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SYSTEMATIC REVIEWS

Influence of methyl donor nutrients as epigenetic regulators in colorectal cancer: A systematic review of observational studies

Lourdes Pilar Chávez-Hidalgo, Silvia Martín-Fernández-de-Labastida, Marian M de Pancorbo, Marta Arroyo-Izaga

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Lourdes Pilar Chávez-Hidalgo, Silvia Martín-Fernández-de-Labastida, Marta Arroyo-Izaga, Department of Pharmacy and Food Sciences, Faculty of Pharmacy, University of the Basque Country UPV/EHU, Vitoria-Gasteiz 01006, Araba/Álava, Spain

Marian M de Pancorbo, Department of Z. and Cellular Biology A., University of the Basque Country UPV/EHU, Vitoria-Gasteiz 01006, Araba/Álava, Spain

Marian M de Pancorbo, Marta Arroyo-Izaga, BIOMICs Research Group, MICROFLUIDICs and BIOMICs Cluster UPV/EHU, Lascaray Research Center, University of the Basque Country UPV/EHU, Vitoria-Gasteiz 01006, Araba/Álava, Spain

Corresponding author: Marta Arroyo-Izaga, PharmD, Department of Pharmacy and Food Sciences, Faculty of Pharmacy, University of the Basque Country UPV/EHU, Paseo de la Universidad, No. 7, Vitoria-Gasteiz 01006, Araba/Álava, Spain. marta.arroyo@ehu.eus

Abstract

BACKGROUND

Dietary methyl donors might influence DNA methylation during carcinogenesis of colorectal cancer (CRC). However, whether the influence of methyl donor intake is modified by polymorphisms in such epigenetic regulators is still unclear.

AIM

To improve the current understanding of the molecular basis of CRC.

METHODS

A literature search in the Medline database, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/), and manual reference screening were performed to identify observational studies published from inception to May 2022.

RESULTS

A total of fourteen case-control studies and five cohort studies were identified. These studies included information on dietary methyl donors, dietary components that potentially modulate the bioavailability of methyl groups, genetic variants of methyl metabolizing enzymes, and/or markers of CpG island methylator phenotype and/or microsatellite instability, and their possible interactions on CRC risk.

CONCLUSION
Several studies have suggested interactions between methylenetetrahydrofolate reductase polymorphisms, methyl donor nutrients (such as folate) and alcohol on CRC risk. Moreover, vitamin B_6, niacin, and alcohol may affect CRC risk through not only genetic but also epigenetic regulation. Identification of specific mechanisms in these interactions associated with CRC may assist in developing targeted prevention strategies for individuals at the highest risk of developing CRC.

Key Words: Colorectal cancer; DNA methylation; Epigenetics; Methyl donors; Microsatellite instability; Nutrients

Core Tip: Dietary methyl donors might influence DNA methylation during the carcinogenesis of colorectal cancer (CRC). However, whether the influence of methyl donor intake is modified by polymorphisms in such epigenetic regulators is still unclear. We conducted a systematic review on this topic to improve the current understanding of the molecular basis of CRC. Several studies have suggested interactions between methylenetetrahydrofolate reductase polymorphisms, methyl donor nutrients (such as folate) and alcohol on CRC risk. Moreover, vitamin B_6, niacin, and alcohol may affect CRC risk through not only genetic but also epigenetic regulation.

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INTRODUCTION

Colorectal cancer (CRC) is the third most frequent type of cancer and is responsible for the second highest mortality rate in cancer patients worldwide[1]. Although screening for early detection of CRC is effective to help decrease the trends in mortality rates, understanding daily life factors is also important to prevent this type of cancer[2]. The main factors which may help prevent CRC are those associated with diet, lifestyle, and prevention of metabolic diseases[3].

With regards to the dietary component, nutrients associated with one carbon (1C) metabolism [including folate, other B vitamins, methionine (Met), and choline] have been recognized as anticarcinogenic and chemotherapeutic agents in the 1C metabolic network[4]. Folate has shown to play a preventive role in CRC, probably because of its involvement in the processes of DNA methylation and synthesis[5]. Other nutrients, such as Met and vitamins B_6 and B_{12}, which interact metabolically with folate in this process, may also influence the risk of CRC[6]. Moreover, in some of those studies, the observed inverse association between folate status and CRC risk was further modified by genetic polymorphisms of the enzymes involved in folate metabolism, most notably methylenetetrahydrofolate reductase (*MTHFR*).

A common C677T substitution in the *MTHFR* gene results in a protein with valine instead of alanine, yielding a more thermolabile enzyme with decreased activity[7]. Numerous studies have shown that this variant (TT) is associated with a decreased risk of CRC, but only when folate status is normal or high. *MTHFR* polymorphism is possibly the best-known gene polymorphism that switches from being a risk factor to a protective one depending on nutrient status. In any case, it is also important to evaluate the joint influence that other polymorphisms in genes involved in folate metabolism might exert. Thus, for example, Met synthase requires vitamin B_{12}, as methylcobalamin, as a cofactor. A variant in this gene, A2756G [in methionine synthase (*MTR*) gene], has been described and results in the substitution of aspartate by glycine. Some studies have shown that the MTR 2756 GG genotype is associated with a decreased risk of CRC; however, the association with diet is still unclear[8,9].

Another relevant example of a mutation in a polymorphism associated with CRC risk, but not consistent with nutrients, is the case of serine hydroxymethyltransferase, a pyridoxal phosphate (B_6)-dependent enzyme, in particular the polymorphism C1420T[10]. An additional relationship between 1C metabolism-related nutrients and CRC risk is related to its influence on DNA methylation. Thus, low folate status or intake is related to a decreasing methylation level[11,12], whereas colonic mucosal DNA methylation increased globally as a result of folate supplementation[13]. A sufficient intake of methyl

donors may also prevent aberrant CpG island promoter hypermethylation. The promoter CpG island hypermethylation that characterizes the CpG island methylator phenotype (CIMP) in CRC is common [14]. Moreover, polymorphisms in enzymes involved in folate metabolism may change the potential impact of methyl donor consumption on DNA methylation[15].

According to the molecular subtype, chromosomal instability, and microsatellite instability (MSI) represent the major pathways for CRC[16]. The inactivation of DNA mismatch repair (MMR) genes, which are responsible for correcting mismatched bases during DNA replication, results in MSI[17]. Microsatellites are short sequences that are dispersed across the genome and are likely to undergo MMR machinery-induced deletion or insertion. Defects in the MMR machinery are associated with CRC[18] and can be affected by epigenetic alterations and deregulation of methylation[19]. In this sense, the associations between methyl donor nutrient intake and CRC risk have been extensively studied, although evidence on their effect is limited[20]. However, whether they act as effect modifiers against a background of deficient DNA repair capacity is unknown.

Until now, there have been few studies on the influence of methyl group donors as epigenetic regulators in CRC[21]. In the present work, we reviewed previous studies that have investigated this matter to improve the current understanding of the molecular basis of CRC, which could contribute to a better design of future research and to better preventive nutritional management in this type of cancer.

MATERIALS AND METHODS

Search strategy

The search terms and search strategy were developed by two researchers. To guide this research, we formulated the following question as the starting point: What is the influence of methyl donor nutrients as epigenetic regulators in CRC? For this purpose, a systematic search in the Medline (through PubMed) database, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/, an artificial intelligence technology-based open multidisciplinary citation analysis database), and a manual reference screening were performed to identify observational studies published from inception to May 20, 2022. A search for relevant keywords and medical subject heading terms related to dietary methyl donors, dietary components that potentially modulate the bioavailability of methyl groups, genetic variants of methyl-metabolizing enzymes, markers of CIMP and/or MSI, in combination with keywords related to CRC events was conducted.

The search was amplified through citation chaining (forward and backward) of the included studies. Reference lists of all identified articles and other related review articles, systematic reviews, and meta-analyses were hand-searched for additional articles. The present search was developed according to the "PRISMA Statement" guidelines (see the PRISMA checklist) (www.prisma-statement.org). For this review, a protocol was not prepared or registered. The search strategy is detailed as follows: (1) Colorectal neoplasms/exp or [(colorectal* or rect* or anal* or anus or colon* or sigmoid) adj3 (cancer* or carcinoma or tumour* or tumor* or neoplas* or adenoma or adenocarcinoma)], abstract (ab), keyword hearing word (kf), original title (ot), title (ti), text word (tw); (2) (observational or case-control or cohort), ab, kf, ot, ti, tw; (3) (incidence or prevalence or risk or odds ratio or hazard ratio), ab, kf, ot, ti, tw; (4) (one-carbon metabolism-related nutrient* or dietary methyl donor* or alcohol), ab, kf, ot, ti, tw; and (5) [gen* or single-nucleotide polymorphism (SNP)* or polymorphism* or methyl metabolizing enzyme* or diet–gene interaction* or hypermethylation* or microsatellite instability*], ab, kf, ot, ti, tw.

Review process and selection criteria

Two researchers independently screened the titles and abstracts of the articles to identify potentially relevant studies. Studies that passed the title/abstract review were retrieved for full-text review. The inclusion and exclusion criteria and the quality of the study were assessed by two researchers with the use of a data extraction form especially designed for this study.

The inclusion criteria consisted of studies: (1) With an observational design (case-control or cohort); (2) that evaluated the exposure to at least one of the following dietary components (dietary nutrient intake and/or plasma levels): Folate, other B vitamins, Met, choline, betaine, and/or alcohol; (3) that included genotyping analyses of methyl-metabolizing enzymes (*MTHFR, MTR,* Met synthase reductase), DN methyltransferase 3 b, euchromatin histone methyltransferase 1 and 2, PR domain zinc finger protein 2; (4) CIMP defined by promotor hypermethylation (calcium voltage-gated channel subunit a1 G, insulin-like growth factor 2, neurogenin1, runt-related transcription factor 3, suppressor of cytokine signalling 1), human *MutL* homolog 1 (*hMLH1*) hypermethylation; (5) MSI using markers [such as mononucleotide microsatellites with quasi-monomorphic allele length distribution in healthy controls but unstable (Bat-26 and/or Bat-25), NR-21, NR-22, NR-24)]; (6) in which the outcome of interest was CRC, colon, or rectal cancer (studies investigating benign adenomas or polyps were excluded); (7) that provided estimates of the adjusted odds ratios or relative risks or hazard ratios with 95% confidence intervals (95%CI); (8) conducted in humans (≥ 18 years old); and (9) written in English or Spanish.

The following types of publications were excluded: (1) Nonoriginal papers (reviews, commentaries, editorials, or letters); (2) meta-analysis studies; (3) off-topic studies; (4) studies lacking specific CRC data; (5) nonhuman research; (6) studies conducted in children, adolescents, or pregnant women; (7) duplicate publications; and (8) low-quality studies (Newcastle-Ottawa scale (NOS)[22] < 4 indicating insufficient study quality).

Study quality assessment

To evaluate the validity of the individual studies, two reviewers worked independently to determine the quality of the included studies based on the use of the NOS for case-control or cohort studies[22]. The maximum score was 9, and a high score (≥ 6) indicated high methodological quality; however, given the lack of studies on the subject under study, it was agreed to select those that had a score equal to or greater than 4. A consensus was reached between the reviewers if there were any discrepancies.

Data extraction

The data extracted for each individual study included the following: Name of the first author, study design, characteristics of the study population (age range or mean age, sex, country), dietary exposure, dietary assessment instrument used, outcomes (including cancer site), comparison, odds ratio or relative risk or hazard ratio (95%CI), adjusted variables, and NOS. For case-control studies, the following additional information was extracted: Number of cases and number of controls. For cohort studies, the following additional information was extracted: Number of participants at baseline, number of CRC cases, and length of follow-up. These variables were judged to be most relevant to the outcome studied. Where multiple estimates for the association of the same outcome were used, the one with the highest number of adjusted variables was extracted. Template data collection forms and data extracted from the included studies will be made available upon request from the corresponding author.

RESULTS

Figure 1 shows the PRISMA flow diagram summarizing the identification and selection of the relevant publications. A total of nineteen studies were included in this systematic review: Fourteen case-control studies[23-36] and five cohort studies[9,37-40]. In total, the case-control studies included 7055 cases and 9032 controls. The cohort studies included 256914 participants, with 1109 cases recorded during follow-up periods that ranged from 7.3 to 22 years. Amongst the case-control studies, nine articles were conducted in the United States, two in the United Kingdom, two in Korea and one in Portugal. With regard to the cohort studies, three were conducted in the Netherlands and two in the United States.

Tables 1 and 2 summarize the main characteristics and findings of the case-control and cohort studies, respectively, on the interactive effect between single-nucleotide polymorphisms in genes encoding methyl-metabolizing enzymes, dietary methyl donors and dietary components that potentially modulate the bioavailability of methyl groups on CRC risk. Tables 3 and 4 show the effects of dietary methyl donors and dietary components that potentially modulate the bioavailability of methyl groups on CRC risk, according to SNPs in genes encoding methyl-metabolizing enzymes and/or mutations in oncogenes, CIMP and/or MSI, in the case-control studies and cohort studies, respectively. Table 5 provides a summary of the results of the studies included in the systematic review.

DISCUSSION

This review summarizes previous studies that have investigated the influence of methyl donor nutrients as epigenetic regulators in CRC. The dietary components that showed a higher association with CRC risk were folate and alcohol. Thus, high folate intake was considered a protective factor, while high alcohol consumption proved to be a risk factor. Several studies have investigated the association between methyl donor nutrients and/or methyl antagonists (*e.g.*, alcohol) and *MTHFR* polymorphisms and have reported significant interactions[23,24,26,29,36]. In one of those case-control studies, those with the *MTHFR* 677 TT genotype, who consume low folate diets, had a greater chance of developing CRC than people with the CC or CT genotype[24]. Two other case-control studies reported that *MTHFR* 677 TT carriers with high (above mean) or adequate folate intake had a low risk of CRC[26,29].

Two case-control studies found that alcohol consumption increased CRC risk among *MTHFR* 677 TT carriers[23,26]. The decreased *MTHFR* enzyme activity among those who carried the T allele, and consumed low methyl donor nutrients and large amounts of alcohol can be utilised to explain the increased CRC risk[25,30]. These dietary habits may alter folate metabolism, especially in people with folate deficiencies[41]. In contrast, several studies have not found an association between *MTHFR* polymorphisms and either folate intake or alcohol intake and CRC risk[25,27]. It has been hypothesized that the differences in folate status among various populations may have influenced the contradictory results on the contribution of *MTHFR* genetic variants in CRC[25]. In addition to *MTHFR* poly-

Table 1 Characteristics of the eight case-control studies included in this systematic review examining the interactive effects between single-nucleotide polymorphisms in genes encoding methyl-metabolizing enzymes and one-carbon metabolism-related dietary compounds on colorectal cancer risk

Ref.	Country	Age (yr)	No. cases (M/W), endpoint	No. controls, type	Gene (SNP)	Nutrient/alcohol	Method for measuring nutrition intake	Outcome (OR, 95%CI)			Adjustments to OR	NOS
								SNP	Nutrient/alcohol	Interaction		
Chen *et al* [23]	United States	40-75	144 M, CRC	627 C	*MTHFR* (677C>T)	Dietary folate, Met, and alcohol	Validated FFQ (self-reported)	No assoc	Alcohol (≥ 5 *vs* ≤ 1 drinks/wk): 1.61 (1.01-2.58)	677TT (*vs* CC/CT)-low alcohol consumption (≤ 1 drinks/wk): 0.11 (0.01-0.85) (*P-interac* = 0.02)	Age, CRC family history	7
Guerreiro *et al*[24]	Portugal	Cases (64.2 ± 11.3), controls (62.2 ± 12.1)	104/92 CRC	200 C	*MTHFR* (677C>T), *MS* (2756A>G), *SHMT* (1420C>T)	Dietary folate, vitamins B_6 and B_{12}, glycine, Met, serine, and alcohol	Validated FFQ (by interview)	677TT (*vs* CC/CT): 3.01, (1.3-6.7); 1420TT (*vs* CC/CT): 2.6, (1.1-5.9)	Folate (> 406.7 mcg/d *vs* < 406.7 mcg/d): 0.67 (0.45-0.99)	677TT (*vs* CC/CT)– folate (< 406.7 mcg/d): 14.0, 1.8-108.5 (*P* = 0.05)	Age, CRC history, and sex	5
Kim *et al* [25]	Korea	30-79	465/322 CRC (363 CCa, 330 RCa)	656 H	*MTHFR* (677C>T)	Dietary folate and alcohol	Validated FFQ	677TT (*vs* CC/CT): 0.60 (0.46-0.78)	Folate (high *vs* low intake): 0.64 (0.49-0.84); alcohol (high *vs* low intake): 1.76 (1.26-2.46)	677CC/CT–Low-methyl diet (folate < 209.69 mcg/d and alcohol ≥ 30 g/d): 2.32 (1.18-4.56) (*P-interac* = no assoc)	Age, BMI, CRC family history, energy intake, multivitamin use, sex, smoking status	7
Ma *et al* [26]	United States	40-84	202 M, CRC	326 C	*MTHFR* (677C>T)	Plasma folate, and alcohol consumption	FFQ (self-reported)	677TT (*vs* CC): 0.45 (0.24-0.86)	Folate (plasma deficiency *vs* adequate levels): No assoc	677TT (*vs* TC/CC)–folate (adequate levels): 0.32 (0.15-0.68)	Age, alcohol consumption, aspirin use, BMI, exercise, multivitamin use, and smoking status	7
									Alcohol: Unk	677TT (*vs* CC)–alcohol (0-0.14 drinks/d): 0.12 (0.03-0.57)	Age	
Murtaugh *et al*[27]	United States	30-79	446/305 RCa	979 C	*MTHFR* (677C>T, 1298A>C)	Dietary folate, riboflavin, vitamins B_6 and B_{12}, Met, and alcohol	FFQ (by interview)	W, 677TT (*vs* CC): 0.54 (0.30-0.98). M&W, 1298CC (*vs* AA): 0.67 (0.46-0.98)	Dietary folate (> 475 mcg/d *vs* < = 322 mcg/d): 0.66 (0.48-0.92). High methyl donor status (*vs* low status): 0.79 (0.66-0.95)	No assoc	Age, BMI, ibuprofen use, intake of energy, fibre and calcium, PA, sex, and smoking status	6
Pufulete *et al*[28]	United Kingdom	38-90	13/15 CRC	76 C	*MTHFR* (677C>T, 1298A>C), *MS* (2756A>G), *CBS* (844ins68)	Plasma folate, vitamin B_{12}, and homocysteine, alcohol and folate intake	Validated FFQ (by interview)	677TT (*vs* CC): 5.98 (0.92-38.66), *P* = 0.06; 1298CC (*vs* AA): 12.6 (1.12-143.70), *P* = 0.04	Folate status score (T_3 *vs* T_1): 0.09 (0.01-0.57), *P-trend* = 0.01	Unk	Age, alcohol consumption, BMI, sex, and smoking status	7
Sharp *et al* [29]	United Kingdom		150/114 (189 CCa, 75 RCa)	408C	*MTHFR* (677C>T,	Dietary folate, riboflavin, vitamins B_6	Validated FFQ (self-reported)	No assoc	No assoc	677CT/TT (*vs* CC)–folate (> mean): *P-interac* =	Age, CRC family history, energy	6

					1298A>C)	and B_{12}, and alcohol				0.029. 677CT/TT (*vs* CC)–vitamin B_6 (> mean): *P-interac* = 0.016	intake, NSAID use, PA, and sex	
Slattery *et al*[30]	United States	30-79	824/849 CC (DCCa 405/303; PCCa 395/327)	1816 C	*MTHFR* (677C>T)	Dietary folate, Met, vitamins B_6 and B_{12}, and alcohol	Validated CARDIA diet questionnaire	677TT: No assoc	Unk	TT-low risk diet (high in folate and Met and without alcohol): 0.4 (0.1-0.9)	Age, BMI, intake of energy and fibre, PA, and smoking intensity	7

Asso: Significant association; BMI: Body mass index; C: Community controls; CBS: Cystathionine synthase; CCa: Colon cancer; CI: Confidence interval; CRC: Colorectal cancer; DCCa: Distal colon cancer; FFQ: Food frequency questionnaire; H: Hospital controls; interac: Interaction; M: Men; Met: Methionine; *MS*: Methionine synthase; *MTHFR*: Methylenetetrahydrofolate reductase; NSAID: Nonsteroidal anti-inflammatory drugs; NOS: Quality Newcastle-Ottawa Scale; OR: Odds ratio; PA: Physical activity; PCCa: Proximal colon cancer; RCa: Rectal cancer; *SHMT*: Serine hydroxymethyltransferase; SNP: Single-nucleotide polymorphism; unk: Unknown; W: Women.

Table 2 Characteristics of the cohort study included in this systematic review examining the interactive effects between single-nucleotide polymorphisms in genes encoding methyl-metabolizing enzymes and one-carbon metabolism-related dietary compounds on colorectal cancer risk

Ref.	Country	Study cohort (age, yr)	No. participants (M/W)	No. incident cases	Follow-up length, y	Gene (SNP)	Nutrient/alcohol	Method for measuring nutrition intake	Outcome (RR, 95%CI)			Adjustments to RR	NOS
									SNP	Nutrient/alcohol	Interaction		
de Vogel *et al*[9]	Netherlands	Netherlands Cohort Study on diet and cancer (55-69)	58279/62573	734 CRC	7.3	*MTHFR* (rs1801133, rs1801131), *MTR* (rs1805087), *MTRR* (rs1801394), *DNMT3B* (rs2424913, rs406193), *EHMT1* (rs4634736), *EHMT2* (rs535586), *PRDM2* (rs2235515)	Dietary folate, Met, vitamins B_2 and B_6, alcohol	Validated FFQ (self-reported)	Unk	Unk	≤ 1 rare allele in folate metabolizing enzymes–vitamin B_2 (T_3 *vs* T_1): 0.30, (0.11-0.81), *P-trend* = 0.005. Rare allele of *DNMT3B* C>T (rs406193)–vitamin B_6 (T_3 *vs* T_1): 1.90 (1.00-3.60), *P-trend* = 0.04. Common allele of *PRDM2* G>A (rs2235515)–vitamin B_6 (T_3 *vs* T_1): 1.49 (1.00-2.22), *P-trend* = 0.03. No assoc	Age, alcohol consumption, BMI, CRC family history, intake of energy and alcohol, sex, and smoking status	9

Asso: Significant association; BMI: Body mass index; CI: Confidence interval; CRC: Colorectal cancer; *DNMT3B*: ADN (cytosine-5-)-methyltransferase 3 ; *EHMT1*: Euchromatin histone methyltransferase 1; FFQ: Food frequency questionnaire; M: Men; *MTHFR*: Methylenetetrahydrofolate reductase; *MTR*: Methionine synthase; *MTRR*: Methionine synthase reductase; NOS: Quality Newcastle-Ottawa Scale; *PRDM2*: PR domain zinc finger protein 2; RR: Relative risk; SNP: Single-nucleotide polymorphism; T: Tertile; unk: Unknown; W: Women.

morphisms, de Vogel *et al*[9] also investigated the modifying effects of polymorphisms of Met synthase reductase, *MTR*, DN methyltransferase 3 b, euchromatin histone methyltransferase 1 and 2, and PR domain zinc finger protein 2 but found no interactions, although some *P-trends* were significant.

Regarding the methylation abnormalities of genes, de Vogel *et al*[37] found that high vitamin B_6 intake was associated with an increased CRC risk caused by hypermethylation of the *hMLH1* promoter among men. Therefore, these authors suggest that vitamin B_6 may have had a tumour-promoting effect by increasing promoter methylation. However, the intake of folate, vitamin B_2, Met and alcohol was not associated with the risk of tumours showing *hMLH1* hypermethylation. In any case, other studies

Table 3 Characteristics of the six case-control studies included in this systematic review examining the interactive effects between single-nucleotide polymorphisms in genes encoding methyl-metabolizing enzymes and/or mutations in oncogenes, CpG island methylator phenotype and/or microsatellite instability, and one-carbon metabolism-related dietary compounds on colorectal cancer risk

Ref.	Country	Age (yr)	No. cases (M/W), endpoint	No. controls and type	Gene (SNP)	CIMP markers	MSI	Nutrient/alcohol	Method for measuring nutrition intake	Outcome (OR, 95%CI), interaction		Adjustments to OR	NOS
										CIMP markers/MSI–nutrient/alcohol	CIMP markers-/MSI–SNP–nutrient/alcohol		
Busch *et al*[31]	United States	40-80 (AAs *vs* EAs)	244/241 CRC	Analyses were only performed in tumour tissue		*CACNA1G, hMLH1, NEUROG1, RUNX3, SOCS1*	Unk	Dietary folate and alcohol	Unk	EAs: High *CACNA1G* methylation tumour (cut point of 5%)–high folate intake: 0.3 (0.14-0.66); high *SOCS1* methylation tumour (cut point of 3%)–high folate intake: 0.3 (0.11-0.80)	Unk	-	4
Curtin *et al*[32]	United States	30-79	518/398 CCa	1972 C	*MTHFR* (677C>T, 1298A>C), *TS* variants (*TSER, TTAAAG* in 3´-UTRs 1494), *MTR* (919D>G), *RFC* (80G>A), *MTHFD1* (R134K, R653Q), *ADH3* (1045A>G)	*MINT1, MINT2, MINT31, p16, hMLH1*	Unk	Dietary folate, Met, vitamin B_{12}, and alcohol	Adaptation of the CARDIA diet history	Unk	*MTHFR* 1298AA–alcohol (high *vs* none): CIMP+, 0.5 (0.3-0.97), $P < 0.01$; *ADH3* (1 or 2 variant, slow catabolizing*2 *vs* homozygous for the common allele)–folate (low): CIMP+, 1.6 (1.03-2.6), $P = 0.02$. *MTHFR* 1298AC or CC-high-risk dietary pattern (low in folate or Met intake, high in alcohol): CIMP+, 2.1 (1.3-3.4), $P = 0.03$	Age, centre, other SNPs, sex, smoking intensity, and race	9
Curtin *et al*[33]	United States	30-79	559/392	1205 C	*MTHFR (* 1298A>C), *TP53, KRAS2,*	*CDKN2A, hMLH1, MINT 1, 2* and *31*		Folate, riboflavin, vitamins B_6, B_{12}, and Met	Adaptation of the CARDIA diet history (by interview)	M: Folate (T_3 *vs* T_1)–CIMP+, 3.2 (1.5-6.7), $P < 0.01$	1298 AC/CC (*vs* AA)–folate (T_3 *vs* T_1): 0.4 (0.2-1.0), $P = 0.04$, for CIMP+	Age, centre, intake of energy and fibre, NSAID use, oestrogen use (W), PA, race, referent year, sex, screening, and smoking	8
Kim *et al*[34]	Korea	30-79	465/322 CRC (363 CCa, 330 RCa)	656 H	*MTHFR* (677C>T)	Unk	2 mononuc-leotide markers (Bat25 and Bat26) and 3 dinucleotide markers (D2S123, D5S346, and D17S250)	Folate, vitamins B_2, B_6, B_{12}, niacin, Met, and choline	Validated FFQ	Unk	DCCa: *hMSH3* (rs41097) AG/GG (*vs* AA)–niacin (> 14.00 mg/d *vs* < 14.00 mg/d)–MSI–MMR status: 0.49 (0.28-0.84), *P-interac* = 0.008	Age, intake of energy and alcohol, BMI, CRC family history, educational level, occupation, income, PA,	7

											sex, and smoking status	
Slattery *et al*[35]	United States	30-79	821/689 CRC	2410 C	Unk	Unk	10 tetranucleotide repeats, 3 Bat-26 and TGFbRII	Dietary folate, and alcohol	Validated CARDIA diet questionnaire	Alcohol–MSI+ (*vs* MSI-): 1.6 (1.0-2.5), *P-trend* = 0.03; liquor–MSI+ (*vs* MSI-): 1.6 (1.1-2.4), *P-trend* = 0.02		Age, BMI, intake of energy, fibre and calcium, intake, PA, sex	7
Slattery *et al*[36]	United States	30-79	638/516 CRC	2410 C	*BRAF* (V600E)	*MINT1*, *MINT2*, *MINT31*, *p16* and *hMLH1*	Unk	Folate, vitamins B_6 and B_{12}, Met, and alcohol	Diet history questionnaire	No assoc	MSI tumour–alcohol (high *vs* none): 1.6 (0.9-2.9), *P-trend* = 0.04, for *p16* unmethylated; 1.7 (0.7-4.3), *P-trend* = 0.06, for $CIMP_{low}$ (< 2 markers); 2.2 (1.2-3.7), *P-trend* = 0.01, for *BRAF* wildtype	Age, alcohol intake, BMI, intake of energy and folate, density of calcium and fibre, NSAIDs use, PA, sex, smoking intensity	7

AA: African Americans; *ADH3*: Alcohol dehydrogenase 3; asso: Significant association; Bat: Mononucleotide microsatellite with quasi-monomorphic allele length distribution in healthy controls but unstable; BMI: Body mass index; *BRAF*: B-Raf proto-oncogene; C: community controls; *CACNA1G*: Calcium voltage-gated channel subunit a1 G; CCa: Colon cancer; *CDKN2A*: Cyclin-dependent kinase inhibitor 2A; CI: Confidence interval; CIMP: CpG island methylator phenotype; CRC: Colorectal cancer; EA: European Americans; FFQ: Food frequency questionnaire; H: Hospital controls; *hMLH1*: Human *MutL* homolog 1; *hMSH3*: Human *MutS* homolog 3; interact: Interaction; *KRAS:* Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; M: Men; Met: Methionine; MINT: Methylated in tumours; MMR: Mismatch repair; MSI: Microsatellite instability; *MTHFD:* Metilentetrahidrofolate dehydrogenase; *MTHFR:* Methylenetetrahydrofolate reductase; *MTR:* Methionine synthase; *NEUROG1*: Neurogenin1; NOS: Quality Newcastle-Ottawa Scale; NSAID: Nonsteroidal anti-inflammatory drugs; OR: Odds ratio; PA: Physical activity; RCa: Rectal cancer; *RFC*: Reduced folate carrier; *RUNX3:* Runt-related transcription factor 3; SNP: Single-nucleotide polymorphism; *SOCS1*: Suppressor of cytokine signalling 1; T: Tertile; *TGFbRII*: Transforming growth factor β receptor type II; TS: Thymidylate synthase; *TSER:* Thymidylate synthase enhancer region; TP53: Tumour protein p53; unk: Unknown; UTR: Untranslated region; W: Women.

showed inverse associations between vitamin B_6 intake and CRC risk, both when the intake level was higher[6] and when it was similar[42] to that in the study of de Vogel *et al*[37]. Therefore, further attention should be given to this association in future studies.

Another interesting finding in this review is the inverse association between dietary folate and Met and B-Raf proto-oncogene mutations among men[37]. A previous study showed that folate may increase the risk of tumours harbouring truncating adenomatous polyposis coli mutations in men[43]. Apparently, relatively high folate intake may confer a growth advantage to mutated tumours independent of the type of mutation. Nevertheless, the occurrence of MSI does not seem to be sensitive to methyl donor intake or to that of alcohol[36-37,44].

In one of the case-control studies that we analysed, an interaction was observed between a high- or low-risk diet and *MTHFR* 1298A>C (but not 677C>T) with regard to CIMP status[32]. This result suggests that a genetic polymorphism at *MTHFR* 1298A>C interacts with the diet (with a low folate and Met intake and a high alcohol consumption) increasing the risk of highly CpG-methylated colon tumours. S-adenosylmethionine binds as an allosteric inhibitor in the *MTHFR* regulatory region, which is where the 1298A>C variant is found. This gives some justification for the stronger associations between *MTHFR* 1298A>C and CIMP rather than the 677C>T SNP, which has an opposite effect on the stability of the enzyme. Due to their high linkage disequilibrium, the *MTHFR* 677C>T and 1298A>C polymorphisms should not be viewed separately. van Engeland *et al*[40] also discovered that people

Table 4 Characteristics of the five cohort studies included in this systematic review examining the interactive effects between single-nucleotide polymorphisms in genes encoding methyl-metabolizing enzymes and/or mutations in oncogenes, CpG island methylator phenotype and/or microsatellite instability, and one-carbon metabolism-related dietary compounds on colorectal cancer risk

Ref.	Country	Study cohort (age, yr)	No. participants (M/W)	No. incident cases	Follow-up length, yr	Gene (SNP)	CIMP markers	MSI	Nutrient/alcohol	Method for measuring nutrition intake	Outcome (RR, 95%CI) interaction			NOS
											CIMP markers/MSI–nutrient/alcohol	CIMP markers–/MSI–SNP–nutrient/alcohol	Adjustments to RR	
de Vogel *et al* [9]	Netherlands	The Netherlands Cohort Study on diet and cancer (55-69)	58279/62573	734 CRC	7.3	*MTHFR* (rs1801133, rs1801131), *MTR* (rs1805087), *MTRR* (rs1801394), *DNMT3B* (rs2424913, rs406193), *EHMT1* (rs4634736), *EHMT2* (rs535586), *PRDM2* (rs2235515)	*CACNA1G*, *IGF2*, *NEUROG1*, *RUNX3*, *SOCS1*	Bat-26, Bat-25, NR-21, NR-22, NR-24	Dietary folate, Met, vitamins B_2 and B_6, alcohol	Validated FFQ (self-reported)	No assoc	Unk	BMI, CRC family history, intake of energy and alcohol, sex, and smoking status	9
de Vogel *et al* [37]	Netherlands	The Netherlands Cohort Study on diet and cancer (55-69)	58279/62573	734 CRC	7.3	*BRAF* (V600E)			Dietary folate, Met, vitamins B_2 and B_6, alcohol	Validated FFQ (self-reported)	M: *BRAF* mut–folate (T_3 *vs* T_1): 3.04 (1.13-8.20), *P-trend* = 0.03; *BRAF* mut–Met (T_3 *vs* T_1): 0.28 (0.09-0.86), *P-trend* = 0.02); *hMLH1* hypermethylation–vitamin B_6 (T_3 *vs* T_1): 3.23 (1.15-9.06), *P- trend* = 0.03	Unk	Age, BMI, CRC family history, intake of energy, meat, total fat, fibre, vitamin C, total iron and calcium, smoking status	9
Schernhammer *et al*[38]	United States	The Nurses' Health Study (W) (30-55) and the Health Professional Follow-up Study (M) (40–75)	47371/88691	669 CCa	22	*KRAS*	Unk	D2S123, D5S346, D17S250, Bat25, Bat26 (14), Bat40, D18S55, D18S56, D18S67, D18S487	Folate, vitamins B_6 and B_{12}, Met, and alcohol	Validated FFQ (self-reported)	Unk	MSI/*KRAS*–folate: No assoc for CCa. MSI/*KRAS*–vitamins B_6 or B_{12}: No assoc for CCa	Age, aspirin use, smoking, BMI, colon polyps, CRC family history, intake of alcohol, energy, beef, calcium, vitamins B_6 and B_{12}, and Met, multivitamin use, PA, sex, screening sigmoidoscopy	9

Schernhammer *et al*[39]	United States	The Nurses' Health Study (30-55)	88691 W	375 CCa		*BRAF*	*CHFR, MGMT, p14, WRN, HTC1, MINT1, MINT31, IGFBP3*	Unk			Folate (Q_4 *vs* Q_1: No assoc with CIMP–high tumour risk; and no assoc with *BRAF* status	Unk			
van Engeland *et al*[40]	Netherlands	Netherlands Cohort Study on Diet and Cancer (55-69)	58279/62573	122 CRC	7.3	Unk	*APC-1A, p14ARF, p16INK4A, hMLH1, O 6-MGMT,* and *RASSF1A*	Unk	Dietary folate and alcohol	Validated FFQ (self-reported)	Low *vs* high-methyl donor intake–promoter methylation (> 1 gene methylated): No assoc	Unk		Age, CRC family history, intake of energy, fibre, vitamin C, and iron, sex	9

APC: Adenomatous polyposis coli; asso: Significant association; Bat: Mononucleotide microsatellite with quasi-monomorphic allele length distribution in healthy controls but unstable; BMI: Body mass index; *BRAF*: B-Raf proto-oncogene; *CACNA1G:* Calcium voltage-gated channel subunit a1 G; CCa: Colon cancer; *CHFR*: RING finger domain protein; CI: Confidence interval; CIMP: CpG island methylator phenotype; CRC: Colorectal cancer; *DNMT3B:* DNA methyltransferase 3 *EHMT:* Euchromatin histone methyltransferase; FFQ: Food frequency questionnaire; *hMLH1*: Human *MutL* homolog 1; *HTC*: Histidine triad with channel; IGF2: Insulin-like growth factor 2; *IGFBP*: Insulin-like growth factor-binding protein; *KRAS:* Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; M: Men; Met: Methionine; *MGMT*: DNA repair enzyme O(6)-methylguanine-DNA methyltransferase; MINT: Methylated in tumours; MSI: Microsatellite instability; *MTHFR:* Methylenetetrahydrofolate reductase; *MTR:* Methionine synthase; *MTRR*: Methionine synthase reductase; mut: Mutation; *NEUROG1*: Neurogenin1; NOS: Quality Newcastle-Ottawa Scale; PA: Physical activity; *PRDM2*: PR domain zinc finger protein 2; Q: Quartile; RASSF1A: Ras association domain family 1 isoform A; RR: Relative risk; *RUNX3:* Runt-related transcription factor 3; SNP: Single-nucleotide polymorphism; *SOCS1*: Suppressor of cytokine signalling 1; T: Tertile; unk: Unknown; W: Women; *WRN*: Werner syndrome gene.

diagnosed with CRC, with low intake of folate and high consumption of alcohol, had a greater prevalence of promoter hypermethylation; however, the difference was not statistically significant due to limited power. Therefore, it was proposed that stratification for functionally significant SNPs in the genes encoding folate metabolism enzymes could strengthen the observed effect of folate deficiency on promoter methylation[40].

Additionally, Curtin *et al*´s study[32] found an interaction between alcohol consumption and *MTHFR* 1298A>C in association with CIMP status. Relative to the AA genotype in non-drinkers, the *MTHFR* 1298 AA genotype was linked to a higher risk of CIMP+ in drinkers. In a previous study by Slattery *et al* [35], in which associations between CIMP status and alcohol use were assessed without taking into regard to genotype, no association was observed. These results imply that the activity of the 1C-metabolism enzyme may alter the risk associated with alcohol in determining the CIMP status of colon cancer. In any case, to date, few published studies have evaluated, CIMP in CRC for possible relationships with 1C-metabolism SNPs[32,45,46]. Moreover, these data raise the possibility that more investigation is required to clarify the function of genetic SNPs in relation to CIMP status and the promoter hypermethylation of particular genes.

In one case-control study[36], an association between long-term alcohol consumption and increased likelihood of having a CIMP-low or B-Raf proto-oncogene-mutated tumour was observed. Among those with unstable tumours, they observed that alcohol was more likely to be associated with CIMP-low rather than CIMP-high tumours. A previous study of these same authors showed that alcohol increased the risk for MSI+ tumours in general[35]. Therefore, these findings suggest that the increased risk of MSI associated with alcohol is limited to those tumours that are unmethylated rather than methylated.

Table 5 Summary of results of the studies included in this systematic review

Gen, SNP/CIMP/MSI	Nutrients/alcohol	CRC risk/CIMP+	Ref.
MTHFR 677 TT	Folate; Adequate folate	CRC risk; CRC risk	Guerreiro *et al*[24]; Sharp *et al*[29]; Ma *et al*[26]
	Alcohol	CRC risk	Chen *et al*[23]; Ma *et al*[26]
	Folate/Met, and without alcohol	CRC risk	Slattery *et al*[30]
	Vitamin B_6	CRC risk	Sharp *et al*[29]
BRAF mutation	Folate	CRC risk (M)	de Vogel *et al*[37]
	Met	CRC risk (M)	
hMLH1 hypermethylation	Vitamin B_6	CRC risk (M)	
MTHFR 1298 AC/CC	Folate/Met, and alcohol	CIMP+	Curtin *et al*[32]
MTHFR 1298 AA	Alcohol	CIMP+ (CCa)	
p16 unmethylated, $CIMP_{low}$ or *BRAF* mut	Alcohol	CRC risk	Slattery *et al*[36]
hMSH3, MSI or MMR status	Niacin	CRC risk (DCCa)	Kim *et al*[34]

BRAF: B-Raf proto-oncogene; CCa: Colon cancer; CRC: Colorectal cancer; CIMP: CpG island methylator phenotype; DCCa: Distal colon cancer; h*MLH1*: Human *MutL* homolog 1; *hMSH3:* Human *MutS* homolog 3; M: Men; Met: Methionine; MMR: Mismatch repair; MSI: Microsatellite instability; *MTHFR:* Methylenetetrahydrofolate reductase; mut: Mutation; SNP: Single-nucleotide polymorphism.
↑: High intake or increased risk or high probability.
↓: Low intake or increased risk.

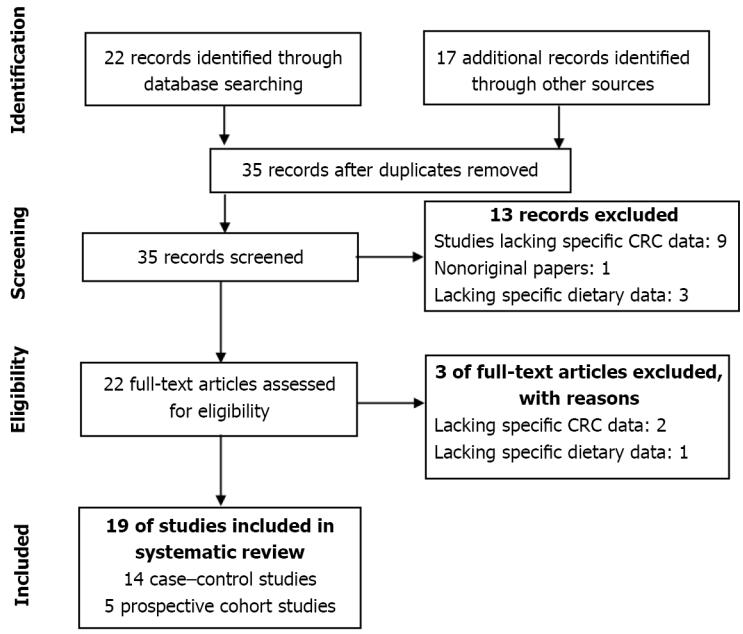

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Figure 1 PRISMA flow diagram summarizing the identification and selection of the relevant publications assessing the influence of methyl donor nutrients as epigenetic regulators in colorectal cancer. CRC: Colorectal cancer.

Finally, regarding the interaction between MMR SNPs and methyl donor nutrient intake on CRC based on MSI status, in a case-control study[34], a strong inverse association was observed for *hMSH3* AG or GG carriers with a high intake of niacin, particularly among patients with CC and microsatellite stability or proficient MMR status. However, to ascertain the processes behind this association with CRC risk, the precise roles of this SNP must be identified.

The importance of interactions between modifiable factors, such as methyl donor nutrients and CRC, is suggested by evidence that colorectal carcinogenesis is generated by numerous molecular pathways in parallel with MSI status, which is caused by a defect in the MMR machinery. In this sense, it is worth

remembering the article mentioned by de Vogel *et al*[37], in which it was reported that high consumption of vitamin B_6 was linked to an increased risk of sporadic CRC with *hMLH1* hypermethylation, indicating that vitamin B_6 affects CRC risk through both genetic and epigenetic mechanisms. Based on the findings of Kim *et al*[34], it may be possible to explain the interactions between dietary methyl donor nutrients, such as niacin, and *hMSH3* genetic variants as predictors of CRC risk.

DNA methylation and microRNA expression levels may be regulated by the MMR machinery's epigenetic relationships with methyl groups[47]. Through the methylation of CpG islands in the promoter region, 1C metabolism mediated by methyl donor nutrients can change how the DNA MMR system is activated. A adequate DNA MMR system with methyl groups may control the equilibrium between the repair and accumulation of short repeat sequences, preventing extensive DNA damage that supports colorectal carcinogenesis.

This systematic review has several strengths: (1) Cohort and case-control studies were identified through a systematic search; (2) a quantitative NOS scale was used to assess the quality of the studies; and (3) most studies (twelve of nineteen) used a validated questionnaire to assess dietary intake. To our knowledge, this is the first systematic review regarding the influence of methyl donor nutrients as epigenetic regulators in CRC.

The limitations of this review include the following: (1) Case-control studies, which are susceptible to recall and selection bias, made up the bulk of the research. However, most studies were based on community controls; thus, they might be a good representation of the frequency of genetic variants or of dietary habits of the overall population; (2) the heterogeneous nature of studies, including the study population characteristics, sample size, study design, and follow-up periods; (3) potential residual confounding because of the observational nature of the studies included or the possibility that not all the studies were adjusted for important nutrient variables; (4) some of the dietary assessments were self-reported, which may affect the reliability of the reported intakes, although the use of validated questionnaires in most studies could reduce this bias; (5) some studies had a relatively limited sample size or effect size, which made it difficult for them to detect the interactions between genetic and nutritional information, which could explain, in part, the lack of results with a statistically significant level; and (6) despite the fact that some research have found differential interactions based on the CRC subtype[34], the majority of studies lacked stratified analysis. Considering these limitations, the conclusions from these researchers should be taken carefully. Consequently, it is difficult for this review to explain the gene-diet interactions and their effects on the development of CRC.

CONCLUSION

In this systematic review of observational studies, some interactions between *MTHFR* polymorphisms, methyl donor nutrients (such as folate) and alcohol on CRC risk are suggested. Moreover, some studies show that vitamin B_6, niacin and alcohol may affect CRC risk through not only genetic but also epigenetic regulation. In any case, this review was not able to clarify which mechanisms underlie the influence of methyl donor nutrients on DNA methylation, as well as the efficacy of methyl uptake, transportation, and the final involvement in methyl-related gene expression. Further prospective studies with large samples and long follow-up periods, as well as clinical trials that take into account the long latency period of CRC, are needed to clarify the influence of methyl group donors as epigenetic regulators, with particular emphasis on differences in CRC subsite-specific risk. Such studies may provide valuable insight into the biological mechanisms with the goal of identifying at-risk subpopulations and promoting primary prevention of CRC.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is the third most frequent cancer and is responsible for the second-highest mortality rate in cancer patients worldwide. The main factors which may help prevent CRC are those associated with diet, lifestyle, and prevention of metabolic diseases. With regards to the dietary component, one-carbon metabolism-related nutrients have been considered anticarcinogenic and chemotherapeutic agents in the one-carbon metabolic network. However, it is still unclear whether the influence of methyl donor intake is modified by polymorphisms in these epigenetic regulators.

Research motivation

Although screening for early detection of CRC is effective to help decrease the trends in mortality rates, understanding daily life factors is also important to prevent this type of cancer. A better understanding of the molecular basis of CRC could contribute to a better design of future research and better preventive nutritional management in this type of cancer.

Research objectives

In the present work, we reviewed previous studies that have investigated this matter to improve the current understanding of the molecular basis of CRC.

Research methods

A literature search in the Medline database, *Reference Citation Analysis* (https://www.referencecitation-analysis.com/, an artificial intelligence technology-based open multidisciplinary citation analysis database), and manual reference screening were performed to identify observational studies published from inception to May 2022. A search for relevant keywords and medical subject heading terms related to dietary methyl donors, dietary components that potentially modulate the bioavailability of methyl groups, genetic variants of methyl-metabolizing enzymes, markers of CpG island methylator phenotype and/or microsatellite instability, in combination with keywords related to CRC events was conducted. The present search was developed according to the "PRISMA Statement" guidelines. To evaluate the validity of the individual studies, two reviewers worked independently to determine the quality of the included studies based on the use of the Newcastle-Ottawa scale for case-control or cohort studies.

Research results

A total of fourteen case-control studies and five cohort studies were identified. In total, the case-control studies included 7055 cases and 9032 controls. The cohort studies included 256914 participants, with 1109 cases recorded during follow-up periods that ranged from 7.3 to 22 years. The dietary components that showed a higher association with CRC risk were folate and alcohol. Thus, high folate intake was considered a protective factor, while high alcohol consumption proved to be a risk factor. Several studies have investigated the association between methyl donor nutrients and/or methyl antagonists (*e.g.*, alcohol) and methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms and have reported significant interactions. In one of those case-control studies, those with the *MTHFR* 677 TT genotype, who consume low folate diets, had a greater chance of developing CRC than people with the CC or CT genotype. Two other case-control studies reported that *MTHFR* 677 TT carriers with high (above mean) or adequate folate intake had a low risk of CRC.

Research conclusions

In this systematic review of observational studies, some interactions between *MTHFR* polymorphisms, methyl donor nutrients (such as folate), and alcohol on CRC risk are suggested. Moreover, some studies show that vitamin B_6, niacin, and alcohol may affect CRC risk through not only genetic but also epigenetic regulation.

Research perspectives

This review was not able to clarify which mechanisms underlie the influence of methyl donor nutrients on DNA methylation, as well as the efficacy of methyl uptake, transportation, and the final involvement in methyl-related gene expression. Further prospective studies with large samples and long follow-up periods, as well as clinical trials that consider the long latency period of CRC, are needed to clarify the influence of methyl group donors as epigenetic regulators, with particular emphasis on differences in CRC subsite-specific risk.

FOOTNOTES

Author contributions: The study was conceived and designed by Chávez-Hidalgo LP, Martín-Fernández-de-Labastida S, M de Pancorbo M, and Arroyo-Izaga M; The data were acquired, collated, and analysed by Chávez-Hidalgo LP and Arroyo-Izaga M; The study was drafted and revised critically for important intellectual content by all authors; The work reported in the paper has been performed by the authors, unless clearly specified in the text; All authors gave final approval of the version to be published and have contributed to the study; No ethical approval was needed.

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Country/Territory of origin: Spain

ORCID number: Lourdes Pilar Chávez-Hidalgo 0000-0002-2766-9009; Silvia Martín-Fdz-de-Labastida 0000-0003-2635-5814; Marian M de Pancorbo 0000-0002-8081-0702; Marta Arroyo-Izaga 0000-0001-5592-4241.

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