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Review Article

Systemic Diseases and Gastrointestinal Cancer Risk

Naila Malkani[1], Muhammad Usman Rashid[2]*

[1]Department of Zoology, Government College University, Lahore, Punjab, Pakistan, [2]Department of Basic Sciences Research, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Punjab, Pakistan

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Correspondence:
Muhammad Usman Rashid, Department of Basic Sciences Research, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Punjab, Pakistan.
E-mail: usmanr@skm.org.pk

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Abstract

Importance: Gastrointestinal (GI) cancers are the second leading cause of cancer-related deaths worldwide. **Observations:** The global challenges GI cancers pose are high, especially in middle- and low-income countries. Patients with these cancers present with symptoms of poor appetite, weight loss, heartburn, abdominal pain, fatigue and anaemia. Several risk factors contribute to GI cancers, including age, gender, obesity, pathogenic infections, smoking cigarettes, alcohol consumption and dietary habits. Most of these cancers are sporadic. However, some patients are at high risk due to a family history of GI cancers. Systemic diseases affect multiple organs, and their chronic occurrence elicits inflammatory responses at various sites. These diseases also contribute to GI cancers. **Conclusion and Relevance:** In this review, we discuss that untreated systemic diseases, including diabetes, hepatitis, acquired immune deficiency syndrome, ulcers and hypertension, can potentially lead to GI cancers if they remain untreated for a longer period. Systemic diseases initiate oxidative stress, inflammatory pathways and genetic manipulations, which altogether confer risks to GI cancers. Here, we describe the association between systemic diseases and their underlying mechanisms leading to GI cancers.

Keywords: Epidemiology, gastrointestinal cancer, global burden, inflammation, risk factors

Introduction

Among humans, the gastrointestinal (GI) tract comprises a series of organs joined in a tube form and provides nutrients, clears toxic waste and maintains immune functions.[1] Due to this significance, a GI tract abnormality may cause serious health consequences. A prolonged illness in the GI tract can also lead to cancer of the GI tract.[2]

Globally, 5 million new GI cancer cases and 3.5 million deaths were estimated in 2020. GI cancers are the second leading cause of cancer-related deaths worldwide. GI cancer refers to the

malignancies of several organs, including the oesophagus, stomach, liver, pancreatic, colon and rectum [Figure 1].

The presenting complaints among individuals with these cancers include poor appetite, weight loss, heartburn, abdominal pain and anaemia.[3] The majority of GI cancers are sporadic, that is, with no family history of cancer. However, up to 10% of GI cancers are hereditary, that is, with a family history of cancer. The chances of recovery increase many folds if diagnosed early.[4] Taken together, the global challenges posed by GI cancers in public health are very high.[5]

Considering the importance of GI cancers, we described major GI cancers, their prevalence and the potential risk factors associated with these cancers. However, the primary focus of the current review is on the association of systemic diseases with the complications of GI cancers.

Classification of GI Cancers

Oesophageal cancer

Oesophageal cancer arises in the oesophagus with symptoms of dysphagia, weight loss, indigestion and cough. Globally, 604,100 new cases and 544,076 deaths were estimated in 2020. It is the sixth leading cause of cancer-related death worldwide. The incidence and mortality of this cancer vary geographically, being common in Eastern Asia and Africa. It is more prevalent in men compared with women.[5]

Histologically, the major subtypes include adenocarcinoma and squamous cell carcinoma. It is an aggressive tumour. The major sites of tumour metastasis include lymph nodes, lungs, liver, bones, adrenal glands and the brain. Early diagnosis can increase the 5-year survival rate up to 45%. Several tumour markers facilitate early diagnosis and prognosis, including the carbohydrate antigen

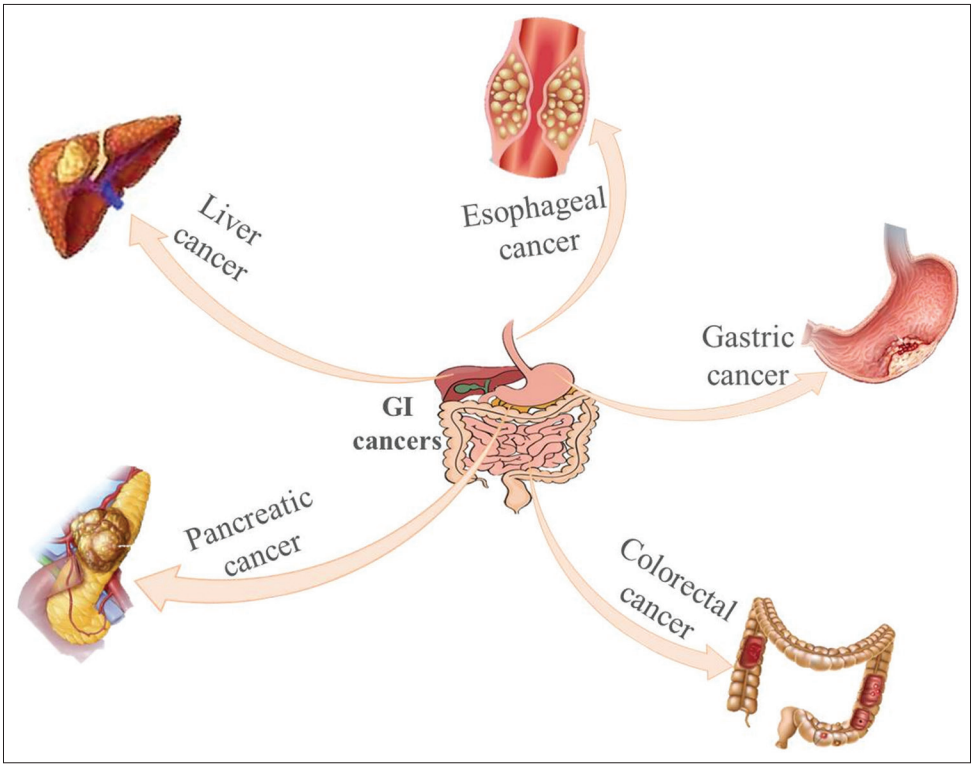

Figure 1: Classification of gastrointestinal cancers

19–9 (CA19–9) and carcinoembryonic antigen (CEA).[6] Multidisciplinary team management is necessary for treating oesophageal cancer patients, including chemotherapy, radiotherapy, surgery and recently emerging targeted therapy.

Gastric cancer

Gastric cancer develops in the stomach, and major sites include cardia (oesophageal-gastric junction) and non-cardia (distal stomach). Initial symptoms include acid reflux, indigestion, loss of appetite, fatigue and a lump in the stomach. Globally, 1,089,103 new cases and 768,793 deaths were estimated in 2020. It is the third leading cause of cancer-related deaths worldwide. The incidence and mortality rates are high in Asia and Africa, followed by Europe. It is more common in men than women.[5] Recently, there has been an unexplained reduction in the mortality rate, possibly due to advanced healthcare facilities, improved hygiene conditions and economic development.[7]

Over 95% of gastric cancers are adenocarcinomas.[8] This aggressive cancer grows in the stomach wall and rarely forms a mass or tumour, therefore challenging to diagnose at an early stage. The metastasis occurs frequently to the liver, peritoneum, lungs and bones. On early diagnosis, localised gastric cancer has a 5-year survival rate of about 70%. The diagnostic tumour markers include CEA, CA19-9 and cancer antigen 72-4 (CA72-4). However, these markers are not very effective, as they lack specificity. Therefore, a new biomarker, monoclonal gastric cancer 7 antigen (MG7-Ag), is emerging as a significant alternative.[9] Multidisciplinary team management is necessary to treat gastric cancer patients, including gastrectomy, chemotherapy, radiation therapy and immunotherapy.

Liver cancer

Liver cancer can arise in the hepatocytes (hepatocellular carcinoma, HCC; 75%), bile duct (cholangiocarcinoma; 10–20%) and blood vessels (liver angiosarcoma; rare). Common early symptoms include yellow skin, eyes, urine, loss of appetite, nausea, vomiting, abdominal swelling and fatigue. Globally, 905,677 new cases and 830,180 deaths were estimated in 2020. It is the fourth leading cause of cancer-related deaths worldwide. Geographical patterns show that it is common in Asia and Africa. It is more common in males as compared to females. Its rates have recently increased in the United States, Australia and Europe. However, they have been decreasing in Asia.[5]

Early diagnosis can increase the 5-year survival rate up to 33%. However, the majority of these cancer patients present at the advanced stage. Serum alfa-fetoprotein is a critical diagnostic tumour marker that is effective in 50% of cases.[10] Multidisciplinary treatment options include surgery, liver transplant, chemotherapy, radiation therapy, transcatheter arterial chemoembolisation, radiofrequency ablation and immune therapy. However, lung and bone metastasis make the treatment difficult.

Pancreatic cancer

Pancreatic cancer arises as an aggressive adenocarcinoma (90%) in pancreatic cells to produce digestive enzymes or as neuroendocrine tumours (1–2%) in pancreatic cells to produce hormones. The symptoms of this cancer rarely appear until it presents at an advanced stage. It includes abdominal pain radiating to the back, weight loss, fatigue, yellow and itchy skin, dark stools and blood clots. Globally, 495,773 new cases and 466,003 deaths are estimated in 2020. It is the seventh leading cause of cancer-related deaths worldwide. It is equally common for both genders. It is most common in Europe, followed by North America, Australia, Asia, and Africa.[5]

Early detection of pancreatic tumours is not possible due to the anatomical location of the pancreas. The 5-year survival rate is lower than other cancers, that is, 5–10% only. It metastasizes to the liver and peritoneum. CA19-9 is the only biomarker available for its prognosis.[11] Multidisciplinary team management is necessary for pancreatic cancer

patients, including total and distal pancreatectomy, chemotherapy, radiotherapy and recently targeted therapy.

Colorectal cancer (CRC)

CRC arises as polyps in the inner lining of the colon and rectum. The most common sites of this cancer include descending colon, sigmoid colon and rectum. The symptoms comprise diarrhoea, constipation, rectal bleeding, prolonged abdominal distress, fatigue and weight loss. Globally, 1,931,590 new cases and 935,173 deaths are estimated in 2020. It is the second leading cause of cancer-related deaths worldwide. CRC is more prevalent among men as compared to women. It is most commonly reported in Australia, New Zealand, North America and Europe and is less common in South-Central Asia.[5]

Early diagnosis of CRC is possible with routine checkups, which increases the 5-year survival rate to 90%. The metastatic sites include the liver, lungs, abdomen, ovaries and brain. The biomarkers used for its prognosis are CA19–9 and CEA.[12] Multidisciplinary treatment options include polypectomy, endoscopic mucosal resection, laparoscopy, a partial colectomy, chemotherapy, radiotherapy, immunotherapy and targeted drug therapy.

Global Burden of GI Cancers

Overall, GI cancers account for 35% of cancer-related deaths worldwide. The incidence and mortality of GI cancers vary geographically and depend on the affected organ, socioeconomic conditions, lifestyle, dietary and hygiene habits. Figures 2a and b illustrate a global burden of GI cancers according to the latest statistics provided by Globocan.[5]

Major Risk Factors of GI Cancers

Obesity

Obesity plays a considerable role in developing oesophageal, liver, pancreatic and CRCs.[13-18] Obese

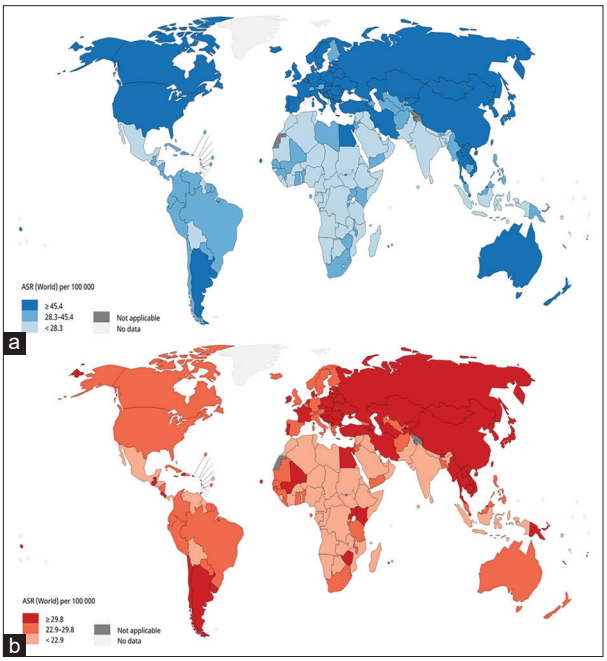

Figure 2: The estimated age-standardized (a) incidence, and (b) mortality rates of gastrointesntinal cancers in 2020.[5]

individuals risk developing gastroesophageal reflux disease, which may lead to oesophageal cancer.[19] Obesity triggers several pathways, including insulin signalling, TNF-α and IL-1 stimulation, and leads to NF-kB activation. These signalling pathways are essential for tumour development, including increased proliferation, angiogenesis and decreased apoptosis.[20] The immune mechanisms of anti-inflammatory cells do not function well during obesity.[21] Obesity mimics low-intensity chronic inflammation by macrophage infiltration of the adipose tissue.[22] Angiogenic markers are highly expressed in adipose tissue.[23] All these factors contribute to the development of GI cancers among obese individuals.

Smoking and alcohol

Smoking and alcohol are considerable etiological factors for GI cancers. Case–control studies showed the association of alcohol consumption with gastric, liver, pancreatic[24] and colorectal[25] cancers. The carcinogens in tobacco smoke and alcohol make the GI tract vulnerable to tumour formation. Acetaldehyde is a potent carcinogen

in tobacco smoke and alcohol metabolite, which causes alterations in the aldehyde dehydrogenase gene. Individuals with compromised DNA repair mechanisms confer an increased risk of GI cancers.[26-28] Smoking also leads to Barrett's oesophagus, which may lead to adenocarcinoma of the oesophagus, the most common but slowly progressing type of oesophageal cancer.[29]

Infections

Prolonged or untreated infections can also lead to GI cancers. Human papillomavirus,[30] Epstein–Barr virus,[31] Herpes simplex 1 virus[32] and cytomegalovirus[33] are associated with the oesophageal, gastric and CRC. A bacterial infection such as Helicobacter pylori increases the risk of developing gastric cancer.[34] Likewise, other pathogens like liver fluke may also infect the GI tract and lead to cancer.[2]

Dietary habits

Dietary habits play a significant role in the overall well-being of individuals. Prior studies have reported the influence of poor diet on the development of stomach and colon cancers.[35] Increased consumption of red meat, high salt and low-fibre diet contributes to the development of GI cancers.

Hereditary factors

Besides environmental factors, a positive family history of GI cancer in first- or second-degree relatives is an important risk factor for GI cancers. About 10% of all GI cancers have a genetic predisposition. Germline mutations in GI cancer susceptibility genes, including MLH1, MSH2, MSH6, APC, CDKN2A, CDH1 and PALB2 are reported.[36-38]

Other GI diseases

Several diseases of the GI tract, if untreated, may develop into cancer. Gastritis, a stomach inflammation, if chronically persists, can cause gastric cancer. Polyps in the lining of the large intestine can also develop colon cancer. A precancerous stage called GI metaplasia in the mucosal lining of the stomach is also associated with an increased risk of developing cancer.[39]

Besides these factors, age above 50 and gender may contribute to GI cancers.

Association of Systemic Diseases with GI Cancers

The modifications of cellular metabolism due to systemic diseases contribute to the initiation and progression of cancers. Multiple systemic diseases have shown an association with GI cancers [Figure 3].

Diabetes

Diabetes is characterised by hyperglycaemia and associated metabolic disorders. Hyperglycaemia activates macrophages to produce inflammatory cytokines and chemokine and further promotes inflammation. It initiates oxidative stress by over-expressing mitochondrial reactive oxygen species and nicotinamide adenine dinucleotide.[40] Oxidative stress is linked to cancer initiation and progression by inducing DNA mutations, which leads to impaired DNA repair, increased cell proliferation and genome instability.[41] Hyperglycaemia also causes hypoxia and supports oxidative stress to initiate tumours. Hyperinsulinemia and insulin resistance can also lead to cancer among type II diabetic patients. Elevated insulin binds to insulin receptors (IR) and activates the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways. This binding of insulin to IR also activates signalling cascades required for mutagenesis, anti-apoptosis, angiogenesis, and tumour-associated lymph angiogenesis. Insulin stimulates the synthesis of insulin growth factor-1, a structural similarity with insulin, activates the PI3K/Akt/mTOR and Ras/Raf/MAPK pathway and promotes cell proliferation.[42]

Several studies have reported the association of diabetes with GI cancers. This association varies with the type of cancer. Dixon *et al*. identified a potential link between diabetes and oesophageal

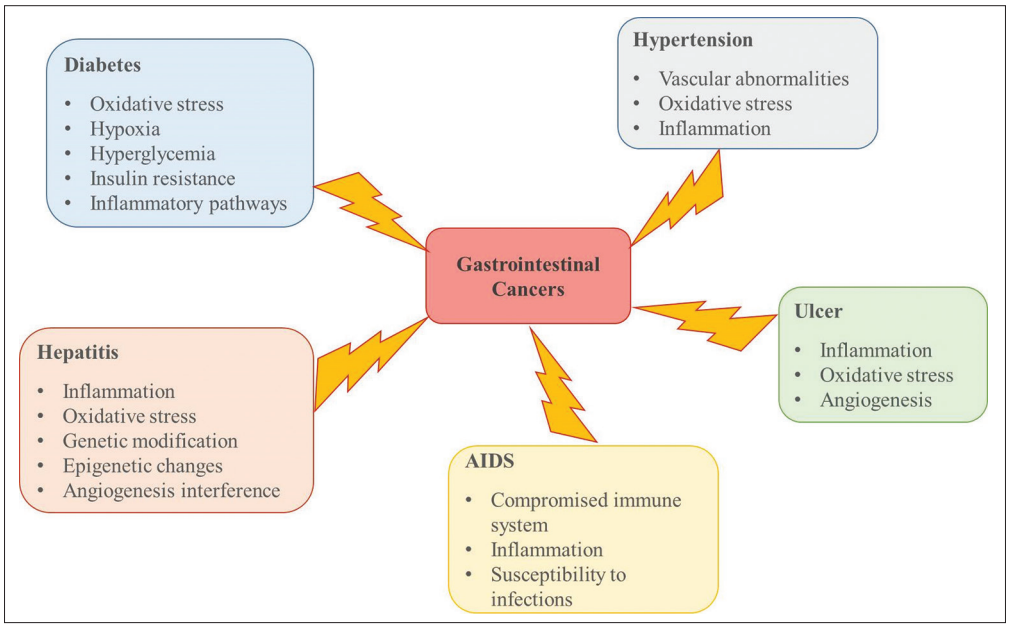

Figure 3: Schematic description of consequences of systemic diseases leading to gastrointestinal cancers

cancer.[43] A meta-analysis of 13 case–control studies[44] showed a correlation between diabetes and oesophageal cancer. The relationship between diabetes and the risk of liver cancer is also noted.[45,46] Obesity plays a significant role in this association.[47] Several observational studies[48,49] also showed high mortality in liver cancer patients with diabetes. There are conflicting reports regarding diabetes and gastric cancer. Few studies[50-52] showed a positive correlation, while others[53,54] showed no association.

Diabetes has also emerged as a prognostic risk factor for pancreatic cancer. Most of these patients (80%) reported impaired glucose levels at the time of diagnosis.[55] Epidemiological investigations reported diabetes is the leading cause of pancreatic cancer, with 1.5–2.0 fold increased risk after smoking and obesity.[56] Similarly, case–control and cohort studies showed an increased risk of CRC development among type 2 diabetics than non-diabetics. It is also linked with increased mortality and poor disease-free survival among CRC patients.[57,58]

Gender differences are pretty straightforward when determining the association between diabetes and GI cancers. Ma *et al*. evaluated the association of the duration of type 2 diabetes with CRC in 87,523 females and 47,240 males.[57] This association was more significant among males than females. Similarly, a meta-analysis of 38 gastric cancer studies showed an increased relative risk of diabetes among females than males. In contrast, a lower risk of hepatic and colon cancers was noted among females than males.[59]

Hepatitis B and C infection

Hepatitis B and C infections are the major causes of liver and other GI cancers. The following mechanisms are involved and lead to cancer.[60-62]

Chronic inflammation (from HBV and HCV infection) induces NF-κB and STAT activation and promotes cancer development.

HBV and HCV infection induces oxidative stress and differential expression of several genes involved in cell-cycle control, repairs DNA damage and promotes a tumour-supportive environment.

Genetic modifications due to the integration of viral sequences in the host genome produce truncated

or mutated proteins. Tumourigenesis is likely if these integration sites are within or near the genes involved in cell proliferation, survival, differentiation or migration.

DNA hypermethylation of promoter regions of onco/suppressor genes or the overexpression of certain miRNAs in response to viral infections is associated with GI cancers, especially HCC.

Angiogenic interference due to viral HBV and HCV proteins may lead to increased expression of VEGF, cyclooxygenase-2, MMPs and other important angiogenesis modulators, leading to tumourigenesis and metastasis.

Of all GI cancers, liver cancer has a significant association with hepatitis. About 25% of HCC cases are attributed to chronic HBV or HCV infection. Chronic liver inflammation and progression of HCC are linked to inflammatory cytokines such as TNF-α, interleukin 1, 6 and 23. Liver cirrhosis and HCC can be promoted by TGF-β induced by untreated or prolonged HCV infection. Stimulation of the PI3K-Akt pathway inhibits apoptosis and increases the survival chances of tumour cells. HCV proteins hamper the expression of tumour suppressor genes like p53 in HCC and lead to defects in cell-cycle control and apoptosis.[63]

Association of hepatitis B and C antigens in pancreatic and gastric cancers is reported. A population-based study from China showed that HBV was differentially associated with GI cancers.[64] Another population-based study from Taiwan showed an association of hepatitis B and C infection with the development of HCC, colorectal and pancreatic cancer.[65] Qadwai *et al*. presented a comprehensive review of the oncogenic potential of HCV in hepatic and extrahepatic cancers. They also reported varied evidence regarding the association between HCV and GI cancers.[66]

Acquired immune deficiency syndrome (AIDS)

Human immunodeficiency virus (HIV) infection causes AIDS with a weakened immune system. This weakened immune system further makes the body susceptible to other infectious diseases and cancer. During HIV infection, GI abnormalities are often observed, which, on prolongation, can lead to cancer.[67]

Regular immune surveillance is indispensable for eliminating pathogens and any circulating cells with tumourigenic potential. Among HIV-infected cases, the immune checkpoints do not function appropriately and let go of the potential targets, which otherwise will be destroyed. HIV infection decreases CD4+, increases CD8+T lymphocytes and causes CD4+/CD8+ imbalance, which is critical in fighting opportunistic tumour cells. Accumulation of mutations in genes involved in oncosuppression is also a key factor for tumour initiation.[68]

A comprehensive study of 16 cancer registry data from 1980 to 2007 showed increased oesophageal and gastric cancer risk in AIDS patients compared to the general population.[69] HIV infection can also cause liver inflammation, but the evidence for cancer development is insufficient. HIV and HBV coinfection are reported to cause liver cancer.[70] Otedo *et al*. showed that HIV and HBV coinfection are common risk factors for liver cancer in Kenya.[71] A multi-centre study from the United States and Canada showed patients with HIV and HBV/HCV coinfection had an increased tendency to present HCC at a young age.[72] The association between HIV infection with pancreatic and CRC is still unknown. A meta-analysis of 27 studies showed a similar rate of CRC in HIV-infected and uninfected individuals.[73] Therapies for GI cancers reduce cellular immunity, which potentially puts HIV patients at risk of opportunistic infections. Therefore, prior knowledge of HIV status is essential before defining treatment strategies.

Ulcers

Ulcers usually develop in the lining of the GI tract, especially in the stomach and small intestine. These ulcers can develop into cancer if they remain untreated or are accompanied by pathogenic

infections, smoking, alcohol consumption and poor dietary habits.

Gastric ulcers provide the site for infection for other pathogens, especially *H. pylori*. *H. pylori* enter the stomach cells and induce decay-accelerating factor (DAF) receptors. The continued DAF expression creates persistent inflammation. *H. pylori* infection causes DNA mutations and damages the cell linings of the stomach. This damaged tissue replaces the fibrous tissue with the initial symptom of stomach cancer. *H. pylori* infection also causes duodenal ulcers.[34,74] Proton-pump inhibitors (PPIs) are the most commonly prescribed medication for treating *H. pylori* infection. PPI usage can induce changes in the gastric environment, including the development of gastric atrophy, hypergastrinaemia and enterochromaffin cell hyperplasia leading to gastric cancer.[75] A recent large population-based study reported the association of PPI usage with an increased risk of gastric cancer.[76] Excessive use of anti-inflammatory drugs like aspirin reduces mucus formation from the stomach lining, accelerates acid production and reduces blood supply to the stomach. These factors collectively increase the risk of developing cancer from ulcers.

Søgaard *et al*. reported a long-term risk of GI cancers with gastric or duodenal ulcers in the Danish population.[77] A comprehensive study from Sweden concluded that gastric ulcers and gastric cancer are closely related, but duodenal ulcers have protective factors against gastric cancer.[78] Molloy and Sonnenberg also showed that gastric ulcers develop into gastric cancer.[79]

Hypertension

Increased cancer risk and cancer-related mortality are also noted among chronic hypertensive individuals.[80] Chronic hypertension causes peripheral resistance and the proliferation of smooth muscle cells in the vasculature. These abnormalities in cell proliferation and apoptosis pathways are due to irregular blood flow. Due to hypertension, oxidative stress in vessels can also contribute to inflammation. A chronic inflammatory response is observed in the endothelium during hypertension. The sustained inflammation in various organs and blood vessel is a definite cause of developing cancer.[81]

Wang *et al*. reported an increased pancreatic cancer risk among postmenopausal women on antihypertensive medications.[82] Conversely, a decreased CRC risk was noted among patients on antihypertensive medication.[83] Few conflicting reports showed an 8% increased colon cancer recurrence risk within 5 years among patients on antihypertensive medications as compared to others on non-hypertensive medications.[84] Kozłowska *et al*. observed higher clinical relevance of early CRC with hypertension, cancer recurrence, and death after treatment.[85]

Christakoudi *et al*. performed a comprehensive study on 307,318 participants to investigate the association of hypertension with various cancers. They concluded that hypertension is strongly associated with colon and oesophageal squamous cell carcinoma. However, no association was observed for oesophageal adenocarcinoma.[86] A meta-analysis of 148 studies showed a significant association of hypertension with oesophageal, liver and colon cancers, while no association was observed with gastric, pancreatic and gallbladder cancer.[84]

Conclusion

Overall, GI cancers account for 26% of the global cancer incidence and 35% of all cancer-related deaths, posing a substantial social and economic burden. Untreated systemic diseases are the constant source of oxidative stress and inflammatory responses. These chronic responses pave the way for cancer initiation in the body. Here, we presented the association of systemic diseases with GI cancers. This review suggests that (i) we should make substantial efforts to study the underlying mechanisms susceptible to GI cancers, (ii) we should appropriately and timely treat systemic diseases, and (iii) we should also

consider the comorbidities at the time of GI cancer diagnosis.

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Authors' Contributions

Conceived and designed the analysis: NM, MUR; Collected the data: NM, MUR; Contributed data or analysis tools: NA; Performed the analysis: NA; Wrote the paper: NM, MUR