Am J Transl Res 2026;18(5):4097-4109
www.ajtr.org /ISSN:1943-8141/AJTR0157181

Review Article

A comprehensive review of gastrointestinal cancers: epidemiology, risk factors, diagnosis, and therapeutic strategies

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Received April 13, 2024; Accepted April 9, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: Objectives: Gastrointestinal cancers, including gastric cancer, colorectal cancer (CRC), and liver cancer, represent a major global health burden. This review aims to provide an integrated overview of their epidemiology, risk factors, molecular mechanisms, diagnostic approaches, and therapeutic strategies, while highlighting recent advances and ongoing challenges. Methods: A comprehensive review of recent literature was conducted to synthesize current evidence on genetic alterations, environmental and lifestyle risk factors, infectious agents such as *Helicobacter pylori*, hepatitis B virus (HBV), and hepatitis C virus (HCV), as well as advances in screening, diagnosis, and treatment. Results: Gastrointestinal cancers arise from complex interactions among genetic, environmental, and lifestyle-related factors. Recent progress in molecular profiling and biomarker discovery has improved understanding of tumor biology and enabled targeted and immune-based therapies. However, clinical benefits remain variable due to tumor heterogeneity, therapeutic resistance, and limitations in biomarker reliability. Conclusions: Despite significant advances, gastrointestinal cancers remain challenging to manage due to late diagnosis and inconsistent treatment responses. Future efforts should focus on improving early detection, developing robust biomarkers, and implementing integrated, precision-based therapeutic strategies.

Keywords: Gastrointestinal cancers, gastric cancer, colorectal cancer, liver cancer, risk factors, diagnosis, therapeutic strategies

Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with its incidence increasing due to population aging and the rising prevalence of lifestyle-related risk factors such as obesity, smoking, and physical inactivity [1, 2].

Among the various malignancies, gastrointestinal cancers account for a substantial proportion of global cancer incidence and mortality. These cancers arise in organs of the digestive system, including the stomach, colon, rectum, and liver. In particular, gastric cancer, colorectal cancer, and liver cancer are among the most prevalent gastrointestinal malignancies and remain major causes of cancer-related death worldwide. Colorectal cancer is one of the most commonly diagnosed cancers globally and is associated with substantial morbidity and mortality [3, 4]. Gastric cancer continues to represent a significant global health problem with more than one million new cases reported annually, particularly in East Asian populations [1]. Similarly, liver cancer, most commonly hepatocellular carcinoma (HCC), is a major contributor to cancer-related mortality and is strongly associated with chronic liver diseases and viral infections [5].

The development of gastrointestinal cancers is a complex and multifactorial process involving interactions between genetic susceptibility, environmental exposures, infectious agents, and lifestyle-related factors. Chronic infections such as *Helicobacter pylori* play a major role in the development of gastric cancer, while hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are important risk factors for hepatocellular carcinoma [6]. In addition, lifestyle factors including diet, alcohol consumption, smok-

https://doi.org/10.62347/CSDV7151

ing, obesity, and physical inactivity have been identified as important contributors to the development and progression of colorectal and other gastrointestinal cancers [7].

Advances in biomedical research have significantly improved the understanding of the molecular mechanisms underlying gastrointestinal carcinogenesis. These advances have also facilitated the development of improved diagnostic techniques and therapeutic strategies, including minimally invasive surgical approaches, chemotherapy, targeted therapy, and immunotherapy [1, 8]. Furthermore, early detection through screening programs and improved diagnostic technologies has played an important role in reducing mortality associated with certain gastrointestinal cancers, particularly colorectal cancer [9].

Recent studies have emphasized the importance of integrating key oncogenic signaling pathways and tumor microenvironment interactions in gastrointestinal carcinogenesis. Central pathways such as Wnt/β-catenin, TP53, and KRAS signaling are frequently dysregulated across gastric, colorectal, and liver cancers, contributing to tumor initiation and progression [4, 11, 12]. In parallel, interactions between tumor cells and the surrounding microenvironment, including immune cells and inflammatory mediators, play a critical role in disease progression and therapeutic response. Incorporating these mechanistic insights is essential for advancing precision oncology approaches.

Importantly, while these cancers share common oncogenic mechanisms such as TP53 mutations, dysregulated Wnt/β-catenin signaling, and aberrant growth factor pathways, they also exhibit substantial biological heterogeneity and disease-specific drivers. Moreover, several unresolved challenges persist, including variability in biomarker performance, resistance to targeted and immunotherapies, and disparities in early detection strategies across populations. Therefore, a critical and integrative evaluation of recent progress is essential to identify gaps and guide future research directions.

Gastric cancer

Gastric cancer remains a significant and challenging clinical issue, with more than 1 million new cases reported worldwide in 2018. It ranks as the fourth most frequently diagnosed cancer in men and the seventh most commonly diagnosed cancer in women. A substantial portion of gastric cancer cases is associated with various pathogenic infections, including but not limited to *Helicobacter pylori (H. pylori)* and Epstein Barr virus (EBV). Efforts are underway to prevent the development of gastric cancer, and strategies such as the eradication of *H. pylori* have proven effective in preventing a significant proportion of gastric cancer cases. Presently, treatments have advanced and have led to better management of this disease. For example, the 5-year survival rates for patients with stage IA and IB tumors who undergo surgery range between 60% and 80%. However, the prognosis becomes much less favorable for patients with stage III tumors who undergo surgery, with 5-year survival rates ranging from 18% to 50% depending on the dataset. These statistics underscore the pressing need for more effective treatment strategies driven by molecular insight to improve the outcomes for individuals affected by gastric cancer [1]. However, the overall survival remains relatively short, especially in advanced cases. The field of molecular research in gastric cancer has led to the development of new targeted therapies. One notable success in targeted treatment is Trastuzumab, an antibody that targets the human epidermal growth factor receptor 2 (HER2). Trastuzumab has shown significant improvements in survival for advanced gastric cancer patients with HER2 overexpression. Second-line treatment options have also emerged. Ramucirumab, an antibody that targets VEGFR-2 (vascular endothelial growth factor receptor 2), either alone or in combination with paclitaxel, has demonstrated beneficial effects in treating advanced gastric cancer. Apatinib, a VEGFR-2 tyrosine kinase inhibitor, has shown promise in improving the survival of advanced gastric cancer patients who have experienced second-line chemotherapy failure. However, it's important to note that some targeted therapies, such as EGFR (epidermal growth factor receptor)-targeting antibodies (cetuximab or panitumumab), VEGF (vascular endothelial growth factor)-targeting monoclonal antibodies (bevacizumab), m-TOR, and drugs targeting the HGF/MET pathway, have not demonstrated significant survival benefits in gastric cancer treatment. Ongoing clinical trials based on molecular markers continue to explore avenues for improved treatment options for gastric cancer patients [6, 8].

In recent years, advances in molecular classification have identified distinct subtypes of gastric cancer, including Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI)-high, genomically stable, and chromosomal instability subtypes. These classifications have improved patient stratification and guided targeted therapies such as human epidermal growth factor receptor 2 (HER2). However, clinical benefits remain limited to selected subgroups, and resistance to targeted agents continues to be a major challenge. Furthermore, although immune checkpoint inhibitors have shown promise, their efficacy is highly variable, highlighting the need for reliable predictive biomarkers and combination strategies.

Molecular mechanisms and biomarkers

Recent translational research has significantly improved the understanding of gastric cancer biology. Several molecular alterations have been identified, including HER2 amplification, MET activation, FGFR2 overexpression, and mutations in TP53 and CDH1 genes. These molecular alterations play important roles in tumor development, progression, and therapeutic response. In addition, biomarkers such as HER2 overexpression have enabled the development of targeted therapies including trastuzumab, which has demonstrated survival benefits in patients with HER2-positive advanced gastric cancer [1, 8].

Targeted therapy and immunotherapy

Translational oncology research has also led to the development of targeted therapies and immunotherapy for gastric cancer. Agents targeting vascular endothelial growth factor receptors (VEGFR), such as ramucirumab and apatinib, have shown promising results in clinical trials. Furthermore, immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) are emerging therapeutic options, particularly for patients with advanced gastric cancer who exhibit high microsatellite instability or PD-L1 expression [6-8].

Colorectal cancer

This includes both colonic and rectal cancer, which affect the large intestine. In all realms of clinical practice and research, colon cancer (CC) and rectal cancer (RC) are commonly regarded as a single tumor entity, collectively referred to as colorectal cancer (CRC). This designation of CRC is based on three distinct factors. First, it stems from the hypothesis that CC and RC originate within the large intestine, which is considered a unified organ. Second, it draws from the shared anatomical structure of the colonic and rectal walls, encompassing similar layers such as the mucosa, muscular layer, and, to some extent, the serosa, as well as their comparable histological characteristics. Lastly, it is influenced by the analogous functions performed by the colorectal tract, including tasks like stool concentration, fluid absorption, stool transportation, and excretion. In terms of statistics, CC accounts for 72% of cases, while RC represents 28% of all CRCs [3, 10]. However, it's common to present statistics for CRC as a whole.

CRC comprises adenocarcinoma of the colon and rectum. It is characterized by the transformation of normal colonic and rectal epithelium into a precancerous lesion (adenomatous intermediate), which eventually progresses to invasive carcinoma (adenocarcinoma). This invasive stage may lead to the development of metastatic lesions, with the liver being the most frequently affected organ. This complex process necessitates the accumulation of genetic mutations, which can be either somatic (acquired) or germline (inherited) over a period of 10-15 years [4]. This concept, often referred to as 'colorectal carcinogenesis', involves a multistep genetic progression in which various gene mutations accumulate during the transition from normal colorectal epithelium to adenoma and, ultimately, invasive carcinoma [11]. Number of colorectal cancer patients and deaths is given in **Table 1**.

Molecular pathways in colorectal carcinogenesis

Colorectal carcinogenesis involves a multistep accumulation of genetic and epigenetic alterations. The well-characterized pathways include the chromosomal instability pathway, microsatellite instability pathway, and CpG island meth-

Table 1. Incidence and mortality of colorectal cancer in selected countries

Country	Male cases	Male deaths	Female cases	Female deaths
Hungary	5,502	2,730	4,291	2,150
Slovakia	2,853	1,450	1,968	1,134
Slovenia	1,297	-	-	-
Portugal	6,418	-	-	-
Croatia	2,230	1,362	-	958
Latvia	854	-	891	-
Netherlands	9,651	-	7,364	-
Spain	24,610	-	-	-
Japan	81,296	-	67,209	-
Denmark	3,155	-	2,614	-
Norway	-	-	2,423	933
New Zealand	-	-	1,603	-
United Kingdom	-	-	23,234	-
Australia	-	-	7,550	-

Note: "-" indicates data not available. Source: Adapted from global cancer statistics databases (e.g., GLOBOCAN).

ylator phenotype. Mutations in key oncogenes and tumor suppressor genes such as APC, KRAS, TP53, and BRAF play central roles in tumor initiation and progression. These molecular insights have provided opportunities for targeted therapy and precision oncology approaches in colorectal cancer management [4, 11].

In colorectal cancer, aberrant activation of the Wnt/β-catenin pathway, driven primarily by APC mutations, represents an early and critical event in tumorigenesis [4, 11]. Subsequent mutations in KRAS and BRAF further promote tumor progression through activation of downstream signaling pathways, including MAPK and PI3K/AKT pathways. Loss of TP53 function contributes to genomic instability and malignant transformation. Furthermore, interactions with the tumor microenvironment, including immune cell infiltration and inflammatory signaling, play an important role in disease progression and response to therapy.

Targeted therapy in colorectal cancer

Advances in translational research have facilitated the development of targeted therapies for metastatic colorectal cancer. Agents targeting epidermal growth factor receptor (EGFR), including cetuximab and panitumumab, have demonstrated clinical benefits in patients with RAS wild-type tumors. Additionally, inhibitors of vascular endothelial growth factor (VEGF), such as bevacizumab, are widely used in combination with chemotherapy to improve treatment outcomes [1, 6, 8].

Recent progress in colorectal cancer research has focused on molecular stratification, particularly the distinction between microsatellite instability (MSI) and microsatellite stable (MSS) tumors, which has significant implications for immunotherapy response. While immune checkpoint inhibitors have demonstrated remarkable efficacy in MSI-high tumors, the majority of patients with MSS tumors derive limited benefit, representing a major unresolved clinical challenge. In addition, resistance to targeted therapies due to KRAS, NRAS, and BRAF mutations continues to limit treatment effectiveness, emphasizing the need for more comprehensive precision medicine approaches.

Liver cancer

Liver cancer can result from chronic liver disease or infection with hepatitis B or C. Liver cancer ranks as the sixth most prevalent cancer on a global scale. Specifically, it stands as the fifth most common cancer among men and the ninth most common cancer among women. In the year 2020, there were an excess of 900,000 newly diagnosed cases of liver cancer. The incidence and mortality rates of liver cancer have seen a decline in certain Eastern Asian countries like Japan, China, and the Republic of Korea. However, rates have witnessed an increase in many countries across the world that previously had low incidence rates. This includes countries such as the United States, Australia, and several European nations. **Table 2** depicts the ten countries with both the highest incidence rates of liver cancer and deaths in the year 2020 [5]. Liver cancer continues to be a significant global health challenge, with its incidence on the rise worldwide.

Table 2. Incidence and mortality of liver cancer in selected countries

Country	Male cases	Male deaths	Female cases	Female deaths
Mongolia	1,279	1,187	957	873
Egypt	18,145	17,211	9,750	9,312
Laos	888	833	384	359
Cambodia	2,080	1,952	1,062	994
China	302,598	288,127	-	-
Thailand	18,268	17,895	9,126	8,809
Guam	26	-	-	-
Vietnam	20,256	19,420	-	-
Gambia	196	189	-	-
Guinea	739	735	673	669
Papua New Guinea	-	-	311	303
Liberia	-	-	178	178
Guinea-Bissau	-	-	69	69
Guatemala	-	-	1,017	974

Note: "-" indicates data not available. Source: Global liver cancer incidence and mortality data (e.g., GLOBOCAN database).

It is estimated that by the year 2025, over 1 million individuals will be affected by liver cancer annually. Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer, accounting for approximately 90% of cases. One of the primary risk factors for the development of HCC is hepatitis B virus (HBV) infection, which is responsible for about 50% of cases. The risk associated with hepatitis C virus (HCV) infection has notably decreased due to the successful achievement of sustained virological response (SVR) through antiviral medications. However, individuals with cirrhosis are still considered to be at a high risk for the incidence of HCC even after clearing the HCV infection [12].

Liver cancer ranks as the sixth most common cancer worldwide, with a total of 841,080 new cases reported in 2018. It also stands as the fourth leading cause of cancer-related deaths globally, as illustrated in **Figure 1** [13]. Exposure to aflatoxins, toxic substances produced by certain molds that can contaminate food, is a risk factor in some regions. Liver cancer can remain asymptomatic in its early stages, making early detection challenging. As it progresses, symptoms may include abdominal pain, jaundice (yellowing of the skin and eyes), unexplained weight loss, fatigue, and loss of appetite. Diagnosing liver cancer typically involves imaging studies like ultrasound, CT scans, or MRI scans. A definitive diagnosis is often made by analyzing a tissue sample obtained through a biopsy. Surgical resection or liver transplantation may be considered if the cancer is confined to a specific part of the liver and the patient is a suitable candidate. Procedures like radiofrequency ablation (RFA) and microwave ablation (MWA) can destroy small liver tumors. Transarterial Chemoembolization (TACE) technique delivers chemotherapy directly to the tumor by the hepatic artery while blocking its blood supply. For advanced cases, systemic treatments like targeted therapy and immunotherapy may be used to slow the cancer's progression [14]. The prognosis for liver cancer varies depending on the stage at diagnosis. Early detection and intervention can improve outcomes. Unfortunately, liver cancer is often diagnosed at advanced stages, which limits treatment options and reduces survival rates. Preventing liver cancer involves reducing risk factors such as hepatitis B and C infections, alcohol abuse, obesity, and exposure to aflatoxins. Hepatitis B vaccination, antiviral treatments, and lifestyle modifications can help prevent liver cancer in high-risk individuals. In conclusion, liver cancer is a challenging disease with a significant global impact. Understanding its risk factors, early detection, and advances in treatment modalities are essential for addressing this growing health concern [15].

Recent therapeutic advances, including the introduction of tyrosine kinase inhibitors and immune checkpoint inhibitors, have improved outcomes in advanced hepatocellular carcinoma. Combination therapies, such as anti-VEGF agents with immunotherapy, have shown encouraging results in recent clinical trials. However, treatment responses remain inconsistent, partly due to underlying liver disease and tumor heterogeneity. Additionally, early detection remains a major limitation, as most

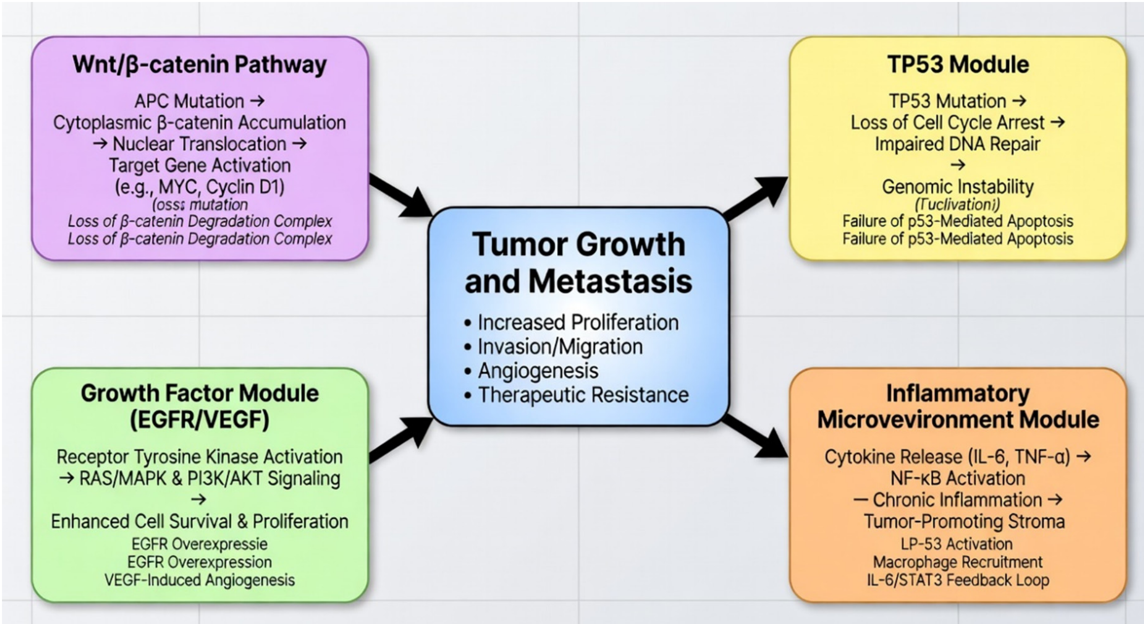

Figure 1. Schematic representation of key molecular pathways involved in gastrointestinal cancers. Dysregulation of Wnt/β-catenin signaling, TP53 pathway, EGFR/VEGF signaling, and chronic inflammation collectively contribute to tumor growth, metastasis, and therapeutic resistance.

cases are diagnosed at advanced stages, underscoring the need for improved surveillance strategies and biomarker development.

Molecular pathogenesis of hepatocellular carcinoma

Hepatocellular carcinoma is characterized by complex interactions between oncogenic signaling pathways and chronic inflammatory microenvironments. Activation of the Wnt/β-catenin pathway and TP53 mutations are among the most frequently observed molecular alterations [12]. Chronic liver injury caused by HBV or HCV infection promotes a pro-tumorigenic microenvironment through persistent inflammation, fibrosis, and immune dysregulation, thereby facilitating tumor initiation and progression.

Emerging therapeutic approaches

Recent translational research has resulted in the development of novel systemic therapies for advanced HCC. Targeted therapies such as sorafenib and lenvatinib have demonstrated improved survival in patients with advanced liver cancer. Furthermore, immune checkpoint inhibitors including nivolumab and pembrolizumab are being investigated as promising treatment options in combination with targeted therapies.

Risk factors for gastrointestinal cancers

Several environmental, lifestyle, and biological factors contribute to the development of gastrointestinal cancers, particularly colorectal, gastric, and liver cancers. Among these, obesity, physical inactivity, smoking, alcohol consumption, aging, and certain chronic diseases have been consistently associated with increased cancer risk (**Figure 2**).

Physical activity

Physical activity has been widely investigated in relation to colorectal cancer risk. Numerous cohort and case-control studies have demonstrated an inverse association between physical activity and colon cancer incidence across different populations and demographic groups [16]. Higher levels of physical activity have been associated with a 10-60% reduction in colon cancer risk, even after adjustment for confounding factors such as age, diet, and obesity [17]. Physical activity may exert protective effects by reducing inflammation, improving metabolic regulation, and limiting abnormal epithelial cell proliferation in the colon.

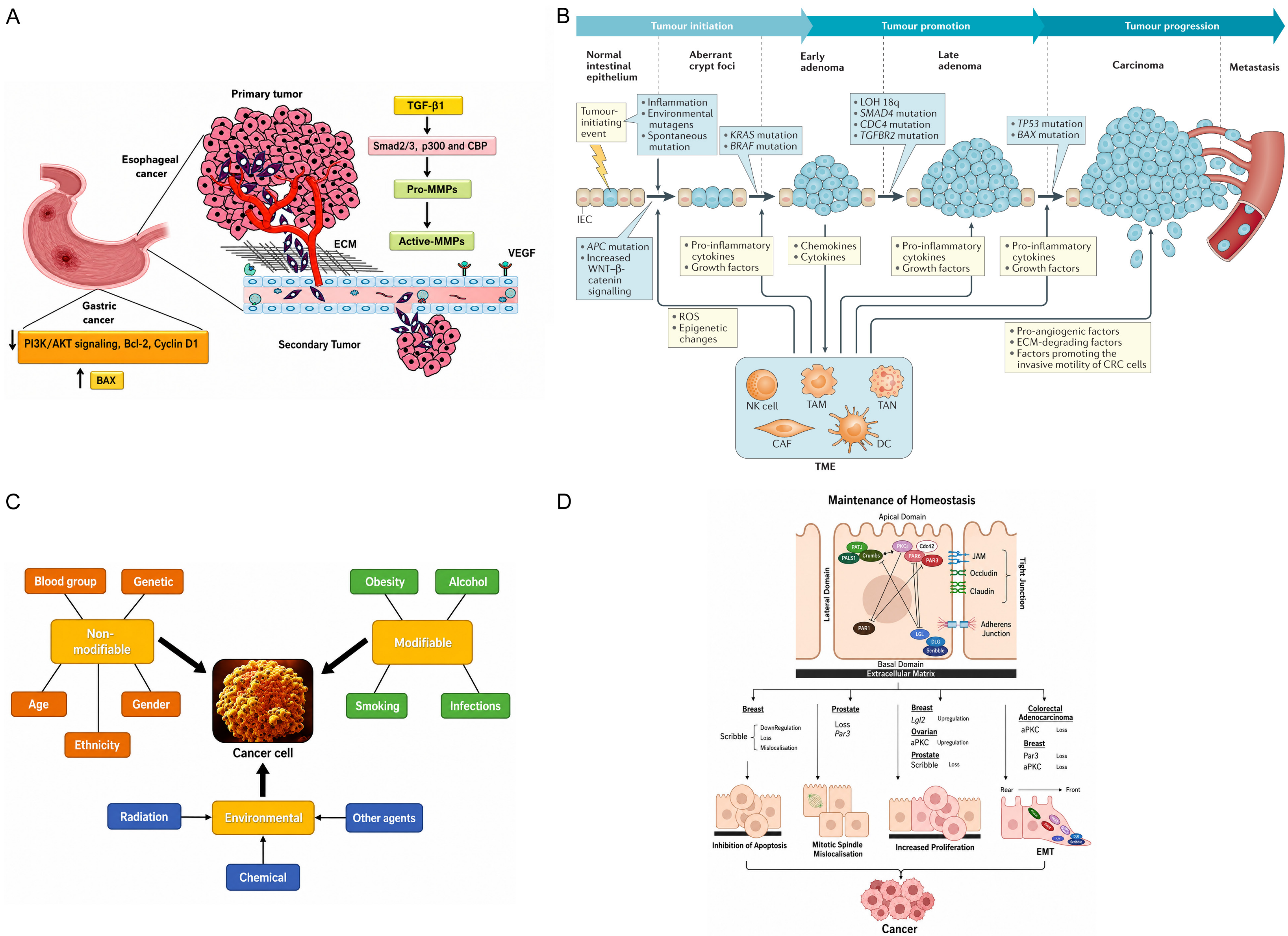

Figure 2. Integrated framework of gastrointestinal cancer development. A: Major environmental, lifestyle, and infectious risk factors associated with gastrointestinal cancers. B: Key molecular mechanisms, including genetic alterations, chronic inflammation, epigenetic changes, and dysregulated signaling pathways. C: Interaction of molecular pathways driving tumor initiation, progression, and therapeutic resistance. D: Organ-specific development of gastric, colorectal, and liver cancers based on distinct etiological drivers.

Obesity and diet

Obesity is a well-established risk factor for colorectal cancer. Epidemiological studies consistently show that increased body mass index (BMI) and abdominal adiposity are associated with higher colorectal cancer risk, particularly in men [18]. Excess body fat contributes to carcinogenesis through chronic inflammation, insulin resistance, and altered hormonal signaling. Dietary patterns also influence colorectal cancer risk. High consumption of red and processed meats has been associated with increased risk, potentially due to the presence of heme iron and the formation of carcinogenic N-nitroso compounds during digestion [19, 20].

Tobacco smoking

Tobacco smoking is another important lifestyle risk factor for colorectal cancer. Studies have demonstrated associations between smoking and the development of colorectal adenomatous polyps, which are considered precursors of colorectal cancer [21]. Recent research has reported elevated odds ratios for hyperplastic and adenomatous polyps among smokers, further supporting the role of tobacco exposure in colorectal carcinogenesis [7].

Age and gender

Age is one of the strongest determinants of colorectal cancer risk. Approximately 90% of colorectal cancer cases occur in individuals older than 50 years. Incidence rates increase significantly after the age of 40 and are generally higher in men than in women across many regions worldwide [22, 23]. Population-based studies in Asian countries have also demonstrated increasing colorectal cancer incidence with longer life expectancy and aging populations.

Alcohol consumption

Alcohol consumption has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC). Excessive alcohol intake has been linked to several cancers, including colorectal and liver cancers [24]. Epidemiologic studies indicate a dose-response relationship between alcohol consumption and cancer risk, with heavy drinkers showing significantly higher risk compared with non-drinkers.

Chronic diseases

Certain chronic diseases, including diabetes mellitus, hypertension, and cardiovascular disease, have also been associated with increased colorectal cancer risk. Studies conducted in several countries have reported higher colorectal cancer incidence among individuals with diabetes and other metabolic disorders, likely due to metabolic dysregulation, chronic inflammation, and shared lifestyle risk factors [25].

Prevention and management strategies of cancer

Recent research suggests that aspirin and other nonsteroidal anti-inflammatory medicines (NSAIDs) may have a role in reducing the risk of developing gastric cancer (GC). Multiple meta-analyses of observational studies have indicated a lower incidence of both cardia and non-cardia gastric cancer associated with NSAID use. However, there are some distinctions to note. For instance, while some studies have shown an inverse correlation with non-cardia gastric cancer but not cardia gastric cancer, there are differences in the observed effects. In general, aspirin use has been found to be inversely associated with various forms of gastric cancer in the most recent meta-analyses. These meta-analyses encompassed 13 and 15 studies, respectively, and included both case-control and cohort studies. However, these examinations did not yield specific findings for the detailed sub-sites of gastric cancer. Despite the promising findings, a pooled analysis of seven clinical studies that investigated the use of daily aspirin for the prevention of vascular events did not demonstrate a reduced risk of gastric cancer-related deaths when compared to the control group. This raises questions and highlights the need for further research to better understand the relationship between aspirin use and gastric cancer risk. Recent meta-analyses have indicated that taking statins may potentially reduce the incidence of gastric cancer (GC) by up to 30% [26]. However, it's important to note that when outlier results were eliminated from the analysis, the risk reduction was around 15%, and the outcomes were consistent across different trials. Interestingly, statin use has also been associated with a reduced risk of other malignancies, such as esophageal adenocarcinoma.

Several mechanisms have been proposed to explain this phenomenon. It's crucial to emphasize that statins do not consistently show a lower risk for all types of cancer incidence or mortality, especially in randomized studies. This highlights the need for further research to fully comprehend the potential connection between statin use and a reduced risk of gastric cancer.

More studies are necessary to explore and understand the complexities of this relationship [27]. The effective control of HBV replication through antiviral treatment and the widespread vaccination against HBV have resulted in a decrease in the incidence of hepatocellular carcinoma (HCC) [28]. Similarly, the high success rate of HCV treatment using direct-acting antiviral (DAA) therapy has led to a reduction in the incidence of HCC in individuals with chronic HCV infection. However, there is limited evidence regarding the impact of alcohol cessation or the reversal of non-alcoholic fatty liver disease (NAFLD) on the risk of HCC. Some studies have explored various therapies, such as vitamin A, vitamin K, and retinol analogues, for the chemoprevention of HCC. Currently, there is growing interest in the potential role of metformin, statins, coffee, and aspirin in preventing HCC, regardless of the underlying liver disease. Although statins have been extensively studied for repurposing in various medical conditions, controlled trials have not provided conclusive evidence of a decreased incidence of HCC with statin use. In contrast, aspirin has shown modest benefits with limitations due to resistance in HCC prevention. For instance, data from nationwide Swedish registries indicated that aspirin use reduced the estimated cumulative incidence of HCC from 8% to 4% after a median follow-up of 8 years. Several cohort and case-control studies have also demonstrated a dose-dependent relationship between coffee consumption and a reduced incidence of HCC in both the general population and individuals with chronic liver disease [29]. Metastatic gastric cancer (GC) cases often manifest in various areas of the stomach mucosa following the endoscopic removal of the primary tumor. A multicenter study on metachronous stomach tumors subsequent to endoscopic resection revealed that the elimination of Helicobacter pylori significantly reduces the risk of developing new GC, especially among individuals already at high risk. This study also found that patients with intestinal metaplasia (IM) and mucosal atrophy benefit from H. pylori eradication. However, contrasting findings from other investigations suggest that *H. pylori* removal is protective against stomach cancer only for individuals without IM or gastric mucosal atrophy.

Retrospective analysis of individuals with early GC who underwent endoscopic resection and developed metachronous GC indicated that the group that retained *H. pylori* had a higher cancer risk compared to the group where the infection was eradicated. Additionally, Kato et al. [30] conducted a separate study demonstrating that effective *H. pylori* eradication reduces the risk of patients developing metachronous stomach cancer after endoscopic resection and significantly lowers cancer rates in the eradicated group compared to the control group. Several studies also indicate that *H. pylori* eradication can effectively slow the progression of stomach mucosal lesions in the precancerous stage. Furthermore, it may have the potential to completely suppress latent tumors, including those too small to be detected by endoscopy, while also delaying tumor growth. Overall, *H. pylori* infection is strongly associated with the development and progression of stomach cancer [31]. **Table 3** shows the gastric screening programs use in different countries [9].

Numerous studies have provided evidence that second-line chemotherapy, involving agents like taxane or irinotecan, offers a survival advantage compared to best supportive care (BSC) in patients with adequate performance status (PS) [32]. Furthermore, the effectiveness of the monoclonal antibody ramucirumab, which targets vascular endothelial growth factor receptor-2 (VEGFR-2), has been established through randomized phase III trials such as REGARD and RAINBOW. Consequently, all major guidelines recommend second-line chemotherapy regimens that include single agents like taxane, irinotecan, or ramucirumab [33].

The major risk factors associated with gastrointestinal cancers vary depending on the specific cancer type but often involve a combination of infectious agents and lifestyle-related factors. Gastric cancer is strongly associated with *H. pylori* infection, smoking, and dietary habits

Table 3. Gastric cancer screening programs implemented in selected countries

Country	Screening program	Screening technique	Implementation details
Japan	Nationwide gastric cancer screening program established since the 1960s; treatment for *Helicobacter pylori* infection is supported but routine screening is not universally implemented.	Photofluorography following barium meal	National screening program initiated in 1960 to facilitate early detection of gastric cancer.
South Korea	Nationwide screening program combining upper gastrointestinal endoscopy and photofluorography.	Upper endoscopy and photofluorography	Integrated screening strategy designed to improve early detection rates of gastric cancer.
Kazakhstan	Biannual upper endoscopy screening for esophageal and gastric malignancies.	Upper endoscopy	Program initiated in 2013 in six regions with plans for nationwide expansion. Implementation structure may require further alignment with organized screening standards.

Source: Adapted from gastric cancer screening studies (e.g., Pasechnikov et al., 2014).

Table 4. Major risk factors of gastrointestinal cancers

Cancer type	Major risk factors
Gastric cancer	*Helicobacter pylori* infection, smoking, high salt diet
Colorectal cancer	Obesity, sedentary lifestyle, red meat consumption
Liver cancer	HBV infection, HCV infection, alcohol abuse

such as high salt intake. Colorectal cancer is commonly linked to lifestyle factors including obesity, sedentary behavior, and high consumption of red or processed meat. In contrast, liver cancer is primarily associated with chronic viral infections, particularly HBV and HCV, as well as excessive alcohol consumption. Understanding these risk factors is essential for developing effective prevention strategies and promoting early detection of gastrointestinal cancers (**Table 4**).

Tumor microenvironment and immune regulation

The tumor microenvironment plays a central role in gastrointestinal cancer progression and therapeutic response. It consists of immune cells, stromal components, cytokines, and extracellular matrix elements that interact dynamically with tumor cells. Chronic inflammation is a key driver of carcinogenesis, particularly in gastric and liver cancers, where persistent infection and tissue injury promote a pro-tumorigenic environment [6, 12].

Immune evasion is another hallmark of gastrointestinal cancers, mediated in part through immune checkpoint pathways such as programmed cell death protein 1 (PD-1) and its ligand PD-L1. Immune checkpoint inhibitors have demonstrated clinical benefit in selected patient populations, including microsatellite instability-high colorectal cancer and subsets of gastric and liver cancers [6-8]. However, responses remain variable, highlighting the need for improved biomarkers and combination therapeutic strategies.

Integrative perspective on gastrointestinal cancers

The development of gastrointestinal cancers is driven by a complex interplay of environmental, lifestyle, and infectious risk factors that activate multiple molecular pathways. As illustrated in **Figure 2**, these factors contribute to genetic alterations, chronic inflammation, epigenetic changes, and dysregulated signaling pathways, ultimately leading to tumor initiation and progression.

However, important differences also exist. Gastric cancer is strongly associated with *H. pylori* infection and molecular subtypes such as HER2-positive disease. Colorectal cancer progression follows a well-defined adenoma-carcinoma sequence, whereas liver cancer is closely linked to chronic liver disease and cirrhosis. These distinctions highlight the need for both shared and cancer-specific therapeutic strategies.

This integrative perspective underscores the importance of developing unified frameworks that combine molecular biology, clinical cha-

Table 5. Comparative overview of gastric, colorectal, and liver cancers, highlighting key risk factors, molecular mechanisms, diagnostic approaches, therapeutic strategies, and major clinical challenges

Cancer type	Key risk factors	Major molecular alterations/pathways	Diagnostic approaches	Current therapeutic strategies	Key challenges
Gastric cancer	*Helicobacter pylori* infection, high-salt diet, smoking	HER2 amplification, TP53 mutation, MET activation, VEGF pathway	Endoscopy with biopsy, imaging (CT/MRI), biomarkers	Surgery, chemotherapy, targeted therapy (trastuzumab, ramucirumab), immunotherapy (PD-1 inhibitors)	Late diagnosis, heterogeneity, limited response to targeted therapy
Colorectal cancer	Obesity, red/processed meat, physical inactivity, smoking, alcohol	APC mutation, KRAS, TP53, BRAF; chromosomal & microsatellite instability	Colonoscopy, fecal occult blood test, imaging, molecular profiling	Surgery, chemotherapy, targeted therapy (EGFR inhibitors, VEGF inhibitors), immunotherapy	Drug resistance, mutation-driven therapy limitations, screening disparities
Liver cancer (HCC)	HBV/HCV infection, alcohol use, cirrhosis, aflatoxin exposure	Wnt/β-catenin activation, TP53 mutation, TERT alterations	Ultrasound, CT/MRI, alpha-fetoprotein (AFP), biopsy	Surgery, liver transplantation, locoregional therapy (TACE, RFA), targeted therapy (sorafenib, lenvatinib), immunotherapy	Late-stage detection, underlying liver disease, limited treatment eligibility

racteristics, and therapeutic responses to improve personalized treatment approaches.

To provide a consolidated overview of the key risk factors, molecular mechanisms, diagnostic approaches, and therapeutic strategies across major gastrointestinal cancers, a comparative summary is presented in **Table 5**. Emerging evidence suggests that the gut microbiome plays a role in gastrointestinal carcinogenesis, particularly in colorectal cancer. Alterations in microbial composition have been associated with chronic inflammation, immune modulation, and metabolic changes that may promote tumor development. However, the clinical relevance of microbiome-targeted interventions remains an area of ongoing investigation [7].

Limitations

A key limitation in current literature is the lack of integration between epidemiological trends, molecular mechanisms, and therapeutic strategies. Gastrointestinal cancers share overlapping oncogenic pathways, including dysregulation of TP53, aberrant activation of Wnt/β-catenin signaling, and alterations in growth factor pathways such as EGFR and VEGF. These shared mechanisms not only drive tumor progression but also influence therapeutic responsiveness. Therefore, integrating molecular insights with clinical management is essential for advancing precision oncology and improving patient outcomes.

Conclusion and future perspective

Gastrointestinal cancers, including gastric, colorectal, and liver cancers, remain a major global health challenge due to their high incidence, late-stage diagnosis, and limited survival outcomes. A key take-home message from this review is that, despite shared oncogenic mechanisms, these cancers exhibit substantial biological heterogeneity, which underlies variable responses to current therapies.

Recent advances in molecular profiling and targeted and immune-based therapies have improved patient management; however, their clinical benefits remain inconsistent and largely restricted to selected subgroups. Persistent challenges, including tumor heterogeneity, unreliable biomarkers, and therapeutic resistance continue to limit treatment efficacy. In addition, delayed diagnosis remains a critical barrier to improving outcomes.

Future research should move beyond single-pathway approaches toward integrated strategies. Priorities include the development of robust, clinically actionable biomarkers, incorporation of multi-omics data into routine clinical decision-making, and the design of rational combination therapies to overcome resistance. Furthermore, improving early detection through non-invasive screening and better understanding tumor-microenvironment interactions will be essential.

Acknowledgements

This study was supported by Major Project of Philosophy and Social Sciences Research in Jiangsu Universities (Grant No. 2023SJZDSZ-017) and Nantong University Clinical Medicine Special Research Fund Project (Grant No. 2025LZ015).

Disclosure of conflict of interest

None.

Abbreviations

BMI, Body Mass Index; CRC, Colorectal Cancer; HCC, Hepatocellular Carcinoma; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HPV, Human Papillomavirus; IARC, International Agency for Research on Cancer; OR, Odds Ratio; RR, Relative Risk; SEER, Surveillance, Epidemiology, and End Results; VO_2 max, Maximum Oxygen Uptake; WHO, World Health Organization; WCRF, World Cancer Research Fund; AICR, American Institute for Cancer Research.

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