rs719725 Polymorphism and Colorectal Cancer Susceptibility: A Meta-analysis

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ABSTRACT

Many studies have suggested an association between 9p24 rs719725 polymorphism and colorectal cancer (CRC) risk, but with inconsistent results. This meta-analysis aimed to summarise the overall association of rs719725 polymorphism with CRC risk. Nine eligible articles with 21 case-control studies (16015 CRC patients and 19341 controls) on the rs719725 polymorphism and CRC susceptibility from four electronic databases (Web of Science, PubMed, SinoMed, and EMBASE) were retrieved and analysed. The association was evaluated with publication bias, pooled OR (odds ratio), and corresponding 95% CI (confidence interval). The pooled results indicated a significant association between the increased CRC risk and rs719725 polymorphism in dominant ([OR] 1.220, [95%CI] 1.161-1.282), recessive (1.166, 1.102-1.234), allele (1.142, 1.102-1.184), homozygous (1.306, 1.212-1.406), and heterozygous (1.18, 1.129-1.234) genetic models. The ethnicity-stratified analyses found a consistently significant association. In the stratification analysis with the source of controls, such significant association was also detected amid the population-based studies under the four former genetic models. Taken together, this meta-analysis indicates that rs719725 genetic variants are associated with an increased risk of CRC among Caucasians and population-based studies. Further relevant research is warranted to confirm these findings.

Key Words: Colorectal cancer, rs719725, Polymorphism, Meta-analysis, Stratification analysis.

INTRODUCTION

Colorectal cancer (CRC) is no doubt one of the most frequently diagnosed malignancies with no gender predisposition and is the third leading cause of cancer-related mortality in recent years worldwide.[1] Biological and epidemiological investigations have demonstrated that CRC is a serious and complex disease resulting from both environmental and genetic factors. Molecular epidemiological studies have largely proved that single nucleotide polymorphisms in genes play a vital role in colorectal carcinogenesis and progression, despite its unclear pathogenesis at present.[2,3] Genome-wide association studies have recognised the responsibility of genetic factors hold for 33% of CRC cases across the globe.[4,5] Among the variants, the single nucleotide polymorphism rs719725 located at the 9p24 locus, has been of great interest in the development of various CRCs.[6] Originally identified in a genome-wide association study and thereafter replicated in a candidate gene association study,[7,8]

The nucleotide 9p24 rs719725 lies within a gene in the presence of several genes nearby. These genes are *TPD52L3* (the gene most proximal to this polymorphism), interleukin 33, *UHRF2*, and glycine dehydrogenase.[8] The associations of rs719725 with colorectal tumours may attribute to the linkage disequilibrium between the true susceptibility allele(s) at neighbouring polymorphisms and genetic markers.[9] Beyond its reportedly potential competence in risk identification, the rs719725 has been pointed out to be significantly associated with the time to recurrence in CRC patients receiving adjuvant therapy.

Over the past few years, evidence from a range of case-control studies has emerged to helpfully interpret the association between the rs719725 polymorphism and CRC risk, but discouragingly with inconsistent and inconclusive findings. This may be partially on account of the presence of insufficient power, small effect on CRC risk from the polymorphism, phenotypic heterogeneity, population stratification, and publication bias. Therefore, with the increasing investigations and related reports, the aim of this meta-analysis of the publications was to analyse the relationship between the rs719725 polymorphism and CRC susceptibility.

METHODOLOGY

The enrolled articles in this meta-analysis were obtained by searching the four online databases, Web of Science, PubMed, SinoMed (Chinese Biomedical Literature Database), and

EMBASE, without language restriction. Keywords focusing on chromosome 9p24 (*e.g.*, 9p24, rs719725) along with words relating to CRC/colorectal adenoma (*e.g.*, colorectal cancer, colorectal adenoma, colorectal neoplasm, rectal cancer, colon cancer, or colorectal adenomatous polyps) were used as search term combinations. The latest included study, as of the initiation of this meta-analysis, was published on March 3, 2022. All references in each included article were searched manually for additional literature of relevance.

Cohort or case-control studies investigating the association between CRC risk and rs719725 polymorphism, enriched with sufficient data for calculating the ORs (odds ratios) and corresponding CIs (confidence intervals) and genotype frequencies complying with Hardy-Weinberg equilibrium (HWE) in controls, were enrolled into the meta-analysis. Abstracts, review articles, case reports or case-only studies, or the studies not concerning cancer risk, or studies with no available data were excluded from this meta-analysis.

Two investigators (Zhou and Chen) independently performed the screening and data extraction of all candidate publications. Any disagreements during data collection were resolved *via* discussion with the third author (Zhang). The data from each eligible study involved year of publication, first author's surname, country, origin, ethnicity, cancer type, genotype frequency, genotyping methods, source of controls, number of controls or CRC cases, and the evidence of HWE among controls.

STATA 12.0 software (Stata Corp., United States) was applied for all statistical analyses. HWE of genotype distribution among the controls was assessed in each study using the χ^2 goodness-of-fit test, with a significant deviation from HWE (set at p <0.01). The strength of the target association was evaluated with OR (95% CI). The statistical significance of pooled ORs was evaluated by the Z test. The association was measured based on five different genetic models, dominant (AA+AC *vs.* CC), recessive (AA *vs.* AC+CC), allele (A *vs.* C), heterozygote (AC *vs.* CC), and homozygote (AA *vs.* CC) models. The heterogeneity among eligible studies was evaluated using both I^2 statistics and Cochran's Q test. The random-effects model with the DerSimonian-Laird approach was applied to calculate the pooled OR in the presence of statistical heterogeneity (p <0.1 or I^2 ≥50%) among included studies.[10] While a fixed-effects model with the Mantel-Haenszel method was used in the absence of statistical heterogeneity.[11] The source of controls and ethnicity were taken for subset stratification analysis. The potential publication bias was evaluated by Egger's linear regression test along with Begg's funnel plot.[12] The influence of one study on the pooled OR and corresponding 95% CI was investigated through sensitivity analyses.[13]

RESULTS

A total of nine eligible publications with 21 case-control studies (including 16015 CRC patients and 19341 controls) were finally included in this meta-analysis.[6-8,14-19] The main characteristics and genotype distribution are summarised in Table I. The enrolled studies were published between August 2007 and August 2020 in international journals. Of these, there were five

studies conducted on the Asian population, 15 on the Caucasian population, and 1 on a population with mixed ethnicity. The genotype distribution of the rs719725 polymorphism was consistent with HWE in the control population in the 21 eligible studies. Figure 1 exhibits the literature selection process.
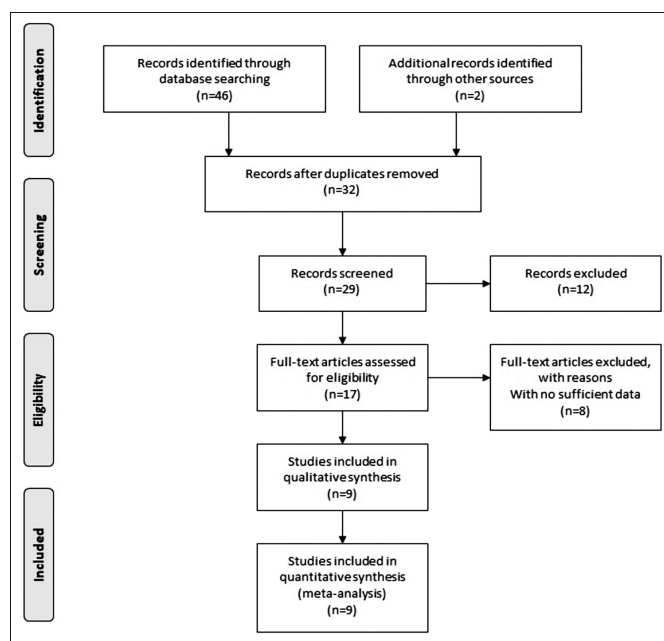

Figure 1: Flow chart of the selection process.

The main results for the association between CRC risk and the rs719725 polymorphism are shown in Table II. The pooled results indicated a significant association between the increased CRC risk and the rs719725 polymorphism in all five genetic models, namely, dominant (AA+AC *vs.* CC, [OR] 1.220, [95%CI] 1.161-1.282), recessive (AA *vs.* AC+CC, 1.166, 1.102-1.234), allele (A *vs.* C, 1.142, 1.102-1.184), homozygous (AA *vs.* CC, 1.306, 1.212-1.406), and heterozygous (AC *vs.* CC, 1.18, 1.129-1.234) models (Figure 2). In the ethnicity-stratified subset analysis (in the Asian and Caucasian populations), the pooled ORs indicated the existence of a similar significant association among Caucasians (A *vs.* C, 1.065, 1.028-1.104; AA *vs.* CC, 1.123, 1.041-1.211; AA *vs.* AC+CC, 1.090, 1.036-1.146; AA+AC *vs.* CC, 1.079, 1.006-1.158). After taking the source of controls into stratification analysis, the same significant associations were detected in the population-based studies under four genetic models (A *vs.* C, 1.052, 1.017-1.088; AA *vs.* CC, 1.109, 1.032-1.192; AA *vs.* AC+CC, 1.061, 1.011-1.113; AA+AC *vs.* CC, 1.089, 1.024-1.158).

Begg's funnel plot was created to detect potential publication bias. Its symmetrical shape shown in Figure 3 suggested the absence of publication bias in the enrolled studies. The reliability of the findings was evaluated through leave-one-out sensitivity analyses (by sequentially removing any one study at a time). As shown in Figure 4, no substantial alteration in the statistical results, when any single enrolled study was removed, which demonstrated the reliability of the authors findings.

Table I: Characteristics of enrolled studies in the meta-analysis.

Author (Year)	Country	Ethnicity	Genotyping Method	Cases (n)	Controls (n)	Sample Origin	Genotypes of Cases (n)			Genotypes of Controls (n)			HWE
							CC	AC	AA	CC	AC	AA	
Kim (2020)	Korea	Asia	MassARRAY	691	1396	PB	102	323	266	192	626	578	Y
Li (2012)	China	Asia	MassARRAY	223	225	HB	18	90	115	22	104	99	Y
D. Kocarnik (WHI) (2010)	America	Caucasian	MassARRAY	619	637	HB	75	281	263	92	310	235	Y
D. Kocarnik (DALS) (2010)	America	Caucasian	MassARRAY	1453	1790	PB	207	659	587	258	808	724	Y
Win (2013)	America/ Canada/ Australia	Caucasian	MassARRAY	327	736	PB/HB	40	145	142	92	337	307	Y
Holst (2010)	Sweden	Caucasian	TaqMan	1724	1719	PB	231	821	672	253	797	669	Y
Poynter (PB) (2007)	America/ Australia	Mixed	MassARRAY	1285	2122	PB	157	630	498	319	992	811	Y
Poynter (Clinic-based) (2007)	America/ Australia	Mixed	MassARRAY	277	491	HB	35	140	102	68	241	182	Y
Abe (Derivation study) (2017)	Japan	Asia	TaqMan	558	1116	HB	58	255	245	132	506	478	Y
Abe (Replication study) (2017)	Japan	Asia	TaqMan	547	547	HB	68	277	202	69	257	221	Y
Zanke (Ontario) (2007)	Canada	Caucasian	Affymetrix GeneChip	1148	1179	PB	138	502	508	159	581	439	Y
Zanke (Newfoundland) (2007)	Canada	Caucasian	Affymetrix GeneChip	436	362	PB	66	208	162	64	156	142	Y
Zanke (Seattle) (2007)	America	Caucasian	Affymetrix GeneChip	685	691	PB	83	324	278	101	337	253	Y
Zanke (Scotland 3) (2007)	Scotland	Caucasian	Illumina GeneChip	880	900	PB	117	410	353	139	447	314	Y
Zanke (Scotland 4) (2007)	Scotland	Caucasian	TaqMan	1912	1969	PB	264	895	753	301	955	713	Y
Zanke (France/Nantes) (2007)	France	Caucasian	Illumina GeneChip	1038	1101	PB	165	510	363	175	537	389	Y
Zanke (France/Familial) (2007)	France	Caucasian	Illumina GeneChip	379	547	PB	60	175	144	78	249	220	Y
Zanke (EPIC) (2007)	Europe	Caucasian	Illumina GeneChip	764	766	PB	121	354	289	108	379	279	Y
Curtin (UK-Sheffield) (2009)	United Kingdom	Caucasian	SNPlex	397	400	PB	56	193	148	49	202	149	Y
Curtin (UK-Leeds) (2009)	United Kingdom	Caucasian	SNPlex	244	216	PB	30	98	116	31	99	86	Y
Curtin (Utah) (2009)	America	Caucasian	SNPlex	428	431	PB	62	203	163	72	189	170	Y

HB = Hospital-based; PB = Population-based, HWE = Hardy-Weinberg equilibrium, Y = Yes.

Table II: Main results of five genetic models in the meta-analysis.

Variables (n)	Allele A vs. C				Homozygous AA vs. CC				Heterozygous AC vs. CC				Recessive AA vs. AC+CC				Dominant AA+AC vs. CC			
	OR (95% CI)	Z	P	I² (%)	OR (95% CI)	Z	P	I² (%)	OR (95% CI)	Z	P	I² (%)	OR (95% CI)	Z	P	I² (%)	OR (95% CI)	Z	P	I² (%)
Total (21)	1.054 (1.022, 1.087)	2.08	0.005	21.9	1.115 (1.043, 1.191)	3.22	0.001	0	1.068 (1.001, 1.139)	2.0	0.046	0	1.062 (1.017, 1.109)	2.74	0.006	34	1.089 (1.024, 1.158)	2.73	0.006	0
Asian (4)	0.987 (0.908, 1.072)	0.31	0.755	38.1	0.992 (0.827, 1.191)	0.08	0.935	0	1.051 (0.878, 1.258)	0.54	0.586	0	0.965 (0.861, 1.082)	0.61	0.534	44	1.024 (0.863, 1.214)	0.27	0.789	0
Caucasian (15)	1.065 (1.028, 1.104)	3.47	0.001	21.1	1.123 (1.041, 1.211)	2.99	0.003	0	1.045 (0.971, 1.126)	1.17	0.241	0	1.090 (1.036, 1.146)	3.34	0.001	32.6	1.079 (1.006, 1.158)	2.14	0.032	0
Population-based (15)	1.052 (1.017, 1.088)	2.93	0.003	30.8	1.109 (1.032, 1.192)	2.81	0.005	11	1.063 (0.991, 1.140)	1.17	0.087	0	1.061 (1.011, 1.113)	2.43	0.015	40.2	1.089 (1.024, 1.158)	2.36	0.018	0
Hospital-based (5)	1.067 (0.983, 1.159)	1.56	0.119	24	1.162 (0.968, 1.396)	1.61	0.107	0	1.116 (0.932, 1.336)	1.20	0.232	0	1.069 (0.955, 1.197)	1.46	0.246	42	1.139 (0.960, 1.352)	1.49	0.136	0

OR = Odds ratio, CI = Confidence interval.

DISCUSSION

Genetics have been reported to serve a dominant role in colorectal carcinogenesis and progression. Since single nucleotide polymorphisms account for most human genetic variation, their connection to individual CRC risk has gained considerable attention. Inconsistent findings were reported in recent epidemiological studies on the relationship between CRC risk and rs719725 polymorphism. Zanke *et al.*, and Kocarnik *et al.*, pointed out an association of rs719725 polymorphism with the increased risk of CRC.[7,17] While later research by Curtin *et al.*, Holst *et al.*, and Kim *et al.*, failed to detect any such association. Thus, the authors performed this up-to-date meta-analysis to obtain a comprehensive conclusion.[14-16]

To the authors' knowledge, this work is a new meta-analysis within at least the last ten years to evaluate the relationship between CRC risk and rs719725 polymorphism.

This meta-analysis critically retrieved all the relevant published studies and ultimately selected 21 eligible case-control studies comprising 16015 CRC patients and 19341 healthy controls. This meta-analysis finally found a significant association between an increased CRC risk and rs719725 polymorphism. In the ethnicity-stratified subset analysis, rs719725 polymorphism was also detected to be significantly associated with the increased incidence of CRC among Caucasians. However, no such association was detected in the Asian population. Such results may be partially on account of a limited number of studies involving Asians. After stratification analysis with the sources of controls, the same significant association was detected among the population-based studies. The sensitivity analyses further confirmed the significance of the above-detected associations. In addition, no significant publication bias was detected in the meta-analysis.
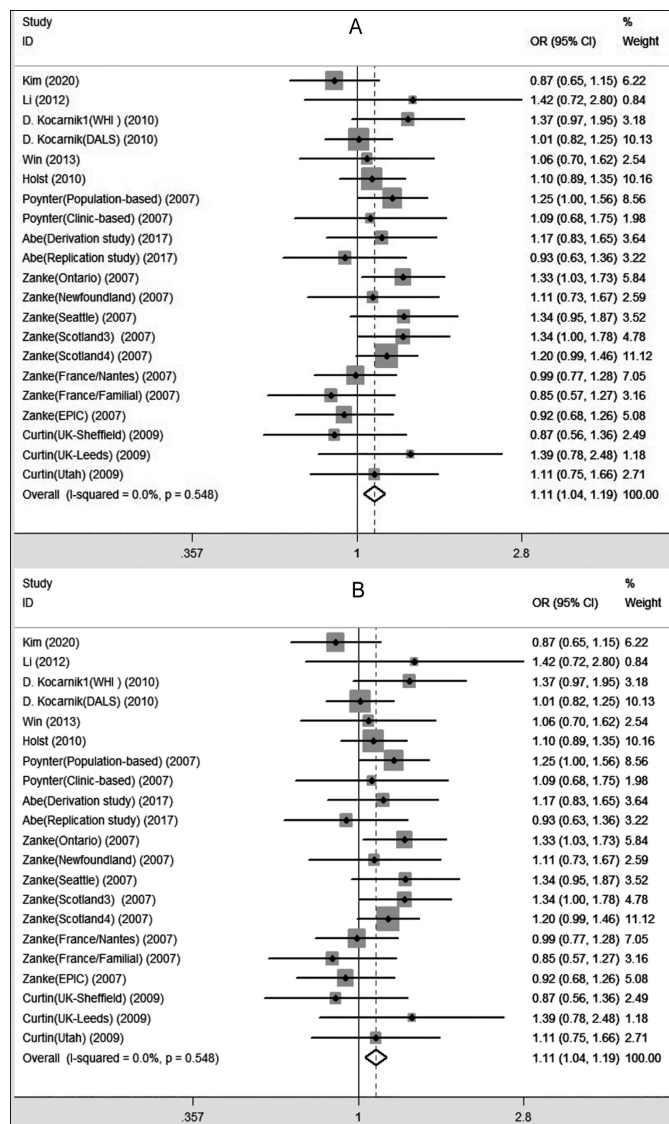
Figure 2: Forest plots for the rs719725 polymorphism and colorectal cancer risk ((A): AA vs. CC; (B): AA *vs.* AC+CC).
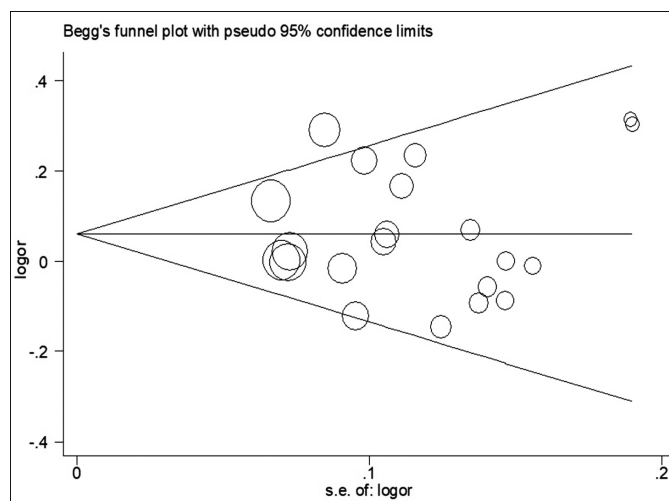

Figure 3: Begg's funnel plot for assessing potential publication bias (AA *vs.* AC+CC).
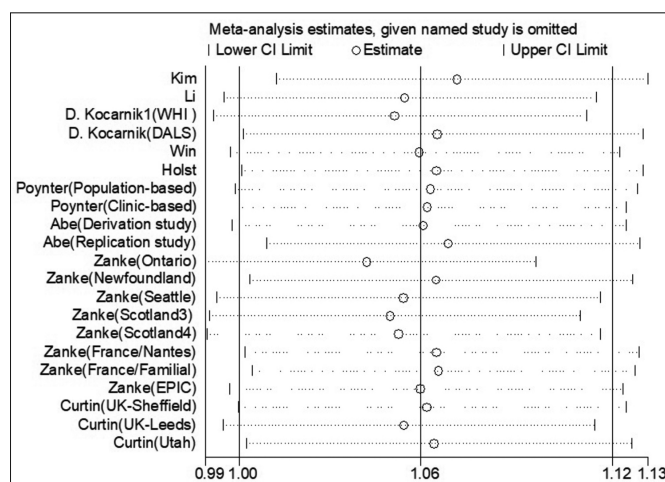

Figure 4: Sensitivity analysis (AA *vs.* AC+CC).

Several mutations in oncogenes and tumour suppressor genes, predominantly in adenomatous polyposis coli (APC), Kirsten-ras, and p53 are contributable to a sizeable fraction of CRC.[20-22]

The tumour suppressor gene APC has been determined to be a major contributor to hereditary CRC.[23] Various SNPs in APC have been observed in CRC. Huang *et al.* in their case control study observed a significant difference in genotype frequency for the rs2019720 polymorphism in APC between CRC and normal control (p = 0.004), indicating this SNP might be correlated with the susceptibility to CRC in the Chinese Han population.[24] In the same racial population, Ying *et al.* found the rs1804194 polymorphism in APC and its interactions with body mass index and smoking are associated with CRC risk in the dominant and recessive models (all p <0.001).[25] In this meta-analysis, the strength of the association between genotype frequency and CRC risk in all genetic models indicated a powerful conclusion.

Notably, consideration of some limitations should be given when interpreting the meta-analysis. First, potential publication bias may still be an issue when without including the unpublished data and ongoing studies in the meta-analysis, even though the statistical test did not indicate such bias. Second, the ethnicity-stratified subset analysis was limited to the Caucasian and Asian populations, thus these conclusions may not be extrapolated to other populations. Third, the number of included studies or the subjects in some subsets (especially Asian and hospital-based groups) was relatively small, and insufficient statistical power might produce significant or insignificant associations by chance. Nevertheless, the sample size in this investigation was the largest ever since the initiation of this meta-analysis.

CONCLUSION

This meta-analysis strongly indicates that rs719725 polymorphism is significantly associated with increased CRC

risk, particularly among Caucasians. Further investigation on the association across different ethnic populations is warranted.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
XZ: Designed the study and analysed the data.
XZ, AC: Searched the literature.
XZ, AC, TZ: Collected the data and provided interpretations of the results.
TZ: Drafted the manuscript.
All the authors have approved the final version of the manuscript to be published.

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