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From carcinogenesis to cure: Challenges and advances in colorectal cancer

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Abstract
Colorectal cancer (CRC) remains one of the most prevalent and lethal malignancies worldwide, representing a major public health challenge. This review summarizes the current understanding of CRC carcinogenesis, highlights epidemiological trends, outlines established and emerging risk factors, and evaluates advances in prevention, diagnosis, and treatment. Particular emphasis is given to the global burden of disease, molecular insights, screening strategies, and therapeutic innovations, including immunotherapy and targeted agents. Despite significant progress, challenges persist in early detection, disparities in healthcare access, and treatment resistance. Future directions involve precision oncology, integration of artificial intelligence (AI) in screening, and personalized prevention strategies.

Keywords: Colorectal cancer, Carcinogenesis, Epidemiology, Risk factors, Prevention, Treatment strategies

1. Introduction

Colorectal cancer (CRC) is one of the most significant malignancies worldwide, both in terms of incidence and mortality. It ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related death globally, according to the latest GLOBOCAN estimates. The worldwide incidence exceeded 1.9 million new cases in 2020, with nearly one million deaths reported, and projections indicate a continued rise in burden, especially in developing regions. This increase is driven by demographic transitions, lifestyle changes, and limited access to preventive healthcare [1].

CRC arises from the epithelial lining of the colon or rectum and typically follows a multi-step carcinogenesis pathway involving the accumulation of genetic, epigenetic, and environmental alterations. Classically, the adenoma–carcinoma sequence describes the transition from benign adenomatous polyps to invasive carcinoma through progressive genetic instability, particularly involving tumor suppressor genes such as APC and TP53, as well as oncogenes like KRAS. In addition, microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) represent alternative molecular pathways, highlighting the heterogeneity of this disease. The identification of consensus molecular subtypes (CMS) has further refined our understanding of CRC biology and therapeutic responses, laying the foundation for precision medicine [1].

From a public health perspective, CRC reflects the impact of both non-modifiable factors (age, genetics, and family history) and modifiable risk factors such as diet, obesity, alcohol consumption, smoking, and physical inactivity. Rising rates of early-onset CRC (diagnosis before age 50) in many countries are particularly concerning, raising questions about environmental and lifestyle influences, as well as the adequacy of current screening guidelines [1].

Despite advances in screening programs—such as colonoscopy, fecal immunochemical testing (FIT), and stool DNA assays—significant gaps remain in early detection, particularly in low- and middle-income countries (LMICs). These disparities contribute to later-stage diagnoses and poorer survival outcomes compared to high-income nations. In regions with established screening and surveillance programs, CRC mortality has declined, demonstrating the value of prevention and early intervention [2].

Therapeutically, the management of CRC has evolved considerably in recent decades. Surgery remains the cornerstone for localized disease, while adjuvant and neoadjuvant

chemotherapy, radiotherapy for rectal cancer, and the advent of targeted therapies and immunotherapy have transformed outcomes for advanced disease. However, treatment resistance, tumor heterogeneity, and the high cost of novel therapies remain major challenges [2].

The rising global burden of CRC, together with evolving insights into its biology, underscores the urgent need for comprehensive strategies encompassing primary prevention, early detection, precision treatment, and survivorship care**.** This review synthesizes current knowledge on CRC carcinogenesis, epidemiology, risk factors, prevention strategies, and therapeutic advances, while also highlighting the persisting challenges and future opportunities in the global fight against colorectal cancer [2].

2. Carcinogenesis of Colorectal Cancer

Colorectal cancer (CRC) develops through a multistep, multiyear process that transforms normal colonic epithelium into invasive carcinoma. This progression is driven by the accumulation of genetic mutations, epigenetic alterations, and interactions with environmental and host factors**,** including the gut microbiome and immune system. Unlike some malignancies that emerge abruptly, CRC typically evolves over a decade or longer, offering a critical window for prevention and early detection [3].

2.1 The Adenoma–Carcinoma Sequence

The classical model of CRC development is the adenoma–carcinoma sequence**,** first described by Fearon and Vogelstein in 1990. According to this model, malignant transformation results from a stepwise accumulation of mutations in oncogenes, tumor suppressor genes, and DNA repair pathways. The earliest event is often the loss of function of the adenomatous polyposis coli (APC) gene**,** leading to dysregulation of the WNT signaling pathway and uncontrolled cell proliferation. Subsequent mutations in KRAS promote adenoma growth, while alterations in TP53 and SMAD4 contribute to progression from adenoma to carcinoma [3].

2.2 Genetic Pathways in Carcinogenesis

CRC is a genetically heterogeneous disease that can develop through distinct but overlapping molecular pathways:

a. **Chromosomal Instability (CIN) Pathway**
   CIN is present in approximately 70–85% of sporadic CRCs. It is characterized by widespread chromosomal gains, losses, and structural abnormalities. Key events include mutations in APC, KRAS, and TP53. CIN tumors usually follow the adenoma–carcinoma sequence and are commonly left-sided [3].
b. **Microsatellite Instability (MSI) Pathway**
   MSI accounts for 15–20% of CRCs and results from defects in DNA mismatch repair (MMR) genes, such as MLH1, MSH2, MSH6, and PMS2. Germline mutations cause Lynch syndrome, while somatic hypermethylation of MLH1 is frequent in sporadic MSI-high cancers. MSI tumors accumulate insertion-deletion mutations in microsatellite regions, generating frameshifts in growth-regulatory genes. These tumors often have distinct clinicopathologic features, including right-sided location, poor differentiation, and a pronounced immune infiltrate [4].
c. **CpG Island Methylator Phenotype (CIMP) Pathway**
   CIMP tumors are characterized by widespread promoter hypermethylation, leading to silencing of tumor suppressor genes. CIMP is often associated with BRAF V600E mutations and overlaps with sporadic MSI-high cancers.

Mutational Landscape

Next-generation sequencing has identified frequent alterations in WNT, MAPK, PI3K/AKT, TGF-β, and DNA repair pathways. This genomic heterogeneity has direct implications for targeted therapy development.

2.3 Epigenetic Alterations

Beyond genetic mutations, epigenetic modifications play a key role in CRC pathogenesis. DNA methylation, histone modification, and dysregulation of non-coding RNAs (miRNAs, lncRNAs) contribute to gene silencing and oncogene activation. Epigenetic changes are potentially reversible, making them attractive targets for therapy and biomarkers for early detection [5].

2.4 Consensus Molecular Subtypes (CMS)

To integrate genetic, epigenetic, and transcriptomic features, the Consensus Molecular Subtypes (CMS) classification was developed, dividing CRC into four distinct groups:

a. **CMS1 (MSI-Immune, ~14%)**: Characterized by hypermutation, MSI, strong immune infiltration, and frequent BRAF mutations. Prognosis is favorable in early stages but poor after relapse.
b. **CMS2 (Canonical, ~37%)**: Defined by WNT and MYC pathway activation, chromosomal instability, and epithelial phenotype. Often left-sided with better prognosis.
c. **CMS3 (Metabolic, ~13%)**: Exhibits metabolic dysregulation, KRAS mutations, and intermediate prognosis.
d. **CMS4 (Mesenchymal, ~23%)**: Associated with stromal invasion, angiogenesis, TGF-β activation, and poor prognosis [5].

This classification reflects the biological heterogeneity of CRC and guides research into tailored therapeutic approaches.

2.5 Tumor Microenvironment (TME)

CRC development is not solely dictated by tumor cell–intrinsic changes. The tumor microenvironment (TME)—including fibroblasts, immune cells, endothelial cells, and extracellular matrix—plays a critical role. Tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T-cells can promote immune evasion. Meanwhile, the gut microbiota influences carcinogenesis through production of carcinogenic metabolites (e.g., secondary bile acids), induction of chronic inflammation, and modulation of host immunity. Specific bacterial strains, such as *Fusobacterium nucleatum*, have been implicated in CRC progression and chemotherapy resistance [6].

2.6 Inflammation and Carcinogenesis

Chronic inflammation contributes significantly to colorectal tumorigenesis. Patients with inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, face an increased CRC risk. Persistent inflammatory signaling through NF-κB and STAT3 pathways promotes DNA damage, epithelial proliferation, and angiogenesis.

3. Global Epidemiology and Trends

a. CRC incidence is highest in developed nations (North America, Europe, Oceania), but rising rapidly in Asia**,** Latin America**,** and Africa due to westernized diets and sedentary lifestyles.

b. **Age distribution:** Traditionally a disease of the elderly, but early-onset CRC (<50 years) is increasing globally.

c. **Sex differences:** Slight male predominance, partly attributable to lifestyle factors.

d. **Survival rates:** Five-year survival exceeds 65% in high-income countries but is <20% in some LMICs, highlighting disparities in access to screening and treatment [7].

4. Risk Factors

4.1 Non-modifiable factors

- Age >50 years
- Family history of CRC
- Genetic syndromes (Lynch syndrome, Familial Adenomatous Polyposis)

4.2 Modifiable factors

- Diet rich in red/processed meat and low in fiber
- Obesity, physical inactivity
- Alcohol and tobacco use
- Type 2 diabetes and metabolic syndrome
- Gut microbiota dysbiosis [8]

Table 1: Types of Risk factors

Category	Factors	Effect on CRC Risk
Non-modifiable factors	Increasing age (>50 years)	Increase
	Family history, Hereditary syndromes (Lynch syndrome, FAP, MAP)	Increase
Medical conditions	Inflammatory bowel disease (ulcerative colitis, Crohn's disease)	Increase
	Diet high in red and processed meat	Increase
	Low fiber, fruit, and vegetable intake	Increase
	High-fat, Westernized diet	Increase
	Obesity and central adiposity	Increase
Modifiable factors	Tobacco smoking, Excessive alcohol consumption	Increase
Protective factors	High dietary fiber, fruits, vegetables, and whole grains	Decrease
	Regular physical activity	Decrease
	Adequate calcium and vitamin D intake	Decrease
	Fish and omega-3 fatty acids	Decrease
	Long-term aspirin/NSAID use (in select populations)	Decrease
	Hormone replacement therapy in postmenopausal women (controversial)	Decrease
Emerging/novel factors	Gut microbiota composition (e.g., Fusobacterium nucleatum)	Variable
	Chronic inflammation and immune dysregulation	Variable

5. Prevention Strategies

Colorectal cancer (CRC) is among the few malignancies where the natural history from premalignant lesion (adenoma) to invasive carcinoma is well characterized. This knowledge provides a valuable opportunity for effective prevention and early intervention**.** Prevention strategies are generally categorized into primary, secondary, and tertiary prevention**,** focusing on lifestyle modification, screening, and recurrence risk reduction, respectively [9].

5.1 Primary Prevention: Lifestyle and Behavioral Modifications

Primary prevention aims to reduce the incidence of CRC by addressing modifiable risk factors.

5.1.1 Dietary Modifications

a. **Reduce red and processed meat intake:** Epidemiological studies consistently link high consumption of processed and red meats with increased CRC risk.

b. **Increase dietary fiber:** Diets rich in fruits, vegetables, and whole grains lower risk by improving bowel transit, binding carcinogens, and supporting a protective gut microbiome.

c. **Micronutrients:** Adequate calcium, vitamin D, and folate intake may reduce carcinogenesis by modulating epithelial proliferation and DNA repair.

d. **Mediterranean diet:** Characterized by high intake of plant-based foods, olive oil, and fish, it has been associated with reduced CRC incidence.[10]

5.1.2 Physical Activity

Regular moderate-to-vigorous physical activity reduces CRC risk by improving insulin sensitivity, lowering systemic inflammation, and promoting gastrointestinal motility. WHO recommends at least 150 minutes of physical activity per week for adults.

5.1.3 Weight Management

Obesity, especially visceral adiposity, is a well-established risk factor. Weight reduction through balanced diet and exercise is an essential preventive measure.

5.1.4 Avoidance of Tobacco and Excess Alcohol

a. **Smoking cessation** lowers risk of adenoma recurrence and CRC incidence.

b. **Alcohol moderation:** Limiting alcohol consumption to below recommended thresholds significantly decreases CRC risk [11].

5.2 Secondary Prevention: Screening and Early Detection

Secondary prevention focuses on the detection and removal of precancerous lesions and the diagnosis of early-stage disease, where treatment outcomes are optimal [12].

5.2.1 Colonoscopy

a. **Gold standard screening method**: that allows both detection and removal of adenomas.

b. **Recommended starting age**

- 50 years for average-risk individuals (recent guidelines suggest 45 years due to rising early-onset CRC).

- Earlier and more frequent screening for high-risk individuals (e.g., Lynch syndrome, family history, IBD).

c. Interval: every 10 years if no polyps detected, more frequent if polyps or risk factors are present.

5.2.2 Sigmoidoscopy

Examines only the distal colon but reduces mortality through polyp removal. Usually combined with stool testing to improve detection [13].

5.2.3 Stool-Based Tests

- **Fecal Occult Blood Test (FOBT):** Detects hidden blood in stool; inexpensive but lower sensitivity.
- **Fecal Immunochemical Test (FIT):** Higher sensitivity and specificity than FOBT, widely used in national screening programs.
- **Stool DNA test (e.g., Cologuard®):** Detects genetic and epigenetic alterations; more sensitive but costly [13].

5.2.4 Emerging Screening Tools

a. CT colonography (virtual colonoscopy): Non-invasive but requires bowel prep.

b. Liquid biopsy: Circulating tumor DNA (ctDNA) and exosomal markers under investigation for early detection.

c. Artificial intelligence (AI): Being integrated into colonoscopy for improved adenoma detection.[13]

5.2.5 Screening Impact

Countries with organized screening programs (e.g., USA, UK, Japan) have seen a decline in CRC incidence and mortality. However, disparities in screening uptake remain a major global challenge, particularly in low- and middle-income countries.[14]

5.3 Tertiary Prevention: Prevention of Recurrence and Progression

Patients with previously treated adenomas or CRC require ongoing surveillance and preventive strategies.

a. Colonoscopy surveillance: Regular follow-up colonoscopies to detect metachronous adenomas or cancers.

b. Aspirin and NSAIDs: Long-term, low-dose aspirin use has been shown to reduce adenoma recurrence and CRC risk, particularly in high-risk populations. However, bleeding risks must be considered.

c. Lifestyle interventions post-treatment: Maintaining a healthy weight, regular exercise, and plant-based diets improve survival outcomes and reduce recurrence risk.

d. Chemoprevention in high-risk groups: Studies support aspirin, celecoxib, and vitamin D supplementation, though optimal regimens remain under investigation.[15]

5.4 Chemoprevention

Beyond lifestyle modification, pharmacological agents show promise in CRC prevention:

a. Aspirin: Strong evidence supports its use in reducing CRC incidence and mortality, especially in Lynch syndrome carriers.

b. Non-steroidal anti-inflammatory drugs (NSAIDs): Shown to reduce adenoma formation, but long-term toxicity (GI bleeding, cardiovascular risks) limits widespread use.

c. Metformin: Commonly used in type 2 diabetes; emerging evidence suggests a protective effect via AMPK activation and reduction in insulin resistance.

d. Statins: Some observational studies suggest a protective effect, though results are inconsistent [15].

5.5 Vaccination and Microbiota Modulation (Emerging Approaches)

a. Cancer vaccines: Research is ongoing into vaccines targeting tumor-associated antigens and neoantigens to prevent CRC in high-risk populations.

b. Microbiome-targeted interventions: Probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation (FMT) are under investigation for CRC prevention, particularly in high-risk individuals.[16]

6. Current and Emerging Treatment Strategies

Colorectal cancer (CRC) management has evolved significantly, with treatments tailored to disease stage, molecular profile, and patient comorbidities. Current strategies include surgery, systemic therapy, targeted agents, immunotherapy, and emerging precision medicine approaches**.**

6.1 Surgery

Surgical resection remains the cornerstone of curative treatment for localized CRC.

a. Colon cancer: Standard colectomy with adequate lymphadenectomy.

b. Rectal cancer: Total mesorectal excision (TME) is the gold standard.

c. Minimally invasive approaches: Laparoscopic and robotic-assisted surgery reduce post-operative morbidity and hospital stay while maintaining oncologic outcomes.

d. Considerations: Tumor location, stage, and patient comorbidities guide the surgical approach.[16]

6.2 Chemotherapy

Systemic therapy is indicated for adjuvant treatment in high-risk localized disease and palliative therapy in advanced CRC.

a. Fluoropyrimidines: 5-Fluorouracil (5-FU) and capecitabine remain foundational.

b. Combination regimens: FOLFOX (5-FU + leucovorin + oxaliplatin) and FOLFIRI (5-FU + leucovorin + irinotecan) improve response rates and survival.

c. Neoadjuvant therapy: Particularly for locally advanced rectal cancer, reduces tumor size and improves sphincter preservation.[17]

6.3 Targeted Therapy

Molecular profiling enables the use of targeted agents:

a. EGFR inhibitors (cetuximab, panitumumab): Effective in RAS/BRAF wild-type tumors.

b. VEGF inhibitors (bevacizumab, aflibercept): Inhibit angiogenesis, improving survival in metastatic CRC.

c. BRAF and MEK inhibitors: Useful in BRAF V600E mutant CRC.

d. HER2-targeted therapy: Emerging in HER2-amplified CRC subsets [18].

6.4 Immunotherapy

a. **Checkpoint inhibitors:** Pembrolizumab and nivolumab show durable responses in MSI-high CRC.
b. **Combination approaches:** Trials are evaluating immunotherapy plus chemotherapy or targeted agents for microsatellite stable (MSS) CRC.
c. **Future directions:** Neoantigen vaccines, CAR-T therapy, and microbiota-modulating therapies are under investigation.[18]

6.5 Precision Medicine

- **Next-generation sequencing (NGS):** Guides therapy selection based on tumor mutational profile.
- **Liquid biopsy:** Non-invasive monitoring for minimal residual disease and early detection of resistance mutations.
- **Therapeutic implications:** Personalized therapy enhances efficacy, reduces toxicity, and may improve survival.[19]

7. Current Challenges

Despite advances, CRC management faces multiple challenges:

7.1 Rising Incidence of Early-Onset CRC

- CRC diagnosis in individuals <50 years is increasing globally.
- Early-onset CRC often presents at advanced stages and with aggressive features.[20]

7.2 Screening Gaps and Disparities

- Limited access to colonoscopy and screening programs in LMICs results in late-stage diagnosis.
- Socioeconomic, geographic, and cultural barriers affect participation in preventive programs.

7.3 Treatment Resistance

- Tumor heterogeneity and clonal evolution contribute to chemotherapy and targeted therapy resistance.
- MSI-low and MSS tumors have limited response to immunotherapy.[21]

7.4 Financial and Logistical Barriers

- High cost of novel therapies restricts access in many countries.
- Infrastructure for molecular testing and targeted therapies is limited in resource-poor settings.[21]

7.5 Biological Complexity

- Interaction of genetics, epigenetics, tumor microenvironment, and microbiome complicates treatment response.
- Personalized therapy is promising but requires comprehensive biomarker profiling.[22]

8. Future Directions

Advances in CRC research point toward precision prevention and therapy:

8.1 Artificial Intelligence and Digital Health

- AI algorithms improve polyp detection during colonoscopy, predicting malignancy risk, and optimizing screening intervals.
- Digital pathology and radiomics enhance diagnostic accuracy and treatment planning.[23]

8.2 Liquid Biopsy and Biomarkers

- Circulating tumor DNA (ctDNA) and exosomal markers enable real-time monitoring of tumor burden and recurrence.
- Biomarker-guided therapy selection may improve outcomes and reduce overtreatment [23].

8.3 Personalized Prevention Strategies

- Stratifying individuals based on genetic, epigenetic, and lifestyle risk allows tailored screening and chemoprevention.
- Modulation of gut microbiota and anti-inflammatory interventions are emerging preventive measures [24].

8.4 Novel Therapeutic Approaches

- CAR-T cell therapy targeting tumor-specific antigens.
- Neoantigen vaccines to stimulate anti-tumor immunity.
- Oncolytic viruses to selectively kill tumor cells.
- Combination strategies integrating immunotherapy, targeted agents, and standard chemotherapy.[25]

8.5 Global Health Initiatives

- Expansion of low-cost screening programs in LMICs.
- Training and capacity building to reduce disparities in CRC detection and treatment [25].

9. Conclusion

Colorectal cancer remains a major global health challenge due to its high incidence, significant mortality, and growing prevalence in both developed and developing countries. Advances in molecular understanding have elucidated the complex mechanisms of carcinogenesis, including chromosomal instability, microsatellite instability, epigenetic dysregulation, and tumor–microenvironment interactions. This knowledge has paved the way for more precise risk stratification, early detection, and targeted therapies. Despite these advancements, challenges persist, including the rising incidence of early-onset CRC, disparities in access to screening and treatment, tumor heterogeneity, and resistance to conventional and novel therapies. Public health measures emphasizing lifestyle modification, dietary improvements, and widespread implementation of cost-effective screening programs remain essential components of reducing disease burden.

Looking forward, integrating precision medicine, immunotherapy, and digital health technologies has the potential to transform CRC management. Innovations such as liquid biopsy, AI-assisted diagnostics, neoantigen vaccines, and CAR-T cell therapy offer promising avenues for early detection, personalized treatment, and improved survival outcomes. Global collaboration and equitable distribution of medical resources will be critical to address regional disparities and ensure that advancements benefit all populations. Ultimately, a comprehensive, multidisciplinary approach combining prevention, early diagnosis, tailored therapy, and survivorship care is required to move closer to the long-term goal of reducing colorectal cancer morbidity and mortality worldwide.

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