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Nutritional prevention of colorectal cancer

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The preventability estimate for colorectal cancer (CRC) is approximately 50 %, highlighting the huge potential for altering modifiable lifestyle factors (including diet and body fatness) in order to reduce risk of this common malignancy. There is strong evidence that dietary factors (including intake of wholegrains, fibre, red and processed meat and alcohol) affect CRC risk. The lack of positive intervention trials and limited mechanistic understanding likely explain limited public health impact of epidemiological observations, to date. An alternative strategy for nutritional prevention of CRC is use of supplements that provide higher individual nutrient exposure than obtained through the diet (chemoprevention). There are positive data for calcium and/or vitamin D and the *n*-3 fatty acid EPA from polyp prevention trials using colorectal adenoma as a CRC risk biomarker. Although CRC is an obesity-related malignancy, there remains a paucity of observational data supporting intentional weight loss for CRC risk reduction. Some types of obesity surgeries (Roux-en-Y gastric bypass) might actually increase subsequent CRC risk due to alteration of local intestinal factors. There is intense interest in nutritional therapy of patients after diagnosis of CRC, in order to impact on recurrence and overall survival (now often termed cancer interception). In conclusion, nutritional prevention of CRC continues to hold much promise. Increased mechanistic understanding of the role of individual nutrients (linked to intestinal microbiota), as well as a precision medicine approach to CRC chemoprevention and interception based on both tumour and host factors, should enable translation of nutritional interventions into effective CRC risk reduction measures.

Chemoprevention: Colorectal cancer: *n*-3 PUFA: Intestinal microbiota

Colorectal cancer prevention strategies

A strong case should continue to be made for increased focus on prevention of colorectal cancer (CRC). Despite advances in diagnosis and treatment of CRC, this common malignancy remains a major contributor to deaths from cancer[1]. There were nearly 2 million cases of CRC diagnosed globally in 2018 and nearly 900 000 deaths, accounting for 9·2 % of all cancer deaths[1]. Moreover, there are two features of colorectal carcinogenesis that provide an excellent opportunity to prevent CRC: first, the long natural history of colorectal carcinogenesis (a process that is understood to take approximately 5–10 years), during which CRC is thought to arise via identifiable, pre-malignant lesions (the conventional adenoma or serrated polyp), facilitates identification and removal of benign precursors[2]; secondly, knowledge of multiple host (including age, sex and familial predisposition) and environmental (diet, excess body weight and tobacco use) factors that modulate CRC

Abbreviations: CRC, colorectal cancer; OS, obesity surgery; ONS, oral nutritional supplement.

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risk should allow identification of those at highest risk for targeted risk reduction measures[3]. The preventability estimate for CRC is considered to be approximately 50 %[4,5], highlighting the potential (currently, largely missed) opportunity for CRC prevention based on addressing modifiable risk factors alone.

Several CRC prevention strategies are recognised (Table 1), some of which are established, whereas others have yet to be introduced into clinical practice. Screening of the general population for CRC is established in many countries in different formats depending on health economy and infrastructure[3,6]. Screening programmes are associated with a reduction in CRC mortality[6]. However, population uptake is variable[6], and only a small proportion of CRC cases are actually diagnosed within screening programmes (10 % in the UK)[7]. Moreover, CRC occurs despite colonoscopy screening and surveillance leading to significant post-colonoscopy CRC rates (approximately 7 % of CRC cases are diagnosed in individuals who have undergone colonoscopy in the previous 3 years in the English NHS)[8,9]. Therefore, there continues to be an unmet need for improved CRC prevention, which I argue should be multi-modal, consisting of a set of interventions that I term here 'nutritional prevention' in combination with best-practice population screening and endoscopic surveillance.

In this paper, I will review three areas of nutritional prevention of CRC (dietary factors, chemoprevention and body weight reduction) relevant to primary/secondary CRC prevention, but also tertiary prevention (prevention of cancer metastasis/progression in CRC survivors), which is now increasingly known by the term cancer interception.

Dietary and lifestyle risk factors for colorectal cancers

The Continuous Update Project by the World Cancer Research Fund and American Institute for Cancer Research is a superb summary of the wealth of observational evidence, which links dietary factors, nutritional state and physical activity levels with CRC risk[5]. There is robust evidence that red/processed (smoked, cured, salted or added preservatives) meat intake, alcohol use (>30 g daily), excess body weight and height are associated with increased CRC risk, whereas physical activity (particularly for colon cancer), as well as wholegrains, fibre and dairy product intake is associated with decreased risk[5]. One might argue that there is sufficient evidence for effective public health intervention; however, this has not materialised and there continues to be controversy about dietary guidance related to CRC risk[10]. Continuing uncertainty about 'dose' (recommended daily intake or activity type/level), benefit associated with lifestyle changes at different stages of the life course and poor understanding of the link between dietary pattern (e.g. Mediterranean and vegetarian) and CRC risk, as opposed to individual nutrient intakes, have all probably contributed to poor translation of epidemiological insights into public health changes. In the case of CRC, one may also argue that over-reliance on endoscopic approaches to CRC prevention by healthcare professionals has also limited focus on dietary guidance.

Table 1. Colorectal cancer prevention strategies

Population screening
Faecal occult blood testing (guaiac or immunochemical methods)
Endoscopy (colonoscopy or flexible sigmoidoscopy)
Endoscopic surveillance of known high risk groups
Chemoprevention
Re-purposed drugs (e.g. aspirin)
Nutrients
Lifestyle modification
Diet, body weight control, smoking cessation, reduced alcohol intake
Increased awareness leading to early diagnosis and improved screening uptake
Clinicians and other healthcare professionals (use of teachable moments)
Public ('red flag' symptoms)

It is methodologically challenging to test the effect of a dietary intervention on CRC incidence and mortality, not least due to the size and duration of any randomised trial with a CRC end-point. Therefore, several dietary interventions (including a low-fat, high-fibre (18 g/4184 kJ) intervention, resistant starch (30 g daily), folic acid (0·5–5 mg daily) and antioxidants) have been tested in a so-called polyp prevention trial, in which the colorectal polyp has been used as an established biomarker of CRC risk in individuals undergoing surveillance colonoscopy over a 1- to 5-year period after an initial finding of colorectal neoplasia[11–13]. These trials have, in general, demonstrated null results with positive polyp prevention trials restricted to interventions that are more appropriately classified as 'nutraceutical' or pharmaco-nutrient (see later) formulations (calcium (1–2 g daily), vitamin D (400–1100 IU daily) and the *n*-3 PUFA EPA (2 g daily))[13–15]. Discrepancies between prior observational data and the findings from subsequent null intervention trials have not been explained, to date. One valid explanation is that the observational data are misleading and that there is no causal relationship between dietary factors and CRC risk. However, this author believes that the relatively short duration polyp prevention trial means that a more rational explanation is that the interventions tested were 'too little (size and duration of the intervention), too late (in individuals who already had colorectal polyps)'.

Chemoprevention agents

An alternative strategy for nutritional prevention of CRC is chemoprevention (a term first coined by Michael Sporn in 1976 to define the use of natural, synthetic or biologic chemical agents to reverse, suppress or prevent carcinogenic progression to invasive cancer)[16]. The re-purposed drug aspirin currently shows most promise for primary CRC prevention based on multiple polyp prevention trials that have reported an approximate 20 % decrease in colorectal polyp recurrence[17],

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aligned with post-trial observational data on long-term CRC incidence and mortality[17]. However, the lack of a risk-stratified approach to CRC chemoprevention using a drug that is associated with a small degree of harm has hampered the introduction of aspirin in those at risk of sporadic (not associated with a defined genetic predisposition syndrome or inflammatory bowel disease) colorectal neoplasia. An alternative approach is to use nutrients with anti-CRC activity in a 'nutraceutical' (also known as pharmaco-nutrient) form (a term that implies the use of a nutritional agent at a supra-physiological (pharmacological) dose and/or in a pharmaceutical (capsule, tablet) form). Table 2 lists the nutraceuticals that have been, or will be, tested in polyp prevention trials either in familial adenomatous polyposis patients or in individuals with sporadic colorectal polyps[13,15,16,18–20]. It should be noted that several of these agents (folic acid, calcium and vitamin D preparations and *n*-3 PUFA) can also be considered as re-purposed drugs, each currently used/licensed for other clinical indications. A comprehensive review of CRC chemoprevention by dietary compounds has been provided by Costea and colleagues[21].

The recent seAFOod polyp prevention trial has drawn attention to the fact that a precision medicine approach is almost certainly required for CRC optimal chemoprevention, taking into account the two types of precursor lesions (conventional colorectal adenoma and serrated polyp) that have distinct histological and molecular phenotypes[22]. Use of *n*-3 PUFA EPA 2 g daily for 12 months was associated with a significant reduction in colorectal adenoma number (a finding consistent with efficacy in a previous familial adenomatous polyposis trial)[23],[15], in contrast to aspirin use, which was associated with a reduction in serrated polyp number[15]. Consistent with the different biology of dysplastic adenomas compared with serrated lesions, emerging epidemiological data are now revealing that the two CRC precursor lesions display differential associations with known CRC risk factors[24]. For example, smoking, excess body weight and alcohol intake are more strongly associated with serrated polyp risk than that for conventional adenomas[24].

Another preliminary observation from the seAFOod trial was that the combination of EPA and aspirin treatment appeared to reduce colorectal adenoma number more than either agent alone, raising the fascinating possibility that a nutrient (EPA)-drug (aspirin) interaction might lead to more potent anti-CRC activity[15].

The large (*n* 25 871) VITAL trial tested the effect of mixed marine *n*-3 PUFA (1 g daily including 460 mg EPA and 380 mg DHA) on invasive cancer of any type in a 2×2 factorial trial with vitamin D_3 (2000 IU daily)[25]. The hazard ratio for the *n*-3 group compared with placebo users was 1·23 (95 % CI 0·83, 1·83), but only ninety eight CRC were reported across both groups[25]. However, a pre-specified analysis of colonoscopy outcomes revealed that although mixed marine *n*-3 PUFA use was not associated with an overall reduction in colorectal polyp risk, those individuals who were African-American, or who had low baseline plasma *n*-3 PUFA levels, did demonstrate a reduction in colorectal polyp recurrence, a finding that mirrored the subgroup analysis of cardiovascular outcomes in the primary VITAL trial analysis[26]. This preliminary finding also suggests that a precision medicine approach might be needed to determine the precise role for nutritional CRC prevention interventions, particularly related to how the baseline tissue level of an individual nutrient predicts benefit, or otherwise, from supplementation.

Table 2. 'Nutraceutical' agents evaluated for primary chemoprevention of colorectal cancer

Folic acid[13]
Calcium plus vitamin D[13,14]
n-3 PUFA[15,18]
Curcumin[19,20]
Resveratrol[19]

Excess body weight and colorectal cancer

That CRC is an obesity-related cancer is beyond doubt[27,28]. Epidemiological observations support a dose–response relationship between increasing excess body weight and CRC risk[28] and the relationship holds for biomarkers of visceral fatness (waist circumference and waist:hip ratio)[28]. The fact that a similar relationship holds for colorectal polyp risk implies that avoidance of excess body weight should be associated with reduced CRC risk[24,29,30]. By contrast, there is a paucity of data supporting the notion that intentional weight loss reduces CRC risk, related to the methodological challenges of monitoring body weight over long periods of time in large cohort or intervention studies (including recall bias and reverse causation)[30,31]. Obesity surgery (OS) has been used as a model of rapid, significant weight loss in order to explore the association between intentional weight loss and cancer risk. Meta-analyses of the large cohort studies, which, to date, have included more than 300 000 patients who underwent OS, leave no doubt that OS is associated with overall decreased cancer risk (OR 0·56 compared with obese controls) in keeping with the other metabolic benefits of OS[32]. However, some observational studies have suggested a counter-intuitive increase in CRC risk after OS, which is backed up by mechanistic data[33]. The association appears to be strongest for Roux-en-Y gastric bypass, perhaps related to increased post-operative bile acid exposure in the colon, dietary change and alterations to the intestinal microbiota and bacterial metabolome[33]. Further studies are required to delineate future risk of colorectal neoplasia, including adenomatous and serrated polyps, in the expanding number of individuals who receive OS[34,35].

Colorectal cancer interception

There is increasing interest in the role of nutritional factors and physical activity for prevention of recurrence

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and metastatic spread in CRC survivors, termed tertiary prevention or cancer interception[36,37]. Dietary and lifestyle factors that have been linked to improved CRC survival in large-scale cohort epidemiological studies are generally those that have already been implicated in a primary prevention setting including *n*-3 PUFA, vitamin D, dietary fibre and physical activity[38]. Few of these interventions have been subjected to assessment in a randomised trial setting. Currently, the *n*-3 PUFA EPA is being tested in the double-blind, placebo-controlled, randomised EMT2 trial in patients undergoing CRC liver metastasis surgery, with a primary endpoint of progression-free survival (clinicaltrials.gov NCT03428477), building on the preliminary survival signal from the phase 2 EMT trial and a wealth of pre-clinical and observational data[18,39].

High-energy, high-protein oral nutritional supplement (ONS) drinks are used on a widespread basis for nutritional support in CRC patients. Recent meta-analysis of randomised trials of ONS (in multiple cancer types) has demonstrated benefit for maintenance of body weight and improved quality of life measures during cancer chemo (radio)therapy[36]. There was limited evidence that supplementation of ONS with *n*-3 PUFA provided additional benefit[36]. However, sub-analysis of a trial of ONS supplemented with *n*-3 PUFA suggested overall survival benefit for those who received *n*-3 PUFA-enriched ONS and who had a modified Glasgow Prognostic Score ≥ 1[40]. This suggests that benefit may be greater for those patients with evidence of systemic inflammation and supports the notion that patient stratification for nutritional intervention may be needed based on the systemic inflammatory response[40]. Results are awaited from the ongoing MENAC trial which is testing the effect of multimodal nutritional and anti-inflammatory therapy (ONS plus *n*-3 PUFA, exercise, non-steroidal anti-inflammatory drug) on cancer cachexia outcomes[41].

The mechanism(s) whereby pharmaco-nutrient, dietary and lifestyle interventions might improve cancer outcomes is only beginning to be investigated. Individual interventions may directly interfere with tumour cell biology, support the host anti-tumour response, boost efficacy of existing chemo(radio)therapy regimens, and/or modulate associated cancer cachexia. Multiple, linked mechanisms of action are likely based on the evidence available for *n*-3 PUFA, which have direct anti-tumour activity, anti-inflammatory properties and may also potentiate the host anti-tumour immune response[18,38]. A recent retrospective analysis of dietary *n*-3 PUFA intake and survival in the N0147 trial reported that survival benefit linked to high marine *n*-3 PUFA intake was restricted to colon cancers with wild-type *KRAS*, suggesting that stratification for host and tumour factors may be necessary to target the right individual to the best nutritional risk reduction measure[42].

Nutrients and intestinal microbiota

There is currently intense interest in the interaction between nutritional factors that are linked to CRC risk and the intestinal microbiota[43,44]. Current mechanistic understanding of how the intestinal microbiota link nutritional factors, including fibre, red/processed meat and *n*-3 PUFA, with early- and late-stage colorectal carcinogenesis, as well as the host anti-tumour response, is summarised in the excellent review of Song and Chan[43]. Intervention studies in human subjects that provide mechanistic insights are now starting to be published. For example, *n*-3 PUFA alter the intestinal microbiome in healthy volunteers in favour of higher abundance of bacteria that produce SCFA[45], which have direct pro-apoptotic activity on colorectal epithelial cells and potentiate the host anti-tumour immune response[38,43]. Red meat may be carcinogenic through increased colonic secondary bile acid exposure, increased hydrogen sulphide production and reduced intestinal barrier function, all secondary to changes in the intestinal microbiota[43]. With the advent of cancer immunotherapy, it will be crucial to investigate whether nutritional factors and/or a pharmaco-nutrient approach will potentiate immunotherapy for CRC[38].

A 'preventionist' approach to colorectal cancer

Although there is strong evidence linking nutritional factors with population CRC risk, there continues to be insufficient emphasis on dietary and lifestyle advice, particularly during potential 'teachable moments' linked to the finding of colorectal polyps at colonoscopy in a primary prevention setting[46,47]. Healthcare service pressures undoubtedly contribute to this. However, 'silo-ed' thinking from healthcare professionals about prevention strategies, with major emphasis on population screening and colonoscopy/polypectomy, likely counteracts a more holistic, multi-modal approach to CRC prevention, in which lifestyle modification and chemoprevention could be used in combination with endoscopy. Further research is required about how and when lifestyle interventions are best communicated to patients and the public for maximum interest, uptake and impact. For example, I have used the term nutritional prevention throughout this paper but, strictly speaking, although cohort epidemiology studies quantify CRC prevented, lifestyle change(s) alters individual risk, but does not necessarily prevent development of colorectal neoplasia, usually in concert with several other non-modifiable factors (e.g. age, sex and genetic predisposition). Development of individual risk-stratification tools will no doubt support CRC risk-based decision-making by patients (for change to diet, weight loss and physical activity) and clinicians (chemoprevention) about nutritional interventions.

Conclusion

In conclusion, there is strong evidence linking nutritional factors with CRC risk reduction in the context of primary prevention, but also with benefit in CRC patients undergoing cancer therapy and for CRC survivors.

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Several barriers to further research, as well as to translation to the clinic, continue to exist for nutritional interventions (lifestyle modification and chemoprevention), which include an ongoing either-or approach to prevention strategies rather than a multi-modal risk reduction philosophy, insufficient mechanistic understanding about how nutritional factors impact on colorectal carcinogenesis, and absence of personalised risk-stratification tools in order to inform individual CRC risk and to best direct nutritional interventions to those with most to gain.

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Conflict of Interest

None.

Authorship

The author had sole responsibility for all aspects of preparation of this paper.

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