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Colorectal Cancer: Risk Factors, Novel Approaches in Molecular Screening and Treatment

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ABSTRACT

By 2040 the burden of colorectal cancer will increase to 3.2 million new cases per year and 1.6 million deaths per year. This highlights the importance of improving preventive measures and treatment strategies. This piece concisely overviews the latest therapeutic and diagnostic approaches for colorectal cancer. In 2019, factors such as low milk intake, smoking, insufficient calcium consumption, and alcohol use had a significant impact on colorectal cancer DALYs worldwide. A comprehensive search was conducted in December 2023 using keywords related to drugs, therapeutic agents, colorectal cancer, diagnostic methods, epidemiology, and novel therapeutic approaches in the PubMed and Scopus databases. Initially, 325 articles were identified based on titles, abstracts, and publication dates. After removing duplicates, 170 unique articles were included. Medications like Nimotuzumab, Cetuximab, and Panitumumab target the Epidermal Growth Factor Receptor (EGFR), which EGF activates. HER2, activated by ligands, is the focus of drugs like Trastuzumab and Pertuzumab. The PD-1/PD-L1 and CTLA-4 pathways, as the immune checkpoints, which involve T cells, are targeted by medications like Ipilimumab. Adoptive cell therapy, including CAR-T cell therapy, TCR modification, and enhancing T cell activity through tumor-infiltrating lymphocytes, is used to combat cancer cell growth. In medical advancements, adoptive cell transfer therapy (ACT) and exosomes in the tumor immune microenvironment (TME) are notable treatment methods that boost the immune system. HIF1A-AS1, CRNDE-h, NEAT1, ZFAS1, and GAS5, along with IGFBP-2, have demonstrated significant CRC diagnostic capacity. Compared to CRC patients with low HIF1A-AS1 expression, individuals with high expression levels were linked to a worse 5-year survival rate.

Keywords: Colorectal cancer, epidemiology, screening tests, treatment approaches

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Introduction

As the second most deadly and third most commonly diagnosed cancer worldwide, colorectal cancer (CRC), which includes cancers of the colon and rectum, presents a significant public health challenge. In 2020, colorectal cancer (CRC) accounted for 9.4% of cancer-related deaths. However, because of a substantial increase in cases among the senior population, it is projected that the global incidence of CRC will be more than two-fold by 2035, with the greatest rise expected in less industrialized countries. By 2040 the burden of colorectal cancer will increase to 3.2 million new cases per year (an increase of 63%) and 1.6 million deaths per year (an increase of 73%) (1,2). The incidence of CRC cases is progressively escalating worldwide(2,3). Genetic and environmental elements both exert a considerable influence on an individual's susceptibility to CRC. Moreover, the risk of CRC rises with advancing age and in persons afflicted with chronic ulcerative colitis and Crohn's disease. Research indicates that factors predisposing individuals to CRC encompass dietary patterns, lifestyle choices, familial medical background, and persistent inflammation (4). The development of CRC is a gradual process, typically taking more than ten years for a polyp to transform into a malignant tumor. Therefore, early detection and removal of polyps through regular screening are essential in preventing CRC. At present, existing diagnostic methods can only detect less than 30-40% of cases in the initial phases, with a risk of recurrence post-surgery and treatment. While chemotherapy drugs target cancer cells, they also harm healthy cells. This can lead to resistance in most CRC patients, reducing the effectiveness of anticancer medications and ultimately resulting in chemotherapy failure. Therefore, it is of utmost importance to partake in a comprehensive dialogue regarding the epidemiology, risk factors, and preventive measures for CRC, taking into account the latest evidence-based knowledge. This will enable us to effectively tackle the forthcoming challenges linked to this ailment (5,6).

To effectively minimize CRC and improve death rates on a larger scale, screening average-risk individuals is the most successful approach. Population-based screening initiatives have been implemented in numerous European nations, Canada, and parts of Asia, Oceania, and North and South America. Eligibility for CRC screening is specified by age and geography. Through population-based screening, it becomes possible to identify average-risk individuals with hidden diseases, enabling timely treatment and reducing risks for both individuals and communities (4,6).

Screening people at average risk is the most effective way to prevent colorectal cancer and lower related death rates overall. As a result, some European countries, Canada, and certain areas of Asia, Oceania, and North and South America have started population-based selection programs(7). Suitability for participation in CRC screening is contingent upon time of life and geographical location. Microsimulation modeling outcomes have indicated a decline in CRC morbidity and mortality in the United States, attributable to the application of screening schemes(8). Furthermore, population-based screening endeavors to unearth latent illnesses amongst the average-risk populace, facilitating timely interventions and mitigating risks to individuals and communities most effective way to reduce CRC and lower mortality rates on a larger scale is by evaluating individuals. Eligibility for CRC screening depends on age and location. The goal of population-based screening is to identify undetected diseases in individuals at average risk, allowing for prompt interventions and minimizing risks to both individuals and communities (6,9). Furthermore, it is essential to adopt additional successful approaches, which entail the identification and surveillance of high-

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risk groups. These groups encompass patients with inflammation in the bowel, families with hereditary colorectal cancer syndromes, individuals with familial colorectal cancer predispositions but no identifiable genetic markers, and those displaying phenotypic markers indicating an increased risk. In a recent cases study, the metabolome of a patient suffering from cancer and recurrent infections showed significantly higher homocysteine/methionine and homocysteine/thiodiglycolic acid ratios compared to that of healthy age-matched controls. So, the metabolome has played a crucial role in revealing key biological processes affected by genetic variances. It is also important to consider that the metabolome varies with time, pathology, developmental stage, progression, drug treatment, dietary intervention, environmental factors, and even the microbiome. It is acknowledged that the simultaneous and accurate analytical quantification of the metabolome remains a challenge (8,10,11).

Presently, cancer treatment has been significantly transformed by immunotherapy approaches utilizing immune checkpoint inhibitors and adoptive cell therapy (ACT) besides chemotherapy. Neoadjuvant therapy involves the administration of radiotherapy, chemotherapy, and a combination of different treatment modalities before surgery. Adjuvant systemic therapy can reduce recurrence and improve survival rates by killing cells that may have escaped the primary tumor bed via lymphatics and blood vessels. This has led researchers to hypothesize that giving systemic therapy before surgery (neoadjuvant) might improve outcomes because it would destroy undetectable microscopic circulating cells. This approach aims to lower the tumor staging, thus decreasing the likelihood of local recurrence and improving the overall prognosis(12,13). This review centers on innovative therapeutic compounds developed for cancer-targeted treatments. It provides a succinct overview of the epidemiological research on CRC, including various risk factors. Furthermore, it examines screening techniques and their utilization in targeted therapies aimed at different molecular pathways. Lastly, it offers a prospective analysis of future directions for therapeutic compounds and screening in the realm of targeted therapies.

Literature Search and Selection of Articles

An extensive review of the current literature on recent advancements in therapeutic agents for CRC was undertaken. The inclusion criteria encompassed articles written in English, available in full-text, comprehensive, and directly pertinent to the subject under investigation. A comprehensive search was carried out in the PubMed and Scopus databases in December 2023, utilizing keywords related to drugs, therapeutic agents, colorectal cancer/CRC, diagnostic methods, epidemiology, and novel therapeutic methods. Initially, 325 articles were identified based on their titles, abstracts, and publication dates. After eliminating duplicate entries, 165 distinct articles were retained. These articles were thoroughly analyzed, and a subset of 5 articles relevant to the research question were selected. Subsequently, in March 2024, a supplementary search was conducted using Google Scholar, PubMed, and Scopus, identifying and including nine additional articles directly related to the topic of interest. To enhance the clarity and coherence of our arguments, nine additional references were integrated throughout the writing process (Figure 1).

CRC prevalence and risk factors:

Prevalence

Colorectal cancer (CRC) was responsible for approximately 1.93 million new cases (10%) and 0.94 million deaths (9.4%). Variations in the incidence and mortality rates of CRC are evident among different

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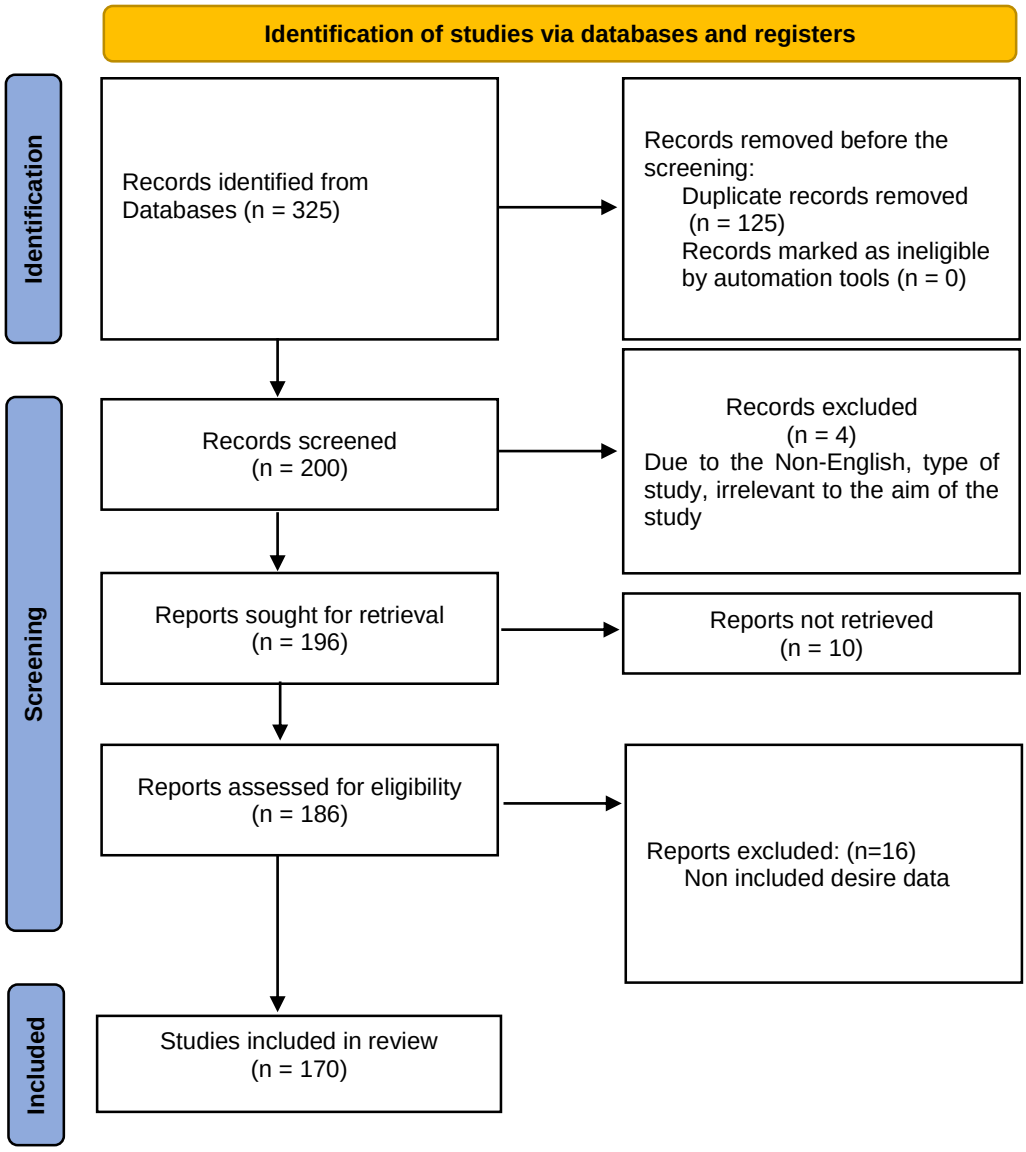

Fig. 1. Flow diagram of the steps for including studies in the review study.

countries and regions, often aligning with the economic status of the respective nations. According to World Bank data, regions with higher income levels tend to have a higher prevalence of new cases and fatalities, whereas lower-income areas tend to report fewer incidences and deaths(6). The incidence rates were found to be at their peak in regions such as Australia/New Zealand and Europe, with figures reaching 40.6 per 100,000 for males, whereas the rates were lowest in various African and Southern Asia, standing at 4.4 per 100,000 for females. A similar trend was observed in terms of mortality rates, with the highest rates recorded in Eastern Europe at 20.2 per 100,000 for males, and the lowest rates in Southern Asia at 2.5 per 100,000 for females(14).

In 2019, the region most impacted by colorectal cancer was East Asia, with 637,096 new cases, 275,604 deaths, and 6.7 million DALYs(11). Australasia had the highest age-standardized incidence rate at 48.3 per

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100,000, while Central Europe had the highest age-standardized mortality rate at 23.6 per 100,000. Central sub-Saharan Africa and South Asia had the lowest age-standardized incidence rates at 7.7 and 8.3 per 100,000 respectively. South Asia also had the lowest age-standardized mortality rate at 7.3 per 100,000. Central Europe had the highest age-standardized DALY rate at 512.6 per 100,000, while South Asia had the lowest at 165.1 per 100,000 in 2019(10,11).

In 2019, China, the USA, and Japan had the maximum number of new cases of the condition for both males and females combined. China reported 607,900 new cases, followed by the USA with 227,242 new cases, and Japan with 160,211 new cases(3,15). The highest number of deaths related to the condition occurred in China with 261,777 deaths, followed by India with 79,098 deaths, and the USA with 84,026 deaths. When it comes to age-standardized incidence rates, Somalia, Niger, and Bangladesh had the lowest rates per 100,000 population. On the other hand, Taiwan, Monaco, and Andorra had the main age-standardized incidence rates(16,17). Regarding age-standardized mortality rates, Greenland, Brunei, and Hungary had the highest rates, while Bangladesh, Somalia, and Nepal had the lowest rates among the 204 countries and territories analyzed in 2019 (15).

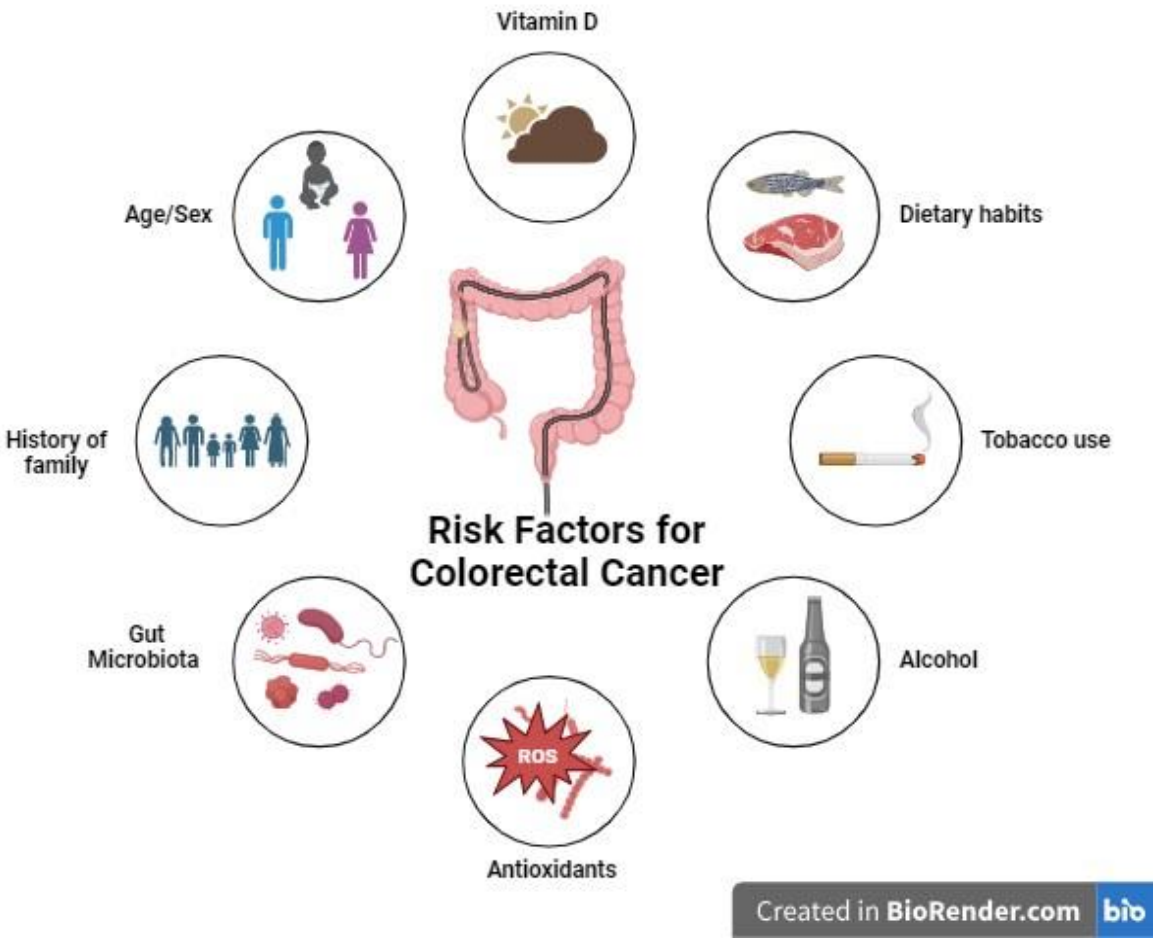

Fig. 2. Risk factors effected on CRC prevalence.

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Looking ahead to the year 2040, it is predictable that the global load of colorectal cancer will considerably escalate, reaching an estimated 3.2 million newly diagnosed patients annually, reflecting a substantial 63% increase. Similarly, the number of deaths attributed to this disease is expected to rise to 1.6 million per year, marking a considerable 73% surge compared to current statistics. This anticipated surge in both incidence and mortality rates underscores the urgent need for enhanced preventive measures, early detection strategies, and innovative treatment approaches to effectively address the growing impact of colorectal cancer on global public health(1,14).

The development of CRC is intertwined with both non-modifiable and modifiable risk factors. Non-modifiable risk reasons encompass personal medical history elements such as gender, time of life, race, history of adenomatous polyps, and a background of inflammatory bowel disease (IBD), along with family history, which individuals have no control over. Conversely, modifiable risk factors pertain to habits and lifestyle choices that individuals can alter. By making changes to these modifiable factors, individuals can potentially lower their risk of developing CRC (Figure 2).

Effect of Sex and Race

The CDC's report reveals that black individuals experienced the highest occurrence and mortality rates, with white individuals, Asians, and American Indians following suit. Non-Hispanic men and women had higher incidence and mortality rates than their Hispanic counterparts. In specific Asian American populations, there was a noticeable decrease in the incidence of late-stage colorectal cancer as opposed to the general population. Black individuals had lower rates of rectal cancer but higher rates of distal and proximal cancers compared to white individuals. White individuals were less prone to tumors and proximal cancers compared to African Americans (18). Although CRC affects both men and women, males are at a higher risk of developing the condition than females. A recent study comparing patients with early-onset CRC (aged 18–49 years) to controls found that males were 1.87 times more likely to have CRC, with a higher prevalence of IBD. Moreover, early-onset CRC patients were 1.44 times more likely to be male compared to those with late-onset CRC (50 years or older), as well as having higher odds of being black or Asian and having IBD. Notably, males exhibited significantly greater odds of developing rectal cancer compared to females(6,19).

Both men and women in developing countries are witnessing a surge in the occurrence and fatality rates of CRC, although the figures are still markedly higher in high-income countries. In contrast, higher-income countries have a lower occurrence rate (42.43%) compared to upper-middle-income countries, but they have significantly fewer recorded deaths (36.40%), possibly due to the presence of advanced healthcare facilities. High-income and upper-middle-income countries together contribute to more than 88% and 85% of the overall occurrence and fatality rates, respectively (3,6,20). During 2020, CRC emerged as the most common cancer diagnosed among men in 18 out of 186 countries worldwide and among women in 6 out of 185 countries(21). In contrast, CRC was identified as the most common cancer in men in 10 out of 185 countries in 2018, while no country reported it as the top cancer among females. The incidence of CRC has doubled from 5% to 10% in men over the last two years, affecting women more in 3.24% of countries. It is worth noting that CRC is more prevalent in men than in women and is more than four times as common in high-income countries. Additionally, mortality rates are about 2.5 times higher in high-income countries (22).

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While mortality rates for colorectal cancer have dropped in many regions across the world, there are still some countries in Latin America, the Caribbean, Asia, and Southern Europe where this decline has not been observed. The improvements in mortality rates are believed to be a result of better access to early detection services and advanced treatment options that can potentially enhance the prognosis of the disease. However, individuals in certain low-income areas may face challenges in obtaining necessary treatment and additional therapies. The percentage of cancer patients in low-income and middle-income countries who can undergo radiotherapy falls between 1.3% and 3.1%, highlighting the limited access to this treatment option in these regions(23,24).

According to a comprehensive study, males saw higher rises in colorectal cancer occurrence, death, and DALYs between 1990 and 2019 than females did. Both absolute numbers and age-adjusted rates reveal that 54.9% (594,176) of deaths related to colorectal cancer and 57.2% (1.2 million) of new cases in 2019 were associated with males. Males' age-standardized occurrence rate was 1.5 times higher in 2019 (33.1 per 100,000 against 21.2 per 100,000)(25). Regarding the age-standardized DALY rate and the age-standardized mortality rate (11.6 per 100,000 for men against 11.2 per 100,000 for women), a comparable difference was seen between the sexes (360.0 per 100,000 in males versus 237.9 per 100,000 in females)(26).

Effect of Age

Although colorectal cancer can affect young adults and teenagers, the highest number of cases is typically seen in individuals who are 50 years old and above. On average, men receive a colon cancer diagnosis at around 68 years old, with women being diagnosed at approximately 72 years old. The average age for both men and women to be diagnosed with rectal cancer is 63 years. Aging is a significant non-modifiable risk factor for CRC, as highlighted in previous studies, where 77% of the 7948 CRC patients were aged between 50 and 79 years(2,27). Based on reports in the year 2023 in the United States, it is assessed that around 153,020 individuals will obtain a diagnosis of colorectal cancer, with approximately 52,550 succumbing to the disease, which includes 19,550 cases and 3750 deaths among those under the age of 50(2). The decrease in the occurrence of CRC has decelerated from an annual rate of 3% to 4% during the 2000s to merely 1% per year from 2011 to 2019. This slowdown can be attributed in part to a rise in the number of cases in persons below 55 years by 1% to 2% annually starting from the mid-1990s(28,29).

As a result, there has been a significant increase in the proportion of cases among individuals below the age of 55, rising from 11% in 1995 to 20% in 2019(30). Since around 2010, there has been an increase in CRC prevalence among individuals under 65 years old. The rate of increase for regional-stage disease is approximately 2% to 3% annually, while for distant-stage disease, it ranges from 0.5% to 3% annually. This marks a reversal in the previous trend of detecting CRC at earlier stages, which was observed from 1995 to 2005. For instance, in 2019, 60% of all new cases were categorized as advanced, in contrast to 52% in the mid-2000s and 57% in 1995, before the widespread implementation of screening programs(31). An observable shift towards left-sided tumors is also noted, with the percentage of rectal cancer cases escalating from 27% in 1995 to 31% in 2019. Although CRC mortality exhibited an overall decrease of 2% annually from 2011 to 2020, it saw an increase of 0.5% to 3% every year in individuals below 50 years of age and among Native Americans below 65 years(2,32).

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The systematic review and meta-analysis showed the highest relative survival rates (RSRs) among populations aged 45–54 years and under 44 years in Asian and North American countries (33,34). Regarding rectal cancer, the age ranges 45–54 and 55–64 exhibit the greatest RSRs. Regarding CRC, those between the ages of 55 and 64 had the greatest RSRs. But in Europe, the 5-year RSRs always go down with age, whether the cancer is colorectal, rectum, or colon cancer. < 44 years old is the age group with the highest survival rate(33,35). The incidence of colon and rectal cancer in people under 50 has grown in some places, including various wealth-level nations. US data shows that between 2000 and 2013, there was a 22% overall rise in incidence among those under 50. In Australia, colon cancer rates rose among the same age group starting in the mid-2000s, with yearly percentage increases ranging from 1.7% to 9.3%; in contrast, rectal cancer rates climbed starting in the early 1990s, rising from 0.9% to 7.1%(36).

Family History

A heightened susceptibility to CRC has consistently been linked to a family history, typically characterized by the presence of a first-degree relative with CRC (37–39). According to a large meta-analysis of 8091 instances of colorectal cancer from 16 studies, those who had a family history of the disease were almost twice as likely to have it as people who did not(40). Determined at 1.80, the risk ratio (RR) has a 95% confidence interval (CI) that spans from 1.61 to 2.02. Furthermore, a retrospective study carried out in the United States that examined risk variables linked to early-onset CRC found that individuals between the ages of 18 and 49 who had a family history of CRC had a noticeably higher risk of the disease than those who did not have such a history. The results showed an odds ratio (OR) of 8.61 with a confidence interval (CI) ranging from 4.83 to 15.75. It is worth mentioning that individuals with early-onset CRC were more inclined to have a family history of the disease in contrast to individuals with late-onset CRC (aged 50 and above), with an odds ratio of 2.87 and a 95% confidence interval of 1.89 to 4.25 (40–43). It follows that one important reason for requiring people to get screened for colorectal cancer is if there is a history of the disease in the family. Furthermore, while genetics undoubtedly contributes to the development of colorectal cancer, this contribution is likely to be small or significant in only a small portion of cases (maybe 20% or so). Familial risk factors are recognized to have a significant impact on the risk of colorectal cancer, especially when family members are affected by early-onset cancer. Inherited forms of colorectal cancer, such as familial adenomatous polyposis (less than 1% of all CRC) and hereditary nonpolyposis colorectal cancer (about 3%), contribute to this familial aggregation. Additionally, genetic factors may influence the development of adenoma or the progression of adenoma to carcinoma. The presence of polymorphisms in the adenomatous polyposis coli gene is linked to increased susceptibility to both adenomas and cancer, supporting this theory. Furthermore, interactions between environmental factors, particularly dietary factors, and polymorphisms in carcinogen-metabolizing enzymes may also play a role(40).

Effect of Body mass index (BMI)

Scientific research has demonstrated that abnormal or excessive accumulation of fat can lead to alterations in the secretion of hormones and cytokines by adipose tissue. In individuals who are overweight or obese, adipose tissue releases a higher quantity of factors such as leptin, resistin, TNF-α, IL-1, IL-6, IL-7, and IL-8. These factors exhibit various effects, including the promotion of cell growth, inhibition of cell death, elevation of oxidative stress, suppression of the immune response, and reduction in the activity of the

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IGF-1 axis. Moreover, they have been implicated in the development and progression of cancer. A meta-analysis of over 66,000 colorectal cancer (CRC) patients across 23 studies found a strong link between body mass index (BMI) and CRC risk, with a 10% increase in risk for every 8 kg/m² rise in BMI. Another study noted that increasing BMI and waist circumference (per 10 cm increase) were associated with colon cancer risk in both genders, with men showing a higher relative risk. Additionally, BMI was significantly correlated with rectal cancer in men but not in women(40). Approximately 9,000,000 participants from various countries were involved in the analysis. The meta-analysis included 41 studies on general obesity and 13 studies on central obesity. The combined Relative Risks (RRs) of CRC for individuals categorized as obese compared to those with normal BMI was 1.334, while for individuals in the highest category of waist circumference (WC) compared to the lowest category, the RR was 1.455. There was observed heterogeneity among the studies on BMI, but not among the studies on WC(44).

Several investigations have explored the correlation between different measures of obesity and the risk of early-onset colorectal cancer (EOCRC). Moore and colleagues discovered that a larger waist circumference (≥99.1 and 101.6 cm for females and males, respectively) was independently linked to a twofold increase in the likelihood of colon cancer, with a notably strong association observed among inactive persons. Previous studies determined that, even after adjusting for BMI, the waist-to-hip ratio did not show a connection with colon cancer in males but did exhibit a slight elevation in risk for females(45). Russo et al. identified a positive association between the waist-to-hip ratio and EOCRC risk, irrespective of BMI. Consequently, further investigation is needed to precisely elucidate the definite impact of excess weight and belly obesity on EOCRC risk in both genders(46).

The connection between obesity and an increased risk of CRC is established through several mechanistic pathways. This pathway involves the development of insulin resistance or hyperinsulinemia, chronic inflammation, oxidative stress, DNA damage, and elevated levels of insulin-like growth factor-1 (IGF-1). These factors collectively promote cell proliferation. On the other hand, physical inactivity has also been associated with a higher risk of CRC, whereas increased levels of physical activity have been found to improve the survival rate among CRC patients (47,48). A meta-analysis encompassing 52 studies demonstrated an inverse relationship between physical exercise frequency and intensity and the risk of CRC(49).

In summary, meta-analysis data offers further evidence of the negative correlation between physical activity and colon cancer. It presents a statistical calculation indicating that engaging in physical activity can potentially decrease the overall risk of CRC. Further studies exploring the nature, level, and duration of physical activity that could provide the most significant risk mitigation will contribute to shaping public health guidelines on specifying particular details of physical activity.

Effect of Diet, Vitamins / Micronutrients, Alcohol Consumption, and Cigarette Smoking

The analysis of the prevalence and impact of colorectal cancer on a global, regional, and national scale across 204 countries and territories from 1990 to 2019 revealed that the colorectal cancer DALYs in 2019 were predominantly influenced by certain factors at a global level. These factors included a low milk intake, smoking, insufficient calcium in the diet, and alcohol use (25).

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Regular alcohol consumption, whether on a weekly or daily basis, has been meaningfully related to an elevated risk of CRC. Individuals engaging in moderate and heavy alcohol consumption (four or more drinks per day) face a 21% and 52% increased risk of CRC, correspondingly. There exists a time-dependent relationship between the duration of alcohol consumption and CRC risk, indicating that a longer period of alcohol consumption is associated with a higher risk of developing CRC(50,51).

In the community population aged 50-74, the research findings suggest a confident association between alcohol consumption and an increased risk of CRC. Women displayed a greater vulnerability to alcohol-related carcinogenesis in CRC compared to men, whereas the association between whisky consumption and CRC risk in men seemed to be influenced by the dosage(52).

The act of smoking cigarettes is a risk factor that can be altered in the development of CRC, with the risk of CRC increasing with the number of cigarettes consumed, as supported by various sources. Research indicates that there is a more pronounced connection between current smoking and rectal cancer (as opposed to proximal or distal cancer) when compared to individuals who have never smoked. Moreover, male smokers have a 39 percent higher risk of distal cancer, while women former smokers face a 20 percent higher risk of proximal cancer compared to women who have never smoked (53,54). Additionally, female smokers exhibit a higher risk of rectal cancer in comparison to their male counterparts. Across 28 prospective cohorts spanning America, Europe, and Asia, a sum of 1,463,796 individuals were enrolled, undergoing a median follow-up duration of 13 years (ranging from 4 to 30 years). Findings indicated that current smokers exhibited a slightly increased risk of CRC in comparison to non-smokers(55). The outcomes of the previous research highlight a strong correlation between cigarette smoking and diminished survival rates in individuals diagnosed with CRC. Consequently, it is crucial to establish an integrated campaign aimed at promoting smoking cessation to effectively reduce mortality associated with CRC.

Multiple prospective epidemiological studies and meta-analyses have collectively shown that the eating of red meat and processed meat increases the risk of CRC by 20–30%(56). It revealed that consuming red meat at a rate of five servings per week is associated with a 13% higher risk of CRC. A cohort study involving over 4000 individuals described that regular consumption of meat was correlated with a higher incidence of proximal colon cancer in males and rectal cancer in females(40,56).

A lower risk of colorectal cancer has been detected in individuals who follow high-fiber dietary patterns that incorporate fruits, vegetables, whole grains, and cereals. Based on prospective research involving more than 2600 cases of colorectal cancer, it was found that those who consumed the highest amount of fiber from bread and morning cereals had a 14% reduced probability of developing colorectal cancer (57). Moreover, studies have linked vitamin D insufficiency to colorectal cancer, suggesting that taking extra calcium and vitamin D may reduce the incidence of this condition. In addition to calcium, another ingredient in milk called vitamin D is thought to help prevent colorectal cancer from developing (46). Since vitamin D improves calcium absorption in the intestines, it plays a major role in preserving calcium homeostasis. The roles of calcium and vitamin D are closely related. The increased blood calcium content linked to vitamin D may be the cause of its anticancer effects. While the recommended daily quantity of vitamin D for people at high risk of CRC remains critical, the recommended daily dose of calcium supplements ranges from 700 to 1250 mg (46). In a study of 2303 randomly chosen healthy postmenopausal older women, the average initial serum

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25-hydroxyvitamin D level was 32.8 ng/mL. Giving these women supplements containing calcium and vitamin D3 did not meaningfully lessen their risk of getting cancer within 4 years when compared to a placebo(58).

Contrary to expectations, in the Aspirin/Folate Polyp Prevention Study RCT, the administration of folic acid supplements did not have a preventive effect on the recurrence of colorectal adenomas(59). In the other study carried out by Jane C Figueiredo et al., there was limited evidence indicating that the initial levels of dietary and overall folate intake, as well as the levels of folate in plasma and red blood cells, did not alter the relationship between the use of folic acid treatment and the risk of developing adenomas or advanced lesions. Nevertheless, individuals in the placebo group demonstrated a protective link between the highest third of dietary and overall folate intake, along with circulating folate, and the risk of developing adenomas, whereas no such connection was observed among those in the folic acid group(60).

Notably, the study uncovered an increased risk of recurrence specifically associated with preneoplastic lesions during the three to five-year follow-up period. In contrast, a different meta-analysis conducted in 2013 demonstrated encouraging findings for selenium. Specifically, the researchers observed that selenium was the sole antioxidant that displayed a favorable impact on reducing the risk of colorectal cancer. Notably, selenium supplementation was linked to a decrease in both colorectal adenoma recurrence and CRC incidence(61–64).

Numerous researches have examined the function of antioxidants, including vitamins A, C, and E in reducing oxidative stress by scavenging free radicals. By conducting a comprehensive analysis of data from prospective cohort studies, it was determined that vitamin A did not exhibit a significant correlation. However, an augmented dietary consumption of vitamins C and E was found to be associated with a modest decrease in the risk of colorectal cancer. However, a meta-analysis of 12 RCTs evaluating the effects of vitamins A, C, and E in addition to other substances found that these drugs were ineffective as chemopreventive agents for colorectal cancer in the general population (61,63,64).

Effect of the gut microbiota

Over the past few years, there has been a surge in studies suggesting that the gut microbiota might have a pivotal role in the initiation of different diseases, including cancer. The gut microbiota consists of a diverse community of microorganisms such as bacteria, viruses, fungi, and protozoa that reside in the human gastrointestinal tract. Recent research focused on the microbiome of individuals with colorectal cancer has revealed that changes in the composition and function of the gut microbiota can contribute to the initiation, promotion, and progression of colorectal cancer. Studies have shown that toxic by-products made by bacteria can damage DNA, disrupt cell cycles, trigger immune responses, and compromise the function of the intestinal barrier. Consequently, an imbalance in the gut microbiota can create an environment conducive to the development of colorectal cancer (65,66).

The microbial composition analysis demonstrated a negative association between tumorigenesis and gram-positive bacteria, particularly the Clostridium group XIVa. On the other hand, the presence of gram-negative bacteria, such as *Alistipes, Akkermansia, Parabacteroides*, and *Bacteroides*, showed a positive correlation with tumor generation. Similarly, probiotics can attach to mutagens, resulting in biotransformation and detoxification (67–69). Furthermore, by interfering with various signaling pathways,

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they can trigger apoptosis. Previous studies have shown that *Propionibacterium acidipropionici* and *P. freudenreichii* produce propionate and acetate, which are short-chain fatty acids capable of inducing cellular apoptosis in human colorectal cancer cell lines. The activation of the caspase 3 enzyme by these particular probiotic strains resulted in chromatin condensation, the formation of apoptotic nuclei bodies, and ultimately, the production of reactive oxygen species that high levels cause damage to proteins, nucleic acids, lipids, membranes, and organelles, leading to cell death. (70).

Diagnosis methods

Fecal immunochemical test and Multitarget DNA test

Most screening programs globally utilize fecal occult blood tests, which have proven to decrease the incidence and mortality of colorectal cancer in randomized trials involving 46,000 to 152,000 average-risk individuals. An improvement on the guaiac method, fecal immunochemical tests (FITs) detect hemoglobin in the stool using antibodies specific for human hemoglobin(71–73).

FIT is a one-sample test, easily completed at home, and unaffected by diet or medications. The sensitivity and specificity of FIT can be adjusted by varying the cut-off for a positive test. The FDA-approved threshold for a positive FIT is 20 μg/g of stool. Varying this threshold can help align colonoscopy demand with supply(72,74). FIT sensitivity for CRC at a threshold of 20 μg/g was recorded at 0.79, with a specificity of 0.94(75). In studies with colonoscopy follow-up, FIT sensitivity for CRC was 0.75 at 20 μg/g and 0.91 at 10 μg/g, with specificities of 0.95 and 0.90 respectively. Sensitivity for advanced adenomas was 0.40 at 10 μg/g and 0.25 at 20 μg/g. With recommendations to start screening at age 45, further research is needed to determine the optimal FIT threshold for positivity(76).

Multiple randomized trials conducted in both the United States and Europe have examined the rates of participation in screening for colorectal cancer using two different methods: fecal immunochemical test (FIT) and colonoscopy. These trials have compared the two methods directly, sequentially, or as a choice between the two. In all scenarios, it has been observed that a greater number of individuals choose to undergo screening when FIT is offered alongside or instead of colonoscopy. Even though a one-time FIT has lower sensitivity compared to a colonoscopy, the higher rates of participation associated with FIT can lead to nearly equivalent detection of CRC. Additionally, when FIT screening is conducted annually or biennially, it has a higher cumulative rate of identifying both CRC and precursor lesions compared to a single FIT. This makes the effectiveness of FIT screening comparable to that of a colonoscopy performed once every 10 years(77,78).

The utilization of a multitarget stool DNA test, which includes detecting methylated and tumor DNA along with occult blood, has shown the potential to increase sensitivity compared to FIT alone. The MT-sDNA test, such as Cologuard by Exact Sciences, has demonstrated high sensitivity for CRC and advanced adenomas in studies. However, it is noted to have lower specificity than other tests like OC-Sensor(79). MT-sDNA, a stool-based screening test, demonstrates high sensitivity and specificity in identifying both CRN and CRC. Following FDA approval, its usage has surged in the past years, appealing to a substantial number of previously non-compliant patients. A significant portion of individuals with a positive test result are subsequently diagnosed with CRN through colonoscopy, predominantly featuring right-sided lesions.

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Although further exploration of potential applications is warranted, MT-sDNA has solidified its position as a convenient, non-invasive, and effective screening tool in the ongoing fight against CRC(80).

Colonoscopy, Flexible sigmoidoscopy, CT colonography, and Colon capsule

In most screening programs, a colonoscopy is often reserved as a follow-up operation following a positive first screening test. The most popular technique for CRC screening is colonoscopy, making it an anomaly in this respect. The screening landscape in 2024 revealed that colonoscopy took the lead as the most prevalent method, with a utilization rate of 63.2%. Following behind were FOBT, accounting for 10.2% of screenings, and sigmoidoscopy, with a utilization rate of 3.2%. Interestingly, the factors influencing the use of colonoscopy within the previous 10 years were found to align with the factors associated with being up to date with any CRC screening(81).

Another method for directly seeing the distal colon is a flexible sigmoidoscopy, which refers patients for a colonoscopy if polyps are found. Numerous large-scale trials with results of lower CRC incidence and death compare a single or repeated flexible sigmoidoscopy against no screening(82). Studies conducted in the UK and Italy, which compared no screening to a one-time flexible sigmoidoscopy for 170,432 and 34,292 persons, respectively, aged 55–64, showed reductions in CRC incidence of 23% and 18% and CRC mortality of 31% and 22%. In addition, there are logistical and practical issues to take into account. Flexible sigmoidoscopy and colonoscopy demand comparable resources; nevertheless, colonoscopy is necessary for patients who have polyps during flexible sigmoidoscopy as well as for follow-up after a positive FIT. The UK changed its CRC screening program in 2021 from flexible sigmoidoscopy to FIT, beginning at age 50, for similar reasons including low adherence, resource requirements, and programmatic efficacy(82–84).

The colon capsule utilizes a wireless, disposable camera capsule that is ingested and becomes operational in the terminal ileum. This capsule captures images of the colonic mucosa without the need for radiation exposure, sedation, or gas insufflation. More recent technological developments have brought improvements to boost the diagnostic output, such as a wider field of vision, a faster and more adaptable capsule frame rate, new algorithms for estimating polyp size, and better data recording. The colon capsule performed better than CTC for both incomplete colonoscopy and average-risk screening in a direct comparative trial including 320 participants. The need for colonic preparation, especially if the colonoscopy cannot be done on the same day, is a barrier to colon capsule testing. The sensitivity and specificity values of Capsule Colonoscopy Examination (CCE) for detecting polyps of 6 mm or larger were 79.2% and 96.3%, respectively, whereas those of Computed Tomographic Colonography (CTC) were 26.8% and 98.9%. In the case of polyps of 10 mm or larger, CCE exhibited a sensitivity of 85.7% and specificity of 98.2%, in contrast to CTC which showed a sensitivity of 50% and specificity of 99.1%. Both procedures were well-tolerated and safe. CCE outperformed CTC in identifying polyps of 6 mm or larger, and showed comparable performance in detecting polyps of 10 mm or larger. It is suggested that CCE could be deemed as effective as, or even more effective than, CTC in screening for colorectal neoplasia, despite both methods not being as efficient as Optical Colonoscopy (OC)(85).

Tests based on blood

A gene known as SEPT9, responsible for producing septin 9, changes early in the progression of colorectal cancer. The sole blood test approved by the FDA for colorectal cancer screening in individuals

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who decline or are unable to undergo more effective screening methods is the evaluation of plasma methylated septin 9 (mSEPT9)(86,87). Despite its limitations in sensitivity, the test has not been included in the latest US Preventive Services Task Force recommendations and is not reimbursed by CMS. An improved version claimed to have a specificity of 80% for all cancer stages and a sensitivity of 68% for colorectal cancer as a whole, with a sensitivity of only 64% for stages I to III. In direct comparison to the FIT test, the mSEPT9 assay demonstrated lower sensitivity but was not found to be inferior(88,89).

Out of the 10,258 individuals included in the clinical validation group, 7861 met the eligibility criteria and were deemed suitable for assessment. The sensitivity of the cfDNA test in diagnosing colorectal cancer was found to be 83.1%, indicating that 83.1% of those individuals who had colorectal cancer detected during colonoscopy tested positive, while 16.9% tested negative. The sensitivity for advanced precancerous lesions was 13.2%, and for colorectal cancer in stages I, II, or III, it was 87.5%. A negative result from the cfDNA blood test led to 89.6% of participants showing no signs of advanced colorectal neoplasia on colonoscopy, while a positive result was seen in 10.4% of participants. These findings suggest a specificity of 89.6% for detecting any advanced neoplasia. Moreover, 89.9% of colonoscopies yielded negative results (NCT0413-6002)(90).

Molecular methods for colorectal cancer screening

It is widely recognized at present that CRC development is dependent on a gradual accumulation of various chromosome mutations. The adenoma-carcinoma progression model, which is based on the buildup of multiple mutations and epigenetic changes, has gained considerable acceptance. In sporadic CRC, there are two main types of mutational occurrences. The first type, affecting approximately 85% of all patients, involves frequent mutations in APC, KRAS, BRAF, TTN, PIK3CA, and SMAD4 genes(91–99). The second type, affecting 15% of CRC-sporadic patients, is distinguished by a significant level of hypermethylation in the MLH1 gene, which is responsible for DNA mismatch repair. The enhancement of genetic understanding in CRC and its associated mutational occurrences can enhance the effectiveness and sensitivity of MT-sDNA tests through an expansion of the targeted DNA genes. Presently, MT-sDNA tests encompass quantitative molecular assessments for KRAS mutations, NDRG4 and BMP3 methylation, and β-actin, incorporating eleven distinct DNA sequences commonly observed in colon polyps and cancers(98,100). Consequently, as evidenced by a retrospective analysis by Weiser et al on 368494 individuals, the MT-sDNA test emerges as the most recommended screening tool for CRC due to its widespread availability and superior sensitivity when compared to previously outlined approaches like FIT and FOBT(98).

Droplet digital polymerase chain reaction (ddPCR) is a dependable technique utilized in clinical oncology research for its notable sensitivity (approximately 74% for CRC) and user-friendly nature. This method is capable of identifying minor mutations through the amplification of individual DNA molecules without the necessity of conventional reference curves(101). ddPCR is frequently employed to detect uncommon alleles as genetic indicators in plasma specimens from both pre-and postoperative colorectal cancer patients, aiding in tracking disease advancement and resistance to medication. The utilization of multiplex ddPCR has proven effective in screening numerous mutations with ample sensitivity to identify mutations in circulating DNA collected through non-invasive blood sampling. Platforms incorporating OncoBEAM technology have exhibited remarkable sensitivity in detecting KRAS mutations in plasma.

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ddPCR has been utilized in the identification and measurement of mutated genes, such as KRAS, BAT26, ITGA6, ITGA6A, hypermethylated GRIA4, VIPR2, and VIM, in both circulating tumor DNA and fecal DNA of colorectal cancer patients(102,103). Nonetheless, a notable drawback of ddPCR is the limited availability of primer/probe sets(103,104).

The Idylla system utilizes a TaqMan reporter system and PlexPCR chemistry to identify various CRC-related mutations in a fully automated manner. This system can be integrated into pathology labs to enhance efficiency by decreasing turnaround time. It is currently capable of testing for KRAS, NRAS, epidermal growth factor receptor mutations in formalin-fixed paraffin-embedded tissues, and BRAF hotspot mutations in plasma samples. Additionally, the Idylla system can provide rapid results to confirm uncertain NGS findings or in situations where tissue material is limited. Research has demonstrated a perfect match of 100% between Idylla and NGS for BRAF and KRAS mutations, and more than 94% for NRAS mutations. This method is known for its precision in sensing common mutations, reducing the risk of contamination, and offering a more cost-effective option compared to NGS or traditional PCR tests. Nevertheless, the system is unable to identify rare or intricate genomic variations, highlighting the need for ongoing enhancement of its biomarker panel to ensure accurate diagnostic outcomes(102,105).

With an AUC of 0.960, HIF1A-AS1, CRNDE-h, NEAT1, ZFAS1, and GAS5 as long noncoding RNA (lncRNA) beside IGFBP-2 demonstrated a significant degree of CRC diagnostic capacity. Compared to CRC patients with low HIF1A-AS1 expression, individuals with high expression levels were linked to a worse 5-year survival rate(106–108)

Therapeutic approaches

Local therapeutic approaches

In rectal cancer, neoadjuvant therapy, which may involve radiotherapy and chemotherapy used separately or together, is often recommended. The main emphasis of neoadjuvant therapy lies in the treatment of locally advanced rectal cancer, along with select resectable metastatic CRC cases. This treatment has been successful in reducing tumor size for patients with intermediate- and advanced-stage cancer (109,110). Radiation therapy's main goals are to increase overall survival and reduce the chance of a local recurrence. For the treatment of stage II and stage III CRC, radiation therapy combined with adjuvant radiation therapy is the best choice. Nevertheless, radiation therapy may have long-term harmful effects on important organs. Research has shown that the overall survival rate following neoadjuvant treatment is not significantly greater than that following surgery (111). Neoadjuvant radiotherapy can enhance the effects of anti-PD-1/PD-L1 therapy by promoting various aspects of the immune response, including T cell activation and recruitment, dendritic cell maturation, antigen exposure, and major histocompatibility complex molecule upregulation (112). Additionally, neoadjuvant chemotherapy may cause PD-1/PD-L1 expression, which would increase the effectiveness of ICI treatment(109–111).

The two pieces of research focus on using neoadjuvant immunotherapy before surgery for colorectal cancer. Neoadjuvant immunotherapy's impact on improving outcomes in nonmetastatic colorectal cancer is evaluated. A meta-analysis of studies is conducted to assess the effectiveness of neoadjuvant immunotherapy in CRC. The analysis shows significant benefits in terms of tumor response and survival rates with neoadjuvant immunotherapy. Different types of immunotherapies, like checkpoint inhibitors, are considered

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for enhancing the immune system against cancer cells. The study points towards neoadjuvant immunotherapy as a promising strategy in the treatment of nonmetastatic colorectal cancer patients(113,114).

The adoption of advanced delivery methods, including intensity-modulated RT (IMRT), has become prevalent in clinical practice. These methods have demonstrated potential benefits for patients with rectal cancer by decreasing toxicity through the reduction of radiation dosage. IMRT utilizes linear accelerators to safely and accurately administer radiation to the tumor while minimizing exposure to nearby healthy tissue(115,116). By employing IMRT, radiation dosages to neighboring healthy organs can be limited, while still effectively targeting the tumor and nearby lymph nodes. Utilizing whole-pelvis IMRT has shown promising results in the treatment of gynecologic malignancy, exhibiting lower toxicity when compared to traditional 3D conformal radiation therapy (3DCRT). In the context of anal cancer, IMRT has been compared to 3DCRT and has demonstrated comparable target coverage while reducing the radiation dose to critical areas such as the genitals, femoral heads, and small bowel (117).

The study by Georgios Kouklidis in 2023 involved 136 patients, with 71 receiving 3D-CRT and 65 receiving IMRT. In terms of toxicity, bladder and skin toxicity showed no notable difference between the two groups. However, patients on a prolonged IMRT regimen had significantly lower acute grade 2 bowel toxicity compared to those on 3D-CRT. Response rates and overall survival did not significantly vary between the two treatments. In conclusion, the study shows that IMRT can effectively decrease acute bowel side effects in patients with locally advanced rectal cancers undergoing neoadjuvant radiotherapy. Further research is needed to validate the clinical benefits of IMRT in rectal carcinoma treatment(118).

In the United Kingdom, a grand total of 947 patients, accounting for 97% of the total, underwent treatment with either 3-dimensional CRT or IMRT. Out of these patients, a staggering 98% received radiation therapy prior to surgery, while 81% underwent definitive resection. The utilization of IMRT has witnessed a remarkable surge, escalating from less than 13% before 2009 to surpassing 30% in 2010 and subsequent years. From 2005 to 2011, a majority of patients with stage 2 or 3 rectal cancer received 3-dimensional CRT. However, there has been a significant and increasing number of patients opting for IMRT. The utilization of IMRT varies greatly among different institutions and is not consistent across sociodemographic groups. Nevertheless, it appears that IMRT is more consistently embraced in specific clinical settings(116).

Systemic therapeutic approach

Chemotherapy

5-FU utilizes the identical facilitated transport mechanism as uracil to penetrate the cell, as indicated by research, and undergoes intracellular conversion into multiple active metabolites, namely fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP), and fluorouridine triphosphate (FUTP), as supported by scientific evidence(119). Leucovorin (LV) is a derivative of folinic acid that functions to increase the cytotoxic effects of 5-FU by impeding the production of thymidylate synthase. LV, with a chemical formula of C20H23N7O7, plays a crucial role in enhancing the effectiveness of 5-FU in cancer treatment by inhibiting the synthesis of thymidylate synthase, an enzyme vital for DNA replication. This interaction ultimately leads to a more potent cytotoxic effect on cancer cells, making the treatment more effective in fighting the disease(120,121).

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Capecitabine, another important oral prodrug in cancer treatment, has a chemical composition of C15H22FN3O6 and is enzymatically converted to 5-FU by thymidine phosphorylase. Capecitabine, a successor to the prodrug doxifluridine, undergoes a series of activation steps within the body to transform into the active drug, FU. This multi-step process involves the enzymatic conversion of capecitabine into 5'-deoxy-S-fluorocytidine (5'-DFCR) and subsequently into 5'-deoxy-S-fluorouridine (5'-DFUR) before finally being converted to FU by thymidine phosphorylase(120,122).

The primary biochemical mechanism of action of cisplatin is centered on the formation of mono-adducts and intra- as well as interstrand crosslinks at specific sites on the DNA molecule. These interactions disrupt the normal processes of transcription and DNA replication, leading to significant interference with the cancer cell's ability to proliferate and replicate. The intricate mechanism of cisplatin's action highlights its effectiveness as a chemotherapeutic agent in targeting cancer cells by inducing DNA damage and inhibiting their growth(120,123).

Oxaliplatin, a third-generation platinum-based anti-cancer agent, is widely utilized as the first-line treatment for metastatic colorectal cancer (CRC). With a chemical formula of C8H14N2O4Pt, oxaliplatin exhibits potent anti-tumor effects by forming DNA adducts that disrupt DNA replication and transcription processes within cancer cells. Its efficacy as a chemotherapeutic agent has made it a cornerstone in the treatment of metastatic CRC, showcasing its importance in improving patient outcomes and survival rates(124).

Irinotecan, with a chemical formula of C33H38N4O6, is derived synthetically from a naturally occurring compound known as camptothecin, which belongs to the quinoline alkaloid class. Its mechanism of action involves the inhibition of an essential enzyme called topoisomerase I (Top I), which plays a crucial role in DNA transcription by cutting, relaxing, and reannealing DNA strands. When metabolized, Irinotecan produces an active form called SN-38, which binds to Top I and forms a complex with DNA, leading to the creation of a stable ternary structure that hinders DNA re-ligation. Consequently, this process promotes DNA damage and triggers programmed cell death, known as apoptosis(28).

The landscape of clinical practice has witnessed significant changes in the past few decades, particularly in the realm of chemotherapeutic drug combinations. Today, regimens featuring irinotecan, a semi-synthetic topoisomerase inhibitor, oxaliplatin, a third-generation platinum compound that induces cell cycle arrest by forming DNA adducts, and capecitabine, a prodrug of 5-FU, have firmly established themselves as preferred options for the first-line, second-line, and sequential treatment of colorectal cancer (120).

Initially developed as a last-resort treatment for patients unresponsive to single-agent 5-FU therapy, combination regimens incorporating oxaliplatin (124)and irinotecan(125) have now become standard treatment options in clinical settings for advanced CRC. Notably, FOLFOX (comprising folinic acid, 5-fluorouracil, and oxaliplatin) and FOLFIRI (126) (comprising folinic acid, 5-fluorouracil, and irinotecan) have shown superior efficacy compared to 5-FU/LV alone in cases of metastatic CRC (127,128). The combination of oxaliplatin with 5-FU/LV (FOLFOX) has demonstrated significant therapeutic potential, resulting in a notable enhancement in progression-free survival rates by approximately 20% and overall survival rates by around 6% among patients with stage II and III CRC(127,128). Phase II trials that have investigated the combination of capecitabine with either irinotecan (XELIRI) or oxaliplatin (XELOX) have

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demonstrated efficacy and toxicity profiles that are comparable to combination regimens involving 5-FU. The XELOX regimen has emerged as an extremely operative first-line therapy for metastatic colorectal cancer, showing response rates, time to progression, and overall survival outcomes that are akin to those achieved with FOLFOX combinations(129). Clinical studies comparing 5-FU/LV and XELOX as adjuvant therapy for stage III colorectal cancer have shown that the administration of XELOX improved disease-free survival by 70.9%, whereas FU/LV improved it by 66.5%. Furthermore, XELOX treatment showed a higher overall survival rate of 77.6% as compared to 5-FU/LV's 74.2% rate(130). Individuals receiving 5-FU/LV had higher rates of stomatitis and neutropenia than did patients getting XELOX therapy. On the other hand, XELOX therapy was linked to greater incidences of thrombocytopenia and hand-foot syndrome compared to individuals receiving 5-FU/LV treatment (131,132).

Target-specific approaches

The expression levels of both epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) have been identified as elevated in a broad spectrum of solid tumors (ST), including colorectal cancer (133). Consequently, a significant amount of scientific investigation has been conducted to explore the potential of inhibiting EGF and VEGF in the context of anticancer therapy. During the period spanning from 2004 to 2006, three innovative monoclonal antibodies targeting EGFR and VEGF, namely bevacizumab, cetuximab, and panitumumab, were granted approval by the United States Food and Drug Administration for treating metastatic CRC(133–135). While EGFR is frequently overexpressed in CRC, mutations in this gene are uncommon. Consequently, tyrosine kinase inhibitors (TKIs) designed to target mutated forms of EGFR have shown limited efficacy when used alone in the treatment of metastatic CRC (mCRC)(136). Instead, the primary focus lies on two monoclonal antibodies (mAbs) that target EGFR: cetuximab and panitumumab. These anti-EGFR mAbs are typically administered alongside fluoropyrimidine-based combination chemotherapy regimens for initial treatment of mCRC, with the condition that there are no activating mutations in the RAS or BRAF genes downstream of EGFR, which could hinder the effectiveness of anti-EGFR therapy(137). Elevated levels of EGFR ligands like epiregulin (EREG) and amphiregulin (AREG) in the plasma might serve as indicators of potential resistance to anti-EGFR therapy. It is worth noting that the use of cetuximab and panitumumab has shown comparable survival benefits in mCRC patients (136).

The use of EGFR-family members other than EGFR/ErbB1/HER1 in guiding treatment decisions is increasingly prevalent. Around 3-5% of cases of mCRC demonstrate an increase in HER2 levels, and this amplification of HER2 is associated with a lower frequency of activating KRAS mutations, particularly in left-sided CRC tumors. Overexpression of HER2 is considered a negative factor, diminishing the efficacy of anti-EGFR treatment. A significant number of cases of mCRC resistant to cetuximab show overexpression of HER2, even in the presence of wild-type KRAS, NRAS, BRAF, and PI3K genes (138,139). The simultaneous blocking of EGFR and HER2 has demonstrated potential in patients with mCRC who have high levels of HER2, although treatment with only the anti-HER2 mAb trastuzumab has shown limited effectiveness. However, when trastuzumab is combined with chemotherapy, it shows promise. Lapatanib also shows encouraging outcomes when used alongside trastuzumab for the treatment of HER2-

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overexpressed mCRC (140,141). Additionally, combining pertuzumab, a mAb that hinders HER2/HER3 dimer formation, with trastuzumab also presents a promising approach for this condition (139–141).

HER3 is a common prognostic factor in metastatic colorectal cancer (mCRC), with increased expression linked to negative outcomes. It requires dimerization with other EGFR-family members or non-EGFR receptors for cell survival and proliferation. HER3 is upregulated in CRC cells due to factors secreted by liver endothelial cells. Various antibody therapies targeting HER3 and HER4 are in progress, with limited direct therapeutic development aimed at HER4 in mCRC(142).

Resistance to anti-EGFR therapy is commonly associated with mutations in downstream signaling pathways, specifically RAS/RAF/MAPK and PI3K/AKT/mTOR (143). One potential therapeutic strategy involves combining anti-EGFR therapy with an MEK inhibitor, such as selumetinib or pimasertib. For tumors harboring ALK fusions or NTRK fusions, treatment with ALK inhibitors like ceritinib or NTRK inhibitors such as larotrectinib or entrectinib can be beneficial (143). Although KRASG12C is only present in less than 4% of mCRC cases, progress has been made in therapeutic approaches targeting this mutation. Investigations into combining selective KRASMT inhibition therapy with anti-EGFR therapy have shown promise. Furthermore, KRASG12C inhibitors are being evaluated in conjunction with MEK inhibitors, anti-AKT medications, and other strategies to disrupt feedback mechanisms and alternative pathways that trigger proliferative and survival signaling (144). The therapeutic promise of targeting the Wnt-pathway for CRC treatment is exemplified by the TNIK inhibitor NCB0846 and mebendazole. In cases of mCRC with activating mutations in the RAS/RAF/MAPK pathway, the anti-VEGF antibody bevacizumab (BEV) is utilized in combination with chemotherapy. In the initial treatment of mCRC, the combination of therapies shows significant potential (145).

Immune checkpoint inhibitors (ICIs)

Immune checkpoint inhibitors, such as atezolizumab and avelumab, are designed to specifically target programmed cell death ligand 1 (PD-L1). Other ICIs like nivolumab, dostarlimab, and pembrolizumab, on the other hand, are focused on programmed cell death protein 1 (PD-1). The ICI ipilimumab is also tailored to target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). These inhibitors play a crucial role as immune regulators by essentially acting as brakes that impede the interaction between checkpoint proteins and their corresponding companion proteins, consequently enhancing the effector activity of T cells in the immune response(144–148). By targeting these specific proteins involved in immune regulation, the ICIs effectively unleash the full potential of the immune system in fighting against various diseases, particularly cancer. This targeted approach offers a promising strategy in immunotherapy by harnessing the body's immune defenses to combat pathological conditions. The intricate mechanisms of action of these ICIs underscore the importance of understanding the complexities of immune regulation for developing novel therapeutic interventions(146,149).

Recently studies revealed that combining chemotherapy with targeted biologic therapy for unresectable CRC-LM resulted in a higher overall response rate (68% compared to 43% with chemotherapy alone). However, it's worth noting that an increase in the overall response rate doesn't always equate to improved overall survival. This review provides an overview of the different targeted therapies and immune checkpoint inhibitors currently employed in the management of metastatic CRC(148) (Table 1).

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Table 1. Summary of FDA-approved targeted drugs, mechanisms, and targets for CRC.

Approved Drug	Categories	Target
Regorafenib	Multikinase inhibitor	VEGFR1-3, TIE2, KIT, RET, RAF, PDGFR-B, FGFR
Fruquinitinib	Small-molecule inhibitors	VEGFR1-3
Bevacizumab	Antibody	VEGF
Cetuximab (Erbitux)	Antibody	EGFR
Ramucirumab	Antibody	VEGFR2
Pembrolizumab	Antibody	PD-1
Nivolumab	Antibody	PD-1
Ipilimumab	Antibody	CTLA-4
Panitumumab (Vectibix)	Antibody	EGFR
Encorafenib	Small molecule BRAF inhibitor	MAPK
Tucatinib	Tyrosine kinase inhibitor	HER2 , HER3, MAPK , AKT
Pertuzumab	Small-molecule inhibitors	HER2
T-DM1 (trastuzumab Emtansine)	Antibody-drug conjugates	HER2
Fruquintinib	Tyrosine kinase inhibitor	VEGFR-1, VEGFR-2, VEGFR-3
Ramucirumab	Fully human monoclonal antibody	VEGFR-2 and VEGF
Aflibercept	Recombinant fusion protein	VEGF-A, VEGF-B, PIG

Adoptive cell transfer therapy (ACT)

T cell amplification therapy, such as adoptive cell therapy, encompasses chimeric antigen receptor T cell therapy (CAR-T), T cell receptor modification (TCR), and enhancing T cell activity through tumor-infiltrating lymphocytes to counteract cancer cell growth. In the realm of medical advancements, adoptive cell transfer therapy (ACT) stands out as a remarkable treatment method that bolsters the immune system. This groundbreaking therapy employs cells from the patient (autologous transfer) or altruistic donors (allogeneic transfer) to optimize immune function(150).

Neoantigens originating from mutations, such as the G12V and G12D mutants, have a close association with pancreatic and colorectal cancers, making them highly promising targets for therapeutic interventions. Mesothelin, glypican-3, GD2, HER2, B7-H3, and claudin18.2 are the key targets of CAR-T cell therapies for solid tumors, including glioma, colorectal, cervical, pancreatic, and lung cancers(151,152). Despite the potential of these targets, ongoing clinical trials have revealed that CAR-T therapies for solid tumors are still in the early stages, mainly encompassing phase 1 or 2 trials. Data available so far indicate that the efficacy of CAR-T cell therapy in ST is relatively inferior compared to hematological malignancies(153).

The HER2-targeted CAR-macrophage (CAR-M) therapy known as CT-0508 exhibited an acceptable safety profile and demonstrated promising antitumor effects in a diverse group of patients with solid tumors,

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as outlined in the results of a phase 1 trial (NCT04660929)(154). CYAD-01, an autologous chimeric antigen receptor (CAR) T-cell product, is designed based on the natural killer (NK) group 2D (NKG2D) receptor, which interacts with eight ligands that are commonly overexpressed in various hematological malignancies but are typically absent in non-neoplastic cells (NCT03018405). In contrast, CYAD-101 represents an innovative non-gene edited allogeneic CAR T-cell therapy, combining the broad tumor-targeting capabilities of the NKG2D-based CAR with a peptide-driven strategy to manage graft versus host disease (GvHD)(155).

NKG2D is a key component of the CYAD-101 therapy. Moreover, the co-expressed T-cell receptor (TCR) inhibitory (TIM) peptide plays a crucial role in disrupting signaling pathways associated with the endogenous TCR(156). An assortment of CYAD-101 cells derived from a single donor underwent thorough evaluation in the AlloSHRINK phase 1 trial (NCT03692429) involving patients grappling with unresectable metastatic colorectal cancer (mCRC)(156). Additionally, a noteworthy trial focusing on Allogeneic NKG2DL-targeting Chimeric Antigen Receptor-grafted γδ T Cells for Relapsed or Refractory Solid Tumors is currently ongoing (NCT04107142)(157). NKG2D-based CAR T-cells Immunotherapy for patients with r/r NKG2DL+ solid tumors clinical trials carried out in phase 1 (NCT05131763 and NCT04270461)(158,159).

Therapy Utilizing Exosomes Derived from Tumors/ Exosomes

Tumor-derived exosomes show potential in triggering a strong anti-tumor immune response due to their antigenicity. Research indicates that these exosomes can serve as vaccines for colorectal cancer, in addition to being a diagnostic marker. A phase I clinical trial with 40 patients demonstrated the safety and tolerability of treating advanced CRC patients with AEX or AEX combined with GM-CSF. Patients in the AEX plus GM-CSF group displayed a significant tumor-specific cytotoxic T lymphocyte response, suggesting that this immunotherapy approach could be beneficial for metastatic CRC patients(96).

The tumor microenvironment (TME) is characterized by the secretion of various soluble molecules and the release of extracellular vesicles, specifically exosomes, by tumor cells and stromal cells. These exosomes, present in different bodily fluids, transport a cargo comprising proteins, DNA, mRNA, miRNA, long noncoding RNA, and viral/prion genetic material. They play a crucial role in facilitating intercellular communication within the context of cancer, enabling both local and long-distance signaling. Additionally, exosomes are an integral component of the TME (95,96). The expression of VEGFR2, ZO-1, occludin, and claudin-5 in endothelial cells is regulated by cancer-derived exosomal miR-25-3p in CRC, leading to the promotion of vascular permeability and angiogenesis. Furthermore, exosomes can serve as blood biomarkers and facilitate tumor metastasis by suppressing DLC-1 expression. The downregulation of DLC-1 expression by CRC-derived exosomal miR-106b-3p also contributes to tumor metastasis. Additionally, exosomal miR-200c-3p plays a negative role in the migration and invasion of CRC induced by lipopolysaccharide (LPS)(92,95–97).

Cell-associated fibroblasts (CAFs) are the primary constituents of the tumor microenvironment (TME) and play a crucial role in driving cancer progression through their interactions with the tumor matrix. The exosomes released by CAFs have been implicated in CRC metastasis and resistance to chemotherapy. These exosomes actively promote stemness, epithelial-mesenchymal transition (EMT), metastasis, and resistance to 5-FU/L-OHP in CRC. Furthermore, exosomes can serve as valuable diagnostic markers for CRC, as they exhibit elevated levels(95,99).

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Discussion

One prevalent disease that has a major impact on cancer death rates is CRC. Due to the intricacy of colorectal carcinogenesis, patient survival results for CRC differ. Finding trustworthy and useful screening methods that support CRC diagnosis and novel therapeutic agents would thus be advantageous. The goal of recent review research has been to find precise and sensitive methods for the diagnosis and prognosis of colorectal cancer. In comparison to traditional biomarkers, further research is necessary to create precise diagnostic, prognostic, and predictive CRC biomarkers besides new methods of therapeutics especially target-specific approaches that may be more therapeutically useful and more patient- acceptable.

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