Association Between Six Genetic Polymorphisms and Colorectal Cancer: A Meta-Analysis

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Objective: The aim of this study was to determine whether six genetic polymorphisms confer susceptibility to colorectal cancer (CRC). **Methods:** A systematic search for candidate genes of CRC was performed among several online databases, including PubMed, Embase, Web of Science, the Cochrane Library, CNKI, and Wanfang online libraries. After a comprehensive filtering procedure, we harvested five genes, including *MGMT* (rs12917 and rs2308321), *ADH1B* (rs1229984), *SOD2* (rs4880), *XPC* (rs2228001), and *PPARG* (rs1801282). Using the REVMAN and Stata software, six meta-analyses were conducted for associations between CRC and the just-mentioned genetic variants. **Results:** A total of 34 comparative studies among 17,289 cases and 54,927 controls were involved in our meta-analyses. Significant association was found between *ADH1B* rs1229984 polymorphism and CRC ($p=0.03$, odds ratio [OR]=1.18, 95% confidence interval [CI]=1.01–1.36). We also found significant association between *PPARG* rs1801282 polymorphism and CRC ($p=0.004$, OR=1.498, 95% CI=1.139–1.970), and this significant association is specific in Caucasians ($p=0.004$, OR=1.603, 95% CI=1.165–2.205). **Conclusions:** The current meta-analysis has established that *ADH1B* (rs1229984) and *PPARG* (rs1801282) are two risk variants of CRC.

Introduction

COLORRECTAL CANCER (CRC) is the second leading cause of cancer deaths in the world (Siegel *et al.*, 2011). Twin studies suggested a heritability of ~35% for CRC (Lichtenstein *et al.*, 2000). CRC is characterized by various forms of gene mutations, accompanied by genome instability, including chromosomal instability and microsatellite instability (Lao and Grady, 2011). CRC development is a multi-step and complex process involving with the accumulation of genetic and epigenetic changes (Lao and Grady, 2011; Migheli and Migliore, 2012), especially at the early stage of CRC (van Engeland *et al.*, 2011). Histopathology classification of CRC is divided into glandular epithelium carcinoma, squamous cell carcinoma, and carcinoid tumor (Armaghany *et al.*, 2012). The major clinical symptoms of CRC include hematochezia, bowel habit changing, and bowel obstruction (Tomlinson *et al.*, 2012). The treatment of CRC is a comprehensive therapy, including surgery, chemotherapy, and radiation therapy (Inoue *et al.*, 2009). Despite the best

efforts and hard work of researchers and clinicians, most CRC patients still have a poor prognosis (Luo *et al.*, 2012).

O⁶-methylguanine-DNA methyltransferase (MGMT) is involved in the direct damage-reversal pathway, which repairs damaged DNA and thus decreases cancer risk (Loh *et al.*, 2011). Aldehyde dehydrogenase-2 (ADH1B) is a major enzyme involved in the alcohol-metabolizing pathways, and ADH1B can metabolize acetaldehyde into acetic acid for detoxification (Yang *et al.*, 2009). Although a meta-analysis reported that *ADH1B* genetic polymorphisms can increase the risk of cancers of the upper aerodigestive tract, including the oral cavity, pharynx, larynx, and esophagus (Guo *et al.*, 2012), there was a lack of summary for *ADH1B* variants in the susceptibility of CRC. Superoxide dismutase 2 (*SOD2*) is a vital gene involved in the oxidative stress pathway, and is implicated in CRC development by affecting cellular processes (Funke *et al.*, 2009). The xeroderma pigmentosum complementation group C (*XPC*) gene plays an important role in DNA damage recognition and repairing (Wu *et al.*, 2011). *PPARG* plays a key role in the regulation of lipid,

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glucose metabolism, and selected insulin-sensitizing and anti-inflammatory effects (Tsilidis *et al.*, 2009).

Associations between six single-nucleotide polymorphisms (SNPs) of the earlier-mentioned five genes and CRC have been reported in different ethnic groups (Smith *et al.*, 2001; Landi *et al.*, 2003, 2005; Krzesniak *et al.*, 2004; Jiang *et al.*, 2005; McGreavey *et al.*, 2005; Murtaugh *et al.*, 2005; Slattery *et al.*, 2005, 2006; Berndt *et al.*, 2006; Huang *et al.*, 2006; Koh *et al.*, 2006; Kuriki *et al.*, 2006; Matsuo *et al.*, 2006; Moreno *et al.*, 2006; Theodoropoulos *et al.*, 2006; Tranah *et al.*, 2006; Hansen *et al.*, 2007; Kang *et al.*, 2007; Stern *et al.*, 2007; Vogel *et al.*, 2007; Yin *et al.*, 2007; Kury *et al.*, 2008; Funke *et al.*, 2009; Khatami *et al.*, 2009; Tsilidis *et al.*, 2009; Yang *et al.*, 2009; Engin *et al.*, 2010; Meplan *et al.*, 2010; Loh *et al.*, 2011; Wu *et al.*, 2011; Crous-Bou *et al.*, 2012; Gil *et al.*, 2012). These six variants comprised rs12917 and rs2308321 of *MGMT*, rs1229984 of *ADH1B*, rs4880 of *SOD2*, rs2228001 of *XPC*, and rs1801282 of *PPARG*.

Numerous studies have shown the association of the just-mentioned genetic polymorphisms with CRC. Since the allelic frequencies of genes often differ substantially in different ethnic groups, meta-analysis may help compare the genetic associations in different populations. In the present study, we perform meta-analyses to evaluate the contribution of the six polymorphisms to CRC susceptibility in different populations. The goal of our study is to summary the contribution of rs12917 and rs2308321 of *MGMT*, rs1229984 of *ADH1B*, and rs4880 of *SOD2*, and to update the meta-analyses for rs2228001 of *XPC* (He *et al.*, 2013) and rs1801282 of *PPARG* (Xu *et al.*, 2010).

Materials and Methods

Literature search

We searched publications in the electronic databases (including PubMed, Embase, Web of Science, the Cochrane Library, CNKI, and Wanfang online libraries) from 2000 to 2013. We used combinations of text words and medical subject headings, including “colorectal cancer” or “colorectal carcinoma” together with “SNP” or “polymorphism” or “variant” or “mutation.” The titles and abstracts were screened to collect the relative case-control or cohort studies.

Full-text articles were read through to get useful information including ORs, 95% confidence intervals (CIs), and genotyping data to estimate the relative risk. References of the articles were also checked for other studies of potential relevance. After a comprehensive literature research, a total of 34 studies on six SNPs were selected in the current meta-analysis. For the meta-analysis of *PPARG* rs1801282, there are four additional association studies of CRC after the previous meta-analysis (Xu *et al.*, 2010). Other meta-analyses were involved with the SNP that was reported by at least three independent association studies and had no previous meta-analysis concerning CRC.

Inclusion criteria

Studies should meet all of the following criteria: (1) be a case-control or cohort study, (2) assess the contribution of the six polymorphisms with CRC risk, (3) provide the allele frequency or genotype distribution data, (4) be an independent study, and (5) be published in the peer-reviewed journal.

Data extraction

The data retrieved from the corresponding articles included first author's name, year of publication, study design, ethnicity, genotyping method, the number of cases and controls, country of the study, and genotyping platform.

Statistical analysis

Meta χ^2 tests were used to calculate the trend, odds ratios (OR), and empirical 95% CIs using REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom) and STATA (version 10.0; Stata Corporation, College Station, TX). We calculated power using PS: Power and Sample Size Calculation (version 3.0, 2009, by William D. Dupont and Walton D. Plummer, Jr.) (Dupont and Plummer, 1990). The power calculation is based on the sample size in the case-control study. Cochran's Q statistic was used to evaluate the heterogeneity of studies involved in the meta-analysis (DerSimonian and Laird, 1986). I^2 statistic was applied to demonstrate the proportion of the total variation owing to heterogeneity. For $I^2 < 50\%$, a fixed-effect

FIG. 1. Flow diagram for selection of studies.

TABLE 1. POLYMORPHISMS AND CHARACTERISTICS OF STUDIES INVOLVED IN THIS META-ANALYSIS

SNP	Author (published year)	Ethnicity	Genotyping platform	Cases		Controls		OR (95% CI)	p
				AA/AB/BB	A/B	AA/AB/BB	A/B		
rs1229984 (Arg47His)	Yin (2007)	Asian	PCR-RFLP	345/294/40	984/374	452/289/37	1193/363	1.24 (0.98, 1.58)	0.03
	Yang (2009)	Asian	PCR-RFLP	205/181/39	591/259	370/319/62	1059/443	1.05 (0.81, 1.36)	
	Matsuo (2006)	Asian	PCR-CTPP	136/102/19	374/140	473/259/36	1205/331	1.36 (0.98, 1.88)	
	Landi (2005)	Caucasian	Microarray	292/54/2	638/58	263/48/3	574/54	0.97 (0.56, 1.67)	
rs4880 (Val16Ala)	Meplan (2010)	Caucasian	KASPar	172/358/189	702/736	165/318/174	648/666	0.98 (0.79, 1.21)	0.33
	Kang (2007)	Caucasian	TaqMan assay	275/578/297	1128/1172	376/686/320	1438/1326	0.89 (0.76, 1.04)	
	Kang (2007)	African	TaqMan assay	31/57/15	119/87	122/194/79	438/352	1.12 (0.72, 1.74)	
	Funke (2009)	Caucasian	PCR-RFLP	136/321/166	593/653	146/294/163	586/620	0.96 (0.77, 1.21)	
	Landi (2005)	Caucasian	Microarray	94/164/77	352/318	88/151/64	327/279	1.06 (0.77, 1.45)	
	Khatami (2009)	Asian	Pyrosequencing	40/160/0	240/160	61/140/0	262/140	1.25 (0.83, 1.87)	
rs12917 (Leu84Phe)	Moreno (2006)	Caucasian	Microarray	213/47/12	473/71	225/63/11	513/85	0.91 (0.56, 1.46)	0.66
	Stern (2007)	Asian	TaqMan assay	251/40/1	542/42	959/194/13	2112/220	0.74 (0.46, 1.21)	
	Tranah (2004)	Caucasian	TaqMan assay	351/80/12	782/104	1964/564/38	4492/640	0.93 (0.68, 1.28)	
	Khatami (2009)	Asian	Pyrosequencing	125/74/1	324/76	146/52/2	344/56	1.44 (0.85, 2.46)	
rs2308321 (Ile143Val)	Moreno (2006)	Caucasian	Microarray	290/63/6	643/75	261/61/1	583/63	1.08 (0.66, 1.77)	0.54
	Tranah (2004)	Caucasian	TaqMan assay	367/76/7	810/90	1962/563/57	2012/677	0.18 (0.12, 0.25)	
	Engin (2009)	Asian	PCR-RFLP	22/63/25	107/113	25/55/36	105/127	0.87 (0.52, 1.47)	
rs2228001 (Lys939Gln)	Hansen (2007)	Caucasian	End-point PCR	141/204/50	486/304	307/392/98	1006/588	1.07 (0.83, 1.37)	0.24
	Gil (2012)	Caucasian	PCR-RFLP	48/71/14	167/99	43/46/11	132/68	1.17 (0.68, 2.01)	
	Berndt (2006)	Caucasian	TaqMan assay	81/110/53	272/216	18,493/8815/1211	45,801/11,237	3.24 (2.51, 4.17)	
	Wu (2011)	Asian	PCR-RFLP	155/204/61	514/326	363/375/104	1101/583	1.19 (0.94, 1.52)	
	Smith (2001)	Caucasian	PCR-based DGGE	37/3/0	77/3	49/11/2	109/15	0.55 (0.14–2.20)	
	Landi (2003)	Caucasian	TaqMan assay	311/46/3	668/52	243/61/5	547/71	1.28 (0.81–2.02)	
rs1801282 (Pro12Ala)	Slattery (2005)	Caucasian	PCR-RFLP	1234/343	NA	1493/478	NA	0.90 (0.80–1.00)	0.004
	Murtaugh (2005)	Caucasian	TaqMan assay	606/188	NA	790/211	NA	1.20 (1.00–1.50)	
	Jiang (2005)	Asian	PCR-RFLP	240/57/4	537/65	230/57/4	517/65	2.15 (1.37–3.39)	
	McGreavey (2005)	Caucasian	End-point PCR	366/80/9	812/98	403/100/10	906/120	2.07 (1.46–2.94)	
	Slattery (2006)	Caucasian	TaqMan assay	1840/496/35	4176/566	2283/645/44	5211/733	2.23 (1.93–2.57)	
	Koh (2006)	Asian	TaqMan assay	345/17	NA	1075/89	NA	0.53 (0.30–0.92)	
	Theodoropoulos (2006)	Caucasian	PCR-RFLP	164/48/10	376/68	118/70/12	306/94	1.44 (0.93–2.22)	
	Kuriki (2006)	Asian	PCR-CTPP	248/9	NA	732/37	NA	0.73 (0.35–1.53)	
	Vogel (2007)	Caucasian	TaqMan assay	252/96/7	600/110	550/190/13	1290/216	2.68 (1.98–3.63)	
	Kury (2008)	Caucasian	TaqMan assay	822/194/7	1838/208	896/212/13	2004/238	2.15 (1.68–2.74)	
	Tsilidis (2009)	Caucasian	TaqMan assay	165/37/1	367/39	295/68/6	658/80	1.96 (1.21–3.16)	
	Crous-Bou (2012)	Asian	Illumina Beadstation and BeadExpress	710/102/0	1522/102	1307/163/9	2777/181	2.19 (1.63–2.95)	

AA, homozygotes for the common allele; AB, heterozygotes; BB, homozygotes for the rare allele; NA, not available; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; PCR-CTPP, polymerase chain reaction with confronting two-pair primers; KASPar, competitive allele specific PCR; PCR-based DGGE, PCR and denaturing gradient gel electrophoresis; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

model was used to calculate the combined ORs and their 95% CIs, otherwise a random-effect model was applied (DerSimonian and Laird, 1986). The primary statistical test is a trend test, and the effect is represented by heterozygote and homozygote ORs. If the ORs show a recessive model, then the model is not well represented by a trend test. Funnel plots were used to show publication bias (Egger *et al.*, 1997). The pooled OR was inferred by a Z-test (Zaykin, 2011).

Results

Characteristics of published studies

A total of 2836 articles were identified during premature searches with our searching strategy of the five databases (PubMed: 2820; Wanfang database: 10; and CNKI: 6). Two thousand eight hundred thirty-six articles were retrieved after excluding overlapping studies. After excluding reviews, animal studies, comments, letters, and studies unrelated to CRC, 545 studies that assess the association between the six

SNPs and CRC were found. Among the remaining 545 articles, 525 studies did not evaluate the five SNPs. Only 34 articles on the six genetic variants met our selection criteria. After searching reference lists, relevant meta-analyses, and reviews, we did not find additional studies. The selection process is illustrated in Figure 1. These 34 studies involved in this meta-analysis comprised 12 studies in the Asian population, 21 studies in the Caucasian population, and 1 study in the African population, covering in total 17,289 cases and 54,927 controls. The characteristics of selected studies are illustrated in Table 1.

Heterogeneity

Our meta-analysis showed that there was minimal heterogeneity for rs1229984 (Arg47His) of *ADH1B* ($I^2=0\%$), rs12917 (Leu84Phe) of *MGMT* ($I^2=0\%$), and rs4880 (V16A) of *SOD2* ($I^2=0\%$, Fig. 2). Large heterogeneities were observed for the meta-analyses of rs2228001 (Lys939Gln) of *XPC* ($I^2=92\%$), rs2308321 (Ile143Val) of *MGMT*

FIG. 2. Forest plots for the case-control studies between five polymorphisms and colorectal cancer (CRC) in our meta-analysis.

FIG. 3. Forest plots for the case-control studies between rs1801282 of *PPARG* and CRC in our meta-analysis.

($I^2=95\%$), and rs1801282 (P12A, 34C>G) of *PPARG* ($I^2=92\%$, Fig. 3).

Publication bias

Begg's regression test was used to detect publication bias for all six polymorphisms. The results are shown in Figures 4 and 5. The publication bias in the "Results" section was also corrected. As shown in Figures 4 and 5, no statistical evidence of publication bias was found using Begg's regression test for the meta-analysis of rs1229984 of the *ADH1B* gene ($p=1$), rs12917 ($p=0.734$) and rs2308321 ($p=0.296$) of the *MGMT* gene, rs2228001 of the *XPC* gene ($p=0.462$), rs1801282 (P12A, 34C>G) of the *PPARG* gene ($p=0.101$), and rs4880 of the *SOD2* gene ($p=0.086$).

Quantitative synthesis

The meta-analysis of rs1229984 was performed among 1709 CRC cases and 2611 controls (Landi *et al.*, 2005; Matsuo *et al.*, 2006; Yin *et al.*, 2007; Yang *et al.*, 2009). As shown in Figure 2, rs1229984 of the *ADH1B* gene was significantly associated with CRC in the Asian and Caucasian populations (the overall OR=1.18, 95% CI=1.01–1.36, $p=0.03$). The meta-analysis of rs1801282/P12A/34 C>G of *PPARG* was involved with 14 studies (Smith *et al.*, 2001; Jiang *et al.*, 2005; Landi *et al.*, 2003; McGreavey *et al.*, 2005; Murtaugh *et al.*, 2005; Slattery *et al.*, 2005, 2006; Koh *et al.*, 2006; Kuriki *et al.*, 2006; Theodoropoulos *et al.*, 2006; Vogel *et al.*, 2007; Kury *et al.*, 2008; Tsilidis *et al.*, 2009; Crous-Bou *et al.*, 2012) among 9132 CRC cases and 12,974 controls. Using the random-effect model, our result indicated that rs1801282-G contributed to the risk of CRC (the overall OR=1.50, 95% CI=1.14–1.97, $p=0.004$) in the Asian and Caucasian populations. Notably, significant association was found in the Caucasian subgroup when stratified

by ethnicity ($p=0.004$, OR=1.603, 95% CI=1.165–2.205, Fig. 3). In addition, no significant association was found between the risk of CRC and the other four genetic polymorphisms (*MGMT* rs12917: the overall OR=0.96, 95% CI=0.78–1.17, $p=0.66$; *MGMT* rs2308321: the overall OR=0.64, 95% CI=0.15–2.69, $p=0.54$; *SOD2* rs4880: the overall OR=0.95, 95% CI=0.86–1.05, $p=0.33$; and *XPC* rs2228001: the overall OR=1.36, 95% CI=0.82–2.25, $p=0.24$).

Power calculation on the combined sample size showed that the statistical powers were all higher than 80% for the meta-analyses except rs12917 of the *MGMT* gene (78.6%).

Discussion

Numerous studies investigated the role of genetic variants in cancer development and progression. In the current meta-analysis, we searched for evidence of associations between six SNPs of five genes and CRC. Our findings supported a significant association of *ADH1B* rs1229984 and *PPARG* rs1801282 with the risk of CRC. Further, we found that the significant association between *PPARG* rs1801282 and CRC was specific to the Caucasian subgroup.

It is recognized that drinking is a risk factor of CRC (Zambirinis *et al.*, 2009). The *ADH1B* gene product is an enzyme involved in metabolizing alcohol. Alcohol is initially oxidized to acetaldehyde by *ADH*, and then further metabolized to acetate by *ALDH1B* (Yin *et al.*, 2007). *ADH1B* rs1229984 (Arg47His) can repress the activity of *ADH1B* in the carriers of *ADH1B* His47His by 40-fold (Yang *et al.*, 2009). The interrupted *ADH1B* gene function may accumulate the quantity of acetaldehyde and reactive oxygen species produced during the metabolic process, and hence increases the toxicity of alcohol and the risk of CRC (Yang *et al.*, 2009). The current meta-analysis has indicated that the mutant allele increases the risk of CRC by 18% ($p=0.03$, OR=1.18, 95%

FIG. 4. Publication bias test of five polymorphisms in our meta-analysis. (A) Publication bias test of rs1229984 of the *ADH1B* gene. (B) Publication bias test of rs4880 of the *SOD2* gene. (C) Publication bias test of rs12917 of the *MGMT* gene. (D) Publication bias test of rs2308321 of the *MGMT* gene. (E) Publication bias test of rs2228001 of the *XPC* gene.

CI=1.01–1.36). This agrees with the previous observation (Yang *et al.*, 2009). The power calculation for rs1229984 suggests that the power is 94.6% to detect a relative risk at a significant level of 0.05. Allele rs1229984-A frequency is minor allele in Asians (24.7%). The allele frequency in the Asian population is consistent with the A allele frequency in the HapMap HCB population (24.4%).

PPARG is a nuclear hormone receptor, which mainly exists in adipose tissue, colon, and immune system (Tontonoz

et al., 1994). *PPARG* plays a key role in adipogenesis, energy homeostasis, and regulation of adipocyte-specific gene expression (Martin *et al.*, 1997). As a tumor-suppressor gene (Kliwer *et al.*, 2001), *PPARG* mutations were detected in CRC, such as rs1801282 (Pro12Ala or 34C>G) (DuBois *et al.*, 1998). *PPARG* gene mutation may increase risk of CRC by interruption of the metabolism of a high-fat diet (Murtaugh *et al.*, 2005). For some studies that had not provided the number of the allele, we applied Stata software to

FIG. 5. Publication bias test of *PPARG* rs1801282 polymorphism in our meta-analysis. (A) Begg's funnel plot of rs1801282 of the *PPARG* gene. (B) Egger's funnel plot of rs1801282 of the *PPARG* gene.

calculate the overall OR and 95% CI. Our meta-analysis indicated that rs1801282-G contributed to the risk of CRC in the Asian and Caucasian populations (the overall OR = 1.50, 95% CI = 1.14–1.97, $p = 0.004$). Notably, significant association was found in Caucasian subgroup ($p = 0.004$, OR = 1.603, 95% CI = 1.165–2.205).

Our results should be interpreted with some caution. First, there is significant heterogeneity for several studies in our meta-analysis, which, along with publication bias and other unknown confounding factors, may distort the current meta-analysis. Second, limited data hampered our attempts to examine associations between these variants and the clinical manifestation of CRC. Therefore, statistical bias may exist in the current meta-analysis. Third, power calculation for rs12917 demonstrated that the meta-analysis was underpowered (78.6%). The moderate sample size in the meta-analysis of *MGMT* rs12917 polymorphism might be still unable to draw a conclusion of the association between rs12917 and CRC. Lastly, positive results are more likely to be published, so there may be potential publication biases in our meta-analysis.

In conclusion, the meta-analysis among 1709 cases and 2611 controls suggests that *ADH1B* rs1229984 is a risk variant in Asian and Caucasian populations. Another meta-analysis among 9132 cases and 12,974 controls established that rs1801282 of *PPARG* contributes to CRC in Asian and Caucasian populations.

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Author Disclosure Statement

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