been suggested to determine the cancer cell's sensitivity toward fluoropyrimidines;[31,32] polymorphism in the methylenetetrahydrofolate reductase gene associates with tumor response to 5-FU monotherapy in patients with advanced colorectal cancer;[33] polymorphism in dihydropyrimidine dehydrogenase associates with toxicity from fluoropymidines treatment;[34–38] and the mutations within the nucleotide excision repair pathway and the detoxifying GST may be correlated to resistance to platinum compounds.[39–41] In this study, we investigated the associations of polymorphisms in *GSTM1* and *GSTT1* with the chemotherapy-related toxicities, tumor response, and prognosis in gastrointestinal cancers for the first time. Pooling analysis revealed no significant association between the polymorphisms and the chemotherapy-related toxicity, tumor response, and prognosis except that *GSTM1* null genotype associated with poor OS. Further subgroup analyses suggested that ethnicity, cancer type, chemotherapy type, patient age, and responder definition might have an important influence on the associations. Notably, GSTs are involved in detoxification via direct glutathione conjugation of xenobiotics, and it might be more reasonable that a null genotype, resulting in no enzyme activity, would lead to better tumor response and prognosis after chemotherapy. However, our results suggested that *GSTM1* null genotype associated with poor OS, and a trend was also observed between *GSTT1* null

type and poor tumor response and prognosis. The underlying mechanisms might be that the null genotypes of *GSTM1* and *GSTT1* reduced the GST activity, then elevated the glutathione levels, and finally decreased DNA binding capability of platinum compounds.[42–45] Besides, *GSTM1* and *GSTT1* might be involved in other signaling pathways that were critical for the metabolism of the chemotherapeutic drugs, which affected the associations and should be explored in the future.

Although we pooled all the potential studies to investigate the association between the polymorphisms of *GSTM1* and *GSTT1* and chemotherapy efficacy in gastrointestinal cancers, the publication number and the sample size were still limited. Another limitation of the meta-analysis was the potential instability of the conclusions resulting from the diversity among the original individual studies. In the present meta-analysis, we investigated the effects of the diversity on the result stability and reliability by performing subgroup analysis according to ethnicity, cancer type, toxicity/response criteria, chemotherapy type, study type, age, and responder definition. Additional factors should be taken into consideration as well. As listed in Table S1, we also extracted the following information, sex radio, ECOG scores, Karnofsky scale, metastatic sites number, disease stage, grade, pre-/postsurgery data, and prechemotherapy/-radiotherapy details, from original studies. The sex radio (male/female) ranged from 1.13 to 3.00. The ECOG scores, Karnofsky scale, metastatic sites, disease stage, and tumor grade were reported in ten, five, seven, seven, and three studies, respectively. The ECOG scores ranged from 0 to 2. Four hundred and thirty-three patients had a cancer at single metastatic site and 554 patients had multiple sites of metastasis, respectively. Two hundred and twenty-three patients were in Stage I–II, 589 patients were in Stage III, 590 patients were in Stage IV, 274 patients were in Grade I–II, and 202 patients in Grade II–IV, respectively. There were seven, nine, and one studies reporting previous/postsurgery, prechemotherapy, and preradiotherapy data, respectively. However, these original data were not sufficient for quantitatively evaluating the impact of the diversity among the included studies on the association of the polymorphisms with chemotherapy efficacy. Thus, further well-designed studies with larger sample size and more detailed information should be conducted to confirm the results.

Conclusion

From the results of the current meta-analysis, it can be observed that the polymorphisms in *GSTM1* and *GSTT1* were not associated with the chemotherapy-related toxicities, tumor response, and prognosis in gastrointestinal cancers, except for *GSTM1* polymorphism being associated with OS. Subgroup analyses suggested that *GSTM1* polymorphism might be associated with neurotoxicity in Asians, with neutropenia in palliative chemotherapy and elder patients, and with OS in Caucasians, Asians, and those with colorectal cancer. *GSTT1* might be associated with tumor response in gastric cancer and with OS in Caucasians and elder patients.

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Disclosure

The authors report no conflicts of interests in this work.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58(2):71–96.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9–29.
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*. 2006;24(14):2137–2150.
4. Macdonald JS. Treatment of localized gastric cancer. *Semin Oncol*. 2004;31(4):566–573.
5. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol*. 2006;24(18):2903–2909.
6. Wohrer SS, Raderer M, Hejna M. Palliative chemotherapy for advanced gastric cancer. *Ann Oncol*. 2004;15(11):1585–1595.
7. Chua W, Kho PS, Moore MM, Charles KA, Clarke SJ. Clinical, laboratory and molecular factors predicting chemotherapy efficacy and toxicity in colorectal cancer. *Crit Rev Oncol Hematol*. 2011;79(3):224–250.
8. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol*. 2003;21(5):807–814.
9. Cortejoso L, Lopez-Fernandez LA. Pharmacogenetic markers of toxicity for chemotherapy in colorectal cancer patients. *Pharmacogenomics*. 2012;13(10):1173–1191.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
11. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088–1101.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
13. Boige V, Mendiboure J, Pignon JP, et al. Pharmacogenetic assessment of toxicity and outcome in patients with metastatic colorectal cancer treated with LV5FU2, FOLFOX, and FOLFIRI: FFCD 2000-05. *J Clin Oncol*. 2010;28(15):2556–2564.
14. Cecchin E, D'Andrea M, Lonardi S, et al. A prospective validation pharmacogenomic study in the adjuvant setting of colorectal cancer patients treated with the 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) regimen. *Pharmacogenomics J*. 2013;13(5):403–409.

15. Goekkurt E, Al-Batran SE, Hartmann JT, et al. Pharmacogenetic analyses of a phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil and leucovorin plus either oxaliplatin or cisplatin: a study of the arbeitsgemeinschaft internistische onkologie. *J Clin Oncol*. 2009;27(17):2863–2873.
16. Kumamoto K, Ishibashi K, Okada N, et al. Polymorphisms of GSTP1, ERCC2 and TS-3′UTR are associated with the clinical outcome of mFOLFOX6 in colorectal cancer patients. *Oncol Lett*. 2013;6(3):648–654.
17. Lecomte T, Landi B, Beaune P, Laurent-Puig P, Loriot MA. Glutathione S-transferase P1 polymorphism (Ile(105)Val) predicts cumulative neuropathy in patients receiving oxaliplatin-based chemotherapy. *Clin Cancer Res*. 2006;12(10):3050–3056.
18. McLeod HL, Sargent DJ, Marsh S, et al. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. *J Clin Oncol*. 2010;28(20):3227–3233.
19. Romero RZ, Morales R, Garcia F, et al. Potential application of GSTT1-null genotype in predicting toxicity associated to 5-fluouracil irinotecan and leucovorin regimen in advanced stage colorectal cancer patients. *Oncol Rep*. 2006;16(3):497–503.
20. Seo BG, Kwon HC, Oh SY, et al. Comprehensive analysis of excision repair complementation group 1, glutathione S-transferase, thymidylate synthase and uridine diphosphate glucuronosyl transferase 1A1 polymorphisms predictive for treatment outcome in patients with advanced gastric cancer treated with FOLFOX or FOLFIRI. *Oncol Rep*. 2009;22(1):127–136.
21. Goekkurt E, Hoehn S, Wolschke C, et al. Polymorphisms of glutathione S-transferases (GST) and thymidylate synthase (TS) – novel predictors for response and survival in gastric cancer patients. *Br J Cancer*. 2006;94(2):281–286.
22. Ruzzo A, Graziano F, Kawakami K, et al. Pharmacogenetic profiling and clinical outcome of patients with advanced gastric cancer treated with palliative chemotherapy. *J Clin Oncol*. 2006;24(12):1883–1891.
23. Ruzzo A, Graziano F, Loupakis F, et al. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. *J Clin Oncol*. 2007;25(10):1247–1254.
24. Ott K, Lordick F, Becker K, et al. Glutathione-S-transferase P1, T1 and M1 genetic polymorphisms in neoadjuvant-treated locally advanced gastric cancer: GSTM1-present genotype is associated with better prognosis in completely resected patients. *Int J Colorectal Dis*. 2008;23(8):773–782.
25. Huang ZH, Hua D, Du X. Polymorphisms in p53, GSTP1 and XRCC1 predict relapse and survival of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy. *Cancer Chemother Pharmacol*. 2009;64(5):1001–1007.
26. Funke S, Timofeeva M, Risch A, et al. Genetic polymorphisms in GST genes and survival of colorectal cancer patients treated with chemotherapy. *Pharmacogenomics*. 2010;11(1):33–41.
27. Shim HJ, Yun JY, Hwang JE, et al. BRCA1 and XRCC1 polymorphisms associated with survival in advanced gastric cancer treated with taxane and cisplatin. *Cancer Sci*. 2010;101(5):1247–1254.
28. Zarate R, Rodriguez J, Bandres E, et al. Oxaliplatin, irinotecan and capecitabine as first-line therapy in metastatic colorectal cancer (mCRC): a dose-finding study and pharmacogenomic analysis. *Br J Cancer*. 2010;102(6):987–994.
29. Lai C-Y, Hsieh L-L, Sung F-C, et al. Tumor site- and stage-specific associations between allelic variants of glutathione s-transferase and DNA-repair genes and overall survival in colorectal cancer patients receiving 5-fluorouracil-based chemotherapy. *PloS One*. 2013;8(7):e69039.
30. Kap EJ, Richter S, Rudolph A, et al. Genetic variants in the glutathione S-transferase genes and survival in colorectal cancer patients after chemotherapy and differences according to treatment with oxaliplatin. *Pharmacogenet Genomics*. 2014;24(7):340–347.
31. Cui YH, Liu TS, Zhuang RY, Gao HJ, Li H. Polymorphism of thymidylate synthase gene and chemosensitivity of 5-fluorouracil regimen in metastatic gastrointestinal cancer. *J Dig Dis*. 2009;10(2):118–123.
32. Arrazubi V, Suarez J, Guerrero D, et al. Prognostic significance of thymidylate synthase polymorphisms in rectal cancer patients treated with neoadjuvant chemoradiotherapy. *Colorectal Dis*. 2013;15(4):428–435.
33. Castillo-Fernandez O, Santibanez M, Bauza A, et al. Methylenetetrahydrofolate reductase polymorphism (677 C>T) predicts long time to progression in metastatic colon cancer treated with 5-fluorouracil and folinic acid. *Arch Med Res*. 2010;41(6):430–435.
34. Deenen MJ, Tol J, Burylo AM, et al. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. *Clin Cancer Res*. 2011;17(10):3455–3468.
35. Saif MW. Dihydropyrimidine dehydrogenase gene (DPYD) polymorphism among Caucasian and non-Caucasian patients with 5-FU- and capecitabine-related toxicity using full sequencing of DPYD. *Cancer Genomics Proteomics*. 2013;10(2):89–92.
36. Loganayagam A, Arenas Hernandez M, Corrigan A, et al. Pharmacogenetic variants in the DPYD, TYMS, CDA and MTHFR genes are clinically significant predictors of fluoropyrimidine toxicity. *Br J Cancer*. 2013;108(12):2505–2515.
37. Froehlich TK, Amstutz U, Aebi S, Joerger M, Largiader CR. Clinical importance of risk variants in the dihydropyrimidine dehydrogenase gene for the prediction of early-onset fluoropyrimidine toxicity. *Int J Cancer*. 2015;136(3):730–739.
38. Li Q, Liu Y, Zhang HM, et al. Influence of DPYD genetic polymorphisms on 5-fluorouracil toxicities in patients with colorectal cancer: a meta-analysis. *Gastroenterol Res Prac*. 2014;2014:827989.
39. Huang D, Zhou Y. Nucleotide excision repair gene polymorphisms and prognosis of non-small cell lung cancer patients receiving platinum-based chemotherapy: a meta-analysis based on 44 studies. *Biomed Rep*. 2014;2(4):452–462.
40. Qin Q, Zhang C, Yang X, et al. Polymorphisms in XPD gene could predict clinical outcome of platinum-based chemotherapy for non-small cell lung cancer patients: a meta-analysis of 24 studies. *PloS One*. 2013;8(11):e79864.
41. Chen YC, Tzeng CH, Chen PM, et al. Influence of GSTP1 I105V polymorphism on cumulative neuropathy and outcome of FOLFOX-4 treatment in Asian patients with colorectal carcinoma. *Cancer Sci*. 2010;101(2):530–535.
42. Voso MT, D'Alo F, Putzulu R, et al. Negative prognostic value of glutathione S-transferase (GSTM1 and GSTT1) deletions in adult acute myeloid leukemia. *Blood*. 2002;100(8):2703–2707.
43. Ekhart C, Rodenhuis S, Smits PH, Beijnen JH, Huitema AD. An overview of the relations between polymorphisms in drug metabolising enzymes and drug transporters and survival after cancer drug treatment. *Cancer Treat Rev*. 2009;35(1):18–31.
44. Tew KD. Glutathione-associated enzymes in anticancer drug resistance. *Cancer Res*. 1994;54(16):4313–4320.
45. Ishikawa T, Ali-Osman F. Glutathione-associated cis-diamminedichloroplatinum(II) metabolism and ATP-dependent efflux from leukemia cells. Molecular characterization of glutathione-platinum complex and its biological significance. *J Biol Chem*. 1993;268(27):20116–20125.

Supplementary material

Table S1 Additional information of included studies

Reference	ECOG score				Karnofsky scale			Metastatic sites			Tumor stage				Tumor grade				Pre-/ postsurgery	Prechemotherapy	Preradiotherapy	Responder definition
	0	1	2	3	100	90	80	70	1	2	3	I	II	III	IV	1	2	3	4			
Goekkurt et al[21]					27		25		7	18	27									37/52	3/52		CR + PR
Lecomte et al[17]	34	25	5											6	52					6/64	13/64		
Romero et al[19]					37	12	2		8	43					51						24/51		
Ruzzo et al[22]					116		59		75	55	45					40	80	55					CR + PR
Ruzzo et al[23]					122		44		99	45	22					11	119	32			74/167		
Ott et al[24]																24		115		133/139			CR
Goekkurt et al[15]	32	94	8						33	44	57												CR + PR
Huang et al[25]												3	15	73	11					102/102			
Seo et al[20]																					81/149		CR + PR
Boige et al[13]	154	151	51						185	161													CR + PR
Funke et al[26]												5	48	187	98								
McLeod et al[18]	496		24																		78/520		
Shim et al[27]					77		123													102/200	34/200		CR + PR
Zarate et al[28]	54		6																		18/60		CR + PR + SD
Cecchin et al[14]																				144/144	13/144	19/144	
Cortejoso et al[9]	91	65	6									1	12	31	118								
Kumamoto et al[16]	39	21	3						26	37													CR + PR
Lai et al[29]													74	267	150					491/491			
Kap et al[30]													65	25	110								

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, standard deviation.