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# Lifestyle and dietary environmental factors in colorectal cancer susceptibility

Neil Murphy[a], Victor Moreno[b,c,d,e], David J. Hughes[f], Ludmila Vodicka[g,h,i], Pavel Vodicka[g,h,i], Elom K. Aglago[a], Marc J. Gunter[a], Mazda Jenab[a,*]

[a] International Agency for Research on Cancer (IARC-WHO), Lyon, France
[b] Unit of Biomarkers and Susceptibility, Oncology Data Analytics Program, Catalan Institute of Oncology (ICO). Hospitalet de Llobregat, Barcelona, Spain
[c] Colorectal Cancer Group, ONCOBELL Program, Bellvitge Biomedical Research Institute (IDIBELL). Hospitalet de Llobregat, Barcelona, Spain
[d] Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Spain
[e] Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona, Spain
[f] Cancer Biology and Therapeutics Group, School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Dublin, Ireland
[g] Department of the Molecular Biology of Cancer, Institute of Experimental Medicine, Czech Academy of Sciences, Prague, Czech Republic
[h] Institute of Biology and Medical Genetics, First Faculty of Medicine, Charles University, Prague, Czech Republic
[i] Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic

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ABSTRACT

Colorectal cancer (CRC) incidence changes with time and by variations in diet and lifestyle, as evidenced historically by migrant studies and recently by extensive epidemiologic evidence. The worldwide heterogeneity in CRC incidence is strongly suggestive of etiological involvement of environmental exposures, particularly lifestyle and diet. It is established that physical inactivity, obesity and some dietary factors (red/processed meats, alcohol) are positively associated with CRC, while healthy lifestyle habits show inverse associations. Mechanistic evidence shows that lifestyle and dietary components that contribute to energy excess are linked with increased CRC via metabolic dysfunction, inflammation, oxidative stress, bacterial dysbiosis and breakdown of gut barrier integrity while the reverse is apparent for components associated with decreased risk. This chapter will review the available evidence on lifestyle and dietary factors in CRC etiology and their underlying mechanisms in CRC development. This short review will also touch upon available information on potential gene-environment interactions, molecular sub-types of CRC and anatomical sub-sites within the colorectum.

## 1. Introduction

Colorectal cancer (CRC) shows a wide global variation in incidence. Overall, it ranks 3rd in men and 2nd in women in incidence with an estimated number of over 1.8 million diagnoses worldwide in 2018 (Bray et al., 2018). CRC incidence patterns vary considerably by world regions, with notable changes over the past few decades - increasing with economic development, Westernization of dietary and lifestyle habits (i.e. high intakes of fats, red/processed meats, refined grains, sugary foods, alcoholic beverages, and low intakes of dietary fibre, fruits, vegetables; overweight, obesity and physical inactivity), affluence, and with age (Brenner and Chen, 2018). In fact, the observed changes in CRC incidence over time and by variations in lifestyle patterns have been evidenced historically in migrant studies and more recently by a large body of epidemiologic evidence (Hughes et al., 2017). Although incidence rates appear to have stabilized in high-income countries, rates in low-to middle-income countries are predicted to increase dramatically in coming decades, likely due to on-going economic and nutrition transitions, Westernization of lifestyle patterns and demographic ageing (Brenner and Chen, 2018). According to a recent review by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) expert panel, there is strong evidence that increased consumption of processed meats, red meats and alcoholic drinks, smoking, physical inactivity, greater body fatness and adult attained height contribute to increased CRC development, while reduced risk of CRC is associated with high consumption of wholegrains, foods containing dietary fibre, dairy products and calcium supplements (Vieira et al., 2017). Additional modifiable risk factors are regular aspirin use and hormone therapy, both of which show inverse risk associations (Green et al., 2012; Algra and Rothwell, 2012). CRC heritability is estimated to range between 7 and 35% with a likely wide range of genetically susceptible individuals who have multiple low risk

* Corresponding author.
*E-mail address:* Jenabm@iarc.fr (M. Jenab).

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variants (Lichtenstein et al., 2000; Jiao et al., 2014; Graff et al., 2017). There is strong evidence for a role of inflammation, oxidative stress and metabolic dysfunction as underlying, interactive mechanisms in CRC. Additionally, there are also likely to be further, inter-related mechanisms particularly for anatomical sub-sites of the disease. The impact of short- and long-term dietary and lifestyle exposures on the gut microbiome, and its impact on colonic health have long been suspected but are only now beginning to be explored. CRC development is complex, multi-factorial, and multi-mechanistic, likely involving interactions of environmental and genetic factors, although much about interactions in CRC etiology remains unknown. Lifestyle factors that affect CRC development, such as obesity, physical inactivity or alcohol drinking, may also affect treatment efficacy and overall survival, but more research is needed in this area. The involvement of environmental factors in the etiology of a large majority of CRC means that this disease is likely to be highly amenable to prevention by prudent dietary and lifestyle choices.

## 2. Epidemiologic evidence on the link between dietary and lifestyle factors and colorectal cancer and potential underlying mechanisms

### 2.1. Alcohol

Alcohol has been identified as a risk factor for CRC development and CRC-related death with little variation by sex or anatomical colorectal sub-site (Fedirko et al., 2011; Cai et al., 2014; Wang et al., 2015). A meta-analysis of cohort study findings indicates the magnitude of the association is an approximate 7% increased risk with each daily intake of 10 g of ethanol (Vieira et al., 2017).

### 2.2. Red and processed meats

The same meta-analysis mentioned above suggests a 12% increased CRC risk for each 100 g/day intake of red and processed meats (Vieira et al., 2017) – a food group consistently associated with a dose-response increase in CRC development (Bouvard et al., 2015). The current evidence is stronger for processed meats than for red meats (Vieira et al., 2017), likely due to carcinogenic exposures from preservation methods (smoking, curing or salting). However, experimental studies trying to define the mechanisms for this association are inconsistent and inconclusive (Turner and Lloyd, 2017). These exposures have been hypothesized to be associated with increased CRC risk due to their content of N-nitroso compounds (NOCs; derived from curing of meats), heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH; derived from smoking of meat) and other meat-derived carcinogens that are generated by high temperature cooking (Cascella et al., 2018). A recent comprehensive review and meta-analysis of epidemiologic studies on the dietary intake of these compounds noted a paucity of research, but concluded that current findings suggest a moderate increase in risk of colorectal adenoma and CRC with higher comparative dietary exposures to some of these carcinogens (Chiavarini et al., 2017). The increased CRC risk associated with high intake of red meats has also been partly attributed to its content of heme iron (Cascella et al., 2018). Free iron can participate in Fenton reactions, producing high levels of reactive oxygen species and lipid peroxidation products in the digestive tract which may induce considerable cellular damage, although the epidemiologic data is inconsistent (Ashmore et al., 2016). Additionally, some novel mechanisms concerning the role of meats in colorectal carcinogenesis, such as the ability of N-glycolylneuraminic acid (a non-human sialic acid in meat) to trigger immune responses, inflammation and subsequent oxidative stress (Turesky, 2018) have also been proposed – but much work is required to establish these as conclusive underlying mechanisms linking consumption of red and processed meats with CRC development.

### 2.3. Dietary fibre

High consumption of foods containing dietary fibre and whole grains have been consistently associated with inverse CRC risk associations (Vieira et al., 2017), particularly in findings from large prospective cohort studies where data are collected prior to cancer diagnoses, and are hence less subject to recall bias observed in traditional case-control studies (Bingham et al., 2003). Despite robust inverse associations observed in prospective epidemiologic studies for dietary fibre and CRC, findings from several randomized controlled trials (RCT) have been inconclusive (Song et al., 2015a).

Potential mechanisms underlying the beneficial properties of dietary fibre for CRC prevention include an increase in the consistency of faecal matter, reduction of the transit time, and consequently a reduction of the contact time between potential toxic carcinogens and the colonic epithelium. Dietary fibre may also bind harmful by-products of digestion including secondary bile acids (Aune et al., 2011). Moreover, fermentable substrates derived from dietary fibre can promote microbiome diversity and increase the biomass of beneficial bacteria, hence decreasing gut permeability and reducing exposure of colonocytes to deleterious compounds from the colonic milieu (Kieffer et al., 2016). For example, fermentation of dietary fibre produces short-chain fatty acids which can influence metabolic signalling pathways and inflammation in the gut (Simpson and Campbell, 2015; Makki et al., 2018).

### 2.4. Dairy products, calcium and vitamin D

The WCRF/AICR expert review panel has also concluded the existence of “strong evidence” linking higher dairy product consumption with lower CRC risk (Vieira et al., 2017) - an association that has been largely attributed to their calcium content (Thorning et al., 2016). In fact, inverse CRC risk associations have long been observed for calcium itself, but observations for colorectal adenoma are inconsistent as are findings from several RCT on calcium supplementation and incidence of colorectal adenoma or CRC (Song et al., 2015a; Garland et al., 1985). Calcium is thought to be able to bind compounds such as free fatty acids and bile acids within the colonic milieu, limiting their carcinogenic potential, but it has also been shown to inhibit cell proliferation, induce differentiation and apoptosis, and suppress DNA damage (Thorning et al., 2016).

A nutrient often related to calcium is vitamin D. There is robust epidemiologic evidence, particularly from prospective cohort studies, for a strong inverse risk association between levels of circulating 25-hydroxyvitamin D and reduced risk of CRC (McCullough et al., 2019) – although findings from the few RCT that have been conducted on the topic have not corroborated these results (Song et al., 2015a; Manson et al., 2019). The observed inverse CRC risk association of circulating vitamin D appears to be stronger in women than in men (McCullough et al., 2019). The biological explanation for this potential sex-difference is not immediately clear based on vitamin D's proposed antineoplastic mechanisms of action (i.e. modulation of cellular growth, differentiation and apoptosis, by reducing angiogenesis, as well as anti-inflammatory and immune regulatory properties) but may be suggestive of possible etiological differences between men and women. Interestingly, high vitamin D status prior to diagnosis has also been shown to be associated with longer survival in patients with CRC (Fedirko et al., 2012).

### 2.5. Lifestyle and dietary patterns

More recently, interest has grown in studying dietary patterns and dietary risk scores generated by combination of specific foods or lifestyle habits (Tabung et al., 2017). Among those, the Mediterranean diet has attracted the most attention with a markedly reduced CRC risk with greater adherence to the dietary pattern, though there is not a clear

agreement on the precise definition of this diet and debate about the inclusion of wine in studies pertaining to cancer development (Farinetti et al., 2017; Schwingshackl et al., 2017). In contrast, a Western diet has been associated with increased risk of CRC (Castello et al., 2018). Other dietary patterns studied include the adherence to the WCRF/AICR recommendations (see dietandcancerreport.org), which has shown strong inverse risk associations in cohort studies based on different populations (Romaguera et al., 2012; Hastert and White, 2016), or various other dietary indices based on healthy eating patterns, where higher compliance is associated with decreased CRC development (Petimar et al., 2018). Interestingly, the observed inverse CRC risk associations with these patterns appear to differ by sex, lending further evidence to the suggestion that men and women may have some etiological differences in development of this disease (Hastert and White, 2016; Petimar et al., 2018). Furthermore, adherence to healthy dietary and lifestyle patterns may also be associated with improved survival post-diagnosis (Romaguera et al., 2015).

Dietary patterns or scores derived from mechanistic approaches have also been assessed in association with CRC. For example, the inflammatory diet index, based on literature evidence to weight nutrients with respect to their correlation with inflammatory markers (Shivappa et al., 2014), has been consistently associated with an increased CRC risk (Zamora-Ros et al., 2015; Shivappa et al., 2017; Zhang et al., 2018). Conversely to the promoting role of inflammation, the Non-Enzymatic Antioxidant Capacity (NEAC) index has proven to be a useful tool to estimate the total dietary antioxidant capacity encompassing antioxidants and bioactive compounds present in the diet and their synergistic effects (Serafini and Del, 2004). Analyses of these scores have been associated with decreased CRC risk in various study settings (Vece et al., 2015; Amiano et al., 2018). Among antioxidant nutrients, flavonoids and polyphenols have been intensively studied, but show inconsistent and heterogeneous results (Zamora-Ros et al., 2017, 2018; Chang et al., 2018). Null results have been observed with measures of circulating vitamin C and carotenoids, another complex group of nutrients with some antioxidant properties (Leenders et al., 2014).

### 2.6. Smoking

Smoking has long been considered an established risk factor for CRC incidence and mortality (Botteri et al., 2008). Data from prospective studies have shown that ever smokers have a 15% greater risk of developing CRC with a clear dose-response effect (Liang et al., 2009), and with possibly stronger associations for rectal cancer (Cheng et al., 2015). Very similar associations have been observed for passive smoking, although it is much less studied (Yang et al., 2016). Smoking may have a stronger effect on the development of serrated polyps (Figueiredo et al., 2015) or tumors with microsatellite instability compared to other molecular CRC sub-types (Carr et al., 2018), and may decrease the preventive effect of aspirin (Wang et al., 2018).

### 2.7. Overweight, obesity and physical inactivity

Overweight and obesity are similarly considered established causes of CRC (Lauby-Secretan et al., 2016). Some observational findings also suggest that they may be associated with decreased survival from CRC (Fedirko et al., 2014). Data from an earlier large meta-analysis of epidemiologic studies comprising almost 100,000 CRC cases showed an overall cancer risk increase of 18% for every 5 units rise in BMI with stronger associations observed in men than women, and for colon compared to rectal cancers (Ning et al., 2010). Similar findings have been observed in more recent meta-analyses (Abar et al., 2018), particularly for the association with abdominal obesity (Ma et al., 2013; Dong et al., 2017). Further research is necessary to determine whether abdominal obesity is an independent CRC risk factor from overweight and obesity (Dong et al., 2017). Sex differences in CRC risk have also been observed with weight gain (Keum et al., 2015), stressing a need for more research on variable etiology for CRC between men and women. The observed positive CRC risk associations with height indicate the likely involvement and importance of early life factors in CRC etiology (Abar et al., 2018), which has received very little research attention to date. The meta-analysis findings also suggest an increased CRC risk association with obesity for Asian populations compared to other populations (Ning et al., 2010), further highlighting the need for a deeper understanding of CRC etiology in different populations.

In contrast to excess energy consumption, overweight and obesity, physical activity has been inversely associated with CRC risk, with a likely dose-response effect (Boyle et al., 2012; Moore et al., 2016; Keum et al., 2016; Kyu et al., 2016), as well as risk of mortality post CRC diagnosis (Qiu et al., 2019). While physical activity is considered as major preventive factor for weight gain in adults (Physical Activity Guideli, 2018), further epidemiological and mechanistic research is required to determine whether, and to what degree, its inverse association with CRC risk may be independent from the CRC promotive effects of obesity. Interestingly, a sedentary lifestyle is positively associated with CRC risk independently of physical activity and may be stronger for colon than for rectal cancer (Cong et al., 2014).

Despite the observed strong associations with obesity, the underlying biological mechanisms are not fully elucidated and under intense study. Obesity is clearly associated with substantial metabolic and endocrine disturbances. The growth promoting effects of insulin signalling, insulin-like growth factors, hyperinsulinemia and hyperglycemia, have been implicated and supported by a considerable volume of evidence from cell culture, animal, clinical and epidemiological studies (Bruce et al., 2000; Gallagher and LeRoith, 2015; Murphy et al., 2018a; McKeown-Eyssen, 1994). Obesity is also associated with chronic inflammation and has been shown to increase adipose tissue-derived inflammatory factors and adipokines such as TNF, leptin, IL-1beta and IL-6. These compounds promote oxidative stress, suppression of the immune system, aberrant cell signalling, increased cell growth, and angiogenesis (Murphy et al., 2018a). In men and postmenopausal women, adipose tissue is central to estrogen synthesis and obesity has been associated with higher levels of circulating estradiol and estrone (Key et al., 2011). It has been hypothesized that the weaker positive obesity and CRC association found among women compared to men may be a consequence of higher circulating estrogens in women mitigating the potential tumorigenic effects of obesity on the colorectum (Terry et al., 2002; Murphy et al., 2015). Epidemiological data on the association of endogenous sex hormones and CRC are relatively limited. Initial studies generally reported null results (Gunter et al., 2008; Clendenen et al., 2009; Lin et al., 2013), although a nested case-control study of postmenopausal women (non-menopausal hormone therapy users) within the Women's Health Initiative found that endogenous circulating estradiol and estrone levels were inversely, and sex hormone binding globulin (SHBG) levels were positively associated with CRC risk (Murphy et al., 2015). Another hormone possibly involved in CRC development is ghrelin, which has numerous metabolic and inflammatory functions and whose levels are lower in obese persons compared to lean. Findings from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study show an increased CRC risk with low serum ghrelin concentrations (Murphy et al., 2018b), but these results remain to be confirmed in other settings. Other potential mechanisms related to obesity include decreased diversity of the gut microbiome, increased permeability of the gut mucosal barrier to pro-inflammatory and toxic compounds from the colonic milieu, and alteration of gut-derived immunity (Kong et al., 2016; Tilg et al., 2018).

### 2.8. Infectious agents and the microbiome

The colon hosts a large and diverse population of microorganisms that exert vital metabolic functions. As noted earlier, gut bacteria are responsible for fermentation of dietary fibre, and the protective effect of foods containing fibre has been hypothesized to be partly related to the

bacterial production of short chain fatty acids such as butyrate (Zeng et al., 2014). It is not clear whether certain microbiome compositional profiles may promote CRC compared to other profiles, but some specific bacteria, such as *Fusobacterium nucleatum*, have been associated with CRC in several studies. *Fusobacterium nucleatum* has been shown to be overabundant in fecal and tumor tissue samples of CRC patients compared to control subjects, and its presence appears predictive of poorer CRC prognosis (Hussan et al., 2017). Evidence from in vitro experiments, animal models, and human studies suggest that *Fusobacterium nucleatum* is involved in colorectal carcinogenesis through promotion of an immunocompromised pro-inflammatory microenvironment conducive to tumor progression (Rubinstein et al., 2013; Kostic et al., 2013; Mima et al., 2015; Abed et al., 2016). However, due to a lack of prospective data on the potential association of this bacterium, it is debatable whether it is an opportunistic invader flourishing in the harsh hypoxic conditions of developing tumors or a causal agent. *Helicobacter pylori* has also been extensively studied in relation to CRC, with inconsistent results (Nam et al., 2017; Fernandez et al., 2017), although recent results from a large consortium of prospective cohort studies suggest a moderate increased association, particularly in African American populations (Butt et al., 2019). Recently, antibodies against *Streptococcus gallolyticus* have been associated with CRC in both case-control (Butt et al., 2017) and prospective settings (Butt et al., 2018a). However, the causal role of this infectious agent is debatable, since some cohort studies only show associations for recent exposure (Pasquereau-Kotula et al., 2018; Butt et al., 2018b). There have been numerous other bacterial species and strains implicated in either promoting (including *pks* + *Escherichia coli*, enterogenic toxin producing *Bacteroides fragilis*) or protecting (e.g., *Faecalibacterium prausnitzii, Akkermansia muciniphila*) against colorectal carcinogenesis (Tilg et al., 2018; Niederreiter et al., 2018), although it is perhaps the interactive microbial balance, strain balance, and the overall bacterial function that is important rather than the specific relative abundance of any single species (Scott et al., 2017). Other infectious agents, such as JC virus, human papillomavirus, and Epstein-Barr virus have also been studied, but with often contradictory results (Chen et al., 2015).

## 3. Prescription medications and CRC risk

Aspirin has been long studied as a potential chemopreventive strategy for CRC. A meta-analysis of case-control and cohort studies of aspirin use (up to 2011) has shown an overall 27% CRC risk reduction (Bosetti et al., 2012), which may be more evident with longer term use (Bosetti et al., 2012; Giovannucci, 2018). The daily use of low dose aspirin has been recommended by a US expert committee for CRC prevention in adults aged 50–59 years (Bibbins-Domingo, 2016), and may even be effective as an adjuvant therapy in cancer patients (Burn and Sheth, 2016). This is supported by evidence of protective effects of aspirin towards increased survival post CRC diagnosis (Veettil et al., 2018). The chemopreventive effect of aspirin is largely due to its anti-inflammatory properties, specifically the inhibition of cyclooxygenase (COX) enzymes which synthesize prostaglandins, although it may also act via COX-independent pathways to induce apoptosis, inhibit NF-kB factor and up-regulate tumor suppressor genes (Burn and Sheth, 2016).

The data on a potential CRC protective effect of statin use are unclear, with observational studies showing a reduced risk of CRC among statin users, while clinical trials do not (Lytras et al., 2014; Joo et al., 2018; Dobrzycka et al., 2018). Hormonal therapies, though controversial because of their broad effects in the cardiovascular system and probable increased risk of breast cancer, have shown a reduced risk of CRC (Gartlehner et al., 2017). Other drugs that have shown a reduced risk of CRC or colorectal adenomas are bisphosphonates (Vogtmann et al., 2017), and metformin (Jung et al., 2017), though it is difficult to rule out confounding by indication or residual confounding by body mass index (BMI). The findings for metformin are encouraging given the increasing incidence of type 2 diabetes mellitus worldwide, because the data appear to support an inverse association with CRC incidence and prolonged survival of CRC patients with type 2 diabetes mellitus (Joo et al., 2018). However, some of the findings on metformin use in CRC are conflicting and further research is warranted (Kobiela et al., 2018). Data on the role of proton pump inhibitors in CRC are controversial and may even be adverse (Joo et al., 2018; Ahn et al., 2012; Graham et al., 2016). Though chemoprevention of the general population is not justified, subjects using these drugs to treat or prevent other conditions may benefit from a reduced CRC risk.

## 4. Etiological differences between molecular sub-types of CRC and anatomical sub-sites within the colorectum

It has been hypothesized that CRC at different anatomical locations may have differential etiologies and risk factors (Iacopetta, 2002; Wei et al., 2004; Limsui et al., 2010; Siegel et al., 2014; Lee et al., 2015; Murphy et al., 2018c). A recent analysis in the European Prospective Investigation into Cancer and Nutrition (EPIC) study comprehensively investigated how 14 established or suspected lifestyle, anthropometric, and reproductive and menstrual risk factors were associated with tumors located at the three main anatomical sites (proximal colon, distal colon, and rectum) (Murphy et al., 2018c). Low levels of physical activity and greater height and body mass index (BMI) were primarily associated with an increased risk of distal or proximal colon cancer, with weaker or null relationships found for rectal cancer. Smoking was primarily associated with an increased risk of proximal colon and rectal cancers. The increasing availability of tumor samples in epidemiological studies allows the relationships for CRC risk factors to be investigated by tumor molecular pathological characteristics (molecular sub-types). For example, smoking has been associated with CIMP positive (CIMP+) and BRAF-mutated tumors (Limsui et al., 2010; Samowitz et al., 2006), and obesity has been associated with microsatellite stable (MSS) and microsatellite instability (MSI)-low CRC tumors, but not MSI-high tumors (Hughes et al., 2012). A recent review and meta-analysis of lifestyle factors by molecular CRC sub-types however, shows a statistically significant association for BMI only with MSS tumors, whereas hormone replacement therapy is inversely associated with risk of MSS but not associated with other molecular subtypes (Carr et al., 2018). The same review also showed that although ever smoking is associated with higher CRC risk for MSS, MSI-low and MSI-high sub-types, the risk is substantially stronger for MSI-high tumors (Carr et al., 2018).

Most recently, in a case-control analysis, regular NSAID use was associated with decreased risk of MSI-high tumors with the strongest effect observed in the absence of *KRAS* and *BRAF* mutations (Amitay et al., 2018). For dietary marine ω-3 polyunsaturated fatty acids, higher intake has been associated with lower risk for MSI-high tumors, with no relationship found for MSS tumors (Song et al., 2015b). A Western dietary pattern (characterized by low intake of fruit and vegetables and high intake of alcohol and red and processed meat consumption) has been found to be positively associated with tumors located in the distal colon and rectum, and for wildtype (non-mutant) *BRAF*, *KRAS*, and CIMP-low/negative tumors (Mehta et al., 2017). Data from the Nurses' Health Study, a long-running American prospective cohort study of over 88,500 female nurses, suggests variability by tumor molecular characteristics for dietary calcium intake, with strongest inverse associations observed for tumors with negative/low CpG island methylator (CIMP) phenotype, and possibly in non-MSI-high subtypes (Keum et al., 2019). Intriguingly, tumor molecular subtypes may also be associated with varying microbiome enrichment with recent data showing that B*acteroides fragilis* and sulfidogenic *Fusobacterium nucleatum* are significantly more enriched in tumors that are deficient in terms of mismatch repair (MMR) gene status compared to those that are proficient (Hale et al., 2018).

These subsite and molecular subtype analyses offer intriguing insights into the possible heterogeneity of CRC etiology. However, larger

and more comprehensive analyses of CRC risk factors by tumor molecular pathological characteristics are now required in different populations to both validate earlier findings and to better understand the variability in associations and the biological pathways underlying the processes of tumor development.

## 5. Interactions between environmental and genetic factors constituting individual susceptibility to colorectal cancer development

Although the majority of CRCs are sporadic, inherited susceptibility is estimated to account for up to as much as 35% of CRC with high-risk germline mutations in the *MMR* genes, and the *APC, MUTYH, SMAD4, BMPR1A and STK11/LKB1* genes only account for about 6% of all cases (Houlston, 2012). Thus, it is likely that CRC may develop in genetically susceptible individuals due to the co-inheritance of multiple low-risk variants. It has been suggested that even subtle alterations in specific proteins of the DNA repair pathways may contribute to CRC susceptibility and clinical outcome (Jiraskova et al., 2018). The multi-factorial nature of CRC etiology implies that environmental and genetic factors are likely to interact at various points along the course of CRC development, from initiation to promotion. Following from this, it has been postulated that weak environmental effects may emerge more clearly in subgroups with enhanced susceptibility (Bermejo and Hemminki, 2007).

Nuclear DNA is constantly exposed to endogenous or exogenous DNA damaging agents that are either physical (UV or ionizing radiation) or chemical (reactive oxygen species, alkylating and aralkylating agents). The resulting DNA damage, via strand breaks, mutations, chromosomal rearrangements or deletions, if not effectively repaired, may become permanent during DNA replication resulting in synthesis of altered proteins (Vilenchik and Knudson, 2003; Vodicka et al., 2006; Pearl et al., 2015). DNA damage is increased under situations of oxidative stress, lipid peroxidation and inflammation (Collins et al., 2012) – such as in the processes of obesity, diabetes, or inflammatory bowel diseases which are closely linked to CRC development. In fact, some clinical studies have shown that supplementation with antioxidant compounds or antioxidant rich foods can reduce DNA oxidation and damage (Moller and Loft, 2006; Chakraborty et al., 2009). For example, fruit consumption has been suggested to increase DNA repair capacity and decrease DNA damage, likely due to antioxidants and bioactive compounds in fruits (Slyskova et al., 2014).

Modified genome-wide association studies (GWAS) approaches to examine gene environment-wide interaction studies (GEWIS) have revealed further significant interactions with several environmental risk factors, including dietary components. These include the SNP rs16892766 at 8q23.3 (*EIF3H/UTP23*), identified by GWAS studies for CRC risk association, in interaction with vegetable intake (Hutter et al., 2012). The study showed that the magnitude of the main positive CRC risk association of the SNP (the minor C allele) increased with increasing levels of vegetable intake - although the functional significance of the SNP and its observed interaction with vegetable intake remains to be elucidated (Hutter et al., 2012). Further examples are processed meat (with rs4143094; possibly indicating involvement of GATA binding protein 3 gene, for which silencing of its expression has been described in CRC), and combined estrogen-progestogen postmenopausal hormone use (with rs964293, which may be involved in vitamin D metabolism) (Figueiredo et al., 2014; Garcia-Albeniz et al., 2016). An illustration of the importance of biological and environmental context in considering nutrient levels and genetic interactions with cancer risk is the micronutrient selenium. Experimental and observational evidence indicate that sub-optimal dietary intakes of selenium may contribute to increased risk for several tumors including CRC, through oxidative and inflammatory response selenoproteins which require selenium for their biosynthesis (Meplan and Hesketh, 2014). However, consistent with the pattern of worldwide selenium bio-availability, nutritional intervention trials and observational studies suggest that selenium-associated CRC risk is most relevant for populations with low selenium status and/or in individuals with variant selenoprotein genotypes (including functional variants in genes coding for core redox glutathione peroxidase enzymes) (Meplan and Hesketh, 2014; Hughes et al., 2015). Additionally, circulating levels of the selenium carrier protein selenoprotein P (SELENOP) appear to be a more sensitive physiological biomarker of selenium status for risk assessment than total selenium measurements (Schomburg and Hughes, 2017). Mouse models show an interaction of disrupted Gpx1 and Gpx2 selenoprotein genes with bacteria-induced intestinal cancer, suggesting an interaction of nutrient-mediated peroxidative stress and dysbiosis (Chu et al., 2004).

The potential of gene-environment interactions in CRC development may also extend to the microbiome. Genetic variation and altered expression of DNA repair or immuno-inflammatory genes may influence the microbiome and, vice-versa, dietary/lifestyle induced microbiome profiles may influence these genes. Immuno-inflammatory genes likely include innate immunity genes, TLR-4 receptors with which the gut barrier integrity biomarker lipopolysaccharide (LPS; an outer membrane component of gram-negative bacteria) interacts, β-catenin/Wnt and NFkB2 signalling pathways, and candidate bacterial response genes IL-1β, TNF-α, IL-10, IL8, ATF6, MBL2, and STAT3 (Rubinstein et al., 2013; Warren et al., 2013; Singh et al., 2016; Coleman et al., 2018). Much further work is needed, particularly from studies providing greater statistical power such as those derived from large collaborative consortia and very large databases, in order to better assess interactions between environmental exposures and genetic factors involved in CRC and to better determine the extent to which they contribute to CRC development, and whether they may identify novel CRC prevention or treatment options.

## 6. Conclusions

This short review has summarized some of the existing evidence linking environmental exposures, particularly dietary and lifestyle, to development of CRC – the majority of which are likely to be sporadic and hence highly amenable to public health strategies promoting sensible eating habits, increased physical activity, weight reduction, smoking cessation and reduced alcohol consumption. Very little is known about potential (and highly likely) gene-environment interactions that may modulate the risk of CRC development in either direction. Similarly, more effort is required to better elucidate and comprehend potential differential risk associations and underlying mechanisms by tumor anatomical sub-sites within the colorectum and by tumor molecular characteristics. Much more research is also required to clearly understand the etiology of this complex and high incidence chronic disease in different populations, not only to guide public health strategies towards its prevention, but also to provide insight into better therapeutic efficacy and post-treatment management for longer term survival in CRC patients.

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## Disclaimer

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## Appendix A. Supplementary data

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