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ORIGINAL RESEARCH

Association between lncRNA CASC8 polymorphisms and the risk of cancer: a meta-analysis

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Objective: To explore the relationship between single-nucleotide polymorphisms (SNPs) in one of the long noncoding RNA (lncRNA), cancer susceptibility candidate 8 (*CASC8*) gene and the risk of cancer.

Materials and methods: A meta-analysis was conducted to summarize the relationship between common SNPs (rs10505477 and rs7837328) in the lncRNA *CASC8* gene and the risk of cancer. The relevant references were retrieved from several authoritative databases. Rigorous inclusion and exclusion criteria were adopted to ensure the credibility of the results. The fixed effects or random effects model was used to calculate the OR and 95% CI. We tested for publication bias.

Results: Fifteen articles containing 20 datasets (24,504 cases and 22,969 controls) were finally included in the meta-analysis. Compared to the individuals carrying the rs10505477 TT genotype, those with the TC or CC genotype had a decreased risk of cancer (TC vs TT: OR 0.876, 95% CI 0.832–0.923, $P<0.001$; CC vs TT: OR 0.748, 95% CI 0.703–0.795, $P<0.001$). Allele C of rs10505477 might be a protective factor for decreasing susceptibility to cancer (OR 0.866, 95% CI 0.840–0.893, $P<0.001$). As for rs7837328, the GA and AA genotypes were associated with increased risks of cancer as compared to the GG genotype (ORs 1.209 and 1.336; 95% CIs 1.127–1.298 and 1.202–1.484, respectively); its A allele could significantly increase the risk of cancer compared with the G allele (OR 1.169, 95% CI 1.114–1.227, $P<0.001$).

Conclusion: The rs10505477 and rs7837328 polymorphisms might be associated with risk of cancer.

Keywords: lncRNA, CASC8, single-nucleotide polymorphism, cancer, meta-analysis

Background

Long non-coding RNA (lncRNA) is a noncoding RNA class with a length of more than 200 nucleotides (nt). Previous studies have shown that lncRNA plays an important role in many cellular processes such as cell cycle, apoptosis, epigenetics, and regulation of gene expression; in addition, lncRNA has become a research hotspot in the genetic and molecular epidemiology fields.[1,2] In recent years, it has been found that lncRNA expression or functional abnormalities are closely related to the occurrence of human diseases, including several serious diseases that harm human health such as cancer and degenerative neurological diseases; specific manifestations were presented in the abnormal expression of lncRNA in sequential and spatial structures. A previous study showed that lncRNAs could be regarded as noninvasive tumor biomarkers in urologic malignancies, and their alterations could promote tumor development in prostate, bladder, and kidney cancers.[3] In fact, it is worth deeply studying not only tumors of

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the urinary system but also the relationship between lncRNA and other tumors. The focus of this study is to explore the association between the genetic variants located in one lncRNA (cancer susceptibility candidate 8 [CASC8]) and the risks of various types of cancer.

The *CASC8* gene is located in the 8q24 – a non-protein-coding region including plenty of genetic loci. Recent studies have revealed that the lncRNAs originating from the human 8q24 locus play important roles in MYC regulation, which is known to be a key contributor to the development of many human tumors.[4] The expression of CASC8 is suggested to be significantly correlated with increased cancer susceptibility. Moreover, this study found that the MYC enhancer region physically interacts with the active regulatory region of the CASC8 promoter, suggesting that long-range interaction of the MYC enhancer with the CASC8 promoter regulates CASC8 expression. Finally, Kim et al demonstrated that CARLo-5 has a function in cell-cycle regulation and tumor development.[5] Genome-wide association studies (GWAS) and several case–control studies have proved that some particular variants in CASC8 had correlation with carcinomas such as breast cancer, colorectal cancer (CRC), prostate cancer (pCa), upper gastrointestinal cancer, lung cancer, and gastric cancer.[6–10] The single-nucleotide polymorphism (SNP) of rs10505477 – located in the intron of the lncRNA of *CASC8* gene – had an intimate correlation with CRC susceptibility,[11–13] the risk of lung cancer, the prognosis for gastric cancer,[14,6] and so on. Rs7837328 – another polymorphism in CASC8 – was associated with pCa and CRC susceptibility.[7,15] Although the above studies have reported the association between polymorphisms in the *CASC8* gene and risks of cancer, the results were not consistent. Thus, the effect of polymorphisms in the *CASC8* gene on cancer is still unclear. Therefore, we conducted an updated meta-analysis on all available studies to assess the overall cancer risk with rs10505477 and rs7837328.

Materials and methods

Data collection

We searched related references from PubMed, Web of science, Chinese National Knowledge Infrastructure(CNKI), China Science and Technology Journal Database, and the Chinese Wanfang Data Knowledge Service Platform. The search keywords were "LncRNA AND cancer", "CASC8", "rs10505477", and "rs7837328". A total of 164 references were retrieved. After examination by title and abstract, 119 articles were retrieved for further evaluation. One hundred studies were excluded because of the absence of detailed genotype frequency, reviews, and cell line or animal studies. Two studies were excluded because of no specified cancer risk. One paper was removed because its full text could not be obtained. One study did not accord with the Hardy–Weinberg equilibrium (P=0.015) and, then, was excluded from the study. Finally, 15 articles containing 20 datasets (24,504 cases and 22,969 controls) were included and used in quantitative synthesis for systematic review. A flowchart of the study selection process is shown in Figure 1.

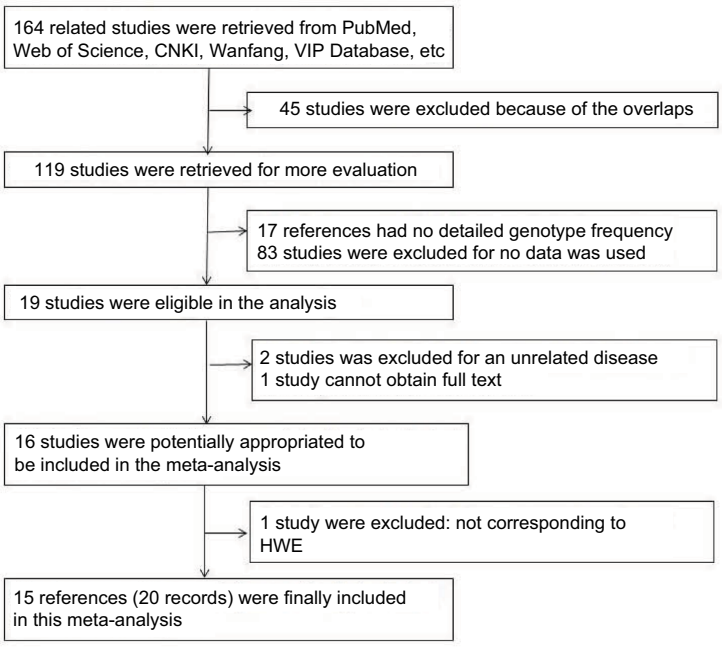

Figure 1 Flow diagram of study identification with criteria in the meta-analysis.

Inclusion/exclusion criteria

Studies included in this meta-analysis had to meet the following criteria: 1) cases were diagnosed with carcinomas at any stage; 2) a clinical case–control study; 3) published in Chinese or English language; and that 4) the distribution of genotype in controls was consistent with the Hardy–Weinberg equilibrium (HWE). Exclusion criteria were as follows: 1) comprehensive data on one type of cancer with other cancers were excluded in the stratified analyses by cancer types; 2) no definite genotype or allele frequency; 3) case–control studies that were family based; and 4) the document type was a summary or a review.

Statistical analysis

This meta-analysis describes the relationship between lncRNA CASC8 SNPs and various type of cancers with ORs and 95% CIs. For each SNP, we estimated five genetic models of ORs and 95% CIs, involving additive model, dominant model, and recessive model as well as homozygous and heterozygous comparisons. Subgroup analysis was conducted according to ethnicity, source of controls, genotyping methods, and cancer types.

The Hardy–Weinberg equilibrium test was conducted on the allele frequency of the control group. The study population were regarded as originating from the same Mendelian genetic group when $P>0.05$. The stability and effect of the results were assessed by the chi-square test as well as by calculating ORs and 95% CI. The combined ORs were calculated by the additive model (rs10505477 C vs T and rs7837328 A vs G), and the statistical significance was evaluated by the Z test. Cochran's Q test and I^2 were used to test the heterogeneity. If I^2 <50% and $P>0.1$, the fixed effects model was used to calculate the ORs and the 95% CI; in contrast, the random effects model was applied. Publication bias was estimated by Begg funnel and Egger regression tests. All statistical analyses were conducted on STATA software (version 11.0), and $P<0.05$ of the two-tailed probability was considered to be statistically significant.

Results

Eligible studies

According to the inclusion/exclusion criteria, 15 articles containing 20 datasets (24,504 cases and 22,969 controls) were finally included in the meta-analysis. In these papers, nine articles including 14 records (16,238 cases and 16,594 controls) were related to rs10505477, and six studies including six datasets (8,266 cases and 6,375 controls) were concerned with rs7837328. The characteristics of all studies are summarized in Table 1. The nine articles of rs10505477 were included in this meta-analysis.[11,14,16–22] Among these, 11 records were Caucasian-based (13,652 cases and 14,221 controls), and three records were Asian-based (2,586 cases and 2,373 controls). In the same way, six articles about rs7837328 were selected in this study.[15,23–27] Caucasians had two records (1,341cases and 1,260 controls), whereas Asians had four records (6,925 cases and 5,115 controls).

Meta-analysis

Rs10505477 and cancer susceptibility

The relationship between the rs10505477 locus in the lncRNA *CASC8* gene and the risk of all cancers is shown in Table 2. Compared to individuals carrying the TT genotype, those with the TC or CC genotype were at decreased risk of developing cancer (TC vs TT: OR 0.876, 95% CI 0.832–0.923, $P<0.001$; CC vs TT: OR 0.748, 95% CI 0.703–0.795, $P<0.001$). The same results were suggested in the dominant model (TC+CC vs TT: OR 0.834, 95% CI 0.794–0.875, $P<0.001$) and the recessive model (CC vs TC+TT: OR 0.817, 95% CI 0.776–0.860, $P<0.001$). In the additive model (C vs T), allele C might be a protective factor for decreasing the susceptibility to cancer (OR 0.866, 95% CI 0.840–0.893, $P<0.001$). The heterogeneity test is shown in Table 2 ($I^2>50\%$ and $P>0.10$), and the fixed effects model was used for the analyses.

The results of subgroup analysis are summarized in Table 3. In the ethnicity analysis, decreased cancer risk was found in either the Caucasian or Asian population. According to the source of controls, all the five models based on population-based studies showed statistical significance with regard to decreasing the risk of cancers (OR<1, $P<0.001$), whereas no significant difference was found in hospital-based studies ($P>0.05$). In studies using Taqman as the genotyping method, all models had a marked association with lower cancer susceptibility. For studies using the MassARRAY method, a significant relationship was found in homozygote comparison – recessive model and additive model. Significant correlations with decreased CRC risk were observed in all the models. Subject to the amount of included studies, other types of cancer have not been analyzed.

Rs7837328 and cancer susceptibility

Rs7837328 – another locus on lncRNA *CASC8* – is associated with the risk of cancer susceptibility as shown in Table 4. Com-

Table 1 Characteristics of the studies included in this meta-analysis

References	Year	Ethnicity	Source	Cancer	Genotying method	Case/control	Genotyping distribution						HWE
							Case			Control			
Rs10505477 (T>C)							TT	TC	CC	TT	TC	CC	
Hashemi et al[22]	2016	Caucasian	PB	ALL	PCR-RELP	110/120	40	43	27	35	56	29	0.481
Hu et al[14]	2016	Asian	HB	LC	MassARRAY	484/210	152	243	89	63	101	46	0.645
Zhou et al[19]	2014	Asian	HB	GC	MassARRAY	242/227	52	120	70	45	107	75	0.542
Haerian et al[20]	2014	Caucasian	HB	CRC	Taqman	380/335	88	182	110	58	182	95	0.555
Hutter et al[16]	2010	Caucasian	PB	CRC	MassARRAY	1,453/1,797	405	741	307	461	912	424	0.512
Hutter et al[16]	2010	Caucasian	PB	CRC	MassARRAY	636/646	169	323	144	156	328	162	0.692
Curtin et al[21]	2009	Caucasian	PB	CRC	SNPlex	1,071/1,040	304	544	223	273	519	248	0.965
Schafmayer et al[17]	2008	Caucasian	PB	CRC	SNPlex	2,713/2,718	780	1,359	574	638	1,374	706	0.543
Zanke et al[11]	2007	Caucasian	PB	CRC	Taqman	761/749	222	372	167	195	365	189	0.489
Zanke et al[11]	2007	Caucasian	PB	CRC	Taqman	1,415/1,656	395	696	324	384	842	430	0.472
Zanke et al[11]	2007	Caucasian	PB	CRC	Taqman	2,809/2,912	836	1,410	563	755	1,444	713	0.665
Zanke et al[11]	2007	Caucasian	PB	CRC	Taqman	1,859/1,882	579	890	390	487	913	482	0.197
Zanke et al[11]	2007	Caucasian	PB	CRC	Taqman	445/366	129	213	103	105	176	85	0.499
Gruber et al[18]	2007	Asian	PB	CRC	GeneChip	1,860/1,936	535	936	389	531	932	473	0.110
Rs7837328 (G>A)						GG	GA	AA	GG	GA	AA		
Yang et al[27]	2014	Asian	HB	CRC	Taqman	90/132	26	37	27	49	61	22	0.684
Zhang et al[15]	2014	Asian	PB	PCa	PCR	388/344	122	210	56	115	173	56	0.501
San Francisco et al[24]	2013	Caucasian	HB	pCa	Taqman	83/21	29	45	9	9	10	2	0.743
Cui et al[23]	2010	Asian	PB	CRC	Illumina	6,163/4,494	2,487	2,886	790	2,040	1,970	484	0.796
Zheng et al[26]	2010	Asian	PB	pCa	MassARRAY	284/145	99	133	52	59	64	22	0.502
Salinas et al[25]	2008	Caucasian	PB	pCa	SNPlex	1,258/1,239	387	639	232	451	590	198	0.828

Notes: Hardy–Weinberg equilibrium test was conducted on the allele frequency of the control group. The study population were regarded as coming from the same Mendelian genetic group when $P>0.05$.
Abbreviations: HB, hospital-based; PB, population-based; LC, lung cancer; GC, gastric cancer; CRC, colorectal cancer; EOC, epithelial ovarian cancer; pCa, prostate cancer.

Table 2 Relationship between SNP of rs10505477 and cancer susceptibility

SNP	No.	Pooled OR (95% CI)	*P* value	Phet*	I^2	Model#
TC vs TT	14	0.876 (0.832–0.923)	<0.001	0.617	0.0	F
CC vs TT	14	0.748 (0.703–0.795)	<0.001	0.801	0.0	F
TC+CC vs TT	14	0.834 (0.794–0.875)	<0.001	0.609	0.0	F
CC vs TC+TT	14	0.817 (0.776–0.860)	<0.001	0.888	0.0	F
C vs T	14	0.866 (0.840–0.893)	<0.001	0.763	0.0	F

Notes: *P-value of the heterogeneity test. #The fixed effects model was used.

pared to the wild genotype (GG), the heterozygote genotype (GA) and the homozygote genotype (AA) were associated with increased risks of cancer (ORs were 1.209 and 1.336, 95% CIs were 1.127–1.298 and 1.202–1.484, respectively). Moreover, we drew the same conclusion in a dominant model (OR 1.236, 95% CI 1.156–1.322, $P<0.001$) and a recessive model (OR 1.204, 95% CI 1.092–1.328, $P<0.001$). In an additive model, allele A could significantly increase the risk of cancer as compared with allele G (OR 1.169, 95% CI 1.114–1.227, $P<0.001$). Heterogeneity test results are listed in Table 4; owing to $I^2<50\%$ and $P>0.1$, the fixed effects models were used.

Subgroup analysis was conducted by means of ethnicity, source of controls, genotyping methods, and cancer types. The results were revealed in Table 5. In different ethnicities, the additive, dominant, and genetic models of the Caucasian population had statistical significance in increasing cancer susceptibility ($P<0.05$). All models in the Asian population obtained a significant result in increasing the cancer risk ($P<0.001$). Significant results were found in all the genetic models for population-based studies ($P<0.001$). For the pooled results in hospital-based studies, in addition to a dominant model ($P=0.151$) and heterozygote comparison ($P=0.489$), other models showed a statistically significant effect on the cancer risk ($P<0.05$). In a subgroup analysis of cancer types, dominant models in CRC and pCa had a statistical association with increasing cancer susceptibility

Table 3 The subgroup analysis of rs10505477 and cancer susceptibility

Subgroup	No.	Homozygote		Heterozygote		Dominant model		Recessive model		Additive model	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Ethnicity	14										
Caucasian	11	0.737 (0.689–0.788)	<0.001	0.857 (0.810–0.906)	<0.001	0.817 (0.775–0.862)	<0.001	0.817 (0.772–0.864)	<0.001	0.859 (0.831–0.888)	<0.001
Asian	3	0.814 (0.694–0.954)	0.011	0.995 (0.870–1.137)	0.938	0.933 (0.823–1.059)	0.284	0.817 (0.715–0.934)	0.003	0.905 (0.836–0.981)	0.015
Source	14										
PB	11	0.746 (0.700–0.794)	<0.001	0.877 (0.832–0.925)	0.001	0.834 (0.793–0.877)	<0.001	0.812 (0.770–0.856)	<0.001	0.864 (0.837–0.892)	<0.001
HB	3	0.788 (0.602–1.031)	0.082	0.852 (0.674–1.077)	0.179	0.833 (0.668–1.040)	0.107	0.900 (0.728–1.113)	0.333	0.899 (0.787–1.026)	0.115
Method	14										
Taqman	6	0.729 (0.667–0.797)	<0.001	0.848 (0.787–0.914)	<0.001	0.809 (0.753–0.868)	<0.001	0.815 (0.757–0.878)	<0.001	0.854 (0.817–0.893)	<0.001
MassARRAY	4	0.820 (0.705–0.953)	0.010	0.932 (0.821–1.058)	0.279	0.896 (0.896–1.009)	0.071	0.858 (0.757–0.973)	0.017	0.907 (0.842–0.978)	0.011
tagSNP	1	–	–	–	–	–	–	–	–	–	–
SNPlex	2	0.702 (0.617–0.799)	<0.001	0.845 (0.758–0.942)	0.002	0.812 (0.692–0.953)	0.011	0.785 (0.705–0.873)	0.947	0.840 (0.788–0.895)	<0.001
Genechip	1	–	–	–	–	–	–	–	–	–	–
Cancer	14										
CRC	11	0.745 (0.700–0.794)	<0.001	0.875 (0.829–0.922)	<0.001	0.832 (0.791–0.875)	<0.001	0.816 (0.774–0.860)	<0.001	0.865 (0.838–0.892)	<0.001
ALL	1	–	–	–	–	–	–	–	–	–	–
LC	1	–	–	–	–	–	–	–	–	–	–
GC	1	–	–	–	–	–	–	–	–	–	–

(P<0.05). The additive model of pCa suggested a similar result (OR 1.147, 95% CI 1.045–1.258, P=0.004).

Influential analysis

In this study, we used the "influence analysis-metaninf" method as a sensitivity analysis method to assess the reliability of this meta-analysis. After individually excluding studies, the combined effect of the OR value revealed no significant change; therefore, the results of this analysis are reliable.

Publication bias

Both Begg's and Egger's tests were used to estimate publication bias of rs10505477 and rs7837328 in this meta-analysis. Begg's funnel plots of both polymorphisms were basically symmetrical; therefore, no publication bias was found in both loci. By Egger' test, P-values were 0.061 and 0.746 for rs10505477 and rs7837328, respectively, but none of them had statistical significance.

Discussion

This is an updated meta-analysis on all available studies to assess the overall cancer risk with rs10505477 and rs7837328 polymorphisms in the *CASC8* gene. The results showed that rs10505477 (T>C) and rs7837328 (G>A) polymorphisms were related to the risk of all kinds of cancers. In a subgroup analysis of cancer types, significant correlations of rs10505477 with decreased CRC risk were observed. Rs7837328 was suggested to be associated with the risks of CRC and pCa.

A malignant tumor that develops between the dentate line of the digestive tract and the sigmoid colon, CRC is the third most commonly diagnosed cancer in males and the second in females, with more than 1.2 million new patients and 608,700 deaths evaluated to have occurred in 2008.[28] pCa refers to epithelial malignancies that occur in the prostate. It was reported that pCa was the second most common cause of cancer in US men among non-cutaneous cancers.[29] Molecular epidemiology has increasingly shown that SNPs play a crucial role in the progression of cancer, including CRC and pCa.

In recent years, GWAS have authenticated five SNPs (rs6983267, rs10505477, rs7837328, rs10505477, and rs16892766) located in the 8q23–8q24 chromosome region, which had a strong correlation with the development of CRC.[13,30–32] SNPs, as third-generation genetic biomarkers, are widely distributed in the human genome and have good stability and high density. They can effectively reflect the differences of individuals to a certain extent, which has

Table 4 Relationship between SNP of rs7837328 and cancer susceptibility

SNP	No.	Pooled OR (95% CI)	*P* value	Phet[a]	I^2	Model
GA vs GG	6	1.209 (1.127–1.298)	<0.001	0.993	0.0	F
AA vs GG	6	1.336 (1.202–1.484)	<0.001	0.478	0.0	F
GA+AA vs GG	6	1.236 (1.156–1.322)	<0.001	0.941	0.0	F
AA vs GA+GG	6	1.204 (1.092–1.328)	<0.001	0.335	12.5	F
A vs G	6	1.169 (1.114–1.227)	<0.001	0.514	0.0	F[b]

Note: [a]Heterogeneity test; [b]the fixed effects model.

gradually become an important tool for medical research and molecular biology studies.

The mechanism by which the *CASC8* gene modifies cancer susceptibility is still unknown. The possible role of CASC8 in cancer development is as follows: *CASC8* is located near the *MYC* gene in the region of 8q24.1 – a known gene desert containing multiple enhancer elements in the proximity of the *MYC* gene, associated with several cancers, including pCa and CRC.[33] These enhancers regulate transcription of the *MYC* gene through an interaction with the CASC8 promoter.[5] The pathogenesis is speculated to be as follows: First, the rs10505477 allele could disrupt the correlation between CASC8 and the cognate gene *POU5F1B* (POU class 5 homeobox 1 pseudogene 1), whose carcinoma susceptibility is well known.[34] Thus, the mutant allele suppresses some transcription elements to act as the promoter of the *POU5F1B* gene.[14] Second, it was reported that a strong linkage disequilibrium (LD) was found between several loci (rs10505477,[35] rs7837328,[27] and rs7014346[36]) and rs6983267, which is located at 8q24 and has confirmed to be related to CRC, pCa, and kidney cancer susceptibility, among others.[13,37,38] Resequencing and detailed determination of the regional LD indicated that rs6983267 could be a casual variation in disease. However, the variant is located in a gene desert.[39] The oncogene *MYC*, the proximal gene, is ~335 kb telomeres from the risk region, which is abnormally expressed in several cancers, including CRC.[40] Therefore, the rs10505477 and rs7837328 loci might indirectly affect the risk of CRC through their LD link with the cancer susceptibility-related rs6983267 locus.

Multiple polymorphisms in the 8q24 region have been proved to have a significant association with pCa risk that could be drawn in both case–control association and genetic linkage studies. Salinas et al confirmed that several 8q24 SNPs of western European descent and the centromeric-specific boundary of the 8q24 region are significantly associated with the risk of pCa, including rs6983267.[25]

In an ethnicity subgroup analysis, we validated positive results in both Caucasian and Asian populations, wherein the aberrant expression of the mutant allele of rs10505477 indeed increased the risk of cancers. The ethnicity analysis of rs7837328 drew a significant conclusion in the Caucasian population, but negative results in the Asian population. The reason may be that although rs7837328 and the risk of CRC had been confirmed by GWAS, its correlation with pCa is still uncertain in Asians, particularly the Chinese. In southern Chinese, rs7837328 was reported to not be associated with PCa.[26] Interestingly, a statistically significant result was found in the northern Chinese Han population, for both of the alleles (P=0.004) and genotypes (P=0.008).[15] This discrepancy may be explained by daily lifestyle, dietary habits, geographic climate, ethnic diversity, and so on.

According to the relevant literature so far, in addition to another meta-analysis of 8q23-24-related loci and CRC in 2015,[41] this is the first study on the relationship between these loci and cancer susceptibility. Besides, our data are relatively new, with the latest data from 2016. In addition, we conducted a detailed subgroup analysis of ethnicity, source, genotyping, and cancer types, with high reliability.

The limitations of this study are as follows: first, the sample size was not large, and unpublished studies may exist that could introduce a potential publication bias; second, the research only studied the relationship between gene polymorphisms and cancer risks, ignoring environmental factors and the interaction of gene–environment; and third, due to data limitations, no tumor staging was discussed.

In conclusion, our meta-analysis showed that the rs10505477 (T>C) and rs7837328 (G>A) polymorphisms were related to the risk of cancer. Although limitations exist, future more rigorous studies are warranted to confirm this result.

Table 5 The subgroup analysis of rs7837328 and cancer susceptibility

Subgroup	No.	Homozygote		Heterozygote		Dominant model		Recessive model		Additive model	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Ethnicity	6										
Caucasian	2	1.366 (1.084–1.721)	0.008	1.266 (1.064–1.506)	0.008	1.291 (1.096–1.521)	0.002	1.188 (0.966–1.461)	0.102	1.182 (1.058–1.321)	0.003
Asian	4	1.328 (1.180–1.495)	<0.001	1.199 (1.109–1.295)	<0.001	1.226 (1.139–1.319)	<0.001	1.209 (1.082–1.351)	0.001	1.166 (1.105–1.230)	<0.001
Source	6										
Population-based	4	1.320 (1.187–1.469)	<0.001	1.210 (1.126–1.299)	<0.001	1.233 (1.152–1.319)	<0.001	1.188 (1.076–1.312)	0.001	1.163 (1.108–1.222)	<0.001
Hospital-based	2	2.126 (1.077–4.195)	0.030	1.207 (0.708–2.059)	0.489	1.439 (0.876–2.363)	0.151	1.960 (1.073–3.577)	0.028	1.468 (1.047–2.057)	0.026
Method	6										
Taqman	2	2.126 (1.077–4.195)	0.030	1.207 (0.708–2.059)	0.489	1.439 (0.876–2.363)	0.151	1.960 (1.073–1.073)	0.028	1.468 (1.047–2.057)	0.026
Illumina	1	–	–	–	–	–	–	–	–	–	–
PCR	1	–	–	–	–	–	–	–	–	–	–
SNPlex	1	–	–	–	–	–	–	–	–	–	–
MassARRAY	1	–	–	–	–	–	–	–	–	–	–
Cancer	6										
CRC	2	1.360 (1.200–1.542)	<0.001	1.201 (1.107–1.302)	<0.001	1.232 (1.141–1.331)	<0.001	1.474 (0.873–2.488)	0.146	1.260 (0.989–1.604)	0.061
pCa	4	1.279 (1.054–1.553)	0.013	1.238 (1.071–1.430)	0.004	1.249 (1.090–1.432)	0.001	1.127 (0.947–1.341)	0.178	1.147 (1.045–1.258)	0.004

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Disclosure

The authors report no conflicts of interest in this work.

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