

Diet and Food chemicals increasing the risk of colorectal cancer – literature review

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ABSTRACT



Colorectal cancer is a common form of cancer nowadays. There are many risk factors in the pathogenesis of colorectal cancer. The malignant proliferation is caused by one or more genetic mutations, which activate oncogenes and deactivate tumor suppressor genes. Some factors cannot be changed, such as a person's age or family history. An essential aspect in the pathogenesis of colorectal cancer is the choice of lifestyles, such as a high-fat diet, smoking, and excess alcohol. Carcinogens can be either natural or chemical. The mechanisms by which carcinogens initiate tumor formation are genetic or non-genotoxic. The most common form of colorectal cancer is found in people who ingest chemicals that, once ingested, reach the large intestine, thus causing malignant lesions. The Western diet and the metabolic syndrome are risk factors for colorectal cancer, due to gut microbiota changes and low-grade chronic inflammation. Among the most important diet carcinogens are nitrosamines, hydrazines, organophosphates, acetaldehyde, and heterocyclic amines. Screening programs, especially among people over 50 years of age, and with multiple risk factors are extremely important in detecting colorectal cancers in the early stages and in improving the long-term prognosis in such patients.

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Introduction

Colorectal cancer is currently the third type of cancer in terms of prevalence worldwide, with 1.93 million new CRC cases diagnosed in 2020. Its prevalence is on a continuously ascending trend, the statistics models estimate around 3.2 million new cases in 2040 [1]. Despite the benefits of global screening procedures that have led to a significant decline of CRC epidemiologic rates in the last decades, this type of cancer still remains a major cause of mortality worldwide [2].

In Romania, colorectal cancer is the most common gastrointestinal malignancy, representing the third leading cause of cancer death after lung and breast cancer [3]. Epidemiological studies showed that colorectal cancer is the second most common type of cancer in women and the third most common type of cancer in men, generating an increase in the number of operations and subsequent complications such as anastomotic leaks [4,5]. Consequently, the colorectal cancer represents a significant economic burden in the healthcare systems [6].

Recently, the Covid-19 pandemic overburdened the national healthcare systems, being considered the most severe sanitary crisis since the Spanish flu which occurred 100 years ago [7]. National healthcare systems reported significant delays and disruptions in the oncological screening programs and ambulatory routine check-ups [8-10]. There are concerns regarding the negative effects, resulting in more cases diagnosed as an emergency, in advanced stages and significant loss of years in the lives of these patients [8,11].

While some risk factors are related to the genetic predisposition, age, family history, there is strong evidence that the Western style diet, smoking, changes in gut microbiota and metabolic syndrome may play a significant role in carcinogenesis [12-14]. Most colorectal cancers start with a polyp. Some types of polyps can develop into cancer over several years, but not all types of polyps turn into cancer. The malignant proliferation is caused by one or more genetic mutations, which activate oncogenes and deactivate tumor suppressor genes. The incidence of synchronous colorectal cancers varies between 1.8% and

12.4% from the total amount of colon cancers [15]. In some cases, they are correlated with microsatellite instability (MSI), either inherited, such as Lynch syndromes, or by de novo mutations of the repair genes [16]. However, in many cases, the co-existence of gastrointestinal tumors is due to the chronic exposure to the same toxic agents along the gastrointestinal tract.

Discussion

The Western diet and the risk for colorectal cancer

Epidemiological data show the link between colon cancer and its distribution in certain geographical areas. Currently, large bowel cancer has the highest incidence of all human neoplastic diseases in the United States. It has an equally high incidence in other Western countries, while on the African continent, Central and West Latin America and Japan, it has a low incidence. In both high-risk and low-risk individuals, significantly different levels of certain key bacterial enzymes in the flora are even more important. There are significant differences in neutral sterols and bile acids, with the high-risk population having higher levels in their stools. Experimental studies revealed that animals on a high-fat diet excrete more neutral sterols and bile acids than control subjects. Bile acids exert a promoting effect on colon carcinogenesis in animal models, thus highlighting the possible role of bile acids in the development of human cancer [17-20].

The Western diet, rich in highly processed meat, fat and sugars is associated with changes in the gut microbiota, metabolic syndrome and insulin resistance. The chronic low-grade inflammation, involving multiple pathways, along with NLRP3 inflammasome, are associated with a favorable tumor microenvironment, tumor microenvironments having a great impact on tumor development and immunity, representing a key factor in the response to therapy [21,22]. While obesity is a well-known factor associated with an increased risk of colorectal cancer, the current knowledge is still scarce regarding the outcomes of obese patients who underwent bariatric surgery. Bariatric surgery is associated with a rapid improvement in insulin resistance, cholesterol level, arterial hypertension, as well as a decrease in systemic inflammation status [23]. However, some studies showed a higher risk for colorectal cancer in obese people that underwent bariatric surgery [24], while others experienced a significantly decreased risk [25,26].

The association between type II diabetes mellitus and digestive neoplasms has been on an upward trend lately due to common risk factors, as well as to mutually potentiating effects on the evolution of the two conditions. DM seems to be a risk factor for interval CRC and advanced adenomatous lesions by accelerating the colorectal epithelial proliferation rate [2,27].

Food chemicals and colorectal carcinogenesis

Carcinogenic factors play a special role in colorectal cancer. Carcinogens can be natural, such as aflatoxin, or they can be chemical, man-made. Carcinogens interact with the DNA of a cell and induce genetic mutations. As a result of these mutations, tumors appear, which have the ability to metastasize and cause the dysfunction of other tissues, culminating in organ failure and even death [28-30].

The mechanisms by which carcinogens initiate tumor formation are complex and may be classified as genetic mechanisms - consisting in producing DNA changes and triggering cell death, and non-genotoxic mechanisms - do not involve the interaction with the DNA, but produce immunosuppression and specific inflammation in the tissues [31,32].

Aside from grilled foods which have a charred coating, the foods that have been heat-treated contain preservatives or have been contaminated with pesticides; they all have the potential to cause colon cancer. The foods fried in the same oil that has already been used more than twice have been found to contain cancer-causing chemicals, due to the deterioration in the oil quality. When such chemicals accumulate in the body, it can increase the risk of cancer occurring in the digestive system [33-35].

Carcinogenic chemical compounds

Hydrazines

Two of these naturally occurring compounds are 1,1-dimethylhydrazine, a tobacco ingredient, and methylhydrazine, a chemical found in the wild edible fungus *Gyromitra esculenta*.

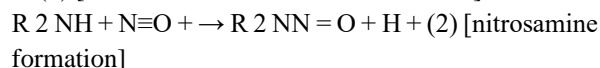
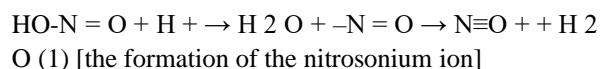
Therefore, the human population is considerably exposed to them. In addition, both compounds are manufactured and used in missile fuel. The other three chemicals, 1,2-dimethylhydrazine dihydrochloride, 1-methyl-2-butylhydrazine dihydrochloride and trimethylhydrazine hydrochloride, are only synthetically produced and, apparently, are not found in large amounts in the environment [36,37].

Nitrosamines

The consumption of foods treated with preservatives almost constantly causes the majority of the population to develop colon cancer. Food preservatives have an extremely high content of nitrites. The combination of nitrites and biogenic amines in the gut leads to the formation of nitrosamines, with a definite carcinogenic effect. Nitrosamines are a group of organic compounds that have a general structural formula: $R1N(-R2)-N=O$, which means that in their structure there is a nitrous group directly linked to an amine functional group. Most nitrosamines are carcinogenic, and are components of the cigarette smoke. One such example is dimethylnitrosamine $(CH_3)_2N-N=O$ [38].

Nitrosamines are obtained by reacting nitrites with a secondary amine, which may also be present in a protein structure [39]. This happens when protein foods containing nitrates or nitrites are cooked, such as meat products with preservatives E 249 to E 252. These additives are nitrites or nitrates, which, in turn, can be converted into nitrites.

Nitrosonium is the chemical species that will react with the amine to produce protonated nitrosamine which is then deprotonated by the solvent. The effect of high temperatures can also promote the formation of nitrosamines. By schematizing the whole reaction, the following two phases can be described:



Nitrosamines are chemical compounds with low or medium toxicity, but with an extremely high carcinogenic potential. They can be formed not only from exogenous sources (e.g., food), but also from endogenous sources (e.g., in the stomach). The *in vivo* (endogenous) formation occurs when exogenous or endogenous nitrate/ nitrite levels stay above 1 mg%. The synthesis of nitrosamines in the digestive tract takes place mainly in the stomach, where the acidic environment is conducive to the nitrosation process. At the intestinal level, even if the pH is close to neutral or under certain alkaline conditions, the nitrosation process can continue under the catalytic action of the microbial flora [40].

Fertilizing the soil with nitrogen fertilizers can lead to their accumulation in vegetables and later, after ingesting them and accumulating over time, the carcinogenic effect is very important.

Animal studies have shown that nitrosamines promote the development of stomach and pharyngeal cancer and are therefore suspected of causing it in humans [41]. Foods with the highest nitrate content are smoked foods. Cereals, alcoholic beverages and dairy products have an average nitrite content. The content in spinach, radish, beets is about ten times higher. Due to the infiltration of fertilizers into the soil, groundwater also has a high nitrogen content.

Nitrosamine metabolism

Nitrosamines formed in the gastrointestinal tract are absorbed into the blood at a level of 0.1 µg/ kg, depending on the amount of nitrogen products ingested with food or endogenously formed.

The metabolism of nitrosamines and their transformation into active metabolites takes place through enzymatic processes. Nitrosamines require metabolism for their biological actions and the enzymes involved have been considered to be somewhat atypical microsomal mixed function oxidases [42]. Many nitrosamines are metabolized by cytochromes P450, one of which

(P450IIE1) has received much attention because of its role in the metabolic activation of N-nitrosodimethylamine. In addition, P450IIE1 is the most active P450 species known in the metabolism of N-nitrosoethylmethylamine and N-nitrosopyrrolidine. P450IIB1 also catalyzes the alpha-oxygenation of both the pentyl and methyl groups of N-nitrosopentylmethylamine, forming pentaldehyde and formaldehyde at a rate ratio of 2:1, as well as oxygenation at other carbons of the pentyl group. Many nitrosamines are effectively activated in non-hepatic target tissues [43].

The appearance of malignant lesions caused by nitrosamines could be due to the formation of free radicals, as a result of their metabolism. For example, N-Methyl-N-nitrosamines are well-known carcinogens and DNA-methylating agents. DNA alkylation by this class of compounds involves metabolic oxidative activation, followed by decomposition to yield alkylating species. The natural product dephostatin, isolated from *Streptomyces*, is a tyrosine phosphatase inhibitor that contains the N-methyl-N-nitrosamine functional group. It has been suggested that the inhibition of tyrosine kinases resulted from the nitroso group-transfer to a cysteine thiol of these enzymes. It can serve as a substrate for appropriate oxygenases, alkylation of DNA and other biomolecules by this natural product is a possibility. In addition, the semiquinone form may decompose with the loss of nitric acid which, in the presence of molecular oxygen, can cause DNA damage [44].

Nitrosamine toxicity

Bartzatt et al. demonstrated that the toxic effect of nitrosamines can be established immediately *in vivo*, leading to the alkylation of substrates [45]. Pei XF shows that nitrosamines have had the effect of DNA synthesis in a number of cultures. The carcinogenic potential of nitrosamines has been tested in laboratory animals [46]. The results showed that only the esophagus is affected [45].

Acute nitrosamine toxicity and the carcinogenic potential were determined on rat studies [47]. Thus, certain nitrosamines have extremely high toxicity: for imethylnitrosamine LD50 is 40 mg/ kg, and for diethylnitrosamine LD50 is 200 mg/ kg. Other nitrosamines are very toxic: methylnitrosamine (LD50 is 18 mg/ kg). the nitrosamines with the lowest toxicity are ethyl-2-hydroxyethylnitrosamine (LD50 7,500 mg/ kg), di-2-hydroxyethylnitrosamine (LD50 5,000 mg/ kg), nitrosoprolidine (LD50 900 mg/ kg).

The higher the toxicity and concentration of nitrosamines, the shorter the time of the onset of malignancies. For the same type of nitrosamines, at low concentrations, the appearance of tumors occurs after a long period (1.5-2 years). However, the exact doses of nitrosamines that cause carcinogenicity are not known. Nitrosamines have a specific carcinogenic effect on each organ. Thus, dimethylnitrosamine causes nasal sinus

cancer, liver cancer and kidney cancer, and diethylnitrosamine causes lung cancer. Dibutylnitrosamine causes bladder cancer and ethylbutylnitrosamine leads to gastric cancer [48-50].

No specific treatment exists for nitrosamine intoxication. Supportive and symptomatic treatment should be provided. Since nitrosamines and their precursors are present in the food, exposure to nitrosamines cannot be avoided.

Undergoing colon screening can help reduce the rate of fatalities that occur from this form of cancer. Such screening is especially advisable for high-risk groups, such as people with a family history of cancer or those who enjoy foods that may trigger the occurrence of cancer.

Other chemicals involved in colorectal cancer

The Organophosphate (OPEs) compound can be found as a pesticide, in contaminated fruits and vegetables. Surveys have found that out of the insecticides used in the agricultural industry, the most common ones are those containing organophosphate [51,52]. The studies about the potential association between OPEs and gastrointestinal cancer were limited. However, a recent study by Li et al. found that the elderly male patients with gastric cancer were more sensitive to the exposure of 2-ethylhexyl diphenyl phosphate (EHDPP), while the triethyl phosphate (TEP) exposure was more sensitive to the relatively young gastrointestinal cancer patients [51].

Acetaldehyde is a chemical metabolite in ethanol metabolism. This can eventually lead to the denaturation of proteins and the destructions of cellular DNA. Moreover, it can stimulate the production of numerous types of cancer-causing genes [53].

Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are chemicals found in grilled foods that have become charred. Several studies have analyzed the risk of colorectal cancer associated with the consumption of red meat, the total meat intake and the exposure to individual heterocyclic amines. Individual measures of specific heterocyclic amines exposure provided little additional value to the risk assessment when compared to the measurement of the meat consumption, thus suggesting that the exposure to other environmental or dietary carcinogens such as nitrosamines may contribute to colorectal cancer risks [54,55].

Acrylamide is a chemical that can be found in the food that has been deeply fried or baked at high temperatures. Some studies revealed that when this chemical is allowed to build up in the body in time, it can increase the risk of cancer in the digestive system [56-58].

Hogervorst et al. [57] found that dietary acrylamide intake increases the risk of colorectal cancer with specific mutations in KRAS and adenomatous polyposis coli (APC) genes, 2 key genes in colorectal carcinogenesis. However, currently, acrylamide is classified as a probable human

carcinogen. While in experimental studies on rats, the incidence of colorectal tumors was higher after the exposures of humans to large amounts of food containing acrylamide, such as coffee, bread crust or fries, and it was not associated with significantly increased carcinogenic risks [58].

Diet protective factors

Several studies showed that dietary fibers may prevent tumor formation at the colonic epithelium [59-61]. They are further metabolized by the gut microbiome into short chain fatty acids, with local anti-inflammatory and anti-proliferative effects. Healthy microbiome associated with high alimentary intake of dietary fibers and phytochemicals could decrease cell proliferation by regulating the epigenetic events which activate proto-oncogenes and the oncogenic pathways [60]. In a study by Castello et al., the high adherence to the Mediterranean diet, rich in fresh fruits and vegetables, olive oil, nuts and fish could prevent colorectal cancer [62].

Highlights

- ✓ The diet in economically developed countries comprises a multitude of carcinogens, either from farming and conserving the aliments, or from unhealthy means of preparation.
- ✓ Screening programs, especially in people over 50 years of age, and with multiple risk factors are extremely important in detecting colorectal cancers in the early stages.

Conclusions

The diet in economically developed countries contains a variety of carcinogens, either from farming and conserving the food, or from the unhealthy means of preparation. On the other hand, a high number of calories and a high fat diet may lead to the metabolic syndrome, and a favorable environment for tumor development. Screening programs, especially in people over 50 years of age, and with multiple risk factors are extremely important in detecting colorectal cancers in the early stages and in improving the long-term prognosis in such patients.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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