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Genetic polymorphism of *RAD51* influences susceptibility to colorectal cancer in Chinese population

J. ZHONG[1], S.-Q. LIU[2], J.-C. TANG[2]

[1]Department of Gastrointestinal Surgery, Chongqing University Jiangjin Hospital, Chongqing, China
[2]Department of Hepatobiliary Surgery, Chongqing University Jiangjin Hospital, Chongqing, China

J. Zhong and S.-Q. Liu are equal contributors and co-first authors

Abstract. – OBJECTIVE: The present study aimed to explore whether *RAD51* polymorphism confers risk to colorectal cancer.

PATIENTS AND METHODS: A total of 240 patients with colorectal cancer were selected. 390 healthy people who participated in normal physical examinations during the same period were selected as the control group. The polymorphism of *RAD51* gene was detected by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. An updated meta-analysis was also conducted.

RESULTS: Meta-analysis found no significant association between the *RAD51* polymorphism and CRC risk (all $p>0.05$). PCR-RFLP method detected three kinds of genotypes (GG, GC, and CC) in both the colorectal cancer group and the control group. A significant association was only found in GC genotype ($p<0.05$).

CONCLUSIONS: Our results demonstrated that *RAD51* polymorphism has a crucial role in colorectal cancer risk and that GC genotype confers an increased risk of colorectal cancer in the Chinese population. The updated meta-analysis indicates that *RAD51* polymorphism contributes no risk to colorectal cancer.

Key Words:
Colorectal cancer, *RAD51*, Gene polymorphism, Novel marker.

Introduction

Colorectal cancer is one of the most common malignant tumors. Statistics[1-3] show that its mortality rate ranks second among malignant tumors in Europe, especially in developed countries, and third after lung cancer and breast cancer. In the last decade, colorectal cancer incidence and mortality presented a rising trend. Relative statistics[4-6] indicate that its incidence rate in women will soon exceed that of stomach cancer, while its mortality rate in men will rank third only after lung cancer and stomach cancer. At present, the pathogenesis of colorectal cancer has not been fully elucidated, but related articles[4-5] have been reported: age, dietary factors, tumor history, genetics, smoking, alcohol consumption, and genetic mutations increase the risk of colorectal cancer. Further studies[5-6] have shown that its occurrence and development are closely related to the inactivation of tumor suppressor genes, oncogene mutation, cell proliferation, and apoptosis imbalance.

There are two repair pathways, homologous recombination, and non-homologous terminal junction, but homologous recombination plays a more important role as the main repair pathway after double-strand breakage. Under normal circumstances, homologous recombination can repair the damage in time and resist various internal and external damage factors. It plays a crucial role in maintaining chromosome integrity, the stability of genomes, and the inhibition of cell carcinogenesis. In recent years, the correlation between single nucleotide polymorphisms and malignant tumors has been widely researched, and the relationship between repair gene polymorphisms and malignant tumors has also attracted more and more attention[7-17]. As an important repair gene, it plays a crucial role in the process of homologous recombination. Studies[3-4] have shown that overexpression will lead to an imbalance of recombination repair, resulting in the loss of genome stability and chromosome integrity. This will lead to the occurrence and development of

Corresponding Author: Juncheng Tang, MD; e-mail: juncheng6412@sina.com

tumors, and even affect the therapeutic effect by reducing the sensitivity of tumor cells to radiotherapy, chemotherapy, and other treatments, thus affecting the survival of patients.

RAD51 gene and single nucleotide polymorphism have been studied[18] as high-risk factors for a variety of tumors, and rs1801320G/C single nucleotide polymorphism located in its 5' end non-coding region has been confirmed[19] to be associated with gene transcription. Over the past decade, numerous studies[18-25] in literature have shown that *RAD51* gene polymorphism is related to the development of head and neck tumors and breast tumors. In addition to high expression detected in breast cancer, pancreatic cancer, lung cancer, and head and neck cancer, the high expression has also been confirmed in colorectal cancer tissues[18-20], but its relationship with *RAD51* rs1801320 polymorphism and the development of colorectal cancer is still controversial in China and abroad. To date, the association of *RAD51* rs1801320G/C polymorphism with the risk of colorectal cancer in China has not been investigated or reported.

Patients and Methods

Study Subjects

The experimental group consisted of 240 patients who were pathologically diagnosed with colorectal cancer in the Chongqing University Jiangjin Hospital without receiving any preoperative treatment, while the control group consisted of healthy people who underwent physical examination in the hospital during the same period. This experiment, after receiving the consent of patients or their families, recorded in detail: basic situation, past history, family history, smoking history, drinking history, etc. Smoking was defined as smoking a cigarette a day for a year and drinking alcohol as drinking white wine at least once a week for a month. All subjects signed written informed consent, completed the epidemiological investigation, and voluntarily provided a 5 ml peripheral blood sample. All samples and research programs were approved by the Ethics Committee of Chongqing University Jiangjin Hospital.

DNA Extraction and Gene Polymorphism Detection

5 ml venous blood was extracted from all subjects on an empty stomach and frozen at -20°C for use. The *RAD51* polymorphism was investigated by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, and the traditional phenol-chloroform extraction method was used to extract genomic DNA. Primer sequences of *RAD51* codon 135 are 5'-CACCTAACTGGCATCTTCACTT-3' and 5'-ACAGGATAAGGAGCAGGGTT-3'.

- PCR anti-reaction line: 50 ng genomic DNA in 20 μl, 12.5 pmol/μl each primer, 0.1 mmol/L every single nucleotide, 1.8 mmol/L $MgCl_2$, 1.0 U Taq enzyme, 1×PCR reaction buffer.
- PCR reaction conditions: pre-denaturation for 5 min; 40 cycles at 95°C 30 s, annealing 45 s, 72°C 60 s; extend for 6 min at 72°C. All PCR products were incubated with endonuclease at 37°C and tested for 100 min on 3.0% agarose gel 80 V electrophoresis. The enzyme digestion products were analyzed by electrophoresisand ethidium bromide staining to determine the genotypes. In this study, two people interpreted the genotypes respectively by blind method and retested the genotypes of the samples with inconsistent interpretation.

Literature Source

English and Chinese studies from PubMed, Cochrane, Embase, China Biomedicine Network, China National Knowledge Network, Wanfang and VIP database were carefully searched and reviewed. The retrieval span is from the establishment of the database to January 28, 2023. "*RAD51*", "single nucleotide polymorphism" and "colorectal cancer" were the search terms.

Inclusion and Exclusion Criteria

All the eligible studies must conform to all these conditions: (a) the reported literature which evaluated the association between *RAD51* rs1801320 polymorphism and colorectal cancer risk; b) embracing sufficient data or information to obtain OR and 95% CI. Studies were excluded when conformed to one of these conditions: (a) not a case-control study on humans; (b) insufficient data to obtain OR and 95% CI.

Data Extraction and Methodological Quality Assessment

Two authors were responsible for the search, review, and evaluation of all data and information, which includes the author's name, publication year, sample size, genotype number of case

Table I. The participants' characteristics of both the colorectal cancer group and control group.

Basic information		Control (N = 390)	Colorectal cancer (N = 240)	*p*
Age		38.4 ± 8.9	36.9 ± 11.3	0.28
Sex	Male	242	155	0.42
	Female	148	85	
Smoking status	Yes	215	135	0.41
	No	175	107	
Alcohol consumption	Yes	158	83	0.53
	No	232	157	
BMI	BMI < 18.5 kg//m^2	125	35	0.09
	BMI ≥ 18.5 kg//m^2	265	205	

BMI, body mass index.

and control, and Hardy-Weinberg equilibrium (HWE). Newcastle-Ottawa Scale (NOS) score was also applied to evaluate the literature quality according to the above information[26].

Statistical Analysis

Statistical analysis was based on SPSS 17.0 (SPSS Inc., Chicago, IL, USA). All measurement data was shown by (±S) and *t*-test was applied to compare two independent samples. c^2 test was used for enumeration data. OR together with 95% CI were counted to judge the association between risk factors and colorectal cancer risk. $p<0.05$ suggested that the present difference was statistically significant. OR value, 95% CI, Q-statistic and I^2 statistics were applied to obtain the corresponding association power and heterogeneity degree[27-29]. Sensitive analysis and publication bias were based on the previous meta-analysis[30]. The current meta-analysis was conducted and reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist. The PROSPERO registration number was 20220184.

Results

General Information of Study Subjects

Table I shows the details of general information. No significant difference was observed between the colorectal cancer group and the control group in the above information which was referred to in Methods ($p>0.05$).

Genotyping and Allele Distribution of RAD51 rs1801320 Polymorphism

The PCR-RFLP method detected three kinds of genotypes (GG, GC, and CC) in both the colorectal cancer group and control group. The significant association was only found in GC genotype. OR (95% CI): 1.98 (1.09-3.59) ($p<0.05$). The detailed information is shown in Table II.

Literature Search

PRISMA 2009 Flow Diagram (Figure 1) shows the flow diagram of the present meta-analysis search process. There were nine studies[31-39] in the literature included in the meta-analysis altogether. Main data and information of all studies are listed in Table III. In total

Table II. Comparison of genotype and allele frequency between colorectal cancer group and control group.

RAD51 rs1801320	Control group (N = 390)		Colorectal cancer group (N = 240)		OR (95% CI)[a]	*p*[a]
	N	Percentage (%)	N	Percentage (%)		
GG	192	49.2	84	30.0	1.00[REF]	
GC	156	40.0	135	35.0	**1.98 (1.09-3.59)**	**0.024**
CC	42	10.8	21	35.0	1.14 (0.42-3.14)	0.795
G	540	69.2	303	63.1	1.00[REF]	
C	240	30.8	177	36.9	1.31(0.87-1.99)	0.197

OR, odds ratio; CI, confidential index. [a]Adjusted for sex and age by logistic regression model.

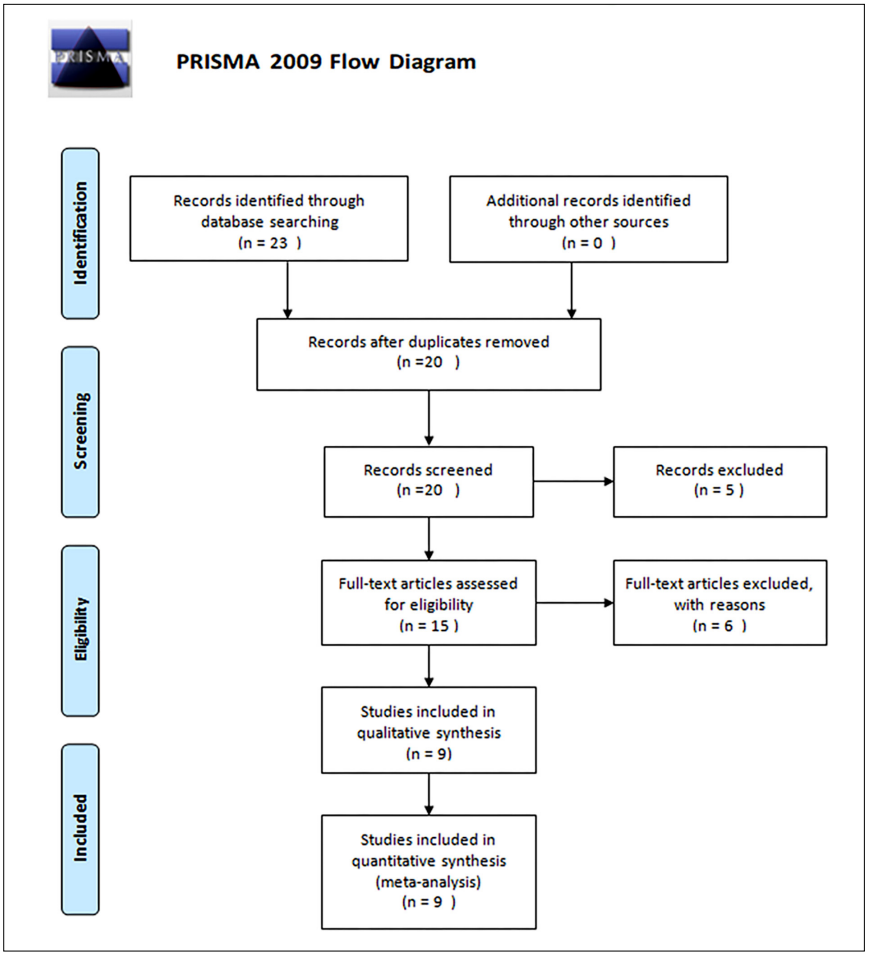

Figure 1. PRISMA 2009 flow diagram.

six studies[31-32,34,36,38-39] were from the Caucasian population; three studies[33,35,37] were from the Asian population. The results of NOS are shown in Table IV.

Allele and Genotype-Wide Meta-Analysis

No positive findings were found between *RAD51* rs1801320 polymorphism and colorectal cancer risk by allele contrast (C *vs.* G: OR=0.97, 95% CI=0.54-1.73, p=0.910, Table V and Figure 2), homozygote comparison (CC *vs.* GG: OR=0.77, 95% CI=0.27-2.18, p=0.623, Table V and Figure 3), heterozygote comparison (GC *vs.* GG: OR=0.82, 95%CI=0.42-1.64, p=0.581, Table V and Figure 4), recessive genetic model (CC *vs.* GG/GC: OR=0.85, 95% CI=0.25-2.83, p=0.788, Table V and Figure 5), and dominate genetic model (CC/GC *vs.* GG: OR=0.93, 95% CI=0.57-1.53, p=0.783, Table V and Figure 6). The main results between interleukin (IL)-8 rs4073 polymorphism and sepsis risk are shown in Table V.

Discussion

In recent years, with the continuous improvement of people's living standards and the changes in diet structure, the morbidity and mortality of malignant tumors are rising, and this has become one of the main causes of human death. However, the pathogenesis of malignant tumors is not clear at present. Studies[40-44] have found that its occurrence and development is a multi-factor, multi-step, multi-stage process, which is related to the mutation and inactivation of tumor suppressor genes and the activation and overexpression of oncogenes. When the regulation of cell differentiation and growth is out of control, the inductor group becomes cancerous due to mutation and abnormal growth. Although tumor pathogenesis has been deeply understood and its diagnosis and treatment have made great progress, incidence, and death rates are still high; therefore, the study of tumors has been one of the research hotspots for scholars. With the further deepening

Table III. Main characteristics of all case-control studies included in meta-analysis.

Literature	Ethnics (country)	Genotyping methods	Source of control	Sample size	HWE conformity	NOS	Genotype frequency (case)			Genotype frequency (control)			Year
							GG	GC	CC	GG	GC	CC	
Wiśniewska-Jarosińska et al[38]	Caucasian (Poland)	PCR-RFLP	PB	100/236	Yes	8	61	36	3	169	44	23	2009
Krupa et al[36]	Caucasian (Poland)	PCR-RFLP	PB	100/100	Yes	8	61	36	3	36	35	29	2011
Gil et al[34]	Caucasian (Poland)	PCR-RFLP	PB	320/320	Yes	9	100	29	4	73	27	0	2011
Romanowicz-Makowska et al[32]	Caucasian (Poland)	PCR-RFLP	PB	116/94	Yes	8	51	26	213	91	164	65	2012
Mucha et al[39]	Caucasian (Poland)	PCR-RFLP	PB	200/200	Yes	8	161	34	5	157	37	6	2012
Nissar et al[37]	Asian (India)	PCR-RFLP	PB	100/120	Yes	9	25	56	19	60	25	35	2014
Cetinkunar et al[31]	Caucasian (Turkey)	PCR-RFLP	PB	71/86	Yes	9	39	11	21	21	54	11	2015
Yazdanpanahi et al[35]	Asian (Iran)	PCR-RFLP	PB	100/100	Yes	9	72	27	1	69	26	5	2018
Hridy et al[33]	Asian (Bangladesh)	PCR-RFLP	PB	200/200	Yes	9	7	61	117	5	43	115	2020

PB: Population-based; HB: Hospital-based; HWE: Hardy-Weinberg equilibrium; RFLP: Restricted Fragment Length Polymorphism; NOS: Newcastle-Ottawa Score.

Table IV. Quality assessment of the seven case-control studies according to the Newcastle-Ottawa Scale.

Literature	Selection of enrolled study subjects	Between-group comparability	Exposure outcomes and factors	Total
Wiśniewska-Jarosińska et al[38]	3	2	3	8
Krupa et al[36]	3	2	2	7
Gil et al[34]	4	3	2	9
Romanowicz-Makowska et al[32]	2	2	3	7
Mucha et al[39]	3	2	3	8
Nissar et al[37]	2	3	2	7
Cetinkunar et al[31]	3	2	2	7
Yazdanpanahi et al[35]	2	3	2	7
Hridy et al[33]	3	3	2	8
Average	2.8	2.4	2.3	7.5

Table V. Meta-analysis of the *RAD51* rs1801320G/C polymorphism and colorectal cancer risk.

Comparison	Population	N	Test of association			Mode	Test of heterogene		
			OR	95% CI	*p*		χ^2	*p*	I^2
C *vs.* G	Overall	6	0.97	0.54-1.73	0.910	Random	149.32	0	94.6
	Caucasian	3	1.01	0.43-2.33	0.013	Random	132.13	0	96.2
	Asian	2	0.90	0.56-1.42	0.641	Random	7.08	0.029	71.7
CC *vs.* GG	Overall	6	0.77	0.27-2.18	0.623	Random	73.56	0	89.1
	Caucasian	3	0.87	0.19-3.97	0.861	Random	64.10	0	92.2
	Asian	2	0.78	0.32 -1.89	0.580	Random	3.32	0.190	39.7
GC *vs.* GG	Overall	6	0.82	0.42-1.64	0.581	Random	83.47	0	90.4
	Caucasian	3	0.57	0.27-1.23	0.154	Random	49.80	0	90.0
	Asian	2	1.82	0.53-6.21	0.338	Random	14.43	0.001	86.1
CC *vs.* GC/GG	Overall	6	0.85	0.25-2.83	0.788	Random	164.29	0	95.1
	Caucasian	3	1.20	0.22-6.48	0.003	Random	91.71	0	94.5
	Asian	2	0.58	0.40-0.83	0.011	Fixed	1.06	0.589	0
CC/GC *vs.* GG	Overall	6	0.93	0.57-1.53	0.783	Random	54.82	0	85.4
	Caucasian	3	0.80	0.44-1.47	0.476	Random	40.75	0	87.7
	Asian	2	1.31	0.50-3.41	0.586	Random	10.23	0.006	80.5

OR, odds ratio; CI, confidence interval.

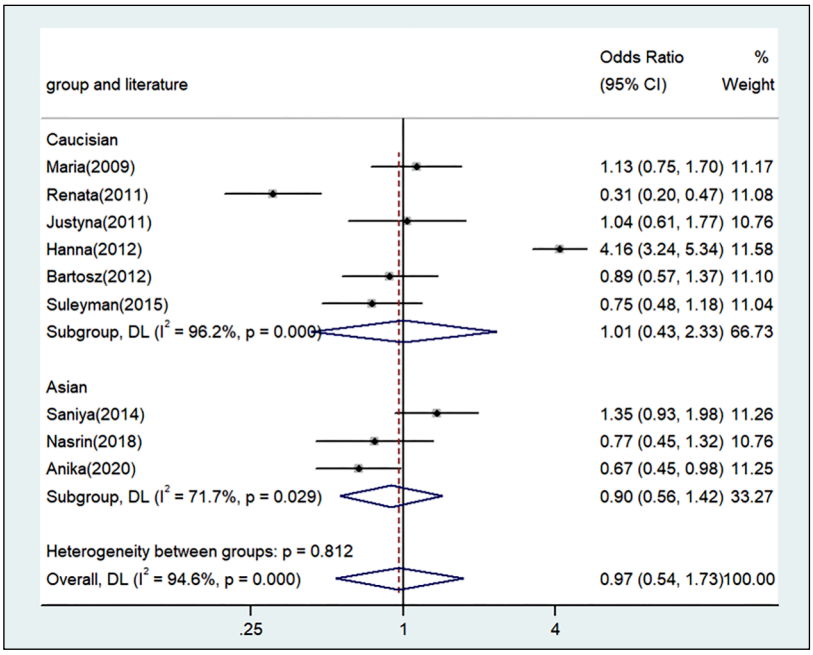

Figure 2. Forest plot for the associations between *RAD51* gene rs1801320 polymorphism and colorectal cancer risk through allele contrast (C *vs.* G). OR, odds ratio; CI, confidence interval.

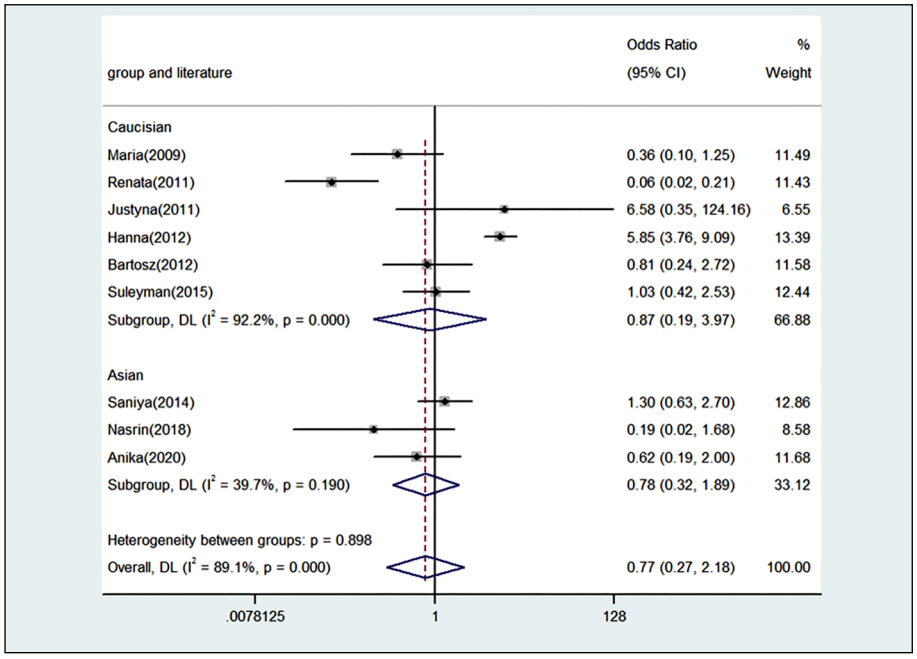

Figure 3. Forest plot for the associations between *RAD51* gene rs1801320 polymorphism and colorectal cancer risk through homozygote comparison (CC *vs*. GG). OR, odds ratio; CI, confidence interval.

of the research on the pathogenesis of cancer, the correlation between the polymorphism of mononucleotide and the malignant tumor gradually becomes the hot point of the research. Among these polymorphic genes, the correlation between the polymorphism of repair genes and the tumor receives more and more attention. The genome instability is one of the main reasons for tumor

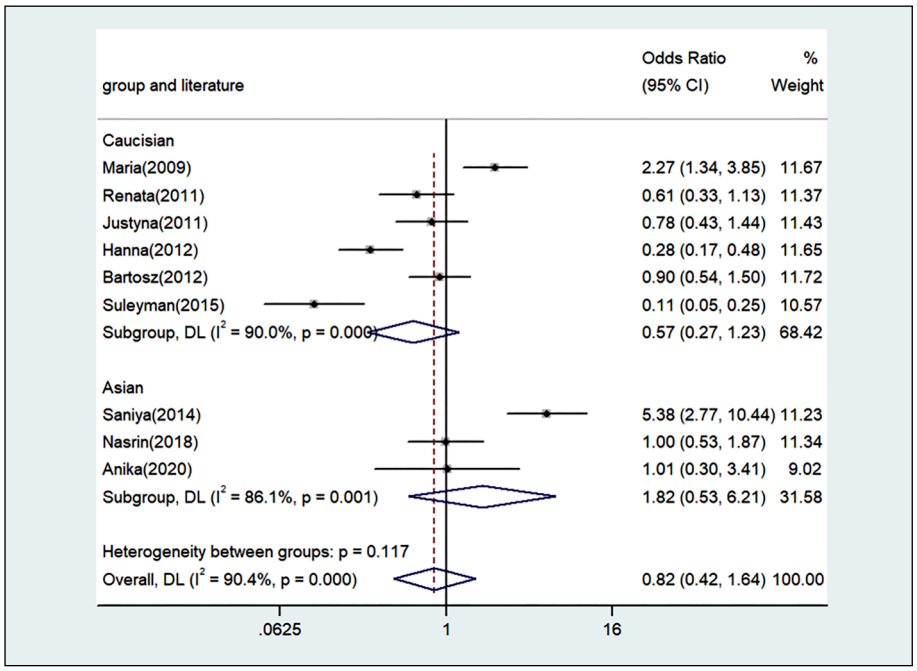

Figure 4. Forest plot for the associations between *RAD51* gene rs1801320 polymorphism and colorectal cancer risk through heterozygosis comparison (GC *vs*. GG). OR, odds ratio; CI, confidence interval.

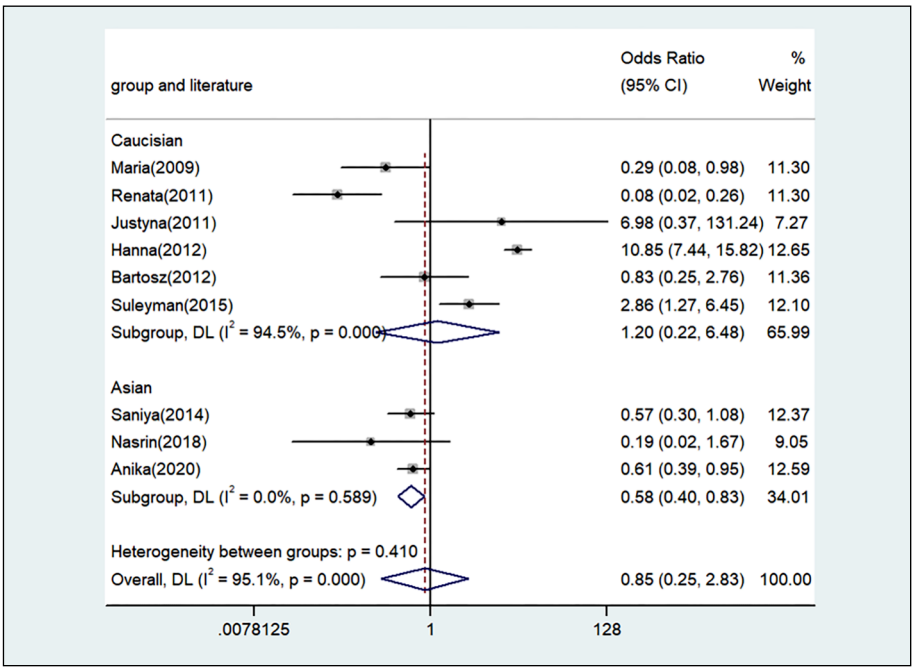

Figure 5. Forest plot for the associations between *RAD51* gene rs1801320 polymorphism and colorectal cancer risk through recessive genetic model (CC *vs.* GC/GG). OR, odds ratio; CI, confidence interval.

occurrence and development. As an important repair factor, *RAD51* plays an important role in maintaining genome stability and chromatids completion. Its expression level is low in normal human cells, but studies[18,19] have shown that it has high expression levels in a variety of malignant tumors, and this abnormal expression is speculated to be closely related to the development of

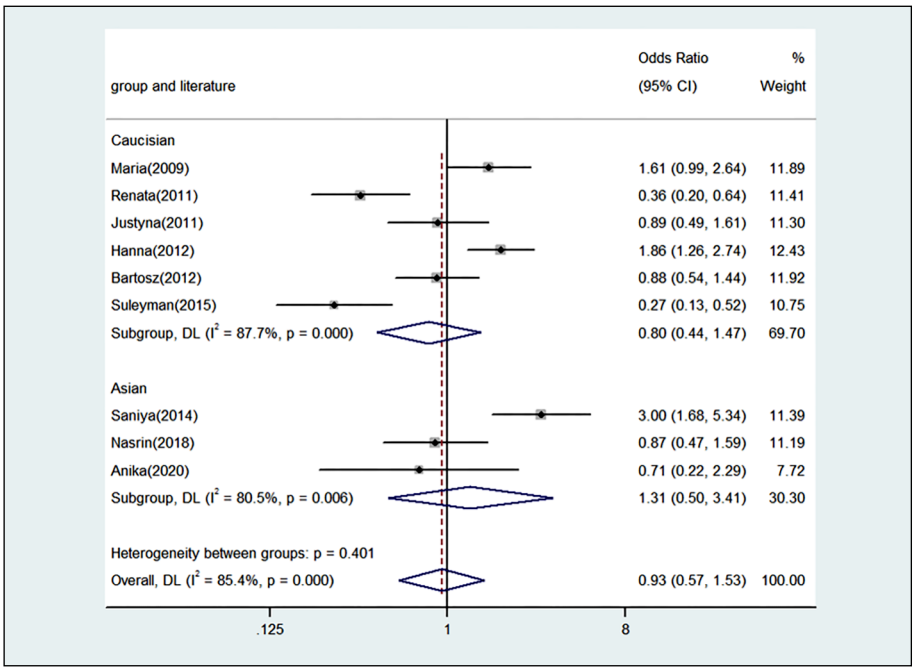

Figure 6. Forest plot for the associations between *RAD51* gene rs1801320 polymorphism and colorectal cancer risk through dominant genetic model (CC *vs.* GC/GG). OR, odds ratio; CI, confidence interval.

tumors. The relationship between high expression and malignant tumors has attracted more and more attention from scholars. The *RAD51* polymorphism has been a hot topic in recent years. In the literature on endometrial cancer in Polish women, the polymorphism of gene locus was positively correlated with endometrial cancer[38]. More importantly, several recent reports[31-33] have shown that polymorphism plays an important role in the development of colorectal cancer, and other studies[36,38] have found that genotypes can reduce the risk of colorectal cancer in Poland, but colorectal cancer grading and staging are not associated with *RAD51* gene polymorphism. As far as we know, this is the first study that investigates this association in the Chinese population. Our results demonstrate that *RAD51* polymorphism has a crucial role in colorectal cancer risk and GC genotype confers an increased risk of colorectal cancer in the Chinese population. The updated meta-analysis indicates that *RAD51* polymorphism contributes no risk to colorectal cancer. All the above results suggest that different races or populations have different genetic polymorphisms and backgrounds. Although China belongs to Asia, Chinese Han people have different genetic backgrounds from other Asian countries, such as Iran, India, Japan, Korea, and Bangladesh.

Conclusions

Our results demonstrate that *RAD51* polymorphism has a crucial role in colorectal cancer risk and GC genotype confers an increased risk of colorectal cancer in the Chinese population. The updated meta-analysis indicates that *RAD51* polymorphism contributes no risk to colorectal cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Authors' Contribution

JT conceived the study design; JT conceived the content concept; JZ and SL performed the data collection, extraction and analyzed the data. JZ and SL interpreted and reviewed the data and drafts. JT reviewed the final draft. All authors were involved in the literature search, writing the paper and had final approval of the submitted and published versions.

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Ethics Approval

All samples and research programs were approved by the Ethics Committee of Chongqing University Jiangjin Hospital (Approval No. KY2022008).

Informed Consent

All patients, control subjects and their family members provided informed consent.

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