Early-onset colorectal cancer: initial clues and current views

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Abstract

Over the past several decades, the incidence of early-onset colorectal cancer (EOCRC; in patients <50 years old) has increased at an alarming rate. Although robust and scientifically rigorous epidemiological studies have sifted out environmental elements linked to EOCRC, our knowledge of the causes and mechanisms of this disease is far from complete. Here, we highlight potential risk factors and putative mechanisms that drive EOCRC and suggest likely areas for fruitful research. In addition, we identify inconsistencies in the evidence implicating a strong effect of increased adiposity and suggest that certain behaviours (such as diet and stress) might place nonobese and otherwise healthy people at risk of this disease. Key risk factors are reviewed, including the global westernization of diets (usually involving a high intake of red and processed

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meats, high-fructose corn syrup and unhealthy cooking methods), stress, antibiotics, synthetic food dyes, monosodium glutamate, titanium dioxide, and physical inactivity and/or sedentary behaviour. The gut microbiota is probably at the crossroads of these risk factors and EOCRC. The time course of the disease and the fact that relevant exposures probably occur in childhood raise important methodological issues that are also discussed.

Early-onset colorectal cancer (EOCRC) is the second most common cancer and the third leading cause of cancer mortality in people <50 years of age in the USA[1]. The incidence of EOCRC has been on the rise over the past four decades[1] and is expected to increase by >140% by 2030 (refs[2,3]). Incidence rates are inversely associated with age[4], and the rise in incidence and mortality from EOCRC is global[2,5,6].

Despite a lack of complete datasets and rigorous research, established cancer drivers have been linked to EOCRC (such as diet, sedentary lifestyle, smoking and alcohol)[1,5,7–9]. In addition, consensus exists that EOCRC is a pathologically, epidemiologically, anatomically, metabolically and biologically different disease to late-onset colorectal cancer (LOCRC; in patients >50 years old)[10]. Therefore, EOCRC must be investigated, evaluated and managed differently to LOCRC. We suggest that several known and unknown-but-suspected risk factors might explain this alarming trend in the younger population. Important to this discussion, bio-behaviours (that is, behaviours that affect biological process, such as diet, stress and exercise) have undergone a generational shift, including the westernization of diets (calorie-dense and nutrient-sparse) and an increase in physical inactivity, leading to poor (colonic) health. Several solutions to address these bio-behavioural risk factors are outlined in detail throughout this Review.

To fully appreciate the genesis of EOCRC (and the premise underlying this Review), it is essential to fully understand what is known about exposomal elements and the putative mechanisms by which the exposome[11,12] (possibly at critical periods of development) drives this disease. The exposome encompasses the totality of human environmental (that is, nongenetic) exposures from conception onwards. The exposome consists of three overlapping domains: the general external environment (for example, socioeconomic factors, education, climate factors, social capital and stress); specific external environment (such as radiation, infections, tobacco, alcohol, prescription drugs and antibiotics, diet and physical activity); and internal environment (for example, metabolic factors, hormones, gut microbiota, inflammation and oxidative stress)[11]. We contend that the general external environment, such as perceived stress and low socioeconomic status associated with poor nutrition, probably contribute to the increased incidence of EOCRC. We also discuss the possibility that specific external environmental factors such as antibiotics, diet and physical activity contribute to EOCRC and explore putative mechanisms. Given that the microbiome and inflammation are key internal exposome players, and are widely recognized as being guardians of colorectal cancer (CRC)[13], we focus on these players as mechanisms at the crossroads of the exposome and EOCRC.

Anatomy and pathology of EOCRC

The most consistent observation about EOCRC borne out by the epidemiology is presentation at an advanced stage — not only because of a more aggressive pathology but often as a result of a delay of up to 6 months from symptom onset to diagnosis[14]. EOCRCs are typically found in the rectum and distal colon (left side) with a high percentage of mucosal and signet cell pathology relative to LOCRC (although percentages remain small)[15,16]. The appearance of EOCRC on the left side gives clues as to the behaviour, causes and treatment of such cancers. For example, left-sided colon cancers are smaller, have lower recurrence rates, and longer disease-free survival than right-sided colon cancers[17,18]. Left-sided tumour size tends to correlate positively with lymph node involvement, and left-sided and right-sided CRCs respond differently to treatment[17].

Cancers in the distal colon and rectum (important in the context of EOCRC) are associated with a high intake of red and processed meat, high lifetime alcohol intake, and low fish and poultry intake[19–23]. Risk is decreased on the left side by consumption of dark yellow vegetables and fruits, including apples[24]. Micronutrients such as calcium, dietary polyphenols, garlic, choline and vitamin D tend to be more closely associated with reduced risk of left-sided colon cancer[25–31]. Fibre intake and dairy consumption reduces CRC risk throughout the colon[26], and zinc reduces rectal cancer risk in women[32]. Interestingly, cyclooxygenase 2 (COX2) inhibitors are chemopreventive in familial adenomatous polyposis (a disease of the distal colon and rectum)[33,34] but not Lynch syndrome (a disease of the right and/or proximal colon)[35]. Aspirin (which targets both COX1 and COX2) seems to be a chemopreventive for the proximal colon, but not the distal colon or rectum[36]. Such findings are worth considering when deciding which putative exposomal elements to pursue as prime suspects, for delineating the mechanisms by which they behave, and for addressing primary and secondary chemopreventive measures.

Finally, although obesity does not seem to be anatomically selective for driving proximal colon versus distal colon versus rectal cancers[37], it substantially increases the risk of CRC in patients with Lynch syndrome; this increased CRC risk is abrogated by aspirin[38]. Of particular importance to this discussion is that the rise in incidence of EOCRC is largely because of increased rates of rectal cancer[39]. Indeed, rectal cancer differs from distal colon cancer with regard to tissue histology, cancer pathology and aggressiveness[35]. Although molecular similarities exist between colon and rectal cancers, molecular differences exist at the somatic and proteomic levels[40,41], and therefore the exposomal elements might be divergent. Delineation of exposomal elements affecting the rectum versus the colon is a critical step to understanding this disease for chemoprevention and treatment strategies.

Genetic and epigenetic elements in EOCRC

Hereditary syndromes and family history

Family history and hereditary conditions account for ~30% of EOCRCs[1,42,43]. The total prevalence of mutational burden is estimated at 16% in EOCRC, with half of these being Lynch syndrome mutations and the other half being other mutations (including adenomatous polyposis coli (APC), monoallelic and biallelic MutYH, and BRCA1/BRCA2 (REF.[43])).

Importantly, a negative family history does not exclude cancer hereditary syndromes[44] (for example, owing to poor communication among families or other yet-to-be discovered inherited genes). Thus, more research is needed to fully elucidate the genetic profiles of patients with EOCRC.

Having a first-degree relative with a large or histologically advanced adenoma increases the lifetime risk of CRC by up to fourfold[45,46]. Therefore, guidelines recommend that such individuals initiate CRC screening at 70 years of age[47]. Unfortunately, adherence to this recommendation in the young is low[48]. Improving identification of — and screening in — this population is an immediate step to curb the rising rates of EOCRC. Barriers involved in such efforts need to be addressed, including patient and provider awareness of the risk on the basis of family history[49]. Additionally, educational efforts to promote CRC screening in average-risk individuals starting at 50 years of age might have unintentionally deterred age-appropriate screening in those at high risk. Physicians must recognize the risks and convey these risks to their patients as well as promote individual knowledge of family background. A concerted educational effort for both the general public and health-care providers to routinely initiate a risk assessment for CRC and develop a plan for age-appropriate CRC screening prior to 40 years of age would save lives.

Although we might discover new genes coming from Mendelian inheritance in certain families at high risk of EOCRC, these factors would be unlikely to exert a materially large effect on reversing the trend in EOCRC in entire populations. Certainly, the advancement of deep learning tied to whole-genome deep sequencing might shed more light on the genetics of EOCRC[50]. However, regardless of genetic background, the problem of recognition, awareness and education in this cohort remains. For example, many patients find out they have Lynch syndrome after a CRC diagnosis[51]. Even screening adherence rates in known mutation carriers are highly variable and often sub-par (as low as 53%)[52,53]. Ongoing efforts to recognize these high-risk families and improve screening adherence in mutation carriers can have a major effect on familial cancer risks, which should, in turn, have an effect on the overall rate of EOCRC. Just as these educational deficiencies are being addressed in innovative ways (such as social media campaigns and personalized web-based interfaces)[54,55], accurate and appropriate screening techniques are also needed for these families. Guidelines for the genetic evaluation and management of hereditary CRC syndromes have been reviewed, assessed and updated on the basis of current knowledge and rigorous science[56–59]. To this end, deep learning algorithms that consider surrogate biomarkers and exposomal factors in combination with genetic profiling, as well as the integration of microbiome profiles, inflammatory load and other mechanisms that drive EOCRC, will advance our understanding of the disease. Indeed, such risk models have been developed for LOCRC cohorts[60–63] and for hereditary cancer syndromes such as Lynch syndrome[56,64,65]. However, sensitivity and specificity are far from perfect even in these models.

EOCRC has a different signature to LOCRC

EOCRCs tend to be microsatellite stable (MSS) and neardiploid, and multiple alterations of chromosome number, chromosomal rearrangements, or gene amplification and/or deletion

of oncogenes and/or tumour suppressors continue to be identified. Up to 63% of EOCRCs with MSS are euploid (chromosomal instability-negative)[66]. EOCRC is also associated with a higher percentage of synchronous (5.8% versus 1.2% for LOCRC) and metachronous (4.0% versus 1.6% for LOCRC) tumours[67]. Microsatellite and chromosome-stable tumours are common in EOCRC and are associated with a positive family history and rectal location (60% of microsatellite and chromosome-stable tumours are rectal)[68]. Another recognized feature of EOCRC is genome-wide hypomethylation in a subset of patients[1,42,69], which seems to be correlated with chromosomal instability and poor prognosis[66,69]. Some of the key players involved in LOCRC, including *KRAS* codon 12 mutations, have been identified as drivers of EOCRC[66,70]. Indeed, it would also be wise to catalogue differences in molecular signatures of rectal versus distal colon cancer. To this end, subclassifications of EOCRC on the basis of genomic signatures have been proposed[71]. For more details on molecular changes associated with EOCRC the reader is guided to other reviews[2,42,44,72]. Interesting and consistent findings in young people with CRC include a relatively high rate of *KRAS* mutations, LINE-1 hypomethylation and *TP53* mutations[69,70,73]. *BRAF*[V600E] mutations and/or *APC* mutations occur infrequently in EOCRC[73–76].

Exposomal elements in EOCRC

Although genetic predisposition is extremely relevant in EOCRC, it does not account for the observed trends in diagnosis. Approximately 70% of EOCRCs might be driven by the exposome in the presence or absence of a previous somatic mutation(s), or rare gene variants (with variable degrees of penetrance). Exposome science suggests that certain windows of vulnerability (for disease risk) and opportunity (for health promotion) can be leveraged for prevention purposes. As for CRC in older individuals, epidemiological studies of EOCRC have identified diet[77–79], alcohol[80], smoking[14,81] and lack of physical activity[82] as risk factors. As some of these factors are becoming more predominant early in life and, therefore, becoming more prevalent in successive generations, questions arise as to whether exposomal elements — especially in the early years of life[79] — could interact with underlying genetic background factors to trigger EOCRC. Indeed, for an algorithm that generates a lifestyle index (encompassing smoking, alcohol consumption, diet, waist–hip ratio and exercise participation), a high score is associated with a 27% reduction in risk of rectal cancer in Chinese men[83]. Given the increasing incidence of rectal cancer in the young[8,39,84,85], similar studies are worth pursuing in other parts of the world.

To sift out the suspects affecting EOCRC, the following facts about the disease must be considered: one, EOCRC incidence and mortality have been increasing since the 1980s[8,39,84,85]; two, EOCRC is a global phenomenon[2,6]; three, CRC development is linked to chronic inflammation[86] and dysbiosis[87]; four, EOCRC occurs mostly in the distal colon and rectum[39]; five, evidence suggests that CRC can develop as a result of insult years earlier[88,89]; six, specific early-life exposomal elements (some linked to EOCRC such as diet and obesity) effect the onset of disease later in life[90,91]; and seven, people across the BMI spectrum develop EOCRC (although there is a propensity towards patients with EOCRC being overweight)[39,81,92,93].

With this knowledge, it makes sense to focus on the exposomal elements that meet the following metrics: first, the exposomal element must have a similar temporal trend to that of EOCRC; second, the trend should be global; third, the exposomal element must have inflammatory or microbiome-modifying properties or evidence of an effect on the distal colon or rectum; and fourth, the exposomal element should be present during development (conception to adulthood). With such benchmarks in mind, some unusual suspects might become prime suspects. Although alcohol and smoking seem to be associated with EOCRC, this link is demonstrated mostly in the older EOCRC subcohort[94]. Substantial direct exposure from alcohol and cigarettes that affects the pathology of the colon during childhood is unlikely. Epidemiological studies have, so far, failed to reach a conclusion regarding physical activity. Some studies suggest that physical activity does not distinguish between the right and left colon[95], whereas other studies suggest that physical activity suppresses cancers of the right colon but neither those of the left colon nor rectum[96–99]. Independent of exercise and obesity, prolonged sedentary television viewing time (a surrogate for an inactive lifestyle) is associated with risk of EOCRC, particularly of the rectum[9].

Against this backdrop, the exposomal elements that match all four metrics are shown in TABLE 1. Although additional information and many more experiments are necessary to imply causation[100], these benchmarks provide an initial, logical framework for identifying putative exposomal factors driving EOCRC and a rational scientific premise for study. Importantly, new exposomal factors and new mechanisms will probably be discovered in experiments moving forward. Given the increasing rates of EOCRC, such discoveries within and outside the purview of the four metrics will be welcome news to those with EOCRC. Several examples that did not reach the metrics are outlined in BOX 1.

Obesity

Globally, 2.16 billion adults are predicted to be overweight, and 1.12 billion to be obese, by 2030 (REFS[101,102]). Food habits have deteriorated worldwide owing to cheap, readily available high-calorie sweeteners, advances in food processing, and the influence of technology on food and behaviour. There is no question that obesity is increasing globally[101–103]. Unsurprisingly, therefore, many studies have linked obesity to EOCRC[39,81,92,93]. A reasonable hypothesis (at least for a portion of EOCRC cases) is that the increased EOCRC incidence rates are a result of the generational shift towards a higher BMI[104]. Supporting this understanding (and key to EOCRC) is the fact that obesity and body fatness have been linked to CRC later in life[105–107]. Owing to the decade(s)-long process of carcinogenesis, a further hypothesis is that the diagnosis of cancer in the second to fourth decade of life might be a consequence of exposure decades earlier (that is, before adulthood). However, studies have yet to be published linking body fatness in infancy or maternal obesity to EOCRC; furthermore, datasets for such studies are difficult to find, and need to be identified or created.

The mechanisms linking obesity and EOCRC are poorly understood but might involve an interaction with the internal exposome (for example, microbiome and inflammation) and other specific exposomal elements (such as food additives and low-quality foods). Indeed,

obesogenicity is associated with dysbiosis and inflammation in humans[108,109]. Moreover, body fatness during childhood and/or adolescence has been associated with unfavourable metabolic profiles that might exacerbate the development of CRC[93,110]. Thus, a reasonable hypothesis is that the detrimental role of body fatness and/or obesity on later CRC risk might have started earlier in life (such as through maternal obesity or obesity during infancy and childhood). Dysbiosis and/or inflammation might be at the mechanistic crossroads of obesity and EOCRC.

Notably, although obesity is associated with colon cancer[37], evidence is weaker that it drives rectal cancer[92,96,106,111]. This finding is important because the observed increase in EOCRC is largely driven by an increased incidence of rectal cancers[4,112,113]. Furthermore, both nonobese and obese people develop EOCRC. These findings all support the scientific premise that exposomal elements outside of the worldwide obesity epidemic contribute to EOCRC. Complicating this picture, evidence exists that caloric restriction in childhood can increase CRC risk later in life[110,114].

Perceived stress

Perceived stress (individual perception of psychosocial stress) is an external exposomal element that requires particular attention in the context of EOCRC. Not only does stress increase the risk of rectal cancer[115], but stress during pregnancy can increase the risk of CRC in offspring[116]. The scientific premise for this hypothesis is strong given the following factors: first, global increases in perceived stress (including childhood and maternal perceived stress) parallel increases in EOCRC in the past four decades[39,117–119]; second, a reduced amount of sleep drives stress, obesity and CRC (and vice versa)[116,120–122]; third, obesity is linked to EOCRC and prenatal stress is associated with obesity in the offspring[116]; fourth, psychosocial stress increases the risk of diabetes and diabetes is linked to EOCRC[116,123]; fifth, stress is associated with reduced physical activity and deterioration in diet[124]; and sixth, the inflammatory milieu, innate immunity, function of immune cells and the microbiome are compromised under stress[116], and a compromised immune system helps drive CRC[125]. Stress also causes genetic, epigenetic and microbial changes not only in the stressed individual but in the offspring of that stressed individual[116]. Such generational transfer, including aberrant DNA methylation, has been linked to the genesis of CRC[126]. Because psychosocial stress modulates microbiota signatures in the gastrointestinal tract[127], and gut microbiota have a key role CRC development[128], stress-induced dysbiosis and inflammatory load might also have a mechanistic role in EOCRC[116].

Diet

A large and consistent body of literature shows that the adoption of a western diet, which is rich in red meat, high in saturated fat and low in fibre, exerts a negative effect on the colon and that healthier regimens, such as a Mediterranean diet, promote a healthy colon[129]. Interestingly, a western dietary pattern increases risk specifically in the distal colon and rectum[129,130] (EOCRC tends to affect the distal colon or rectum), whereas a Mediterranean diet seems to protect the entire colon and rectum from CRC. A western dietary pattern also has been shown to be associated with tumours that are *KRAS* wild-type, *BRAF* wild-type, have no or a low CpG island methylator phenotype (CIMP) and are MSS[130]. Given that a

large subset of patients with EOCRC tend to have tumours that are *KRAS*^{+/+} (refs[73,131]), *BRAF*^{+/+} (refs[66,73,76,132–134]), CIMP[lo] (refs[74,75,135–137]), and MSS[42,75], linking diet to molecular features of EOCRC (and subsets of EOCRC) would advance our knowledge.

A western diet also drives gut dysbiosis[138] and inflammation[139], and an increasing number of children (worldwide) are eating diets high in refined carbohydrates, added sugars, fats and animal sources[140]. Arguing against linking a western diet to EOCRC is the understanding from an epidemiological standpoint that EOCRC is increasing both in areas with heavy consumption of a western diet (such as the USA and Canada)[8,85,141] and of a Mediterranean diet (for example, Egypt)[142]. However, global food supplies are increasingly homogeneous[143], and countries with people traditionally consuming a Mediterranean diet have been adopting an increasingly westernized diet[144,145]. Likewise, we have observed this trend in other parts of Africa, Asia and Latin America[145,146].

Augmenting the unhealthy nature of a westernized diet is the cooking style typically used. For example, frying (especially deep-frying) can generate pro-inflammatory and pro-carcinogenic advanced glycation end-products (AGEs)[147]. These molecules are highly oxidant compounds formed through the nonenzymatic reaction between reducing sugars and free amino acids. Animal-derived foods that are high in fat and protein are generally AGE-rich and prone to new AGE formation during cooking. By contrast, nutrient-rich foods such as vegetables, fruits, whole grains and milk contain relatively few AGEs, even after cooking[147]. Cooking time, cooking style, cooking temperature and the presence of moisture also dictate the level of AGEs. AGEs contribute to metabolic syndrome[147], drive gut dysbiosis[148] and might have a role in type 2 diabetes mellitus, cardiovascular disease and even Alzheimer disease[149]. Additionally, AGEs are transferred through maternal blood, prematurely raising levels of AGEs in children to adult norms, preconditioning them to abnormally high oxidative stress and inflammation and thus possibly to early onset of disease, such as diabetes[147] and possibly EOCRC.

The Dietary Inflammatory Index (DII) was developed to characterize the inflammatory potential of diet. Just as a Mediterranean diet has low AGE levels[150], the same diet has a particularly low DII[151]. Diet-associated inflammation, as measured by the DII, is strongly and consistently related to CRC incidence and mortality across a wide variety of racial and ethnic groups[152]. The DII has also been used to quantify the relationship between food and inflammation and other risk factors including weight gain and obesity[153–155]. Given the evidence linking diet, inflammation and CRC, a higher DII score might contribute to EOCRC, as we have seen in numerous studies among older individuals with CRC[156]. However, this hypothesis has not been tested in a direct and rigorous manner.

Red and processed meat

A role for red and processed meat in CRC development has been proposed, largely on the basis of evidence from epidemiological studies, especially in those populations consuming a westernized diet[20,157,158]. Red and processed meat reaches the four metrics for study in that consumption and production have increased globally and in children since the 1960s[159]. In addition, red and processed meats have pro-inflammatory and dysbiosis-promoting

properties[160,161]. We predict that inferring causation of EOCRC by red or processed meat will be supported by future mechanistic studies.

Antibiotics

Antibiotic over-use is a serious public health concern. More than 1 million doses of antibiotics are prescribed unnecessarily in the USA every year, and 50% of infants are exposed directly to antibiotics for >5 days[162]. Furthermore, indirect antibiotic exposure through pregnancy is high and can have persistent effects on the infant microbiota after birth[163]. Antibiotic overexposure at an early age has been correlated with multiple health disorders, including obesity[164,165]. Epidemiological studies support an association between antibiotic exposure and CRC[166–168].

Adding to the scientific premise that antibiotics influence colon health and CRC genesis, repeated short-term or long-term exposure (possibly at windows of vulnerability) contributes to antibiotic resistance and alters the gut microbiota with pro-inflammatory and pro-carcinogenic consequences[169–171]. The suggestion of developmental windows of vulnerability to antibiotics is supported by studies consistently showing that antibiotic use in infancy increases the risk of childhood obesity[172,173] (which is linked to EOCRC). Although animal models support the notion that heavy antibiotic use can drive gastrointestinal cancers[174], studies are not always consistent[175–177]. Some studies have shown that antibiotics can protect against CRC, probably owing to the fact that specific microorganisms (for example, *Fusobacterium*) can drive CRC[178] . Thus, inconsistencies across studies are not surprising and highlight the need for carefully controlled, scientifically rigorous studies that consider and delineate 'bad' versus 'good' bacteria, developmental timing and exposure, and type and dose of antibiotic. Addressing this knowledge gap is critical to counter the effects of repeated exposure or long-term antibiotic use. Notably, other drugs targeting the gastrointestinal tract, such as proton-pump inhibitors, have also been associated with gut dysbiosis[179], and thus might also affect the risk of EOCRC.

Dietary additives

Changes in agricultural practices over the past four decades have resulted in a considerable shift in food quality and consumption both globally and regionally (reviewed in detail elsewhere[180]). The health consequences resulting from these changes are only beginning to be understood; however, the consequences generally fit with the models proposed here in that the result is an increase in consumption of energy-dense foods (leading to obesity) and a decline in nutrient content (which affects everyone, regardless of weight). Furthermore, some of the fillers and additives are themselves carcinogenic[181].

Ingredients that have found their way into our food supply range from thoroughly tested chemicals that, so far, have been found to be inert, to known carcinogens or pre-carcinogens such as nitrates and nitrites in processed meats. Indeed, nitrate exposure through drinking water has been shown to be associated with CRC[182], and intake of nitrite-containing processed meat is associated with increased CRC risk[183]. Mechanistically, nitrite consumption can lead to the formation of *N*-nitroso compounds, some of which are carcinogenic. The addition and subtraction of food ingredients is too vast to cover in this

Review, and the historical nature of changes in food content over the past 40 years has been covered elsewhere[184]. Indeed, many of the new exposomal elements found in contemporary diets meet our four metrics as summarized in TABLE 1 and outlined below.

Synthetic food colouring.—Toxicity and carcinogenicity studies on synthetic food colouring have been reviewed elsewhere[185–188]. Synthetic dyes are added to our food and consumed throughout the world. Three dyes (Allura Red, tartrazine and Sunset Yellow) account for 90% of all dyes used in food in the USA[189]. They are used to attract consumers and are especially attractive to children. Importantly, dye consumption per person has increased fivefold since 1955 (REF[185]). Thus, in the context of EOCRC, these synthetic products are highly suspect and require scientific scrutiny. Synthetic food dyes are in breakfast cereals, candy, snacks, beverages, vitamins, and other products aimed at children. In 2010, the European Union placed warning labels on foods that contain synthetic food dyes. Although the implications of such measures are yet to emerge (for EOCRC), it is concerning that measures have not been taken in the USA, nor in most other countries outside of the European Union. This fact is alarming because of the scientific premise supporting a role for synthetic dyes in carcinogenesis.

Allura Red is used as an example because it is a highly common synthetic dye[189] and meets all metrics outlined in TABLE 1. Allura Red (like tartrazine, Sunset Yellow and other synthetic food colourings) is a sulfonated mono azo dye and, as such, is metabolized by intestinal bacteria[190,191] through azo-reduction and has pro-inflammatory properties[185–187,192,193]. The Acceptable Daily Intake (ADI) for Allura Red is currently set at 7 mg/kg daily on the basis of antiquated data[194]. Although this ADI was confirmed by a joint Food and Agriculture Organization–WHO Expert Committee on Food Additives in 2016 (REF[187]), the lack of scientifically rigorous original studies regarding the impact of Allura Red on health is clear; the committee could draw from only seven original studies since 2010. Strikingly (and consistent with our findings from searching the biomedical literature), original data examining the effect of Allura Red on carcinogenesis is lacking. Of the four studies regarding the effect of Allura Red on the colon[191,195–198], three of these studies (albeit conducted by one group) found colonic DNA damage in rats following consumption of 10 mg/kg daily of Allura Red[191,197,198]. The other study found negative results, although the authors were affiliated with the International Association of Color Manufacturers and The Coca-Cola Company[195]. Regarding human exposure, 10 mg/kg daily in rats is the equivalent of 72 mg daily for a 30-kg human child[199]. Although average human exposure to Allura Red is below the ADI[187], one serving of some popular beverages that children consume contains >50 mg Allura Red[187,200]. Considering these facts, we suggest that Allura Red is a key prime suspect that needs scientific attention and has been understudied in the context of carcinogenesis and EOCRC.

Monosodium glutamate.—Monosodium glutamate (MSG) is produced through the fermentation of starch, sugar beets, sugar cane or molasses and was introduced as a food flavouring in the early 1900s. It is a common food additive used to intensify and enhance the flavour of savoury dishes. It is found in a variety of processed foods such as frozen dinners, salty snacks and canned soups, and is also often added to restaurant foods. MSG is worth

considering as an ingredient stimulating EOCRC as it meets the metrics for hypothesis testing (TABLE 1). In particular, global consumption of MSG has increased in the past 50 years[195], and it has pro-inflammatory properties[196]. Additionally, MSG is used to induce obesity and diabetes (both of which are linked to EOCRC)[39,93,123] in animal models[201]. Interestingly, the MSG diabetes model renders mice more susceptible to azoxymethane-induced CRC[202].

Titanium dioxide.—Titanium dioxide (TiO_2) is a naturally occurring metal oxide and is an engineered nanomaterial commonly used in daily consumer products, including food. The food additive TiO_2 (also known as E171) is commonly used as a whitening and brightening agent in confectionery, white sauces and icing (all foods typically targeted towards, and consumed by, children). In the USA, the FDA approved the use of food-grade TiO_2 in 1966 with the stipulation that levels must not exceed 1% of the food weight[203]. However, the increasingly common use of TiO_2 leads to substantial levels of daily dietary intake. Human exposure analyses on foods consumed among American and British populations report that children <10 years of age have higher exposure to TiO_2 than adults[204,205]. Although the reader is guided to other reviews on the subject of TiO_2 in food and health[204,205], insufficient research is being carried out regarding the impact of TiO_2 on colon carcinogenesis. Importantly in the context of EOCRC, TiO_2 as a food additive has been demonstrated to facilitate growth of colitis-associated colorectal tumours in animals[206,207]. In addition, food-grade TiO_2 changes the expression of colonic genes involved in immune responses, oxidative stress, DNA repair, xenobiotic metabolism, cancer pathway signalling and, interestingly, genes involved in olfactory and serotonin signalling[207–209]. As with the other suspects discussed, TiO_2 reaches the metrics already outlined (TABLE 1) to support the scientific premise of studying the effect of TiO_2 on EOCRC.

High-fructose corn syrup.—High-fructose corn syrup (HFCS) has been used in beverages for decades. The technology to produce it was developed in the 1960s and it was introduced to the food and beverage industry as a liquid sweetener alternative to sucrose (sugar) in the 1970s. Made from abundant corn, by the mid-1980s HFCS had fully replaced sucrose in most beverages in the USA[210]. Recognizing that EOCRC is linked to obesity[39,81,92,93] and that obesity is associated with high consumption of HFCS[211], examining the effect of HFCS on EOCRC makes sense. The literature provides a compelling scientific premise for study. Consumption of fructose-rich beverages leads to increased gain in body weight[212], and intermediate biomarkers associated with obesity can be reversed if HFCS is replaced by glucose[213]. The harmful effects of fructose also can be found from the first months of life. Children of mothers who consume fructose have increased body weight, food intake and circulating levels of leptin, and decreased insulin sensitivity[214]. Importantly, HFCS meets the four metrics for investigation (TABLE 1). In particular, consumption has increased in the USA and globally since the early 1970s[215]. HFCS also has pro-inflammatory and dysbiotic properties[216] and children are generally exposed to higher doses than adults[217]. Only in the past few years have mechanistic animal experiments started to reveal the effect of HFCS on the gut. HFCS-treated mice show a substantial increase in gut tumour size and tumour grade in $Apc^{min/+}$ mice in the absence of obesity and metabolic syndrome[218,219]. The effect of HFCS on the distal colon and rectum is unknown.

Microbiome link to EOCRC

The scientific premise supporting a mechanistic link between gut microbial dysbiosis and CRC is strong[87,220,221]. Approximately 1,000 different species of microorganisms, comprised of trillions of cells, reside in the gut[221]. Although the overall picture remains blurry, the microbiota provides many targets for the exposome. Indeed, specific microorganisms (such as *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis* and *Salmonella enterica*) have been identified as having a key role in colon carcinogenesis[178,222]. Infection with pathogens could contribute to neoplastic development through different mechanisms, including intestinal dysbiosis, inflammation, evasion of tumoural immune response and activation of protumoural signalling pathways, such as β-catenin[222].

Gut microbiota and their host share a symbiotic and intricate relationship that benefits both the microbiome and the host. Microorganisms maintain gastrointestinal homeostasis and (under healthy circumstances) protect the gut against inflammation and cancer. However, certain elements of the exposome (that is, any general external exposomal element (such as stress), specific exposomal elements (such as antibiotics and synthetic food dyes), or internal exposomal elements (for example, inflammation))[11,12] can affect the gut microbiome leading to dysbiosis (FIG. 1). In turn, dysbiosis can have a direct effect on the mechanisms that lead to CRC. For example, certain microbiota can mediate the effects of diet on colon cancer risk by their generation of butyrate, folate and biotin (molecules known to have a key role in the regulation of epithelial proliferation). Colorectal cancer-associated microbiota contributes to oncogenic epigenetic signatures[223]. High-fat diets can cause intestinal dysbiosis, leading to the accumulation of harmful bacterial products such as lipopolysaccharides that can enter the intestinal circulation and cause inflammation[224]. As another example, dietary emulsifiers (used to aid texture and extend the shelf-life of processed foods) modulate the gut microbiota and drive colitis and metabolic syndrome[225]. Given that both colitis and obesity are associated with EOCRC[93,105–107,226,227], a reasonable hypothesis is that dietary emulsifiers drive EOCRC as well. Initial studies have shown that these agents cause dysbiosis and increase the incidence of CRC in animal models[228].

Exposomal elements that modulate the gut microbiome include not only those elements meeting the above metrics (such as stress, antibiotics and dietary factors) but also elements previously thought to be disconnected from colon health, such as birth mode, breastfeeding behaviours and maternal stress and nutrition[116,229,230]. Exposure to antibiotics, stress and harmful dietary components can lead to microbial dysbiosis, and these exposures can occur during development. Furthermore, the degree to which the microbiome is at the crossroads of the exposome and EOCRC might be dictated by the timing of exposure. However, testing the hypothesis that dysbiosis in early human development causes molecular changes and dangerous lesions that render the colon at increased risk of transformation in early adulthood is a particular challenge. For example, samples would need to be collected (stool and preferably colonic tissue, and preferably at multiple times during development) during a specific (yet unknown) time frame, and then linked to CRC development decades later. As yet we are unaware of the existence of such a valuable resource. The integration of

other confounding exposomal elements during development (probably involving diet) adds to the complexity of solving the EOCRC problem in the context of microbial dysbiosis. The advancement of machine learning and artificial intelligence in biomedical research and personalized medicine might help to address these issues.

Conclusions

Regrettably, the alarming rise in EOCRC described by epidemiological studies has yet to be followed up by well-designed observational and intervention studies in humans or mechanistic animal experiments. A working group, Fight Colorectal Cancer, has been convened to determine priorities for research of EOCRC[231]. Consistent with this Review, recommendations were made for prioritizing targeted, large, epidemiological studies and the need to tease out the causative factors and the genes involved in a scientifically rigorous fashion. Here, we have complemented these recommendations by rationally identifying prime suspects worth further investigation. To address the rise in EOCRC, some solutions can be deployed now (for example, awareness through educating physicians and patients), some can be deployed with additional work to overcome barriers (such as novel or modified screening techniques and surrogate end points, and improved protocols and guidelines); and some solutions can be deployed with money, time, ingenuity and scientific rigour (for example, to arrive at a better understanding of the mechanisms and gene–environment interactions) (FIG. 2).

Our understanding of how ingredients that have become common in foods over the past four decades might individually increase or combine to increase the risk of EOCRC is woeful. This factor is highlighted by the finding that, despite a wide swathe of the (global) population (particularly children) being exposed[200], only four articles relevant to the effect of Allura Red on colon carcinogenesis could be identified[191,195–198]. Importantly, food constituents rarely exert their effects individually and so these agents should be considered as part of larger (usually unhealthy) dietary patterns (which is why the DII was developed).

How this global nutrition transition affects the colon remains confusing. Future efforts should explore the effect of timing and dose of suspected elements, and the mechanisms by which they might drive EOCRC. Does one or more of the exposomal elements highlighted in Table 1 drive CRC at a young age? Do these elements interact with the genetic background of the individual? What genetic factor(s) increase the risk for sporadic EOCRC? Is age at exposure critical to risk? We hope that such questions will be answered, and that this Review sparks additional questions and hypothesis testing. On the basis of the evidence and logical clues outlined above, the globalization of western diets, fast-food cooking styles, the infiltration of our food by poorly understood artificial ingredients and processing techniques might help to explain the increasing incidence of EOCRC. Until mechanistic studies are carried out, however, we will not know for sure. In addition, high levels of stress and the increasing use of antibiotics place the colon at increased risk of cancer development. The microbiome and/or the inflammasome are likely to be at the crossroads of the link between these exposomal elements and EOCRC.

We posit that if other elements of the exposome are uncovered as prime suspects through attaining all four EOCRC metrics (TABLE 1), then they should be seriously investigated. With access to big data, other exposomal suspects might become clear moving forward. Only after the hypotheses are tested and the clues are investigated can we tackle this challenging disease in a specific and deliberate manner. In the interim, aiming for a healthy lifestyle index (restricting a western-style diet and encouraging a Mediterranean or other mainly plant-based diet), reducing consumption of low-nutrient additives (such as artificially coloured foods and synthetic food colourings), reducing stress, maintaining a healthy weight, and reducing gastrointestinal-targeting drug consumption (especially antibiotics) will probably reduce EOCRC risk. An attainable goal is to use machine and deep learning (that is, artificial intelligence) algorithms in connecting exposomics to taxonomics to generate a weighted-risk signature for targeted chemoprevention of EOCRC.

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Box 1 |

potential exposomal elements affecting early-onset colorectal cancer

Dietary emulsifiers

- Can modulate the gut microbiota and inflammation[225,228,232]

- Can drive colitis, colon cancer and the metabolic syndrome[233–235]

- Children are exposed[236,237]

***Trans*-fatty acids**

- High levels in fast foods and deep-fried foods, bakery products, packaged snacks, and margarines[238]

- Global *trans*-fatty acid production and consumption (including children) has been steadily increasing over the past several decades[157,239]

- Might increase colorectal cancer (CRC) risk[240–242]

Acrylamide

- Prevalent in fast foods[243]

- Drives CRC in animal models

- Exposure occurs during development[244,245]

Sodium nitrate/nitrite

- Associated with activating *KRAS* mutations in humans[246]

- Exposure occurs during development[247,248]

A1 β-caseins

- In cow's milk, are difficult to digest and exposure during development[249]

- Exacerbate gut inflammation and the microbiome[250]

- Drive DNA damage and CRC in animal models[251,252]

Key points

- The alarming rise in early-onset colorectal cancer (EOCRC) over the past four decades described by epidemiological studies and cancer registry data requires coordination and follow-up with mechanistic in vitro testing, animal experimentation and human intervention studies.

- EOCRC occurs in both people who are obese and those who are nonobese, and the rising incidence is global.

- Some solutions to EOCRC can be deployed now (for example, awareness campaigns); some can be deployed with additional work to overcome barriers (such as identifying surrogate end points); and some can deployed with money, time, ingenuity and scientific rigour (for example, uncovering mechanisms and gene–environment interactions).

- Key elements driving EOCRC are exposed when four metrics are fulfilled: one, a temporal relationship exists that follows that of EOCRC; two, exposure is global, as with EOCRC; three, evidence exists of inflammatory or microbiome-modifying properties or evidence of an effect on the distal colon or rectum; and four, exposure occurs during development from conception to adulthood.

- The following elements reach all four of the above metrics: a westernized diet including red and processed meats; consumption of monosodium glutamate, titanium dioxide, high-fructose corn syrup and synthetic dyes; obesity; stress; and widespread use of antibiotics.

- Delineation of exposomal elements attacking the rectum versus colon and their interactions with genetics is a critical step to understanding this disease for purposes of chemoprevention and treatment.
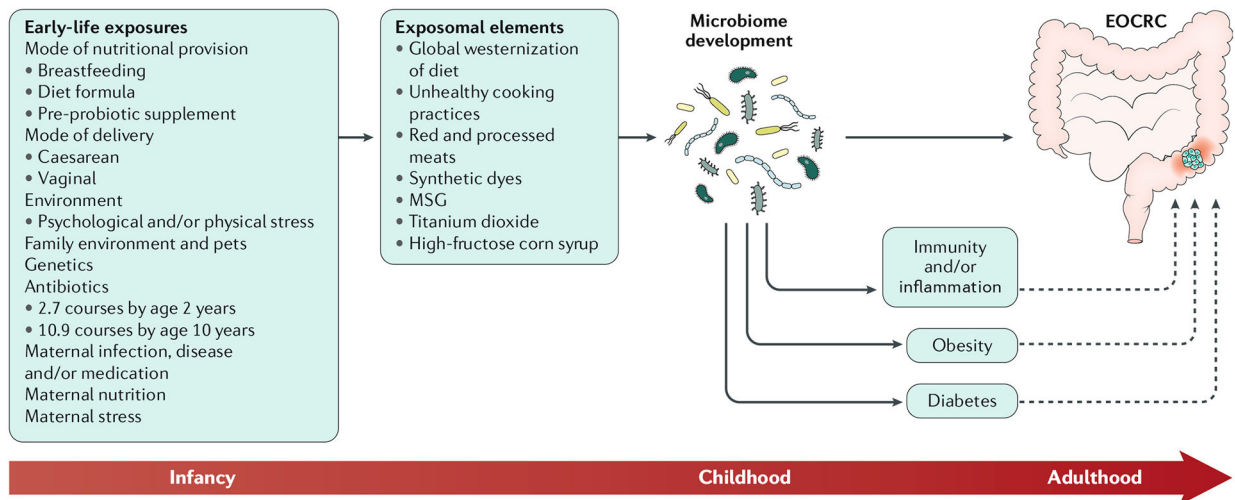
Fig. 1 |. The effect of the exposome and early-life environmental exposures on microbiome health. Exposomal elements that modulate the gut microbiome include not only those elements meeting the four metrics discussed in this Review (such as stress, antibiotics and dietary factors; TABLE 1) but also elements previously thought to be disconnected from colon health, such as birth mode, breastfeeding behaviours and maternal stress and nutrition. In turn, given the role of the microbiome in disease genesis (and the role of the microbiome in maintaining gut health) it probably has a key role in guiding colonic health and development of colorectal cancer. This role might or might not be mediated by obesogenic pathologies. EOCRC, early-onset colorectal cancer; MSG, monosodium glutamate.

Deploy now
- Education and awareness (physician and patient)
- Genetic testing (for all family members with CRC)
- Re-evaluate screening guidelines for EOCRC
- Streamline and coordinate care and communication

Deploy but barriers
- Whole-genome sequencing for high-risk patients
- Whole-genome sequencing for all
- Gene testing for all with family member with CRC
- Colonoscopy and/or widespread screening and/or cost effectiveness
- Risk-adapted screening
- Streamline and coordinate care and communication
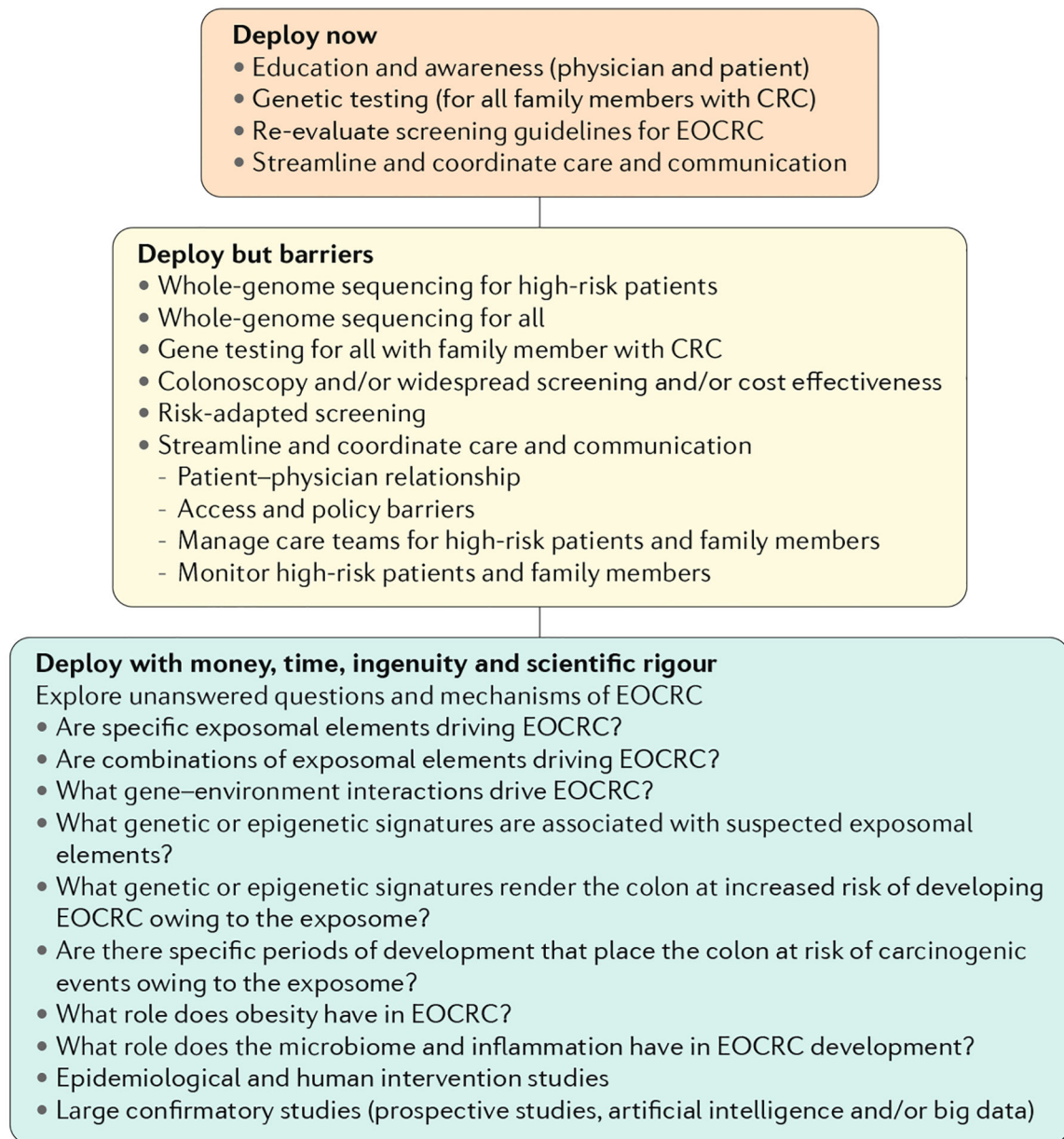 - Patient–physician relationship
  - Access and policy barriers
  - Manage care teams for high-risk patients and family members
  - Monitor high-risk patients and family members

Deploy with money, time, ingenuity and scientific rigour
Explore unanswered questions and mechanisms of EOCRC
- Are specific exposomal elements driving EOCRC?
- Are combinations of exposomal elements driving EOCRC?
- What gene–environment interactions drive EOCRC?
- What genetic or epigenetic signatures are associated with suspected exposomal elements?
- What genetic or epigenetic signatures render the colon at increased risk of developing EOCRC owing to the exposome?
- Are there specific periods of development that place the colon at risk of carcinogenic events owing to the exposome?
- What role does obesity have in EOCRC?
- What role does the microbiome and inflammation have in EOCRC development?
- Epidemiological and human intervention studies
- Large confirmatory studies (prospective studies, artificial intelligence and/or big data)

Fig. 2 |. Solutions for EOCRC.
To address the rise in early-onset colorectal cancer (EOCRC), solutions can be deployed now, deployed with additional work to overcome barriers and deployed with money, time, ingenuity and scientific rigour. CRC, colorectal cancer.

Table 1 |

Exposomal elements driving EOCRC

Exposomal element	Temporal trend	Global trend	Effect on inflammation/microbiome or known effect on distal colon or rectum	Exposure during development (conception to adulthood)
Westernized diets	Yes[140]	Yes[140]	Yes[138,148]	Yes[129,130]
Red and processed meat	Yes[20,140,157,158]	Yes[20,140,157,158]	Yes[160,161,253,254]	Yes[20,157,158]
Obesity	Yes[101,103,140]	Yes[101,103,140]	Yes[108,109]	Yes[105–107]
Stress	Yes[118]	Yes[117]	Yes[255,256]	Yes[118,119,257]
Antibiotics	Yes[258]	Yes[168]	Yes[169–171]	Yes[162]
Synthetic dyes	Yes[186,200]	Yes[186,200]	Yes[192,193,259,260]	Yes[200]
Monosodium glutamate	Yes[261,262]	Yes[261,262]	Yes[201,202,263–265]	Yes[261]
Titanium dioxide	Yes[266]	Yes[266]	Yes[206,208,209,267]	Yes[206,207,266]
High-fructose corn syrup	Yes[210,215,268]	Yes[210,215,268]	Yes[216,269]	Yes[217]

Key exposomal suspects driving early-onset colorectal cancer (EOCRC) emerge when four metrics are fulfilled: first, a temporal relationship exists, similar to EOCRC; second, exposure is global, as is EOCRC; third, molecular evidence exists of inflammatory or microbiome-modifying properties or evidence of an effect on the distal colon or rectum; and four, exposure occurs at any time during development from conception until adulthood.