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Risk Factors and Carcinogenesis of Colorectal Cancer

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Aim: to present current research data on the epidemiology and carcinogenesis of colorectal cancer.
Key points. Colorectal cancer (CRC) ranks third in the incidence of malignant tumors in most countries of the world, including Russia. At the same time, the incidence rate continues to grow both globally and in Russia, where CRC accounts for 12.2 % of the total oncological incidence. It is possible to stop the growth and achieve a significant reduction in the incidence of CRC only by identifying proven causes and risk factors for CRC and introducing effective measures for its prevention into the healthcare system. The review includes three sections of research: 1) CRC prevalence in populations and the dynamics of CRC incidence; 2) causes and modifiable and non-modifiable risk factors of CRC; 3) mechanisms of CRC carcinogenesis. The majority of CRC cases, 90 to 95 %, are sporadic and largely due to a combination of modifiable environmental and lifestyle risk factors, such as certain dietary characteristics, gut microbiota, body weight, physical activity, alcohol consumption, tobacco use, precancerous diseases of the colon and rectum, and the level of knowledge about the causes of CRC and measures to prevent them. It is estimated that approximately 30 % of CRC cases are due to varying degrees of genetic predisposition or non-modifiable risk factors, but only 5 % of all CRC cases develop in the context of known genetic syndromes that are caused by a specific germline mutation.
Conclusion. The information presented in the review on proven modifiable and non-modifiable risk factors for CRC and the mechanisms of their participation in CRC carcinogenesis will contribute to the development of effective methods for the prevention of CRC and their implementation in practical health care.
Keywords: colorectal cancer, epidemiology, carcinogenesis, modifiable and non-modifiable risk factors
Conflict of interest: the author declares no conflict of interest.

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Факторы риска и канцерогенез колоректального рака

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Цель: представить данные о факторах риска и их участии в канцерогенезе колоректального рака.
Основные положения. Колоректальный рак (КРР) занимает третье место в структуре заболеваемости злокачественными опухолями в большинстве стран мира, включая Россию. При этом заболеваемость продолжает расти и в мире, и в России, где КРР составляет 12,2 % в общей онкологической заболеваемости. Остановить рост и добиться существенного снижения заболеваемости КРР возможно только на основе определения доказанных причин и факторов риска КРР и внедрения в систему здравоохранения эффективных мер его профилактики. Обзор включает три раздела исследований: распространение КРР в популяциях и динамика показателей заболеваемости; причины и модифицируемые и немодифицируемые факторы риска КРР; механизмы канцерогенеза КРР. Большинство случаев КРР (90–95 %) носит спорадический характер и в значительной степени обусловлено совокупностью модифицируемых факторов риска окружающей среды и образа жизни, таких как определенные характеристики питания, микробиота кишечника, вес, физическая активность, употребление алкоголя, табакокурение, предопухолевые заболевания ободочной и прямой кишки, уровень знаний о причинах злокачественных новообразований и мерах их профилактики. Предполагается, что около 30 % случаев заболеваний КРР в разной степени обусловлено наследственной предрасположенностью или немодифицируемыми факторами риска, но лишь 5 % всех случаев КРР развиваются на фоне известных наследственных синдромов, которые вызваны определенной герминальной мутацией.
Заключение. Представленные в обзоре данные о доказанных модифицируемых и немодифицируемых факторах риска КРР и механизмах их участия в канцерогенезе злокачественных новообразований толстой или прямой кишки будут способствовать разработке и внедрению в практическое здравоохранение эффективных методов профилактики и снижению заболеваемости КРР.

Ключевые слова: колоректальный рак, эпидемиология, канцерогенез, модифицируемые и немодифицируемые факторы риска
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Introduction

In the world statistics on the incidence of malignant tumors, colorectal cancer (CRC) ranks third in terms of the number of newly diagnosed cancers among the adult population of the world and is also the third leading cause of cancer death in both men and women. Every year, 1.9 million cases of CRC are detected worldwide (10 % of all new cancer cases in the world) and about 900,000 deaths from it [1]. The incidence of CRC is traditionally the highest in Western countries.

In Russia, CRC also ranks third in terms of prevalence among malignant neoplasms. In the structure of the incidence of all diseases, colon cancer accounts for 7.1 %, tumors of rectum, rectosigmoid junction and anus — 5.1 %. All these localizations, collectively referred to as CRC, account for 12.2 % of the total incidence of cancers. The absolute number of people with newly diagnosed CRC increased from 49,470 in 2011 to 71,001 in 2021. The incidence rate per 100,000 population increased from 41.6 in 2011 to 48.67 in 2021. The increase in gross incidence rates over a 10-year period was 25.3 % for colon cancer and 15.5 % for rectal, rectosigmoid junction and anus cancers [2]. In most countries of the world, including Russia, the incidence of CRC continues to grow [3, 4]. It is expected that without the introduction of effective CRC prevention measures into practical healthcare, 2.4 million new cases of CRC will be detected worldwide by 2035 [5].

The aim of this literature review is to provide data on risk factors and their involvement in CRC carcinogenesis.

A literary review of articles published in the period from January 2018 to February 2024 devoted to the study of the epidemiology, etiology and carcinogenesis of CRC has been performed. A systematic literature search on the target research topics was carried out on the basis of electronic data by searching in international scientific databases: PubMed/MEDLINE, Google, Library, RusMed. A manual search was also conducted in the lists of primary sources of the analyzed studies.

Proven causes and risk factors of CRC

In the development of CRC, the combined action of carcinogens and carcinogenesis promoters, which are designated as risk factors, is of decisive importance, since they do not individually determine the development of a malignant tumor, but to one degree or another increase the likelihood of its development. Risk factors are divided into assumed and proven. In relation to the latter, on the basis of special analytical studies, confirmation of their statistically reliable cause-and-effect or dose-dependent relationship with the development of a certain form of oncological neoplasm has been obtained. In preventive medicine, non-modifiable risk factors are traditionally distinguished, the elimination or correction of which is impossible or limited, and modifiable risk factors that can be eliminated or their characteristics changed. To date, a causal relationship has been established between a number of both non-modifiable and modifiable risk factors.

Non-modifiable risk factors for CRC

Heredity

Summation of data from 20 analytical epidemiological studies of CRC showed that the presence of first-degree relatives with CRC in the family history increases the relative risk (RR) of developing CRC by more than 4 times (RR = 4.21; 95 % confidence interval (95%CI): 2,61–6,79) [6]. It is assumed that about 30 % of cases of CRC are caused by a hereditary predisposition, but only 5 % of all CRC cases develop against the background of known hereditary syndromes that are caused by a certain germinal mutation: Lynch syndrome, familial adenomatosis of the colon, MUTYH-associated polyposis, juvenile polyposis, hereditary mixed polyposis syndrome, Peitz — Jeghers syndrome and serrated polyposis [7]. The most common hereditary syndrome causing CRC is Lynch syndrome, which is associated with up to 3 % of all CRC cases [8]. Currently, there are ~20 identified genes that are associated with an increased risk of developing CRC. In a large-scale genome-wide association study of CRC, which included 35,145 cases of CRC and 288,934 individuals from control groups from different populations, the results of a targeted meta-analysis confirmed a significant relationship between polygenic CRC risk assessment scales and the incidence of CRC. Individuals with moderate and high polygenic risk were 2.11 and 3.88 times more likely to develop

CRC than those in the low-risk subgroup, respectively [9]. Indicative data on the association of the risk of developing CRC with a hereditary predisposition to this form of malignant tumors were obtained in a study where a quantitative assessment of genetic risk based on 140 single-nucleotide polymorphisms associated with CRC was performed in a population cohort. Smoking history was also considered. In individuals with polygenic risk values above the 90th percentile, the risk of CRC was increased several times compared with those with polygenic risk values below the 10th percentile, in those who had never smoked, smoked in the past and continued to smoke, the risk was increased by 3.6, 4.3 and 6.4 times, respectively. Multivariate analysis has shown that both polygenic risk and smoking have an independent effect on the risk of CRC [10].

A burdened family history, that is, the presence of cases of CRC diseases among relatives of 1st–2nd degrees of kinship is noted in 30–35 % of patients with CRC. At the same time, the family history of the disease may be related to both genetic factors and family-wide lifestyle disorders. Genetic factors play a more significant role in the etiology of CRC in families where there are carriers of germinal mutations that cause CRC, they account for only 5–10 % of CRC cases [7, 10].

Gender

According to statistics, in almost all populations, CRC develops more often in men than in women. The standardized incidence rate of CRC per 100,000 men in Russia is 31.87 and 21.86 for women [2]. In another population, the ratio of men and women with CRC is 1.25:1.0 [4].

Age

Up to 40 years of age, cases of CRC are rare. As a rule, it affects people after the age of 40, and in 85 % of cases CRC is detected after the age of 65 [11]. In Russia, the age-related incidence rates per 100,000 population of the corresponding age for colon cancer are: <40 years — 7.3; 40–49 years — 20.4; 50–59 years — 56.8; 60–69 years — 155.2; 70–79 years — 168.0; 80 and older — 229.2 [2]. These data confirm the presence of a pronounced trend of an increase in the incidence of CRC with increasing age, which is also found in many other populations. The incidence rates in the age groups over 60 years are ten times higher than those in the age groups <40 years and 40–49 years. In recent decades, in some countries, there has been an increase in the number of cases of CRC among people under the age of 50, which causes additional concern, but does not change the main trend of a marked increase in the risk of CRC with increasing age [12]. Thus, age appears to be one of the most significant risk factors for CRC. Age, or rather the aging of the population, is one of the main reasons for the increase in the incidence of CRC in most countries of the world in absolute terms.

Height

A systematic review with meta-analysis of data from 47 observational studies, including 280,644 cases of CRC, showed that adults with every 10 cm taller had a slight but significant increase in the risk of CRC (RR = 1.14; 95% CI: 1.11–1.17). The comparison of the incidence of CRC between adults with the highest growth percentiles and those with the lowest growth percentiles varied in individual studies within the risk ratio values from 1.24 (95% CI: 1.19–1.30) to 1.07 (95% CI: 0.92–1.25) [13]. Thus, the risk ratio for developing CRC was significantly higher in individuals with the highest height compared to those with low height. Another meta-analysis of the results of more than 40 studies, which included data on 50,936 cases of CRC in a population of 7,393,510 adults, also confirmed the presence of a significant positive association between growth and the risk of CRC. The total RR value was 1.04 (95% CI: 1.02–1.05) with each 5 cm increase in height [14]. A large-scale randomized, placebo-controlled intervention study conducted in China also investigated a number of known risk factors for CRC, including height, to assess the preventive effectiveness of vitamin supplements. The study cohort included 29,553 healthy individuals aged 40 to 69 years. After 5.25 years of follow-up, all cases of CCR were recorded. A multifactorial analysis assessing the association of CRC disease with various risk factors showed that the cumulative risk of CRC increases significantly with increasing height, regardless of other known risk factors [11].

Ethnicity

The incidence of CRC varies from country to country and in different racial/ethnic groups of the population. In the United States, compared with the non-Hispanic white population, the morbidity and mortality rates among the African American population are 28 and 60 % higher, respectively. Hispanics have an overall lower incidence rate of CRC than non-Hispanic whites, with standardized incidence rates of CRC for the former and latter being 35.5 and 40.2 per 100,000 population, respectively. Japanese Americans have the highest incidence of CRC among all Asian Americans [15]. The highest incidence rate of CRC among tribal and racial groups in the United States was recorded in 2018 among American Indians and Alaska Natives — 61.9 per 100,000 population. This indicator was higher than in any other country in the world, with the exception of Hungary, where men had a higher incidence of CRC than men in

Alaska, 70.6 per 100,000 and 63.6 per 100,000, respectively [16]. It is assumed that racial and ethnic differences in the incidence of CRC are due to a complex of risk factors — genetic, environmental, lifestyle-related, which are associated with both the country of origin and the country of residence, as well as with different levels of implementation of preventive medicine in healthcare, in particular, CRC screening.

Modifiable risk factors

Nutrition characteristics

Numerous studies have shown that nutrition, depending on its specific characteristics, can play both a causal and protective role in the development of CRC. Thus, excessive consumption of animal protein and fats, especially red and processed meat, can increase the risk of developing CRC, while fiber or dietary fiber (vegetables, fruits, greens), dairy products can protect against CRC carcinogenesis [17].

The analytical case-control study conducted in the Omsk region involved 609 people aged 30 to 85 years (average age — 51.2 years). Twenty-three parameters characterizing the nutrition and eating habits of the study participants were evaluated. A univariate analysis of the data obtained confirmed the significance for the risk of developing CRC only in relation to the following six parameters: alcohol consumption more than twice a month with a predominance of strong alcohol; the frequency of consumption of red meat more than 10 times a month; the amount of fresh fruit consumed less than 100 g at a time; preference for fatty foods; and a body mass index of more than 25 [18].

A systematic review covering fourteen cohort studies and seven case-control studies, including a total of >60,000 cases of CRC and comparable controls, showed a significant reduction in the risk of CRC associated with high consumption of total **dairy products** [19].

Studies of the relationship between the consumption of **various types of fruits** and the risk of CRC have yielded contradictory results. A meta-analysis of 24 relevant studies with a total participation of 1,068,158 adults showed that, compared with low, higher consumption of certain fruits reduces the risk of developing CRC: citrus fruits — by 9 % (odds ratio (OR) — 0.91; 95% CI: 0.85–0.97), apples — by 25 % (OR = 0.75; 95% CI: 0.66–0.85), watermelon — by 26 % (OR = 0.74; 95% CI: 0.58–0.94) and kiwi — by 13 % (OR = 0.87; 95% CI: 0.78–0.96). No reliable association with the risk of CRC has been established for other types of fruits [20].

In a prospective cohort study in Malmö, 923 cases of CRC were identified during 502,136 person-years of follow-up of the study participants. An analysis of the relationship between various dietary components and the risk of CRC showed that **dietary fiber** intake at the level of the highest quintile reduced the risk of CRC by 23 % compared with the lowest quintile (hazard ratio (HR) — 0.77; 95% CI: 0,61–0,98), [17].

A meta-analysis of the results of 7 observational and case-control studies of the possible association of the risk of developing CRC with the level of dietary anthocyanins (plant components and pigments, most of which are contained in the skin of berries and fruits), showed the presence of significant feedback between the total consumption of anthocyanins and the risk of CRC. High consumption of anthocyanins compared with low consumption reduced the risk of CRC according to observational studies by 22 % (RR = 0.78; 95% CI: 0.64–0.95), according to case-control studies — by 31 % (RR = 0.69; 95% CI: 0.60–0.78) [21].

A case-control study was conducted to study the relationship between different types of **plant-based diets** and the risk of CRC in the Chinese population. The study included relevant data on 2,799 cases of CRC and 2,799 paired controls of comparable age, gender, place of residence, and other possible risk factors. To collect nutrition data, a validated questionnaire on the frequency and composition of food intake was used, based on which a plant-based nutrition index was derived, which makes it possible to assess compliance with common, healthy and unhealthy plant-based eating patterns. Compared to the lowest quintile of index values with the highest quintile, the adjusted OR scores for the risk of developing CRC were: 0.79 (95% CI: 0.66–0.95) for all dietary patterns, 0.45 (95% CI: 0.38–0.55) for healthy eating patterns, and 1.45 (95 % CI: 1.18–1.78) while following an unhealthy eating pattern. In general, the results confirm the recommendations that switching to a healthy plant-based diet is important for the prevention of CRC [20].

A study using UK Biobank data on 114,217 individuals assessed the intake of types and sources of carbohydrates based on detailed dietary characteristics collected. Over a multi-year follow-up period (median follow-up time was 9.4 years), 1,193 individuals from the study cohort were diagnosed with CRC. It has been established that there is a significant inverse association of CRC risk with the consumption of non-free sugar and whole grain fiber [22].

The systematic review analyzes current data on the relationship between dietary **calcium and vitamin D** and the risk of CRC based on case-control

studies. Selected, 32 studies assessed calcium intake, and 23 studies assessed vitamin D. In total, data on 19,076 cases of CRC and 36,746 control individuals were used. With respect to dietary calcium intake, a 6 % reduction in the risk of CRC was found for every 300 mg of calcium taken daily (OR = 0.94; 95% CI: 0.92–0.97). With regard to vitamin D intake, a 4 % reduction in the risk of developing CRC was found per 100 IU/day of vitamin D (OR = 0.96; 95% CI: 0.93–0.98). Higher dietary intake of calcium and vitamin D is associated with a significant reduction in the risk of CRC [23].

In a prospective study, 26,218 adults were interviewed using a standardized questionnaire regarding their diet. With subsequent long-term follow-up (median follow-up period — 13.3 years), all cases of cancer among the study participants were recorded. Analysis using a multivariate regression model with covariant adjustment and stratification by age and gender showed that in women, high consumption (4th quartile) of processed red meat was associated with an increased risk of gastrointestinal cancer, with an adjusted risk ratio of 1.68 (95% CI: 1.09–2.57) and individually for CRC, it was 1.90 (95% CI: 1.12–3.22). No statistically significant associations were observed with regard to consumption of red meat or processed meat from non-red meat [24].

In the prospective study of the association of various dietary components with the risk of CRC mentioned above, it was found that consumption of any processed meat at the level of the highest quantile increased the risk of CRC by 31 % compared with the lowest quantile (HR = 1.31; 95% CI: 1.05–1.63) [17].

Since different foods are usually consumed together and in different complexes, it is important to explore the importance of not only individual nutrients, but also holistic diets or dietary patterns. The largest and most significant study of the association of a low-carbohydrate diet with the risk of CRC is the Singapore-based Chinese prospective cohort study, which included data on 61,321 Chinese people who were between 45 and 74 years old at the beginning of the study. On average, over 19.5 years of follow-up, 2,520 participants developed CRC. The structure of the diet took into account the consumption of carbohydrates, proteins and fats. At the same time, the scores assessed how many carbohydrates were consumed from plant products and how many from animals. Overall, there was no association between total or plant-based low-carbohydrate diet scores and the risk of CRC ($p \geq 0.28$). The number of animal-derived carbohydrate scores was moderately positively associated with the risk of colon cancer ($p = 0.02$), but not with rectal cancer. Compared with the lowest quartile of animal carbohydrate intake, HR indicators for colon cancer for quartiles 2, 3 and 4 were respectively: 1.12 (95% CI: 0.98–1.29), 1.27 (95% CI: 1.10–1.46) and 1.14 (95% CI: 0.99–1.31). Thus, low-carbohydrate diets with high levels of animal protein and fat were associated with a moderate increased risk of colon cancer among Chinese Singaporeans [25].

When analyzing data from the diet and cancer cohort study in Malmö, the Diet Quality Index (DQI) for CRC prevention was used, based on consumption of processed meat, fiber, and dairy products. Higher DQI values indicated a higher content of protective products and were associated with a lower risk of CRC. The risk of CRC in the group with the highest quintile of DQI values was 43 % lower than in the group with the lowest quintile of DQI (HR = 0.57; 95% CI: 0.43–0.75). Adherence to a diet with a higher DQI, taking into account several significant nutritional components for CRC, had a stronger association with CRC than when taking into account individual nutritional components [17].

A prospective study conducted in the Netherlands examined the relationship between adherence to the Mediterranean diet and the risk of CRC. At the beginning of the study, 120,852 adults completed a basic questionnaire that included 150 items. During the 20.3 years of follow-up in the study cohort, 1993 cases of CRC were detected in men and 1574 in women. A multifactorial analysis of the collected data showed that higher adherence to Mediterranean diet was not associated with a reduced risk of CRC [26]. At the same time, a meta-analysis that included data from 13 prospective cohort studies showed a significant 10 % reduction in the risk of CRC, with the highest adherence to Mediterranean diet compared with the lowest (RR = 0.90; 95% CI: 0.84–0.96) [27].

Overweight and obesity

Epidemiological data consistently demonstrate a significant relationship between the degree of obesity and the risk of developing CRC. Obesity in adults, both general and abdominal, is a risk factor for developing CRC, and this association is more pronounced in men than in women [6, 14]. In most studies, the degree of overweight and obesity was assessed by body mass index (BMI) and waist circumference [28].

A review was conducted with a meta-analysis of 47 studies, together including 50,936 cases of CRC detected in populations totaling 7,393,510 people. The results of the generalized data analysis confirm the existing evidence of a positive association between an increase in total and abdominal

body fat and the risk of CRC. The calculation of dose-effect dependence showed that per 5 kg/m² increase in BMI increased the risk of CRC by 6 % (RR = 1.06; 95% CI: 1.04–1.07), every 10 cm of waist circumference increased the risk of CRC by 3 % (RR = 1.03; 95% CI: 1.01–1.05) [14].

A study was conducted in Germany to assess the association of overweight during life with the cumulative risk of CRC. In the case-control study, 5,635 people with CRC and 4,515 people in the control group received and analyzed data on measurements of their weight and height, starting at the age of 20 and every subsequent 10 years until the analysis of the relevant data. Special calculations were used to determine the weighted number of years spent overweight (BMI over 25). The results of the study indicate that the more years a person lives with excess weight or obesity, the higher their risk of developing CRC during their lifetime [29].

Hypodynamia — a sedentary lifestyle

Physical inactivity is a sedentary lifestyle. In population-based cohort studies, there was a statistically significant inverse relationship between the incidence of CRC and the level of physical activity in all age groups of both sexes [30, 31].

A total of 33,403 people participated in the Korean National Health and Nutrition Examination Survey. Sedentary lifestyle was assessed by two values: < 10 hours per day and ≥ 10 hours per day. Three types of physical activity were considered: leisure-time, occupational, and transportation physical activity. According to the results of the study, a sedentary lifestyle (≥ 10 hours per day) was significantly associated with an increased risk of CRC (OR = 1.64; 95% CI: 1.22–2.21) [32].

A systematic review with a meta-analysis of studies on the association of physical activity degree with the risk of developing digestive-system cancer showed that the values of risk ratio in individuals with high physical activity decreased compared with those with low physical activity: for colon cancer — by 19 % (RR = 0.81; 95% CI: 0.76–0.87), for rectal cancer — by 12 % (RR = 0.88; 95% CI: 0.80–0.98), for CRC — by 23 % (RR = 0.77; 95% CI: 0.69–0.85). A meta-analysis of data from 9 studies, which took into account three levels of physical activity — low, moderate and high — showed that, compared with low physical activity, moderate activity also reduced the risk of developing digestive-system cancer by 11 % (RR = 0.89; 95% CI: 0.80–1.00). When comparing high physical activity with moderate one, no significant difference was found in relation to the digestive-system cancer risk (RR = 1.11; 95% CI: 0.94–1.32) [30].

Tobacco consumption

Tobacco smoke is the most common proven carcinogen for humans. A cause-and-effect relationship of tobacco smoking with 15 forms of malignant neoplasms, including CRC, has been established. A review of numerous cohort and case-control studies of the association of tobacco smoking with the risk of CRC showed that most of these studies confirm the causal relationship of smoking with CRC. At the same time, a dose-dependent relationship was established between the intensity of tobacco smoking (duration, age of onset smoking, number of cigarettes smoked per day) and the risk of developing CRC [33].

A large population-based case-control study in Germany included 5,086 patients with CRC and 4,120 patients in the control group. Smokers had a 48 % higher risk of developing CRC than non-smokers (adjusted OR = 1.48; 95% CI: 1.27–1.72). Both smoking and the polygenic risk of CRC carry essentially independent information about the risks of CRC, and their joint consideration provides a powerful risk stratification. At the same time, abstinence from smoking can compensate for a significant proportion of the genetically determined risk of CRC [10].

Alcohol consumption

The International Agency for Research on Cancer has confirmed the carcinogenicity of alcohol consumption for humans. The main carcinogenic components of alcohol are ethanol and its derivative in the human body, acetaldehyde. A causal relationship between alcohol consumption has been established with 7 forms of cancer, including CRC [34].

In a multiethnic cohort study, the association of alcohol consumption with the risk of developing CRC, taking into account race/ethnicity, as well as gender and risk factors related to lifestyle and type of alcoholic beverage consumed, was investigated based on relevant data for 190,698 people living in Hawaii and California. During 16.7 years of follow-up, 4,923 cases of CRC were detected in the study cohort. According to the results of a multidimensional analysis of the relevant data, the hazard ratio index of CRC development increased at different levels of alcohol consumption compared with non-drinkers: in men — by 16 % with alcohol consumption of 15.0–29.9 g/day (HR = 1.16; 95% CI: 1.01–1.34) and by 28 % with alcohol consumption ≥30.0 g/day (HR = 1.28; 95% CI: 1.12–1.45); in women — by 6 % with a lower dose of alcohol (HR = 1.06; 95% CI:

0.85–1.32) and by 15 % with a higher dose of alcohol (HR = 1.15; 95% CI: 0.92–1.43) [35].

In a population-based case-control study, the association between alcohol consumption and CRC was assessed based on relevant data in relation to 5,104 cases of CRC and 4,131 individuals in the control group. In addition to alcohol consumption, the level of polygenic risk was assessed based on 140 loci associated with the development of CRC. The corresponding analysis was carried out separately for the early (<55 years) and late (≥55 years) development of CRC. Compared with low alcohol consumption during life (<25 g/day), average alcohol consumption (≥25 g/day) was more strongly associated with early CRC (OR = 1.8; 95% CI: 1.2–2.8) than with late onset (OR = 1.3; 95% CI: 1.1–1.4) [36].

Dysfunction of intestinal microflora

The microecology of the human intestine is a complex system consisting of numerous microbial communities with a complex structure. Studies show that certain changes in the composition of the microbiota, leading to its imbalance, can play a significant role in the occurrence and development of CRC [37, 38]. Microbes have both prooncogenic and oncoprotective properties. Bacteria such as *Fusobacterium nucleatum, Escherichia coli,* and *Bacteroides fragilis* contribute to the development of CRC, and such as *Clostridium butyricum, Streptococcus thermophilus*, and *Lacticaseibacillus paracasei* can protect against it [39]. In 45 % of patients, CRC is associated with the presence of the bacterium *Fusobacterium nucleatum* in the intestine. A systematic review, which included 57 articles with meta-analysis of generalized data, showed that *F. nucleatum* is present in CRC tumor tissue samples 4.6 times more often than in control samples of healthy tissue (OR = 4.56; 95% CI: 3.31–6.27) and over 3 times more often than in control samples of colorectal adenoma (OR = 3.24; 95% CI: 2.35–4.46) [40]. Based on these data, *F. nucleatum* is designated as one of the risk factors at the beginning of tumor development and during the progression of CRC. *F. nucleatum* is also recognized as a marker of early warning and prediction of CRC, and as a target for its prevention and treatment [41, 42].

Precancerous diseases

In most cases, CRC develops against the background of already existing pathological changes in the intestinal mucosa. In the oncogenesis of CRC, there are three variants of precancerous changes: colorectal adenoma, serrated papillomatosis, and an inflammatory process. The risk of tumor cells is especially high in people suffering from colon adenomatosis, MUTYH-associated polyposis, Lynch syndrome, and chronic inflammatory bowel diseases (Crohn's disease, ulcerative colitis, and colon diverticula) [43, 44].

Patients with colorectal adenoma have a 4-fold higher risk of developing CRC than the rest of the population, with approximately 80 % of CRC cases occurring against the background of colorectal adenoma [37, 43]. Patients with progressive colorectal adenoma (≥1 cm, high grade dysplasia) are significantly more likely to develop CRC than those without it (RR = 2.7; 95% CI: 1.9–3.7). There was no significant difference in the risk of developing CRC between individuals with non-progressive colorectal adenoma (<1 cm) and those without it (RR = 1.2; 95% CI: 0.8–1.7) [45].

A meta-analysis of 31 studies involving 50,445 patients with a history of diverticulitis showed that the risk of developing CRC was significantly higher in patients with complicated diverticulitis than in patients with uncomplicated diverticulitis [44].

A systematic review of studies on the relationship between inflammatory bowel disease (IBD) and CRC reviewed 26 papers, which included data on 531,449 patients with IBD and more than 65 million reference patients. A meta-analysis of the relevant data, stratified by cancer location, showed that IBD mainly increased the risk of bowel cancer rather than stomach cancer. Crohn's disease significantly increases the risk of developing both small bowel cancer and CRC, while ulcerative colitis increases the risk of CRC alone [46]. Population data show that the risk of developing CRC among patients with inflammatory bowel diseases is 2–3 times higher than in the general population [47].

Low level of health literacy

Many analytical epidemiological studies of CRC risk factors have shown a significant relationship between the level of general education and health literacy with the risk of developing CRC. The lower the level of education and knowledge regarding health and hygiene, the higher the risk of developing CRC [48, 49].

The study of the relationship between the level of education and the incidence of CRC, conducted in China, involved 2502 patients with newly diagnosed CRC and 2538 people in the control group, comparable by gender, age, and place of residence. A multidimensional analysis taking into account the proven risk factors of CRC confirmed that the level of education was inversely related to the risk of developing CRC. People who graduated from college or universities had a significantly lower risk of CRC than those who studied only in elementary school (adjusted OR = 0.42; 95% CI: 0.34–0.52) [48].

In another study, 1,200 persons participated in a cross-targeted survey targeting the Lebanese

population aged 50 and over. In the sample, 38.3 % of the respondents knew about any screening test for CRC, and only 7.5 % had ever used it. This national study highlights the alarmingly low level of knowledge about CRC screening tests and the clearly insufficient coverage of the population by CRC screening, despite the fact that CRC is one of the most common cancers in Lebanon [50].

For comparison, in Canadian province of British Columbia, a region with a higher average educational level of the population and a lower incidence of CRC, the adherence of respondents to CRC screening was 62.4 % [51].

Mechanisms of action of risk factors in the carcinogenesis of CRC

Various pathophysiological mechanisms are involved in the carcinogenesis of CRC, such as abnormal cell proliferation, cell differentiation, resistance to apoptosis, invasion of structures adjacent to CRC cells, and distant metastasis. These processes are initiated by the complex interaction of a number of genetic factors and environmental and lifestyle factors [52]. For most of the proven CRC risk factors, the mechanisms of their involvement in CRC carcinogenesis have been investigated.

Gender

It has been suggested that sex hormones may be the cause of gender differences in the incidence and mortality of CRC, but observational studies of the possible relationship between the level of endogenous sex hormones and the risk of CRC have yielded contradictory results [53].

In one of the latest studies using a large-scale resource of the British Biobank, the relationship between the concentration of testosterone in the blood serum and sex hormone binding globulins with the risk of CRC was investigated. No convincing evidence has been obtained for the independent role of hormones in gender differences in the incidence of CRC. Given the widespread use of testosterone supplements in older men to compensate for the age-related decrease in their endogenous concentrations, large and long-term randomized controlled trials are needed to clarify the effect of testosterone on the risk of CRC [53].

Exposure to estrogen may be inversely related to the risk of CRC. A large-scale prospective study in Denmark examined the relationship between women's history of oophorectomy, which reduce the level of estrogen circulating in the body, and the risk of CRC. The study involved 25,698 women (aged ≥ 45 years) from the Danish cohort of nurses. During 542,140 person-years of follow-up, 863 (3.4 %) nurses were diagnosed with CRC. Multifactorial analysis showed that history of bilateral ovariectomy was associated with 79 % increased risk of CRC (adjusted RR = 1.79; 95% CI: 1.33–2.42). The history of unilateral ovariectomy also showed a slight increase in the risk of CRC, but statistically unreliable (RR = 1.25; 95% CI: 0.86–1.82) [54].

Old age

The close association of the likelihood of developing CRC with age is explained by an increase in the duration of action of other risk factors with age, including exposure to direct carcinogens and promoters of CRC oncogenesis and, accordingly, the accumulation of somatic mutations in genes and the formation of tumor cells. With age, the body's defense systems against cancer cells weaken. Experimentally, it was also found that the infiltration of macrophages in CRC tissues increases with age. Macrophages from the aged host were more likely to polarize to pro-tumor phenotype and more powerful in promoting tumor cell proliferation [55].

Height

The effect of high height on the risk of developing CRC is mediated by the metabolic features characteristic of individuals with tall stature, in particular through the endocrine system and growth hormone [13].

Nutrition

It is assumed that there are four main metabolic pathways involved in the interaction of diet-related genes and directly involved in CRC carcinogenesis: folic acid metabolism, lipid metabolism, oxidative stress response, and inflammatory response [56].

The mechanism of influence of **meat products** on the risk of developing CRC can be associated with several ways. Thus, contamination of meat products during their high-temperature cooking with polycyclic aromatic hydrocarbons, which undergo biotransformation and activation in the body, can cause changes in the DNA structure in cells of the colorectal mucosa. DNA adducts specific for polycyclic aromatic hydrocarbons have been identified in CRC tissues [57].

It is known that heme iron, which is an essential component of red meat, also contributes to the carcinogenesis of CRC. The DNA-damaging property of heme iron with the release of DNA adducts related to the etiology of CRC has been established. The products of red meat decomposition, affecting the microbiome, create a pro-inflammatory microenvironment in the colon, which also stimulates the carcinogenesis of CRC [58].

A **high-fat diet** increases the risk of developing CRC by stimulating bile acid metabolism. Bile acids are synthesized in the liver in response to dietary fats. Entering the colon, they undergo a

complex biotransformation carried out by intestinal bacteria, resulting in the formation of secondary bile acids, in particular deoxycholic acid which can activate carcinogenesis in the intestine. This mechanism combines the action of dietary, microbial, and genetic risk factors for CRC [59].

The protective effect of **dietary fiber** against CRC is due to the fact that it stimulates the butyrogenic activity of the intestinal microbiota, providing a high content of butyrate (butyric acid, a waste product of intestinal bacteria), a substance with significant antitumor effect. Therefore, diets with fiber supplementation and fat restriction can be an effective measure to reduce the risk and prevent CRC [59]. Data from a prospective population study confirm the importance of butyrate production in reducing the risk of CRC when consuming whole grain products [22].

Anthocyanins with their antioxidant properties can also inhibit the development of colon cancer by interfering with the cell cycle with the effect of antiproliferation and apoptosis. The formation of cytoplasmic vacuoles in cells also indicates that anthocyanins can induce autophagy [21].

Overweight and obesity

The role of insulin resistance and metabolic syndrome is assumed in relation to the mechanisms of the association of obesity with an increased risk of CRC. It is also suggested that a large waist circumference is a risk factor for CRC due to the possible involvement in CRC carcinogenesis of elevated levels of cytokines and hormones produced in visceral abdominal fat [60].

Physical inactivity

Low physical activity can increase the risk of developing a number of diseases, including CRC, by reducing insulin sensitivity and antitumor activity of the immune system, as well as by prolonging the period of exposure to food carcinogens on the digestive tract, due to impaired motility of the gastrointestinal tract and increased transit time of food [30].

Tobacco consumption

The mechanisms and consequences of tobacco intoxication have now been studied in sufficient detail. The chemical composition and biological activity of tobacco smoke components have been determined. The latter contains about 4,000 components and chemical compounds, several dozens of which are proven carcinogens to humans. A number of special experiments and studies have confirmed the ability of tobacco smoke and its components to have direct genotoxic and mutagenic effects on cell DNA [33].

The carcinogenic components of tobacco smoke enter the bloodstream and reach various organs and tissues of the body, including the colon. This is confirmed by the detection of tobacco compounds and their metabolites in sufficiently high concentrations in urine samples from smokers. More recent biological studies indicate that tobacco consumption may affect macrophage functions and their polarization, thereby contributing to tumor progression. In particular, the association of smoking with the incidence of CRC was studied, taking into account and depending on the number of macrophages, with the identification of common, M1-polarized and M2-polarized macrophages in the tumor. It was found that the relationship between "pack-years", the quantitative indicator of tobacco consumption, and the incidence of CRC differed in subgroups with different densities of stromal macrophages (heterogeneity — 0.003). This association was stronger for tumors with a lower number of stromal macrophages, which indicates the interaction of tobacco consumptions and macrophages in colorectal carcinogenesis [61].

Intestinal microbiota

The human gut microbiota consists of numerous microbial communities that are involved in many essential functions such as immunity, protection against pathogens, metabolism of food compounds, and maintenance of homeostasis. There is increasing evidence that the gut microbiome, acting as an important metabolic and immunological regulator, may play a key role in the initiation and progression of CRC. The data from certain studies demonstrate the ability of the intestinal microbiota to interact with the colon epithelium and host immune cells by releasing a wide range of metabolites, proteins, and macromolecules that regulate the development of CRC [62]. "Harmful" metabolites include some primary bile acids and short-chain fatty acids, while ursodeoxycholic acid and butyrate are beneficial and prevent the development and progression of tumors. Pathogenic bacteria involved in the carcinogenesis of CRC cause chronic irritation and inflammation, oxidative stress. Bacterial metabolites form biofilms in the intestine and produce genotoxins [39]. *F. nucleatum* promotes the development of CRC through several mechanisms: invasion, colonization, and secretion of proinflammatory cytokines. *F. nucleatum* is regarded as one of the risk factors at the beginning of tumor development and during the progression of CRC by affecting the immune system and modulating inflammation [41].

Precancerous diseases

Benign neoplasms of the colon, rectum, anus, and anal canal are true neoplasms of the intestinal mucosa and are associated with a high risk of developing CRC. The adenoma-carcinoma sequence

is generally accepted in relation to the stages of development of sporadic CRC.

A team of Chinese specialists sequenced 54,788 cells from tissue samples collected from patients, including blood, normal tissue, precancerous, polyp, and CRC. At each stage of carcinogenesis, cell types, transcription signatures, and differentially expressed genes of different cell populations were determined. Populations of adenoma and carcinoma progenitor cells were identified and characterized. Modern knowledge about the evolution of the colorectal epithelium in the process of carcinogenesis with single-cell resolution has been obtained [63].

In chronic inflammation (in inflammatory bowel diseases), various cytokines and chemokines are secreted in the intestine, which are involved in the pathogenesis of CRC by influencing tumor growth and immunosuppression of colitis-associated tumor formation. Inflammation can also induce mutagenesis, and the recurrent nature of inflammation, along with epithelial regeneration, can accelerate carcinogenesis. The molecular pathogenesis of "inflammatory bowel disease → CRC" occurs in the sequence "inflammation → dysplasia → carcinoma" and is well described [64].

Conclusion

CRC is one of the most common and one of the most preventable types of cancer, with great untapped potential for primary and secondary prevention. The global trend in the incidence of CRC determines the need for the development of preventive technologies in relation to CRC. To date, the main risk factors that have a proven causal relationship with the development of CRC have been identified. The mechanisms of influence of these factors on the risk of developing CRC have been investigated. The results of these studies open up opportunities for the development of effective CRC prevention measures and their implementation in public health.

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