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## Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2020-320990>).

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Received 26 February 2020

Revised 15 April 2020

Accepted 21 May 2020

Published Online First

28 September 2020

## ABSTRACT

Colorectal cancer (CRC) is one of the most common and lethal malignancies in Western countries. Its development is a multistep process that spans more than 15 years, thereby providing an opportunity for prevention and early detection. The high incidence and mortality rates emphasise the need for prevention and screening. Many countries have therefore introduced CRC screening programmes. It is expected, and preliminary evidence in some countries suggests, that this screening effort will decrease CRC-related mortality rates. CRC prevention involves a healthy lifestyle and chemoprevention—more specifically, oral chemoprevention that can interfere with progression from a normal colonic mucosa to adenocarcinoma. This preventive effect is important for individuals with a genetic predisposition, but also in the general population. The ideal chemopreventive agent, or combination of agents, remains unknown, especially when considering safety during long-term use. This review evaluates the evidence across 80 meta-analyses of interventional and observational studies of CRC prevention using medications, vitamins, supplements and dietary factors. This review suggests that the following factors are associated with a decreased incidence of CRC: aspirin, non-steroidal anti-inflammatory drugs, magnesium, folate, a high consumption of fruits and vegetables, fibre and dairy products. An increased incidence of CRC was observed with frequent alcohol or meat consumption. No evidence of a protective effect for tea, coffee, garlic, fish and soy products was found. The level of evidence is moderate for aspirin,  $\beta$ -carotene and selenium, but is low or very low for all other exposures or interventions.

## INTRODUCTION

Colorectal cancer (CRC) remains the third most commonly diagnosed cancer among both men and women in the US,<sup>1</sup> with a cumulative lifetime risk of developing CRC of 5% in the general population.<sup>2</sup> In the USA, it is the second leading cause of cancer-related deaths in men and the third in women.<sup>1</sup> Its global burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths by 2030.<sup>3</sup> Whereas CRC mortality has been declining in most developed countries, diverging trends have been observed for incidence rates, with some countries having noted a decrease, such as in the USA, France or Japan, while others have reported an increase, such as in Canada, the UK or the Netherlands.<sup>3</sup> As CRC has a natural history that spans over more than 15 years, from normal mucosa to overt cancer, it provides a window of opportunity for effective prevention.<sup>4</sup>

Randomised clinical trials (RCTs) have shown that biennial screening with faecal occult blood testing reduces mortality by 15% through the detection and subsequent removal of advanced adenomas or by diagnosing CRC at an early stage.<sup>5</sup> Nevertheless, there is a wide heterogeneity in screening uptake across countries (ranging from 21% to 73%),<sup>6</sup> and indeed across different population groups, including heterogeneity according to socioeconomic factors.<sup>7</sup> In addition to increasing screening uptake, promotion of a healthy lifestyle is of great importance.

The following work is an umbrella review of systematic reviews and meta-analyses of interventions targeting chemopreventive products for CRC, specifically in an average-risk population.

## METHODS

## Search strategy

We performed a systematic review searching Embase, Medline and ISI Web of Knowledge using a highly sensitive search strategy to identify meta-analyses or systematic reviews. The following combination of controlled vocabulary and text words, related to (1) colon or colorectal cancer (neoplasia, carcinoma, tumour, metastasis, malignancy) and (2) chemoprevention agents, were used, including medications (aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), statin), vitamins or supplements (magnesium, calcium, folic acid, vitamin A, B, C, E, D,  $\beta$ -carotene and selenium), as well as dietary factors (coffee, tea, fish, dairy products, fibre, fruits and vegetables, meat and alcohol). All citations were independently reviewed by two authors (MB and MM) and any discrepancies were resolved through discussion. Recursive searches and cross-references were carried out using a 'similar articles' function and hand searches of identified articles.

## Study selection and patient population

We identified all meta-analyses assessing the risk of colon, rectal or colorectal cancer and chemoprevention agents in an average-risk population. Any studies on specific high-risk populations, such as those with previous adenoma removal, diabetes mellitus, chronic inflammatory bowel disease or a genetic background that increases CRC risk, were excluded. We included all studies published in French or English between September 1980 and June 2019, and more specifically all meta-analyses that performed a complete systematic search of the literature coupled with a pooled analysis, with reported odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs) and corresponding 95%



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**To cite:** Chapelle N, Martel M, Toes-Zoutendijk E, et al. *Gut* 2020;**69**:2244–2255.

confidence intervals (95% CIs). Meta-analyses that reported adjusted risk ratios (aRRs), or summary relative risk estimates (SRREs) were also included.

Data were extracted by two independent reviewers (NC and MM) with the following information: authors, year of publication, search string, databases searched and dates of search, study inclusion and exclusion criteria, outcomes, number and design of included studies, number of patients, measure and category of exposure or intervention, type of cancer, study quality, heterogeneity, publication bias, effect size and 95% CI. Specific data for men and women, colon subsites and dose and/or duration of intake for each studied component were also extracted, when available.

### Data analysis and quality assessment

Owing to the heterogeneity of the collected information and comparisons, the overall effect on the incidence of CRC was analysed qualitatively and categorised as protective or no effect. Chemoprotective agents were qualified as 'protective effect' if the included meta-analysis showed an overall significant effect for the primary outcome and 'no effect' if no statistical difference was noted. We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) rating of evidence to characterise the evidence of the effect of each studied factor on colorectal cancer incidence.<sup>8</sup> Information on quality scores, publication bias and heterogeneity was included. Heterogeneity reported in the included meta-analyses was considered as low, moderate or severe for  $I^2 < 25\%$ ,  $25\text{--}75\%$  and  $> 75\%$ ,

respectively. When an  $I^2$  value was not provided, heterogeneity was defined as significant or not, based on a p value below or above 0.05, respectively. The quality of each meta-analysis is reported using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for meta-analyses and the AMSTAR (assessment of multiple systematic reviews) checklist for systematic reviews (data available on request).

### Patients and public involvement

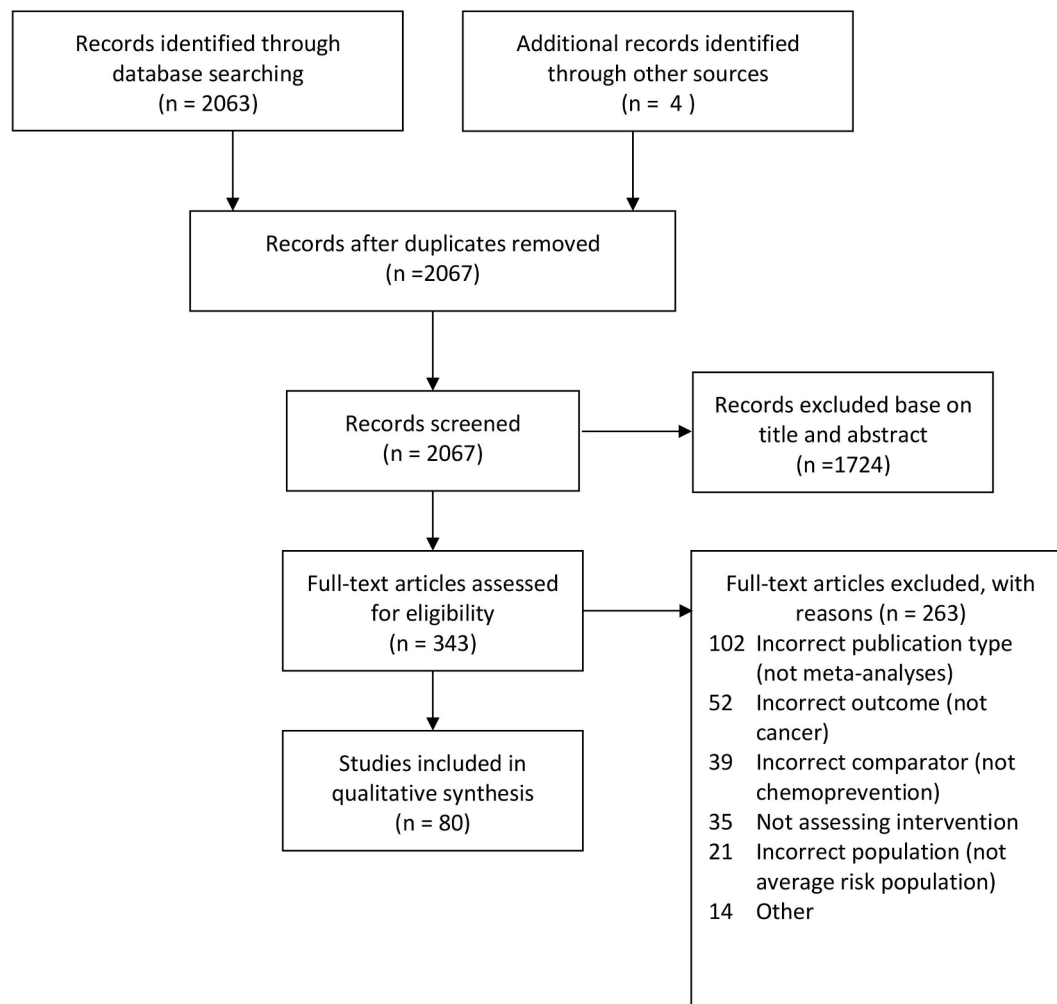
This paper is a systematic review for which we did not identify a specific need for patient involvement.

### Research ethics approval: human participants

This paper is a systematic review of already published articles. Ethics approval was considered unnecessary as ethics approval had been considered by the original publications.

### RESULTS

From the 2063 records initially identified, 343 full text articles were assessed for eligibility; 80 articles were finally included in the qualitative analysis of this umbrella review (figure 1). Summary of results, with the GRADING of evidence, is presented separately for medications, vitamins or nutrient supplements intake, any combination of vitamins and nutrient supplements, and for dietary factors (table 1). They have been classified according to



**Figure 1** Quorum diagram. From: Moher D *et al.*<sup>97</sup>

**Table 1** Summary of results of each component

| Component                                     | Number and type of meta-analyses (reference)                                | Grade of overall certainty of evidence  | Overall effect on colorectal cancer incidence             | Range of the effect* (if significant) |
|---|---|---|---|---------------------------------------|
| Components with protective effect on CRC risk |   |   |   |                                       |
| Aspirin                                       | 4 Observational, <sup>9–12</sup> 1 RCT, <sup>14</sup> 1 mixed <sup>13</sup> | ⊕⊕⊕○<br>Moderate<br>(serious inconsistency and suspected publication bias)                      | Protective  | –14% to –29%                          |
| Low-dose aspirin                              | 2 Observational, <sup>10,12</sup> 1 RCT <sup>13</sup>                       | ⊕⊕○○<br>Low<br>(serious inconsistency and suspected publication bias)                           | Protective (observational)<br>No effect in RCT            |                                       |
| NSAIDs  | 3 Observational <sup>10,15,16</sup>   | ⊕⊕○○<br>Low<br>(serious inconsistency and suspected publication bias)                           | Protective  | –27% to –43%                          |
| Magnesium                                     | 3 Observational <sup>17–19</sup>  | ⊕⊕○○<br>Low   | Protective  | –11% to –22%                          |
| Folic acid                                    | 3 Observational <sup>20–22</sup>  | ⊕○○○<br>Very low<br>(serious inconsistency and indirectness, strong suspected publication bias) | Protective  | –12% to –15%                          |
| Folic acid combination                        | 2 RCT, <sup>23,24</sup> 1 mixed <sup>25</sup>                               | ⊕○○○<br>Very low<br>(very serious indirectness)   | No effect   | NA                                    |
| Dairy products                                | 3 Observational <sup>26–28</sup>  | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | Protective/no effect                                      | –13% to –19%                          |
| Fibre   | 5 Observational <sup>26,29–32</sup>   | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | Protective effect (4) no effect (1)                       | –22% to –43%                          |
| Fruits and vegetables                         | 9 Observational <sup>26,30,33–39</sup>                                      | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | Protective effect (5) no effect (4)                       | –8% to –52%                           |
| Soy   | 3 Observational <sup>38–40</sup>  | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | Protective (2)/no effect (1)                              | –8% to –15%                           |
| Components with no effect on CRC risk         |   |   |   |                                       |
| Vitamin E                                     | 5 RCT, <sup>41–45</sup> 2 observational <sup>21,22</sup>                    | ⊕⊕○○<br>Low<br>(serious indirectness)   | No effect (6)/protective (1 Obs)                          | –12%                                  |
| Vitamin C                                     | 2 Observational, <sup>21,22</sup> 1 RCT <sup>44</sup>                       | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | No effect   | NA                                    |
| Antioxidant combinations                      | 4 RCT, <sup>41,42,44,45</sup> 1 observational <sup>21</sup>                 | ⊕○○○<br>Very low<br>(very serious indirectness)   | No effect (4)/protective (one obs, vitamin C combination) | –17%                                  |
| β-Carotene                                    | 3 RCT <sup>42,45,46</sup>   | ⊕⊕⊕○ Moderate<br>(serious inconsistency)  | No effect   | NA                                    |
| β-Carotene combinations                       | 5 RCT <sup>42,44–47</sup>   | ⊕○○○<br>Very low<br>(very serious indirectness)   | No effect   | NA                                    |
| Selenium                                      | 3 RCT <sup>42,44,45</sup>   | ⊕⊕⊕○ Moderate   | No effect   | NA                                    |
| Tea   | 5 Observational <sup>26,48–51</sup>   | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | No effect (4)/protective effect (1)                       | –18%                                  |
| Garlic and allium                             | 4 Observational <sup>21,52–54</sup>   | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | No effect/protective (1)                                  | –24%                                  |
| Vitamin D                                     | 3 Observational, <sup>21,22,55</sup> 1 RCT <sup>55</sup>                    | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | No effect/Protective (2 Obs)                              | –12% to –13%                          |
| Vitamin D+calcium                             | 2 RCT <sup>55,57</sup>  | ⊕○○○<br>Very low<br>(very serious indirectness)   | No effect   | NA                                    |
| Components with unclear effect on CRC risk    |   |   |   |                                       |
| Coffee  | 7 Observational <sup>26,58–63</sup>   | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | No effect (4)/protective effect (3)                       | –17% to –24%                          |
| Fish and omega-3                              | 7 Observational <sup>26,33,64–68</sup>                                      | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | No effect (4)/Protective (3)                              | –7% to –13%                           |

Continued

Table 1 Continued

| Component                                     | Number and type of meta-analyses (reference)                                 | Grade of overall certainty of evidence  | Overall effect on colorectal cancer incidence                   | Range of the effect* (if significant)        |
|---|--|---|---|--|
| Calcium                                       | 3 Observational, <sup>21 72 73</sup> 2 RCT <sup>70 71</sup>                  | ⊕○○○<br>Very Low<br>(serious inconsistency and serious indirectness, serious imprecision)       | Protective (observational)<br>No effect or increased risk (RCT) | Protective: –14% to –24%<br>Increased<br>+7% |
| Vitamin A                                     | 2 Observational <sup>21 22</sup>   | ⊕⊕○○<br>Low<br>(very serious indirectness)  | Protective (1)/no effect (1)                                    |  |
| Group B vitamins                              | 2 Observational <sup>22 69</sup>   | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | Protective (1)/no effect (1)                                    | –10% (Vitamin B6)                            |
| Statins                                       | 6 Mixed, <sup>76–81</sup> 1 RCT, <sup>74</sup> 1 observational <sup>75</sup> | ⊕⊕○○<br>Low<br>(serious inconsistency and serious indirectness)                                 | Unclear   | –6% to –14%                                  |
| Components associated with increased CRC risk |  |   |   |  |
| Meat  | 7 Observational <sup>26 33 39 82–85</sup>                                    | ⊕○○○<br>Very low<br>(serious inconsistency and very serious indirectness)                       | Increased risk  | +12% to +21%                                 |
| Alcohol                                       | 9 Observational <sup>86–94</sup>   | ⊕○○○<br>Very low<br>(serious inconsistency and indirectness, strong suspected publication bias) | Increased risk  | +12% to +20%                                 |

CRC, colorectal cancer; NA, Not applicable; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised clinical trial.

their effect on CRC prevention as (i) protective, (ii) no effect, (iii) unclear effect or (iv) increasing risk of CRC. The characteristics and quality of included studies and the effect of each factor on CRC incidence are shown in table 2. Large variations were observed in quality, publication bias and between-study heterogeneity (table 2).

### Exposures or interventions associated with a protective effect on CRC prevention (supplementary table 1)

#### Aspirin

Six meta-analyses, published between 2006 and 2017, evaluated the effect of aspirin. Four pooled results of observational studies only,<sup>9–12</sup> one assessed both RCTs and observational studies,<sup>13</sup> and the last RCTs only.<sup>14</sup> Aspirin dose, frequency and treatment duration were reported separately in the meta-analysis by Ye *et al*,<sup>12</sup> while the effect of low-dose aspirin (daily intake  $\leq 325$  mg/day) on CRC prevention was evaluated in three meta-analyses.<sup>10 12 13</sup>

A statistically significant protective effect of aspirin intake overall (RRs ranging from 0.71 to 0.86) was reported in the meta-analyses of both observational studies,<sup>9 11–13</sup> and RCTs.<sup>14</sup> The magnitude of the protective effect was similar for colon cancer (RR=0.71 to 0.76) and rectal cancer (RR=0.68 to 0.74) when analysed separately.<sup>11 12</sup> The protective effect in the colon may be limited to proximal colon cancers (RR=0.58; 95% CI 0.46 to 0.74) as results for distal colon cancer did not reach statistical significance (RR=0.77, 95% CI 0.58 to 1.04).<sup>14</sup> Increases in dosing, frequency and duration of intake were all independently associated with a decreased risk (RR ranging from 0.80 to 0.84), but were based on only one meta-analysis.<sup>12</sup> Meta-analyses of low-dose aspirin (up to 325 mg/day) found conflicting results, with either no protective effect,<sup>13</sup> or a protective effect for a daily intake of aspirin as low as 75 mg/day,<sup>10</sup> with a possible dose–response effect and with RR ranging from 0.90 to 0.80 for daily intakes ranging from 75 mg to 325 mg, respectively.<sup>12</sup> Heterogeneity within the meta-analysis was noted in two of the studies included (with one quantified as strong).<sup>9 11</sup>

Despite serious inconsistencies across the meta-analyses and possible publication bias, the level of overall certainty was

graded as moderate since the meta-analyses that included RCTs reported the strongest effects.

**Summary:** Based on RCT and observational studies, aspirin is protective in most of the included meta-analyses, the relative risks range from 0.71 to 0.86. The protective effect may be observed even for doses as low as 75 mg/day, with a dose–response effect reported up to 325 mg/day. Certainty of evidence is moderate.

#### Non-steroidal anti-inflammatory drugs (NSAIDs)

Three meta-analyses of observational studies published between 2007 and 2018 were included.<sup>10 15 16</sup> Overall, NSAID intake was associated with a protective effect against CRC (RR ranging from 0.57 to 0.74).<sup>10 15 16</sup> The optimal duration for the observed protective effect of NSAIDs is uncertain, with two meta-analyses suggesting a need for an intake of at least 5 years,<sup>10 16</sup> whereas the third, suggested a protective effect after the first year.<sup>10</sup> Moderate to strong heterogeneities were reported in only one meta-analysis.<sup>16</sup> The level of overall certainty was graded low (table 2).

**Summary:** Based on observational studies, NSAID use is associated with a significant decrease in CRC incidence, with RR ranging from 0.57 to 0.74. The effect was consistently significant over n intake of at least 5 years. Certainty of evidence is low.

#### Magnesium

Three meta-analyses of observational studies compared the lowest with the highest level of magnesium intake (from dietary sources or supplements).<sup>17–19</sup> All three meta-analyses found a protective effect against CRC (RR ranging from 0.78 to 0.87).<sup>17–19</sup> A dose–response analysis was performed in two meta-analyses; one reported a RR of 0.93 (95% CI 0.88 to 0.99) for colon cancer for each incremental intake of 50 mg/day,<sup>18</sup> whereas the other found no statistically significant differences when assessing 100 mg/day increments, RR=0.87 (95% CI 0.75 to 1.01).<sup>17</sup>

Low to moderate heterogeneity was found within the three meta-analyses.<sup>17–19</sup> The level of overall certainty was graded low (table 2).

**Table 2** Grading assessment of the certainty of evidence of each component

| Certainty assessment   |               |               |                |             |                                       |                               | Summary of findings      |
|--|---------------|---------------|----------------|-------------|---------------------------------------|-------------------------------|--------------------------|
| No of participants (studies) follow-up   | Risk of bias  | Inconsistency | Indirectness   | Imprecision | Publication bias                      | Overall certainty of evidence | Relative effect (95% CI) |
| Aspirin user compared with non-aspirin user in prevention of colorectal cancer                 |               |               |                |             |                                       |                               |                          |
| 6 Meta-analyses  | Not serious a | Serious b     | Not serious c  | Not serious | Publication bias strongly suspected d | ⊕⊕⊕○ Moderate                 | 0.71 to 0.86             |
| Low dose aspirin user compared with control in prevention of colorectal cancer                 |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Serious e     | Not serious    | Not serious | Publication bias strongly suspected   | ⊕⊕○○ Low                      | 0.71 to 1.02             |
| NSAIDs compared with no NSAIDs for prevention of colorectal cancer                             |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Serious f     | Not serious    | Not serious | Publication bias strongly suspected d | ⊕⊕○○ Low                      | 0.57 to 0.74             |
| Magnesium compared with control for prevention of colorectal cancer                            |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Not serious   | Not serious g  | Not serious | None                                  | ⊕⊕○○ Low                      | 0.78 to 0.89             |
| Folic acid compared with control for prevention of colorectal cancer                           |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Serious h     | serious i      | Not serious | Publication bias strongly suspected j | ⊕○○○ Very low                 | 0.85 to 0.88             |
| Folic acid in combination with other antioxidants for the chemoprevention of colorectal cancer |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Not serious   | very serious k | Not serious | None                                  | ⊕○○○ Very low                 | 0.96 to 1.15             |
| Dairy products compared with control for prevention of colorectal cancer                       |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Serious l     | very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.81 to 0.87             |
| Fibre compared with control for prevention of colorectal cancer                                |               |               |                |             |                                       |                               |                          |
| 5 Meta-analyses  | Not serious   | Serious n     | very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.57 to 0.94             |
| Fruits and vegetables  |               |               |                |             |                                       |                               |                          |
| 9 Meta-analyses  | Not serious   | Serious o     | very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.48 to 1.00             |
| Soy products   |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Serious p     | very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.85 to 1.01             |
| Vitamin E  |               |               |                |             |                                       |                               |                          |
| 7 Meta-analyses  | Not serious   | Not serious   | serious m      | Not serious | None                                  | ⊕⊕○○ Low                      | 0.82 to 1.05             |
| Vitamin C  |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Serious q     | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.84 to 0.92             |
| Combinations of vitamins A, C, E, D or antioxidants  |               |               |                |             |                                       |                               |                          |
| 5 Meta-analyses  | Not serious   | Not serious   | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.92 to 1.00             |
| β-Carotene   |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Serious r     | Not serious    | Not serious | None                                  | ⊕⊕⊕○ Moderate                 | 0.99 to 1.09             |
| β-Carotene in combination with other products  |               |               |                |             |                                       |                               |                          |
| 5 Meta-analyses  | Not serious   | Not serious   | Very serious s | Not serious | None                                  | ⊕○○○ Very low                 | 0.96 to 1.15             |
| Selenium   |               |               |                |             |                                       |                               |                          |
| 3 Meta-analyses  | Not serious   | Not serious   | Not serious    | Not serious | None                                  | ⊕⊕⊕○ Moderate                 | 0.48 to 0.77             |
| Tea  |               |               |                |             |                                       |                               |                          |
| 5 Meta-analyses  | Not serious   | Serious t     | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.82 to 0.99             |
| Garlic   |               |               |                |             |                                       |                               |                          |
| 4 Meta-analyses  | Not serious   | Serious u     | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 1.03 to 1.24             |
| Vitamin D  |               |               |                |             |                                       |                               |                          |
| 4 Meta-analyses  | Not serious   | Serious v     | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.87 to 0.92             |
| 2 Meta-analyses  | Not serious   | Not serious   | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.62 to 1.08             |
| Coffee or caffeine   |               |               |                |             |                                       |                               |                          |
| 7 Meta-analyses  | Not serious   | Serious w     | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.76 to 1.00             |
| Fish and omega-3   |               |               |                |             |                                       |                               |                          |
| 7 Meta-analyses  | Not serious   | Serious x     | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.88 to 1.03             |
| Vitamin A  |               |               |                |             |                                       |                               |                          |
| 2 Meta-analyses  | Not serious   | Not serious   | Very serious m | Not serious | None                                  | ⊕⊕○○ Low                      | 0.77 to 0.87             |
| Vitamin B  |               |               |                |             |                                       |                               |                          |
| 2 Meta-analyses  | Not serious   | Serious y     | Very serious m | Not serious | None                                  | ⊕○○○ Very low                 | 0.86 to 1.18             |
| Calcium  |               |               |                |             |                                       |                               |                          |
| 5 Meta-analyses  | Not serious   | Serious z     | Serious aa     | Serious bb  | None                                  | ⊕○○○ Very low                 | 0.34 to 1.38             |

Continued



Table 2 Continued

| Certainty assessment   |              |               |                |             |                                     |                               | Summary of findings      |
|--|--------------|---------------|----------------|-------------|-------------------------------------|-------------------------------|--------------------------|
| No of participants (studies) follow-up                                   | Risk of bias | Inconsistency | Indirectness   | Imprecision | Publication bias                    | Overall certainty of evidence | Relative effect (95% CI) |
| <b>Statin</b>  |              |               |                |             |                                     |                               |                          |
| 8 Meta-analyses  | Not serious  | Serious cc    | Serious dd     | Not serious | None                                | ⊕⊕○○Low                       | 0.74 to 1.02             |
| <b>Meat</b>  |              |               |                |             |                                     |                               |                          |
| 7 Meta-analyses  | Not serious  | Serious ee    | Very serious m | Not serious | None                                | ⊕○○○Very low                  | 1.04 to 1.25             |
| <b>Alcohol compared with control for prevention of colorectal cancer</b> |              |               |                |             |                                     |                               |                          |
| 9 Meta-analyses  | Not serious  | Serious ff    | Serious gg     | Not serious | Publication bias strongly suspected | ⊕○○○Very low                  | 1.03 to 1.52             |

a. Source of bias was difficult to assess as included meta-analyses included observational studies and did not perform standard risk of bias tools nor any other biases.

b. Heterogeneity was noted in three of the five meta-analyses<sup>9,10</sup> (only for case-control); and<sup>11</sup>, not reported in one<sup>13</sup> and no heterogeneity noted in one.<sup>12</sup>

c. All meta-analyses, any dose aspirin definition.

d. Publication bias was detected but no value provided in the meta-analysis.

e. Heterogeneity was noted in one of the three meta-analyses,<sup>10</sup> not reported in two.<sup>12,13</sup>

f. Heterogeneity was noted in one of the three meta-analyses,<sup>16</sup> not reported in two.<sup>10,15</sup>

g. Intervention and control are based on highest category compared with lowest category of magnesium intake as opposed to primary question, similar quartiles.

h. Heterogeneity reported in one meta-analysis<sup>22</sup> but not in two others.<sup>20,21</sup>

i. Intervention and control are based on different controls as well as high vs low intake.

j. Publication bias was detected in two meta-analyses.<sup>20,22</sup>

k. Different intervention and comparison within each meta-analysis included.

l. Heterogeneity found in one meta-analysis.<sup>27</sup>

m. Different intervention and comparison within each meta-analysis included.

n. Heterogeneity was reported in one meta-analysis<sup>20</sup> none in two<sup>26,29</sup> and not reported in one.<sup>31</sup>

o. Varying heterogeneity in meta-analyses.

p. Heterogeneity was noted in Zhu 2015.<sup>38</sup>

q. Strong heterogeneity was reported in one meta-analysis.<sup>21</sup>

r. Two meta-analyses reported heterogeneity<sup>42,46</sup> and one did not report any results.<sup>45</sup>

s. Different intervention and comparison within each meta-analysis included.

t. Heterogeneity was reported in three meta-analyses<sup>26,50,51</sup> but none in one.<sup>48</sup>

u. Heterogeneity was noted in one meta-analysis.<sup>54</sup>

v. Heterogeneity was reported in two meta-analyses<sup>21,22</sup> none in one<sup>56</sup> and not reported in another.<sup>55</sup>

w. Heterogeneity noted in five meta-analyses.<sup>58,60,26,61,63</sup>

x. Heterogeneity was noted in three meta-analyses<sup>65,66,68</sup> none was noted in four.<sup>26,33,64,67</sup>

y. Heterogeneity was found in one meta-analysis.<sup>69</sup>

z. Heterogeneity was noted in two meta-analyses,<sup>21,73</sup> none was noted for three.<sup>70,71,72</sup>

aa. Intervention and control are based on different controls as well as high vs low intake.

bb. Imprecision due to wide confidence interval in one meta-analysis.<sup>70</sup>

cc. Heterogeneity was reported in two meta-analyses<sup>80,81</sup> no heterogeneity in two,<sup>74,75</sup> varying strength of heterogeneity between publication type in two<sup>77,78</sup> or not reported in the last two meta-analyses.<sup>76,79</sup>

dd. Databases used in meta-analyses are population based therefore include all population, not only average-risk population.

ee. Heterogeneity was reported in two meta-analyses,<sup>82,84</sup> not in five.<sup>26,33,39,83,85</sup>

ff. All included meta-analyses for this outcome reported heterogeneity.

gg. Different intervention and comparison within each meta-analysis included. Doses standard.

**Summary:** Meta-analyses of observational studies suggest a significant protective effect associated with the highest versus lowest magnesium intake (RR ranging from 0.78 to 0.87). The effect was observed when at least 255 mg/day was consumed. Certainty of evidence is low.

### Folic acid (vitamin B9)

Three meta-analyses of observational studies,<sup>20–22</sup> were reviewed. All compared highest to lowest doses of folate intake, and found total (ie, dietary and supplement) folate intake to be associated with a protective effect against CRC (RR ranging from 0.85 to 0.88).<sup>20–22</sup> One meta-analysis provided results by cancer location (rectal or colon) and type of study (cohort or case-control). A protective effect for colon cancer was only described in a pooled analysis of nine cohort studies, (RR=0.75; 95% CI 0.57 to 0.99).<sup>20</sup> Heterogeneity within the meta-analyses was low,<sup>20,21</sup> to moderate.<sup>22</sup> The overall certainty of evidence was graded very low.

Three meta-analyses published between 2010 and 2015, two including RCTs exclusively,<sup>23,24</sup> and one combining RCTs with a cohort study,<sup>25</sup> have evaluated the effect of folic acid (supplementation of 0.4 mg/day, or 0.5 to 2.5 mg/day) combined with other vitamins or aspirin on CRC incidence (online supplementary table 2). No significant effect on CRC was observed in any of these meta-analyses. Heterogeneity was low in all studies.<sup>23–25</sup> The level of overall certainty was graded very low.

**Summary:** Based on meta-analyses of observational studies, high intake of folic acid is associated with a significant decrease in CRC

risk (RR=0.85 to 0.88). A protective dose cannot be determined. However, meta-analyses of RCTs investigating folate in combination with various other components did not report any effect on CRC incidence. Certainty of evidence is very low.

### Dairy products

Three meta-analyses of observational studies, published between 2012 and 2017, were included.<sup>26–28</sup> Results are presented below according to the type of dairy products investigated.

Aune *et al*<sup>27</sup> reported a RR for CRC of 0.81 (95% CI 0.74 to 0.90) associated with high versus low consumers of dairy products. The effect appeared to be dose related, with any 400 g/day increase being associated with a RR reduction of 0.83–0.87.<sup>26,27</sup>

The protective effect persisted when the analysis was restricted to milk consumption, both for CRC as a whole (RR=0.83; 95% CI 0.74 to 0.93) and colon cancer in particular (RR=0.82; 95% CI 0.72 to 0.94), but not rectal cancer.<sup>27</sup> A similar protective effect against CRC (RR=0.85; 95% CI 0.77 to 0.93) was reported in high consumers of non-fermented milk.<sup>28</sup> The effect was statistically significant in men (RR=0.79; 95% CI 0.69 to 0.93) but not in women (RR=0.83; 95% CI 0.68 to 1.02).<sup>28</sup> In a dose-response analysis, RRs ranged from 0.90 to 0.94 for CRC and from 0.92 to 0.93 for colon cancer alone, both for a 200 g/day increase of milk consumption.<sup>26,27</sup> For rectal cancer, only one of the two meta-analyses showed a statistically significant protective effect (RR=0.94; 95% CI 0.91 to 0.97).<sup>27</sup>

None of the meta-analyses described a protective effect associated with cheese consumption.<sup>26–28</sup>

Heterogeneity was low to moderate in all the meta-analyses. The level of overall certainty was graded very low.

**Summary:** Based on observational studies, consumption of dairy products is associated with a decrease in CRC risk (RR=0.81 to 0.87). However, the small number of available meta-analyses, and the multiplicity of outcomes and variety of dairy products do not allow any confident conclusion to be reached about dose or duration necessary for protection. Certainty of evidence is very low.

## Fibres

Five meta-analyses of observational studies published between 1990 and 2018 were included.<sup>26–29–32</sup>

The highest intakes of total dietary fibres showed a protective effect against CRC (RR ranging from 0.57 to 0.88).<sup>29–30</sup> One meta-analysis focused on colon cancer only and also reported a significant protective effect (RR=0.82; 95% CI 0.73 to 0.92).<sup>32</sup> Each incremental 10 g/day of whole grain consumption was associated with a significant risk reduction in both CRC (RR ranging from 0.83 to 0.90),<sup>26–29</sup> and colon cancer (RR=0.82; 95% CI 0.73 to 0.92).<sup>26</sup> Significant heterogeneity was reported in three studies.<sup>29–30–32</sup> The level of overall certainty was graded very low.

**Summary:** Based on observational studies, fibre consumption is associated with a significant reduction in CRC risk, ranging from 0.57 to 0.78. Nevertheless, optimal daily dose and duration of intake cannot be defined due to significant heterogeneity across studies. Certainty of evidence is very low.

## Fruits and vegetables

Nine meta-analyses published from 1990 to 2017, all of observational studies only, were included.<sup>26–30–33–39</sup> Results are presented below according to the type of fruit and/or vegetable investigated.

Considered altogether, high consumption of fruits and vegetables was associated with a significant decreased risk in both colorectal (RR=0.92; 95% CI 0.86 to 0.99) and colon (RR=0.91; 95% CI 0.84 to 0.99) cancers in one meta-analysis.<sup>34</sup>

High fruit consumption was associated with a protective effect for both CRC (RR=0.90; 95% CI 0.83 to 0.98) and colon cancer (RR=0.89; 95% CI 0.81 to 0.98), but not for rectal cancer (RR=0.91; 95% CI 0.76 to 1.09).<sup>34</sup> Conflicting results were reported by Huxley *et al*, where the only significant effect was found for rectal cancer (RR=0.78; 95% CI 0.63 to 0.97), but not colorectal (RR=0.99; 95% CI 0.90 to 1.08) or colon cancer (RR=1.01; 95% CI 0.86; 1.18).<sup>33</sup>

Three of six meta-analyses reported a significantly decreased CRC risk in those having high vegetables intake,<sup>30–34–37</sup> (RR ranging from 0.48 to 0.91); the other three meta-analyses found no statistically significant effects.<sup>33–36–39</sup> Two of the four meta-analyses reported significant protective effects for colon cancer (RR ranging from 0.84 to 0.87),<sup>34–36</sup> but none for rectal cancer.

A significant dose–effect against CRC was found for any 100 g/day incremental fruit and vegetable intake (RR=0.98; 95% CI 0.97 to 0.99), and for vegetable intake only (RR=0.90; 95% CI 0.85 to 0.95),<sup>34</sup> (RR=0.98; 95% CI 0.96 to 0.99).<sup>26</sup> For the fruit consumption dose–effect analysis, controversial results have been reported. Indeed, a significant dose–effect for any increment of 100 g/day was reported by Aune *et al*<sup>34</sup> (RR=0.89; 95% CI 0.81 to 0.98), whereas results from Vieira *et al*<sup>26</sup> failed to reach statistical significance either for CRC, colon cancer or rectal cancer.

High consumption of legume, cabbage and cruciferous vegetables was associated with a significantly decreased CRC risk (RR ranging from 0.76 to 0.91).<sup>35–38</sup> However, no effect was found in the dose–response analysis for legume consumption.<sup>26</sup>

Heterogeneity was reported to be low to moderate,<sup>26–35–39</sup> or low.<sup>30–33–34</sup> The overall level of certainty was graded very low.

**Summary:** Several meta-analyses of observational studies suggest a protective effect of fruit and/or vegetable consumption against CRC risk, with RR ranging from 0.48 to 0.92, with also an incremental benefit for any 100 g/day incremental intake. More specific conclusions about type, dose and duration cannot be made. Certainty of evidence is very low.

## Soy

Three meta-analyses of observational studies were published between 2014 and 2016.<sup>38–40</sup> A significant protective effect of soy or soybean consumption against CRC was reported in two meta-analyses (RR=0.85; 95% CI 0.73 to 0.99),<sup>38</sup> and (OR=0.92; 95% CI 0.87 to 0.97)<sup>40</sup>, whereas another reported no significant effect.<sup>39</sup> The noted beneficial effect was significant for colon (OR=0.92; 95% CI 0.96 to 0.99) but not rectal cancer.<sup>40</sup>

Heterogeneity was low to moderate.<sup>38–40</sup> The level of overall certainty was graded very low.

**Summary:** Observational studies suggest a modest but significant decrease in colon cancer risk associated with soy consumption (RR=0.85 to 0.92). Certainty of evidence is very low.

## Components with no protective effect on CRC prevention (SUPPLEMENTARY TABLE 2)

### Vitamin E

Seven meta-analyses, five including RCTs only,<sup>41–45</sup> and two comprising cohort studies,<sup>21–22</sup> were published between 2007 and 2015, investigating the effects of vitamin E consumption on CRC risk.

None of the studies reported any significant effect of vitamin E intake on CRC. Only one meta-analysis of five cohort studies comparing highest with lowest intake reported a significant protective effect against colon cancer (RR=0.82; 95% CI 0.67 to 0.99).<sup>21</sup> Heterogeneity was low to moderate in all the meta-analyses. The level of overall certainty was graded low.

**Summary:** RCT and observational studies suggest that vitamin E supplementation is not protective for CRC. Certainty of evidence is low.

### Vitamin C

Three meta-analyses, two of observational studies only,<sup>21–22</sup> and one of RCTs,<sup>44</sup> published between 2011 and 2015, investigated the effect of vitamin C consumption on CRC prevention.

No protective effect of vitamin C intake on CRC or colon cancer risk was shown in any of the meta-analyses.<sup>21–22–44</sup>

Heterogeneity was low in the study by Papaioannou *et al*,<sup>44</sup> moderate in Liu *et al*,<sup>22</sup> and strong in Heine-Bröring *et al*.<sup>21</sup> The level of overall certainty was graded very low.

**Summary:** RCT and observational studies do not suggest a protective effect of vitamin C in CRC prevention. Certainty of evidence is very low.

## Antioxidants combination or combination of vitamins with other components

Five meta-analyses, four of RCTs only,<sup>41–42–44–45</sup> and one of cohort studies,<sup>21</sup> were published between 2007 and 2015. These investigated antioxidants or vitamin combinations with other components.

Only one of these five meta-analyses reported a significant protective effect of multivitamin supplementation on CRC risk (RR=0.92; 95% CI 0.86 to 0.98).<sup>21</sup>

Heterogeneity was low in four of the meta-analyses,<sup>21 42 44 45</sup> and not reported in the fifth.<sup>41</sup> The level of overall certainty was graded very low.

**Summary:** RCT and observational studies do not suggest that multivitamin intake, either alone or in combination with other components, exerts a protective effect on CRC risk. Certainty of evidence is very low.

### β-Carotene

Eight meta-analyses of RCT published between 2004 and 2013 have been included. Among them, three assessed β-carotene alone<sup>42 45 46</sup> and five β-carotene in combination with other supplements or medication, including aspirin and various 'other components' (such as vitamin C, selenium or vitamin E).<sup>42 44–47</sup>

None of the pooled analyses, overall or by subgroups (according to gender or incremental dosing), found any significant protective effect of β-carotene consumption alone, or in association with other agents, on CRC risk.

Heterogeneity was strong in one study,<sup>46</sup> moderate in two others,<sup>42 44</sup> and not provided in the two others.<sup>45 47</sup> The level of overall certainty was graded moderate for β-carotene alone and very low for β-carotene in combination.

**Summary:** Meta-analyses of RCTs provide no evidence to support the use of β-carotene, either alone or in combination with other products, in the primary prevention of CRC. Certainty of evidence is moderate for β-carotene alone and very low for β-carotene in combination.

### Selenium

The effect of selenium supplementation on CRC risk was assessed in three meta-analyses of RCTs.<sup>42 44 45</sup>

None of the meta-analyses showed any significant effect of selenium on CRC incidence, either taken alone or in combination with other agents.

Heterogeneity was moderate in Papaioannou *et al*,<sup>44</sup> low in Pais *et al*<sup>45</sup> and not assessed in the Bjelakovic *et al*.<sup>42</sup> The level of overall certainty was graded moderate.

**Summary:** Meta-analytical data of RCT suggest no protective effect of selenium on CRC risk. Certainty of evidence is moderate.

### Products noted to have an unclear effect on CRC prevention (SUPPLEMENTARY TABLE 3)

#### Tea

Five meta-analyses of observational studies published between 2006 and 2017 were reviewed.<sup>26 48–51</sup>

Overall, high tea consumption (green, black and mixed tea) was not associated with a significant protective effect for CRC in two meta-analyses.<sup>49 50</sup> Two meta-analyses investigated the effect of green tea consumption on CRC risk, with the first reporting a significant effect,<sup>51</sup> but not the second.<sup>48</sup>

In subsite analysis, the protective effect was found in rectal cancer only (OR=0.91; 95% CI 0.85 to 0.99).<sup>50</sup> In gender subgroup analysis, high consumption of tea and black tea (1 to 5 cups/day) were both reported to be protective against CRC in women (OR=0.86; 95% CI 0.78 to 0.94<sup>50</sup> and OR=0.82; 95% CI 0.70 to 0.95,<sup>51</sup> for any type of tea and black tea, respectively). In the three remaining meta-analyses, no protective effect of tea consumption was reported.<sup>26 48 49</sup>

Heterogeneity was moderate in three studies,<sup>48–50</sup> strong in one<sup>26</sup> and significant in the last two.<sup>42 51</sup> The level of overall certainty was graded very low.

**Summary:** Conclusions from meta-analyses of observational studies are disparate, with the effect of tea consumption on CRC risk remaining unclear. Certainty of evidence is very low.

#### Allium and garlic

Four meta-analyses of observational studies, published between 2013 and 2014, investigated the role of allium vegetable, and garlic consumption, or garlic supplementation in CRC prevention.<sup>21 52–54</sup>

When the effect of allium and garlic as a whole was assessed, no protective effect was reported. However, when studied separately, one meta-analysis found that garlic and onion consumption were both associated with a significant CRC risk reduction (RR=0.76; 95% CI 0.67 to 0.85 and RR=0.74; 95% CI 0.56 to 0.98, for garlic and onion, respectively), and garlic alone with a decreased incidence of rectal cancer (RR=0.76; 95% CI 0.59 to 0.98).<sup>54</sup> Study heterogeneity was moderate in one meta-analysis,<sup>54</sup> and low in the others.<sup>21 52 53</sup> The level of overall certainty was graded very low.

**Summary:** Meta-analyses of observational studies yield disparate results to support any protective effect of allium and garlic consumption on CRC incidence. Certainty of evidence is very low.

#### Vitamin D

Four meta-analyses, published between 2011 and 2015, evaluated the effect of vitamin D on CRC prevention. One included RCTs only,<sup>55</sup> and three assessed observational studies only.<sup>21 22 56</sup>

Two of the meta-analyses of observational studies, comparing the highest with the lowest range of vitamin D intake, reported significant CRC risk reductions (RR ranging from 0.87 to 0.88).<sup>22 56</sup> Conversely, no significant protective effect was reported by the third meta-analysis of observational studies,<sup>21</sup> nor the meta-analysis of RCTs only.<sup>55</sup>

None of two meta-analyses of RCT investigating the combination of vitamin D and calcium reported a significant protective effect on CRC incidence.<sup>55 57</sup>

Heterogeneity was low<sup>56</sup> to moderate,<sup>21 22 57</sup> or not reported in one meta-analysis.<sup>55</sup> The level of overall certainty was graded very low.

**Summary:** Meta-analyses of RCTs and observational studies yield disparate results to support any protective effect for vitamin D alone or in combination with calcium in CRC prevention. Certainty of evidence is very low.

#### Coffee and caffeine

Seven meta-analyses of observational studies, published between 1998 and 2017, assessed coffee or caffeine intake and CRC risk.<sup>26 58–63</sup>

Four of the seven meta-analyses reported no significant protective effect associated with coffee consumption on CRC risk.<sup>26 59 61–63</sup> Two others reported a significant decrease in CRC risk among drinkers versus no drinkers (OR=0.83; 95% CI 0.73 to 0.95),<sup>60</sup> or drinkers of greatest versus lowest volumes (RR=0.76; 95% CI 0.66 to 0.89).<sup>58</sup> The seventh meta-analysis by Li *et al*<sup>61</sup> reported a significant protective association for the colon cancer subgroup (OR=0.79; 95% CI 0.67 to 0.95), whereas the effect was not significant in rectal cancer.

Among the three meta-analyses that performed a dose-response analysis,<sup>26 60 63</sup> one reported a protective association



for an incremental consumption of 1 cup/day on CRC, as well as on colon and rectal cancer when analysed individually (OR ranging from 0.94 to 0.97).<sup>60</sup> The second reported a protective association for an incremental consumption of 6 to 8 cups/day (RR ranging from 0.87 to 0.93),<sup>63</sup> while the third found no significant association.<sup>26</sup>

Heterogeneity was low in one meta-analysis,<sup>59</sup> moderate in three,<sup>26 61 63</sup> high in two meta-analyses<sup>58 60</sup> and not reported in the last study.<sup>62</sup> The level of overall certainty was graded very low.

**Summary:** Meta-analyses of observational studies and site-specific subgroup analyses yield disparate results for any protective effect for coffee and caffeine intake in CRC prevention. Certainty of evidence is very low.

### Fish and omega-3

Seven meta-analyses of observational studies published between 2007 and 2017 were reviewed.<sup>26 33 64–68</sup>

In two of these, fish consumption was associated with a significant CRC risk reduction (RR ranging from 0.87 to 0.93) compared with non-/lowest-consumers.<sup>65 68</sup> A protective effect was also observed for rectal cancer (RR=0.79; 95% CI 0.65 to 0.97 and RR=0.85; 95% CI 0.75 to 0.95),<sup>65 68</sup> and colon cancer alone (RR=0.95; 95% CI 0.91 to 0.98).<sup>68</sup> In a third meta-analysis, the results were significant when assessing the pooled results of case-control studies (OR 0.83 to 0.84) but not of cohort studies.<sup>67</sup> Three other meta-analyses did not report any significant associations when comparing highest and lowest consumption of fish or omega-3 fatty acids.<sup>33 64 66</sup> In a dose-response analysis of the seventh meta-analysis, any incremental 100 mg/day of fish consumption was associated with a significant decrease in CRC risk (RR=0.89; 95% CI 0.80 to 0.99), but the protective effect was lost when colon or rectal cancers were assessed separately.<sup>26</sup> None of the other meta-analyses reporting incremental levels of fish consumption (20 g/day once a week and 100 g/week) found any significant dose-response protective effects on CRC.<sup>64 68</sup>

Heterogeneity was low in four meta-analyses,<sup>26 33 64 67</sup> moderate in two<sup>66 68</sup> and significant in the last.<sup>65</sup> The level of overall certainty was graded very low.

**Summary:** Meta-analyses of observational studies and site-specific subgroup analyses yield disparate results to support any protective effect for fish and omega-3 consumption in CRC prevention. Certainty of evidence is very low.

### Vitamin A

Two meta-analyses of observational studies evaluating the association between vitamin A consumption and CRC,<sup>22</sup> or colon cancer risk,<sup>21</sup> were published in 2015.

No significant association was found when comparing low intake with high intake of vitamin A either for CRC or colon cancer sites.<sup>21 22</sup> However, a significant protective association for colon cancer was found when comparing any vitamin A consumption with no intake (RR=0.77; 95% CI 0.62 to 0.94).<sup>21</sup>

There was no heterogeneity in any of the meta-analyses. The level of overall certainty was graded low.

**Summary:** Two meta-analyses of observational studies yielded inconsistent results when assessing any protective effect of vitamin A intake in CRC chemoprevention. Certainty of evidence is low.

### Vitamin B group (folic acid excluded)

Two meta-analyses of observational studies, published in 2010 and 2015, were reviewed, one assessing intake of vitamin B2, vitamin B3, vitamin B6 and vitamin B12,<sup>22</sup> while the second focused exclusively on vitamin B6 intake.<sup>69</sup> The first meta-analysis compared highest with lowest intake, and noted that vitamin B2 and vitamin B6 were associated with a decreased risk of CRC (RR=0.86; 95% CI 0.76 to 0.97 and RR=0.88; 95% CI 0.79 to 0.99 for vitamins B2 and B6, respectively).<sup>22</sup> The second meta-analysis did not suggest any protective effect associated with vitamin B6 consumption.<sup>69</sup>

Heterogeneity was reported as moderate,<sup>22</sup> or strong.<sup>69</sup> The level of certainty was graded very low.

**Summary:** Two meta-analyses of observational studies yielded inconsistent results for any protective effect of the intake of vitamins B in CRC chemoprevention. Certainty of evidence is very low.

### Calcium

Five meta-analyses published between 2008 and 2015 were reviewed, two of RCTs only,<sup>70 71</sup> and three of observational studies.<sup>21 72 73</sup>

No significant effect of overall calcium supplementation on CRC incidence was reported in the meta-analyses that included two RCTs,<sup>70</sup> and seven RCTs<sup>71</sup> (study-level analysis), but an increased CRC risk (HR=1.63; 95% CI 1.01 to 2.64) was reported in patients receiving more than 500 mg/day of calcium supplementation in the results of four RCTs at a patient-level analysis.<sup>71</sup> In contrast, a significant protective association was reported in two meta-analyses of observational studies (RR=0.76; 95% CI 0.65 to 0.89) and (RR=0.86; 95% CI 0.79 to 0.95).<sup>21 72</sup> An association with decreased CRC risk was noted for calcium dose ingestion for every 300 mg/day increase (RR=0.91; 95% CI 0.86 to 0.98).<sup>73</sup>

Heterogeneity was moderate in two meta-analyses,<sup>21 73</sup> and low in the others.<sup>70–72</sup> The level of overall certainty was graded very low.

**Summary:** Although a modest protective effect on CRC incidence was found in observational studies of increased calcium ingestion, no protective effect, and even an increased CRC risk was reported in a meta-analysis of RCTs. Certainty of evidence is very low.

### Statins

Eight meta-analyses, published between 2006 and 2014 were reviewed, one of RCT only,<sup>74</sup> two of observational studies only<sup>75 76</sup> and five that included RCTs and observational studies.<sup>77–81</sup>

None of the meta-analyses with pooled results of RCTs reported any significant protective effect of statin consumption on CRC incidence as compared with placebo or no treatment.<sup>74 75 77 78 80 81</sup> In contrast, significant risk reductions of CRC were observed in pooled results of meta-analyses assessing only case-control or cohort studies (RR ranging from 0.86 to 0.92).<sup>77 78 80 81</sup> and in pooled results grouping both RCTs and observational studies (RR 0.90 and 0.91).<sup>80 81</sup>

Heterogeneity was low to moderate in the pooled analyses of RCTs,<sup>74 77 78 80 81</sup> while moderate or strong heterogeneity was reported in the meta-analyses comprising observational studies,<sup>75 78 80 81</sup> except for one reporting low heterogeneity.<sup>77</sup> The level of overall certainty was graded low.

**Summary:** Disparate evidence exists for any protective effect of statin administration on CRC risk. Although meta-analyses of

observational studies suggest a protective association, no beneficial effect was noted in meta-analyses of RCTs. Certainty of evidence is low.

#### Products yielding a consistent increased risk of CRC (SUPPLEMENTARY TABLE 4)

##### Meat

Seven meta-analyses of observational studies, published between 2001 and 2017, assessed meat/fat animal consumption on CRC risk.<sup>26 33 39 82–85</sup>

A large amount of meat consumption and incremental 100 g/day of total meat consumption were both significantly associated with an increased CRC risk (RR ranging from 1.21 to 1.25).<sup>39 82</sup>

High versus low red meat intake was significantly associated with increased CRC risk (RR ranging from 1.12 to 1.21).<sup>26 33 84 85</sup> A similar effect was also reported for incremental intakes of 100 g/day of red meat, and for each incremental serving of meat per day (RR=1.12; 95% CI 1.00 to 1.25),<sup>26</sup> OR=1.30; 95% CI 1.13 to 1.49),<sup>82</sup> and each incremental serving per week (SRRE=1.02; 95% CI 1.00 to 1.04<sup>84</sup>). An increased association with colon cancer was also noted (RR ranging from 1.11 to 1.22),<sup>26 33 84 85</sup> whereas only one meta-analysis suggested such a deleterious association for rectal cancer (RR=1.28; 95% CI 1.02 to 1.60).<sup>33</sup>

In two meta-analyses a significantly increased association was reported between processed meat consumption and CRC (RR=1.17 to 1.19<sup>33 85</sup>), or colon cancer risks (RR=1.21 to 1.23)<sup>33 85</sup>). Each incremental intake of 50 g/day of processed meat led to significant increases in CRC, colon and rectal cancer risks (RR ranging from 1.08 to 1.23), the magnitude of the association being greatest for colon cancer.<sup>26</sup>

In contradiction to red and processed meat consumption, a significant risk reduction in rectal cancer (RR=0.80; 95% CI 0.67 to 0.96) was reported for high versus low consumers of poultry.<sup>85</sup> No dose–effect was found in the meta-analysis by Vieira *et al*<sup>26</sup> for any of cancer location.

No significant effect was reported with animal fat or protein intake.<sup>83</sup>

Heterogeneity was low to moderate in two meta analyses<sup>26 39</sup> and reported as 'significant' in two others.<sup>82 84</sup> The level of overall certainty was graded very low.

**Summary:** Most of the available meta-analyses of observational studies report a significant association (RR ranging from 1.12 to 1.21) between meat consumption (particularly red and processed) and increased CRC incidence. Dose–effect studies report a 10–30% increased risk for each increment of 100 g/day of total or red meat, with no clear limit threshold identifiable. Certainty of evidence is very low.

##### Alcohol

Nine meta-analyses of observational studies, published between 1990 and 2015, were reviewed.<sup>86–94</sup>

Three meta-analyses comparing no/occasional drinkers with regular drinkers showed a significant increase in CRC risk (RR ranging from 1.12 to 1.20).<sup>90 93 94</sup> Investigating a dose–effect and considering the no/occasional drinkers as controls, the lowest ingestion category of drinking ( $\leq 1$  drink/day) was associated with a modest but significant increase in CRC risk (RR=1.07; 95% CI 1.02 to 1.13) in one meta-analysis.<sup>93</sup> A clear dose–effect relationship was reported in the meta-analysis of Bagnardi *et al*,<sup>88</sup> in which the RR for CRC increased with alcohol consumption (from 1.08 to 1.38 for daily intake of 25 g to 100 g, respectively).

For moderate drinkers (daily intake of two drinks, up to 25 g/day of alcohol), two meta-analyses reported a significant association between alcohol intake and CRC risk (RR from 1.08 to 1.10).<sup>86 88</sup> With intakes of 2–3 drinks/day (12.6 g/day) up to 50 g/day, all meta-analyses consistently reported a significant increase of CRC risk (RR between 1.17 and 1.23).<sup>88 90 92 93</sup>

Higher relative risks were reported in the highest exposure categories (heavy drinkers >4 drinks/day, more than 50 g/day) (RR ranging from 1.38 to 1.53).<sup>88 90 92–94</sup> The relative risk for rectal cancer tended to be greater than for colon cancer.<sup>86–94</sup>

When stratified by gender, significant increases in CRC risk were observed for men only.<sup>90 93</sup> When assessed, the risk for CRC in men increased proportionally to the amount of alcohol intake.<sup>90 92 93</sup>

Heterogeneity was moderate or 'significant' in all the meta-analyses.<sup>86–94</sup> The level of overall certainty was graded very low.

**Summary:** Alcohol intake is associated with a significantly increased risk of CRC. The effect is dose-dependent and appears even at the lowest consumption doses investigated (1–2 drinks/day). For similar intakes, men tend to have greater CRC risk. Certainty of evidence is very low.

#### CONCLUSIONS

This contemporary umbrella review has confirmed decreased CRC incidences associated with some CRC chemopreventive agents, such as aspirin, NSAIDs, magnesium, folate, dairy products, fibre, soy or fruits and vegetables, suggesting that their use should be encouraged to reduce CRC incidence in average-risk individuals. On the other hand, meat consumption and alcohol intake were associated with increased CRC risks in almost all the meta-analyses published. Nevertheless, it should be kept in mind that the level of evidence is low or very low in most cases, mainly due to marked heterogeneity across published studies, and the type of study. Furthermore, in most cases, we were unable to identify an optimal dose and duration of exposure/intake for any of the products, even in the case of low-dose aspirin and other compounds that have been extensively assessed. Although the present study synthesises the available data in the literature for chemoprevention of CRC, even in the case where all the meta-analyses provide congruent data (going in the same direction, whether protective or deleterious for the occurrence of CRC), the aforementioned limitations prevent us from providing high level of evidence for the consumption of any of the medications, vitamins, supplements and dietary factors discussed.

Since colorectal carcinogenesis is a process that spans several years or decades,<sup>95</sup> designing RCTs specifically to assess the prevention of CRC in an average-risk population may not be feasible, and the effects of many molecules and foods can be studied only using long-term follow-up cohorts or case control studies—and this despite the difficulties in adjusting for many confounders as is needed in these types of studies that are more subject to bias. Additionally, in most of the RCTs, CRC incidence was usually not the primary endpoint of the trial (probably owing to feasibility and sample size considerations), while the populations investigated probably do not reflect a true general population, as patients known to be at a greater risk were often excluded.

The adverse events implications of any recommendations for large populations need also be considered and may outweigh benefits with regards to CRC incidence, such as has been the case in guidelines that have moved away from primary prevention of cardiovascular disease using ASA.<sup>96</sup>

We were not able to identify any subgroups in the general population that would particularly benefit or suffer from a particular chemopreventive agent owing to the average-risk population targeted, and the source data availability of stratified analyses above and beyond what we report.

One major limitation of the present umbrella meta-analysis was the impossibility of pooling the results of the different meta-analyses included for each component because of high between-study heterogeneity for patient selection, dosing and duration of exposure or intervention, follow-up time, and type of molecule/food investigated. Although we proceeded systematically for every agent, grading of the evidence is usually performed for meta-analyses based on pooled estimates and therefore was not fully applicable in the present case. It is important for readers to understand that we completed an umbrella meta-analysis of published meta-analyses. We did not perform a systematic review of recent RCTs which may have been published after the end date of our literature review (2019).

It is our hope that despite all aforementioned limitations, this comprehensive umbrella meta-analysis will assist clinicians in counselling patients, and help to guide the future research on the topic that is required in many instances, to better characterise the impact of a nutritional, supplement, or chemical intervention in CRC prevention in an average-risk population.

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**Acknowledgements** ANB is the holder of the DG Kinnear Chair in Gastroenterology at McGill University. Writing assistance was funded by the Direction of Clinical Research and Innovation (DRCI) of Dijon-Bourgogne University Hospital.

**Contributors** MB and MM carried out the literature search and selection, NC and MM extracted the data, NC, MB and MM drafted the manuscript. ANB reviewed the data extraction, ANB and ET-Z provided a scientific assessment and substantially contributed to manuscript preparation, for initial and revised submissions.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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