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REVIEW

Genetic polymorphisms of *CASR* and cancer risk: evidence from meta-analysis and HuGE review

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Background: *CASR* gene appears to be involved in cancer biology and physiology. However, a number of studies investigating *CASR* polymorphisms and cancer risks have presented inconclusive results. Thus, a systematic review and a meta-analysis of the effect of *CASR* polymorphisms on several cancer risks were performed to suggest a statistical evidence for the association of *CASR* polymorphisms with cancer risks.

Methods: MEDLINE, EMBASE, Web of Science, Scopus, and the HuGE databases were searched. Nineteen articles of case–control and cohort studies were included for the final analysis.

Results: The colorectal cancer risk was reduced in proximal (odds ratio [OR] =0.679, *P*=0.001) and distal (OR =0.753, *P*=0.026) colon sites with GG genotype of *CASR* rs1042636 and increased in distal colon site (OR =1.418, *P*=0.039) with GG genotype of rs1801726 by additive genetic model. The rs17251221 demonstrated noticeable associations that carrying a homozygote variant increases breast and prostate cancer risk considerably.

Conclusion: The significant association of *CASR* polymorphisms with several cancer risks was observed in this review. In particular, the act of *CASR* polymorphisms as a tumor suppressor or an oncogene differs by cancer site and can be the research target for tumorigenesis.

Keywords: rs1042636, rs1801725, rs1801726, systematic review, colorectal cancer

Introduction

The effect of calcium intake on various cancer risks is an ongoing topic of investigation. Besides the physiologic calcium level, the calcium-sensing receptor (CaSR), through which calcium balance is regulated, is thought to play an important role in the regulation of cancer expression. The activated CaSR can stimulate intracellular signal pathways including mitogen-activated protein kinase, phosphatidylinositol 3 kinase/protein kinase B, and cy-mic and cyclin D1 pathways; these processes are involved in cellular secretion, proliferation, differentiation, chemotaxis, and apoptosis.[1] The CaSR expression is related to the *CASR* gene that seems to have a role in cancer cells, acting both as a tumor suppressor and an oncogene, depending on the cancer site and environmental condition. In colonic epithelial cells, high calcium intake could reduce the risk of colorectal cancer development.[2] E-cadherin stimulated by CaSR can interact with β-catenin, an important protooncogene, contribute to reducing the cancer cell activity, and downregulate cell proliferation.[3] Whereas, the increased expression of CaSR by high calcium levels promoted MCF-7, PC-3, and C4-2B breast and prostate cancer cells known to metastasize to the bone and the cancer cell proliferation process is linked to extracellular signal-regulated kinases 1 and 2 (ERK 1/2) phosphorylation.[4]

The *CASR* gene contains seven exons and is located on chromosome 3q13. Among the single-nucleotide polymorphisms (SNPs) in the *CASR* gene, rs1801725

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(A986S, 2956G>T) causes an amino acid change from alanine (A) to serine (S), and the T allele is associated with higher levels of serum calcium.[5] The rs1042636 (R990G, 2968A>G) polymorphism causes an amino acid change from arginine (A) to glycine (G) and induces a gain-of-function mutation associated with primary hyperparathyroidism and calcium stone formation.[6–8] The rs1801726 (Q1101E, 3403C>G) is a common polymorphism in African ethnicity whose functional characteristics need further investigation;[9,10] glutamine (Q) to glutamic acid (A) change is observed.

The rs17251221 (1378–1412A>G) in introns, which is in high linkage disequilibrium with rs1801725,[11] induces a gain-of-function mutation associated with total serum calcium concentration[11] and stone multiplicity in patients with nephrolithiasis.[12]

Recently, many studies have focused on the association between *CASR* gene polymorphism and multiple cancer risks. Three common nonsynonymous SNPs (rs1801725, rs1042636, and rs1801726) have been the primary research targets for cancer risk, but inconsistent results have been reported. Dong et al[13] reported that *CASR* variants are not associated with colorectal cancer risk, whereas Jenab et al[14] suggested possible association between *CASR* rs1042636 variations with colorectal cancer risk. Additional genetic variants of the large *CASR* gene (102 kb), which cannot be sufficiently explained by the three nonsynonymous SNPs, are also the research targets of cancer risks. Thus, a systematic review on the effect of *CASR* polymorphisms with several cancer risks and a meta-analysis on colorectal cancer risk were performed to suggest statistical evidence for the clinical use of cancer markers.

Methods

Search strategy and eligibility criteria

The electronic databases of MEDLINE, EMBASE, Web of Science, Scopus, and the HuGE Published Literature database were searched with the following keywords: ("calcium sensing receptor" OR "casr protein" OR "*CASR*" OR "Calcium sensing receptor gene") AND ("cancers" OR "neoplasia"). The references of included articles were checked to include any additional relevant articles.

A systematic search for relevant literature was performed to include studies published up to July 26, 2014, by two independent reviewers (JS and KJ) without language restrictions. Any disagreement was resolved by discussion between the authors. Inclusion criteria for article selection were as follows: 1) case–control studies or cohort studies and 2) sufficient data reporting odds ratio (OR) with 95% confidence interval (CI) or sample frequency with which the appropriate calculations could be done. Studies were excluded if they were 1) duplicate or previously published, 2) letters, reviews, or editorials, and 3) *CASR* gene studies on cell lines or animals by PRISMA flow diagram.

Data extraction

The following information was extracted from included studies: first author, year of publication, country of study site, ethnic group, genotyping method, number of genotyped cases and controls, genotype frequencies for cases and controls, selection pool of control population (population-based controls and hospital-based controls) and Hardy–Weinberg equilibrium (HWE) in any population, tumor type and site, OR, and corresponding 95% CI. Ethnicity was classified as Caucasian, Asian, or African. When the study did not specify the ethnicity, the term "mixed ethnicity" was used. Any discrepancies in the extracted information were resolved by discussion among the authors.

Quality score assessment

Two reviewers (JS and KJ) independently evaluated the quality of the selected studies using the quality assessment scoring tool developed for genetic association studies by Thakkinstian et al,[15] which was modified from previous meta-analyses of observational studies[16–19] considering traditional epidemiologic and genetic issues[20,21] (Table S1).

Statistical analysis

The association of three nonsynonymous *CASR* SNPs with colorectal cancer risk was examined by unconditional logistic regression to obtain ORs with 95% CIs in additive, dominant, and recessive genetic models and represented by forest plot. The pooled ORs were calculated for each genetic model and different cancer sites (eg, proximal colon, distal colon). Whenever ORs and 95% CIs were not reported, appropriate data were selected and calculated to produce OR with 95% CI. Between-study heterogeneity was assessed by the Q-statistic (heterogeneity was considered statistically significant if $P<0.1$)[22] and quantified by the I^2 value. Both fixed- and random-effects models were used to combine the aggregate data determined by the I^2 value. When I^2 was >50%, the random-effects model was used for analysis. Potential publication bias was assessed with the linear regression method of Egger's test[23] and funnel plot.[24] Statistical analyses were performed

using Comprehensive Meta-Analysis (Version 2; Biostat, Inc., Engelwood, NJ, USA) and PASW (Version 21; IBM Corporation, Armonk, NY, USA). All tests were two-sided, and $P<0.05$ was considered significant unless otherwise specified.

Results

Study selection

Twenty out of 1,309 publications were found to be eligible for systematic review as shown in Figure S1.

Among eligible publications, the study by Speer et al[25] was excluded due to an overlapping population with another study by the same author.[26] Also, a study for esophageal cancer[27] was excluded due to insufficient SNP information. By hand search, a study by Mahmoudi et al[28] was added, and the final number of studies included for systematic review was 19 (Table 1).

In meta-analysis, two articles that reported colorectal cancer risk of rs1801725 were excluded because the reported frequency of homozygote variants was 0. Meta-analyses for colorectal cancer risk included 4,209 cases and 4,801 controls for rs1801725 and 5,557 cases and 5,552 controls for rs1042636 and rs1801726, respectively.

Synthesis of result by meta-analysis on the colorectal cancer risk

The association between rs1801725, rs1042636, rs1801726 and colorectal cancer risk, stratified by genetic model and cancer site, is presented in Table 2.

Figures 1–3 demonstrate the pooled associations between three nonsynonymous *CASR* polymorphisms and colorectal cancer risk in forest plot.

T allele polymorphisms of rs1801725 did not show any association with colorectal cancer risk compared with the wild-type homozygous GG genotype. With the additive genetic model (TT vs GG), the pooled OR was 1.152 (95% CI: 0.859–1.543, I^2: 25.769) (Table 2, Figure 1).

The colorectal cancer risk was significantly reduced in GG genotype of rs1042636 compared with the wild type in both proximal and distal colon sites with additive genetic model (OR =0.679 [95% CI: 0.536–0.859], I^2: 42.519) in proximal colon and (OR =0.753 [95% CI: 0.587–0.967], I^2: 0) in distal colon. With the dominant genetic model, the association was not significant (Table 2, Figure 2). GG genotype of rs1801726 showed increased colorectal cancer risk in the distal colon site with additive genetic model (OR =1.418 [95% CI: 1.017–1.977], I^2: 0) (Table 2, Figure 3).

Systematic reviews of the association of *CASR* polymorphisms with cancer risks

From 19 studies that reported *CASR* polymorphisms and cancer risks, we extracted significant SNPs associated with several cancer risks that could not be assessed by meta-analysis for future research targets stratified by cancer type and cancer site (Table 3).

CASR SNPs

Having a T allele of rs1801725 is associated with clinical stage 4 (P=0.002) and the histological subgroup of undifferentiated neuroblastomas (P=0.046).[29] Patients with this polymorphism had significantly lower overall survival rates (P=0.022) and event-free survival rates (P=0.01) than those who had GG homozygotes.

African–American prostate cancer patients having advanced disease were approximately six times less carrying the homozygote minor allele of rs1801726 than were controls (P=0.01).[30]

The polymorphism of rs17251221 demonstrated a noticeable association with prostate and breast cancer risk; carrying a homozygote variant increases the risk of breast and prostate cancer considerably.[31,32]

Haplotype and diplotypes

Colorectal adenoma risk was associated with diplotype (GAC/GAG) of rs1801725, rs1042636, and rs1801726 (OR =0.56 [95% CI: 0.36–0.88]).[33] The polymorphism of rs1801726 on this diplotype reduced distal colon adenoma risk by half compared with the diplotype only composed of wild types (GAC/GAC). The haplotype (CC) of rs4678174 and rs2270916 was associated with cancer risk compared with the wild-type haplotype (TT) in the proximal colon (OR =0.80 [95% CI: 0.67–0.97]).[13] TAC haplotype of *CASR* rs1801725, rs1042636, and rs1801726 was compared with the wild-type GAC haplotype, and the increased incidence of stage 4 neuroblastoma (OR =5.52 [95% CI: 1.78–17.18]) and inferior overall survival (hazard ratio =2.74 [95% CI: 1.20–6.25]) was reported with TAC haplotype.[29]

Diet effects and *CASR* polymorphisms

The polymorphisms of rs2270916, rs10934578, rs12485716, and rs4678174 were not associated with colorectal cancer risk;[34] however, with low calcium intake, the genetic association was significant. This correlation was also valid in a study for prostate cancer;[35] several SNPs were significant only under low calcium levels or low plasma vitamin D levels.

Table 1 Main characteristics of included studies of *CASR* associated with cancer risks

Cancer type	Reference	Country (ethnicity)	Study design	Cases (n)	Controls (n)	Genotyping method (HWE)	SNP	Tumor site
Colorectal	Speer et al[26]	Hungary (Caucasian)	Hospital-based case–control	56	112	PCR (HWE: N/A)	rs1801725 (A986S)	Rectum
	Peters et al[33]	USA (94% Caucasian)	Population-based nested case–control	716	729	Taqman (HWE: A986S [*P*=0.92], A990G [*P*=0.69] Q1101E [*P*=0.62])	rs1801725 (A986S), rs1042636 (A990G), rs1801726 (Q1101E)	Distal colorectum
	Fuszek et al[81]	Hungary (Caucasian)	Population-based case–control	70	201	PCR (HWE: N/A)	rs1801725	Colorectum
	Fuszek et al[81]	Hungary (Caucasian)	Population-based case–control	70	201	PCR (HWE: N/A)	rs1801725	Colorectum
	Bácsi et al[76]	Hungary (Caucasian)	Population-based case–control	278	260	Taqman (HWE: N/A)	rs1801725	Colorectum
	Dong et al[13]	USA (Mixed, Caucasian predominant)	Population-based case–control	1,600	1,949	MALDI-TOF (HWE: *P*>0.01)	17 SNPs	Proximal colon, distal colon
	Jenab et al[14]	Europe (Caucasian)	Population-based nested case–control	1,160	1,248	Taqman (meet HWE)	rs1801725	Colorectum, colon, rectum
	Jacobs et al[79]	USA, Australia (mixed, Caucasian predominant)	Population-based discordant sibship case–control	1,802	2,874	Illumina Golden gate platform (HWE: N/A)	36 SNPs	Proximal colon, distal colon, rectum
	Safaei et al[77]	Iran (Caucasian)	Hospital-based case–control	105	105	PCR-RFLP (HWE: N/A)	rs1801725	Colorectum
	Fedirko et al[82]	Europe (Caucasian)	Population-based cohort	1,137	N/A	Taqman (HWE: N/A)	rs1801725	Colorectum
	Hibler et al[78]	USA Caucasian (white)	Population-based cohort	1,439	N/A	Illumina Golden gate platform (meet HWE)	35 SNPs	Proximal colon, distal colon
	Kim et al[34]	Korea (Asian)	Hospital-based case–control	420	815	Taqman (meet HWE)	rs10934578, rs12485716, rs4678174, rs2270916	Proximal colon, distal colon, rectum
	Mahmoudi et al[28]	Iran (Caucasian)	Hospital-based case–control	350	510	PCR-RFLP (HWE: N/A)	rs1801725	Colorectum
Prostate	Schwartz et al[30]	USA (African–American)	Population-based case–control	458	248	Illumina Beadlab system: rs1042636, rs1801726; Taqman: rs1801725 (meet HWE)	rs1801725, rs1042636, rs1801726	Prostate
	Szendroi et al[54]	Hungary (Caucasian)	Hospital-based case–control	204	102	PCR (HWE >0.05)	rs1801725	Prostate
	Shui et al[35]	USA (Caucasian with European decent)	Population-based nested case–control	1,193	1,244	Open-array SNP genotyping platform (HWE: *P*>0.01)	18 SNPs	Prostate
	Jorde et al[31]	Norway (Caucasian)	Population-based case–cohort	370	1,647	KBioscience competitive allele-specific PCR (meet HWE)	rs17251221, rs1801725	Prostate, lung, breast, colorectum
Breast	Li et al[32]	People's Republic of China (Asian)	Hospital-based case–control	217	231	Taqman (HWE: *P*>0.05)	rs17251221	Breast
Pancreas	Anderson et al[53]	Canada (Caucasian)	Population-based case–control	628	1,193	MassARRAY, iPLEX Gold sequenom Platform (meet HWE)	13 SNPs	Pancreas
Neuroblastoma	Masvidal et al[29]	Spain (Caucasian)	Cohort	65	N/A	RT-PCR (meet HWE)	Haplotype of rs1801725, rs1042636, rs1801726	Nerve

Abbreviations: HWE, Hardy–Weinberg equilibrium; PCR, polymerase chain reaction; N/A, not applicable; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; SNP, single-nucleotide polymorphism; RFLP, restriction fragment length polymorphism; RT, reverse transcription.

Table 2 Stratified analysis of the three nonsynonymous SNPs (rs1801725, rs1042636, rs1801726) in *CASR* and colorectal cancer risk by three genetic models and cancer sites

Variable		N*	n (case/control)	Association			Heterogeneity			Publication bias	
Genetic model	Site			OR	95% CI	*P*-value	I^2	*P*(*Q*)-value	Model	Funnel plot	Egger's *P*-value
rs1801725											
TT vs GG	Colorectal	6	4,209/4,801	1.152	0.859–1.543	0.379	25.769	0.345	Fixed	None	0.181
rs1042636											
GG vs AA	Proximal	3	4,841/4,823	0.679	0.536–0.859	0.001**	42.519	0.176	Fixed	None	0.634
	Distal	4	5,557/5,552	0.753	0.587–0.967	0.026**	0	0.396	Fixed	None	0.957
AG + GG vs AA	Proximal	3	4,841/4,823	0.797	0.505–1.260	0.332	83.839	0.002	Random	None	0.175
	Distal	3	4,841/4,823	0.854	0.710–1.029	0.097	44.491	0.165	Fixed	None	0.451
rs1801726											
GG vs CC	Proximal	3	4,841/4,823	1.137	0.820–1.575	0.441	0	0.408	Fixed	None	0.601
	Distal	4	5,557/5,552	1.418	1.017–1.977	0.039**	0	0.676	Fixed	None	0.770
CG + GG vs CC	Proximal	3	4,841/4,823	1.095	0.882–1.360	0.411	0	0.481	Fixed	None	0.987
	Distal	3	4,841/4,823	1.073	0.857–1.344	0.537	59.415	0.085	Random	None	0.414

Notes: *Number of studies included in the meta-analysis. **Significant result.
Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Quality score assessment

The quality score of each study was graded: 13 studies were graded 8 and over and six studies were under 8 (Table S2), and overall included studies are well designed: 13 studies have over 500 research subjects and 12 studies have population-based recruiting methods.

Publication bias

As a widely accepted tool for publication bias, Egger's linear regression methods and funnel plot were used. Overall, Egger's linear regression methods and funnel plots in rs1801725, rs1042636, and rs1801726 polymorphisms did not detect publication bias (Table 2, Figures 1–3).

Discussion

In this review, we presented the novel findings of significant association between *CASR* rs1042636, rs1801726, and rs17251221 polymorphisms; rs1042636 decreased the colorectal cancer risk in proximal and distal sites, but rs1801726 increased the risk in distal colon site. The rs17251221 considerably increased the cancer risk in prostate and breast. The *CASR* encodes a polypeptide of 1,078 amino acids with seven membrane spanning helixes characteristic of G protein-coupled receptors (GPCRs).[36,37] GPCRs have been known to have a direct link with cellular transformation with the discovery of *MAS* oncogene.[38] Wild-type GPCRs could become oncogenic by the excessive exposure to local or circulating agonists.[39–41] The G protein-coupled CaSR, through which calcium mediates its carcinogenesis, has been implicated in parathyroid gland cancer.[42] CaSR is also distributed through the entire gastrointestinal tract[43–46] and reacts to the calcium concentrations in the lumen of the colon as well as circulating concentrations.[47,48] Evidence from several studies[49–51] suggests that risk factors differ by site within the colorectum, and molecular and functional

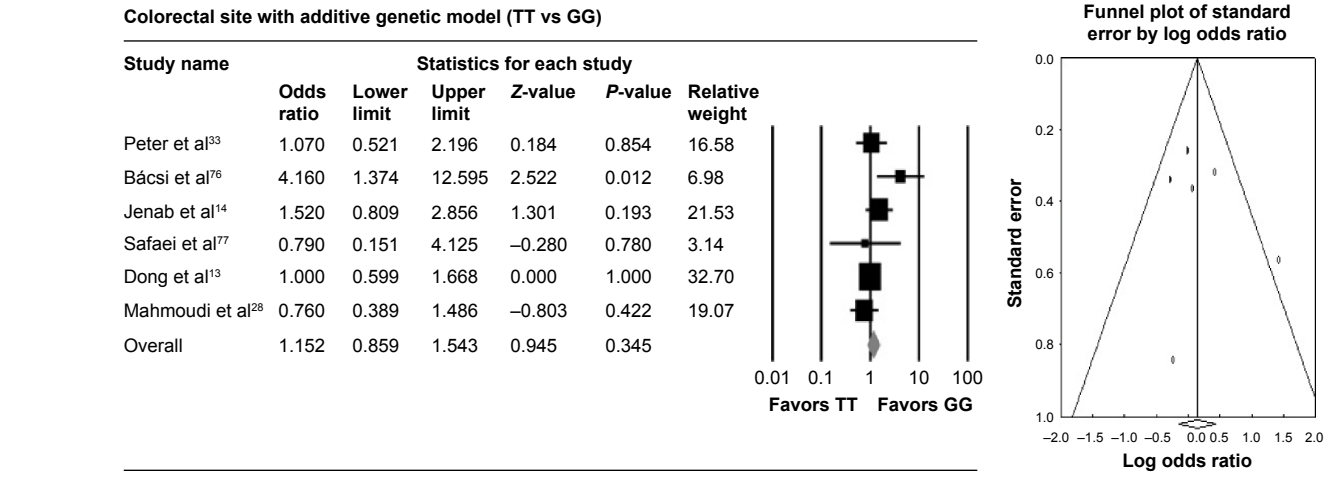
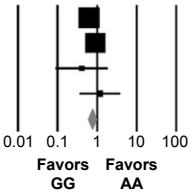
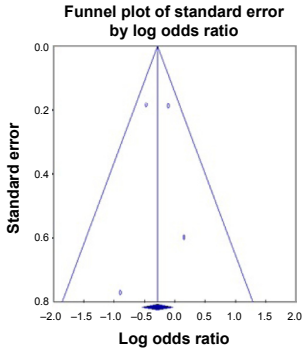


Figure 1 Association of rs1801725 polymorphism with colorectal cancer risk by additive genetic model.

Distal colon site with additive genetic model (GG vs. AA)

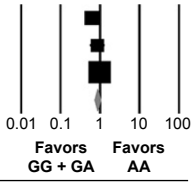
Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	0.630	0.438	0.906	–2.492	0.013	47.26
Jacobs et al[79]	0.900	0.622	1.303	–0.558	0.577	45.52
Dong et al[13]	0.410	0.090	1.864	–1.154	0.248	2.72
Peter et al[33]	1.170	0.361	3.796	0.261	0.794	4.50
Overall	0.753	0.587	0.967	–2.225	0.026	

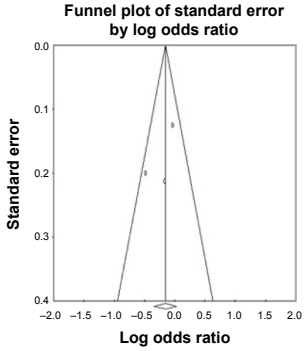




Distal colon site with dominant genetic model

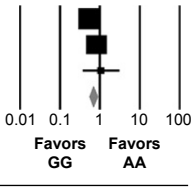
Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	0.620	0.419	0.918	–2.390	0.017	22.48
Jacobs et al[79]	0.850	0.560	1.290	–0.763	0.445	19.85
Dong et al[13]	0.970	0.759	1.239	–0.244	0.807	57.67
Overall	0.854	0.710	1.029	–1.658	0.097	

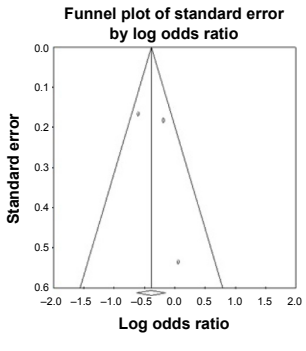




Proximal colon site with additive genetic model (GG vs. AA)

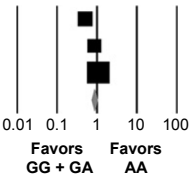
Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	0.550	0.396	0.763	–3.578	0.000	51.88
Jacobs et al[79]	0.830	0.579	1.189	–1.016	0.309	43.09
Dong et al[13]	1.060	0.370	3.033	0.109	0.914	5.03
Overall	0.679	0.536	0.859	–3.220	0.001	





Proximal colon site with dominant genetic model

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	0.510	0.358	0.726	–3.734	0.000	23.95
Jacobs et al[79]	0.880	0.602	1.285	–0.661	0.508	20.85
Dong et al[13]	1.090	0.864	1.376	0.725	0.468	55.20
Overall	0.869	0.731	1.033	–1.590	0.112	



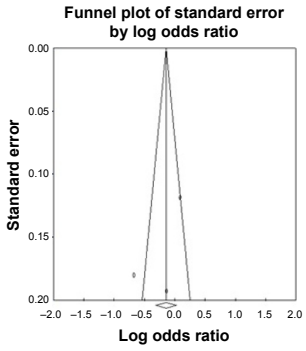


Figure 2 Association of rs1042636 polymorphism with colorectal cancer risk stratified by cancer sites and three genetic models.

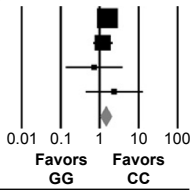
differences result in different susceptibility to exposures and environment, such as diet. Thus, colorectal cancer risk was analyzed by proximal and distal colon sites in our research.

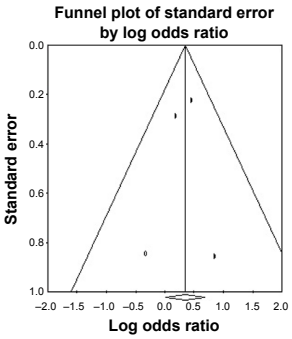
The *CASR* gene carries three common nonsynonymous SNPs, each expressed at a much different allele frequency in three ethnic populations: rs1801725 (A986S) in Europeans (minor allele frequency: 13.3%), rs1042636 (R990G) in Asians (minor allele frequency: 50.4%), and rs1801726 (Q1011E) in Africans (minor allele frequency: 23.3%).[52]

The most frequent SNP in the Caucasian ethnicity, rs1801725, did not show any association with colorectal cancer risk. This finding is consistent with studies included in this systematic review on pancreatic[53] and prostate cancers[35,54] in Caucasians. The functional significance of this variant is small

Distal colon site with additive genetic model (GG vs. CC)

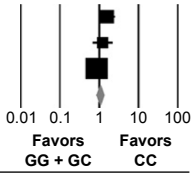
Study name	Statistics for each study					
	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	1.580	1.019	2.449	2.046	0.041	57.56
Jacobs et al[79]	1.210	0.687	2.131	0.660	0.509	34.50
Dong et al[13]	0.720	0.137	3.781	–0.388	0.698	4.02
Peter et al[33]	2.350	0.439	12.578	0.998	0.318	3.93
Overall	1.418	1.017	1.977	2.060	0.039	

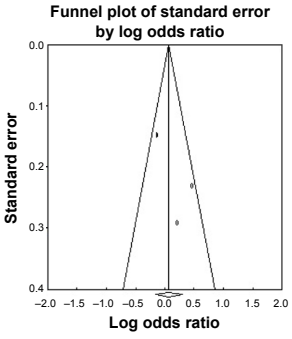




Distal colon site with dominant genetic model

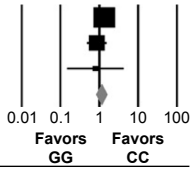
Study name	Statistics for each study					
	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	1.590	1.011	2.502	2.006	0.045	24.63
Jacobs et al[79]	1.240	0.699	2.198	0.736	0.462	15.43
Dong et al[13]	0.880	0.658	1.177	–0.862	–0.388	59.94
Overall	1.073	0.857	1.344	0.617	0.537	

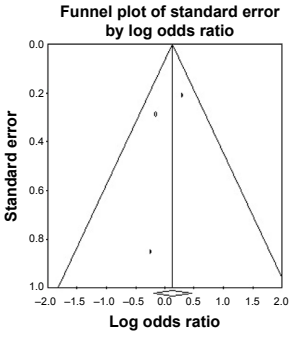




Proximal colon site with additive genetic model (GG vs. CC)

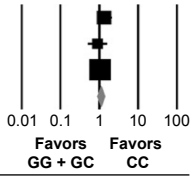
Study name	Statistics for each study					
	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	1.350	0.894	2.039	1.427	0.154	62.59
Jacobs et al[79]	0.860	0.490	1.510	–0.525	0.599	33.60
Dong et al[13]	0.790	0.149	4.195	–0.277	0.782	3.82
Overall	1.137	0.820	1.575	0.770	0.441	





Proximal colon site with dominant genetic model

Study name	Statistics for each study					
	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Hibler et al[78]	1.350	0.880	2.071	1.375	0.169	25.63
Jacobs et al[79]	0.900	0.510	1.589	–0.363	0.716	14.50
Dong et al[13]	1.050	0.794	1.389	0.342	0.733	59.87
Overall	1.095	0.882	1.360	0.822	0.411	



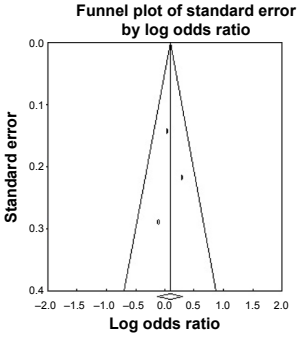


Figure 3 Association of rs1801726 polymorphism with colorectal cancer risk stratified by cancer sites and three genetic models.

by amino acid substitution,[55,56] such that the outcome of cancer risk could be negligible.[13] The study of Masvidal et al[29] is the only one to demonstrate that having a T allele of rs1801725 is associated with later stage with significantly low overall and event-free survival in patients with neuroblastoma.

The rs1042636 (R990G) variant, which is frequently found in the Asian population, seems functionally relevant, as evidenced by cross-species evolutionary conservation.[57] Based on physical properties, the change from positively charged arginine (R) to hydrophilic glycine (G) at codon 990 results in different functionality.[58] This property is consistent with the results of this meta-analysis that GG genotype showed a decreased cancer risk by 25% compared to the wild-type AA genotype in the distal colon and by 32% in the proximal colon.

Table 3 Significant SNPs or haplo/diplotype of *CASR* found in selected studies stratified by cancer sites

Cancer (specified by included studies)	SNP/haplotype/diplotype	Genotype	Case	Control	OR	95% CI	*P*-value	Cofactor other than *CASR*	References
Colorectum	rs1801725 (G/T)	GG + GT vs TT	278	260	4.01	1.33–12.07	0.026	–	Bácsi et al[76]
	rs1801725 (G/T)	GG vs TT	105	105	0.56	0.31–0.99	0.04		Safaei et al[77]
	rs2270916 (T/C)	TT vs CC	420	815	2.11	1.27–3.51	NA	With low Ca intake	Kim et al[34]
	rs10934578 (T/G)	TT vs GG	420	815	1.84	1.12–3.00	NA	With low Ca intake	Kim et al[34]
	rs12485716 (G/A)	GG vs AA	420	815	1.89	1.14–3.11	NA	With low Ca intake	Kim et al[34]
	rs4678174 (T/C)	TT vs CC	420	815	1.73	1.06–2.83	NA	With low Ca intake	Kim et al[34]
	rs1042636 (A/G)	AA vs GG	1,439	0	0.63	0.47–0.85	0.002 (0.104)*	–	Hibler et al[78]
	rs1042636 (A/G)	AA vs AG + GG	1,439	0	0.61	0.45–0.83	0.002 (0.091)*	–	Hibler et al[78]
Proximal colon	rs12485716 (G/A)	GG vs GA + AA	1,600	1,949	0.84	0.71–1.00	NA	–	Dong et al[13]
	rs4678174 (T/C)	TT vs TC + CC	1,600	1,949	0.83	0.70–0.98	NA	–	Dong et al[13]
	rs4678174 (T/C)	TT vs CC	1,600	1,949	0.83	0.69–0.99	NA	–	Dong et al[13]
	rs10934578 (T/G)	TT vs GG	1,600	1,949	1.35	1.01–1.81	NA	–	Dong et al[13]
	rs2270916 (T/C)	TT vs CC	1,600	1,949	0.43	0.19–0.97	NA	–	Dong et al[13]
	rs4678174 (T/C), rs2270916 (T/C)	Haplotype CC/TT	1,600	1,949	0.80	0.67–0.97	NA	–	Dong et al[13]
	rs17203502 (A/G)	AA + AG vs GG	1,802	2,874	0.55	0.40–0.78	0.001 (0.036)*	–	Jacobs et al[79]
	rs1501900 (A/T)	AA vs TT	1,802	2,874	0.71	0.54–0.94	0.017 (0.514)*	–	Jacobs et al[79]
		AA vs AT + TT	1,802	2,874	0.71	0.52–0.98	0.035 (0.744)*	–	
	rs17282022 (A/G)	AA + AG vs GG	1,802	2,874	0.62	0.45–0.85	0.003 (0.136)*	–	Jacobs et al[79]
	rs3845918 (A/G)	AA vs GG	1,802	2,874	1.30	1.01–1.66	0.041 (0.789)*	–	Jacobs et al[79]
		AA vs AG + GG	1,802	2,874	1.51	1.12–2.02	0.006 (0.257)*	–	
	rs4678013 (G/T)	GG vs TT	1,802	2,874	0.69	0.52–0.90	0.007 (0.285)*	–	Jacobs et al[79]
		GG vs GT + TT	1,802	2,874	0.69	0.51–0.94	0.020 (0.566)*	–	
	rs6764205 (C/T)	CC vs CT + TT	1,802	2,874	1.42	1.06–1.91	0.020 (0.565)	–	Jacobs et al[79]
	rs1042636 (A/G)	AA vs GG	1,439	0	0.55	0.40–0.77	<0.001 (0.022)*	–	Hibler et al[78]
		AA vs AG + GG	1,439	0	0.51	0.36–0.73	<0.001 (0.011)*	–	
	rs12635478 (A/C)	AA vs CC	1,439	0	0.82	0.69–0.97	0.017 (0.523)	–	Hibler et al[78]
		AA vs AC + CC	1,439	0	0.74	0.59–0.92	0.008 (0.299)*	–	
	rs3749208 (C/T)	CC vs TT	1,439	0	0.82	0.69–0.97	0.020 (0.563)*	–	Hibler et al[78]
		CC vs CT + TT	1,439	0	0.74	0.59–0.92	0.008 (0.30)*	–	
Distal colon	rs1801725 (G/T)–rs1042636 (A/G)–rs1801726 (C/G)	Diplotype GAC-GAG /GAC-GAC	410	369	0.56	0.36–0.88	NA	–	Peters et al[33]
	rs10222633 (A/G)	AA vs AG + GG	1,802	2,874	0.69	0.48–0.98	0.036 (0.757)*	–	Jacobs et al[79]
	rs1802757 (C/T)	CC vs CT + TT	1,802	2,874	0.68	0.47–1.00	0.050 (0.850)*	–	Jacobs et al[79]
	rs1042636 (A/G)	AA vs GG	1,439	0	0.63	0.44–0.91	0.015 (0.478)*	–	Hibler et al[78]
		AA vs AG + GG	1,439	0	0.62	0.42–0.92	0.017 (0.511)*	–	
	rs1801726 (C/G)	CC vs GG	1,439	0	1.58	1.02–2.45	0.042 (0.802)*	–	Hibler et al[78]
		CC vs CG + GG	1,439	0	1.59	1.01–2.50	0.048 (0.841)*	–	
Rectum	rs1801725 (A/T)	AA vs TT	32	0	0.107	0.018–0.635	0.012	ERBB2, EGFR, p53, *ras* coexpressed	Speer et al[26]
	rs1801726 (C/G)	CC vs GG	1,802	2,874	0.53	0.29–0.96	0.036 (0.755)*	–	Jacobs et al[79]

	rs17282008 (C/G)	CC vs GG	1,802	2,874	1.31	1.01–1.72	0.045 (0.820)*	–	Jacobs et al[79]
	rs4678174 (T/C)	TT + TC vs CC	1,802	2,874	0.60	0.37–0.98	0.041 (0.794)*	–	Jacobs et al[79]
	rs7644390 (C/T)	CC vs CT + TT	1,802	2,874	1.38	1.00–1.91	0.050 (0.847)*	–	Jacobs et al[79]
Prostate	rs1801726 (C/G)	CC vs GG	458	248	0.16	0.03–0.74	0.01	–	Schwartz et al[30]
	rs17251221 (G/A)	GG vs AA	370	1,647	2.32	1.24–4.36	<0.01	–	Jorde et al[31]
	rs6438705 (G/A)	GG vs AA	113	1,244	0.65	0.42–0.99	0.04	–	Shui et al[35]
	rs13083990 (T/C)	TT vs CC	113	1,244	0.65	0.47–0.89	0.008	Low plasma 25(OH)D, low Ca intake	Shui et al[35]
	rs2270916 (T/C)	TT vs CC	113	1,244	1.55	1.09–2.20	0.01	Low plasma 25(OH)D, low Ca intake	Shui et al[35]
	rs1801725 (G/T)	GG vs TT	73	614	0.54	0.31–0.95	0.03	Low plasma 25(OH)D	Shui et al[35]
	rs1979869 (C/T)	CC vs TT	73, 74	614, 829	0.59	0.38–0.94	0.03	Low plasma 25(OH)D, low Ca intake	Shui et al[35]
	rs7637874 (C/T)	CC vs TT	74	829	1.62	1.11–2.35	0.01	Low Ca intake	Shui et al[35]
Breast	rs17251221 (G/A)	GG vs AA	403	2,256	1.948	1.216–3.120	0.007	–	Jorde et al[31]
		GG vs GA + AA	217	231	10.957	1.374–87.393	0.007	–	Li et al[32]
Pancreas	rs3804592 (G/A)	GG vs AA	628	1,193	0.81		0.043	–	Anderson et al[53]
Neuroblastoma	rs1801725 (G/T), rs1042636 (A/G), rs1801726 (C/G)	Haplotype TAC	65	0	2.74 (HR)	1.20–6.25	0.016	–	Masvidal et al[29]

Notes: *P-values were adjusted for multiple comparisons using a modification of P_{ACT} for correlated tests developed by Conneely and Boehnke.[80]

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; NA, not applicable; HR, hazard ratio; P_{ACT} *P*-value adjusted for correlated tests.

According to a report by the Center for Disease Control in 2011, Africans had the highest rate of colorectal cancer, followed by Caucasian, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native.[59,60] The results of our study that represent decreasing cancer risk by variant rs1042636 (high frequency in Asian) and increasing cancer risk by variant rs1801726 (high frequency in African) might explain part of the colorectal cancer risk by genetic causality.

One of the major risk factors of colorectal cancer is diet.[61] Specifically, calcium and dairy product intake have been studied, and high calcium intake is associated with decreased colorectal cancer risk.[62–67] According to the study by Kim et al[34] on colorectal cancer and Shui et al[35] on prostate cancer, several SNPs are significant only under low calcium intake or low plasma vitamin D level and that SNPs of *CASR* are under strong influence of epigenetic factors and regulation of calcium and vitamin D intake is a vital factor in tumorigenesis. In fact, methylation of *CASR* was shown in 69% of colorectal cancer tissues and 90% of lymph node metastatic tissues and was strongly associated with reduced CaSR expression.[68] Both prostate and breast cancers of high mortality are strongly related to bone metastasis.[69] Approximately 75% of patients who develop advanced breast cancer will have secondary tumors in the bone, while in the case of prostate cancer, ~90% of patients who die of advanced prostate cancer develop bone metastases.[70,71] Overexpression of CaSR can serve as a major target of calcium in facilitating the formation and growth of skeletal metastasis of prostate and breast cancers.

One of the important aspects of CaSR research is that CaSR is highly correlated with the response of chemotherapeutics. CaSR signaling regulates the expression of thymidylate synthase and survivin and facilitates 5-fluorouracil treatment, which is one of the drugs of choice in colon cancer chemotherapy.[72,73] The treatment of paclitaxel, a mitotic inhibitor used in chemotherapy is also related with CaSR. Knocking down the tumor suppressor gene *BRAC1* leads to a downregulation of CaSR expression and results in upregulation of survivin which reduced the cancer cell's sensitivity.[74]

Therefore, *CASR* gene polymorphisms can be the research target for the cancer causality and improvement of chemotherapeutics.

The limitations of this study should be acknowledged. First, most of the studies were mainly on colorectal cancers in Caucasians, ethnic factors could not be evaluated in the meta-analysis. Second, the total number of cases and controls is ~10,000, which is not enough for a meta-analysis of genetic association study under Venice guidelines[75] to elucidate robust evidence. Third, several studies were performed under

hospital-based control population, which could modulate population characteristics by selection bias.

Conclusion

In summary, *CASR* polymorphisms are highly associated with cancer risks in various sites. The evaluation of *CASR* in clinical aspect as a cancer biomarker and in therapeutics should consider the ethnicity, environment and diet effects concomitantly. Further research stratified by cancer site, environmental impact, and ethnicity should be undertaken.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Methodological tool of quality assessment of individual studies included for *CASR* polymorphisms and cancer risk

Criteria	Quality score
Representativeness of cases	
Consecutive/randomly selected from case population with clearly defined sampling frame	2
Consecutive/randomly selected from case population without clearly defined sampling frame or with extensive inclusion/exclusion criteria	1
No method of selection described	0
Representativeness of controls	
Controls were consecutive/randomly drawn from the same sampling frame (ward/community) as cases	2
Controls were consecutive/randomly drawn from a different sampling frame as cases	1
Not described	0
Ascertainment of cancer diagnosis	
Clearly described objective criteria for diagnosis of asthma	2
Diagnosis of asthma by patient self-report or by patient history	1
Not described	0
Ascertainment of controls	
Controls were tested to screen out cancer	2
Controls were subjects who did not report cancer; no objective testing	1
Not described	0
Genotyping examination	
Genotyping done under "blinded" condition	1
Unblinded or not mentioned	0
Hardy–Weinberg equilibrium	
Hardy–Weinberg equilibrium in control group	2
Hardy–Weinberg disequilibrium in control group	1
No checking for Hardy–Weinberg equilibrium	0
Association assessment	
Assess association between genotypes and cancers with appropriate statistics and adjustment for confounders	2
Assess association between genotypes and cancers with appropriate statistics without adjustment for confounders	1
Inappropriate statistics used	0

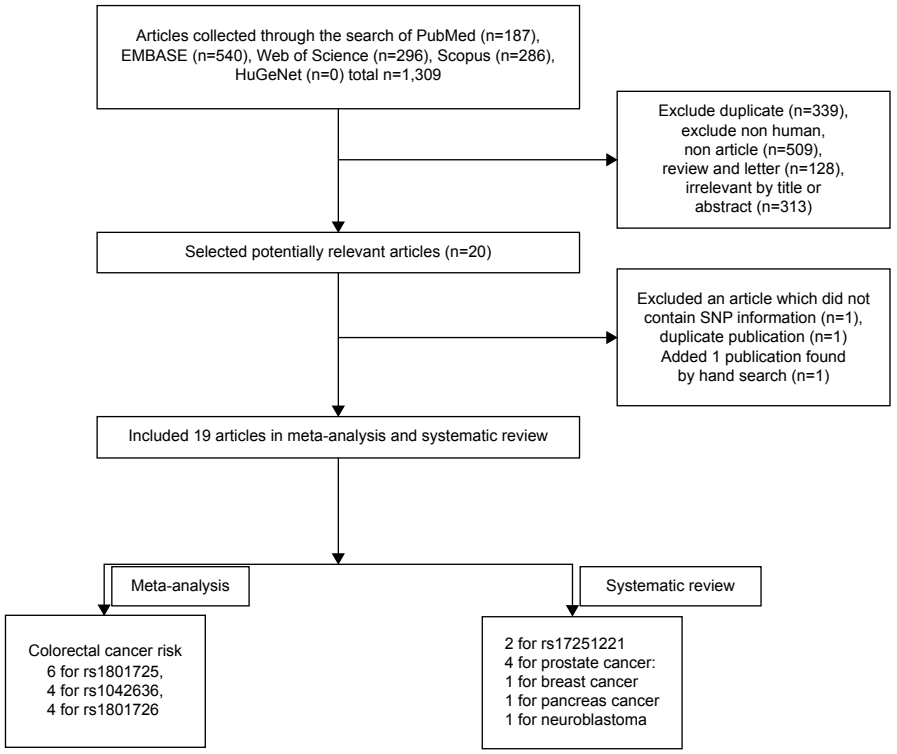

Figure S1 The literature search and selection process by PRISMA flow diagram: 19 studies were included for meta-analysis and systematic review.
Abbreviation: SNP, single-nucleotide polymorphism.

Table S2 Results of comprehensive quality assessment of included studies for the meta-analysis and systematic review

References	Representativeness of cases	Representativeness of controls	Ascertainment of cancer diagnosis	Ascertainment of controls	Genotyping examination	HWE	Association assessment	Total score
Speer et al[1]	1	2	0	1	0	2	1	7
Peters et al[2]	2	2	1	2	1	2	2	12
Fuszek et al[3]	2	1	1	0	0	0	1	5
Bácsi et al[4]	2	1	1	1	1	2	1	9
Dong et al[5]	2	2	1	1	1	2	2	11
Jenab et al[6]	2	2	1	1	1	2	2	11
Jacobs et al[7]	2	2	1	1	0	0	2	8
Schwartz et al[8]	2	2	1	2	1	2	2	12
Szendroi et al[9]	2	2	1	1	0	2	2	10
Safaei et al[10]	2	2	1	2	0	1	1	9
Fedirko et al[11]	2	N/A	1	N/A	0	0	2	5
Shui et al[12]	2	2	1	2	1	2	2	12
Hibler et al[13]	2	N/A	1	N/A	0	2	2	7
Anderson et al[14]	2	2	1	1	0	2	2	10
Kim et al[15]	2	1	0	1	0	2	1	7
Jorde et al[16]	2	2	1	2	0	2	2	11
Masvidal et al[17]	2	N/A	1	N/A	0	2	1	6
Mahmoudi et al[18]	2	2	1	2	0	2	2	10
Li et al[19]	2	1	1	2	0	2	2	10

Abbreviations: HWE, Hardy–Weinberg equilibrium; N/A, not applicable.

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