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Impact of processed and ultra-processed foods on colorectal cancer risk: Mechanisms, dietary factors, and protective compound

Impacto dos alimentos processados e ultraprocessados no risco de câncer colorretal: Mecanismos, fatores dietéticos e compostos protetores

Impacto de los alimentos procesados y ultraprocesados en el riesgo de cáncer colorrectal: Mecanismos, factores dietéticos y compuestos protectores

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Abstract
Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide, linked to behavioral factors such as a sedentary lifestyle and smoking, environmental factors like pollution, and nutritional factors including a diet rich in red and processed meats. Some foods are associated with potential carcinogenicity, while others act as protective factors. This review aims to report the contribution of processed and ultra-processed foods to the etiopathogenesis of CRC and explore the role of protective diets. The article is an integrative review conducted in PubMed and VHL databases using the descriptors "colorectal cancer" and "processed foods." Studies published in the last five years addressing the relationship between these foods and CRC development were included. Potentially carcinogenic substances in processed foods, such as heterocyclic amines, nitrosamines, heme iron, industrial fatty acids, aromatic hydrocarbons, sialic acid sugar, and additives like titanium dioxide, were associated with colon and rectal neoplasms. Additional associations were found with the human microbiome, packaging materials, and food preparation methods. Conversely, several food components can protect against CRC. The consumption of processed and ultra-processed foods can significantly increase CRC risk through mechanisms like inflammation, oxidative stress, gene expression changes, and genetic material damage. The intestinal flora profile may be protective against CRC but is altered when processed and ultra-processed foods are included in the diet. Fiber, phytochemicals, and spices present in plant foods are consistently reported to have anticarcinogenic effects.
Keywords: Colorectal cancer; Processed foods; Neoplasm; Carcinogens.

Resumo
O câncer colorretal (CCR) é a terceira neoplasia maligna mais comum no mundo, relacionado a fatores comportamentais como sedentarismo e tabagismo, fatores ambientais como poluição, e fatores nutricionais como uma dieta rica em carnes vermelhas e processadas. Alguns alimentos estão associados a uma possível carcinogenicidade, enquanto outros atuam como fatores protetores. Esta revisão visa relatar a contribuição dos alimentos processados e ultraprocessados na etiopatogenia do CCR e explorar o papel das dietas protetoras. O artigo é uma revisão integrativa conduzida nas bases de dados PubMed e BVS utilizando os descritores "colorectal cancer" e "processed foods". Foram incluídos estudos publicados nos últimos cinco anos que abordam a relação entre esses alimentos e o

desenvolvimento do CCR. Substâncias potencialmente cancerígenas em alimentos processados, como aminas heterocíclicas, nitrosaminas, ferro heme, ácidos graxos industriais, hidrocarbonetos aromáticos, açúcar de ácido siálico e aditivos como dióxido de titânio, foram associadas a neoplasias de cólon e reto. Associações adicionais foram encontradas com o microbioma humano, materiais de embalagem e métodos de preparo dos alimentos. Por outro lado, vários componentes alimentares podem proteger contra o CCR. O consumo de alimentos processados e ultraprocessados pode aumentar significativamente o risco de CCR por meio de mecanismos como inflamação, estresse oxidativo, mudanças na expressão gênica e danos ao material genético. O perfil da flora intestinal pode ser protetor contra o CCR, mas é alterado quando alimentos processados e ultraprocessados são incluídos na dieta. Fibras, fitoquímicos e especiarias presentes em alimentos vegetais são consistentemente relatados por seus efeitos anticarcinogênicos.
Palavras-chave: Câncer colorretal; Alimentos processados; Neoplasia; Carcinógenos.

Resumen
El cáncer colorrectal (CCR) es la tercera neoplasia maligna más común a nivel mundial, vinculado a factores conductuales como el estilo de vida sedentario y el tabaquismo, factores ambientales como la contaminación y factores nutricionales como una dieta rica en carnes rojas y procesadas. Algunos alimentos están asociados con una posible carcinogenicidad, mientras que otros actúan como factores protectores. Esta revisión tiene como objetivo informar sobre la contribución de los alimentos procesados y ultraprocesados en la etiopatogenia del CCR y explorar el papel de las dietas protectoras. El artículo es una revisión integradora realizada en las bases de datos PubMed y VHL utilizando los descriptores "colorectal cancer" y "processed foods". Se incluyeron estudios publicados en los últimos cinco años que abordan la relación entre estos alimentos y el desarrollo del CCR. Las sustancias potencialmente carcinógenas en los alimentos procesados, como las aminas heterocíclicas, las nitrosaminas, el hierro hemo, los ácidos grasos industriales, los hidrocarburos aromáticos, el azúcar de ácido siálico y los aditivos como el dióxido de titanio, se asociaron con neoplasias de colon y recto. Se encontraron asociaciones adicionales con el microbioma humano, los materiales de envasado y los métodos de preparación de alimentos. Por otro lado, varios componentes alimenticios pueden proteger contra el CCR. El consumo de alimentos procesados y ultraprocesados puede aumentar significativamente el riesgo de CCR a través de mecanismos como la inflamación, el estrés oxidativo, los cambios en la expresión génica y el daño al material genético. El perfil de la flora intestinal puede ser protector contra el CCR, pero se altera cuando se incluyen alimentos procesados y ultraprocesados en la dieta. Las fibras, los fitoquímicos y las especias presentes en los alimentos vegetales son reportados consistentemente por sus efectos anticancerígenos.
Palabras clave: Cáncer colorrectal; Alimentos procesados; Neoplasia; Carcinógenos.

1. Introduction

Colorectal cancer (CRC) is the third most common neoplasm worldwide and the second leading cause of cancer-related mortality2 (Katsidzira et al., 2018; El Kinany et al., 2022). It's a malignant proliferation with disorganized and uncontrollable cell growth and can invade adjacent tissues or organs at a distance. The CRC is related to behavioral, environmental, and nutritional factors (Watson et al., 2022), which is reflected in the geographic variation of its incidence.

The CRC incidence has been increasing, along with mortality rates, in underdeveloped and developing countries, linked to social and economic development (El Kinany et al., 2022). Therefore, it is crucial to determine modifiable risk factors related to incidence and survival (Sofi et al., 2019). The characteristics of the tumor, as well as the etiology of CRC, may differ according to anatomical location. Still, there are few data on dietary associations and the subtypes of this cancer (Bradbury, Murphy & Key, 2019). As the global consumption of processed and ultra-processed foods rises, it is essential to comprehend their negative impacts and encourage diets that mitigate the risks linked to CRC. This understanding can shape public policy, train healthcare providers, and educate the public on healthier food choices.

Fiber-rich foods, non-starchy products, fruits, milk, calcium, and vitamin D have been associated with reduced risk of developing cancer (Katsidzira et al., 2018; Sofi et al., 2019). Processed and ultra-processed foods, industrially produced with food derivatives and additives, contain a lower proportion of whole foods, have low nutritional value, and are rich in unsaturated fatty acids (UFA) (Pu et al., 2023). These characteristics, designed to facilitate transportation and extend shelf life, are related to health damage, including CRC (Sofi et al., 2019; Pu et al., 2023).

The International Agency for Research on Cancer (IARC) classifies foods with carcinogenic potential into four

groups: carcinogens (group 1) - foods that have been proven to be associated with cancer risk; probably carcinogenic (group 2A) - foods whose evidence is not sufficient to prove their association; possibly carcinogenic (group 2B) – foods that may be associated with cancer, but evidence is limited – and foods not classified for cancer risk (group 3). Red meat was classified in 2023 as probably carcinogenic (2A), while a variety of processed and ultra-processed foods was arranged between groups 1 and 2A of the list of carcinogenic foods.

According to the Food Processing Classification System (NOVA), foods are divided into 4 groups (Kliemann et al., 2023). They are classified as: unprocessed or minimally processed foods (NOVA 1) - natural foods altered or not by freezing, pasteurization, and other processes without added substances, such as dried or frozen fruits and vegetables; Processed Culinary Ingredients (NOVA 2) - substances obtained directly from food; processed foods (NOVA 3) – industrial products produced using methods such as bottling and canning, such wines, beers and smoked fish; and ultra-processed foods (NOVA 4) - substances made from a series of industrial processes and with the addition of salt, sugar, and fats, such as processed meats, soft drinks, and chocolates (Kliemann et al., 2023).

Given the high incidence, severity and lethality of CRC, this review aims to report the contribution of processed and ultra-processed foods in the etiopathogenesis of CRC, as well as explore the role of protective diets.

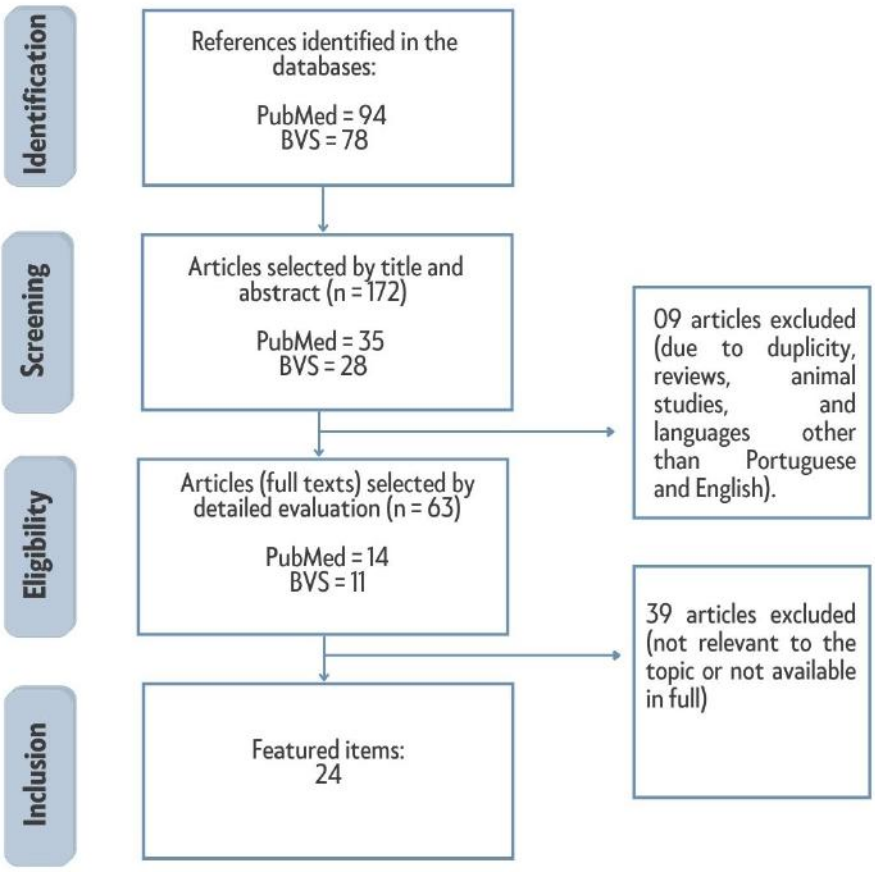
2. Methodology

This integrative review, according to the steps proposed by Sousa et al. (2021), was elaborated based on searches in PubMed and Virtual Health Library (VHL) databases, using the descriptors colorectal cancer and processed foods, connected by the Boolean operator "and". The search resulted in 94 and 78 articles, respectively. The inclusion criteria were full-open access articles, in English and Portuguese, published in the last five years prior to the research date (2023) and relevant to the theme involving the relationship between processed foods and CRC. Duplicate publications, those inconsistent with the objective of the research, and/or those showing biases, as well as integrative reviews, case reports, theses, and animal experimentation studies were excluded.

The initial analysis was performed by title, keywords and abstract, and 35 publications were selected from the PubMed databases and 28 from the VHL. After reading the articles in full, 24 publications were chosen as bibliographic references for this review (Figure 1).

Due to the breadth of subtopics and substances discussed, a categorization was implemented to organize the content effectively: (i) potentially carcinogenic substances involved in the risk of CRC, encompassing compounds, additives, and methods of food preparation/packaging, (ii) alterations to the microbiome relevant to CRC, (iii) epigenetic alterations associated with CRC, and (iv) CRC-protective food components.

Figure 1 - PRISMA flowchart of the applied methodology.



Source: Author's collection.

3. Results and Discussion

Potentially carcinogenic substances involved in the risk of CRC

Several characteristics of ultra-processed food products may contribute to the onset of cancer, including the addition of potentially carcinogenic substances to make the food more palatable, cooking methods and packaging (Figure 2). In addition, before being marketed, products go through industrial processes that include hydrogenation, hydrolysis, extrusion, molding, remodeling, and pre-processing by frying, as well as the addition of emulsifiers, colorants, flavorings, sweeteners, and numerous other additives (Kliemann et al., 2023; Fiolet et al., 2018). Thus, ultra-processed foods stand out for their high content of total and saturated fats, sugar, and salt, high energy density, and low nutritional quality. Obesity, cancer, and other persistent, non-communicable diseases can be exacerbated by these traits.

Other substances found in ultra-processed foods are fatty acids, generated by chemical processes to hydrogenate oils to facilitate transportation and storage. Among these, only trans fatty acids or those from industrial products, found in hydrogenated oils and snacks, showed an association with an increased risk of CRC. However, there was no significant correlation with fatty acids found in natural products, such as dairy products and meat. The possible mechanisms related to neoplastic formation induced by these fatty acids include increased cell proliferation, anti-apoptotic mechanisms, and cell invasion, as well as pro-inflammatory and pro-carcinogenic actions (Seyyedsalehi et al., 2022).

Figure 2 - Carcinogenic substances, additives and constituents of packaging associated with the development of colorectal cancer.

Potentially carcinogenic substances	Food Additives
Industrial fatty acids	Titanium dioxide
Sialic acid sugar	Polysorbate 80
Nitrosamines	Carboxymethylcellulose
Nitrous compounds	Nitrates and nitrites
Aromatic hydrocarbon	**Constituents of packaging**
Heme iron	Bisphenol A
Heterocyclic amines	Ethyhexyl phthalate

Source: Author's collection.

Peroxidized lipids and hemoproteins derived from excessive consumption of red and processed meat induce the generation of reactive oxygen species (ROS) in the digestive tract. These ROS are responsible for initiating lipid peroxidation in the membranes of colonic epithelial cells, a process involved in the etiology of colon carcinogenesis (Morales et al., 2018). The hemeprotein present in red meat catalyzes nitrosation in nitrolyzed heme (N-heme), forming N-nitroso compounds (NOCs) which are a potential risk factor for colon carcinogenesis (van Breda et al., 2021). The binding of nitric oxide to the central iron atom of the heme molecule is a pH-dependent process, so it is assumed that the slightly acidic conditions prevailing in the proximal colon can trigger its release, inducing other pro-carcinogenic effects. Furthermore, heme iron can lead to intestinal carcinogenesis through induction of colonic and preneoplastic cell hyperproliferation, modulation of immune cells, and promotion of intestinal dysbiosis (Wang et al., 2022).

Sialic acid sugar (Neu5Gc) is a negatively charged nine-carbon monosaccharide found at the ends of carbohydrate chains (glycans), glycoproteins and glycolipids, abundant in red meat and dairy products (Bashir et al., 2021). This sugar can be synthesized by most mammals but is not synthesized by humans. A study on humans demonstrated the presence of polyclonal anti-Neu5Gc antibodies produced against epitopes containing Neu5Gc in human tissues (Bashir et al., 2021). These IgG antibodies against to Neu5Gc could serve as biomarkers of carcinoma, and their high levels have been associated with an increased risk of CRC (Bashir et al., 2021).

Most ultra-processed foods contain many additives in their preparation. Although the maximum permitted level does not normally pose an individual risk, the cumulative intake of processed foods can lead to damage to genetic material. Among these additives, titanium dioxide, a substance used as a bleaching agent, with antimicrobial properties and the ability to improve food texture, has been associated with the development of inflammatory bowel processes and pre-neoplastic colonic lesions (Kliemann et al., 2023). Sugars added to food during preparation may also be associated with an increased risk of colon cancer, as excessive sugar intake can lead to insulin resistance and an increase in oxidative markers, stress, and DNA damage (Wang et al., 2022).

Nitrites and nitrates are also commonly added to food as preservatives to extend shelf life and prevent bacterial growth, or as colorants to give processed meats a red color. Studies show that both nitrites and nitrates, when transformed into

nitrites by the oral microbiota, lead to the formation of NOCs (N-nitroso compounds). When NOCs are activated by cytochrome P450 liver enzymes, they can become potential carcinogens (Niedermaier et al., 2023).

Food preparation strongly influences its carcinogenic potential. Ultra-processed foods and red meats, when heat-treated because of the Maillarde reaction, undergo the formation of neoformed contaminants. Some of these contaminants are potentially carcinogenic, such as acrylamide, heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) (Kliemann et al., 2023). Regarding red meat, there is also the formation of a specific mutagen, 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline (MeIQX) (Mosley et al., 2020), which together with the formation of carcinogenic nitrosamines generated by the process of carbonization or cooking at high temperatures, is associated with CCR17 (Fiolet et al., 2018). HCAs and PAHs are generated during high-temperature cooking of meat, the metabolites of which can cause DNA damage (Chazelas et al., 2022). The mutagenic activity of these reactive metabolites varies based on several factors, such as the cooking method, cooking time and temperature, as well as depending on the bioactivity of specific enzymes in the body (Mosley et al., 2020). HCAs become capable of damaging DNA when they are activated by specific enzymes in the body. The bioactivity of these enzymes differs between people and may contribute to the cancer risk associated with exposure to HCAs. A potential mechanism of mutagenicity of HCAs and PAHs is the formation of DNA adducts (covalent bonds of substances to DNA) (Chazelas et al., 2022; Boldo et al, 2022).

In addition to the substances contained in food and the processes used to prepare it, packaging can have carcinogenic and endocrine disrupting properties when in contact with food. Among the constituents of packaging are bisphenol A and ethylhexyl phthalate (Kliemann et al., 2023; Fiolet et al., 2018). It is suspected that these contaminants may migrate from plastic packaging to food compounds, something that is corroborated by the presence of increased urinary levels of phthalates (Viennois & Chassaing, 2021). These substances have been associated with the proliferation of cancer cells and the weakening of the inhibition capacity of the chemotherapeutic agent camptothecin, factors that may be related to its carcinogenic potential (Viennois & Chassaing, 2021).

Microbiome changes relevant to CRC

The human microbiome has around 30 trillion bacteria, being altered by the environment and the relationship between the host and symbiotic organisms. The microflora, mostly composed of the Firmicutes and Bacteroides phyla, can produce metabolites and bioproducts, promoting a protective effect against the infiltration of intestinal pathogens and the development of pathologies. Compromise of the microbiota, in turn, can lead to dysbiosis, associated with tumorigenesis (Dacrema et al., 2022).

Therefore, some components of the diet, such as saturated fats, processed carbohydrates, red meat, and ultra-processed foods, associated with changes in the microbiome, can lead to inflammation, a factor known as a driver of carcinogenesis, and associated with CRC (Dacrema et al., 2022). Such factors increase the local pro-inflammatory potential, which, in turn, favors carcinogenesis by altering the cell proliferation/apoptosis balance (Viennois & Chassaing, 2021). Dietary emulsifiers, another subtype of additive, are added to processed foods to promote stability and improve texture. Two of these were related to CRC: Carboxymethylcellulose (CMC) and Polysorbate 80 (P80). Both interact and alter the intestinal microbiota, promoting, respectively, inflammation of the intestinal mucosa and increased bacterial translocation in the epithelium (Viennois & Chassaing, 2021). Hydrogen sulfide (H2S), one of the metabolites arising from the microbial metabolism of sulfur-containing foods, is a potentially pro-carcinogenic substance (Nguyen et al., 2020). Intestinal colonization of H2S-producing bacteria is mainly associated with processed meats and some preservatives, providing a high risk of CRC.

Evidence has shown that the consumption of red meat causes the enrichment of *Alistipes* and *Oscillibacter* microbiota, which are resistant to bile and putrefactive (Farsi et al., 2023). *Alistipes* bacteria are associated with both health and disease, while *Oscillibacte*r is linked to weight gain, metabolic dysfunction, and leaky gut (Santos & Padilha, 2022). When replacing red meat in the diet with mycoprotein, an alternative to meat, rich in fiber and produced from the fungus *Fusarium venenatum*, an increase in the relative abundance of the genera of bacteria *Lactobacilli*, *Roseburia*, and *Akkermansia* was observed (Farsi et al., 2023).

Lactobacilli bacteria exert significant protection against chemically induced tumors and enhance intestinal barrier function, improving tight junction integrity and increasing colonic mucin production (Farsi et al., 2023). The butyrate-producing *Roseburia* bacteria, which had reduced abundance after meat consumption, suppresses intestinal inflammatory processes and is reduced in CRC. The *Akkermansia* bacteria acts by degrading intestinal mucin, paradoxically increasing cellular mucus production (Farsi et al., 2023).

Epigenetic changes associated with CRC

Epigenetics is the study of mechanisms related to reversible changes in gene expression that do not involve changes in the DNA sequence. Imbalances in epigenetic phenomena are related to cancer, through alterations such as DNA methylation and histone modifications, which can modify the expression of oncogenes and tumor suppressor genes, leading to the development of neoplasms (Santos & Padilha, 2022). Epigenetic modifications such as hypermethylation of the MLH1 gene result in the loss of the nitrogenous base repair system, and this event may be a longitudinal biomarker of CRC (Khil et al., 2021).

Four genes (*GREM, CA7, AKR1B10* and *RASAL1*) play roles in the colon and/or CRC due to changes in gene expression after consumption of processed red meat. The *CA7*, *AKR1B10* and *RASAL1* genes are involved in the development of CRC, while the *GREM2* gene interferes with the differentiation of normal colonic tissue. The downregulated *CA7* gene encodes a metalloenzyme that catalyzes the conversion of CO2 into bicarbonate ions and protons, a reaction involved in tumorigenicity. Its expression is downregulated in CRC, both at the level of messenger RNA (mRNA) and at the level of protein. Low levels correlate with the progression of CRC and an unfavorable clinical prognosis, due to reduced cell differentiation and reduced protection against oxidative stress. The *AKR1B10* gene encodes an oxidoreductase enzyme of the aldo-keto reductase superfamily. This enzyme catalyzes the reduction of electrophilic carbonyl compounds to less toxic alcoholic metabolites, protecting the intestinal cells against DNA damage. *AKR1B10* is expressed specifically in the small intestine and colon and is directly regulated by tumor suppressor protein p53. However, consumption of processed red meat leads to and is downregulated of *AKR1B10*. This downregulation may contribute to the development of CRC and worsen the clinical prognosis by inhibiting p53-induced apoptosis and the loss of proliferative suppression of cancer cells (van Breda et al., 2021). Furthermore, there is a negative correlation between the consumption of red meat and the expression of the *TP53* gene, which is responsible for encoding the p53 protein (Khil et al., 2021). The consumption of processed red meat has been shown to upregulate the *RASAL1* gene, which plays a crucial role in controlling cell proliferation and differentiation. On the other hand, processed red meat consumption to the downregulation of the *GREM2* gene, which expresses a protein that acts as an antagonist of BMP (bone morphogenic protein) signaling, thereby inhibiting of differentiation of basal crypt epithelial cells (van Breda et al., 2021).

CCR protective food components

Antioxidant compounds, present mainly in fruits and vegetables, act as natural inhibitors of the formation of NOCs,

therefore, they can reduce the carcinogenic potential of nitrites and nitrates (Chazelas et al., 2022). In addition to this mechanism, these substances can also contribute to reducing the formation of mutagens resulting from lipid peroxidation, reducing oxidative stress in colonic cells, and preventing CCR (Kliemann et al., 2023). A diet enriched with legumes and other vegetables may be associated with a decrease in sulfur-metabolizing bacteria. Such foods are also a rich source of glucosinolates, compounds with anti-inflammatory effects and possibly preventive properties for carcinogenesis, associated with a reduced risk of CRC and colorectal adenomas (Nguyen et al., 2020).

The fermentation of plant foods rich in soluble fibers such as fructooligosaccharides and inulin, by colonic bacteria, increases short-chain fatty acids (acetic, propionic, and butyric) in the intestine. These substances are associated with the inhibition of histone deacetylase and the promotion of apoptosis, related factors to antineoplastic activity. Furthermore, it also increases activated microbial phytochemicals, with anti-inflammatory and antioxidant properties, related to protection against cancer (Kliemann et al., 2023).

Soluble fibers also prevent bacterial adhesion and translocation in the colonic epithelium, thus blocking inflammation and epithelial changes caused by it. It was observed that the protective effect of fiber is mainly due to pectin, present in this food group. Pectins are rapidly fermented in the colon, mediated by the action of the intestinal epithelium itself, becoming a barrier to bacterial effects (Rhodes, 2020).

Biologically active compounds, also called phytochemicals, include a wide range of chemical classes such as tocopherols, flavonoids, carotenoids, glycolic alkaloids, and vitamins. Its beneficial effects occur through different mechanisms, including the inhibition of NOC formation, effects on the kinetics of carcinogenic compounds in the colon, and the level of cellular protection (van Breda et al., 2021). Phytochemicals, fiber, and spices can also modulate microbial cells and prevent their adhesion to the epithelium and translocation, protecting colonic cells from inflammation and cancer (Rhodes, 2020).

Rutin (3,3',4',5,7-pentahydroxyflavone-3-rutinoside), a plant flavonoid derived from quercetin, is mainly present in buckwheat, parsley, tomatoes, wine, and apricots. In the colon, the microflora releases quercetin from rutin, which will be absorbed or degraded, resulting in fission products such as 3,4-dihydroxyphenylacetic acid (DHPAA), 3,4-dihydroxybenzoic acid (protocatechuic acid: PCA) and 3,4-Dihydroxytotulene (DHT). These products appear to exert a cancer-preventive effect through a variety of molecular mechanisms, including antioxidant action (Morales et al., 2018). Treatment of cells with quercetin and DHT had a protective effect against lipid peroxidation and significantly elevated the level of the protein Nrf-2 (Prx-6 protein transcription factor), possibly involved in the antioxidant defense of the intestinal mucosa (Morales et al., 2018).

Another food group associated with anti-cancer effects is spices, such as turmeric, black cumin, ginger, ginseng, garlic, and black pepper. Due to their natural aromatic bioactives (curcumin, thymoquinone, piperine, and capsaicin), they appear to inhibit the development of CRC. They do this by regulating the intestinal microbiome and effects such as reducing oxidative stress, the inflammatory cascade, and apoptosis, as well as regulating epigenetics. These aromatic substances also have antioxidant and anti-inflammatory properties, stimulate digestion, lower lipid levels, and possess antilithogenic, and antidiabetic properties, factors contribute to their antimutagenic and anticarcinogenic potential (Dacrema et al., 2022).

Table 1 presents the research corpus, listing the articles selected after a thorough filtration process. The table includes details such as the title, reference, goals and conclusions of investigation of processed and ultra-processed foods in the etiopathogenesis of colorectal cancer.

Table 1 - Presentation of the synthesis of articles organized by title, reference, objectives and conclusions.

Title	Reference	Goals	Conclusions
Inhibitory effect of catecholic colonic metabolites of rutin on fatty acid hydroperoxide and hemoglobin dependent lipid peroxidation in Caco-2 cells.	Mukai *et al.*, 2018	This study aims to evaluate the antioxidant effect of catechol-type colonic metabolites of rutin on lipid peroxidation in colon epithelial cells.	Among the colonic metabolites of rutin, 3,4-dihydroxytoluene (DHT) has been identified as a possible candidate to suppress oxidation damage to intestinal epithelial cells.
Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort.	Fiolet *et al.*, 2018	To assess the prospective associations between consumption of ultra-processed food and risk of cancer.	In this large prospective study, a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer. Further studies are needed to better understand the relative effect of the various dimensions of processing (nutritional composition, food additives, contact materials, and neoformed contaminants) in these associations.
Dietary patterns and colorectal cancer risk in Zimbabwe: A population based case-control study.	Katsidzira *et al.*, 2018	The study sought to establish the association between dietary patterns and colorectal cancer in Zimbabwe.	A shift away from protective, traditional African dietary patterns may partly explain the rising incidence of colorectal cancer in sub-Saharan Africa.
Dietary and lifestyle associations with microbiome diversity.	Morales *et al.*, 2018	To evaluate the interaction between the patient's clinical factors, their oral, fecal and mucosal microbiome and adenoma burden, through a cohort of patients undergoing screening colonoscopy.	Associations were shown between dietary habits, the mucosal microbiome and the modifiable risk for adenoma formation and development of colorectal neoplasia.
Fecal microbiome as determinant of the effect of diet on colorectal cancer risk: comparison of meat-based versus pesco-vegetarian diets (the MeaTIc study).	Sofi *et al.*, 2019	To test in a randomized clinical trial whether the effects of diet on colorectal cancer risk are mediated by interaction with the intestinal microbiota, and whether meat-based and pesco-vegetarian diets have different modulation of risk biomarkers.	At the time of writing, there were no studies available that evaluated the effects on colon carcinogenesis of a meat-based diet and a diet that excludes meat and meat products but includes fish. The objective of the project will be to understand the role of the intestinal microbiota as a determinant of this effect.
Diet and colorectal cancer in UK Biobank: a prospective study	Bradbury *et al.*, 2019	The objective of the current study is to systematically examine the associations of colorectal-cancer risk with the intake of foods and food groups included in the short food-frequency touchscreen questionnaire: meat, fish, fruit, vegetables, milk, cheese, alcohol, tea and coffee, as well as fibre intake, and to use re-measured dietary intakes to quantify the risk at actual levels of intake in UK Biobank. They also examined the associations between intakes of food and food groups with anatomical sub-sites of colorectal cancer.	Consumption of red and processed meat at an average level of 76 g/d that meets the current UK government recommendation (≤90 g/day) was associated with an increased risk of colorectal cancer. Alcohol was also associated with an increased risk of colorectal cancer, whereas fibre from bread and breakfast cereals was associated with a reduced risk.
Meat intake, meat cooking methods, and meat-derived mutagen exposure and risk of sessile serrated lesions.	Mosley *et al.*, 2020	Meat doses, cooking methods and inferred mutagenic effects with the risk of serrated sessile lesion (SSR) - CRC's precursor - were evaluated in comparison to the risk of other polyps.	Ingestion of large amounts of red and processed meats is strongly associated with the risk of SSL and part of the association may be due to the intake of heterocyclic amine – formed during cooking.
Association between Neu5Gc carbohydrate and serum antibodies against it provides the molecular link to cancer: French NutriNet-Santé study	Bashir *et al.*, 2020	To investigate the dietary effects on the global burden of worldwide CRC, and the effects of N-glycolylneuramine (Neu5Gc) - a carbohydrate derived from red meat - on the levels of IgG anti-Neu5Gc antibodies in humans.	There is a dose-dependent positive effect between Neu5Gc and circulating anti-Neu5Gc antibody levels. . High levels of anti-Neu5Gc IgG have been suggested to increase the risk of CRC.
Nutrition and gut health: the impact of specific dietary components – it's not just five-a-day. Proceedings of the Nutrition Society.	Rhodes *et al.*, 2020	Analysis of the impact of specific food components on intestinal health, and their relationship with colorectal cancer.	The literature review shows some associations such as: dietary fibers can act as prebiotics; dietary fructans may have a pro-inflammatory effect; and emulsifiers can increase bacterial translocation and alter the microbiota.

Association Between Sulfur-Metabolizing Bacterial Communities in Stool and Risk of Distal Colorectal Cancer in Men.	Nguyen *et al.*, 2020	They identified a dietary pattern associated with sulfur-metabolizing bacteria in stool and then investigated its association with risk of incident CRC using data from a large prospective study of men.	In an analysis of participants in the Health Professionals Follow-up Study, we found that long-term adherence to a dietary pattern associated with sulfur-metabolizing bacteria in stool was associated with an increased risk of distal CRC. Further studies are needed to determine how sulfur-metabolizing bacteria might contribute to CRC pathogenesis.
Replacement of Nitrite in Meat Products by Natural Bioactive Compounds Results in Reduced Exposure to N-Nitroso Compounds: The PHYTOME Project.	Breda *et al.*, 2021	This study evaluates the effect of consumption of red meat products with reduced nitrite levels and enriched with phytochemicals on exposure to N-nitroso compounds (NOCs) - a potential risk factor for CRC - in the human diet.	The introduction of natural bioactivated compounds associated with reduced amounts of nitrite in meat products results in a decrease in the formation of NOCs.
Consumption of Select Dietary Emulsifiers Exacerbates the Development of Spontaneous Intestinal Adenoma.	Viennois *et al.*, 2021	Investigate the impact of dietary emulsifier consumption on cancer initiation and progression in a genetic model of intestinal adenomas.	The responses reinforce the hypothesis that emulsifiers may be a modifiable risk factor for colorectal cancer and that changes in the interaction between microbiota and host may favor gastrointestinal carcinogenesis in genetically predisposed individuals.
Time trends of colorectal cancer incidence and associated lifestyle factors in South Korea.	Khil *et al.*, 2021	Identify predominant factors underlying the escalating incidence rates of CRC in South Korea.	Patterns in CRC incidence and major etiologic contributors may be highly heterogeneous by sex and age in South Korea. While decreasing physical activity appears to be a common driver of increasing CRC across all sex and age groups of South Koreans, obesity and alcoholic drinks may be more relevant CRC contributors to men, and processed meat to middle-aged adults. Efforts to increase calcium intake and CRC screening uptake may help control increasing distal colon cancer in South Korea.
The role of diet in genotoxicity of fecal water derived from IBD patients and healthy controls.	Wang *et al.*, 2022	This study compares fecal water from patients with inflammatory bowel disease and healthy controls to investigate the direct effect of DNA damage disease on epithelial cells, and its potential protective effects against hydrogen peroxide-induced DNA changes. The study also investigated the association between fecal water genotoxicity, gut inflammation, and dietary factors.	The presence of intestinal inflammation was associated with increased fecal water genotoxicity. The results of the food intake analysis indicate the potential of dietary factors for patients with the disease to prevent CRC.
Meat Intake, Cooking Methods, Doneness Preferences and Risk of Gastric Adenocarcinoma in the MCC-Spain Study.	Boldo *et al.*, 2022	Elucidate the role of meat intake in the incidence of GAC, including type of meat, meat cooking methods and doneness preferences, overall and by histological subtypes and anatomical subsites, within the MCC-Spain multicase–control study.	Reducing red and processed meat intake could decrease gastric adenocarcinoma risk, especially for intestinal and non-cardia tumors. Meat cooking practices could modify the risk of some gastric cancer subtypes.
Nitrites and nitrates from food additives and natural sources and cancer risk: results from the NutriNet-Santé cohort.	Chazelas *et al.*, 2022	The objective was to investigate the relationship between nitrate and nitrite intakes (natural food, water and food additive sources) and cancer risk in a large prospective cohort with detailed dietary assessment.	Food additive nitrates and nitrites were positively associated with breast and prostate cancer risks, respectively. Although these results need confirmation in other large-scale prospective studies, they provide new insights in a context of lively debate around the ban of these additives from the food industry.
Spice-Derived Bioactive Compounds Confer Colorectal Cancer Prevention via Modulation of Gut Microbiota.	Dacrema *et al.*, 2022	This study is designed to summarize the reciprocal interactions between dietary spices and the gut microbiota, and highlight the impact of dietary spices and their bioactive compounds on colorectal carcinogenesis by targeting the gut microbiota.	The available literature data suggest that spices and their phytochemicals could be one of the dietary factors that may prevent the risk of CRC development by affecting tumor behavior and targeting numerous molecular mechanisms. Thus, the exploration of other spice-derived phytochemicals is essential to provide further insights into the interesting relationship between spice-derived phytochemicals and gut microbiota in CRC.

Food processing groups and colorectal cancer risk in Morocco: evidence from a nationally representative case–control study.	El Kinany *et al.*, 2022	The aim of this study was to investigate the association between the consumption of foods and drinks from different food processing categories using the NOVA classification and CRC risk among Moroccan adults.	This is the first study to evaluate the association between the NOVA classification groups and CRC risk in an African country. Our results suggest that the consumption of ultra-processed foods and drink products may be associated with an increased risk of developing CRC, but longitudinal studies are needed to confirm these results.
Mecanismos Epigenéticos no Surgimento do Câncer: uma Revisão Bibliográfica.	Santos & Padilha, 2022	Carry out a literature review on the relationship between epigenetic mechanisms and the emergence of different types of cancer.	The results show that changes in DNA methylation in gene regions and CpG islands are related to the emergence of cancer.
Dietary Ruminant and Industrial Trans-Fatty Acids Intake and Colorectal Cancer Risk.	Seyyedsalehi *et al.*, 2022	Assessment of the relationship between the intake of industrial and ruminant trans fatty acids and the development of colorectal cancer.	Industrial fatty acids found in semisolid or solid hydrogenated oils may be associated with the risk of colorectal cancer, while ruminant fatty acids appear to be associated with a lower risk.
Impact of Reducing Intake of Red and Processed Meat on Colorectal Cancer Incidence in Germany 2020 to 2050—A Simulation Study.	Niedermaier *et al.*, 2023	Estimate the potential impact of a reduction in or elimination of red or processed meat intake on numbers of CRC cases in the German population from 2020 until 2050.	The reduction in red and processed meat intake would most likely have a modest positive impact on CRC incidence in Germany.
Prediagnosis ultra-processed food consumption and prognosis of patients with colorectal, lung, prostate, or breast cancer: a large prospective multicenter study.	Pu *et al.*, 2023	To evaluate the relationship between the consumption of ultra-processed foods before the diagnosis of colorectal, lung, prostate or breast cancer, and all-cause mortality.	Consumption of ultra-processed foods before diagnosis was significantly associated with an increased risk of all-cause mortality in lung and prostate cancer patients. Colorectal cancer showed a significant association in the group analysis only in stages I and II.
Food processing and cancer risk in Europe: results from the prospective EPIC cohort study.	Kliemann et al., 2023	This study investigated the association between dietary intake according to amount of food processing and risk of cancer at 25 anatomical sites using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study.	This study suggests that the replacement of processed and ultra-processed foods and drinks with an equal amount of minimally processed foods might reduce the risk of various cancer types.
Substituting meat for mycoprotein reduces genotoxicity and increases the abundance of beneficial microbes in the gut: Mycomeat, a randomised crossover control trial.	Farsi *et al.*, 2023	The study explores the effects of replacing red and processed meat with the ingestion of the mycoprotein, produced by the fungus *Fusarium venenatum*, on intestinal markers of genotoxicity and gut health.	Replacing red and processed meat with microprotein-rich meat significantly reduces fecal genotoxicity and genotoxin excretion and increases the abundance of microbial genera with purported gut health benefits.

Source: Author's collection.

4. Conclusion and Suggestions

The mechanisms related to neoplastic induction vary and include induction of cell proliferation, activation of anti-apoptotic mechanisms, pro-inflammatory actions, oxidative stress in cell membranes, changes in the intestinal microbiota, damage to genetic material, and epigenetic changes.

Diet has a major influence on the risk of developing CRC. Excessive consumption of ultra-processed foods, red meat, sugar, and certain dietary emulsifiers has been linked to carcinogenesis. In addition to the composition of the food, high temperatures cooking methods and the carcinogenic properties of the packaging also increase its carcinogenic potential.

Conversely, antioxidant compounds, primarily found in fruits and vegetables; biological compounds, known as phytochemicals, soluble fibers, and aromatic bioactives have been associated with protection against carcinogenesis. They reduce the formation of carcinogenic compounds and exhibit anti-inflammatory and antioxidant properties. Moderation in the consumption of processed foods and the regular inclusion of fiber- and phytochemical-rich plant foods are recommended.

Although this review highlights the significant role of processed and ultra-processed foods in the risk of developing colorectal cancer, further research is essential to understand the underlying mechanisms. Future studies should focus on the

long-term effects of specific additives and industrial ingredients, the interactions between dietary components and the human microbiome, and the impact of various food preparation methods on carcinogenic potential. Additionally, longitudinal cohort studies and randomized controlled trials are needed to establish causal relationships and to develop evidence-based dietary recommendations for CRC prevention. These insights will be crucial in formulating public health policies and nutritional guidelines aimed at reducing the global burden of colorectal cancer.

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