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REVIEW ARTICLE

# Association Between the hOGG1 1245C>G (rs1052133) Polymorphism and Susceptibility to Colorectal Cancer: a Meta-analysis Based on 7010 Cases and 10,674 Controls

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## Abstract

**Background** The 1245C>G (rs1052133) polymorphism of human 8-oxoguanine DNA glycosylase 1 (hOGG1) gene has been indicated to be correlated with colorectal (CRC) susceptibility, but studies have yielded conflicting results. Thus, the present meta-analysis was performed to derive a more precise estimation between hOGG1 1245C>G polymorphism and CRC risk.

**Methods** Data were collected from several electronic databases such as PubMed, EMBASE, and Google Scholar databases, with the last search up to September 01, 2020. Pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to assess the strength of the association.

**Results** A total of 24 case-control studies with 7010 CRC cases and 10,674 controls were selected. Pooled data showed that the hOGG1 1245C>G polymorphism was significantly associated with CRC risk under three genetic models, i.e., homozygote (GG vs. CC: OR = 1.229, 95% CI 1.031–1.465, $p = 0.022$); heterozygote (GC vs. CC: OR = 1.142, 95% CI 1.008–1.294, $p = 0.037$); and dominant (GG+GC vs. CC: OR = 1.162, 95% CI 1.034–1.304, $p = 0.011$). When stratified analysis by ethnicity, a significant association of the hOGG1 1245C>G polymorphism with risk of CRC was found in the Caucasians, but not in Asians. Moreover, there were significant associations between hOGG1 1245C>G polymorphism and CRC by PCR-RFLP and hospital-based subgroups.

**Conclusions** Inconsistent with the previous meta-analysis, these meta-analysis results revealed that the hOGG1 1245C>G polymorphism might be associated with an increased risk of CRC, especially in Caucasians.

**Keywords** Colorectal cancer · hOGG1 gene · Polymorphism · Meta-analysis

## Introduction

Colorectal cancer is one of the leading causes of cancer death worldwide, which its incidence and mortality in young adults has been increasing [1, 2]. Worldwide CRC is considered the third most common cancer and ranks second worldwide with regard to mortality [3, 4]. The global CRC burden by 2030 is estimated to have risen to more than 2.2 million new cases and 1.1 million deaths. There is a higher incidence of CRC, about two-thirds, in developed countries compared with developing

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countries [1, 2]. The highest incidence rates are found in Australia, North America, and Western Europe, while the lowest are found in developing countries [5]. The CRC sex-adjusted incidence showed that the incidence of cancer of the proximal colon is higher in women than in men while men have a higher incidence of cancer in the distal colon and rectum [1]. Approximately 2–8% of CRC is caused by genetic predisposition, due to pathogenic germline variants in genes associated with high cancer risk [6, 7]. It is estimated that the lifetime risk of developing CRC may approach 50–80% for certain mutation carriers in the absence of diagnostic and treatment interventions [7–9].

The human 8-oxoguanine DNA glycosylase 1 (hOGG1) belongs to the base excision repair (BER) pathway of DNA repair and has a DNA glycosylase/AP-lyase activity [10, 11]. The hOGG1 plays a key role in maintaining genome integrity and preventing tumorigenesis [11, 12]. The hOGG1 gene is located in chromosome 3p26.2 and highly polymorphic among humans and is also mutated in cancer cells [13, 14]. Various mutations in the hOGG1 gene sequences have frequently been detected missing or deleted in various tumors. A C>G polymorphism (rs1052133) at 1245 bp (C1245G) in exon 7 of the hOGG1 is one of the key variants caused due to a substitution of serine to cysteine residue at codon 326 (Ser326Cy) of the exon and has been extensively studied for its association with different types of cancer risk [15–17]. To date, several epidemiological studies have been performed to evaluate the association of the hOGG1 Ser326Cys polymorphism with risk of CRC [18], but the results remain conflicting rather than conclusive, which might be due to small sample size or other causes. Meta-analysis can be used to pool data from these studies to obtain sufficient statistical power to detect the potential effect of small to moderate sizes associated with the hOGG1 1245C>G polymorphism. Thus, we performed an update meta-analysis at the aim of precisely verifying the association of the hOGG1 1245C>G polymorphism with CRC risk in global population.

## Materials and Methods

### Publication Search

An ethical approval or patient consent was not needed because this is a meta-analysis in which all data were extracted from published literature. We performed a computer-based literature research using PubMed, Research Gate, Web of Knowledge, Web of Science, EMBASE, Scientific Information Database (SID), Scientific Electronic Library Online (SciELO), WanFang, China Biological Medicine Database (CBMD), China/Asia on Demand (CAOD), VIP, Chinese Biomedical Database (CBD), and China National Knowledge Infrastructure (CNKI) database for all eligible studies that evaluated the association of the hOGG1 1245C>G polymorphism with risk of CRC up to September 01, 2020. The following MeSH terms and keywords were used in various combinations in this search: ("Colorectal Cancer" OR "CRC" OR "Colon Cancer" OR "Bowel Cancer" OR "Rectal Cancer" OR "Colorectal Adenocarcinoma" OR "Tumor" OR "Cancer" OR "Neoplasm") AND ("human 8-oxoguanine DNA glycosylase 1" OR "hOGG1" OR "1245C>G" OR "rs1052133" OR "Ser326Cys" OR "C8069G") AND ("Gene" OR "Genotype" OR "Allele" OR "Polymorphism" OR " Single nucleotide polymorphisms" OR "SNP" OR "Variation" OR "Mutation"). We also manually searched the reference list of all relevant articles or reviews to identify more potential eligible studies. The whole search process was carried out in English, Chinese, and Persian. When overlapping data on the same cases were included in more than one population or publications, only the one with the larger sample size was included to the meta-analysis.

### Inclusion and Exclusion Criteria

Eligible studies were included in the meta-analysis while they met the following criteria: (1) studies with case-control or cohort design; (2) studies evaluated the association of the hOGG1 1245C>G polymorphism with CRC risk; (3) studies with sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). Accordingly, studies with the following characteristics were excluded: (1) case only studies (no control population); (2) studies without sufficient data or lacking of genotypes distribution data; (3) not relevant to the hOGG1 1245C>G polymorphism polymorphisms or CRC; (4) linkage studies and family-based studies (twins and sibling); (5) case reports, abstracts, comments, conference abstracts, editorials, reviews, meta-analysis; and (6) duplicated studies or data. Publications involved with two or more case-control groups were regarded as two or more different studies.

### Data Extraction

Two authors (Mohammad Hosein Antikchi and Seyed Alireza Dastgheib) carefully screened the relevant articles and extracted data independently according to the criteria. Any disagreement was resolved by discussion or consensus by a third author (Hossein Neamatzadeh) when required. The authors collected the following data from each study: first author, publication year, country, ethnicity, source of controls, genotyping method, numbers of cases and controls, genotype frequency of cases and controls, minor allele frequencies, minor allele frequency (MAF) in controls, and Hardy-Weinberg equilibrium (HWE) in controls. Different ethnicities were categorized as Caucasian, Asian, African, and mixed descent. All eligible studies were defined as population-based (PB) or hospital-

based (HB) according to the source of control subjects. If a publication did not present the necessary information, we contacted the corresponding authors by email to request those data.

### Statistical Analysis

The odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were used to assess the strength of the hOGG1 1245C>G polymorphism with susceptibility to CRC in the global population. The significance of the genetic association was measured using a $Z$ test and $p < 0.05$ was considered statistically significant. The association of the hOGG1 1245C>G polymorphism with CRC risk was evaluated under five genetic models, i.e., allele (G vs. C), homozygote (GG vs. CC), heterozygote (GC vs. CC), dominant (GG+GC vs. CC), and recessive model (GG vs. GC+CC), respectively. The existence between-study heterogeneity was assessed using Cochran's $Q$ test. A $p$ value of < 0.1 was interpreted as presence of significant heterogeneity. Moreover, the $I^2$ statistics was used to quantify the variation caused by the heterogeneity, in which $I^2$ value of > 50% was represented as having significant heterogeneity. A fixed-effect model (Mantel-Haenszel method) was used to pool ORs and 95% CI when there was no significant heterogeneity. Otherwise, a random effects model (the DerSimonian and Laird method) was used. Pearson's $\chi^2$ test was applied to test the Hardy-Weinberg equilibrium (HWE) in healthy controls with the significance set at $p < 0.05$. Sensitivity analysis was performed by iteratively deleting one study at a time to identify individual study on overall data and check the stability and robustness of the results. Moreover, sensitivity analysis was performed by removing those studies that were not in agreement with HWE in control groups. Stratification analysis was performed based on ethnicity (Caucasians, Asians, African, and mixed populations), source of controls (HB or PB), genotyping methods, and HWE status. The publication bias was assessed visually inspecting Begg's funnel plot for asymmetry and Egger's linear regression test statistical. An asymmetric plot and $p$ value less than 0.05 suggest a possible publication bias. Statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided $p$ values < 0.05 were considered statistically significant.

## Results

### Characteristics of Studies

Through the primary literature research in online databases, 138 studies were identified. All the fields of the retrieved publications were checked through titles and abstracts. After manually screening the titles, 34 studies were excluded for the reason of duplicates. The flow of study identification, inclusion, and exclusion is shown in Fig. 1. Finally, a total of 24 case-control studies with 77,010 CRC cases and 10,674 controls were selected [19–42]. Table 1 presents the characteristics of all the eligible studies and genotype frequency distributions of the hOGG1 1245C>G polymorphism included in the current meta-analysis. Of the studies included, 13 case-control studies with 4161 CRC cases and 5376 controls were on Caucasians and 11 case-control studies with 2860 CRC cases and 5224 controls were on Asians (Table 1). All the included studies were published between 2003 and 2018 in English (21 studies) and Chinese (three studies). The CRC cases' sample size ranged from 68 to 1582. The included studies were conducted in Korea, Norway, Spain, Singapore, Japan, Czech, the USA, China, Poland, Denmark, Turkey, Pakistan, and Taiwan. Genotyping methods used included PCR-RFLP (11 studies), TaqMan (10 studies), Microarray (one study), PCR-MSSCP (one study), and PCR-CTPP (one study). Thirteen matching for the controls were hospital-based (HB), ten were population-based, and one study did not stated. The distributions of genotypes in the controls of the studies were in Hardy-Weinberg equilibrium except for four studies.

### Quantitative Data Synthesis

Table 2 lists the main results of the meta-analysis of the hOGG1 1245C>G polymorphism and CRC risk. We pooled all the 24 case-control studies to assess the overall association of the hOGG1 1245C>G polymorphism with CRC risk. The combined results showed that the hOGG1 1245C>G polymorphism was significantly associated with an increased risk of CRC under three genetic models, i.e., homozygote (GG vs. CC: OR = 1.229, 95% CI 1.031–1.465, $p = 0.022$; Fig. 2a); heterozygote (GC vs. CC: OR = 1.142, 95% CI 1.008–1.294, $p = 0.037$; Fig. 2b); and dominant (GG+GC vs. CC: OR = 1.162, 95% CI 1.034–1.304, $p = 0.011$; Fig. 2c). In the subgroup analysis by ethnicity, a significant association of the hOGG1 1245C>G polymorphism with susceptibility to CRC was found in the Caucasian populations under three genetic models, i.e., allele (G vs. C: OR = 1.229, 95% CI 1.060–1.415, $p = 0.006$); heterozygote (GC vs. CC: OR = 1.421, 95% CI 1.027–1.966, $p = 0.034$); and dominant (GG+GC vs. CC: OR = 1.239, 95% CI 1.049–1.463, $p = 0.012$), but not in Asian populations (Table 2).

The studies were further stratified on the basis of genotyping technique, source of control subjects, and HWE status. In the PCR-RFLP group, a significantly increased association between the hOGG1 1245C>G polymorphism and CRC risk was observed only under dominant model dominant (GG+GC vs. CC: OR = 1.392, 95% CI 1.038–1.742, $p = 0.019$), but not in the TaqMan subgroup. Moreover, when stratifying by source of controls, we found that the hOGG1 1245C>G polymorphism was significantly associated with increased risk of

**Table 1** Main characteristics of studies included in this meta-analysis

| First author (year) | Country (ethnicity) | Genotyping method | SOC | Case/ control | Cases | | | | | Controls | | | | | MAFs | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Genotype | | | Allele | | Genotype | | | Allele | | | |
| | | | | | CC | CG | GG | C | G | CC | CG | GG | C | G | | |
| Kim 2003 | Korea (Asian) | PCR-RFLP | PB | 125/247 | 24 | 66 | 35 | 114 | 136 | 52 | *131* | *64* | 235 | 259 | 0.524 | 0.320 |
| Hansen 2005 | Norway (Caucasian) | TaqMan | PB | 165/396 | 101 | 55 | 9 | 257 | 73 | 208 | 164 | 24 | 580 | 212 | 0.267 | 0.262 |
| Moreno 2006 | Spain (Caucasian) | Microarray | HB | 362/323 | 225 | 114 | 23 | 564 | 160 | 210 | 104 | 9 | 524 | 122 | 0.188 | 0.360 |
| Stern 2007 | Singapore (Asian) | TaqMan | PB | 303/1159 | 35 | 152 | 116 | 222 | 384 | 183 | 537 | 439 | 903 | 1415 | 0.610 | 0.380 |
| Park 2007 | Korea (Asian) | TaqMan | PB | 439/676 | 91 | 220 | 128 | 402 | 476 | 120 | 333 | 223 | 573 | 779 | 0.576 | 0.823 |
| Kasharan 2008 | Japan (Asian) | PCR-RFLP | PB | 68/121 | 17 | 38 | 13 | 72 | 64 | 39 | 54 | 28 | 132 | 110 | 0.454 | 0.002 |
| Pardini 2008 | Czech (Caucasian) | PCR-RFLP | HB | 532/532 | 336 | 168 | 28 | 840 | 224 | 331 | 181 | 20 | 843 | 221 | 0.207 | 0.437 |
| Curtin 2009 | USA (Caucasian) | TaqMan | PB | 1582/1951 | 918 | 570 | 94 | 2406 | 758 | 1172 | 686 | 93 | 3030 | 872 | 0.223 | 0.563 |
| Ming-Juan 2008 | China (Asian) | PCR-RFLP | PB | 197/835 | 42 | 95 | 60 | 179 | 215 | 179 | 395 | 261 | 753 | 917 | 0.549 | 0.196 |
| Aizhong 2008 | China (Asian) | TaqMan | HB | 345/670 | 68 | 176 | 101 | 312 | 378 | 160 | 338 | 172 | 658 | 682 | 0.508 | 0.810 |
| Sliwinski 2009 | Poland (Caucasian) | PCR-RFLP | HB | 98/100 | 52 | 46 | 2 | 150 | 50 | 68 | 28 | 4 | 164 | 36 | 0.180 | 0.607 |
| Hansen 2009 | Denmark (Caucasian) | TaqMan | PB | 373/776 | 220 | 137 | 16 | 577 | 169 | 467 | 277 | 32 | 1211 | 341 | 0.219 | 0.253 |
| Engine 2010 | Turkey (Caucasian) | PCR-RFLP | HB | 110/116 | 50 | 43 | 17 | 143 | 77 | 51 | 47 | 18 | 149 | 83 | 0.357 | 0.203 |
| Obtulowicz 2010 | Poland (Caucasian) | PCR-SSCP | PB | 74/97 | 38 | 19 | 17 | 95 | 53 | 63 | 33 | 1 | 159 | 35 | 0.180 | 0.139 |
| Brevik 2010 | USA (Caucasian) | TaqMan | PB | 308/362 | 172 | 117 | 19 | 461 | 155 | 217 | 127 | 18 | 561 | 163 | 0.225 | 0.916 |
| Canbay 2011 | Turkey (Caucasian) | PCR-RFLP | HB | 79/247 | 31 | 40 | 8 | 102 | 56 | 171 | 69 | 7 | 411 | 83 | 0.168 | 0.990 |
| Gil 2012 | Poland (Caucasian) | PCR-RFLP | HB | 132/100 | 87 | 41 | 4 | 215 | 49 | 67 | 33 | 0 | 167 | 33 | 0.165 | 0.048 |
| Sameer 2012 | Pakistan (Asian) | PCR-RFLP | HB | 114/200 | 66 | 41 | 7 | 173 | 55 | 100 | 89 | 11 | 289 | 111 | 0.277 | 0.121 |
| Yan 2012 | China (Asian) | PCR-RFLP | HB | 95/80 | 14 | 55 | 26 | 83 | 107 | 22 | 49 | 9 | 93 | 67 | 0.418 | 0.020 |
| Przybylowska 2013 | Poland (Caucasian) | PCR-RFLP | HB | 172/200 | 102 | 67 | 3 | 271 | 73 | 142 | 54 | 4 | 338 | 62 | 0.155 | 0.664 |
| Zhang 2014 | China (Asian) | PCR-CTPP | HB | 247/300 | 44 | 111 | 92 | 199 | 295 | 48 | 139 | 113 | 235 | 365 | 0.608 | 0.631 |
| Lai 2016 | Taiwan (Asian) | TaqMan | HB | 727/736 | 93 | 363 | 258 | 549 | 879 | 125 | 324 | 281 | 574 | 886 | 0.606 | 0.059 |
| Zhang 2018 | China (Asian) | TaqMan | HB | 200/200 | 36 | 82 | 82 | 154 | 246 | 29 | 98 | 73 | 156 | 244 | 0.610 | 0.672 |
| Kabzinski 2018 | Poland (Caucasian) | TaqMan | NS | 174/176 | 52 | 109 | 13 | 213 | 135 | 72 | 84 | 20 | 228 | 124 | 0.352 | 0.543 |

*Abbreviations*: *PCR-RFLP*, polymerase chain reaction restriction fragment length polymorphism; *PCR-SSP*, polymerase chain reaction with sequence-specific primer; *HB*, hospital-based; *PB*, population-based; *NR*, not stated; *MAFs*, minor allele frequencies; *HWE*, Hardy-Weinberg equilibrium

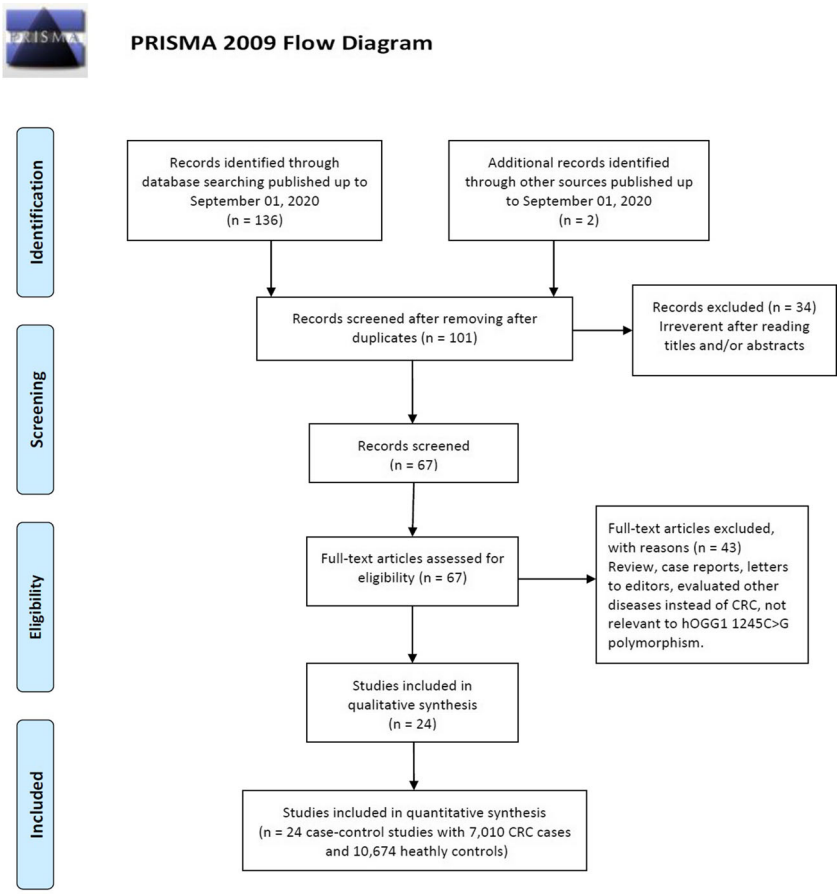


**Fig. 1** Flow chart depicting exclusion/inclusion of individual studies for meta-analysis

CRC risk in the HB subgroup under three genetic models, i.e., homozygote (GG vs. CC: OR = 1.259, 95% CI 1.057–1.833, $p = 0.025$); heterozygote (GC vs. CC: OR = 1.142, 95% CI 1.029–1.540, $p = 0.037$); and dominant (GG+GC vs. CC: OR = 1.251, 95% CI 1.000–1.564, $p = 0.050$), but not in the PB subgroup (Table 2).

## Heterogeneity Test

Between-studies heterogeneity was identified in overall estimations under all five genetic models, i.e., allele (G vs. C: $I^2 = 88.93$, $P_H \leq 0.001$), homozygote (GG vs. CC: $I^2 = 46.47$, $P_H = 0.007$), heterozygote (GC vs. CC: $I^2 = 73.65$, $P_H \leq 0.001$), dominant (GG+GC vs. CC: $I^2 = 73.65$, $P_H \leq 0.001$), and recessive (GC vs. CC: $I^2 = 73.65$, $P_H = 0.002$, Table 2). To examine the potential source of heterogeneity, a subgroup was performed based on ethnicity, source of control, genotyping method, and HWE status. The results revealed that Asians, TaqMan, and population-based (PB) studies contributed to the substantial source of between-study heterogeneity in the present meta-analysis.

## Sensitivity Analysis

Leave-one-out sensitivity analysis was performed to explore individual study's influence on the pooled data. The results revealed that there was no material alteration in corresponding pooled ORs for the hOGG1 1245C>G polymorphism and CRC risk, indicating that the no individual study affected the pooled OR significantly (data not shown). Furthermore, we also performed a sensitivity analysis by excluding those four studies' departure from HWE in healthy subjects. After excluding those studies, there were no changes in the pooled data and still presented a positive under the three genetic models.

## Publication Bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias. In the funnel diagram, publication bias did not exist and the shapes of the plots did not show any evidence of obvious asymmetry under four genetic models, except in the recessive model (Fig. 3). Moreover, Egger's linear regression also did not find significantly statistical evidence of publication bias under four genetic models, i.e., allele

**Table 2** Summary risk estimates for association of hOGG1 polymorphism with CRC risk

| Subgroup | Genetic model | Type of model | Heterogeneity | | Odds ratio | | | | Publication bias | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $I^2$ (%) | $P_H$ | OR | 95% CI | $Z$ test | $P_{OR}$ | $P_{Beggs}$ | $P_{Eggers}$ |
| Overall | G vs. C | Random | 88.93 | ≤ 0.001 | 1.063 | 0.913–1.237 | 0.785 | 0.433 | 0.118 | 0.284 |
| | GG vs. CC | Random | 46.47 | 0.007 | 1.229 | 1.031–1.465 | 2.297 | 0.022 | 0.205 | 0.076 |
| | GC vs. CC | Random | 58.41 | ≤ 0.001 | 1.142 | 1.008–1.294 | 2.082 | 0.037 | 0.286 | 0.285 |
| | GG+GC vs. CC | Random | 56.27 | ≤ 0.001 | 1.162 | 1.034–1.304 | 2.532 | 0.011 | 0.086 | 0.139 |
| | GG vs. GC+CC | Random | 43.96 | 0.012 | 1.111 | 0.966–1.278 | 1.472 | 0.141 | 0.130 | 0.020 |
| Ethnicity | | | | | | | | | | |
| Caucasians | G vs. C | Random | 70.53 | ≤ 0.001 | 1.225 | 1.060–1.415 | 2.749 | 0.006 | 0.023 | 0.107 |
| | GG vs. CC | Random | 50.62 | 0.018 | 1.421 | 1.027–1.966 | 2.120 | 0.034 | 0.582 | 0.222 |
| | GC vs. CC | Random | 67.55 | ≤ 0.001 | 1.183 | 0.993–1.414 | 1.882 | 0.060 | 0.200 | 0.208 |
| | GG+GC vs. CC | Random | 66.30 | ≤ 0.001 | 1.239 | 1.049–1.463 | 2.525 | 0.012 | 0.017 | 0.082 |
| | GG vs. GC+CC | Random | 49.18 | 0.023 | 1.316 | 0.963–1.798 | 1.723 | 0.085 | 0.760 | 0.323 |
| Asians | G vs. C | Random | 92.60 | ≤ 0.001 | 0.888 | 0.689–1.146 | −0.911 | 0.362 | 1.000 | 0.847 |
| | GG vs. CC | Fixed | 39.23 | 0.087 | 1.109 | 0.962–1.279 | 1.426 | 0.154 | 0.755 | 0.435 |
| | GC vs. CC | Fixed | 45.42 | 0.050 | 1.109 | 0.974–1.262 | 1.564 | 0.118 | 0.876 | 0.811 |
| | GG+GC vs. CC | Fixed | 39.35 | 0.086 | 1.080 | 0.957–1.220 | 1.246 | 0.213 | 0.640 | 0.834 |
| | GG vs. GC+CC | Fixed | 21.18 | 0.242 | 0.996 | 0.899–1.104 | −0.072 | 0.942 | 0.212 | 0.105 |
| Genotyping methods | | | | | | | | | | |
| PCR-RFLP | G vs. C | Random | 92.87 | ≤ 0.001 | 1.133 | 0.779–1.647 | 0.652 | 0.514 | 0.275 | 0.013 |
| | GG vs. CC | Random | 46.69 | 0.043 | 1.411 | 0.976–2.039 | 1.832 | 0.067 | 0.275 | 0.221 |
| | GC vs. CC | Random | 68.16 | 0.001 | 1.282 | 0.982–1.675 | 1.824 | 0.068 | 0.212 | 0.135 |
| | GG+GC vs. CC | Random | 68.87 | ≤ 0.001 | 1.344 | 1.038–1.742 | 2.241 | 0.025 | 0.161 | 0.095 |
| | GG vs. GC+CC | Fixed | 35.30 | 0.116 | 1.160 | 0.946–1.422 | 1.425 | 0.154 | 0.436 | 0.276 |
| TaqMan | G vs. C | Random | 80.19 | ≤ 0.001 | 0.965 | 0.840–1.109 | −0.501 | 0.616 | 0.370 | 0.237 |
| | GG vs. CC | Fixed | 9.88 | 0.352 | 1.137 | 0.991–1.304 | 1.834 | 0.067 | 0.210 | 0.413 |
| | GC vs. CC | Random | 58.74 | 0.009 | 1.109 | 0.948–1.296 | 1.295 | 0.195 | 0.850 | 0.850 |
| | GG+GC vs. CC | Fixed | 40.12 | 0.090 | 1.081 | 0.993–1.177 | 1.789 | 0.074 | 1.000 | 0.750 |
| | GG vs. GC+CC | Fixed | 7.95 | 0.369 | 1.007 | 0.906–1.120 | 0.137 | 0.891 | 1.000 | 0.828 |
| Source of controls | | | | | | | | | | |
| HB | G vs. C | Random | 83.77 | ≤ 0.001 | 1.127 | 0.927–1.371 | 1.196 | 0.232 | 0.246 | 0.366 |
| | GG vs. CC | Random | 47.52 | 0.029 | 1.392 | 1.057–1.833 | 2.355 | 0.019 | 0.200 | 0.246 |
| | GC vs. CC | Random | 68.82 | ≤ 0.001 | 1.197 | 0.962–1.490 | 1.616 | 0.106 | 0.582 | 0.506 |
| | GG+GC vs. CC | Random | 66.79 | ≤ 0.001 | 1.259 | 1.029–1.540 | 2.235 | 0.025 | 0.360 | 0.241 |
| | GG vs. GC+CC | Random | 47.14 | 0.030 | 1.251 | 1.000–1.564 | 1.959 | 0.050 | 0.427 | 0.047 |
| PB | G vs. C | Random | 92.86 | ≤ 0.001 | 0.982 | 0.759–1.271 | −0.138 | 0.890 | 1.000 | 0.790 |
| | GG vs. CC | Fixed | 48.91 | 0.040 | 1.124 | 0.882–1.432 | 0.945 | 0.345 | 0.720 | 0.234 |
| | GC vs. CC | Fixed | 14.34 | 0.311 | 1.047 | 0.952–1.151 | 0.940 | 0.347 | 0.858 | 0.865 |
| | GG+GC vs. CC | Fixed | 33.32 | 0.141 | 1.064 | 0.971–1.165 | 1.334 | 0.182 | 0.283 | 0.711 |
| | GG vs. GC+CC | Fixed | 42.60 | 0.074 | 1.020 | 0.899–1.157 | 0.306 | 0.760 | 0.474 | 0.146 |

*Abbreviations*: *PCR-RFLP*, polymerase chain reaction restriction fragment length polymorphism; *HB*, hospital-based; *PB*, population-based

(G vs. C: $P_{Beggs}$ = 0.118 and $P_{Eggers}$ = 0.284), homozygote (GG vs. CC: $P_{Beggs}$ = 0.205 and $P_{Eggers}$ = 0.076), heterozygote (GC vs. CC: $P_{Beggs}$ = 0.286 and $P_{Eggers}$ = 0.285), and dominant (GG+GC vs. CC: $P_{Beggs}$ = 0.086 and $P_{Eggers}$ = 0.139). However, Egger's test showed a significant publication bias under the recessive genetic model (GC vs. CC: $P_{Beggs}$ = 0.130 and $P_{Eggers}$ = 0.020). In addition, subgroup analysis by genotyping method in PCR-RFLP studies showed that there was a significant publication bias in the allele model ($P_{Beggs}$ = 0.275 and $P_{Eggers}$ = 0.013, Table 2). Therefore, we performed the Duval and Tweedie non-parametric "trim and fill" method to adjust for publication bias. The results showed that the

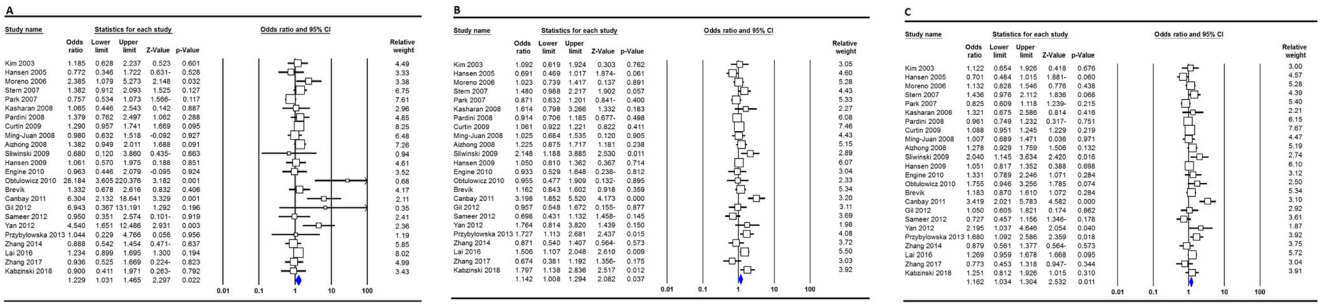


**Fig. 2** Forest plots for association of hOGG1 1245C>G polymorphism with risk of CRC in overall population. a Homozygote model (GG vs. CC). b Heterozygote model (GC vs. CC). c Dominant model (GG+GC vs. CC)

meta-analysis with and without "trim and fill" did not draw different outcomes, indicating that the current meta-analysis results were statistically robust.

## Minor Allele Frequencies

The minor allele frequencies (MAFs) of the hOGG1 1245C>G polymorphism by ethnicity are presented in Table 1. The allele and genotype distributions of the hOGG1 1245C>G polymorphism showed ethnic variations. The hOGG1 1245G allele frequencies in the Asians and Caucasians were 44.35% (27.70–61.0%) and 25.60% (15.50–35.70%), respectively. Therefore, the MAFs of the hOGG1 1245C>G polymorphism in Caucasians were less than Asians.

## Discussion

CRC is determined by the complex interaction between strong genetic components and environmental factors. Genetic variations in a component of base excision repair (BER) pathway may represent a suitable marker for identifying individual's susceptibility to CRC. The hOGG1 gene is an important part

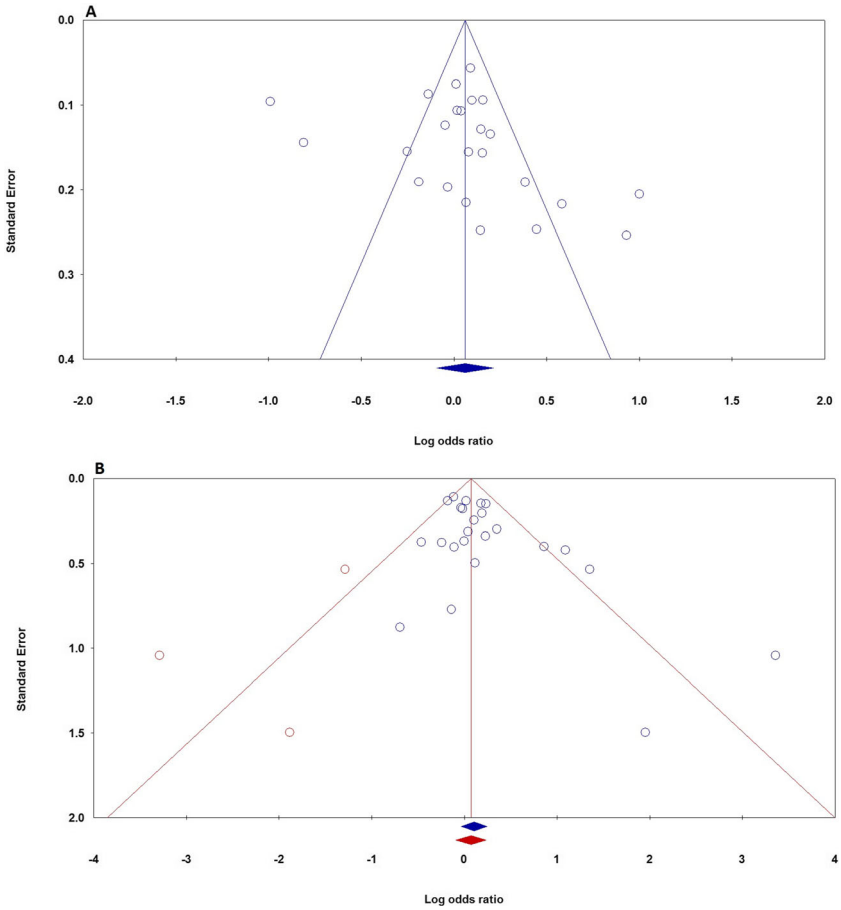


**Fig. 3** Funnel plot for the detection of the publication bias for association of the hOGG1 1245C>G polymorphism with CRC risk in the overall population. a Allele model (G vs. C). b Recessive model (GG vs. GC+CC)

in the BER pathway of DNA repair. An increasing number of studies suggested that hOGG1 1245C>G polymorphism may play an important role in susceptibility to CRC. However, those study results on the association of the hOGG1 1245C>G polymorphism with CRC susceptibility had controversial results due to the small sample size and subsequently suffer from too low power. Anyway, none of the published meta-analyses has enrolled all the available studies and newly published data. In the present meta-analysis, a total of independent 24 case-control studies including 7021 CRC cases and 10,600 controls were recruited, and then identified the association the hOGG1 1245C>G polymorphism with CRC risk. In addition, in a stratified analysis by ethnicity, in the three genetic models, significant increased risks of CRC were found in Caucasians, but not in Asians. The last finding might be explained by a possible role of ethnic differences in genetic background. In addition, the relevant environmental exposure in Asia may differ from that in Caucasian populations. Further well-designed studies involving different ethnicities may help answer this finding.

At present, several meta-analyses have been performed to identify the association of the hOGG1 1245C>G polymorphism with CRC based on previous published studies. However, our results are different from most recently published meta-analyses. In 2015, Sun et al. performed a meta-analysis of 16 studies including 4866 CRC cases and 7363 controls to evaluate the hOGG1 1245C>G polymorphism and the susceptibility to CRC. However, their results did not show any evidence of significant association between the hOGG1 1245C>G polymorphism and CRC risk [43]. However, when including ten additional studies which have strong significant association of the hOGG1 1245C>G polymorphism with CRC risk, our meta-analysis revealed statistically significant association between the hOGG1 1245C>G and CRC risk. Similarly, in 2014, Wang et al., in a meta-analysis of 14 case-controls, have found a significant association between the hOGG1 1245C>G polymorphism and the risk of CRC only under the dominant genetic model (GG+GC vs. CC: OR = 1.17, 95% CI 1.00–1.37, $p \leq 0.001$) [44]. However, considering the limited number of case-control studies, those meta-analyses' results on the hOGG1 1245C>G and CRC risk essentially might be underpowered. Moreover, compared with those meta-analyses, we have also performed stratified analysis by ethnicity, genotyping method, and source of controls.

As a meta-analysis, between-studies heterogeneity should be considered and finding the source of heterogeneity is very important for the final outcomes of a meta-analysis [45–47]. Some of the most important potential sources of heterogeneity in a genetic association meta-analysis are the genetic backgrounds for cases and controls, selection criteria for the cases and controls, genotyping methods, source of controls, diverse genotype distribution of a SNP, environmental exposures, and sample size. In the present meta-analysis, a significant between-study heterogeneity was found under all five genetic models in the overall estimation. Through conducting subgroup analyses, we found that ethnicity (Asians), genotyping method (TaqMan), and source of controls (population based) might be contributed to the substantial observed heterogeneity in the present meta-analysis. Another potential problem which may have a negative effect on the current meta-analysis was the publication bias. However, after adjustment using the "trim and fill" method, the result was stable in the direction of the effect, and still presented a significant association, indicating that the publication bias has little effect on our results and the present meta-analysis conclusions are relatively stable and reliable.

To the best of our knowledge, we have included significantly more number of studies to the previous meta-analysis study by using a strict searching strategy which combines online databases with manual search making the eligible studies included as much as possible. In addition, in this meta-analysis, we have well designed and performed the process of literature search, data extraction, and statistical analysis. Nevertheless, there were still several limitations that should be taken into consideration in the current meta-analysis. First, as only Caucasian and Asian populations were involved in the present meta-analysis, this meta-analysis was in lack of African and mixed populations; the results might not suit for other ethnicities. Therefore, more studies based other ethnicities were required to be included in this study to obtain a more comprehensive result. Second, there was a significant heterogeneity under all five genetic models, although we performed the pooled analysis with severe inclusion criteria and explicit extraction data. Third, publication bias may exist in the present meta-analysis; however, after adjustment using the "trim and fill" method, the result was stable in the direction of the effect, and still presented a significant association. Fourth, the result of this meta-analysis was based on unadjusted ORs due to lack of relevant data across the included studies, and stratified analysis cannot be conducted by age, sex, smoking, physical activity, overweight or obesity, alcohol use, and other factors. Fifth, because of the complex etiology of CRC, it is unlikely that a single polymorphism in the hOGG1 gene would be obviously associated with an increased risk of CRC, and whether additional polymorphisms of this gene or other susceptible genes may lead to underestimation of its overall genetic effect on susceptibility to CRC. Finally, the interaction of different susceptibility genes and environment factors lead to CRC, but our study could not assess gene-gene and gene-environment interactions due to the limited information of included studies.

In summary, the current meta-analysis indicated that the hOGG1 1245C>G polymorphism might be a risk factor for susceptibility to CRC, especially in Caucasians. In the future, more well-designed studies that consider confounding factors in larger sample sizes should be conducted to re-evaluate the

associations of the hOGG1 1245C>G polymorphism with CRC risk in different ethnicities.

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**Author Contribution** Y.G. and F.A. are responsible as the guarantor of integrity of the entire study, study design and concepts, definition of intellectual content, and literature research. M.H.A. and S.A.D. are responsible for the clinical studies, experimental studies, data acquisition, and manuscript preparation. S.H.S and J.J.N. are responsible for the data analysis, statistical analysis, and manuscript review. H.N and Y.G are responsible for the manuscript editing. All authors have read and agreed with the final version of this manuscript.

## Compliance with Ethical Standards

An ethical approval or patient consent was not needed because this is a meta-analysis in which all data were extracted from published literature.

**Conflict of Interest** The authors declare that they have no conflict of interest.

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