

Original Research Article

Dietary patterns and colorectal cancer risk: Global Cancer Update Programme (CUP Global) systematic literature review



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ABSTRACT

Background: The 2018 World Cancer Research Fund/American Institute for Cancer Research Third Expert Report, including studies up to 2015, determined limited–no conclusion evidence on dietary patterns and colorectal cancer (CRC) risk due to insufficient data and varying pattern definitions.

Objectives: This updated review synthesized literature on dietary patterns and CRC risk/mortality.

Methods: PubMed and Embase were searched through 31 March, 2023, for randomized controlled trials (RCTs) and prospective cohort studies on adulthood dietary patterns. Patterns were categorized by derivation method: a priori, a posteriori, or hybrid, and were then descriptively reviewed in relation to the primary outcomes: CRC risk or mortality. The Global Cancer Update Programme Expert Committee and Expert Panel independently graded the evidence on the likelihood of causality using predefined criteria.

Results: Thirty-two dietary scores from 53 observational studies and 3 RCTs were reviewed. Limited–suggestive evidence was concluded for higher alignment with a priori–derived patterns: Mediterranean, healthful plant-based index, Healthy Eating Index (HEI)/alternate HEI, and Dietary Approaches to Stop Hypertension (DASH), in relation to lower CRC risk. Common features across these diets included high plant-based food intake and limited red/processed meat. Hybrid-derived patterns: the empirical dietary index for hyperinsulinemia (EDIH) and the empirical dietary inflammatory pattern (EDIP), showed strong–probable evidence for increased CRC risk. Evidence for a priori–derived low-fat dietary interventions and a posteriori–derived patterns was graded as limited–no conclusion. By cancer subsite, higher alignment with Mediterranean diet showed limited–suggestive evidence for lower rectal cancer risk, and that with HEI/alternate HEI and DASH showed limited–suggestive evidence for lower colon and rectal cancer risks. EDIH and EDIP showed strong–probable evidence for increased colon cancer risks. All exposure–mortality pairs and other pattern–outcome associations were graded as limited–no conclusion.

Conclusions: This review highlights the role of dietary patterns in CRC risk/mortality, providing insights for future research and public health strategies. This review was registered at PROSPERO as CRD42022324327 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022324327).

Abbreviations: AICR, American Institute for Cancer Research; AHEI, Alternative Healthy Eating Index; CRC, colorectal cancer; CUP, Cancer Update Programme; DASH, Dietary Approaches to Stop Hypertension; EDIH, Empirical Dietary Pattern for Hyperinsulinemia; EDIP, Empirical Dietary Inflammatory Pattern; HEI, Healthy Eating Index; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; PDI, plant-based diet index; PDQS, Prime Diet Quality Score; RoB-NObs, Risk of Bias for Nutrition Observational Studies; RoB, risk of bias; RR, relative risk; WCRF, World Cancer Research Fund; WHI, Women's Health Initiative.

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Keywords: adult, colorectal cancers, dietary patterns, epidemiology, incidences, mortalities, prospective studies, public health, randomized controlled trial, review

Introduction

Diet plays an important role in colorectal cancer (CRC) risk. Research suggests that factors such as alcohol use, low calcium intake, and low milk intake are among the largest contributors to global disability-adjusted life years (DALYs) lost to CRC. In 2017, globally, the top three factors contributing to DALYs for both sexes were low calcium intake (20.5%), alcohol consumption (15.2%), and low milk intake (14.3%) [1]. The 2018 World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) Third Expert Report [2], incorporating studies up to April 2015, provided strong evidence (subgrade: convincing or probable) that foods containing whole grains, fiber, dairy products, and calcium supplements have protective effects against CRC, whereas red/processed meat and alcoholic drinks are associated with an increased risk of CRC [3].

Decades of diet and cancer research primarily focused on individual nutrients or foods, but this approach has limitations. Considering the combined effects of foods and analyzing diet holistically as a pattern is crucial for a more realistic reflection of real-world eating habits [4]. Moreover, pattern-based dietary guidelines are often more practical for individuals to follow than isolated nutrient or food group recommendations [5].

Various dietary patterns based on different approaches have been developed to assess the quality and intake of diets. A priori patterns are derived based on established scientific evidence linking dietary components to disease risks, whereas a posteriori patterns are derived from data of a specific population through statistical modeling without previous knowledge. Other approaches involve hybrid methods of combining both a priori and posteriori methods by incorporating disease-related intermediate variables and extracting exposure patterns from available data. However, despite the growing number of studies on dietary patterns, the 2018 WCRF/AICR Third Expert Report concluded limited–no conclusion evidence on the association between dietary patterns and CRC risk due to insufficient research and inconsistencies in defining the patterns [3].

As part of the ongoing Global Cancer Update Programme (CUP Global), previously referred to as the WCRF/AICR Continuous Update Project, an updated systematic literature review was performed to summarize current evidence on dietary patterns and their associations with CRC risk and mortality, including analysis by anatomic subsite [colon (proximal colon and distal colon) and rectal cancer]. This updated review improved upon the WCRF/AICR Third Expert Report by using a clearer methodologic approach with detailed investigations into dietary pattern components. Dietary patterns were categorized by derivation methods, and their associations with CRC risk/mortality were reviewed. The objective of this review was to provide a better understanding of the current state of knowledge including an independent assessment of the strength of the evidence and identify areas for further investigations. This article presents evidence solely on dietary patterns, whereas evidence on dietary-lifestyle patterns is presented in the accompanying article [6].

Methods

The review protocol is available at <https://osf.io/z9naw/>. The systematic review was registered in PROSPERO on 9 May, 2022, and

further updated on 6 July, 2023, to extend the literature search up to 31 March 2023 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022324327).

Search strategy

The CUP Global research team at Imperial College London conducted searches on PubMed and Embase from the inception of each database until 31 December, 2018, using the WCRF CUP Global search strategy. Relevant lifestyle factors and cancer data were then extracted into the in-house CUP Global database. Search terms are listed in Appendix A. The study selection process involved an initial screening of all titles and abstracts, followed by a thorough examination of full-text articles and reference lists. A subsequent search, using the same strategy, was conducted for articles published between 1 January, 2019, and 31 March, 2022, with an extension for articles published up to 31 March, 2023.

Study selection

Inclusion criteria involved peer-reviewed studies that investigated the following: 1) males and females aged 18 y or older, free of cancer (except nonmelanoma skin cancer); 2) alignment with dietary patterns (defined as the quantities, proportions, variety or combination of different foods, drinks, and nutrients in diets, and the frequency with which they are habitually consumed) assessed using data-driven, pre-defined, or mixed methods—defined indices or scores, with details on the components and their cutoff points; 3) comparison/control groups that aligned with varying dietary patterns or differing levels of the same pattern; and 4) incidence or mortality related to CRC. In this review, mortality specifically refers to the incidence of fatal CRC in populations initially free of cancer. Types of studies for inclusion were randomized controlled trials (RCTs), prospective cohort studies, nested case–control studies, case–cohort studies, and pooled analyses of studies with these designs. Studies must report relative risk (RR), hazard ratio, or odds ratio along with its corresponding measure of variability. Studies were excluded if published in languages other than English, if participants were younger than 18 y (children/adolescents), if they exclusively involved individuals with diseases (except diabetes) or hospitalized patients due to illness or injury, if participants had previous cancer diagnoses, or if the dietary patterns were solely based on nutrient intakes. The exclusion of participants with previous cancer diagnoses ensures consistency across studies evaluating both CRC risk and mortality outcomes. Although this exclusion might remove studies derived from CRC patient cohorts examining survival, our focus was specifically on population-based studies assessing dietary patterns and their association with the development of fatal CRC, rather than survival following a diagnosis. When multiple publications reported on the same or overlapping populations, the publication with the largest number of events and longer follow-up periods was selected for inclusion.

Data extraction

Data extracted from each study included the following: 1) the last name of the first author, year of publication, and country; 2) study name, design, and participant characteristics; 3) number of cases, study sample size, and follow-up period; 4) case ascertainment method; 5) method for exposure assessment, including the name and a brief description of each pattern including its components; 6) types of

outcome (incidence or mortality and cancer site); 7) RR estimates along with their corresponding 95% CIs or *P* values for the exposure comparisons; and 8) variables included in any adjusted analysis. A second reviewer independently assessed $\geq 10\%$ of the study selection and conducted data extraction. Any discrepancies were resolved by consensus through discussion.

Risk of bias assessment

Risk of bias (RoB) in each included study was evaluated and graded according to pre-established criteria. The tools used were the Cochrane RoB2 tool for RCTs [7] and a modified version of the Risk of Bias for Nutrition Observational Studies (RoB-NObs) tool (Appendix B). The RoB-NObs tool was originally developed by the United States Department of Agriculture Nutrition Evidence Systematic Review [8], based on modifications to the Cochrane's collaboration Risk of Bias in Nonrandomized Studies of Interventions [9]. The RoB-NObs tool (version dated 9 March, 2022) was optimized and tested by the Imperial College London review team, and additional confounding factors were incorporated for further adaptation (Appendix B). For RCTs, the following 5 domains are covered in RoB assessment: 1) randomization process; 2) deviations from intended interventions; 3) missing outcome data; 4) outcome measurement; and 5) selection of reported results. For observational studies, 7 domains are covered as follows: 1) confounding; 2) participant selection; 3) exposure classification; 4) departure from intended exposures; 5) missing data; 6) outcome measurement; and 7) selection of reported results.

Data synthesis

Studies were grouped by the methods used to derive dietary patterns (3 main methods—a priori, a posteriori, or hybrid) and study design (observational studies or RCTs): 1) a priori patterns from observational studies of culturally defined dietary habits or dietary guidelines; 2) a priori patterns from RCTs of dietary interventions, such as low-fat diets; 3) a posteriori patterns from observational studies derived using principal component analysis, exploratory factor analysis, or cluster analysis; and 4) hybrid patterns from observational studies derived from biological markers or bacterial composition.

All studies were summarized narratively. A meta-analysis was not conducted due to heterogeneity in components and cutoff points across the identified patterns within groups. The approach undertaken involved summarizing measures of associations using descriptive statistics (i.e., range) and vote counting based on direction of reported associations (null, positive, or inverse), which was applied after grouping studies based on predefined characteristics (i.e., types of patterns and outcome). A descriptive synthesis was conducted separately for each investigation of dietary patterns with risk of all CRC combined, colon cancer, rectal cancer, colon cancer subsites [i.e., proximal (or right-sided) colon cancer, distal (or left-sided) colon cancer] and CRC-related mortality.

Forest plots were generated (for patterns investigated in a minimum of 3 studies) to visually present all data and facilitate narrative summary. The forest plots present RR estimates and 95% CIs for comparisons between the highest and lowest exposure categories, without calculating an overall summary effect. For studies comparing the lowest with the highest exposure categories, an inversion of the effect estimates was performed. When studies reported separate RR estimates for each outcome category (total CRC, colon cancer, rectal cancer, or colon subsites) within subgroups (e.g., females or males; nonsteroidal anti-inflammatory drugs users or nonusers), and overall population data were unavailable, we used a fixed-effect model to pool the estimates and calculate an overall estimate for each outcome category (marked with an

asterisk in the forest plots). These pooled estimates were then included in the descriptive evidence synthesis with other studies. For studies reporting only continuous (linear-dose response) associations, the results are presented in Supplemental Table 1A–D and within the text.

We explored potential sources of heterogeneity by performing predefined subgroup/sensitivity analyses (when ≥ 2 studies were available in each subgroup). Forest plots were presented to visually assess the range of RRs and their 95% CIs across studies. The subgroups investigated were as follows: sex (females and males), geographical location of the studies by continent (North America, Europe, and Asia), and alcohol (included or not as a scoring component).

Although a meta-analysis was not feasible, we assessed potential small-study effects, such as publication bias, by using visual inspection of funnel plots and Egger regression asymmetry test for patterns with ≥ 10 included studies [10]. Statistical analyses were conducted using Stata 18 (StataCorp LLC, College Station, TX, USA).

Grading the quality of evidence

The quality of evidence was evaluated and graded independently by the CUP Global Expert Committee on Cancer Incidence and Expert Panel according to the predefined WCRF/AICR evidence grading criteria (Supplemental Table 2) [11]. Grades indicating strong evidence (with subgrades for likelihood of causality: convincing, probable, or substantial effect on risk unlikely) or limited evidence (with subgrades for likelihood of causality: limited–suggestive or limited–no conclusion) were assigned. Factors considered in the evaluation and grading were quantity, consistency, magnitude and precision of the summary estimates, presence of a dose–response relationship, study design and RoB, generalizability, and mechanistic plausibility of the results.

Results

Figure 1 illustrates a flow diagram for the study selection process. We screened 27,464 publications from the new searches (for articles published between 2019 and 2023), and identified 28 additional publications. Major reasons for exclusion were that the publication type or study design did not align with the specified inclusion criteria. Additionally, we excluded studies that were outside the scope of the research topic, such as those investigating nutrient-based dietary patterns [12–19], organic food consumption [20], ultraprocessed food intake [21], and specific eating behaviors [22]. By combining these 28 publications with 48 articles from the in-house CUP Global database that met the eligibility criteria, we identified 76 publications assessing dietary and lifestyle patterns, with 56 of these reporting dietary pattern components included in this review [23–78].

Study characteristics

The included studies were published between 2001 and 2023, comprising 53 observational studies [23–75] and 3 RCTs [76–78]. Detailed results and main characteristics of each study are presented in Supplemental Table 1A–D. Supplemental Figures A1–A3 provide details on dietary pattern components. Twenty-eight studies were from North America [23–25,28,30,31,35–37,40,42,43,46,49,50,52,53,56,57,62,64,67,69,70,73,76–78], 22 from Europe [26,27,29,32–34,38,41,44,45,51,54,55,58,59,63,65,66,68,72,74,75], and 6 from Asia [39,47,48,60,61,71]. In observational studies, cohort sizes ranged from 8050 [35] to 492,382 [69] participants (median: 94, 217), and the number of diagnosed CRC cases ranged from 118 [44] to 10,702 [32] (median: 1700). The 3 RCTs from the Women's Health Initiative (WHI) included

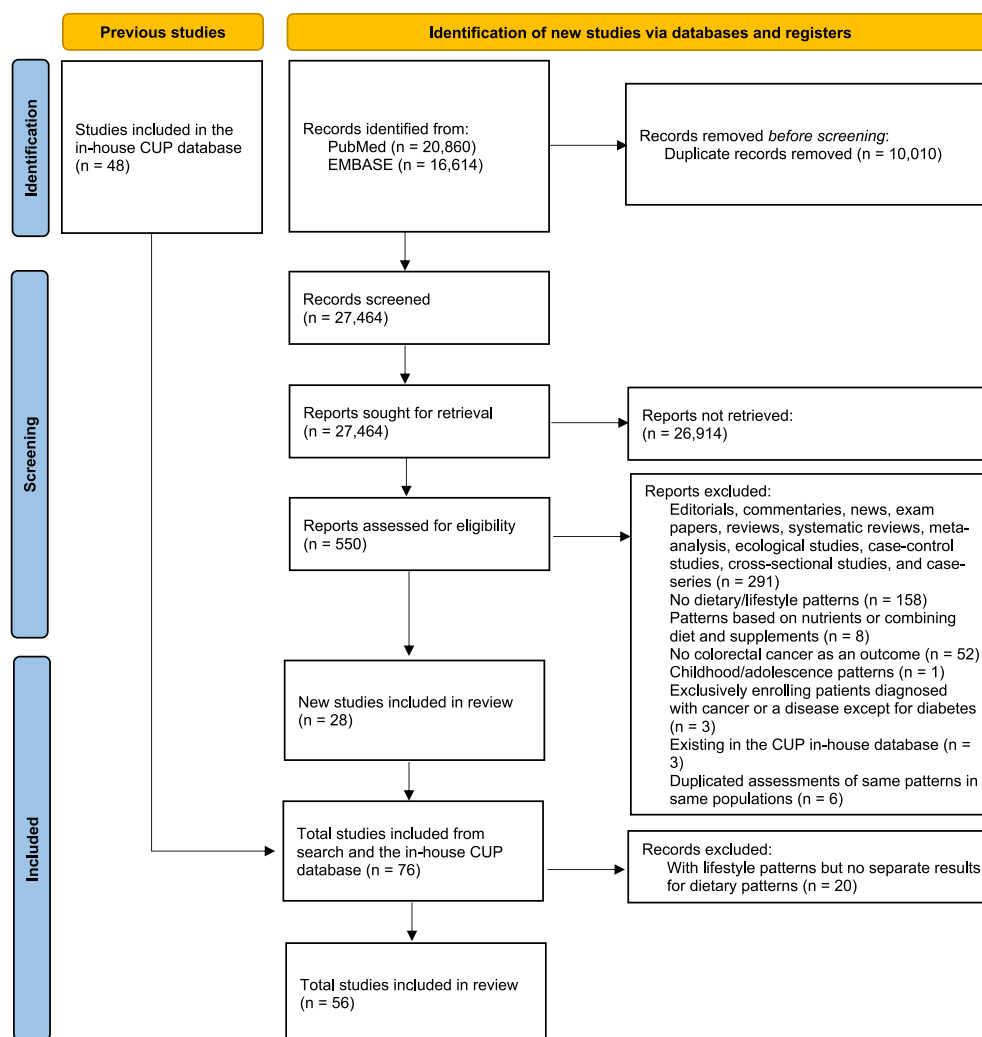


FIGURE 1. PRISMA flow chart of study selection. CUP, Cancer Update Programme.

48,834 [77] to 48,835 [76,78] participants. Thirty-five observational studies reported a follow-up duration of >10 y [23–25,28,30,31,33–43, 46,47,49–57,59–63,65,74], whereas 18 studies reported ≤ 10 y [26,27, 29,32,44,45,48,58,64,66–73,75], with a median follow-up duration of 12.3 y across all observational studies. Two RCTs reported a follow-up duration of >10 y [76,77], while 1 reported ≤ 10 y [78], with a median follow-up duration of 17.5 y across all RCTs.

RoB assessment

Summary RoB assessments for observational studies and RCTs on dietary patterns and CRC associations are shown in [Appendixes B and C](#), respectively. Forty-two percent of the studies presented serious-to-critical bias concerning confounding factors (study biased due to either unadjusted or nonvalidated key confounders, such as energy intake and socioeconomic status.) A detailed list of all confounders is available in [Appendix C](#). Note that adjustment for alcohol was mandatory if not already included in the dietary pattern components. Moreover, 92% showed moderate participant selection bias (no studies demonstrated serious-to-critical bias); 11% presented serious bias in exposure classification (primarily due to a lack of validation and replication data for self-reported measurements or lack of lag time analysis); 79% had critical bias due to departure of intended exposures (as most studies examined dietary factors only

once at baseline, without considering possible fluctuations during follow-up); 13% had serious bias in handling missing data (mainly because proportions of missing participants differed substantially across exposures); 9% had serious bias in outcome measurement (authors reported some differences in outcome ascertainment); and lastly, all studies had moderate bias in selection of reported result (due to absence of preregistered protocols or analysis plans, a common issue in observational studies). All RCTs conducted intention-to-treat analyses and demonstrated low RoB across domains 1–4 (randomization process, deviations from intended interventions, missing outcome data, and measurement of the outcome), with some concerns in domain 5 (deviations from selective reporting) ([Appendix D](#)).

Evidence grading

[Table 1](#) shows the summary findings and judgment of the CUP Global Expert Committee on Cancer Incidence and Expert Panel. A visual summary of the quality-of-evidence matrix is presented in [Figure 2](#). Detailed judgments on the evidence concluded for a priori patterns are provided in [Supplemental Table 3A–C](#) (based on culturally defined dietary habits, based on dietary guidelines, and RCTs of dietary interventions, respectively); for a posteriori patterns in [Supplemental Table 3D](#); and for hybrid patterns in [Supplemental Table 3E](#).

A priori patterns from observational studies

Thirty-seven observational studies assessed a priori dietary patterns and CRC risk: 24 prospective cohorts [23–32,34,35,39–46,48,51,52,54,56–59,62–66,69,73], 1 pooled analysis of prospective cohorts [55], and 1 case-cohort study [38]. The components of each culturally defined habits and guideline-based dietary pattern are summarized in [Supplemental Figure A1](#). Common food components across the various dietary patterns include a higher intake of fruits, vegetables, and whole grains. These patterns also emphasize a lower intake of red and processed meats. Legumes, nuts, and fish also appear frequently as recommended components [e.g., Mediterranean diet, overall plant-based diet index (PDI), Programme National Nutrition Santé-Guidelines Score 2, Prime Diet Quality Score (PDQS)]. Five studies investigated dietary patterns based on both culturally defined dietary habits and dietary guidelines: Petimar et al. [43] [Alternate Mediterranean Diet and Alternate Healthy Eating Index (AHEI)-2010], Lavalette et al. [44] (Mediterranean diet and AHEI-2010), Vargas et al. [56] [Alternate Mediterranean diet, HEI-2010, and Dietary Approaches to Stop Hypertension (DASH)], Park et al. [52] (Alternate Mediterranean diet, HEI-2010, and DASH); and Reedy et al. [69] (Mediterranean diet and Recommended Food Score).

A priori dietary patterns based on culturally defined dietary habits

Sixteen publications from 14 observational studies [28,31,35,38,43–46,52,54,56,58,63,65,66,69] on culturally defined a priori dietary patterns were included, one of which examined both CRC incidence and mortality [56], while another solely investigated CRC-related mortality [66]. No strong evidence of small-study effects (publication bias) was found ($P = 0.841$) ([Supplemental Figure 1](#)). Overall, no sources of heterogeneity were observed regarding sex, geographical regions, and alcohol component across studies assessing a priori dietary patterns based on culturally defined dietary habits ([Supplemental Figures 2–4](#)).

The evidence for an inverse association between alignment with Mediterranean diet and both CRC (10 associations; RRs ranged from 0.77 to 1.02; in 4 of the 7 inverse associations, 95% CIs excluded 1) and rectal cancer risks (8 associations; RRs ranged from 0.38 to 1.21; in 3 of the 6 inverse associations, 95% CIs excluded 1) ([Figure 2](#)) was graded as limited–suggestive evidence. No strong evidence of an association between alignment with Mediterranean diet and colon cancer risk was found (6 associations; RRs ranged from 0.85 to 1.03; all 95% CIs included 1), resulting in a limited–no conclusion grading. In sex-stratified analysis, among males, 5 associations with CRC risk reported RRs ranging from 0.72 to 1.07 (in 3 of the 4 inverse associations, 95% CIs excluded 1); among females, 8 associations with CRC risk reported RRs ranging from 0.82 to 1.01 (all 95% CIs included 1) ([Supplemental Figure 2](#)). Mediterranean diet excluding alcohol from the scoring system showed similar RR estimates to the main findings on CRC risk (3 associations, RRs ranged from 0.80 to 1.02; in 1 of the 2 inverse associations, 95% CIs excluded 1) ([Supplemental Figure 4](#)). For colon cancer subsites, 7 associations between alignment with Mediterranean diet and proximal colon cancer risk reported RRs ranging from 0.83 to 1.66, with all 95% CIs including 1, and 7 associations with distal colon cancer reported RRs ranging from 0.76 to 1.35, with 1 of the 5 inverse associations showing 95% CIs excluding 1 ([Supplemental Figure 5](#)).

The evidence for alignment with healthful plant-based diet index (hPDI) and lower risk of CRC was graded as limited–suggestive (RRs ranged from 0.82 to 0.92; in 2 of the 4 inverse associations, 95% CIs excluded 1) ([Figure 3](#)). One study [28] presented results for distal colon cancer risk, with RR of 0.80 (95% CI: 0.67, 0.96) for hPDI and RR of

0.78 (95% CI: 0.65, 0.95) for overall PDI. There was no strong evidence of an association between any plant-based diet and proximal colon cancer risk ([Supplemental Figure 5](#)).

The evidence for alignment with the Healthy Nordic Food Index (HNFI) [58,63] and CRC risk was graded as limited–no conclusion (2 associations, RRs ranged from 0.75 to 1.09; in 1 of the 2 associations, 95% CIs excluded 1) ([Figure 3](#)). Only 1 study each found limited evidence for PDQS (RR: 0.80; 95% CI: 0.57, 1.11) [35] and evolutionary-concordance diet score (RR: 1.01; 95% CI: 0.85, 1.19) [46] in relation to CRC risk, hence both patterns were graded as limited–no conclusion.

Evidence for the remaining associations [i.e., pro-PDI/overall PDI (for CRC and rectal cancer risk); hPDI (for rectal cancer risk); unhealthful PDI (for CRC and rectal cancer risk); Healthy Nordic Food Index (for colon and rectal cancer risk); PDQS (for rectal cancer risk)] was limited and sparse, thus graded as limited–no conclusion ([Figure 2](#), [Supplemental Table 3A](#)).

Only 2 studies examined CRC-related mortality outcome for alignment with Mediterranean diet [56,66] ([Supplemental Table 1A](#)). Analyzing the dietary patterns as either categorical (alternate Mediterranean diet—RR: 0.90; 95% CI: 0.57, 1.43) [56] or continuous (modified Mediterranean diet—RR: 0.99; 95% CI: 0.89, 1.11) [66] scores did not show evidence of a strong association, hence graded as limited–no conclusion.

A priori dietary patterns based on dietary guidelines

Twenty-seven publications from 19 individual observational studies [23–27,29,30,32,34,38–44,48,51,52,56,57,59,62,64,69,73], 1 pooled cohort analysis [55], and 1 case-cohort study [38] evaluated dietary patterns aligned with country-specific or chronic disease (including cancer) prevention guidelines. All studies investigated CRC risk, and 2 additionally examined CRC-related mortality [56,73]. The most studied dietary patterns were the HEI/AHEI [23,24,39,40,43,44,52,56,64,69], the WCRF/AICR dietary recommendations score [25,27,38,42,55,57], and the DASH diet [39,43,52,56,62]. No strong evidence of publication bias was detected ($P = 0.471$) ([Supplemental Figure 6](#)). No sources of heterogeneity were noted overall by sex, geographical location, or alcohol component ([Supplemental Figures 7–9](#)).

The evidence for alignment with the Healthy Eating Index (HEI) and AHEI was graded as limited–suggestive for risks of CRC (7 associations; RRs ranged from 0.74 to 1.04; in 2 of the 5 inverse associations, 95% CIs excluded 1), colon cancer (4 associations; RRs ranged from 0.78 to 1.03; in 2 of the 3 inverse associations, 95% CIs excluded 1), and rectal cancer (5 associations; RRs ranged from 0.51 to 1.28; in 2 of the 4 inverse associations, 95% CIs excluded 1) ([Figure 4](#)) with generally consistent results showing inverse associations. By colon subsite, 5 associations examined HEI/AHEI with proximal colon cancer (RRs ranged from 0.80 to 1.00; in 1 of the 4 inverse associations, 95% CIs excluded 1), and 4 associations examined distal colon cancer risks (RRs ranged from 0.68 to 1.03; in 2 of the 3 inverse associations, 95% CIs excluded 1) ([Supplemental Figure 10](#)). One publication [24] presented associations using only continuous variables, reporting no strong evidence of an association between a 20% increment in HEI-2010 score and CRC risk (RR: 0.90; 95% CI: 0.71, 1.14).

The evidence for alignment with the DASH index and its variation was graded as limited–suggestive for risks of CRC (6 associations; RRs ranged from 0.78 to 0.98; in 4 of the 6 associations, 95% CIs excluded 1), colon cancer (4 associations; RRs ranged from 0.77 to 1.02; in 2 of the 3 inverse associations, 95% CIs excluded 1), and rectal cancer (5 associations; RRs ranged from 0.63 to 1.24; in 2 of the 4 inverse

TABLE 1

Evidence grades and main findings from the descriptive synthesis of dietary patterns and colorectal cancer risk/mortality.

Evidence grades	Pattern	Colorectal cancer or subsites	Summary of findings	Conclusions
Decreases risk Limited evidence Suggestive	A priori dietary patterns based on culturally defined dietary habits (Mediterranean diet and Healthful plant-based diet index)	CRC	Mediterranean diet: For the highest vs. lowest level of alignment, 10 RRs (from 9 publications) ranged 0.77–1.02: 4/7 inverse associations; 95% CIs excluded 1 3 positive associations; 95% CIs included 1 Healthful plant-based diet index: For the highest vs. lowest level of alignment, 4 RRs (from 3 publications) ranged 0.82–0.92: 2/4 inverse associations; 95% CIs excluded 1	Evidence based on somewhat consistent direction of inverse associations. Low evidence of publication bias. Supported by plausible mechanistic evidence for pattern components (healthful plant-based diet), with evidence for the Mediterranean diet lowering inflammation, insulin, and oxidative stress. RoB concerns due to confounding in studies.
	Mediterranean diet	Rectal	For the highest vs. lowest level of alignment, 8 RRs (from 7 publications) ranged 0.38–1.21: 3/6 inverse associations; 95% CIs excluded 1 2 positive associations; 95% CIs included 1	Evidence based on generally consistent direction of inverse associations. Low evidence of publication bias. Supported by plausible mechanistic evidence for Mediterranean diet lowering inflammation, insulin, and oxidative stress. RoB concerns due to confounding in studies.
	A priori dietary patterns based on dietary guidelines (HEI/AHEI and DASH)	CRC	HEI/AHEI: For the highest vs. lowest level of alignment, 7 RRs (from 6 publications) ranged 0.74–1.04: 2/5 inverse associations; 95% CIs excluded 1 2 positive associations; 95% CIs included 1 For each 1-unit increment in the score, 1 RR (95% CI): 0.90 (0.71, 1.14) DASH: For the highest vs. lowest level of alignment, 6 RRs (from 5 publications) ranged 0.78–0.98: 4/6 inverse associations; 95% CIs excluded 1	Evidence based on somewhat consistent direction of inverse associations. Low evidence of publication bias. Some observational mechanistic evidence from IARC for inflammation and oxidative stress (and insulin in DASH). RoB concerns due to confounding in studies.
	(HEI/AHEI and DASH)	Colon	HEI/AHEI: For the highest vs. lowest level of alignment, 4 RRs (from 3 publications) ranged 0.78–1.03: 2/3 inverse associations; 95% CIs excluded 1 1 positive association; 95% CIs included 1 DASH: For the highest vs. lowest level of alignment, 4 RRs (from 3 publications) ranged 0.77–1.02: 2/3 inverse associations; 95% CIs excluded 1 1 positive association; 95% CIs included 1	Evidence based on somewhat consistent direction of inverse associations. Low evidence of publication bias. Some observational mechanistic evidence from IARC for inflammation and oxidative stress (and insulin in DASH). RoB concerns due to confounding in studies.
	(HEI/AHEI and DASH)	Rectal	HEI/AHEI: For the highest vs. lowest level of alignment, 5 RRs (from 4 publications) ranged 0.51–1.28: 2/4 inverse associations; 95% CIs excluded 1 1 positive association; 95% CIs included 1	Evidence based on somewhat consistent direction of inverse associations. Low evidence of publication bias. Some observational mechanistic evidence from IARC for inflammation and oxidative stress (and insulin in DASH). RoB concerns due to confounding in studies.

(continued on next page)

TABLE 1 (continued)

Evidence grades	Pattern	Colorectal cancer or subsites	Summary of findings	Conclusions
Increases risk Strong evidence Probable	Hybrid dietary patterns derived from biological markers [EDIH (hyperinsulinemic), EDIP (proinflammatory)]	CRC	DASH: For the highest vs. lowest level of alignment, 5 RRs (from 4 publications) ranged 0.63–1.24: 2/4 inverse associations; 95% CIs excluded 1 1 positive association; 95% CIs included 1 EDIH: For the highest vs. lowest level of alignment, 4 RRs (from 3 publications) ranged 1.19–1.67: 3/4 RRs; 95% CIs excluded 1 1 RR; 95% CIs on 1 For each 1-unit increment in the score, 1 RR (95% CI): 1.20 (1.01, 1.41) EDIP: For the highest vs. lowest level of alignment, 4 RRs (from 3 publications) ranged 1.07–1.44: 3/4 RRs; 95% CIs excluded 1 1 RR; 95% CIs on 1 For each 1-unit increment in the score, 1 RR (95% CI): 1.28 (1.10, 1.49)	Evidence based on overall consistent direction of positive associations. Mechanisms not reviewed by IARC, but pattern is derived from biological markers suggesting mechanistic basis. Some RoB concerns due to confounding in studies.
		Colon	EDIH: For the highest vs. lowest level of alignment, 3 RRs (from 2 publications) ranged 1.21–1.32: 2/3 RRs; 95% CIs excluded 1 1 RR; 95% CIs on 1 EDIP: For the highest vs. lowest level of alignment, 3 RRs (from 2 publications) ranged 1.30–1.37: all RRs; 95% CIs excluded 1	Evidence based on overall consistent direction of positive associations. Mechanisms not reviewed by IARC, but pattern is derived from biological markers suggesting mechanistic basis. Some RoB concerns due to confounding in studies.
No conclusion Limited No conclusion	A priori dietary patterns based on culturally defined dietary habits: Mediterranean diet (colon cancer risk and CRC-related mortality), healthful plant-based diet index (rectal cancer risk), pro-/overall plant-based diets (CRC risk), unhealthy plant-based diet index (CRC and rectal cancer risks), Healthy Nordic Food Index (CRC risk) A priori dietary patterns based on dietary guidelines: HEI/AHEI (CRC-related mortality), WCRF/AICR dietary recommendations (CRC, colon, and rectal cancer risks), ACS (CRC risk), Recommended Food Score (CRC risk), Dutch Dietary Guidelines (CRC risk), Healthy dietary quality index (CRC risk), colorectal cancer dietary score (CRC risk) A priori dietary patterns based on RCT: Low-fat Dietary Intervention in the WHI (CRC risk and CRC-related mortality) A posteriori dietary patterns: Prudent/healthy/vegetable-rich (CRC, colon, and rectal cancer risks) Western (CRC, colon, and rectal cancer risks), meat (CRC, colon, and rectal cancer risks), alcohol (CRC, colon, and rectal cancer risks), traditional/ethnic/mixed (CRC, colon, and rectal cancer risks) Hybrid dietary patterns derived from biological markers: EDIH (rectal cancer risk), EDIP (rectal cancer risk) A priori dietary patterns based on culturally defined dietary habits: Pro-/overall plant-based diets (rectal cancer risk), unhealthy plant-based diet index (rectal cancer risk), Healthy Nordic Food Index (rectal cancer risk), Prime Diet Quality Score (CRC and rectal cancer risks), evolutionary-concordance diet score (CRC risk) A priori dietary patterns based on dietary guidelines: DASH (CRC-related mortality), Recommended Food Score (rectal cancer risk and CRC-related		The evidence is based on 2 or more estimates from cohort studies or pooled analyses but showing inconsistency in the associations.	
				The evidence is based on 1 estimate from a cohort study or pooled analysis.

(continued on next page)

TABLE 1 (continued)

Evidence grades	Pattern	Colorectal cancer or subsites	Summary of findings	Conclusions
			mortality), Chinese Food Pagoda (CRC, colon, and rectal cancer risks), healthy dietary quality index (colon and rectal cancer risks), 2013 Danish Dietary Guidelines Index score (CRC, colon, and rectal cancer risks), PNNS-GS2 (CRC), colorectal cancer diet quality index (CRC, colon, and rectal cancer risks), colorectal cancer dietary score (rectal cancer risk), Lifelines Diet Score (CRC risk), global diet quality score and healthful or unhealthful Global diet quality score (CRC and rectal cancer risks), and dietary recommendations for cardiometabolic health (CRC risk)	
	A priori dietary patterns based on RCT:			
	Low-fat dietary intervention in the WHI (colon and rectal cancer risks)			
	Hybrid dietary patterns derived from biological markers:			
	Dietary inflammation scores (CRC risk)			
	Hybrid dietary patterns derived from bacteria:			
	Sulfur Microbial Diet Score (CRC risk)			

Note: The level of confounding between exposure-outcome pairs is categorized as follows:

- Moderate confounding in all studies: some RoB.
- Moderate and serious confounding in studies: RoB concerns.
- Critical confounding for RoB in studies: substantial RoB concerns.

Abbreviations: ACS, American Cancer Society; AHEI, Alternate Healthy Eating Index; CRC, colorectal cancer (which includes both colon cancer and rectal cancer); DASH, Dietary Approaches to Stop Hypertension; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIP, Empirical Dietary Inflammatory Pattern; HEI, Healthy Eating Index; IARC, International Agency for Research on Cancer; PNNS-GS2, Programme National Nutrition Santé-Guidelines Score 2; RCT, randomized controlled trials; RoB, risk of bias; RR, relative risk; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; WHI, Women’s Health Initiative.

Results					
Summary of evidence matrix	Dietary patterns	CRC risk	Colon cancer risk	Rectal cancer risk	CRC mortality
A priori					
	Mediterranean diet (MDS and modifications)				
Based on culturally defined dietary habits	Pro-/overall plant-based diets				
	Healthful plant-based diet index (hPDI)				
	Unhealthful plant-based diet index (uPDI)				
	Healthy Nordic Food Index (HNFI)				
	The prime diet quality score (PDQS)				
	Evolutionary-concordance diet score				
	Healthy Eating Index (HEI) and alternate HEI (AHEI)				
	Dietary Approaches to Stop Hypertension (DASH)				
	WCRF/AICR dietary recommendations scores				
	American Cancer Society (ACS) diet				
Based on dietary guidelines	Recommended Food Score (RFS)				
	The Chinese Food Pagoda (CHFP) score				
	Dutch Dietary Guidelines (DDG) Index				
	Healthy dietary quality index				
	2013 Danish Dietary Guidelines Index score				
	Programme National Nutrition Santé-Guidelines Score 2 (PNNS-GS2)				
	Colorectal cancer diet quality index (CDQI)				
	Colorectal cancer dietary score (CRC score)				
	The Lifelines Diet Score (LLDS)				
	Global diet quality score (GDQS)				
	healthful Global diet quality score (hGDQS)				
	unhealthful Global diet quality score (uGDQS)				
	Dietary recommendations for cardiometabolic health				
	Low-fat diet RCT (WHI-DM trial)				
A posteriori					
Derived by PCA, EFA, or cluster analysis	Prudent/Healthy/Vegetable-rich				
	Western/Meat/Alcohol				
	Traditional/Ethnic/Mixed				
Hybrid					
Derived from biological markers	Empirical Dietary Index for Hyperinsulinemia (EDIH)				
	Empirical Dietary Inflammatory Pattern (EDIP)				
	Dietary inflammation scores (DIS)				
Derived from bacteria	Sulfur Microbial Diet Score				
Decreases risk		Conclusions key		Increases risk	
Strong – Convincing	Strong – Probable	Limited – Suggestive	Limited – No conclusion	Limited – Suggestive	Strong – Probable
					Strong – Convincing

Note: Empty (white) cells represent exposure-outcome pair not reviewed and no evidence grading assigned.

FIGURE 2. Summary quality-of-evidence matrix from the systematic literature review on alignment with dietary patterns and CRC outcomes. CRC, colorectal cancer; EFA, exploratory factor analysis; PCA, principal component analysis; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; WHI-DM, Women’s Health Initiative-Dietary Modification.

associations, 95% CIs excluded 1) (Figure 4). For DASH index and colon subsites, 3 associations with distal colon cancer risk showed RRs ranging from 0.62 to 0.89, with 2 associations showing 95% CIs excluding 1; while 3 associations with proximal colon cancer risk showed RRs ranging from 0.96 to 1.08, with all 95% CIs including 1 (Supplemental Figure 10).

The evidence for alignment with WCRF/AICR dietary recommendations score and CRC risk was graded as limited–no conclusion due to lack of strong evidence of an association (4 associations; RRs ranged from 0.74 to 0.93; in 1 of the 4 associations, 95% CIs excluded 1) (Figure 4). Similarly, evidence for colon cancer (3 associations; RRs ranged from 0.73 to 1.00; in 1 of the 2 inverse associations, 95% CIs

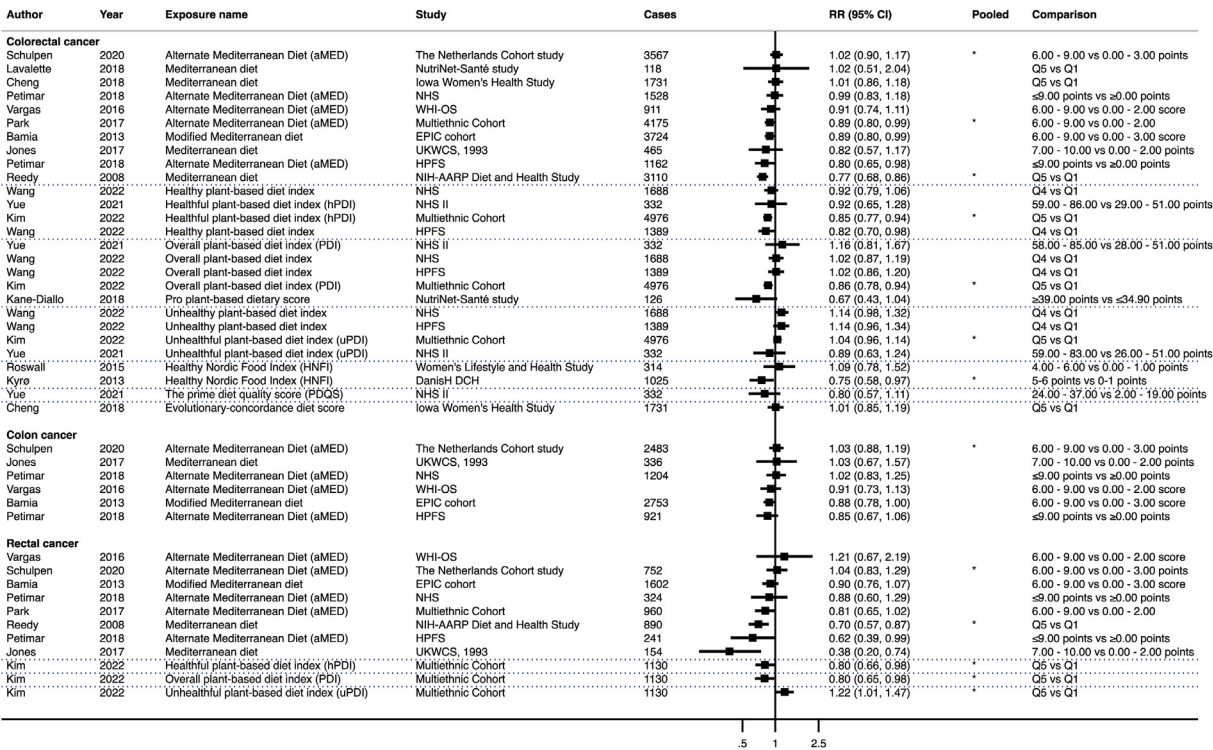


FIGURE 3. RR (95% CI) of colorectal cancer incidence for the highest compared with the lowest level of alignment with culturally defined a priori dietary patterns—Mediterranean, plant-based (healthful, pro-/overall, unhealthful), and others, as ordered by pattern groups and RR for trend observation. The blue dotted horizontal reference lines indicate distinct dietary pattern groups. *Pooled estimates from subgroup RRs reported in the publications, calculated using a fixed-effect model before being presented in the forest plot. Note: Missing values in cases refer to studies with no available information. DCH, Danish Diet, Cancer and Health study; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; JPHC, Japan Public Health Center-Based Prospective Study; NHS, Nurses' Health Study; RR, relative risk; UKWCS, UK Women's Cohort Study; WHI-OS, Women's Health Initiative-Observational Study.

excluded 1) and rectal cancer risks (2 associations; RRs: 0.79 and 0.80; all 95% CIs included 1) were also graded limited–no conclusion. For colon subsites, 2 associations between WCRF/AICR dietary recommendations score and distal colon cancer risk reported RRs ranging from 0.60 and 0.79, with 1 association showing 95% CIs excluding 1 (Supplemental Figure 10), whereas 2 associations with proximal colon cancer showed RRs ranging from 0.84 to 1.07, with all 95% CIs including 1. Two studies [38,55] analyzed the associations between alignment with WCRF/AICR dietary recommendations score and CRC risk using only continuous variables: Jankovic et al. [55] reported an RR of 0.84 (95% CI: 0.80, 0.89) per 1-point increase in the WCRF/AICR score, whereas Schulpen et al. [38] reported RR (95% CI) of 1.00 (0.92, 1.07) for females and 0.95 (0.88, 1.02) for males per 1-point increase.

The evidence for the remaining associations [i.e., American Cancer Society guideline, Dutch Dietary Guidelines index, Programme National Nutrition Santé-Guidelines Score 2, Lifelines Diet Score, Dietary recommendations for cardiometabolic health (for CRC risk); Recommended Food Score, Chinese Food Pagoda score, Healthy dietary quality index/healthy diet, 2013 Danish Dietary Guidelines Index score, CRC diet quality index, CRC dietary score, Global diet quality score, healthful Global diet quality score, unhealthful Global diet quality score (for CRC, colon and/or rectal cancer risk)] was graded as limited–no conclusion owing to the scarcity of studies on risk of CRC-related outcomes (Figure 2, Supplemental Table 3B, Supplemental Figure 11).

One publication [56] reported associations of HEI/AHEI and DASH index with CRC-related mortality risk, yet none of these

associations showed strong evidence (3 associations; RRs ranged from 0.91 to 1.09; all 95% CIs included 1) (Supplemental Table 1A). Another study [73] examined the Recommended Food Score and CRC-related mortality, reporting an RR of 0.49 (95% CI: 0.29, 0.84). However, due to the low number of studies, the evidence for these guideline-based dietary patterns and CRC-related mortality was graded as limited–no conclusion.

A priori patterns from RCT dietary interventions

Three publications [76–78], originating from a single RCT—the Dietary Modification clinical trial within the WHI—examined a low-fat dietary intervention (Supplemental Table 1B). Kato et al. [77] solely investigated CRC risk as an outcome, whereas Beresford et al. [78] assessed both CRC incidence and CRC-related mortality. The remaining publication by Chlebowski et al. [76] examined only CRC-related mortality.

Neither of the 2 publications on the low-fat dietary intervention and CRC risk showed strong evidence of an effect; thus, the intervention was graded as limited–no conclusion (Supplemental Table 3C). One of the studies followed participants for a mean of 8.1 y during the intervention period (RR: 1.08; 95% CI: 0.90, 1.29) [78], while the other followed them up for 18 y, covering both intervention and post-interventional periods (RR: 0.95; 95% CI: 0.62, 1.45) [77] (Supplemental Figure 12).

Only 1 study [78] examined the effectiveness of the low-fat dietary intervention with colon cancer risk (Supplemental Figure 12) and its subsites (proximal and distal colon cancer) (Supplemental Figure 13),

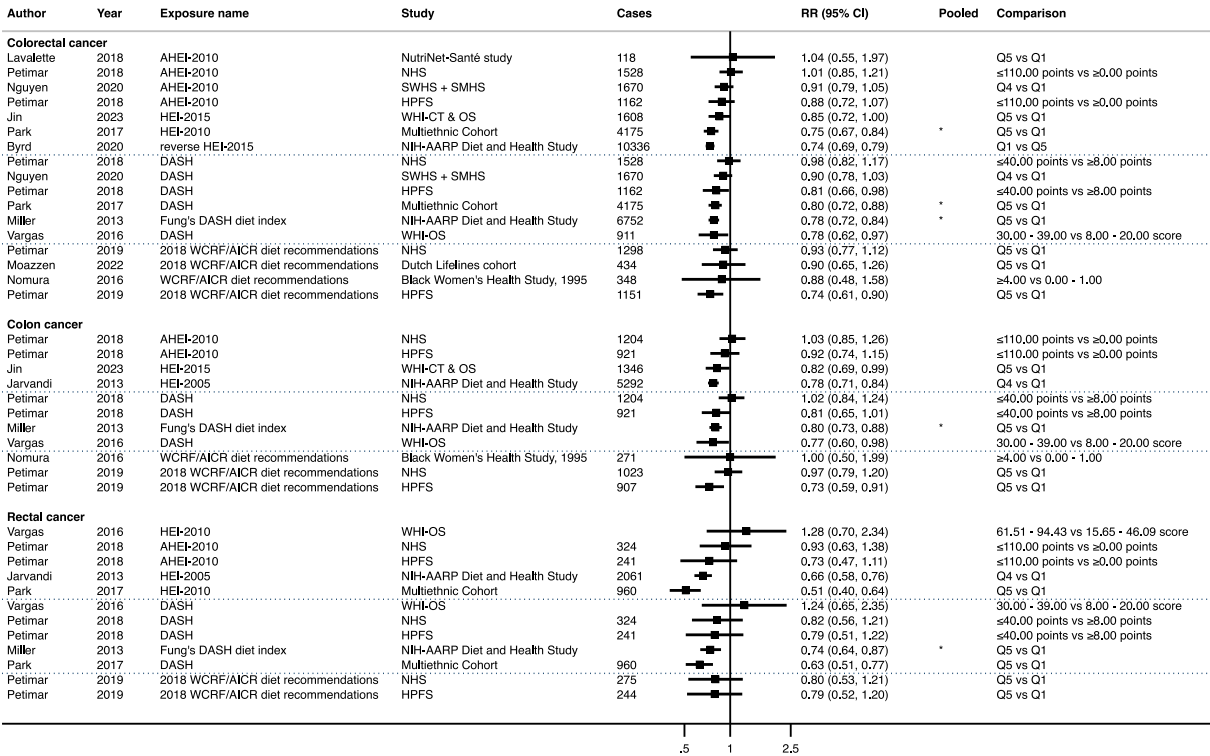


FIGURE 4. RR (95% CI) of colorectal cancer incidence for the highest compared with the lowest level of alignment with guideline-based a priori dietary patterns—HEI/AHEI, DASH, and WCRF/AICR, as ordered by pattern groups and RR for trend observation. The blue dotted horizontal reference lines indicate distinct dietary pattern groups. *Pooled estimates from subgroup RRs reported in the publications, calculated using a fixed-effect model before being presented in the forest plot. Note: Missing values in cases refer to studies with no available information. AHEI, Alternate Healthy Eating Index; BCDDP, Breast Cancer Detection Demonstration Project; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index; HPFS, Health Professionals Follow-up Study; MDCS, Malmö Diet and Cancer Study; NHS, Nurses' Health Study; RR, relative risk; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; WHI-CT & OS, Women's Health Initiative-Clinical Trial & Observational Study.

demonstrating no strong evidence of an effect for any of these risks (colon—RR: 1.05; 95% CI: 0.85, 1.30; proximal colon—RR: 1.25; 95% CI: 0.96, 1.61; distal colon—RR: 0.86; 95% CI: 0.56, 1.19).

Two studies [76,78] investigating the low-fat dietary intervention on CRC-related mortality risks reported no strong evidence of an effect. One study [78] covered only the intervention period, with a mean follow-up of 8.1 y, reporting an RR of 1.26 (95% CI: 0.85, 1.85). The other study [76], which included both the intervention and post-interventional periods with a median follow-up of 17.7 y, reported an RR of 1.09 (95% CI: 0.86, 1.38) (Supplemental Table 1B).

A posteriori patterns from observational studies

Twelve publications, featuring 35 different a posteriori dietary patterns from 10 prospective cohorts [33,47,60,61,67,68,70–72,75] and 1 pooled study [74] were identified. Most studies used principal component analysis or factor analyses to derive a posteriori dietary patterns, with 2 exceptions using cluster analyses [67,68] (Supplemental Table 1C). The dietary patterns were categorized into 3 groups: prudent/healthy/vegetable-rich (high intake of fruits and vegetables); western/meat/alcohol (high intake of red and processed meat or alcohol); and traditional/ethnic/mixed (high intake of poultry, dairy products, fish, seafood, snacks, sweets, and ultraprocessed foods). In general, prudent/healthy/vegetable-rich group comprised healthier diets, while western/meat/alcohol group comprised less healthy dietary patterns; patterns that did not fit into either of these 2 groups were

classified as traditional/ethnic mixed. Components of these patterns are summarized in Supplemental Figure A2. No strong evidence of publication bias was found for studies of the 3 a posteriori dietary patterns and CRC risk (prudent/healthy/vegetable-rich, $P = 0.139$; western/meat/alcohol, $P = 0.685$; traditional/ethnic/mixed, $P = 0.940$) (Supplemental Figure 14).

Prudent/healthy/vegetable-rich dietary patterns

The evidence for the prudent/healthy/vegetable-rich dietary patterns was graded as limited—no conclusion for risks of CRC (11 associations; RRs ranged from 0.76 to 1.03; in 3 of the 9 inverse associations, 95% CIs excluded 1), colon cancer (7 associations; RRs ranged from 0.76 to 0.92; in 3 of the 7 inverse associations, 95% CIs excluded 1), and rectal cancer (9 associations; RRs ranged from 0.51 to 1.26; in 1 of the 7 inverse associations, 95% CIs excluded 1), largely due to an inconsistent direction of associations (Figure 5, Supplemental Table 3D). No appreciable differences were noted between sexes or across continents and by inclusion of alcohol in the dietary patterns (Supplemental Figures 15–17). However, in males, 5 associations with CRC risk reported RRs ranging from 0.78 to 1.11, with 2 of the 4 inverse associations showing 95% CIs excluding 1. Conversely, among females, 7 associations with CRC risk reported RRs ranging from 0.77 to 1.06, with all 95% CIs including 1. In North America, 3 associations with CRC risk reported RRs ranging from 0.78 to 0.90, with 2 of the 3 associations showing 95% CIs excluding 1. In Asia, 3 associations reported RRs ranging from 0.76 to 1.02, with 1 of the 2 inverse

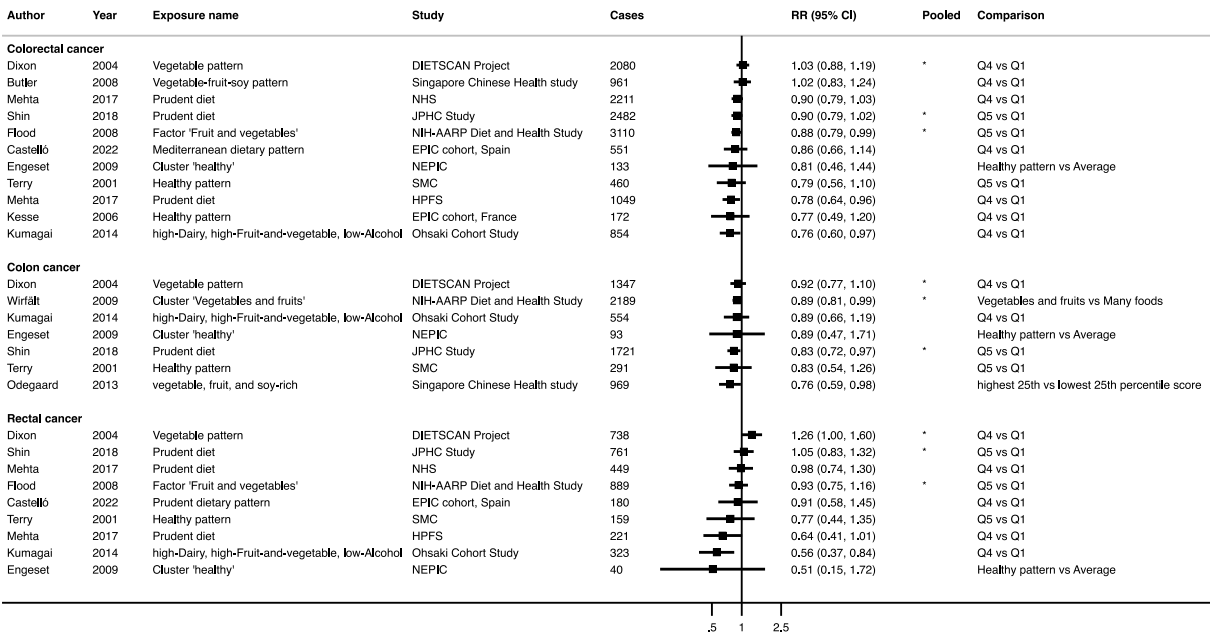


FIGURE 5. RR (95% CI) of colorectal cancer incidence for the highest compared with the lowest level of alignment with a posteriori dietary patterns—prudent/healthy/vegetable-rich diets, as ordered by RR for trend observation. *Pooled estimates from subgroup RRs reported in the publications, calculated using a fixed-effect model before being presented in the forest plot. DFA, high-dairy, high-fruit-and-vegetable, low-alcohol; HPFS, Health Professionals Follow-up Study; EPIC, European Prospective Investigation into Cancer and Nutrition; JPHC, Japan Public Health Center-Based Prospective Study; NHS, Nurses' Health Study; RR, relative risk; SMC, Swedish Mammography Cohort.

associations showing 95% CIs excluding 1. Conversely, in Europe, 5 associations with CRC risk reported RRs ranging from 0.77 to 1.03, with all 95% CIs including 1. For distal colon cancer risk, 7 associations with RRs ranging from 0.66 to 1.24 showed that 2 of the 6 inverse associations had 95% CIs excluding 1 (Supplemental Figure 18). For proximal colon cancer risk, 7 associations showed RRs ranging from 0.62 to 1.17, with all 95% CIs including 1.

Western/meat/alcohol dietary patterns

Evidence for all western/meat/alcohol dietary patterns was graded as limited–no conclusion for risks of CRC, colon cancer, and rectal cancer due to an inconsistent direction of associations. For western dietary patterns (Figure 6, Supplemental Table 3D), 7 associations with CRC risk reported RRs ranging from 0.86 to 1.31 (in 2 of the 5 positive associations, 95% CIs excluded 1); 3 associations with colon cancer risk reported RRs ranging from 0.74 to 1.06 (all 95% CIs included 1); and 6 associations with rectal cancer risks reported RRs ranging from 0.86 to 1.53 (all 95% CIs included 1). For meat dietary patterns, 5 associations with CRC reported RRs ranging from 0.97 to 1.58 (in 1 of the 3 positive associations, 95% CI excluded 1); 4 associations with colon cancer risk reported RRs ranging from 0.87 to 1.14 (all 95% CIs included 1); and 4 associations with rectal cancer reported RRs ranging from 0.91 to 1.36 (in 1 of the 3 positive associations, 95% CIs excluded 1). For alcohol dietary patterns, 3 associations with CRC risk reported RRs ranging from 1.04 to 1.36 (all 95% CIs included 1); 2 associations with colon cancer risk reported RRs of 0.78 and 1.14 (all 95% CIs included 1); and 2 associations with rectal cancer risks reported RRs of 1.03 and 1.73 (all 95% CIs included 1). No sources of heterogeneity were found by sex and geographical location (Supplemental Figures 19 and 20). When comparing western/meat/alcohol dietary patterns by the inclusion of alcohol, 8 associations between diets without alcohol and CRC risk reported RRs ranging from 0.97 to 1.58 (in 3 of the 6 positive associations, 95% CIs excluded 1). Additionally, 6 associations and

rectal cancer risk reported RRs ranging from 1.04 to 1.53 (in 1 of the 6 associations, 95% CIs excluded 1). Conversely, 7 associations between diets including alcohol component and CRC risk reported RRs ranging from 0.86 to 1.36 (all 95% CIs included 1) (Supplemental Figure 21). By colon subsite, 7 associations between western/meat/alcohol dietary patterns and distal colon cancer risk reported RRs ranging from 0.99 to 1.55, with 2 of the 6 positive associations showing 95% CIs excluding 1; whereas proximal colon cancer risk reported RRs ranging from 0.70 to 1.17, with all 95% CIs including 1 (Supplemental Figure 22).

Traditional/ethnic/mixed dietary patterns

The evidence for the traditional/ethnic/mixed dietary patterns was graded as limited–no conclusion for risks of CRC (7 associations; RRs ranged from 0.63 to 1.04; in 1 of the 4 inverse associations, 95% CIs excluded 1), colon cancer (6 associations; RRs ranged from 0.41 to 1.05; all 95% CI included 1), and rectal cancer (7 associations; RRs ranged from 0.56 to 1.41; in 2 of the 3 inverse associations, 95% CIs excluded 1), due to an inconsistent direction of associations (Supplemental Figure 23, Supplemental Table 3D). No sources of heterogeneity were found when analyzed by sex, geographical location, or inclusion of alcohol (Supplemental Figures 24–26). No strong evidence of associations was found for proximal or distal colon cancer risk (Supplemental Figure 27).

Hybrid patterns from observational studies

Seven publications from 5 prospective cohorts [23,35,36,40,49,50] and 1 pooled cohort analysis [37] conducted in North America examined hybrid methods of dietary patterns and CRC risk. These patterns were categorized into 2 groups: one based on intermediate response variables, such as biological markers (e.g., C-peptide) [23,35,37,50] or inflammatory biomarkers [23,37,40,49], and the other based on sulfur-metabolizing bacteria [36] (Supplemental Table 1D). The dietary components of hybrid patterns are summarized in Supplemental

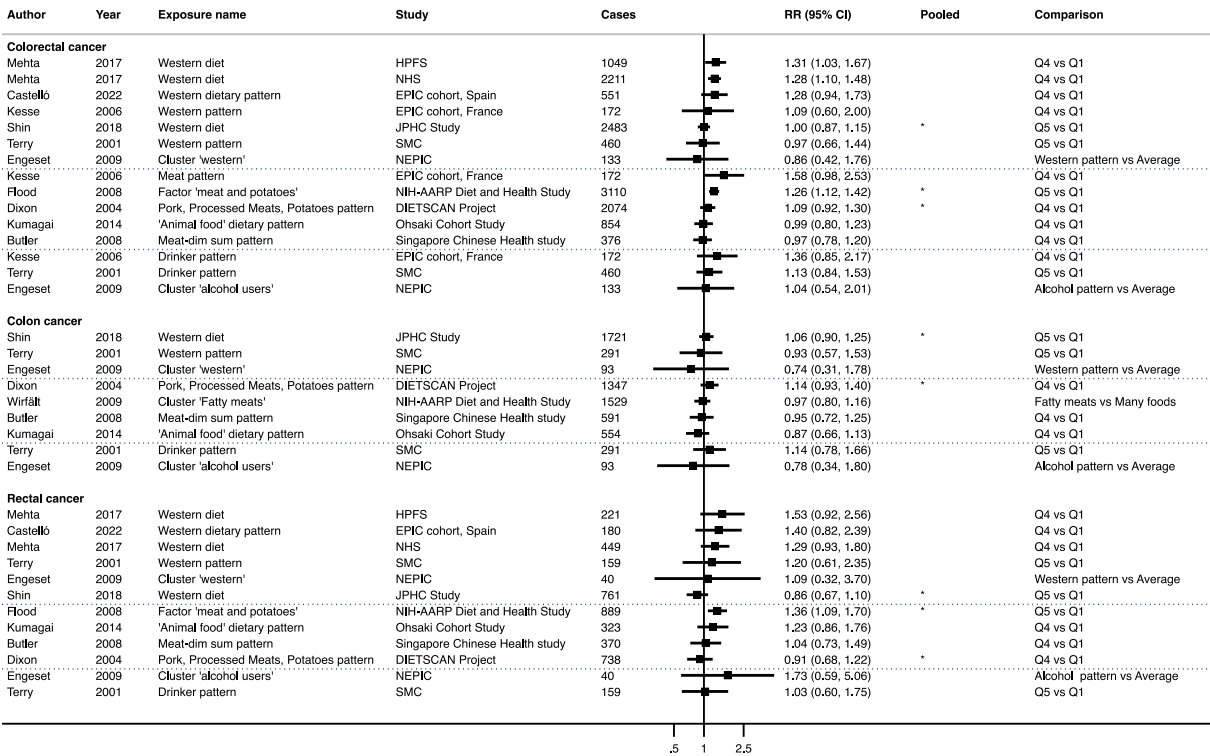


FIGURE 6. RR (95% CI) of colorectal cancer incidence for the highest compared with the lowest level of alignment with a posteriori dietary patterns—western/meat/alcohol, as ordered by RR for trend observation. *Pooled estimates from subgroup RRs reported in the publications, calculated using a fixed-effect model before being presented in the forest plot. EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; JPHC, Japan Public Health Center-Based Prospective Study; NEPIC, Norwegian European Prospective Investigation into Cancer and Nutrition; NHS, Nurses' Health Study; RR, relative risk; SMC, Swedish Mammography Cohort.

Figure A3. Publication bias was not assessed for the hybrid patterns as there were fewer than 10 included studies for each index.

Derived from biological markers

Three patterns were derived from biological markers: empirical dietary index for hyperinsulinemia (EDIH) [23,35,37,50], empirical dietary inflammatory pattern (EDIP) [23,37,49], and dietary inflammation scores [40].

The evidence for the association of EDIH was graded as strong–probable with consistent increased risks of both CRC (4 associations; RRs ranged from 1.19 to 1.67; in 3 of the 4 associations, 95% CIs excluded 1, and 1 association on 1) and colon cancer (3 associations; RRs ranged from 1.21 to 1.32; in 2 of the 3 associations, 95% CIs excluded 1, and 1 association on 1) (Figure 7, Supplemental Table 3E). Similarly, the evidence for the association of EDIP was graded as strong–probable for increased risks of CRC (4 associations; RRs ranged from 1.07 to 1.44; in 3 of the 4 associations, 95% CIs excluded 1, and 1 association on 1) and colon cancer (3 associations; RRs ranged from 1.30 to 1.37; all associations, 95% CIs excluded 1). One publication was identified for each EDIH [50] and EDIP [49], each reporting 2 associations for rectal cancer risk (EDIH—RR: 1.63; 95% CI: 1.09, 2.44, and 0.88; 95% CI: 0.60, 1.29; EDIP—RR: 1.70; 95% CI: 1.14, 2.54, and RR: 0.84; 95% CI: 0.57, 1.24), with evidence graded as limited–no conclusion due to lack of strong evidence of an association and inconsistent direction of associations. One study [37] analyzed only continuous variables, reporting higher CRC risks per 1-point increase in EDIH (RR: 1.20; 95% CI: 1.01, 1.41) and EDIP (RR: 1.28; 95% CI: 1.10, 1.49), consistent with the evidence based on categorical measures.

In sex-stratified analysis, EDIH and EDIP scores indicated associations with increased risks of CRC and colon cancer for both females and males (Supplemental Figure 28). Positive associations for rectal cancer were observed solely in males (EDIH—RR: 1.63; 95% CI: 1.09, 2.44; EDIP—RR: 1.70; 95% CI: 1.14, 2.54), while no such associations were found in females (EDIH—RR: 0.88; 95% CI: 0.60, 1.29; EDIP—RR: 0.84; 95% CI: 0.57, 1.24). There was no evidence of heterogeneity among studies examining hybrid dietary patterns with and without alcohol on CRC risk (Supplemental Figure 29). By colon subsite, both EDIH and EDIP consistently showed a positive direction of association with both proximal (EDIH: RRs ranged from 1.15 to 1.41; EDIP: RRs ranged from 1.35 to 1.44) and distal colon cancer risks (EDIH: RRs 1.46 and 1.63, EDIP: RRs 1.44 and 1.47); however, all 95% CIs included 1 (Supplemental Figure 30). Only 1 study [40] assessed dietary inflammation scores with CRC risk (RR: 1.21; 95% CI: 1.14, 1.29), with evidence graded as limited–no conclusion due to limited data (Figure 7).

Derived from bacterial composition

The evidence for a positive association between alignment with the sulfur microbial diet score and CRC risk (RR: 1.27; 95% CI: 1.12, 1.44) was graded as limited–no conclusion due to limited number of studies [36] (Figure 7). By sex, results for the sulfur microbial diet and CRC risk were consistent in females (RR: 1.18; 95% CI: 1.01, 1.37) and males (RR: 1.45; 95% CI: 1.18, 1.77) (Supplemental Figure S28). The sulfur microbial diet was assessed for its association with proximal colon cancer risk only, and no strong evidence of an association was observed (RR: 1.13; 95% CI: 0.93, 1.39) (Supplemental Figure 30).

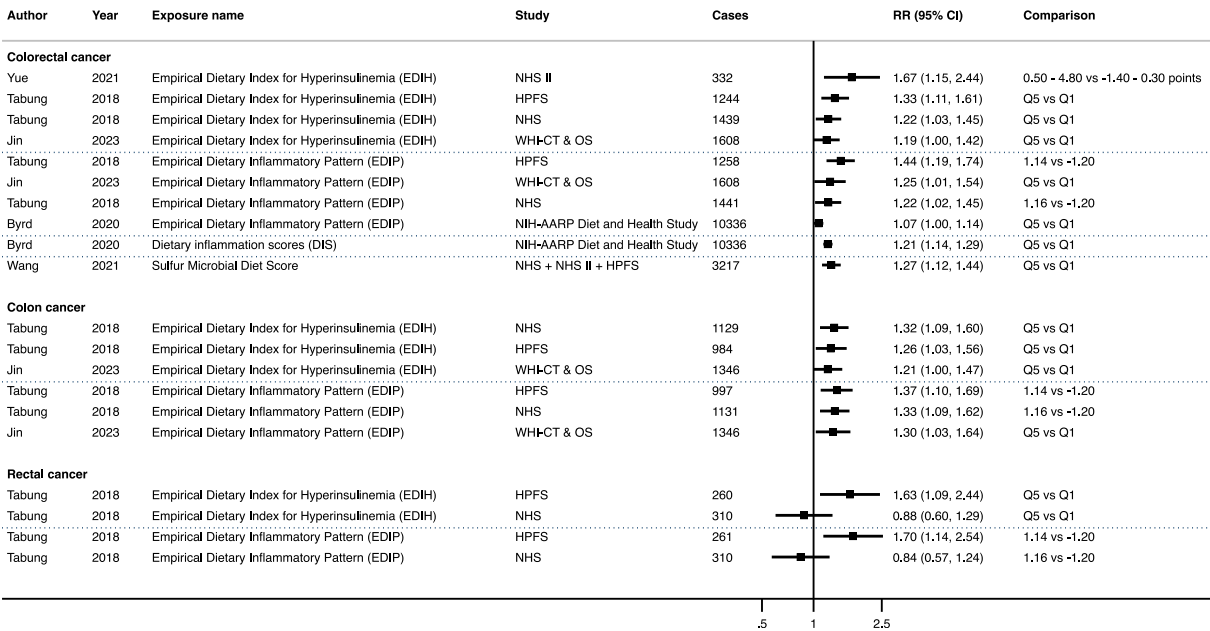


FIGURE 7. RR (95% CI) of colorectal cancer incidence for the highest compared with the lowest level of alignment with hybrid dietary patterns, as ordered by RR for trend observation. The blue dotted horizontal reference lines indicate distinct dietary pattern groups. HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; RR, relative risk; WHI-CT & OS, Women's Health Initiative-Clinical Trial & Observational Study.

Discussion

This review presents limited–suggestive evidence linking Mediterranean, healthful PDI, HEI/AHEI, and DASH dietary patterns to lower CRC risk, whereas EDIH (hyperinsulinemic) and EDIP (proinflammatory) show strong–probable evidence for increased CRC risk. By subsite, limited–suggestive evidence suggests that Mediterranean diets are associated with lower rectal cancer risk, and HEI/AHEI and DASH are associated with lower colon and rectal cancer risks. Other dietary patterns and CRC risk/CRC-related mortality associations showed limited–no conclusion evidence.

Despite differing derivations (cultural habits or dietary guidelines), a priori–derived patterns (Mediterranean, hPDI, HEI/AHEI, and DASH) consistently showed inverse associations with CRC risk, emphasizing higher fruit/vegetable and whole-grain intake with limited red/processed meat. Notably, although some guideline-based patterns (e.g., HEI-2015, and DASH) penalize alcohol consumption, a major CRC risk factor [79], certain cultural-based approaches (e.g., hPDI) also do not consider alcohol intake, whereas others (e.g., Mediterranean and AHEI) are less restrictive. Dietary recommendations balancing structure and cultural sensitivity can strengthen public health strategies. HEI/AHEI and DASH additionally emphasize low sodium, with HEI/AHEI updates (e.g., HEI-2015) recommending to reducing saturated fat and added sugar [80]. Stronger inverse associations were noted for HEI than those for AHEI. HEI emphasizes overall diet quality by including dairy, seafood, and plant-based proteins, whereas AHEI highlights nuts, polyunsaturated fats, moderate alcohol, and reduced red/processed meat and sugar-sweetened beverages. Although there was limited–no conclusion evidence between WCRF/AIRC dietary patterns and CRC risk (inverse directions, mostly null associations), the broader WCRF/AIRC dietary-lifestyle patterns integrating adiposity, activity, and smoking received a strong–probable grading (described in the accompanying dietary-lifestyle article) [6], likely due to combined mechanisms beyond diet alone [81–84].

The WHI's low-fat diet trial showed limited–no conclusion evidence due to weak effects [76–78]. Without specific biomarkers for low-fat intakes, assessing adherence is challenging. Typically, low-fat/high-carbohydrate diets raise plasma triglycerides and lower HDL levels [85,86], but minimal changes were observed across intervention/comparison groups in the WHI at 3-year follow-up [87]. Similarly, a meta-analysis found short-term lipid improvements with low-carbohydrate diets that diminished over time [88]. Long-term impacts remain uncertain, partly due to delayed CRC outcomes. Associations with CRC precursors or metabolic indicators may provide earlier insights into dietary effects. Moreover, unblinding in the WHI trial [89] may have attenuated the intervention's effectiveness.

A posteriori–derived patterns showed inconsistent associations with CRC risk. Inverse trends were noted for prudent/healthy/vegetable-rich patterns and CRC risk in males and specific regions (reflecting cultural differences). No clear associations emerged for meat patterns, contrary to previous meta-analyses [90–92]. Nonetheless, processed meat is classified as carcinogenic, and red meat as probably carcinogenic [93, 94]. WCRF recommends limiting cooked red meat (350–500 g weekly) and avoiding processed meat [3]. Despite variations in food preparation, further research on specific red/processed meat types is needed to refine risk assessments. Traditional/ethnic/mixed diets, rooted in cultural food traditions, combining healthy (e.g., fish and vegetables) and less healthy (e.g., snacks/sweets/ultraprocessed foods) components, showed mixed CRC risk results.

Hybrid-derived patterns, such as EDIH and EDIP, showed strong–probable evidence for increased CRC and colon cancer risks. Developed in the Nurses' Health Study (NHS) and validated in the NHS II and Health Professionals Follow-up Study (HPFS) [95,96], these indices correlate at 0.5 to 0.6 [97] and are based on food groups predictive of insulinemic and inflammatory biomarkers. Notably, EDIH includes animal foods high in fat and protein. Although more research is needed for CRC and other cancer end points, these indices showed stronger associations with inflammatory biomarkers [98] and type 2

diabetes [99] in Hispanic and African-American participants than those in White participants (including NHS participants) [98], likely due to greater insulin resistance susceptibility (e.g., obesity). These associations may be underestimated in NHS and HPFS cohorts due to higher health literacy. As empirical lifestyle index for hyperinsulinemia/EDIH scores are primarily based on United States diets (and similar ones in Europe) [100], further validation in different geographical populations is important. Likewise, the empirical lifestyle index for hyperinsulinemia, incorporating BMI and physical activity, shows strong–probable evidence for increased CRC risk in the accompanying dietary-lifestyle patterns article [6].

Associations between dietary patterns and CRC risks varied by tumor location and sex. For instance, there is limited–suggestive evidence linking Mediterranean diet alignment to lower rectal cancer risk but not colon cancer. These variations may stem from embryonic development, anatomical features [101,102], gut microbiota [103], and metabolite exposure [104]. Sex-specific differences, such as the association of EDIH/EDIP with increased rectal cancer risk in males (HPFS) but not females (NHS) [49,50], merit further investigation. Potential mechanisms may involve sex hormones [49,50] and gut microbiota [105].

There is limited–no conclusion evidence on CRC-related mortality, mainly due to insufficient data. However, studies suggest that patterns such as Mediterranean diet, hPDI, HEI/AHEI, and DASH diet, linked to lower CRC risk, may also reduce CRC-related mortality, aligning with using mortality data as a proxy for incidence [106]. Mortality data in this review were primarily derived from healthy baseline cohorts with diets assessed years before diagnosis, emphasizing the long-term impact of prediagnosis diets but not accounting for dietary changes around/after treatment, which could influence survival outcomes. However, as most CRC-related mortality occurs within 5 y post-diagnosis, with risk factors largely overlap with those for incident CRC [107], it is important to address common determinants for reducing CRC incidence/CRC-related mortality.

Existing literature supports inflammation, insulin, and oxidative stress as key biological processes linking dietary patterns (i.e., Mediterranean, HEI, and DASH) to CRC risk, although causality between inflammation/oxidative stress and CRC remains unclear. Meta-analyses of predominantly RCTs suggest that Mediterranean and DASH diets reduce inflammation, oxidative stress, and insulin, while HEI decreases inflammation and oxidative stress [108–119]. Prospective cohort studies also support these processes in CRC risk [110,120]; and Mendelian randomization analysis provides evidence linking elevated fasting insulin levels to CRC risk [121].

Strengths and limitations

This review examined dietary patterns and CRC risk/CRC-related mortality within the CUP Global framework and included long-term prospective studies (median follow-up: 12.3 y for observational studies; 17.5 for RCTs). Established methods assessed publication bias (none detected) and subgroup/sensitivity analyses explored variations in associations. Most studies used validated food frequency questionnaires and confirmed cancer diagnoses via registries or medical records. An independent CUP Global Expert graded the evidence strength using standardized criteria.

However, a meta-analysis was unfeasible due to variability in pattern scoring. Construction of scoring methods for some a priori dietary patterns (e.g., tertiles and quartiles) was based on the specific distribution of dietary variables within the population, hindering cross-study comparisons.

Categorical exposure comparisons prevented dose–response analyses. Lack of adjustment for energy intake and confounders (e.g., previous endoscopic screening) may affect the magnitude and even possibly the direction of associations. Baseline-only dietary assessment may risk regression dilution, and recall-based methods may introduce measurement errors. However, given the prospective design, potential misclassification is likely nondifferential, possibly attenuating observed associations. Finally, limited data from diverse racial/ethnic (e.g., Black and African descent) and younger age groups may affect generalizability.

Future studies should prioritize well-designed prospective cohort studies with consistent dietary pattern definitions, repeated exposures/confounders assessments, and validated scoring. Standardized reporting items/checklists for dietary pattern studies are needed. Dose–response analyses, subgroup stratifications, and adjustment for energy intake and screening history are important. Trial emulation studies and pooled analyses can strengthen causal evidence. Research across diverse populations is needed to ensure equitable dietary recommendations. Investigating biological pathways and refining optimal diets (e.g., understanding specific roles of low-fat/high-fat dairy and fruits/vegetables) can inform CRC prevention dietary guidance.

Conclusions

This review suggests limited–suggestive evidence linking Mediterranean, hPDI, HEI/AHEI, and DASH diets to lower CRC risk. Strong–probable evidence associates EDIH/EDIP with higher CRC and colon cancer risks. The strongest evidence supports mechanism-informed dietary patterns, highlighting a promising path to pursue. Recommendations from this review can guide health professionals, policymakers, researchers, and stakeholders in adopting healthful dietary patterns. Future effort will involve WCRF and the CUP Global Expert Panel developing dietary guidance for CRC prevention based on these conclusions.

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Author contributions

The authors' responsibilities were as follows—DHL, ELG: were the coauthors to the development of the protocol for this work; KL, AHYC: did the literature search, study selections, and data extraction; assessed risk of bias; and synthesized and interpreted the data; NB-T: did the data extraction; DSMC: checked the data; AHYC, KL, DHL, ELG: wrote the draft of manuscript; MPW, SJL, HC, SK, EMG-G, DSMC, NB-T, NA, LD, YP: critically revised the manuscript; ELG: supervised the study; and all authors revised and approved the manuscript. JK was the Chair of the CUP Global Panel. MPW was the Co-chair of the CUP Global Panel. MLB was the Chair of the CUP Global Expert Committee on cancer incidence. YP was the Deputy Chair of the CUP Global Expert Committee on cancer incidence. SJL, JCS, EC, RC, and LH were CUP Global Expert Panel members. All members of the Expert Panel provided input into the judgments on the evidence and advised on the interpretation of the review, with the Expert Committee providing the preliminary evidence interpretation, the public representative (LH) did not contribute to the final decisions made by the panel. LD, EMG-G were CUP Global collaborators on biological processes and provided input into the biological mechanism citations in the manuscript. HC was the Head of the CUP Global Secretariat.

Conflict of interest

The authors declare no conflict of interests. International Agency for Research on Cancer disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer/WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/WHO.

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Data availability

For this review, only publicly published data were used. All information on data sources and handling is described in Methods section and Supplemental Material. Further details could be available from the corresponding author upon request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajcnut.2025.02.021>.

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