Research Article

Individual and combined effects of \textit{GSTM1} and \textit{GSTT1} polymorphisms on colorectal cancer risk: an updated meta-analysis

Liang Song\textsuperscript{1,}\textsuperscript{*}, Chen Yang\textsuperscript{2,}\textsuperscript{*} and Xiao-Feng He\textsuperscript{3}

\textsuperscript{1}Endoscopy Room, Heping Hospital Affiliated to Changzhi Medical College, Shanxi, Changzhi, 046000, People’s Republic of China; \textsuperscript{2}Teaching Reform Class of 2016, First Clinical College, Changzhi Medical College, Shanxi, Changzhi, 046000, People’s Republic of China; \textsuperscript{3}Department of Science and Education, Heping Hospital Affiliated to Changzhi Medical College, Shanxi, Changzhi, 046000, People’s Republic of China

Correspondence: Xiao-Feng He (393120823@qq.com)

Background. The presence or absence of glutathione S-transferase M1 gene (\textit{GSTM1}) and glutathione S-transferase T1 gene (\textit{GSTT1}) polymorphisms, and their combined effects have been suggested as a risk factor for colorectal cancer (CRC). However, the results are inconsistent.

Objectives. An updated meta-analysis was performed to solve the controversy.

Methods. Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines were used.

Results. Overall, the \textit{GSTM1} null genotype was associated with an increased CRC risk in Caucasians (odds ratio (OR) = 1.14, 95% confidence interval (CI): 1.05–1.23), Asians (OR = 1.19, 95% CI: 1.08–1.32), high-quality studies (OR = 1.12, 95% CI: 1.06–1.18). Moreover, the \textit{GSTM1} null genotype was also associated with an increased colon cancer risk (OR = 1.32, 95% CI: 1.16–1.51). The \textit{GSTT1} null genotype was also associated with an increased CRC risk in Asians (OR = 1.08, 95% CI: 1.02–1.15) and Caucasians (OR = 1.24, 95% CI: 1.09–1.41). Moreover, The \textit{GSTT1} null genotype was associated with an increased rectal cancer risk (OR = 1.13, 95% CI: 1.01–1.27, $I^2 = 8.3\%$) in subgroup analysis by tumor location. Last, the \textit{GSTM1} null/\textit{GSTT1} null genotype was associated with an increased CRC risk in Asians.

Conclusion. This meta-analysis indicates that the \textit{GSTM1} and \textit{GSTT1} null genotypes are associated with increased CRC risk in Asians and Caucasians, and the \textit{GSTM1} null/\textit{GSTT1} null genotype was associated with increased CRC risk in Asians.

Introduction

Colorectal cancer (CRC) is a common form of cancer, with more than 1.5 million new patients diagnosed every year worldwide [1]. It is a complex chronic disease whose development is affected by genetic and environmental factors [2,3]. CRC incidence rates differ between countries indicating that environmental factors may be associated with an increased cancer risk, although. A twin study indicated that the role of genetic factors is around 35% in CRC [4]. A previous genome-wide association study also indicated that single-nucleotide polymorphisms are important risk factors [5].

Glutathione S-transferases (\textit{GSTs}) are a large family of enzymes that catalyze the conjugation of electrophiles to glutathione and the conversion of toxic compounds to hydrophilic metabolites [6,7]. \textit{GSTM1} maps to chromosome 1p13.3 contains 10 exons, while \textit{GSTT1} maps to chromosome 22q11.23 and contains six exons. \textit{GSTM1} present/null and \textit{GSTT1} present/null polymorphisms have been reported in human [8–11]. The null genotypes are the most common polymorphisms in \textit{GSTM1} and \textit{GSTT1}, and have been proven to be associated with the loss of enzyme activity [12,13].
To date, many studies have evaluated the association between \textit{GSTM1} present/null and \textit{GSTT1} present/null polymorphisms, and their combined effects with CRC risk [14–107,108–114]. Additionally, 13 meta-analyses [115–125,126,127] have been conducted. However, a lot of studies have been published on these associations with CRC risk, therefore, an updated meta-analysis was performed to explore the association between \textit{GSTM1} present/null, \textit{GSTT1} present/null, and their combined effects on CRC risk in all populations.

### Materials and methods

#### Search strategy

Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines were used [128]. PubMed, Chinese Biomedical Medical databases (CBM), China National Knowledge Infrastructure (CNKI), and WanFang databases (up to March 15, 2020) were searched to identify eligible studies that analyzed the \textit{GSTM1} present/null, \textit{GSTT1} present/null, and their combined effects with CRC risk. The following keywords were used: (\textit{GSTT1} OR glutathione S-transferase T1 OR \textit{GSTM1} OR glutathione S-transferase M1) AND (polymorphism OR variant OR mutation) AND (colorectal OR rectal OR rectum OR colon). The search strategy was designed to be sensitive and broad. We first carefully reviewed the title and abstract of the search results, and then downloaded full articles to identify possible articles. These were evaluated in detail to identify relevant articles. The reference lists of identified articles and reviews was also examined as appropriate. The corresponding author may be contacted by e-mail if only the abstract was available online or the data was incomplete.
Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) articles on the \textit{GSTM1} present/null, \textit{GSTT1} present/null, and their combined effects with CRC risk; (2) sufficient genotype data to calculate ORs and 95% CIs; and (3) case–control studies. Exclusion criteria were as follows: (1) no raw data; (2) no control; (3) review articles, case reports, editorials, or animal research; (4) duplicate and insufficient data.

Data extraction and quality score assessment

Two investigators independently extracted data using Excel. Any disagreement was solved by iteration, discussion, and consensus. The following data were extracted from eligible studies: (1) first author’s name, (2) publication year, (3) country, (4) source of controls (hospital-based and population-based case–control studies), (5) sample size, (6) genotyping method, and (6) genotype distribution of the \textit{GSTM1}, \textit{GSTT1}, and their combined effects in cases and controls.
controls. Different ethnicities included “Caucasians”, “Asians”, “Indians”, and “Africans”. If ethnicity was not stated or if the sample size could not be separated, the term “Mixed populations” was used. Two investigators independently assessed the quality of each individual study. The quality assessment criteria (Table 1) were obtained from two previous meta-analyses [129,130]. The highest value is obtained from the quality assessment was nine; studies of quality scoring ≥ 6 were considered as high quality.

### Statistical analysis

We used crude odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the association on the above issues. The genetic model of the individual GSTM1 and GSTT1 polymorphisms was null vs. present. Their combined effects used the following five genetic models: −− vs. + +, −− vs. + −, −− vs. − +, −− vs. (+ −) + (− +), and −− vs. (+ −) + (− +) + (+ +). −− referred to the GSTM1 null/GSTT1 null genotype, −− referred to the GSTM1 null/GSTT1 null genotype, − + referred to the GSTM1 null/GSTT1 present genotype, and ++ referred to the GSTM1 present/GSTT1 present genotype. Heterogeneity among studies was tested using the $I^2$ value [131]. A fixed-effects model (Mantel–Haenszel method) was used when $I^2 \leq 50\%$ [132]; otherwise, a random-effects model (DerSimonian and Laird method) was considered [133] if $I^2 > 50\%$. However, these studies cannot be pooled into

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**Figure 3. Forest plot of the association between GSTM1 present/null polymorphism and CRC risk in Asians**

| Study  | OR (95% CI) | % Weight |
|--------|-------------|----------|
| Luo [93] 2006 | 1.10 (0.58, 2.10) | 1.83 |
| Yang [103] 2003 | 2.76 (1.32, 5.79) | 1.48 |
| Yoshida [37] 2007 | 1.14 (0.63, 2.08) | 2.05 |
| Katch [75] 1996 | 1.54 (0.91, 2.60) | 2.49 |
| Lee [73] 1996 | 0.79 (0.54, 1.14) | 3.76 |
| Yang ZF [48] 2008 | 2.99 (1.64, 5.46) | 2.04 |
| Huang [107] 2007 | 2.22 (1.06, 4.65) | 1.49 |
| Huang [92] 2003 | 2.46 (1.31, 4.63) | 1.90 |
| Zhang [105] 2001 | 0.79 (0.37, 1.72) | 1.58 |
| Zhou [96] 2000 | 1.42 (0.68, 2.98) | 1.49 |
| Gao [106] 1998 | 1.05 (0.37, 3.01) | 0.81 |
| Guo [74] 1996 | 1.65 (0.44, 6.17) | 0.54 |
| Zeng [101] 2016 | 1.93 (1.20, 3.11) | 2.81 |
| Hu [98] 2012 | 1.15 (0.68, 1.94) | 2.47 |
| Lin LM [95] 2006 | 1.71 (1.09, 2.70) | 2.98 |
| Xia [61] 2007 | 1.82 (1.10, 3.01) | 2.62 |
| Zhu [59] 2002 | 0.66 (0.38, 1.15) | 2.32 |
| Yoshioka [69] 1999 | 1.55 (0.89, 2.68) | 3.23 |
| Cong [35] 2014 | 1.57 (1.13, 2.18) | 4.21 |
| Zhang SS [52] 2010 | 1.18 (0.83, 1.66) | 4.03 |
| Fan [43] 2006 | 1.11 (0.74, 1.65) | 3.46 |
| Yeh [49] 2005 | 0.98 (0.80, 1.21) | 5.79 |
| Chen [130] 2004 | 0.99 (0.66, 1.49) | 3.34 |
| Fu [100] 2006 | 0.97 (0.70, 1.34) | 4.24 |
| Vogtmann [33] 2014 | 1.03 (0.78, 1.34) | 4.93 |
| Koh [21] 2011 | 1.16 (0.94, 1.43) | 5.69 |
| Yang [26] 2010 | 1.01 (0.79, 1.30) | 5.21 |
| Nisa [80] 2010 | 0.92 (0.75, 1.13) | 5.79 |
| Probst-Hensch [41] 2006 | 0.96 (0.75, 1.24) | 5.12 |
| Seow [58] 2002 | 1.25 (0.83, 1.87) | 4.65 |
| Piao [79] 2009 | 1.02 (0.90, 1.17) | 6.75 |
| Overall (I-squared = 52.7%, p = 0.000) | 1.19 (1.08, 1.32) | 100.00 |

**NOTE:** Weights are from random effects analysis.

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Table 1 Scale for quality assessment

| Criteria                                      | Score |
|-----------------------------------------------|-------|
| Representativeness of cases                   |       |
| Selected from cancer registry or multiple cancer center sites | 2     |
| Selected from oncology department or cancer institute | 1     |
| Selected without clearly defined sampling frame or with extensive inclusion/exclusion criteria | 0     |
| Source of controls                            |       |
| Population or community based                 | 2     |
| Both population-based and hospital-based/healthy volunteers/blood donors | 1.5   |
| Hospital-based controls without colorectal cancer | 1     |
| Cancer-free controls without total description | 0.5   |
| Not described                                 | 0     |
| Ascertainment of colorectal cancer            |       |
| Histological or pathological confirmation     | 2     |
| Diagnosis of colorectal cancer by patient medical record | 1     |
| Not described                                 | 0     |
| Sample size                                   |       |
| >1000                                         | 2     |
| 200–1000                                      | 1     |
| <200                                          | 0     |
| Quality control of genotyping methods         |       |
| Clearly described a different genotyping assay to confirm the data | 1     |
| Not described                                 | 0     |

together when $I^2$ value > 75%. Subgroup analyses were performed by ethnicity, source of controls, tumor location, smoking history, gender, quality score, and tumor site. Then, a sensitivity analysis was carried out to assess the stability, a single study was excluded one at a time. Publication bias was tested by using Begg's funnel and Egger's test (significant publication bias was considered if $P < 0.05$). A nonparametric "trim and fill" method was applied to accredit missing studies if publication bias was detected. Finally, a meta-regression analysis was applied to assess the heterogeneity source. All results were calculated using Stata version 9.0 (Stata Corporation, College Station, TX, U.S.A.).

Results

Study characteristics

A flowchart of study selection is shown in Figure 1. Overall, 472 articles were identified by electronic database searching. Of these, 115 full-text articles were selected after carefully screening titles and abstracts. Fourteen articles were excluded because they were not case-control studies, while the data of fourteen articles [18,25,37,43,61,79,84,92,94,95,100,110] overlapped with those of another nine articles [26,41,47,48,93,105,107,108,114]. Hence, a total of 87 articles were included in the present meta-analysis.

The main study characteristics are listed in Tables 2 and 3. Eighty-five publications involving eighty-six case–control studies [14–17,19–24,26–36,38–42,44–60,62–64,67–70,73,74,76–78,80–82,87–90,93,96–99,102,105,109,111–114] were included on the GSTMI present/null polymorphism (24,931 cases and 36,537 controls; 44 studies on Caucasians, 31 on Asians, one on Africans, one on Indians, and nine on mixed populations) with CRC risk. Sixty-three articles of sixty-four case–control studies [15–17,19,21–24,26,27,30,31,33,34,36,38–42,45,47,48–52,54–58,62–64,67–70,73,74,76–78,80–82,87–90,93,96–99,102,105,109,111–114] were eligible concerning the GSTT1 present/null polymorphism (19,725 cases and 28,725 controls; 34 studies on Caucasians, 23 on Asians, one on Indians, one on Africans, and five on mixed populations) with CRC risk. Thirty-two publications of thirty-three case–control studies [15,19,22–24,26,27,31,33,38,39,41,42,45,49,52,55–57,63,67,68,70–76,78,90,96,97,99,105,109,112] were included regarding their combined effects (8270 cases and 14,381 controls; 11 studies on Caucasians, 17 on Asians, one on Indians, one on Africans, and three on mixed populations) with CRC risk. Fifty-five studies had a quality score ≥ 6 and the remaining 31 had a quality score < 6 regarding the GSTMI present/null polymorphism; 48 high-quality studies were examined and the remaining 16 were low-quality concerning the GSTT1 present/null polymorphism; a total of 25 high-quality and eight low-quality studies were included on their combined effects with CRC risk.
Table 2 The data between the GSTM1 and GSTT1 polymorphisms and colorectal cancer risk

| First author/Year | Country     | Ethnicity | SC | Sample size (case/control) | Genotyping methods                  | GSTM1 genotype distribution | GSTT1 genotype distribution | Quality scores |
|-------------------|-------------|-----------|----|----------------------------|-------------------------------------|-----------------------------|-----------------------------|----------------|
| Stojkovic [111]   | Serbia      | Caucasian | HB | 509/399                    | Multiplex PCR                       | Present: 249 Null: 260       | Present: 204 Null: 195     | 145: 364 91: 308       | 6              |
| Rodrigues-Fleming | Brazil      | Mixed     | HB | 232/378                    | Multiplex PCR and PCR-RFLP          | Present: 100 Null: 132       | Present: 385 Null: 353     | 192: 40 573: 165       | 6.5            |
| Wang [113]        | Poland      | Caucasian | HB | 279/233                    | PCR                                 | Present: 151 Null: 128       | Present: 133 Null: 100     | 220: 59 189: 44        | 6              |
| Klusek [114]      | Poland      | Caucasian | HB | 197/104                    | TaqMan                              | Present: 105 Null: 92        | Present: 57 Null: 47       | 166: 31 83: 21        | 6              |
| Gorukmez [49]     | Turkey      | Caucasian | HB | 92/116                     | Multiplex PCR                       | Present: 65 Null: 27         | Present: 67 Null: 49       | 58: 34 91: 25        | 4              |
| Khabaz [32]       | Saudi Arabia| Caucasian | HB | 83/35                      | PCR                                 | Present: 14 Null: 69         | Present: 12 Null: 23       | NA: NA NA: NA         | 3              |
| Zeng [99]         | China       | Asian     | HB | 108/215                    | PCR                                 | Present: 38 Null: 70         | Present: 110 Null: 105     | 48: 60 117: 98        | 6              |
| Dnjegasurova [34] | Kazakhstan  | Mixed     | HB | 249/245                    | Site-specific PCR                   | Present: 124 Null: 125       | Present: 158 Null: 87      | 171: 78 164: 81        | 4.5            |
| Cong [33]         | China       | Asian     | PB | 264/317                    | Multiplex PCR                       | Present: 122 Null: 142       | Present: 182 Null: 135     | 125: 139 190: 127      | 6              |
| Procopciuc [85]   | Romania     | Caucasian | HB | 150/162                    | PCR-RFLP                            | Present: 60 Null: 90         | Present: 97 Null: 65       | NA: NA NA: NA         | 6              |
| Vogtmann [81]     | China       | Asian     | PB | 340/673                    | Real-time PCR                       | Present: 134 Null: 201       | Present: 259 Null: 379     | 164: 173 350: 318      | 8              |
| Kassab [76]       | Tunisia     | Caucasian | HB | 147/128                    | Multiplex PCR                       | Present: 43 Null: 104        | Present: 41 Null: 87       | 90: 57 65: 63        | 6              |
| Saeed [14]        | Saudi Arabia| Caucasian | HB | 100/79                     | PCR                                 | Present: 98 Null: 2          | Present: 79 Null: 0        | NA: NA NA: NA         | 5              |
| Chhila [15]       | Romania     | Caucasian | HB | 19/19                      | Multiple PCR                        | Present: 14 Null: 5          | Present: 15 Null: 4        | 15: 4 16: 3         | 3              |
| Hezova [16]       | Czech       | Caucasian | HB | 197/218                    | Duplex PCR                          | Present: 97 Null: 100        | Present: 117 Null: 101     | 157: 40 179: 39       | 6.5            |
| Rudolph [17]      | Germany     | Caucasian | PB | 1796/1806                  | Multiplex PCR                       | Present: 822 Null: 932       | Present: 844 Null: 923     | 1433: 313 1459: 308    | 6              |
| Huang [96]        | China       | Asian     | HB | 130/100                    | PCR                                 | Present: 71 Null: 59         | Present: 58 Null: 42       | 63: 67 52: 48        | 6              |
| Darazi [20]       | Lebanon     | Lebanese  | HB | 67/70                      | PCR                                 | Present: 32 Null: 25         | Present: 58 Null: 12       | NA: NA NA: NA         | 3.5            |
| Wang [23]         | India       | Indian    | PB | 302/291                    | Multiplex PCR                       | Present: 202 Null: 100       | Present: 215 Null: 76      | 245: 57 247: 44       | 6              |
| Koh [19]          | China       | Asian     | PB | 480/1167                   | TaqMan                              | Present: 246 Null: 234       | Present: 641 Null: 526     | 294: 186 691: 476     | 8              |
| Cleary [21]       | Canada      | Caucasian | PB | 1174/1293                  | Multiplex PCR                       | Present: 550 Null: 616       | Present: 608 Null: 684     | 953: 213 1,067: 223    | 9              |
| Yang [24]         | China       | Asian     | PB | 322/1251                   | Real-time PCR                       | Present: 133 Null: 189       | Present: 521 Null: 730     | 158: 164 639: 612     | 8              |
| Nisa [78]         | Japan       | Asian     | PB | 685/778                    | Multiplex PCR                       | Present: 328 Null: 357       | Present: 356 Null: 422     | 347: 338 435: 343      | 8              |
| Zhang SS [50]     | China       | Asian     | PB | 197/599                    | Multiplex PCR                       | Present: 83 Null: 114        | Present: 184 Null: 215     | 150: 47 310: 89       | 6              |
| Hlavata [22]      | Czech       | Caucasian | PB | 495/495                    | PCR-RFLP                            | Present: 228 Null: 267       | Present: 254 Null: 241     | 392: 103 396: 100     | 6              |
| Csepei [28]       | Hungary     | Caucasian | HB | 102/97                     | PCR                                 | Present: 42 Null: 60         | Present: 51 Null: 46       | 68: 34 77: 20        | 4              |
| Piao [77]         | Korea       | Asian     | PB | 1829/1699                  | Real-time PCR                       | Present: 825 Null: 1,004     | Present: 776 Null: 923     | 879: 950 841: 858     | 9              |
| Matakova [27]     | Slovakia    | Caucasian | PB | 183/402                    | PCR                                 | Present: 83 Null: 100        | Present: 202 Null: 220     | 142: 41 329: 93       | 6              |
| Zuupa [28]        | Italy       | Caucasian | HB | 92/121                     | PCR                                 | Present: 31 Null: 61         | Present: 53 Null: 68       | NA: NA NA: NA         | 5              |
| Curtin [29]       | U.S.A.      | Caucasian | PB | 750/1201                   | PCR                                 | Present: 310 Null: 323       | Present: 465 Null: 545     | NA: NA NA: NA         | 8              |

Continued over
Table 2 The data between the GSTM1 and GSTT1 polymorphisms and colorectal cancer risk (Continued)

| First author/Year | Country | Ethnicity | SC | Sample size (case/control) | Genotyping methods | GSTM1 genotype distribution | GSTT1 genotype distribution | Quality scores |
|--------------------|---------|-----------|----|---------------------------|--------------------|-----------------------------|----------------------------|----------------|
| Epplein [30] 2009  | U.S.A.   | Mixed     | PB | 173/313                   | TaqMan             | 82 91                        | 166 147                    | 127 46          |
| Lin LM [93] 2008   | China    | Asian     | HB | 120/204                   | Multiplex PCR      | 51 69                        | 114 90                     | 56 64           |
| Yang ZF [46] 2008  | China    | Asian     | HB | 84/112                    | PCR                | 24 60                        | 61 51                      | 67 68           |
| Cotterchio [88] 2008| Canada  | Caucasian | PB | 836/1249                  | Multiplex PCR      | 395 441                      | 588 661                    | 679 157         |
| Kury [87] 2008     | France   | Caucasian | PB | 1023/1121                 | TaqMan             | 479 544                      | 553 568                    | 840 183         |
| Skjelbred [36] 2007| Norway   | Caucasian | PB | 108/299                   | Multiplex PCR      | 53 55                        | 148 151                    | 93 15           |
| Yoshida [33] 2007  | Japan    | Asian     | PB | 66/121                    | PCR                | 30 36                        | 59 62                      | NA NA           |
| Xia [59] 2007      | China    | Asian     | HB | 112/140                   | PCR                | 45 67                        | 77 63                      | NA NA           |
| Huang [105] 2007   | China    | Asian     | HB | 57/68                     | PCR                | 17 40                        | 33 35                      | 33 24           |
| Martinez [38] 2006 | Spain    | Caucasian | PB | 144/329                   | Multiplex PCR      | 55 87                        | 180 149                    | 68 74           |
| Probst-Hensch [39] 2006 | China | Asian | PB | 300/1169 | TaqMan | 168 132 | 643 525 | 200 100 | 693 475 |
| Little [40] 2006   | U.K.     | Caucasian | PB | 241/383                   | PCR                | 110 131                      | 162 221                    | 192 49          |
| Fan [41] 2006      | China    | Asian     | PB | 140/343                   | PCR                | 58 80                        | 151 188                    | 113 25          |
| Huang [42] 2006    | China    | Caucasian | PB | 315/547                   | Multiplex PCR      | 135 180                      | 258 289                    | 241 74          |
| Huang [42] 2006    | China    | African   | PB | 239/327                   | Multiplex PCR      | 162 77                       | 245 82                      | 187 56          |
| Fu [98] 2006       | China    | Asian     | PB | 315/439                   | PCR                | 86 229                       | 117 321                    | 141 174         |
| Luo [91] 2006      | China    | Asian     | HB | 56/143                    | PCR                | 36 20                        | 95 48                      | NA NA           |
| Rajagopal [39] 2005| U.K.     | Caucasian | HB | 361/881                   | PCR                | NA NA                        | NA NA                      | 265 96          |
| Landi [44] 2005    | Spain    | Caucasian | HB | 176/162                   | PCR                | 77 99                        | 66 96                      | NA NA           |
| Atge [45] 2005     | Turkey   | Caucasian | HB | 181/204                   | Real-Time PCR      | 83 98                        | 116 88                     | 118 63          |
| Yeh [47] 2005      | China    | Asian     | HB | 727/736                   | Multiplex PCR      | 325 402                      | 326 410                    | 331 396         |
| van der Logt [51] 2004 | U.S.A. | Caucasian | PB | 371/415                   | PCR                | 186 184                      | 212 203                    | 299 72          |
| Kiss [49] 2004     | Hungary  | Caucasian | HB | 500/500                   | PCR                | 209 291                      | 258 242                    | 369 131         |
| Chen [109] 2004    | China    | Asian     | HB | 125/399                   | PCR                | 56 69                        | 151 188                    | 102 23          |
| Smits [52] 2003    | Multiple  | Caucasian | PB | 724/1743                  | PCR                | 381 343                      | 821 922                    | NA NA           |
| van der Hel [54] 2003 | U.S.A.  | Caucasian | PB | 212/1756                  | PCR                | 124 88                       | 396 369                    | 154 58          |
| Slattery [107] 2003| U.S.A.   | Mixed     | PB | 801/1013                  | PCR                | 397 404                      | 467 546                    | NA NA           |
| Nascimento [55] 2003| Brazil   | Mixed     | HB | 102/300                   | Multiplex PCR      | 52 50                        | 166 134                    | 85 17           |

Continued over
Table 2 The data between the GSTM1 and GSTT1 polymorphisms and colorectal cancer risk (Continued)

| First author/Year | Country | Ethnicity | SC | Sample size (case/control) | Genotyping methods | GSTM1 genotype distribution | GSTT1 genotype distribution | Quality scores |
|-------------------|---------|-----------|----|---------------------------|-------------------|----------------------------|----------------------------|----------------|
| Huang [90] 2003   | China   | Asian     | HB | 82/82                      | Multiplex PCR      | Present 36, Null 46         | Present 54, Null 28         | 41 41          |
| Yang [101] 2003   | China   | Asian     | HB | 58/65                      | PCR-RFLP           | Present 18, Null 40         | Present 36, Null 29         | 42 40          |
| Zhu [57] 2002     | China   | Asian     | HB | 104/101                    | Multiplex PCR      | Present 56, Null 48         | Present 44, Null 57         | 55 49          |
| Ye [58] 2002      | U.K.    | Caucasian | HB | 41/82                      | Specific PCR       | Present 21, Null 20         | Present 49, Null 33         | 39 2           |
| Tiemersma [60] 2002 | U.S.A. | Mixed     | PB | 102/537                    | PCR               | Present 44, Null 58         | Present 252, Null 285       | NA NA         |
| Sachse [81] 2002  | U.K.    | Caucasian | PB | 490/593                    | PCR               | Present 206, Null 264       | Present 291, Null 302       | 306 184       |
| Zhang [103] 1999  | China   | Asian     | HB | 52/52                      | Multiplex PCR      | Present 30, Null 22         | Present 27, Null 25         | NA NA         |
| Loktionov [64] 2001 | U.K.   | Caucasian | HB | 104/176                    | Multiplex PCR      | Present 125, Null 133       | Present 246, Null 263       | 133 116       |
| Ye [58] 2002      | China   | Asian     | HB | 41/82                      | Multiplex PCR      | Present 21, Null 20         | Present 49, Null 33         | 39 2           |
| Zou [97] 2000     | China   | Asian     | HB | 55/62                      | PCR               | Present 21, Null 34         | Present 29, Null 33         | 24 31          |
| Loktionov [64] 2001 | U.K.   | Caucasian | HB | 52/52                      | Multiplex PCR      | Present 30, Null 22         | Present 27, Null 25         | NA NA         |
| Butler [82] 2001  | Australia | Caucasian | PB | 219/200                    | PCR               | Present 97, Null 106        | Present 92, Null 108        | 123 67         |
| Saadat [83] 2001  | Iran    | Caucasian | HB | 46/131                     | PCR               | Present 21, Null 25         | Present 78, Null 53         | 28 18          |
| Abdel-Rahman [88] 1999 | U.K.   | Caucasian | PB | 196/178                    | PCR               | Present 94, Null 102        | Present 88, Null 90         | 157 39         |
| Zou [97] 2000     | China   | Asian     | HB | 55/62                      | PCR               | Present 21, Null 34         | Present 29, Null 33         | 24 31          |
| Loktionov [64] 2001 | U.K.   | Caucasian | HB | 104/176                    | Multiplex PCR      | Present 125, Null 133       | Present 246, Null 263       | 133 116       |
| Yoo [85] 2001     | China   | Asian     | HB | 104/176                    | Multiplex PCR      | Present 125, Null 133       | Present 246, Null 263       | 133 116       |
| Deakin [52] 1996  | U.K.    | Caucasian | HB | 252/577                    | PCR               | Present 117, Null 135       | Present 261, Null 316       | 189 63         |
| Gao [72] 1999     | U.K.    | Caucasian | HB | 19/23                      | PCR               | Present 12, Null 7          | Present 17, Null 6          | 17 9           |
| Chenevix-Trench [74] 1995 | Australia | Caucasian | HB | 132/200                    | NA                | Present 68, Null 64         | Present 99, Null 101        | 79 15          |
| Zhong [75] 1993   | U.K.    | Caucasian | PB | 196/225                    | PCR               | Present 86, Null 110        | Present 131, Null 94        | NA NA         |
| Strange [106] 1991 | U.K.   | Caucasian | HB | 19/502                     | HSE               | Present 5, Null 14          | Present 249, Null 253       | NA NA         |

Abbreviations: HB, hospital-based study; HSE, horizontal starch gel electrophoresis; PB, population-based study; SC, source of control.
Table 3 The data between combined effects of GSTM1 and GSTT1 polymorphisms and colorectal cancer risk

| First author/Year | Country | Ethnicity | SC | Sample size | +− | +− | −− | +− | ++ | ++ | −− | −− | ++ | +− or ++ | ++ +−, or +− | Quality scores |
|-------------------|---------|-----------|----|-------------|----|----|----|----|----|----|----|----|----|----|-------------------|-------------------|
| Rodrigues-Fleming [112] 2018 | Brazil | Mixed | HB | 232/738 | 19 | 82 | 97 | 270 | 14 | 83 | 68 | 303 | 116 | 352 | 184 | 655 | 6.5 |
| Gorukmez [49] 2016 | Turkey | Caucasian | HB | 92/116 | 31 | 11 | 24 | 35 | 3 | 14 | 34 | 56 | 55 | 46 | 89 | 102 | 4 |
| Zeng [99] 2016 | China | Asian | HB | 108/215 | 25 | 64 | 35 | 71 | 35 | 34 | 13 | 46 | 60 | 135 | 73 | 181 | 6 |
| Kassab [76] 2014 | Tunisia | Caucasian | HB | 147/128 | NA | NA | NA | NA | 45 | 26 | NA | NA | NA | NA | 102 | 102 | 6 |
| Cong [33] 2014 | China | Asian | PB | 264/317 | 22 | 54 | 23 | 44 | 119 | 83 | 100 | 136 | 45 | 98 | 145 | 234 | 6 |
| Vogtmann [31] 2014 | China | Asian | PB | 332/633 | NA | NA | NA | NA | 106 | 169 | 67 | 128 | 159 | 336 | 226 | 464 | 8 |
| Chirila [15] 2013 | Romania | Caucasian | HB | 19/19 | NA | NA | NA | NA | 2 | 3 | 3 | 15 | 14 | 1 | 17 | 16 | 3 |
| Huang [96] 2012 | China | Asian | HB | 130/100 | NA | NA | NA | NA | 15 | 12 | 46 | 42 | NA | NA | 115 | 88 | 6 |
| Wang [23] 2011 | India | Indian | PB | 302/291 | 42 | 37 | 85 | 69 | 15 | 7 | 160 | 178 | 127 | 106 | 287 | 284 | 6 |
| Koh [19] 2011 | China | Asian | PB | 480/1167 | NA | NA | NA | NA | 163 | 421 | 108 | 263 | 209 | 483 | 317 | 746 | 8 |
| Yang [24] 2010 | China | Asian | PB | 322/1247 | NA | NA | NA | NA | 96 | 326 | 65 | 234 | 161 | 687 | 226 | 921 | 8 |
| Nisa [78] 2010 | Japan | Asian | PB | 685/778 | NA | NA | NA | NA | 183 | 189 | NA | NA | NA | NA | 502 | 589 | 8 |
| Hlavata [22] 2010 | Czech | Caucasian | HB | 495/495 | NA | NA | NA | NA | 61 | 46 | 186 | 200 | 248 | 249 | 434 | 449 | 6 |
| Piao [77] 2009 | Korea | Asian | PB | 1829/1699 | 428 | 391 | 477 | 456 | 393 | 467 | 391 | 385 | 905 | 847 | 1296 | 1232 | 9 |
| Matakova [27] 2009 | Slovak | Caucasian | PB | 183/422 | 20 | 35 | 83 | 162 | 19 | 58 | 61 | 167 | 103 | 197 | 164 | 264 | 6 |
| Huang [105] 2007 | China | Asian | PB | 57/88 | 3 | 13 | 19 | 24 | 19 | 24 | 14 | 20 | 22 | 37 | 36 | 57 | 5 |
| Martinez [38] 2006 | Spain | Caucasian | PB | 142/329 | NA | NA | NA | NA | 40 | 24 | 21 | 128 | 81 | 177 | 102 | 305 | 6 |
| Probst-Hensch [39] 2005 | China | Asian | PB | 300/1168 | NA | NA | NA | NA | 45 | 222 | NA | NA | NA | NA | 255 | 946 | 9 |
| Fan [41] 2006 | China | Asian | PB | 138/339 | 5 | 33 | 60 | 152 | 20 | 36 | 53 | 118 | 65 | 185 | 118 | 303 | 6 |
| Huang [42] 2006 | U.S.A. | Caucasian | PB | 315/547 | 36 | 79 | 142 | 206 | 38 | 83 | 99 | 179 | 178 | 285 | 277 | 464 | 6 |
| Huang [42] 2006 | U.S.A. | Caucasian | PB | 239/227 | 37 | 82 | 58 | 55 | 19 | 27 | 125 | 163 | 95 | 137 | 220 | 300 | 6 |
| Ateş [45] 2005 | Turkey | Caucasian | PB | 180/204 | 36 | 34 | 71 | 69 | 27 | 19 | 46 | 82 | 107 | 103 | 150 | 185 | 6 |
| Chen [106] 2004 | China | Asian | PB | 125/339 | 5 | 32 | 51 | 152 | 18 | 35 | 51 | 119 | 56 | 184 | 107 | 303 | 7 |
| Nascimento [55] 2003 | Brazil | Mixed | HB | 102/300 | NA | NA | NA | NA | 9 | 24 | 44 | 138 | 49 | 138 | 93 | 276 | 6 |
| Huang [90] 2003 | China | Asian | HB | 82/82 | 15 | 26 | 20 | 14 | 26 | 14 | 21 | 28 | 35 | 40 | 56 | 68 | 5 |
| Zhu [57] 2002 | China | Asian | HB | 104/101 | 35 | 37 | 31 | 36 | 28 | 11 | 10 | 17 | 66 | 73 | 76 | 90 | 6 |
| Seow [56] 2002 | China | Asian | PB | 213/1190 | NA | NA | NA | NA | 39 | 224 | NA | NA | NA | NA | 174 | 966 | 9 |
| Saadat [63] 2001 | Iran | Caucasian | HB | 46/131 | 9 | 27 | 16 | 39 | 9 | 14 | 12 | 51 | 25 | 66 | 37 | 117 | 5 |
| Zhou [97] 2000 | China | Asian | PB | 55/62 | 14 | 14 | 17 | 16 | 17 | 27 | 7 | 15 | 31 | 30 | 38 | 45 | 5 |
| Yoshida [67] 1999 | Japan | Asian | PB | 106/100 | 20 | 22 | 25 | 23 | 31 | 19 | 30 | 36 | 45 | 45 | 75 | 81 | 6 |
| Abdela-Rahman [68] 1999 | Egypt | Caucasian | HB | 56/49 | 10 | 4 | 18 | 17 | 12 | 17 | 16 | 11 | 28 | 21 | 44 | 32 | 4 |
| Gertig [70] 1998 | U.S.A. | Mixed | PB | 208/220 | NA | NA | NA | NA | 24 | 23 | 83 | 75 | 101 | 122 | 184 | 197 | 7 |
| Deakon [52] 1996 | U.K. | Caucasian | HB | 218/448 | 38 | 37 | 89 | 207 | 26 | 42 | 65 | 162 | 127 | 244 | 192 | 406 | 4 |

Abbreviations: HB hospital-based studies; NA not available; PB population-based studies; SC, source of controls.
Meta-analysis results

**GSTM1 present/null polymorphisms**

Table 4 lists the summary ORs and 95% CIs on the GSTM1 null genotype with CRC risk. The GSTM1 null genotype was associated with an increased CRC risk (OR = 1.17, 95% CI: 1.10–1.23, $I^2 = 55.8\%$) in the overall population. In subgroup analyses by ethnicity, source of controls, and quality score, a significantly increased CRC risk was observed in Caucasians (OR = 1.14, 95% CI: 1.05–1.23, $I^2 = 56.7\%$, Figure 2) and Asians (OR = 1.19, 95% CI: 1.08–1.32, $I^2 = 52.7\%$, Figure 3), hospital-based studies (OR = 1.32, 95% CI: 1.20–1.46, $I^2 = 51.4\%$), high-quality studies (OR = 1.12, 95% CI: 1.06–1.18, $I^2 = 20.4\%$) and low-quality studies (OR = 1.38, 95% CI: 1.17–1.62, $I^2 = 55.8\%$). Moreover, the GSTM1 null genotype was also associated with an increased colon cancer risk (OR = 1.37, 95% CI: 1.00–1.88, $I^2 = 73.0\%$; Figure 2) and Asians (OR = 1.26, 95% CI: 1.09–1.46, $I^2 = 57.7\%$).

**GSTT1 present/null polymorphisms**–

Table 5 lists the summary ORs and 95% CIs on the GSTT1 present/null polymorphism and CRC risk. The included studies could not be merged together because $I^2 > 75\%$ was found between the GSTT1 present/null polymorphism and CRC risk in the overall analysis and Caucasians. In subgroup analysis by ethnicity and quality score, a significantly increased CRC risk was observed in Asians (OR = 1.08, 95% CI: 1.02–1.15, $I^2 = 43.6\%$, Figure 4) and low-quality studies (OR = 1.33, 95% CI: 1.16–1.53, $I^2 = 17.3\%$). The GSTT1 null genotype was also associated with an increased rectal cancer risk (OR = 1.13, 95% CI: 1.01–1.27, $I^2 = 8.3\%$) in subgroup analysis by tumor location.

**Combined effects of GSTM1 and GSTT1 present/null polymorphisms**

Table 6 lists the summary ORs and 95% CIs on their combined effects with CRC risk. The GSTM1 null/GSTT1 null genotype was associated with an increased CRC risk in the overall analysis ($−−$ vs. $++$: OR = 1.42, 95% CI: 1.17–1.73, $I^2 = 68.6\%$; $−−$ vs. $+−$: OR = 1.37, 95% CI: 1.00–1.88, $I^2 = 73.0\%$; $−−$ vs. $(+−) + (+−)$: OR = 1.26, 95% CI: 1.05–1.51, $I^2 = 70.4\%$; $−−$ vs. $(+−) + (+−) + (+−)$: OR = 1.26, 95% CI: 1.09–1.46, $I^2 = 69.0\%$).

In subgroup analyses by ethnicity, source of controls, and quality score, the GSTM1 null/GSTT1 null genotype was associated with an increased CRC risk in Asians ($−−$ vs. $++$: OR = 1.41, 95% CI: 1.15–1.73, $I^2 = 54.4\%$, Figure 5; $−−$ vs. $+−$: OR = 1.38, 95% CI: 1.17–1.62, $I^2 = 58.9\%$; Figure 6).
and colorectal cancer risk analysis did not reveal a source of heterogeneity under any genetic model. Additionally, concerning the

Heterogeneity and sensitivity analyses

Significant heterogeneity was detected in the meta-analysis, as shown in Tables 4-6. A meta-regression analysis revealed that sample size (P=0.002) was the source of heterogeneity for the GSTM1 present/null polymorphism. Concerning the GSTT1 present/null polymorphism and the combined effects of GSTM1 and GSTT1, meta-regression analysis did not reveal a source of heterogeneity under any genetic model. Additionally, I² > 75% as shown in Tables 4-6.

When the study of Laso et al. [82] was excluded, the values of heterogeneity dropped and the GSTT1 null genotype was associated with an increased CRC risk in the following subgroups: Caucasians (OR = 1.24, 95% CI: 1.09–1.41, I² = 70.8%) and hospital-based studies (OR = 1.19, 95% CI: 1.06–1.35, I² = 54.5%). When the study of Martínez et al. [38] was excluded, the I² value dropped and no significant association was found between the combined effects of GSTM1 and GSTT1 polymorphisms and CRC risk in Caucasians (OR = 1.22, 95% CI: 0.83–1.78, I² = 55.6%; −− vs. (+−) + (−+): OR = 0.81, 95% CI: 0.53–1.26, I² = 68.1%; −− vs. (+−) + (−+) + (+−): OR = 0.99, 95% CI: 0.69–1.41, I² = 57.0%) and population-based studies (OR = 1.22, 95% CI: 0.89–1.78, I² = 55.6%; −− vs. (+−) + (−+): OR = 0.81, 95% CI: 0.53–1.26, I² = 68.1%; −− vs. (+−) + (−+) + (+−): OR = 0.99, 95% CI: 0.69–1.41, I² = 57.0%) and population-based studies (−− vs. +−: OR = 1.11, 95% CI: 0.99–1.24, I² = 28.9%; −− vs. (+−) + (−+): OR = 1.16, 95% CI: 0.93–1.45, I² = 73.9%; −− vs. (+−) + (−+) + (+−): OR = 1.08, 95% CI: 0.93–1.26, I² = 63.5%). When the study of Gorukmez [49] was deleted, the I² value dropped and no significant association was observed between the combined effects of GSTM1 present/null and GSTT1 present/null polymorphisms and CRC risk in population-based studies (−− vs. +−: OR = 1.13, 95% CI: 0.98–1.30, I² = 45.6%; −− vs. (+−) + (−+): OR = 1.29, 95% CI: 1.10–1.51, I² = 73.0%).

Table 5: Odds ratios and 95% confidence intervals for the association between GSTT1 present/null polymorphism and colorectal cancer risk

| Variable | No. of studies | No. of cases/controls | No. of GSTT1 null cases/controls | Test of association | Test of heterogeneity |
|----------|----------------|-----------------------|-------------------------------|---------------------|-----------------------|
|          |                |                       |                               | OR  | 95% CI     | Z    | P       | Chi-square | I² (%) |
| Overall  | 64             | 19,725/28,725         | 6512/8888                     | −   | −          | −   | −      | 260.28     | 75.8   |
| Ethnicity|                |                       |                               | −   | −          | −   | −      | 188.52     | 82.5   |
| Caucasian| 34             | 11,337/14,632         | 2896/3205                     | −   | −          | −   | −      | 39.03      | 43.6   |
| Asian    | 23             | 6878/11,659           | 3286/5069                     | 1.08 | 1.02−1.15  | 2.49 | 0.013  | 90.02      | 70.0   |
| Source of controls |         |                       |                               | −   | −          | −   | −      | 154.05     | 77.3   |
| HB       | 36             | 6801/8894             | 2459/2552                     | −   | −          | −   | −      | 18.14      | 17.3   |
| PB       | 28             | 12,924/19,831        | 4053/6336                     | 1.05 | 0.95−1.16* | 0.96 | 0.337  | 9.81       | 8.3    |
| Quality score |        |                       |                               | 4.09 | <0.001  | −   | −      | 234.52     | 80.0   |
| ≥6       | 48             | 17,832/26,262        | 5903/8253                     | −   | −          | −   | −      | 16.48      | 39.3   |
| <6       | 16             | 1893/2463            | 609/635                      | 1.33 | 1.16−1.53  | 4.09 | <0.001 | 18.14      | 17.3   |
| Location |                |                       |                               | −   | −          | −   | −      | 21.46      | 48.7   |
| Colon cancer |        |                       |                               | 1.11 | 0.94−1.32  | 1.22 | 0.224  | 23.33      | 57.1   |
| Rectal cancer |       |                       |                               | 1.13 | 1.01−1.27  | 2.09 | 0.036  | 9.81       | 8.3    |
| Smoking |                |                       |                               | 1.04 | 0.83−1.30  | 0.36 | 0.721  | 23.33      | 57.1   |
| Smokers  | 12             | 2007/2405            | 537/641                      | 0.96 | 0.74−1.25  | 0.28 | 0.777  | 3.12       | 0.0    |
| Non-smokers |        |                       |                               | 1.13 | 0.98−1.30  | 1.71 | 0.087  | 3.51       | 0.0    |
| Gender |                |                       |                               | 0.96 | 0.78−1.39  | 0.27 | 0.786  | 3.51       | 0.0    |
| Males    | 5              | 1900/2401            | 615/752                      | 1.10 | 0.95−1.28  | 1.24 | 0.217  | 10.99      | 45.4   |
| Females  | 5              | 1467/2436            | 493/930                      | 1.24 | 0.91−1.69  | 1.34 | 0.179  | 5.09       | 25.0   |
| Site     |                |                       |                               | 1.04 | 0.78−1.39  | 0.27 | 0.786  | 3.51       | 0.0    |
| Distal   | 7              | 723/1677             | 194/388                      | 1.24 | 0.91−1.69  | 1.34 | 0.179  | 10.99      | 45.4   |
| Proximal | 7              | 340/1677             | 83/368                       | 1.24 | 0.91−1.69  | 1.34 | 0.179  | 10.99      | 45.4   |

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Table 6 Combined genotype analysis of the GSTM1 and GSTT1 polymorphisms on risk of colorectal cancer

| Variables | No. of studies | No. of cases/controls | Test of association | Test of heterogeneity |
|-----------|----------------|-----------------------|--------------------|----------------------|
|           |                |                       | OR                 | 95% CI               | Z       | P       | Chi-squared I² (%) |
| −− vs. ++ | 29             | 3543/5647             | 1.42               | 1.17–1.73*           | 3.50    | <0.001  | 89.24 68.6       |
| Ethnicity |                |                       |                    |                      |         |         |        |
| Caucasian | 10             | 780/1371              | −                  | −                    | −       | −       | 52.35 82.8       |
| Asian     | 14             | 2202/3255             | 1.41               | 1.15–1.73*           | 3.29    | 0.001   | 28.51 54.4       |
| Source of controls | | | | | | | |
| HB        | 18             | 1193/1954             | 1.53               | 1.28–1.83            | 4.66    | <0.001  | 31.24 45.6       |
| PB        | 11             | 2350/3337             | −                  | −                    | −       | −       | 51.81 80.7       |
| Quality score |          |                       |                    |                      |         |         |        |
| ≥ 6       | 21             | 3257/5144             | 1.43               | 1.15–1.77            | 3.19    | 0.001   | 75.95 73.7       |
| < 6       | 8              | 286/503               | 1.38               | 0.85–2.24*           | 1.32    | 0.187   | 12.76 45.1       |
| −− vs. −+ | 20             | 2469/3221             | 1.15               | 0.92–1.44*           | 1.21    | 0.226   | 46.25 58.9       |
| Ethnicity |                |                       |                    |                      |         |         |        |
| Caucasian | 7              | 577/982               | 0.89               | 0.61–1.28*           | 0.64    | 0.522   | 11.35 47.1       |
| Asian     | 10             | 1604/1728             | 1.28               | 1.11–1.48            | 3.42    | 0.001   | 17.16 47.6       |
| Source of controls | | | | | | | |
| HB        | 14             | 878/1392              | 1.21               | 0.99–1.48            | 1.89    | 0.059   | 24.25 46.4       |
| PB        | 6              | 1591/2829             | −                  | −                    | −       | −       | 20.28 75.3       |
| Quality score |          |                       |                    |                      |         |         |        |
| ≥ 6       | 13             | 2154/2727             | 1.20               | 0.91–1.60*           | 1.28    | 0.199   | 40.26 70.2       |
| < 6       | 7              | 315/494               | 1.07               | 0.77–1.47            | 0.39    | 0.693   | 5.99 0.0        |
| −− vs. +− | 20             | 1878/2218             | 1.37               | 1.00–1.88*           | 1.98    | 0.048   | 70.50 73.0       |
| Ethnicity |                |                       |                    |                      |         |         |        |
| Caucasian | 7              | 314/474               | 0.66               | 0.37–1.17*           | 1.42    | 0.154   | 18.89 68.2       |
| Asian     | 10             | 1418/1426             | −                  | −                    | −       | −       | 36.61 75.4       |
| Source of controls | | | | | | | |
| HB        | 14             | 582/790               | 1.32               | 0.83–2.09*           | 1.18    | 0.239   | 44.80 71.0       |
| PB        | 6              | 1296/1428             | −                  | −                    | −       | −       | 24.47 79.6       |
| Quality score |          |                       |                    |                      |         |         |        |
| ≥ 6       | 13             | 1646/1944             | 1.60               | 1.15–2.22*           | 2.82    | 0.005   | 39.67 69.7       |
| < 6       | 7              | 232/274               | 1.07               | 0.77–1.47            | 0.39    | 0.693   | 5.99 0.0        |
| −− vs. (−+) + (+−) | 28       | 4842/7564             | 1.26               | 1.05–1.51*           | 2.45    | 0.014   | 91.18 70.4       |
| Ethnicity |                |                       |                    |                      |         |         |        |
| Caucasian | 10             | 1203/1709             | −                  | −                    | −       | −       | 41.23 78.2       |
| Asian     | 13             | 3070/4836             | 1.50               | 1.20–1.86*           | 3.60    | <0.001  | 40.06 70.0       |
| Source of controls | | | | | | | |
| HB        | 17             | 1563/2293             | 1.23               | 0.92–1.63*           | 1.40    | 0.162   | 39.44 59.4       |
| PB        | 11             | 3279/5271             | −                  | −                    | −       | −       | 50.60 80.2       |
| Quality score |          |                       |                    |                      |         |         |        |
| ≥ 6       | 20             | 4391/6934             | 1.33               | 1.09–1.62*           | 2.85    | 0.004   | 71.8 73.6       |
| < 6       | 8              | 451/630               | 0.91               | 0.53–1.54            | 0.36    | 0.715   | 18.80 62.8       |
| −− vs. (−+) + (+−) + (++) | 33     | 8270/14,381           | 1.26               | 1.09–1.46*           | 3.08    | 0.002   | 103.11 69.0       |
| Ethnicity |                |                       |                    |                      |         |         |        |
| Caucasian | 8              | 1893/2888             | −                  | −                    | −       | −       | 47.52 79.0       |
| Asian     | 17             | 5328/9617             | 1.30               | 1.10–1.53*           | 3.14    | 0.002   | 47.75 66.5       |
| Source of controls | | | | | | | |
| HB        | 19             | 2620/3998             | 1.38               | 1.19–1.60            | 4.17    | <0.001  | 35.47 49.3       |
| PB        | 14             | 5650/10,383           | −                  | −                    | −       | −       | 61.31 78.8       |

Continued over
Table 6 Combined genotype analysis of the GSTM1 and GSTT1 polymorphisms on risk of colorectal cancer (Continued)

| Variables | No. of studies | No. of cases/controls | Test of association | Test of heterogeneity |
|-----------|----------------|-----------------------|---------------------|-----------------------|
|           |                |                       | OR      | 95% CI | Z   | P   | Chi-squared | I^2 (%) |
| Quality score | < 6  | 8             | 623/988       | 1.10  | 0.72–1.70* | 0.45 | 0.656 | 14.27  | 0.047 |
| Quality score | ≥ 6  | 25            | 7647/13,393   | 1.29  | 1.10–1.51* | 3.08 | 0.002 | 88.88  | 73.0 |

+ +: GSTM1 present/GSTT1 present; + −: GSTM1 present/GSTT1 null; − +: GSTM1 null/GSTT1 present; − −: GSTM1 null/GSTT1 null; HB Hospital-based studies; PB Population-based studies

Figure 4. Forest plot of the association between GSTT1 present/null polymorphism and CRC risk in Asians

+ +: OR = 1.13, 95% CI: 0.78–1.65, I^2 = 54.4%; + −: OR = 0.88, 95% CI: 0.65–1.19, I^2 = 55.3%). A single study was excluded each time to assess the stability of the results. Figures 6–12 suggest that the results are stable in the present meta-analysis.

Publication bias

Begg’s funnel plot and Egger’s test were used to assess publication bias in the meta-analysis. The Begg’s funnel plot shape and Egger’s test (P < 0.001) revealed obvious publication bias between the GSTM1 present/null polymorphism
Figure 5. Forest plot of the association between the combined of \textit{GSTM1} present/null and \textit{GSTT1} present/null polymorphisms and CRC risk in Asians

and CRC risk in the overall analysis. Figure 13 shows the Begg's funnel plots by the trim and fill method; 24 missing studies should be added to this. Notably, log OR and 95% CI did not alter significantly when the trim and fill method was used. No significant publication bias was observed for the \textit{GSTT1} present/null polymorphism ($P=0.195$). Concerning their combined effects, no publication bias was detected under any genetic model ($P=0.093$ for $--$ vs. $++$; $P=0.398$ for $--$ vs. $+-$; $P=0.764$ for $--$ vs. $-+$; $P=0.643$ for $--$ vs. $(+ -) + (++)$; $P=0.280$ for $--$ vs. $(+ -) + (++)$).

Discussion

Strange et al. [106] in 1991 first reported an association between the \textit{GSTM1} null genotype and colon adenocarcinoma risk. Chenevix-Trench et al. [21] first analyzed the association between the \textit{GSTT1} null genotype and CRC risk in 1996. Deakin et al. [52] first examined their combined effects with CRC risk in 1996. Since then, many case-control studies have investigated the associations but the results are still inconsistent. Hence, an updated meta-analysis was performed to explore the \textit{GSTM1} null genotype, \textit{GSTT1} null genotype, and their combined effects with CRC risk.

Overall, this meta-analysis indicates that the \textit{GSTM1} and \textit{GSTT1} null genotypes are associated with increased CRC risk in Asians and Caucasians, and the \textit{GSTM1} null/\textit{GSTT1} null genotype was associated with increased CRC risk in Asians, but not in Africans and Indians. In addition, the \textit{GSTM1} null genotype was associated with colon cancer risk but not rectal cancer, while conversely that the \textit{GSTT1} null genotype was associated with rectal cancer but not colon cancer.

Actually, it may not be uncommon that the same polymorphism played different roles in cancer risk among different ethnic population, because cancer is a complicated multi-genetic disease, and different genetic backgrounds...
Figure 6. Sensitive analysis of the null genotype of \textit{GSTM1} on CRC risk in overall population.

Figure 12. Sensitive analysis of the combined effects of \textit{GSTM1} and \textit{GSTT1} on CRC risk in overall population ((+ −) + (− +) + (+ +))
Figure 7. Sensitive analysis of the null genotype of \textit{GSTT1} on CRC risk in overall population.

Figure 8. Sensitive analysis of the combined effects of \textit{GSTM1} and \textit{GSTT1} on CRC risk in overall population (−− vs. + +).
Figure 9. Sensitive analysis of the combined effects of GSTM1 and GSTT1 on CRC risk in overall population (−− vs. +−)

| Study                        | Year | Effect |
|------------------------------|------|--------|
| Abdel-Rahman [70]            | 1999 |        |
| Gorukmez [51]                | 2016 |        |
| Deakin [54]                  | 1996 |        |
| Huang [107]                  | 2007 |        |
| Huang [92]                   | 2003 |        |
| Zhou [99]                    | 2000 |        |
| Saadat [65]                  | 2001 |        |
| Zeng [101]                   | 2016 |        |
| Zhu [59]                     | 2002 |        |
| Yoshioka [69]                | 1999 |        |
| Ate? [47]                    | 2005 |        |
| Wang [25]                    | 2011 |        |
| Huang [44]                   | 2006 |        |
| Cong [35]                    | 2014 |        |
| Fan [43]                     | 2006 |        |
| Matakova [29]                | 2009 |        |
| Huang [44]                   | 2006 |        |
| Rodrigues-Fleming [133]      | 2018 |        |
| Chen [130]                   | 2004 |        |
| Piao [79]                    | 2009 |        |

Figure 10. Sensitive analysis of the combined effects of GSTM1 and GSTT1 on CRC risk in overall population (−− vs. −+)

| Study                        | Year | Effect |
|------------------------------|------|--------|
| Abdel-Rahman [70]            | 1999 |        |
| Gorukmez [51]                | 2016 |        |
| Deakin [54]                  | 1996 |        |
| Huang [107]                  | 2007 |        |
| Huang [92]                   | 2003 |        |
| Zhou [99]                    | 2000 |        |
| Saadat [65]                  | 2001 |        |
| Zeng [101]                   | 2016 |        |
| Zhu [59]                     | 2002 |        |
| Yoshioka [69]                | 1999 |        |
| Ate? [47]                    | 2005 |        |
| Wang [25]                    | 2011 |        |
| Rodrigues-Fleming [133]      | 2018 |        |
| Chen [130]                   | 2004 |        |
| Huang [44]                   | 2006 |        |
| Cong [35]                    | 2014 |        |
| Fan [43]                     | 2006 |        |
| Matakova [29]                | 2009 |        |
| Huang [44]                   | 2006 |        |
| Piao [79]                    | 2009 |        |
Figure 11. Sensitive analysis of the combined effects of GSTM1 and GSTT1 on CRC risk in overall population (−− vs. (+−) + (−+))

Figure 13. The Duval and Tweedie nonparametric "trim and fill" method's funnel plot of the GSTM1 present/null polymorphism
may contribute to the discrepancy [134]. In addition, the differences might arise by chance because studies in Indians and Africans with small sample size may have insufficient statistical power to generate an authoritative risk estimate [135]. Therefore, a large population-based case-control study is required to confirm the GSTM1, GSTT1 and their combined effects with CRC risk in Indians and Africans. Nine [32,33,46,59,90,93,99,101,105] and seven [38,45,48,75,81,83,85] studies indicated that the GSTM1 null genotype was associated with an increased CRC risk in Asians and Caucasians, respectively. Five [33,47,78,93,102] and eight [26,38,49,52,62,80,82,89] studies indicated that the GSTT1 null genotype had a significantly increased CRC risk in Asians and Caucasians, respectively. Moreover, five studies [33,41,57,90,99] reported a significant association between their combined effects and CRC risk in Asians. The results of present study strongly supported these findings.

Subgroup analysis by source of control found a significant association in hospital-based studies, but not in population-based studies in the present meta-analysis. However, hospital-based controls are not likely to replace the general population because they may have more bias than population-based studies [136]. Therefore, the results of hospital-based controls should be carefully explained. Heterogeneity is a common problem in meta-analyses. The present study observed several high levels of heterogeneity ($I^2 > 75\%$), and the results of meta-regression analysis indicated that sample size was the source of heterogeneity between the GSTM1 null genotype and CRC risk. Small sample size studies may be important confounding bias in molecular epidemiological studies, because random error and bias were common in the studies with small sample sizes, and the results were unreliable [137]. Furthermore, small sample studies were easier to accept if there was a positive report as they tend to yield false-positive results because they may be not rigorous and are often of low-quality. In addition, several value of $I^2 > 75\%$ dropped when a single study was excluded, the results indicate that source of heterogeneity also may be from one or multiple small sample or low quality studies. Figure 13 indicates that the asymmetry of the funnel plot was caused by studies with low-quality small samples.

A total of 13 meta-analyses [115–125,126,127] were conducted between 2010 and 2019 on the associations between the GSTM1 present/null and/or GSTT1 present/null polymorphisms with CRC risk. Cai et al. [115] examined 17 studies that included 5907 CRC cases and 9726 controls to explore the association between the GSTM1 null genotype and CRC risk in Asians, reporting that the GSTM1 null genotype was associated with an increased CRC risk. Liao et al. [116] examined 23 studies including 5058 cases and 5999 controls to show that the GSTT1 null genotype was associated with an increased CRC risk in Caucasians and Asians. Wan et al. [117] identified 30 studies of 7635 cases and 12,911 controls in all races, and demonstrated that the GSTT1 null genotype was associated with an increased CRC risk in Caucasians. Teng et al. [118] examined 13 studies (including 2225 cases and 3990 controls) to assess the GSTM1 null genotype with CRC risk and they found that the GSTM1 null genotype was associated with an increased CRC risk in Chinese. Gao et al. [119] assessed the association of the GSTM1 null genotype with CRC risk in all races (including 10,009 cases and 15,070 controls from 36 studies) and indicated that the GSTM1 null genotype was associated with an increased risk of CRC, especially in Caucasians. Qin et al. [120] selected 46 studies including 15,373 cases and 21,238 controls to show that the GSTT1 null genotype may contribute to an increased CRC risk in Asians and Caucasians. Wang et al. [121] (19 studies including 3130 cases and 6423 controls) found that the null genotypes of GSTM1 and GSTT1 and the dual null genotype of GSTM1/GSTT1 were not associated with CRC risk in Chinese population. The examination of 44 studies of GSTM1 (11,998 CRC cases and 17,552 controls) and 34 studies of GSTT1 (8596 CRC cases and 13,589 controls) by Economopoulos and Sergentanis [122] indicated that the GSTM1 and GSTT1 null genotypes were associated with an increased CRC risk in Caucasians. Li et al. [123] analyzed 33 studies (including 8502 CRC Asian cases and 13,699 controls) and indicated that the GSTM1 null genotype conferred susceptibility to CRC, especially in Chinese population. Xu et al. [124] examined 13 publications of 4832 cases and 7045 controls, demonstrating that the GSTT1 null genotype was associated with an increased CRC risk in Asians. Zhong et al. [125] conducted an association of 12 studies involving 4517 cases and 6607 controls, and suggested that the GSTT1 null genotype contributed to an increased CRC risk in Asians. Du et al. [126] examined 12 studies of GSTM1 and 8 studies of GSTT1, and found no association on the GSTM1 or GSTT1 null genotype with CRC risk. Huang et al. [127] selected 55 studies including 17,498 cases and 26,441 controls to show that the GSTM1 null genotype was a risk factor for CRC.

The current meta-analysis has several advantages over previous meta-analyses [115–125,126,127]. First, the sample size was much larger, with 86 case-control studies including 24,931 CRC cases and 36,537 controls evaluated for the GSTM1 present/null polymorphism, 64 case-control studies including 19,725 CRC cases and 28,725 controls for the GSTT1 present/null polymorphism, and 33 case-control studies including 8306 CRC cases and 14,369 controls for their combined effects in all races. Second, this is the first meta-analysis to explore their combined effects in overall population. Third, we used a meta-regression analysis method to explore the source of heterogeneity. Finally, the current meta-analysis included the most recent relevant publications to produce more accurate results.
Similar to previous meta-analyses, our study also has several limitations. First, only published articles were selected. Hence, publication bias may be found as shown in Figure 13. Moreover, positive results are known to be published more readily than negative ones. If negative results were included, an underestimation of the effect may be observed. Second, some case–control studies were based on hospital-based controls. These controls with non-cancerous disease may influence the pooled results in this study. Therefore, the use of population-based control studies may be more appropriate than hospital-based control studies. Third, only one study on Africans and Indians were included in the present study. Further new original studies were need on these issues in Africans and Indians.

In summary, the present study indicates that the GSTM1 null genotype is associated with increased CRC risk in Asians and Caucasians, the GSTT1 null genotype is associated with increased CRC risk in Asians, and the GSTM1 null/GSTT1 null genotype was associated with increased CRC risk in Asians. Further investigations involving large population-based studies should be conducted to explore the associations on the GSTM1 null genotype, GSTT1 null genotype and their combined effects with CRC risk.

Data Availability
All relevant data are within the paper.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
Liang Song: performed research, collected data, check data, and wrote manuscript. Chen Yang: performed research, collected data, check data, and revised manuscript. Xiao-Feng He: designed research, analyzed data, and revised manuscript.

Abbreviations
CBM, Chinese Biomedical Medical; CI, confidence interval; CNKI, China National Knowledge Infrastructure; CRC, colorectal cancer; GSTM1, glutathione S-transferase M1; GSTT1, glutathione S-transferase T1; MOOSE, Meta-analyses of Observational Studies in Epidemiology; OR, odds ratio.

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