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Original Article

Genetic association between *hOGG1* C8069G polymorphism and colorectal cancer risk

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Abstract: Background: *hOGG1* C8069G polymorphism has been extensively investigated in single studies as well as meta-analyses in terms of the association with colorectal cancer (CRC). But the results remain contradictory. This study was undertaken to comprehensively evaluate the association of the commonly studied *hOGG1* C8069G polymorphism and the susceptibility to CRC. Methods: By searching the electronic databases of PubMed, Embase, and Web of science, 16 available publications consisting of 4,866 cases and 7,363 controls were finally included in our meta-analysis. Stratified analyses by ethnicity and source of control were also carried out to further assess the association between *hOGG1* C8069G polymorphism and CRC risk. Results: *hOGG1* C8069G polymorphism was not observed to have statistical significance with the susceptibility to CRC ($OR_{CC\ vs.\ GG}$ = 0.97, 95% CI = 0.91-1.05; *P* = 0.995; $OR_{CC + CG\ vs.\ GG}$ = 0.98, 95% CI = 0.93-1.04; *P* = 0.993; $OR_{CC\ vs.\ CG + GG}$ = 0.96, 95% CI = 0.90-1.02; *P* = 0.339; $OR_{allele\ C\ vs.\ allele\ G}$ = 0.98, 95% CI = 0.94-1.02; *P* = 0.912; $OR_{CG\ vs.\ GG}$ = 0.95, 95% CI = 0.88-1.03; *P* = 0.526). Similarly, no association was found in the subgroup analysis by ethnicity or the source of control. Conclusions: The results of our meta-analysis did not demonstrate any evidence for significant association between *hOGG1* C8069G polymorphism and CRC risk. Future large-scale studies are expected to be conducted to further confirm our findings.

Keywords: *hOGG1*, C8069G, CRC, polymorphism, susceptibility

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide, leading to the overwhelming majority of deaths in relation to cancer [1]. Of the complex etiology of CRC, exposure to assaults from common environmental risk factors and various endogenous and exogenous mutagens or carcinogens have been evidenced to be the major contributions for the susceptibility to CRC [2-4]. Among the threatening agents, oxidant is the most common one that could induce genomic instability, and causes damage to DNA and mutations, activation of oncogenes as well as inactivation of tumor suppressor genes, or carcinogenesis [5, 6]. So the repair of DNA plays a key role in genome stability that is closely related to cancer risk including the CRC.

DNA 8-hydroxydeoxyguanine caused by oxidative stress is mutagenic or carcinogenic, leading to G: C to T: A transversions. The 8-hydroxydeoxyguanine lesions undergo the base-excision repair, particularly by a critical enzyme the 8-oxoguanine DNA glycosylase that is essential in the repair of 8-oxoguanine and other oxidative DNA damages [7]. *hOGG1* gene on chromosome 3p26, plays an important role in DNA repair by various processes [8, 9].

Many previous studies have investigated several polymorphisms of *hOGG1* gene, such as 2 homozygous mutations at codons 85 and 131, codon 46 Arg/Gln, codon 154 Arg/His, codon 229 Arg/Gln, 7143A/G and 11657A/G [10-14]. However, the most frequently explored polymorphism is *hOGG1*, which has been extensively investigated in single studies as well as meta-analysis in terms of the association with CRC.

Table 1. Main characteristics of all studies included in the meta-analysis

First author	Country	Ethnicity	Control source	Genotyping method	Case sample size	Control sample size	HWE
Kim	Korea	Asian	PB	PCR-RFLP	125	247	0.320
Hansen	Norway	Caucasian	PB	TaqMan	165	396	0.262
Moreno	Spain	Caucasian	HB	PCR-RFLP	362	323	0.360
Stern	Singapore	Asian	PB	TaqMan	303	1159	0.380
Park	Korea	Asian	PB	TaqMan	439	676	0.823
Kasahara	Japan	Asian	PB	PCR-RFLP	68	81	0.002
Pardini	Czech	Caucasian	HB	PCR-RFLP	532	532	0.437
Curtin	USA	Caucasian	PB	TaqMan	1582	1951	0.563
Sliwinski	Poland	Caucasian	HB	PCR-RFLP	100	100	0.607
Hansen	Denmark	Caucasian	PB	TaqMan	373	776	0.253
Engin	Turkey	Asian	HB	PCR-RFLP	110	116	0.203
Obtulowicz	Poland	Caucasian	PB	PCR-RFLP	74	97	0.139
Brevik	USA	Caucasian	PB	TaqMan	308	362	0.916
Canbay	Turkey	Asian	PB	PCR-RFLP	79	247	0.990
Gil	Polish	Caucasian	HB	PCR-RFLP	132	100	0.048
Sameer	India	Asian	HB	PCR-RFLP	114	200	0.121

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium.

But the results of them remain contradictory. Some provided evidence for significant association between *hOGG1* polymorphism and CRC risk [15-19], while the others indicated no significance [20-26]. This might be caused by the limited samples in these studies, thus an updated meta-analysis with more study subjects was performed to confirm the association between the *hOGG1* polymorphism and CRC risk.

Materials and methods

Literature search strategy

To extract all publications on the association between *hOGG1*C8069G polymorphism and CRC risk, we searched the electronic databases of the PubMed, Embase, and Web of Science until February 2014. The terms used in the search were "*hOGG1*", or "C8069G", "polymorphism" or "genetic variation", and "colorectal cancer". Additional relevant publications were manually screened in the references of each publication. The eligible studies included in the meta-analysis were limited to English and conducted on human subjects. Moreover, we contacted the authors of the literature when crucial data were not reported in the original papers. If more than one publication were conducted on the same patient populations, only the latest and the largest one was selected.

Inclusion and exclusion criteria

The inclusion criteria used in our meta-analysis were as follows: (1) a case-control design; (2) an investigation of the association between *hOGG1* C8069G polymorphism and colorectal cancer risk; (3) adequate data on the numbers of case and control group; (4) clear numbers of the genotypes. The following were the designed exclusion criteria: (1) the studies on the colon or rectal cancer; (2) case-only study; (3) abstracts, editorials, letters, and review articles. In the end, 16 qualified studies were selected in this meta-analysis.

Data extraction

Two authors extracted the data independently. The extracted data from each study included first author, journal, year of publication, study country, source of control, ethnicity, genotyping method, the numbers of total study subjects in cases and controls, information on the distribution of genotypes, and the selection and characteristics of cancer cases and controls. The differences emerging in the search were resolved by discussion until consensus was reached.

Table 2. Meta-analysis results for *hOGG1* C8069G polymorphism and CRC risk

	CC vs. GG		CC + CG vs. GG		CC vs. CG + GG		Allele C vs. Allele G		CG vs. GG	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Ethnicity										
Asian	0.98 (0.82, 1.16)	0.807	0.98 (0.88, 1.09)	0.723	0.90 (0.77, 1.05)	0.049	0.98 (0.90, 1.07)	0.487	1.02 (0.90, 1.15)	0.999
Caucasian	0.97 (0.90, 1.05)	0.990	0.98 (0.92, 1.05)	0.997	0.97 (0.90, 1.04)	0.902	0.98 (0.93, 1.03)	0.945	0.91 (0.82, 1.01)	0.159
Control source										
Population	0.97 (0.89, 1.06)	0.873	0.98 (0.92, 1.05)	0.854	0.95 (0.88, 1.02)	0.112	0.98 (0.93, 1.02)	0.577	0.95 (0.87, 1.04)	0.133
Hospital	0.98 (0.85, 1.12)	1.000	0.98 (0.88, 1.10)	1.000	0.99 (0.88, 1.12)	0.843	0.99 (0.91, 1.07)	0.985	0.95 (0.80, 1.14)	0.998
Total	0.97 (0.91, 1.05)	0.995	0.98 (0.93, 1.04)	0.993	0.96 (0.90, 1.02)	0.339	0.98 (0.94, 1.02)	0.912	0.95 (0.88, 1.03)	0.526

P_h: *P*-value of heterogeneity test. CI, confidence interval; OR, odds ratio.

Meta-analysis

The odds ratios (ORs) of CRC in relation to *hOGG1* C8069G polymorphism were detected for the single studies separately. As for *hOGG1* C8069G polymorphism, we evaluated the risk of the following five genetic models: CC vs. GG, CC + GG vs. GG, CC vs. CG + GG, allele C vs. allele G, CG vs. GG, respectively. Apart from the comparisons for total subjects, stratified analyses by ethnicity and the source of control were also performed.

Statistical analysis

The crude odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were calculated for each study. We also estimated the between-study heterogeneity across the eligible comparisons using the X^2-based Q test [27] and $P < 0.1$ was considered significant. The combined values of the included studies were estimated by fixed-effects model [28] or random-effects model [29]. The former was adopted if $P > 0.1$, or the latter was used. The funnel plots and Egger's test were used to detect publication bias [30]. Hardy-Weinberg equilibrium (HWE) was tested by the chi-square test. To evaluate the effects of single studies on the overall CRC risk, sensitivity analysis was used by excluding one study each time independently and recalculating the ORs and 95% CIs. All statistical analyses were performed by STATA version 12.0 (Stata Corporation, College Station, TX). All the tests were two-sided and $P < 0.1$ was considered statistically significant.

Results

Studies characteristics

At the end of our literature search, there were actually 21 selected studies in total. But five studies were excluded because three of them failed to provide enough information about genotype distribution [31-33] and two were reviews [34, 35]. Thus this updated meta-analysis was conducted on the basis of 16 case-control eligible studies including 4,866 cases and 7,363 controls. The basic information like first author, year of publication, country, ethnicity, source of control, genotyping methods, numbers of cases and controls, distribution of genotypes and alleles, and HWE were all presented in **Table 1**. Of the included 16 studies, seven were conducted on Asians [18, 21, 25, 26, 36, 37] and 9 on Caucasians [15-17, 20, 22-24, 38, 39]. For the source of control, ten were population-based [16, 17, 21, 23, 39, 40] and six were hospital-based [15, 18, 20, 22, 24-26, 36-38]. All cases were histopathologically confirmed and controls were matched with the cases by age, gender and other variables. The PCR-RFLP was most commonly performed in genotyping among the individual studies.

Meta-analysis results

The genotyping data of *hOGG1* C8069G polymorphism were obtained from 16 publications. There was no between-study heterogeneity across the eligible comparisons in the meta-analysis, so the fixed-effects model was selected to calculate the pooled ORs. As showed in **Table 2**, pooling all eligible studies into the meta-analysis, we observed that there was no evidence for significant association between *hOGG1* C8069G polymorphism and overall CRC risk ($OR_{CC\ vs.\ GG}$ = 0.97, 95% CI = 0.91-1.05; P = 0.995; $OR_{CC + CG\ vs.\ GG}$ = 0.98, 95% CI = 0.93-1.04; P = 0.993; $OR_{CC\ vs.\ CG + GG}$ = 0.96, 95% CI = 0.90-1.02; P = 0.339; $OR_{allele\ C\ vs.\ allele\ G}$ = 0.98, 95% CI = 0.94-1.02; P = 0.912; $OR_{CG\ vs.\ GG}$ = 0.95, 95% CI = 0.88-1.03; P = 0.526). In addition, neither significant association was observed in the stratified analysis based on ethnicity, nor in the

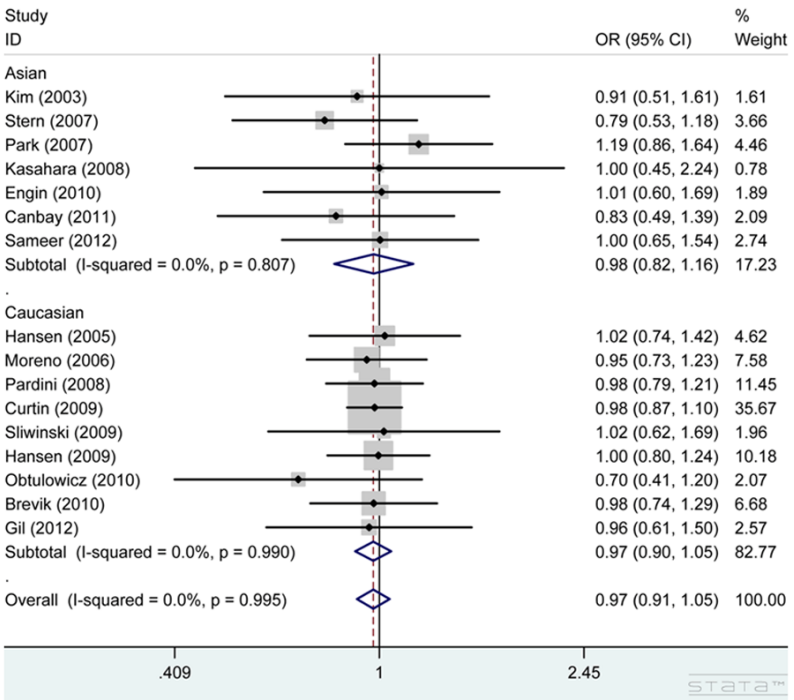

Figure 1. The fixed-effects model.

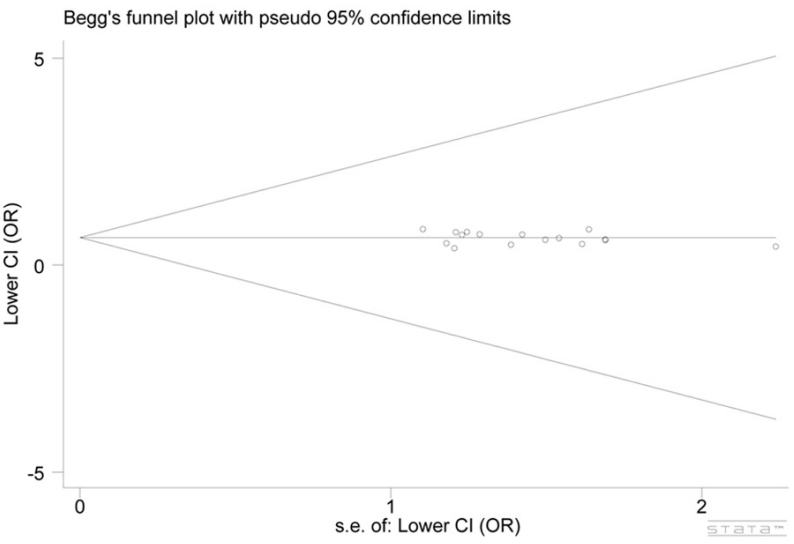

Figure 2. The funnel plot.

subgroup analysis by source of control (**Figure 1**).

Heterogeneity and sensitivity analyses

No between-study heterogeneity was observed among overall studies of *hOGG1* C8069G polymorphism in all genetic models ($P > 0.1$). In the sensitivity analyses, we examined the effects of each study on the pooled OR by repeatedly omitting one study at a time and recalculating the ORs, which confirmed the stability of our results. Two of the 16 studies, whose genotype distributions deviated from HWE, did not apparently affect the overall result of the meta-analysis.

Publication bias

Begg's funnel plot and Egger's test were carried out to evaluate the publication bias of all included studies. The symmetrical shape of the funnel plot suggested that there was no obvious publication bias (**Figure 2**). Meanwhile, the Egger's test further indicated that there existed no significant publication bias in this meta-analysis (the Egger's test: CC vs. GG: $P = 0.284$, Begg's test: $P = 0.344$).

Discussion

In this meta-analysis, all available single studies were summarized to examine the combined association of the well-characterized polymorphism of *hOGG1* C8069G and overall CRC risk. A large number of studies have been devoted to investigating whether *hOGG1* C8069G polymorphism was associated with the susceptibility to CRC. Some authors, such as Curtin et al. suggested that *hOGG1* C8069G polymorphism was not significantly associated with CRC susceptibility [20-26, 36-39]. In contrast, different findings were reported in several other publications [15-18]. Meanwhile, conflicts were also indicated in four meta-analysis. Three of them held the same view with Curtin et al. [41-43], yet one study supported that the *hOGG1* C8069G polymorphism was associated with an increased CRC

susceptibility in different genetic models [40]. The inconsistent results may attribute to the various study designs and the relatively smaller sample of each individual studies and meta-analysis.

Compared with the four previous meta-analyses, the current study has two advantages: (1) we included newly published data; (2) the sample size increased by 246 in CRC cases and 388 in control subjects because of the new data. The strengths provided more convincing evidence for the association between *hOGG1* C8069G polymorphism and CRC risk. Our meta-analysis indicated that *hOGG1* C8069G polymorphism was not a risk factor for the susceptibility to CRC. This is supported by Kim et al. [20-26, 36-43], and simultaneously opposed by other studies [15-19]. The carcinogenesis of cancer including CRC is complicated and multifactorial. The possible explanation for the etiology of CRC is continual exposure to risk factors such as polluted environment and chemical carcinogens, which could lead to gene mutation and carcinogenesis. Therefore, the role of *hOGG1* C8069G polymorphism in CRC risk is expected to be further examined in future gene-to-environment association studies.

To further confirm our finding, we conducted subgroup analyses by ethnicity and the source of control. In the stratified analysis of ethnicity, no association was observed in both Asians and Caucasians under all genetic models. However, Wei et al. found that the *hOGG1* C8069G polymorphism was associated with overall cancer risk in Asians ($OR_{GG\ vs.\ CC}$ = 1.21, 95% CI = 1.10-1.33, $P_{heterogeneity}$ = 0.001) [42]. In addition, Guo et al. indicated that significantly increased risks were found among European plus American subjects, who are mostly Caucasian ($OR_{GG\ vs.\ CG\ +\ CC}$ = 1.444; 95% CI = 1.017-2.05, *P* = 0.04) [41]. The frequencies of allele G differs substantially in Asians and Caucasians (49.3% vs. 77.8%), indicating that the distribution of the allele was obviously different in the ethnic groups. Such a difference might alter the association of *hOGG1* C8069G and the cancer risk, which might provide evidence for the disagreements.

In the subgroup analysis by source of control, neither did we find significant evidence that *hOGG1* C8069G polymorphism was correlated with CRC risk in both hospital-based studies and population-based ones. The selection criteria of control subjects are not the same in the single studies included in our meta-analysis, thus masking the potential association. So it is of great importance to select studies with representative control subjects in the genotype association studies.

There were some limitations in our meta-analysis. Firstly, lack of the original data of the included studies limited our further estimation of the potential interactions like gene-environmental interaction that may contribute to cancer risk, which has been identified in several single studies [22, 37]. Secondly, we included only published studies in the meta-analysis, thus leading to publication bias, even if it was not indicated in the statistical test. Thirdly, in the subgroup analysis, the relatively small sample possibly underpowered the association between *hOGG1* C8069G polymorphism and CRC risk.

In conclusion, our meta-analysis provided no evidence that *hOGG1* C8069G polymorphism was significantly associated with the susceptibility to CRC, neither in the stratification analysis by ethnicity and source of control. Our study focused only on the effects of a single gene, so further multi-gene and gene-environment association studies should be carried out to yield a more comprehensive understanding of the association between the *hOGG1* C8069G polymorphism and cancer susceptibility.

Disclosure of conflict of interest

None.

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