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Association of Dietary Vitamin D and Calcium With Genetic Polymorphisms in Colorectal Neoplasia

REVIEW

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The incidence trends of colorectal cancer have varied over time, and there is wide geographical variation across the world. Regarding colorectal cancer, diverse modifiable environmental or intrinsic risk factors have been investigated. This review summarizes the effects of both dietary intake of vitamin D and calcium in particular and diet-associated genetic factors on colorectal cancer risk. We searched the electronic database PubMed for articles published between January 2000 and March 2015. We reviewed case-control studies that included dietary factors, genetic polymorphisms, and gene-diet interactions in association with colorectal cancer risk. Overall, 21 studies were selected as eligible studies. These studies demonstrated that dietary consumption of vitamin D and calcium may decrease the risk of colorectal cancer or adenoma. Colorectal carcinogenesis was discussed in conjunction with dietary factors and mediating genetic factors. The epidemiological findings suggested that the gene-diet interactions may possibly alter the associations between dietary intake, genetic polymorphisms, and the risk of colorectal cancer. However, the reported effects of the same potential factors on colorectal cancer risk were inconsistent, depending on the study population and geographical location. This finding may imply the necessity of considering the environmental differences and genetic variations existing between individuals or specified populations. Therefore, further studies are required to investigate modifiable risk factors in diverse locations to derive useful implications for colorectal neoplasia.
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Key Words: Colorectal neoplasms, Vitamin D, Calcium, Genetic polymorphism, Environment-gene interaction

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females (10% and 9.2% of the total cancer incidence, respectively), according to GLOBOCAN worldwide estimates of cancer incidence for 2012. There is wide geographical variation in the incidence across the world, and nearly 55% of cases occur in more developed regions.[1] The CRC incidence trends in high-income countries have varied over the past 20 years[2]; for instance, rates have recently tended to decline in the United States, whereas high rates have been reported in newly developed countries around the globe, where the risk was once low.[3] South Korea is one example of a country reporting CRC as the cancer with the second highest incidence in both sexes, excluding thyroid cancer overdiagnosed in Korea.[4] The rates increased continuously from 1999 to 2012[5] in the Korean population and nearly caught up to those in Western countries.[6] This trend in Asian countries may reflect increased risk factors for CRC, including obesity, irregular and inadequate dietary habits adapting westernized lifestyle as well as various environmental factors that may potentially affect people physically or psychosocially.[2,7] As the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) have reported,[8,9] lifestyle factors that very likely confer an increased risk of CRC are physical inactivity, obesity, alcohol consumption, and certain dietary habits or patterns. Among the diverse CRC risk factors, a combination of extrinsic and intrinsic factors may cause differences between individuals; extrinsic factors including a diet

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containing certain nutrients and food compositions, and intrinsic for having different genetic background, which may alter gene expression or may function in carcinogenesis.[10,11]

In this review, we will discuss the dietary factors vitamin D and calcium, which are linked to each other, rather than reviewing factors well known to reduce CRC risk. In the 2012 WCRF/AICR Continuous Update Project Report on Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, the evidence for an effect of vitamin D on decreasing CRC risk was classified as 'limited-suggestive,' and calcium was classified as having a probable effect on decreasing CRC risk.[9] Over the course of actively conducting studies to prove that these two dietary factors have real effects, vitamin D has been reported to be a protective agent that induces pro-differentiation, anti-proliferative, and growth-inhibitory effects on carcinogenesis[12,13] in association with a decrease in CRC risk. Certain previous meta-analyses demonstrated an inverse association between calcium intake and CRC risk.[14] In addition to dietary factors, genetic changes, known as mutations, will also be discussed, including a review of diet-associated single nucleotide polymorphisms (SNPs). The above-described risk factors' association with CRC and the interaction between dietary and genetic factors will be summarized by reviewing relevant studies.

METHODS

An article search was conducted using the electronic database PubMed to identify studies published between January 2000 and March 2015. The search keywords were combinations of following terms: vitamin D, calcium, CRC, and polymorphism. We selected eligible studies based on several inclusion criteria, as follows: (1) epidemiological studies including cases and controls as well as cohort studies; (2) studies investigating the association between dietary factors/genetic variants and CRC including adenoma or polyps; (3) studies assessing the gene-diet interaction effect on CRC; and (4) studies using an OR or relative ratio and a 95% CI to estimate CRC risk. The studies that failed to comply with any of the above conditions were excluded.

We assessed the relevance of the studies using a hierarchical approach based on the title, abstract, and full-text article. A flow chart depicting the literature search and the selection of 21 eligible studies is presented in Figure 1. We excluded experimental studies that aimed to examine the association with colorectal neoplasia risk using non-epidemiological approaches (n = 5), as well as laboratory studies conducted with animals or cell lines (n = 273). The articles comprising a meta-analysis (n = 3) or a systematic review (n = 8) also were not included in the current study. We excluded certain studies consisting of

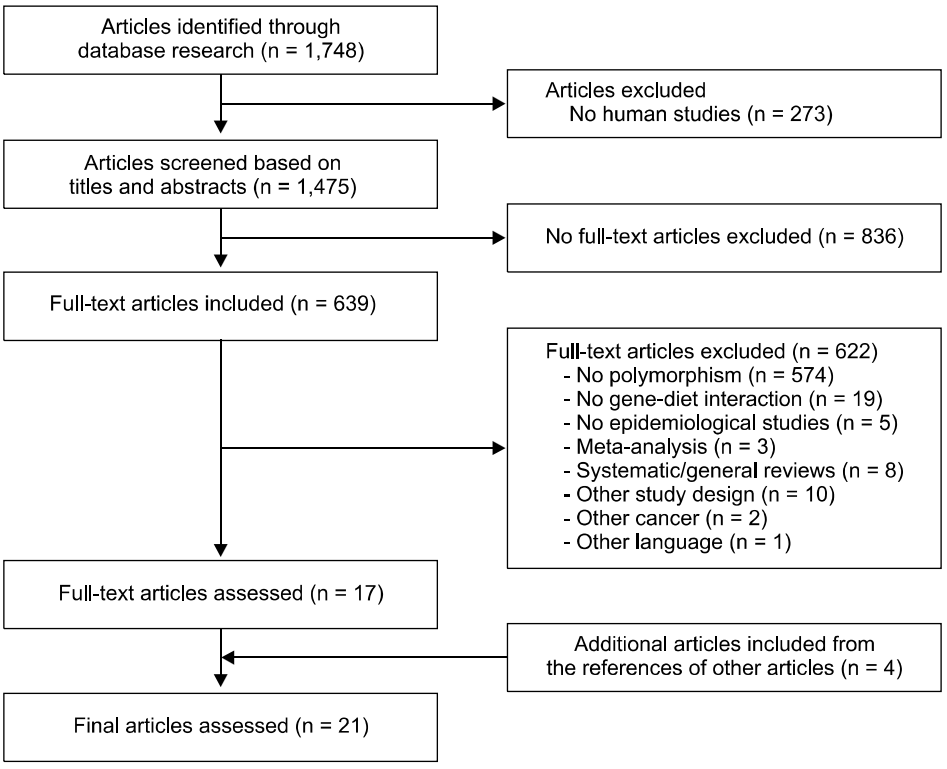

Figure 1. Flow diagram detailing the procedures for selecting eligible studies.

randomized clinical trials or survival analyses of risk association between cancer cases and healthy controls (n = 10). Four articles were additionally included by using the same keywords and checking for eligible references to other articles. We assessed the study objectives and risk of bias of each selected article by using the National Institute for Clinical Excellence methodology checklist for case-control study.[15] The contents of quality assessment included selection of participants, assessment, confounding factors, and statistical analysis. We summarized previous studies based on dietary factors, vitamin D and calcium and collected relevant findings associated with CRC risk. For each eligible study, we extracted the publication year, the study design, the geographical location, the number of study subjects (cases and controls), any diet of interest and related genetic polymorphism, and gene-diet interactions associated with a modified CRC risk.

RESULTS

We identified a total of 21 case-control studies that investigated the association between CRC risk and dietary or genetic factors modified by gene-diet interactions. The majority of the studies were conducted in Western countries (n = 16), such as the United States and European countries, whereas a few studies were performed in non-Western countries (n = 5, mostly Japan). All of the studies were designed as case-control studies, including 5 nested case-control studies. According to the study subject recruitment, the studies were population based (n = 12), clinic based (n = 8), or family based (n = 1). The studies examined dietary and genetic factors in association with CRC risk and also observed gene-diet interactions, mainly focusing on vitamin D and calcium, which share a biological pathway. We grouped the studies by each dietary factor and summarize the findings from the studies in Table 1[16-28] and 2.[29-36] Additional study data that are not mentioned in the tables will be discussed separately.

Both vitamin D and calcium were determined to be protective agents against CRC in many quantitative studies. Several studies showed data with a significant OR to represent cancer risk and with a significant *P*value for the comparison of dietary intake between cases and controls. Generally, it is known that high levels of vitamin D or calcium intake are associated a decreased risk of developing CRC. Atoum and Tchoporyan[16] found that 75% of CRC patients were vitamin deficient, with a significant decrease in serum 25-hydroxy-vitamin D ($P < 0.05$). The same study also reported that vitamin D deficiency was associated with an approximately 19-fold higher risk among Jordanian patients compared with controls ($P \leq 0.05$). Similar to the dietary calcium-related studies listed in Table 2, another study by Gong et al.[17] found that patients with sporadic colorectal adenomas had significantly lower calcium intake compared with the control group, with a *P*value of 0.02. Takeshige et al.[18] found that calcium intake was associated with a decreased risk of colon cancer ($P = 0.06$) and rectal cancer ($P = 0.10$) (the corresponding data from Gong et al.[17] and Takeshige et al.[18] are not shown in the tables).

The effect of genetic factors was determined for several representative gene polymorphisms related to vitamin D, calcium, or both, as follows: vitamin D receptor (VDR), vitamin D 24-hydroxylase (CYP24A1), vitamin D 25-hydroxylase (CYP2R1), calcium sensing receptor (CASR), Transient receptor potential cation channel (TRPM7), and cyclin D1 protein (CCND1) polymorphisms.[37,38] The VDR gene polymorphisms were diversely studied with regard to CRC development. Among the reviewed studies, many examined Tru9I, BsmI, ApaI, TaqI, FokI, and group-specific component/vitamin D-binding protein (GC). Each SNP results in elevated or reduced cancer risk differently. Several, such as Tru9I and BsmI, were found to be reliably associated with a decreased risk, whereas for others, such as TaqI and GC, there was no significant a relationship between the gene polymorphism and CRC risk. Based on the allele frequency in genotypes, the frequency of certain alleles distinctly increased cancer risk. The difference between the VDR FokI Ff and ff genotypes was shown in a study by Wong et al.[29] Boyapati et al.[19] reported that the calcium-colorectal adenoma association varied with the VDR BsmI genotype, indicating that individuals with at least one b allele were at much lower risk, with OR = 0.25 (0.08-0.80), *P*trend = 0.02 (these data are not shown in the tables). However, there have been different results regarding the allelic expression of the same gene (VDR ApaI) in different populations. Takeshige et al.[18] determined that VDR ApaI AA/Aa was associated with a decreased risk of rectal cancer reporting OR = 0.75 (0.56-0.99) in a Japanese population, whereas Kupfer et al.[20] demonstrated that the VDR ApaI T allele was associated with an increased CRC risk reporting OR = 1.15 (1.00-1.33) among the population of African Americans. Two studies listed in Table 2, or those by Dong et al.[30] and Peters et al.[31] (2004), reported significant associations in analyses by cancer anatomic site and diplotype, in which both studies examined the CASR gene polymorphism by stratified analyses due to statistical insignificance. For proximal colon, CASR IVS3 + 1048TT was associated with an increased risk with OR = 1.35 (1.01-1.18) and CASR IVS6+16CC with a decreased reporting OR = 0.43 (0.19-0.97).[30] By the diplotype analysis conducted with CASR, a decreased risk was observed with OR = 0.56 (0.36-0.88).[31]

In combination with dietary and genetic factors, genetic

Table 1. Literatures assessing the interaction between vitamin D and related genetic polymorphisms regarding the risk of colorectal neoplasia (n = 13)

Reference (year)	Study design	No. of subject	Outcome	Diet	Diet-CRC association	Gene polymorphism	Gene-CRC association	Gene-diet interaction OR/RR (95% CI)
Kim et al.[24] (2001)	Case-control (clinic-based, USA)	393/406	Colorectal adenoma	Vitamin D	Not significant	VDR BsmI (rs1544410): BB/Bb/bb	Compared to BsmI bb genotype, BB genotype: OR = 0.71 (0.46-1.11)	Inverse association with colorectal adenoma risk among BsmI BB genotype in the presence of lowest vitamin D intake: OR = 0.24 (0.08-0.76), P = 0.094
Peters et al.[26] (2001)	Case-control (clinic-based, USA)	239/228	Colorectal adenoma	Vitamin D	Serum 25(OH)D: OR = 0.74 (0.60-0.92)	VDR FokI (rs10735810): FF/Ff/ff	No association	No association
Boyapati et al.[19] (2003)	Case-control (clinic-based, USA)	177/228	Colorectal adenoma	Vitamin D	Not determined	VDR BsmI (rs1544410): BB/Bb/bb	No association	VDR genotype Bb having high vitamin D intake: OR = 0.29 (0.09-0.95), $P < 0.01$
Peters et al.[25] (2004)	Nested case-control (population-based, USA)	Genotype analysis: 763/774 Serum levels: 394/397	Colorectal adenoma	Vitamin D: levels of 25(OH)D and $1.25(OH)_2$	The average serum level of 25(OH)D in cases was lower than in controls: $P = 0.06$; Higher serum 25(OH)D levels: OR = 0.27 (0.11-0.69), $P = 0.0002$; Serum levels of 1.25(OH)2D: No association	VDR TaqI (rs731236): TT/Tt/tt	No association	No association
Gong et al.[17] (2005)	Case-control (clinic-based, USA)	171/220	Colorectal adenoma	Vitamin D	Not significant difference in dietary vitamin D intake between cases and controls ($P = 0.16$)	VDR Tru9I G > A: UU/Uu/uu	Tru9I having at least 'u' allele : OR = 0.36 (0.13-0.97) for Sessile shape of adenoma; OR = 0.38 (0.17-0.88) for women	No evidence suggesting an interaction with VDR Tru9I and dietary micronutients
Dong et al.[22] (2009)	Case-control (population-based, USA)	1,600/1,949	Colon cancer	Vitamin D	Higher use of vitamin D supplements in controls; Not significant inverse associations for the highest vitamin D intake	CYP24A1 IVS4 + 1653C > T (rs4809958), IVS5 − 162T > C (rs6013905); CYP27B1	CYP24A1 IVS4+1653C > T GT: OR = 0.82 (0.71-0.96), $P = 0.03$; GG/GT: OR = 0.83 (0.72-0.96), $P = 0.03$; IVS5-162T > C CT: OR = 0.85 (0.72-0.96), $P = 0.06$; CC/CT: OR = 0.85 (0.73-0.99), $P = 0.06$	No statistically significant interactions between genotypes in CYP24A1 and total vitamin D ($P = 0.80$)
Jenab et al.[23] (2009)	Nested case-control (population-based, European countries)	1,248/1,248	Colorectal, colon, and rectal cancer	Vitamin D: level of serum 25(OH)D	Not determined	VDR BsmI (rs1544410), Fok1 (rs2228570); CASR G > T (rs1801725)	Compared to wild-type bb, the BB genotype of VDR BsmI: RR = 0.76 (0.59-0.98), $P = 0.10$ with colorectum: RR = 0.69 (0.45-0.95), $P = 0.05$ with colon;VDR FokI or CASR: No association	No association between VDR BsmI and CRC risk with interaction with serum 25(OH)D ($P = 0.43$); Stratified analysis: BsmI BB genotype at higher serum 25(OH)D: RR = 0.41 (0.24-0.69), $P = 0.03$
Poynter et al.[27] (2010)	Case-control (family-based, USA, Canada, Australia)	585/837	Colorectal cancer	Vitamin D	Similar vitamin D intake in cases and controls	VDR FokI (rs10735810); BsmI (rs154410), CDX2 (rs11568820), ApaI (rs7975232); GC	No association	No association
Kupfer et al.[20] (2011)	Case-control (popoulation-based, USA/Spain)	AA: 795/985 Caucasians: 1,324/990	Colorectal cancer	Vitamin D	Not determined	VDR gene (RFLPs: FokI, BsmI, ApaI, TaqI)	VDR ApaI T allele additive model associated with AA CRC: OR = 1.15 (1.00-1.33), $P = 0.05$ None of other RFLP SNPs: No association	Association of intronic rs11574041 A allele with CRC by vitamin D intake (≥ 100 IU): OR = 0.30, $P = 0.0009$
Theodoratou et al.[21] (2012)	Case-control (population-based, Scotland)	2,001/2,237	Colorectal cancer	Vitamin D	Highest quintiles of 25(OH)D associated with reducing CRC risk: OR = 0.47 (0.39-0.57), $P < 0.0005$	CYP2R1 (rs10741657); GC (rs2282679), CYP24A1 (rs6013897)	No association	CYP2R1 GA associated with a decreased CRC risk for those of low plasma 25(OH)D levels (< 10 ng/ml): OR = 0.74 (0.59-0.94), $P = 0.01$
Yamaji et al.[28] (2012)	Case-control (clinic-based, Japan)	737/703	Colorectal and colon adenoma	Vitamin D	Highest levels of plasma 25(OH)D: OR = 0.64 (0.45-0.92), $P = 0.09$	VDR FokI (rs2228570), TaqI (rs731236)	No association	The interaction between 25(OH)D levels and colorectal adenoma was modified by TaqI Tt/tt polymorphism: OR = 0.43 (0.23-0.79), $P = 0.03$
Atoum and Tchoporyan[16] (2014)	Case-control (clinic-based, Jordan)	93/102	Colorectal cancer	Vitamin D	Significantly lower vitamin D level among cases ($P \leq 0.05$);Only 2.2% optimal vitamin D in cases compared to 23.5% among controls ($P = 0.005$)	VDR TaqI (rs731236): TT/Tt/tt	No association found between TT, Tt, and tt among CRC patients and controls	Lower mean vitamin D level (ng/ml) among cases vs. controls with TT (8.91 ± 4.31) vs. TT (21.3 ± 8.31), $P = 0.01$; Tt (9.15 ± 5.25) vs. Tt (19 ± 7.68), $P = 0.04$
Takeshige et al.[18] (2015)	Case-control (population based, Japan)	685/778	Colorectal, colon, and rectal cancer	Calcium, vitamin D	Vitamin D intake associated with decreased risks for colon cancer ($P = 0.004$), and for reactal cancer ($P = 0.06$)	VDR genes: FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236)	ApaI AA/Aa: OR = 0.75 (0.56-0.99), $P = 0.04$ for rectal cancer:	Among individuals with ApaI AA/Aa having high vitamin D: OR = 0.46 (0.28-0.74), $P = 0.09$ for risk of colon cancer: Among individuals with FokI Ff/ff having high vitamin D intake: OR = 0.53 (0.35-0.78), $P = 0.09$ for risk of colorectal cancer

CRC, colorectal cancer; RR, relative risk; VDR, vitamin D receptor; CYP24A1, cytochrome P450, family 24, subfamily A, polypeptide 1; CYP27B1, cytochrome P450, family 27, subfamily B, polypeptide 1; CASR, calcium-sensing receptor; CYP2R1, cytochrome P450, family 2, subfamily R, polypeptide 1; RFLP, restriction fragment length polymorphism.

Table 2. Literatures assessing the interaction between calcium and related genetic polymorphisms regarding the risk of colorectal neoplasia (n = 8)

Reference (year)	Study design	No. of subject	Outcome	Diet	Diet-CRC association	Gene polymorphism	Gene-CRC association	Gene-diet interaction OR/RR (95% CI)
Ma et al.[36] (2001)	Nested case-control (population-based, USA)	125/318	Colorectal cancer	Calcium from milk	Highest intake of calcium from total milk: RR = 0.66 (0.40-1.09), P = 0.09	IGF-I/IGFBP-3	IGF-1/IGFBP-3: RR = 1.84 (1.12-3.01), P = 0.01	Highest IGF-I/IGFBP-3 molar ratio in nondrinker of low-fat milk: RR = 3.05 (1.29-7.24), P = 0.03; Among men with high IGF-I/IGFBP-3, frequent low-fat milk drinker: RR = 0.40 (0.17-0.87), P = 0.02
Wong et al.[29] (2003)	Nested case-control (population-based, Singapore)	217/890	Colorectal and colon cancer	Calcium	No association	VDR FokI (rs10735810): FF, Ff, and ff	FokI Ff genotype (P = 0.01): OR = 1.51 (1.00-2.29); ff genotype: OR = 1.84 (1.15-2.94) for colorectum FokI Ff genotype (P = 0.01): OR = 1.90 (1.13-3.20); ff genotype: OR = 2.13 (1.19-3.85) for colon	The effect of VDR FokI Ff and ff genotype on risk modified in the presence of lower dietary calcium: OR = 2.10 (1.17-3.78); OR = 2.69 (1.37-5.23), respectively, P = 0.004
Lewis et al.[35] (2003)	Case-control (clinic-based, USA)	161/213	Colorectal adenoma	Calcium	Higher total calcium in controls, P = 0.01	CCND1: (GG/AG/AA)	CCND1 AA + AG: OR = 1.5 (1.0-2.4), P = 0.18	CCND1 GG with high total calcium intake: OR = 0.4 (0.2-0.9)
Peters et al.[31] (2004)	Nested case-control (population-based, USA)	716/729	Colorectal adenoma	Calcium	Not determined	CASR A986S (rs1801725), R990G (rs1042636), Q1011E (rs1801726)	CASR genotype: No association CASR diplotype (000/001)[a]: OR = 0.56 (0.36-0.88)	Protective association between calcium intake (1,000 mg/day) and advanced colorectal adenoma stratified by CASR diplotype (000/000), OR = 0.68 (0.47-0.99)
Guerreiro et al.[32] (2007)	Case-control (population-based, Portugal)	196/200	Colorectal cancer	Calcium	Higher intake in controls: P = 0.01 Calcium: OR = 0.59 (0.49-0.88), P < 0.05	APC D1822V: DD/DV/VV	Not determined	High calcium intake associated with CRC risk among those carrying DV/VV allele: OR = 0.51 (0.28-0.93)
Dai et al.[33] (2007)	Case-control (population-based, USA)	688 (adenoma) + 210 (hyperplastic polyp)/1,306	Colorectal adenoma, hyperplastic polyps	Calcium	Higher total calcium intake associated with colorectal adenoma: OR = 0.56 (0.45-0.71), P < 0.01; associated with hyperplastic polyps: OR = 0.64 (0.45-0.92), P = 0.01	TRPM7 T1482I (rs8042919)	TRPM7 T1482I AG/AA: OR = 1.20 (0.94-1.53), P = 0.23 for adenoma; OR = 1.41 (0.99-2.01), P = 0.03 for polyps	TRPM7 T1482I with high Ca:Mg intake ratio > 2.78: AG/AA, OR = 1.60 (1.12-2.29), P < 0.01 for adenoma; OR = 1.85 (1.09-3.14), P < 0.01 for polyps
Dong et al.[30] (2008)	Case-control (population-based, USA)	1,600/1,949	Colon cancer	Calcium	Higher dietary intake of calcium in controls;The highest quartile of dietary calcium: OR = 0.72 (0.56-0.91) for proximal; OR = 0.63 (0.49-0.80) for distal cancer	CASRIVS3 + 1048 (rs10934578); IVS3-685 (rs12485716); IVS5-90 (rs4678174); IVS6+16 (rs2270916)	No association, but stratified by anatomic site (proximal colon): IVS3 + 1048 TT, OR = 1.35 (1.01-1.81), P = 0.09; IVS3-685 AA/AG, OR = 0.84 (0.71-1.00), P = 0.03; IVS5-90 CC/CT, OR = 0.83 (0.70-0.98), P = 0.05; IVS6 + 16CC OR = 0.43 (0.19-0.97), P = 0.04	No association
Kim et al.[34] (2013)	Case-control (clinic-based, Korea)	420/815	Colorectal cancer	Calcium	Higher energy-adjusted total calcium intake in controls (P < 0.001)	CASR (rs10934578, rs12485716, rs2270916, rs4678174)	No association	Interaction between CASR rs2270916 CC and low calcium intake (CC/low): OR = 2.11 (1.27-3.51), P = 0.375; rs10934578GG/low: OR = 1.84 (1.12-3.00), P = 0.295; rs12485716 AA/low: OR = 1.89 (1.14-3.11), P = 0.769; rs4678174 CC/low: OR = 1.73 (1.06-2.83), P = 0.883

CRC, colorectal cancer; RR, relative risk; TRPM7, transient receptor potential cation channel, subfamily M, member 7; CASR, calcium-sensing receptor; APC, adenomatous polyposis coli; CCND1, cyclin D1; IGF-I, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3. [a]000 = A986, R990, Q1011; 001 = A986, R990, 1011E.

polymorphism can influence the dietary absorption level, which can affect the risk of cancer. Atoum and Tchoporyan[16] found that the absorption of vitamin D among CRC patients can be affected by the T allele of VDR TaqI. Compared with the healthy control group, the case group had a lower level of vitamin D in a comparison based on the frequency of the T allele. Vitamin D absorption levels in TT- and Tt-genotyped cases were significantly lower than those in controls (Table 1). In contrast, the dietary intake level can modify the effect of genetic polymorphism on the risk of cancer development. For instance, Takeshige et al.[18] indicated that VDR FokI did not have a significant association with cancer risk but seemed to be associated with a decreased risk of colon cancer, especially among individuals with high intake of vitamin D. In the same study, it was also found that VDR ApaI AA/Aa showed a decreased rectal cancer risk, with OR = 0.75 (0.56-0.99), $P = 0.04$. Among the cases with the same genotype and a high calcium intake, a higher degree of reduction was detected, with OR = 0.53 (0.36-0.79), $P = 0.05$ (these data are not shown in the tables). In a cohort of Singaporean Chinese, Wong et al.[29] observed the effect of VDR FokI only in the lower dietary calcium category, and this effect depended on the f allele in a gene dose-dependent manner (these data are shown in Table 2).

DISCUSSION

This review summarizes the previous epidemiological studies that have investigated the effects of dietary factors and genetic polymorphisms on CRC risk. To understand the variety of potential factors that may influence CRC risk, the gene-diet interactions among diverse study populations have been examined according to stratification by dietary intake or allele frequency in gene expression.

1. Dietary effect on colorectal cancer risk and diet-associated genetic factors

Dietary factors are commonly recognized as modifiable factors that can have a profound influence on cancer and tumor behavior.[8] Therefore, the relationship between dietary factors and CRC risk has long attracted a great deal of attention. The effects of vitamin D and calcium on CRC risk and its incidence have been extensively studied.[9] Mounting evidence supports an inverse association of vitamin D with colorectal adenoma or cancer incidence,[39-42] and a long-term inadequate vitamin D status might lead to a progressive increase in CRC incidence in humans.[10] High intake of calcium has also consistently been reported to lower the risk of CRC.[14,43-45] As protective nutrients against CRC, vitamin D and calcium are closely related to each other due to the role of vitamin D in maintaining calcium levels. Calcium homeostasis is critical for the inhibition of cancerous tumor development, and the active metabolites of vitamin D, $1,25(OH)_2D_3$ play a mediating role in intestinal calcium absorption to prevent homeostatic disruption.[19,30] In addition to preventing carcinogenesis in the colon and rectum, vitamin D and calcium are diversely linked to biological responses, including DNA synthesis and inhibition of double-strand breaks caused by endogenous or exogenous factors.[10,19] The association between vitamin D and calcium is also well known to account for the physiologic functions and regulation of genes responsible for cell proliferation, differentiation, angiogenesis, and apoptosis.[46-48] Nutrient metabolism-associated gene variants have been studied to investigate their implication in CRC.[49-52] Various genes, such as CASR, CYP2R1, CYP27A1, CYP27B1, CYP24A1, VDR, and GC, have been identified to be activated by different forms of vitamin D metabolites.[21,53] Certain genes, such as VDR and CASR, can mediate the interaction between dietary factors and can possibly modify physiologic pathways. Vitamin D exerts its effects on calcium metabolism through binding the VDR gene, which regulates the transcription of genes involved in calcium absorption[46] and which is involved in the Wnt/β catenin signaling pathway, a central pathway in CRC development.[11,32,53] Additionally, the promoter region of the CASR gene contains a vitamin D response element that may also modify the calcium uptake level.[50,54]

2. Variation in gene-diet interactions

Determination of CRC risk is further complicated by interaction with genetic factors in conjunction with environmental stimuli, such as dietary intake. Previous studies have demonstrated that gene-diet interactions may influence cancer risk. Dietary intake and the polymorphic genotype of different genes interact with each other, modulating CRC risk.[12,16,18,19,29,55,56] The interaction between diet and genes may contribute to modulating the risk of CRC or adenoma. Guerreiro et al.[32] reported that high calcium intake was more markedly associated with lowering CRC risk in those carrying the polymorphic allele (DV/VV) of the APC gene (adenomatous polyposis coli; tumor suppressor gene) than in those without that allele in the Portuguese population. Kupfer et al.[20] reported a significant result in African Americans, suggesting that there was a significant VDR gene-vitamin D interaction in lowering CRC risk. In both studies, dietary intake seemed to modulate the associations that were originally not present in the gene-CRC and diet-CRC comparisons. The frequency of certain alleles that differentiate genetic expression can alter the

absorption level of nutrients in subjects. Atoum and Tchoporyan[16] conducted a study in Jordanians and reported an inverse association with CRC risk in a gene dose-dependent manner. Nutrient absorption may be inhibited based on the frequency of a certain type of allele in both CRC patients and controls. In this study, the expression of more T alleles resulted in a lower level of vitamin D absorption, which was linked to a higher CRC risk. The findings suggest that the type of allele has its own effects; therefore, the allele frequency in a gene may modulate the ultimate results, with additive effects of dietary intake. Boyapati et al.[19] reported that those with at least one b allele, representing the restriction site, appeared to have a reduced risk of colorectal adenoma under the condition of high vitamin D intake. Although many previous epidemiological studies have investigated the association with susceptibility to CRC, the results show wide ethnic variation by location or population.[49,52,53,57-59] Most of the studies discussed above were conducted in different populations with diverse ethnic and environmental backgrounds. Analyses of the effects of the same polymorphisms on CRC association yielded unreliable results, occasionally providing inverse results between different study populations. This may imply that in investigations of CRC, all people do not share the same background. To achieve a better understanding of CRC in specified populations, environmental differences and genetic variations that exist within groups of individuals must be considered. This current study represented the lack of studies related diet-gene interaction in Asian countries, compared to Western countries. This suggests the necessity of further researches on Asian populations that may different from western countries and their culture.

In conclusion, this review demonstrates that dietary consumption of vitamin D and calcium may decrease the risk of CRC or adenoma. The findings suggest that gene-diet interactions may possibly alter the associations among dietary intake, genetic polymorphisms, and CRC risk. However, the observations regarding effect modification are still controversial, which may be partly due to different exposures for each individual or population. Further studies conducted with different target populations are actively needed to investigate the implications of gene-diet interactions for CRC. Identification of modifiable risk factors in various locations may help to effectively and broadly reduce the disease burden from an epidemiological or public health point of view.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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