1 Epidemiology, Microbiome, and Risk Factors Involved in Carcinogenesis of Esophagus, Gastric, and Intestine

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[Aspects of genomic risk factors are covered in Chapter 2].
[Aspects of relevant colorectal data are covered in Chapter 9].

Introduction

Cancers of the gastrointestinal tract (GIT) encompassing esophagus, stomach, and colorectum make up a significant proportion of cancers diagnosed worldwide and contribute to a considerable burden of disability-adjusted life years and years of life lost. (Kocarnik et al. 2022) The increase of GIT malignancies has been linearly associated with the human development index (HDI), likely due to the adoption of an affluent lifestyle with an increase in the consumption of processed meat, fast food, sedentary lifestyle, smoking, and increasing alcohol consumption. Obesity has become a worldwide pandemic and has been linked to the development of GIT cancers through multiple genetic and epigenetic microenvironment changes. Excess adipokines in obesity mediate a state of chronic inflammation resulting in the activation of multiple pathways that promote carcinogenesis. The understanding of the epidemiology and predisposing factors to GIT cancers is crucial in the development of early detection strategies. Screening efforts such as colonoscopy has reduced the burden of CRC worldwide. Similarly, screening of gastric cancers which has been adopted in Japan and Korea has reduced the numbers as well as improved the survival of gastric cancer.

In this chapter, we will discuss the epidemiology, global time trends, burden of disease, risk factors of esophageal, gastric and intestinal cancer, and strategies to reduce the incidence of these malignancies.

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Esophageal Cancer

Epidemiology of Esophageal Cancer

Global Burden and Time Trends of Esophageal Cancer

Esophageal cancer (EC) is the seventh most common cancer globally (Huang et al. 2021) and the sixth leading cause of cancer mortality (Sung et al. 2021). The rates of EC worldwide have increased in the last two decades from 319,969 cases in 1990 to 319,969 cases in 2019 with a relative increase of 67.07% (Li et al. 2021). In 2020 there were 604,100 new cases of EC worldwide with a corresponding age-standardized incidence of 6.3 per 100,000 (Morgan et al. 2022b). The five-year survival of EC remains dismal at less than 20%, owing largely to its late stage of diagnosis (Then et al. 2020). Mortality from EC demonstrated a relative increase of 55.97% from 1990 till 2019 (Li et al. 2021) and resulted in 544,100 deaths in 2020 with a corresponding age-standardized mortality of 5.6 per 100,000 (Morgan et al. 2022b). The highest incidence of EC was observed in East Asia accounting for 59.2% of all EC cases out of which 53.7% occurred in China. EC mortality was observed to be highest in Eastern Asia, accounting for 58.7% of EC-related deaths.

Distribution of Esophageal Adenocarcinoma and Esophageal Squamous Carcinoma

Histologically, EC is divided into adenocarcinoma (EAC) and squamous cell carcinoma (ESCC). The subtype of esophageal cancers varies according to geographic region. ESCC accounts for more than 85% of esophageal cancer cases worldwide (Arnold et al. 2015). There has been a change in the geographic distribution of EC with a rise in EAC, but a reduction in ESCC was noted in Western countries. The incidence rate of ESCC was double in males at 7.8 per 100,000 compared to females at 3.2 per 100,000 (Morgan et al. 2022b). This subtype is commonly seen in regions

with the highest EC rates, such as Eastern Asia, Southern and Eastern Africa where it constitutes 90% of the EC cases (Zheng et al. 2019). Meanwhile, in American and European countries EAC is predominantly seen (Ilson and van Hillegersberg 2018). The incidence of ESCC is declining, however the incidence of EAC has been increasing in the last decade (Li et al. 2021) primarily due to the increase in the rate of obesity. The commonest anatomical locations of EAC are gastroesophageal junction and cardia (Pohl et al. 2010). The geographic variation demonstrates the multi-hit theory that ethnicity, lifestyle, and genetic factors culminate in the development of EC.

Gender Distribution of Esophageal Cancer

There is a male predominance of EC with 70% of EC occurring in males (Sung et al. 2021). The age-standardized rate (ASR) for EC in males is 9.3 per 100,000 and 3.6 per 100,000 for females globally while the ASR mortality is 8.3 for males and 3.2 for females (Sung et al. 2021). Mortality rates were also observed to be two to three times higher in males, a finding that was most pronounced in Eastern Asia whereby rates of male mortality were eight times higher compared to females (Morgan et al. 2022b). Of note, the male-to-female ratio is highest at ages 50 to 54 and then declines thereafter (Mathieu et al. 2014) suggesting a correlation between androgens and EC and a protective effect of estrogen (Thrift 2021). Androgen receptor expression has been demonstrated in EAC tissue (Kim) (Sukocheva et al. 2015) as well as ESCC tissues (Sukocheva et al. 2015) and may be related to the propagation of its growth. A study by Petrick et al. found a high ratio of androgens to estrogen in patients with EAC. Patients with the highest quartile of androgen to estrogen had 2.4 times increased odds of EAC (Petrick et al. 2018).

Risk Factors for Esophageal Cancer

Barrett's Esophagus and Obesity

The incidence of Barrett's esophagus and obesity has been increasing worldwide which parallels the increase in EAC (Alexandre et al. 2014). Visceral obesity is a significant risk factor for gastroesophageal reflux disease (GERD), Barrett's esophagus (BE) and esophageal adenocarcinoma. Obesity is a state of chronic low-grade inflammation termed meta-inflammation whereby there is an increase in acute phase reactants such as leptin and TNF-a which have mitogenic properties and propagate the progression of Barrett's esophagus to EAC (Corley et al. 2007; Roberts et al. 2010). Adipose tissue had been shown to contain inflammatory cells which synthesize reactive oxygen species which have mitogenic properties (Kim et al. 2012). Leptin, an adipokine, also plays a crucial role in the pathogenesis of obesity induced carcinogenesis. Leptin enhanced cell mitosis and reduced cellular apoptosis via extracellular signal-regulated kinase, p38 mitogen-activated protein kinase, phosphatidylinositol 3′ kinase/Akt and Janus tyrosine kinase 2-dependent activation of cyclooxygenase-2 and prostaglandin E2 production in Barrett's derived EAC lineage of cells (Ogunwobi et al. 2006). Chronic inflammation is associated with epithelial metaplasia and promotes carcinogenesis by creating a microenvironment favorable for tumor development as well as progression (Jankowski et al. 2000). Obesity also exerts mechanical consequences promoting GERD.

GERD has a prevalence of 50% in patients with morbid obesity (El-Serag and Thrift 2021). GERD is the strongest risk factor for the development of Barrett's esophagus. The frequency of GERD symptoms influenced the risk of development of EAC whereby weekly symptoms increased the risk by five-fold (OR 4.92, 95% CI 3.90–6.22) and daily symptoms increased the risk seven-fold (OR 7.40, 95% CI 4.94–11.1) (Rubenstein and Taylor 2010). Barrett's esophagus is defined as the replacement of normal squamous epithelium in the lower esophagus by columnar epithelium with evidence of intestinal metaplasia, the hallmark of which is acid mucin-containing goblet cells. Molecularly, this cellular change heightens the risk of EAC through chronic inflammation. Non-dysplastic BE has the lowest risk of progression to EAC with a rate or progression of 0.3% per year (Hvid-Jensen et al. 2011). Once low-grade or high-grade dysplasia develop, the risk increases. Genomic profiling of BE tissue next to EAC revealed that BE cells have a mutational burden that is only marginally reduced than the median burden for EAC (Alexandrov et al. 2013). Telomere length is altered in chronic inflammation and in patients with BE a shorter telomere length was associated with a higher risk of progression to EAC (Vaughan and Fitzgerald 2015). Obesity and BE have synergistic factors on the development of EAC which explains the rise in the incidence of EAC in the recent years.

Smoking and Alcohol Consumption

Smoking also contributes to the risk of EAC with a robust dose-response association with the number of pack years of smoking (Singh et al. 2013). The risk factors for ESCC differ between Western and Asian population. Cigarette smoking and heavy alcohol consumption are risk factors for ESSC in the West (Pandeya et al. 2013). The OR of ESCC in those who smoked more than 30 pack years was 4.1 (95% CI, 2.7 – 6.2) with the rate being higher in men compared to women (5.5 vs 4.0) (Pandeya et al. 2013), whereas in South East Asia these risk factors were less common; instead, consumption of hot tea, opium, betel chewing, poor diet, low socioeconomic status, and inhalation of aromatic hydrocarbons, a by-product of indoor air pollution, are significant risk factors for the development of ESCC in this region (Sheikh et al. 2019). Heavy alcohol intake defined as more than 170 g per week markedly increased the risk of ESCC but not EAC with a similar dose-response relationship (Pandeya et al. 2009). Concomitant smoking further compounded this risk (Pandeya et al. 2009). Ethanol is the main component of alcohol and is broken down into acetaldehyde which has been classified as a human carcinogen by IAARC (Lachenmeier 2007) and is also a local irritant that promotes DNA methylation thereby promoting carcinogenesis.

Dietary Factors

Dietary risk factors associated with ESCC are increased consumption of *N*-nitroso compounds in men but not in women (Keszei et al. 2013). The N-nitroso compounds are carcinogenic and produce alkyl adducts in the DNA thus promoting mutagenesis (Guttenplan 1990). The risk of ESCC increases in micronutrient deficiencies such as vitamin C, E, folate, (Uhlenhopp et al. 2020) selenium (Steevens et al. 2010), and zinc. Zinc deficiency potentiates the carcinogenic effect of nitrosamines thereby promoting ESCC (Abnet et al. 2005). Other environmental factors that contribute to the development of ESCC are opium smoking, exposure to air pollutants, as well as the frequent consumption of hot beverages and a low intake of fruits and vegetables (Morgan et al. 2022b), and a high intake of red and processed meat (Nucci et al. 2021). These risk factors, were commonly observed in areas of high incidence of EC with the intake of hot beverages compounding the effects of smoking and alcohol intake (He et al. 2010).

Genetic Risks

Genomic-profiling of EAC has shown that this malignancy has an elevated mutational burden with one of the most mutated malignancy types (Alexandrov et al. 2013). Somatic mutation in TP53 was found in more than 83% of ESCC specimens (Song et al. 2014). Genetic mutations that regulate the cell cycle (CDKN2A, RB1, NFE2L2, CHEK1, and CHEK 2) and NOTCH 1 and NOTCH 3 mutations have been detected in 1–10% of ESCCs (D.-C. Lin et al. 2014a). Epidermal growth factor receptor (EGFR) was also found to be overexpressed in 59.76% of patients with ESCC and denotes a poor prognosis (Zhang et al. 2014). Single-nucleotide polymorphism DNA microarray has shown that 19% of patients with EAC demonstrate CCNE1 gene amplification. Raised levels of cyclin E were found in BE (5.8%), low-grade dysplasia (19.0%), high-grade dysplasia (35.7%), and EC (16.7%) (Zhou et al. 2014). The pathophysiology of esophageal cancer is depicted in Figure 1.

Esophageal Microbiome and Carcinogenesis

Dysbiosis in the Esophageal Adenocarcinoma cascade

The normal distal esophagus harbors a distinct microbiota that includes six major phyla: *Firmicutes*, *Bacteroides*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *TM7* (Pei et al. 2004). It also includes five major genera: *Streptococcus*, *Prevotella*, *Veillonella*, *Haemophilus, Neisseria* (Sharma et al. 2022). However, patients with gastroesophageal reflux disease (GERD) and Barret's esophagus (BE) have increased abundances of gram-negative bacteria such as *Prevotella*, *Neisseria*, *Campylobacter*,

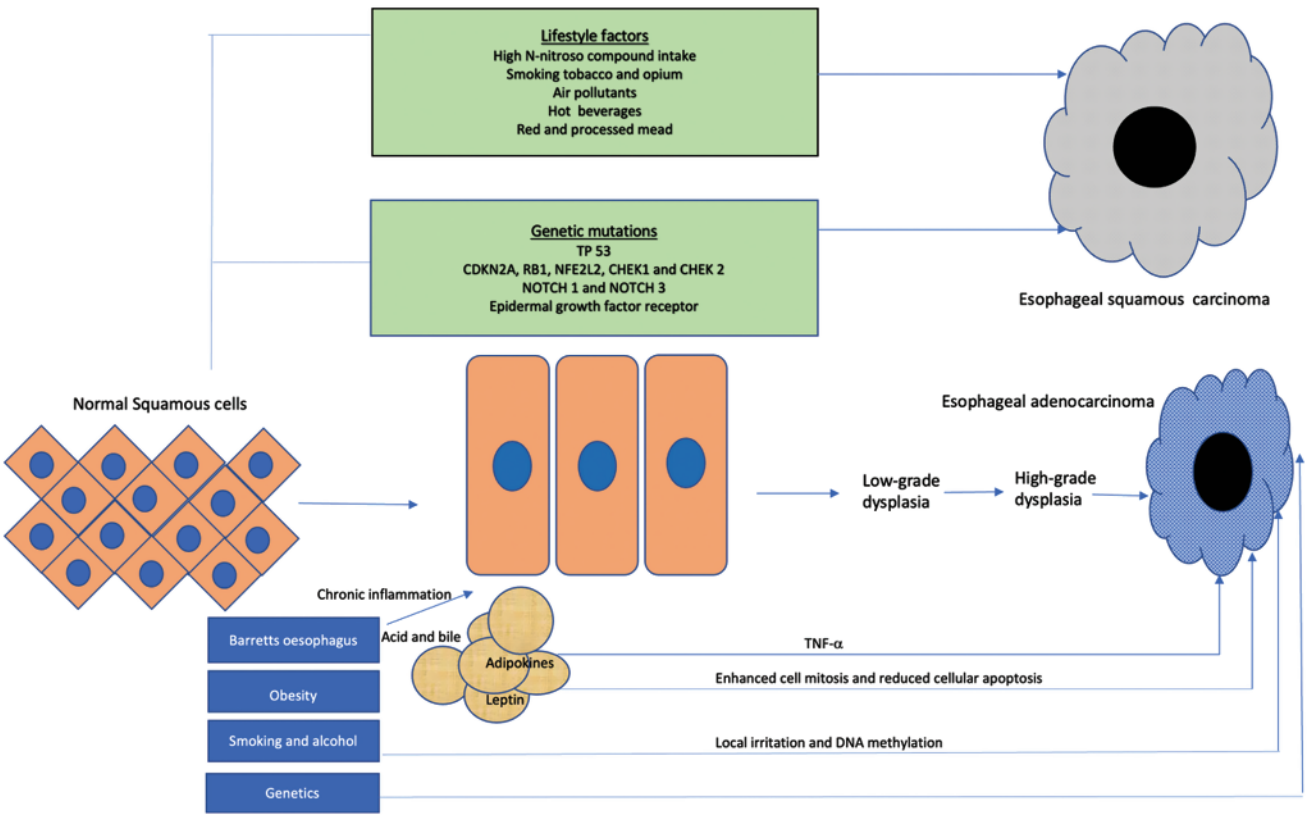

Figure 1 Pathways of esophageal cancer.

Leptotrichia, and *Fusobacterium* and decreased abundance of gram-positive bacteria as compared to the normal esophagus (Blackett et al. 2013; Deshpande et al. 2018; Zhou et al. 2020).

The enrichment of gram-negative bacteria including *Campylobacter*, *Leptotrichia*, *Fusobacterium*, *Rothia*, and *Capnocytophaga* are comparable in the esophageal microbiome of GERD and BE patients. When comparing to the microbiome at the normal mucosa adjacent to the metaplastic tissue of BE, there is decreased abundance of *Prevotella*, *Selenomonas*, *Campylobacter*, and *Fusobacterium* decreased in the latter (Lopetuso et al. 2020). An increasing density of microbial networks were found along the progression of normal esophagus to GERD and BE (Deshpande et al. 2018). This suggests that bacteria become more dependent on each other to sustain their growth along the progression of the disease stages from GERD to BE.

Decreased microbial diversity was found in patients with esophageal adenocarcinoma (EAC) as compared to healthy individuals (Elliott et al. 2017; Snider et al. 2019). While Elliott et al. found that *Lactobacillus fermentum* and lactic acid bacteria were enriched in EAC, Snider et al. found that high grade dysplasia and EAC had increased abundance of *Enterobacteriaceae* and *Akkermansia muciniphila* and decreased abundance of *Veillonella* (Elliott et al. 2017; Snider et al. 2019). In contrast, a recent study showed that *Veillonella* and other bacterial genera including *Atopobium*, *Actinomyces*, *Ralstonia*, *Burkholderia*, and *Lautropia* progressively enriched along the GERD, BE and EAC sequence. These discrepancies of microbial composition in EAC may be caused by the low resolution of 16S rRNA sequencing which is only able to identify bacteria at genus level. It is possible that the species within the same genus may positively or negatively associate with EAC, thus resulting in apparent differences at the higher genus levels.

Apart from bacteria, presence of human papillomavirus (HPV) was more prevalent in dysplasia and EAC but not in BE as compared to healthy controls (Rajendra et al. 2013). The virus was mostly detected at the transformation zone (Rajendra et al. 2013). Moreover, the viral oncogene was highly associated with disease severity in dysplasia and EAC patients with viral positivity than those with viral negativity (Rajendra et al. 2013). This suggests that HPV may contribute to esophageal carcinogenesis.

Dysbiosis and EAC Carcinogenesis

Toll-like receptors (TLR), that recognize pathogen associated molecular patterns, have been suggested to interact with the esophageal microbiota. For example, TLR2 is expressed in the basal keratinocytes in normal squamous esophagus (Verbeek et al. 2016). However, its expression is around the papillae high up in the epithelium in reflux esophagitis (Verbeek et al. 2016). In BE, TLR2 is expressed mostly in superficial epithelial cells and deeper crypts, and in lamina propria as well (Verbeek et al. 2016). In EAC, TLR2 is highly expressed as compared to normal esophagus, reflux esophagitis and BE and its expression is diffuse throughout the biopsy (Verbeek et al. 2016). Interestingly, long term activation of TLR2 together with bile salts in BE epithelial cells (BAR-T) results in higher expression of mitochondrial and lysosomal enzymes and other factors regulating the endocytosis as compared to the cells exposed to bile salt only. Furthermore, TLR2 also heterodimerizes with TLR1 or TLR6 to recognize a wider range of microbial components. Consistent with this, the expression of TLR1 and TLR6 is also increased in BE and EAC (Huhta et al. 2016). This suggests that a wide range of bacteria from the dysbiotic esophageal microbiota may activate the TLR2 signaling pathway under stress conditions, leading to inflammation. This is supported by a recent study that TLR2 stimulation results in induction of pro-inflammatory cytokines, chemokines, and factors that activate the inflammasome in macrophages in BE organoid and early-stage EAC cell models (Flis et al. 2021). Whether this TLR2-mediated inflammation contributes to the EAC progression requires further investigation in *in vivo* models.

Apart from TLR2, TLR4 has been implicated in EAC carcinogenesis. The expression of TLR4 is increased in reflux esophagitis, BE and EAC as compared to the normal squamous esophagus (Verbeek et al. 2014). Inhibition of TLR4 activation by an inhibitory peptide or by TLR4 gene mutation reduces the expression of inflammatory markers including intercellular adhesion molecule-1 and IL-8, and the development of hyperplastic and proliferative response of the esophageal mucosa in the surgical reflux mouse model (Gergen et al. 2021). This suggests that TLR4 activation promotes inflammation in reflux esophagitis, and BE, leading to the progression of EAC. This TLR4 activation could have resulted from LPS, a bacterial cell wall component, present in the dysbiotic esophageal microbiota. LPS has been shown to induce NFkB activation and IL-8 secretion in the BE cell line (BAR-T) via TLR4 (Verbeek et al. 2014). It also induces IL-8 secretion and cyclooxygenase-2 (COX2) expression in *ex vivo* BE cultures (Verbeek et al. 2014). Consistent with this, increased COX2 expression is found in BE mucosa (Buttar et al. 2002) and COX2 inhibitor decreases esophageal inflammation and the risk of EAC development in a BE rat models (Buttar et al. 2002). Taken together, these studies suggest that LPS from the dysbiotic esophageal microbiota activates TLR4 signaling pathway and COX2 expression in the esophageal epithelium. This leads to chronic inflammation and the progression of EAC.

Epidemiology of Gastric Cancer

Global Burden and Time Trends

There has been a significant shift in the global epidemiology of gastric cancer (GC) (Sekiguchi et al. 2022). Gastric cancer demonstrated the second highest incidence and mortality worldwide in 1990, while in 2020 Gastric cancer has become the fifth commonest cancer and the fourth common cause of cancer death worldwide (Sung et al. 2021).

Approximately 1.1 million cases of GC (720,000 males and 370,000 females) were diagnosed globally in 2020 which resulted in 770,000 deaths (65% males) (Morgan et al. 2022a). The global age-standardized incidence decreased by 28.0% in 2017 compared to 1990 while the age-standardized mortality decreased by 48.7% with the most remarkable decrease noted in Japan and South Korea (Etemadi et al. 2020) due to the advancement in diagnosis and treatment (Rawla and Barsouk 2019). However, the decrease in GC was less pronounced in populations such as the US Caucasian population, Canada, Columbia, Denmark, Brazil, Germany, Israel, and India (Luo et al. 2017).

Human Development Index has been shown to correlate with the incidence of gastric cancer. It is estimated that 86% (885,119 of 1,033,701) of new GC cases in 2018 were diagnosed in areas with high as well as very high Human Development Index. Eastern Asia had the highest incidence rates of GC (32.1 per 100,000 men and 13.2 per 100,000 women), followed by Central and Eastern Europe which had 17.1 per 100,000 men and 7.5 per 100,000 women, and then South America which had 12.7 per 100,000 men and 6.9 per 100,000 women. North America had one of the lowest rates of GC (5.6 per 100,000 men and 2.8 per 100,000 women) followed by Africa (~5 per 100,000 men and 3–4 per 100,000 women) (Bray et al. 2018).

Gastric Cancer Survival Trends

The survival rate of gastric cancer is highly dependent upon the stage at diagnosis and also exhibits regional variability. The overall age-standardized five-year survival rate of GC was 31% in the United States (Rawla and Barsouk 2019) and 20.7% in the United Kingdom. Meanwhile, the overall age-standardized five-year survival in South Korea was reported to be 68.9% and 60.3% in Japan (Allemani et al. 2018). The overall 5-year survival has improved over time from. The survival rate for all patients diagnosed in 2000 was 18.8% and it increased to 28.0% in 2010. The survival rate for localized gastric cancer in 2000 was 46% and this increased to 60% for those diagnosed in 2010. Those with regional disease diagnosed in 2000 was 20% while this improved to 30% for those diagnosed in 2010. Unfortunately, the 5-year survival rate for patients diagnosed with distant disease remains dismal at less than 5%.

(Thrift & El-Serag, 2020). References: Thrift, A. P., & El-Serag, H. B. (2020). Burden of gastric cancer. Clinical Gastroenterology and Hepatology, 18(3), 534-542.

Risk Factors for Gastric Cancer

Gastric cancer consists of two main topographic types: Cardia gastric cancer (cancer arising at the area of the stomach next to the esophagogastric junction) and non-cardia gastric cancer (cancer arising from the distal region of the stomach) and can be divided histologically according to the Lauren classification into intestinal and diffuse. *Helicobacter pylori* infection is associated with histologic subtypes and accounts for approximately 89% of non-cardia gastric cancer cases worldwide (Plummer et al. 2015). The intestinal type is the most commonly found in the high gastric cancer incidence populations and is associated with the Correa cascade of inflammation (Correa et al. 1975).

Helicobacter Pylori Infection

It has been reported that an almost a staggering 50% of the world's inhabitants are currently infected with *Helicobacter pylori* (Fan et al. 2021). *Helicobacter pylori* is commonly found in the stomach antrum or body. Numerous elements such as adhesins, urease, flagella, and vacuolating cytotoxin (VacA) promote *Helicobacter pylori* activity and injury to the gastric cells (Gastli et al. 2021). *Helicobacter pylori* infection triggers chronic active gastritis, which, if persists, results in gastric glandular loss termed chronic atrophic gastritis. Atrophy begins in the incisura and, with time, progresses to the anterior and posterior gastric wall, where it is replaced by metaplastic cells. Metaplastic cells then transform into low-grade dysplastic cells, high-grade dysplastic cells, and subsequently, invasive carcinoma (Thrift and Nguyen 2021). On a molecular level, there is an increase in the activity of arginase which acts as a catalyst of L-arginine hydrolysis which results in the formation of ornithine and urea (Alam et al. 2018). Urea then forms ammonia which neutralizes gastric acid thereby promoting an alkaline pH which improves the survival of *Helicobacter pylori* allowing it to propagate (Wu et al. 2021). It has been shown that the Wnt/b-catenin pathway plays an important role in gastric epithelial cell regulation. *Helicobacter pylori* triggers abnormal Wnt/b-catenin pathway signaling via b catenin stabilization in gastric epithelial cells, which results in abnormal cellular proliferation which leads to carcinogenesis (X. Song et al. 2015b) (Song et al. 2015b).

The reduction in incidence and mortality of gastric cancer is due to the decrease in NGC (Rawla and Barsouk 2019), which is attributed to the improved diagnosis and treatment of *Helicobacter pylori*. Most *Helicobacter pylori* infection occurs in early childhood which is transmitted through the orofecal route (Sonnenberg 2013). Globally there has been a decrease in the prevalence of *Helicobacter pylori* infection (Sjomina et al. 2018). Africa (79.1%) had the highest prevalence of *Helicobacter pylori* infection followed by Latin American and the Caribbean (63.4%) and Asia (54.7%) while the lowest prevalence was seen in North America (37.1%) and Oceania (24.2%) (Hooi et al. 2017). A urban-rural disparity was seen in the prevalence of *Helicobacter pylori* infection whereby higher rates of infection were seen in the rural areas and correspondingly higher rates of gastric cancer were also observed (Wen et al. 2017). On the other hand, gastric cardia cancer incidence has been rising, particularly among developed countries (Clinton et al. 2020). This has been attributed

to the increasing rates of smoking in developed countries. Data has shown that 11% of stomach malignancies worldwide and 17% of stomach malignancies in Europe are imputed to smoking (Clinton et al. 2020).

Smoking

Tobacco smoking has been linked with a variety of malignancies including gastric cancer. The Stomach Cancer Pooling Project (StoP) has shown that active smokers had a 25% greater risk of developing gastric cancer than never-smokers (OR, 1.25; 95% CI, 1.11–1.40). There was a linear relationship between cigarettes per day ($P<0.01$) and duration of smoking ($P<0.01$) with an OR od 1.33 (95% CI: 1.14 – 1,54). For 40 years of smoking and above, the risk was seen to be more marked for cardia than non-cardia gastric cancer (Praud et al. 2018). Quitting smoking was associated with a reduced rate of GC. The risk of GC of former smokers who quit more than ten years of tobacco became similar to that of never smokers (Praud et al. 2018).

Carcinogens found in tobacco such as the N-nitroso compound are pivotal to its carcinogenesis. In vitro studies have shown that tobacco smoke has a direct carcinogenic effect in the gastric mucosa. (Tayler and Piper 1977) In endoscopic studies, Tobacco smoking was demonstrated to promote dysplasia of gastric epithelium, chronic atrophic gastritis, and intestinal metaplasia (Kneller et al. 1992). Molecular mechanisms by which tobacco smoking promotes GC may be mediated via the polymorphism in the *GSTT1, SULT1A1, CYP1a1*, and *NAT2* genes which increase susceptibility to GC (Boccia et al. 2007). Smoking also has a compounding effect on the increased risk of susceptibility and persistence of *Helicobacter pylori* infection. Smoking also results in a lower efficacy of antibiotic eradication of *Helicobacter pylori* (Ferro et al. 2019).

Obesity and Lifestyle Factors

Obesity has also been shown to be associated with a modestly increased risk for cardia gastric cancer (X.-J. Lin et al. 2014a). Dietary factors that increase GC risk include a high salt diet (Morais et al. 2022) processed meat (Kim et al. 2019) nitrates (P. Song et al. 2015b). Excessive processed meat intake increased the risk for non-cardia GC but not cardia GC. Salt has been postulated to cause gastric mucosal damage and hypergastrinemia (Furihata et al. 1996) leading to chronic inflammation promoting *H. pylori* infection. Salt also potentiates the carcinogenicity of nitrates by enhancing its penetration. (Eusebi et al. 2020) Heavy alcohol consumption which is defined as more than five drinks per day increased the risk of gastric cancer (OR 3.13, 95% CI 1.15–8-64) (Laszkowska et al. 2021). A meta-analysis by Han et al. showed high total dietary fat intake more than 20 g/day correlated with an increased risk for GC (Han et al. 2015).

Genetic Risk

Hereditary cancer syndromes such as hereditary diffuse gastric cancer (HDCC), Lynch, hereditary breast and ovarian cancer (BRCA), Li-Fraumeni, familial adenomatous polyposis, and Peutz-Jeghers syndromes result in an increased risk for gastric cancer. Persons with HDCC syndrome have a 80% risk of developing GC (Hansford et al. 2015), While GC is usually sporadic, approximately 10% of GC cases have familial aggregation (Pocurull et al. 2021). HDCC is characterized by E-cadherin (CDH1) mutation results in an increased risk of early-onset diffuse gastric cancer and lobular breast cancer. HDCC is inherited in an autosomal dominant manner. The cumulative risk for gastric cancer in those with CDH1 mutations is 70% by 89 years for men and 56% for women (Hansford et al. 2015). It is recommended that any patient with two or more family members with a history of gastric cancer, irrespective of age with at least one diagnosed with gastric cancer, or anyone with a family member with diffuse gastric cancer at any age and lobular breast cancer diagnosed before the age of 70, a family history of two or more relatives with breast cancer diagnosed less than 50 years of age undergo CDH1 testing. Meanwhile, any patients who have been diagnosed with diffuse gastric cancer below the age of 50, have diffuse gastric cancer at any age who are of Maori ethnicity, have diffuse gastric cancer with a history or family history of cleft lip palate, a history of bilateral lobular breast cancer diagnosed before 70, or gastric cancer *in situ* signet ring or pagetoid spread of signet ring diagnosed less than 50 years of age undergo CDH1 testing (Blair et al. 2020).

Li-Fraumeni syndrome is an infrequently encountered hereditary cancer syndrome which is a result of TP53 germline mutation and is inherited in an autosomal dominant manner (Masciari et al. 2011). It is also associated with an increased risk of sarcoma, brain tumors, breast and adrenal cortical carcinomas, and breast cancer (Garber et al. 1991). Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary colorectal cancer syndrome that has a prevalence of 1 in 10,000 (Plawski et al. 2013). FAP is due to a mutation in the adenomatous polyposis coli (APC) gene. The endoscopic features of patients with FAP is multiple polyposis of the stomach. There is an increased prevalence of gastric adenomas, fundic gland polyps, and polyps with high grade dysplasia in these patients. There is a high rate of duodenal adenomas in patients with FAO reaching approximately 88 to 98% with the risk of duodenal malignancy as high as 18% by the age of 75. The risk of gastric adenocarcinoma is 1.3% in patients with FAP. Polyposis usually begins around puberty therefore it is recommended that colonoscopy screening begin at the age of 12 in patients with an affected family member (Bülow et al. 2012), hence it is recommended by international guidelines that screening esophagealgastroduodenoscopy (EGDS) should commence at age 25 (Monahan et al. 2020; van Leerdam et al. 2019; Yang et al. 2020).

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited genetic disorder that results in the development of mucocutaneous pigmentation and multiple hamartomatous polyps in the gastrointestinal tract. It is due to a mutation in the STK11 gene which is located in 19p 13.3 (Aretz et al. 2005). STK11 is a tumor suppressor gene that is responsible for cell cycle and cell proliferation pathways that regulate apoptosis and RAS-related cell transformation (Karuman et al. 2001). The development of GI malignancies in PJS occurs through the hamartoma-adenoma-carcinoma pathway. (Bosman 1999) PJS has an incidence of approximately 1 in 250,000 and carries a 15 to 18-fold increased risk of cancer compared to the general population (Kalloo and Shanahan 2016). A clinical diagnosis of PJS can be made when one of the criteria is met: two or more pathologically ascertained Peutz-Jeghers polyps, detection of Peutz-Jeghers polyps and family history of Peutz-Jeghers in a close relative, characteristic mucocutaneous pigmentation in the mouth, lips, nose, eyes, genitalia, or fingers with a family history of PJS, any Peutz-Jeghers polyps in a patient with a characteristic mucocutaneous pigmentation (Beggs et al. 2010). In view of the increased risk of malignancy, it is advocated that a screening EGDS be performed at eight years of age in those with PJS. If polyps are found, polypectomy should be performed and EGDs should be repeated in one to three-year intervals. If no polyps are found at baseline screening EGDs therefore the next EGD can be performed at 18 years of age (Monahan et al. 2020; van Leerdam et al. 2019).

Other Risk Factors for Gastric Cancer

Other less common risk factors for GC include Epstein-Barr virus infection, Menetrier's disease, and autoimmune gastritis. Epstein Barr Virus was found in approximately 8% of gastric cancers; however, there is inadequate evidence for a direct causal relationship for Epstein Barr Virus in gastric carcinogenesis (Group 2012). Menetrier's disease is a condition where hypertrophic gastropathy develops in the body of the stomach resulting in the formation of giant gastric folds, protein-losing enteropathy, and achlorhydria. Histologically, there is presence of massive foveolar hyperplasia (Toubia and Schubert 2008). Smoking increased the risk of development of Menetrier's disease however alcohol use and *Helicobacter Pylori* did not increase this risk. The risk of GC was 8.9% after 10 years of the diagnosis of Menetrier's disease and the survival was 72.7% at 5 years and 65% at 10 years (Almazar et al. 2021).

Autoimmune gastritis accounts for under 5% of chronic gastritis cases (Lahner et al. 2015). It is the result of autoimmune T-cell mediated destruction of the oxyntic mucosa of the proximal stomach which is mediated by autoantibodies against the parietal cells and intrinsic factor (Zhang et al. 2013). This results in the development of atrophy of the oxyntic gastric mucosa with hypo- or achlorhydria. Complications of B12 malabsorption (Pernicious anemia) and iron deficiency anemia ensue (Coati et al. 2015). Pernicious anemia carries approximately seven-fold higher risk of gastric malignancy (Weise et al. 2020). It is important to note that the hypo- or achlorhydria gives rise to hypergastrinemia and enterochromaffin-like cell hyperplasia which can develop into a neuroendocrine tumor (Bordi et al. 1995). The prevalence of enterochromaffin-like cell neuroendocrine tumors in autoimmune gastritis is markedly elevated compared to *Helicobacter pylori* gastritis (Waldum and Fossmark 2019). The pathophysiology of gastric cancer is depicted in Figure 2.

Factors Protective of Gastric Cancer

The Mediterranean diet which incorporates vegetables, legumes, whole grains, fish, and olive oil which are high in polyunsaturated fat and low in saturated fats and nitrites have been shown to be protective against GC in those with high adherence (Álvarez-Álvarez et al. 2021). The Stomach cancer Pooling (STOP) a global epidemiological study on GC demonstrated that there was a marked decrease in GC risk in those with highest tertile consumption of fruits (0.76, CI 0.64–0.90), vegetables (OR 0.68, CI 0.56–0.84) and fruits and vegetables combined (OR 0.61, CI 0.49–0.75) compared to those in the lowest tertile (Ferro et al. 2020). Other beneficial food include whole grains and nuts (Zhang et al. 2020), Vitamin D levels above 20 ng/ml (Kwak and Paik 2020), and ascorbic acid and polyphenols found in fruits and vegetables was found to lower the risk of GC (Toh and Wilson 2020).

Microbiome and Gastric Cancer

Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes are the major phyla present in the healthy gastric mucus layer (Fakharian et al. 2022). *Prevotella, Veillonella, Streptococcus, Neisseria, Fusobacterium*, and *Haemophilus* are the main genera present in the healthy gastric microbiota, but their abundance varies among human individuals from different geolocations (Fakharian et al. 2022). In general, the overall microbial load of the stomach is around 10^2–10^4 CFU/ml which is lower than that of the colonic microbiota (10^{10}–10^{12} CFU/ml) owing to the acidic environment that limits microbial colonization (J. Yang et al. 2021b).

Helicobacter pylori (*H. pylori*) plays a major role in the progression from atrophic gastritis to intestinal metaplasia to gastric cancer (GC) (Stewart et al. 2020). Chronic *H. pylori* infection induces chronic gastric inflammation, leading to atrophic gastritis (Goldenring and Mills 2022). These effects are mediated by multiple virulence factors of *H. pylori*. Of these, VacA increases the mitochondrial membrane permeability, impairs endocytosis trafficking, and triggers apoptosis in gastric epithelial cells (Gauthier et al. 2005; Matsumoto et al. 2011; Willhite and Blanke 2004). It also

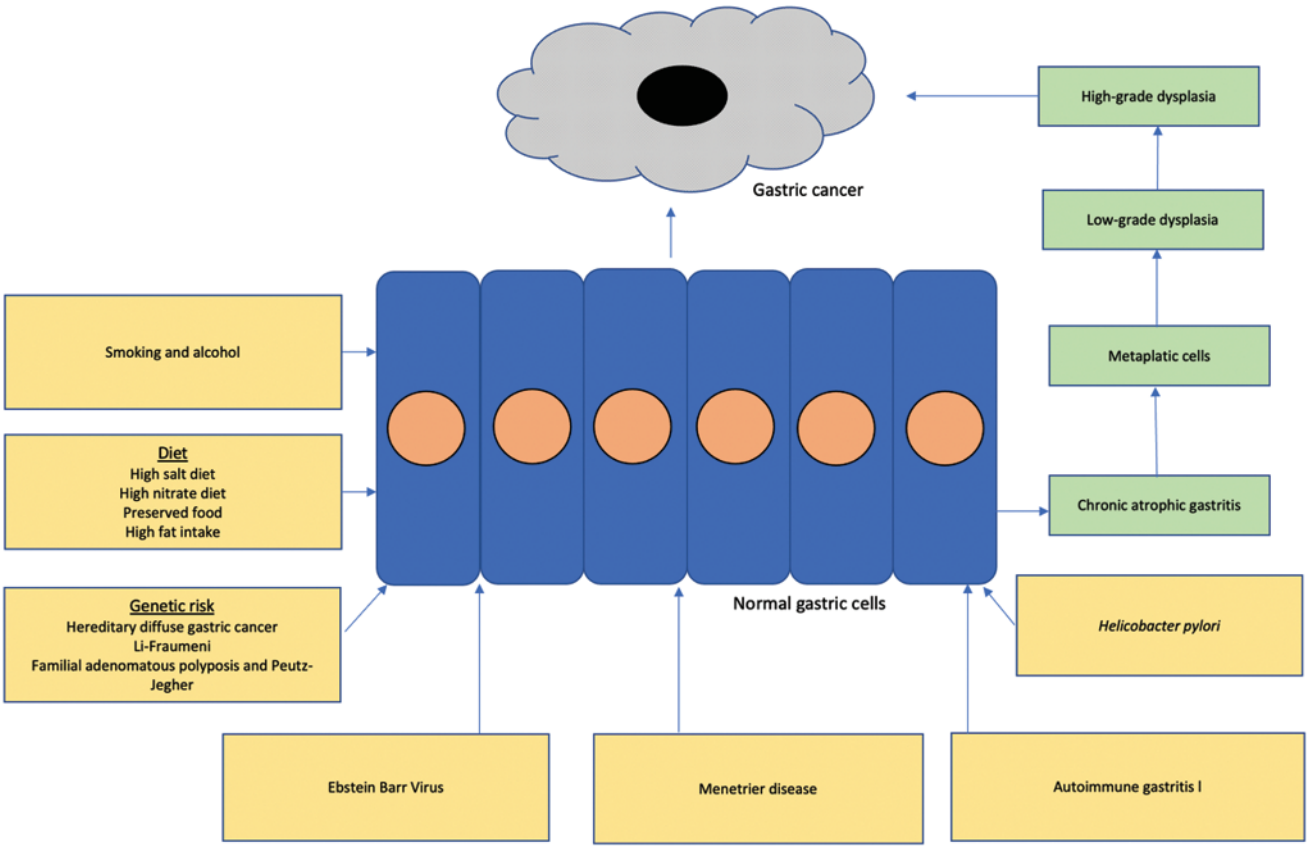

Figure 2 Pathways of gastric cancer.

stimulates mast cells to produce pro-inflammatory cytokines such as IL-6 and TNF-a (Supajatura et al. 2002), leading to the *H. pylori*-associated gastritis. Furthermore, VacA, g-glutamyl transpeptidase and bacterial cholesterol of *H. pylori* induce T_H17 immune responses, contributing to the development of gastritis. On the other hand, CagA and T4SS form a complex that deliver CagA to the infected host cells across the outer and inner bacterial membranes (Chung et al. 2019; Knorr et al. 2019). CagA then induces inflammatory responses and proliferation, inhibits apoptosis, impairs cell-cell junctions, and leads to loss of cell polarity in the gastric epithelial cells, thus promoting gastric carcinogenesis (Bagnoli et al. 2005; Buti et al. 2020, 2011; Yang et al. 2018). This chronic inflammation induced by *H. pylori* virulence factors enhances the production of reactive oxygen species and reactive nitrogen species which damage DNA (Shimizu et al. 2017). *H. pylori* also induces DNA damage via direct adhesion of live bacteria with the host cells and impairs the DNA repair system via the host long noncoding RNAs, SNHG17 (Toller et al. 2011). The DNA damage results in genomic instability and accumulation of mutations, leading to gastric carcinogenesis.

The chronic gastric inflammation results in the death of hydrochloric acid secreting parietal cells. The hypochlorhydria allows the gastric colonization and outgrowth of oral and lower bowel microbes that are not normally present in the acidic condition of the stomach, leading to dysbiosis of the gastric microbiota. The enriched oral bacteria in the mucosa of GC includes *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes* (Coker et al. 2018; Liu et al. 2022). This enrichment only occurs in GC but not in other early stages including superficial gastritis, atrophic gastritis, and intestinal metaplasia (Coker et al. 2018). In addition, *H. pylori* reduces microbial diversity, changes the microbiota composition, and weakens the interactions among gastric microbes (Liu et al. 2022). The first link between gastric dysbiosis and carcinogenesis was demonstrated by Lee et al., using the INS-GAS transgenic mouse model for gastritis with achlorhydria (Lee et al. 2008). Lee et al. treated the INS-GAS transgenic mice with three antibiotics including metronidazole, omeprazole, and clarithromycin prior to *H. pylori* infection (Lee et al. 2008). Killing of *H. pylori* by the antibiotics lowers the severity of gastric dysplasia several weeks post-infection (Lee et al.

2008). Intriguingly, INS-GAS transgenic mice treated with the antibiotics and without *H. pylori* infection also have a reduced severity of dysplasia (Lee et al. 2008). These data suggest that antibiotics not only eradicate *H. pylori* but also the gastric microbiota, protecting the mice from gastric carcinogenesis. This idea is further supported by two later studies. Lofgren et al. demonstrated that germ-free INS-GAS mice have a delayed development of gastric lesions as compared to INS-GAS mice with a more complex microbiota and *H. pylori* infection (Lofgren et al. 2011). Lertpiriyapong et al. further examined if a diverse gastric microbiota is required for the development of gastric lesions (Lertpiriyapong et al. 2014). The risk for gastric cancer development was compared among three groups of INS-GAS mice that were germ-free, had restricted microbiota (only containing *Lactobacillus, Clostridium, Bacteroides*), and had complex microbiota (Lertpiriyapong et al. 2014). They found that the rate of gastric cancer development is similar in mice with a restricted and complex microbiota (Lertpiriyapong et al. 2014). However, mice with a restricted microbiota have enhanced gastric inflammation, epithelial defects, oxyntic gland atrophy, epithelial hyperplasia, and dysplasia as compared to the germ-free mice (Lertpiriyapong et al. 2014). Taken together, these results suggest that *H. pylori* acts synergistically with the bacterial community for potentiating gastric neoplasia development.

Despite the above evidence, it remains unknown if gastric dysbiosis in humans is sufficient to induce gastric carcinogenesis. A recent study addressed this research question by transplanting the microbiota obtained from chronic superficial gastritis, intestinal metaplasia, or GC into germ-free wild type mice (Kwon et al. 2022). They found that the gastric microbiota from patients with intestinal metaplasia or GC colonized the mouse stomachs and induced premalignant lesions including loss of parietal cells, increased inflammation, and enhanced gastric cell proliferation (Kwon et al. 2022). These mice also developed gastric dysplasia after one year of transplantation (Kwon et al. 2022). These results suggest that the gastric dysbiotic microbiota from intestinal metaplasia and GC but not gastritis is sufficient to induce gastric carcinogenesis. They also explain why more than 50% of the world population are infected with *H. pylori* but only 1–3% of these infected individuals develop gastric cancer (Stewart et al. 2020). It is possible that *H. pylori* induces chronic gastritis and hypochlorhydria, providing a favorable environment for the development of gastric dysbiosis which in turn potentiates the gastric carcinogenesis with or without the synergistically carcinogenic effect by *H. pylori*. Further investigation is required to understand the molecular mechanism on how this gastric dysbiotic microbiota promote gastric carcinogenesis and to examine if this gastric dysbiosis could be treated to prevent gastric cancer.

Epidemiology of Colorectal Cancer

Global Burden and Time Trends of Colorectal Cancer

Colorectal cancer is ranked third in worldwide incidence of malignancies in 2020 with 1.9 million new cases diagnosed and accounted for 935,000 cancer-related deaths making it the second deadliest malignancy (Sung et al. 2021). The crude incidence rate was 24.8 per 100,000 and the age-adjusted incidence rate was 19.5 per 100,000 while the crude mortality rate was 12 per 100,000 and the age-standardized mortality rate was 9 per 100,000 (Sung et al. 2021). There is significant geographic variability in CRC incidence and a correlation with the human development index (HDI). The incidence and mortality of CRC in the past two decades in developed countries with high HDI has decreased largely due to established CRC screening programs and polypectomy (Kanth and Inadomi 2021). There has been an increase in the incidence of CRC in Eastern Europe, South America, and South Eastern and South Central Asia which is possibly associated with an affluent lifestyle encompassing higher animal-source food, higher calorie intake, reduced physical activity, and increased obesity (Sung et al. 2021). The highest age-standardized incidence rate was reported in Australasia at 48.3 per 100,000 population, while the lowest was seen in central sub-Saharan Africa at 7.7% per 100,000 (Collaborators 2022). Central Europe has the highest age-standardized mortality rate (23.6 per 100,000). On the other hand, South Asia had the lowest figure for age-standardized mortality rate (7.3 per 100,000) (Collaborators 2022).

Early-onset Colorectal Cancer

Early-onset CRC is defined as CRC occurring before the age of 50. The average age of diagnosis of CRC is 68 years of age in men and 72 years of age in women (Sung et al. 2021). However, there has been a steady increase in the incidence of early-onset CRC and a decrease in late-onset CRC. There has been a rise in early-onset CRC in the last three decades. In the United States there has been an increase of 45% of CRC in adults aged 20 to 49 years from 1992 (8.6 per 100,000) to 2016 (13.1 per 100,000) (Stoffel and Murphy 2020). There has also been an increasing trend of early CRC across Europe. CRC in ages 20 to 29 increased from 0.8 in 1990 to 2.3 per 100,000 in 2016 while in ages 30 to 39 there was an increase from 2.8 in 2006 to 6.4 per 100,000 in 2016 and in ages 40 to 49 an increase from 15.5 in 2005 to 19.2 per 100,000 in 2016 was observed (Vuik et al. 2019). A similar trend was seen in Australia and New Zealand (Siegel et al. 2019) as well as in industrialized Asian countries such as Japan, Hong Kong, South Korea, and Taiwan (Sung et al. 2021). Early onset CRC mortality has also been on the rise with an increase of 1.3% per year from 2008 and 2017 (Siegel

et al. 2019). Decreasing colorectal cancer trends were noted in three developed countries: Italy, Austria, and Lithuania. Of note Austria implemented an earlier CRC screening age commencing at 40 years of age which likely contributes to this trend (Vuik et al. 2019).

In terms of clinical presentation, early-onset CRC usually presents symptomatically in 70 to 95% of cases (Silva et al. 2019) whereas late onset CRC patients are usually diagnosed fortuitously likely during CRC screening colonoscopy (F. W. Chen et al. 2017b). Patients with early onset CRC also report a longer duration of symptoms and have a lengthier delay in diagnosis and are diagnosed at a more advanced stage compared with late-onset CRC (F. W. Chen et al. 2017b). Early onset CRC had a higher frequency of left-sided disease with more aggressive histology with approximately 27.9% having poorly or undifferentiated cancer (F. W. Chen et al. 2017b). Insights into the adenoma-carcinoma pathway have revealed that the most effective way to prevent sporadic CRC is by the removal of colorectal adenomas. According to a 20-year prediction model reported based on Cancer Tomorrow on Global Cancer Observatory (https://gco.iarc.fr), there would be 1.93 million instances of colon, rectal, and anal cancers globally in 2020, and 3.15 million in 2040 (Xi and Xu 2021). This is based on projected aging, population growth, and human advancement. The surge was ascribed to a shift in lifestyle and nutrition toward a more westernized norm (Xi and Xu 2021).

Risk Factors of Colorectal Cancer

Polyps, the Adenoma-carcinoma Sequence and the Risk of Colorectal Cancer

Colorectal cancer is divided into sporadic, colitis-associated, and hereditary colorectal cancer all of which undergo different carcinogenic pathways. It is estimated that 60 to 65% of CRC are sporadic, while 25% have a family history but no genetic cancer syndrome whereas only 5% are hereditary (Keum and Giovannucci 2019; Migliore et al. 2011). The development of CRC undergoes four key phases which encompass initiation, promotion, progression, and metastasis. The process of initiation begins with an irreparable genetic injury that results in neoplastic transformation. The promotion stage ensues when the neoplastic cells proliferate resulting in neoplastic growth. Thereafter the progression phase occurs. Genetic and epigenetic remodeling causes the cells to have a selective growth advantage which results in their metastatic ability. Metastasis then occurs via the bloodstream or lymphatic system (Keum and Giovannucci 2019).

Most CRCs begin with a polyp. There are two major subtypes of polyps: adenomatous (adenomas) and serrated polyps. Approximately 85 to 90% of CRCs arise from adenomas (Conteduca et al. 2013). However, below 10% of adenomas develop into CRC (Conteduca et al. 2013). Adenomas with characteristics of villous histology, high-grade dysplasia, or size being more than 1 cm have been termed high-grade adenomas and possess a greater likelihood of progression to malignancy (30–50%) compared with non-advanced adenomas (1%) (Conteduca et al. 2013). An adenoma develops from mutations in *APC*, the tumor suppressor gene. This results in the overactivation of the Wnt/b-catenin signaling pathway and progresses to dysregulated cell proliferation forming an adenoma (Dow et al. 2015). Thereafter, *KRAS* mutations enhances the adenoma proliferation, and subsequent inactivation of TP53 tumor suppressor gene results in the development of CRC (Armaghany et al. 2012).

Another group of polyps, the serrated polyps encompass traditional serrated adenomas, sessile serrated adenomas, and hyperplastic polyps. The hyperplastic polyp (HP) is the predominant variant that was previously believed to be completely benign, however, recent data have shown that large polyps and/or in the proximal colon may progress to CRC via the serrated pathway (East et al. 2017). An estimated 10–15% of sporadic CRC arise from serrated polyps (Conteduca et al. 2013). One of the critical events in this pathway is mutation of the *BRAF* oncogene which activates the MAPK pathway and results in the development of hyperplastic polyp. Progression to sessile serrated adenoma is propagated by CIMP (Kedrin and Gala 2015). The risk of progression can be halted by removing these adenomas via polypectomy during a colonoscopy thus reducing the CRC risk.

Inflammatory Bowel Disease

Chronic inflammation results in a different carcinogenic pathway. In chronic inflammation, *TP53* mutation occurs early and low-grade dysplasia arises from chronic inflammation and usually occurs in flat mucosa and has an accelerated pathway to high-grade dysplasia and finally CRC (Itzkowitz and Yio 2004). Due to the fact that these lesions occur in flat mucosa, their detection is challenging hence chromoendoscopy or high-definition endoscopy is superior to white light imaging for dysplasia surveillance (Buchner and Lichtenstein 2016).

Risk Factors for Early-onset Colorectal Cancer

Early-onset CRC has been on the rise in highly Westernized countries. Early-onset CRC is genetically, pathologically, and molecularly diverse (Pearlman et al. 2017). An estimated 30% of early-onset CRC patients have a family history of CRC or one first-degree relative with CRC and out of that only 13% had a germline mutation (Pearlman et al. 2017). Early-onset CRC has been found to be MSI-high in 10–30% of the cases of CRC compared with ~15% of overall CRCs (Conteduca et al. 2013). The obesity epidemic among young children and adolescents parallels the rise in early-onset CRC (Keum and Giovannucci 2019). It has been shown that women with a BMI of 23 or above at the age of 18 had almost 60% increased risk

of early-onset CRC compared with women who had a BMI <23. Thus early-onset CRC is multifactorial and personalized screening should be adopted in those aged 45 years and younger (X.-J. Lin et al. 2014a).

Hereditary Colorectal Cancer Syndrome Risk Factors

High penetrance syndromes contribute 2–5% of all CRC cases. These include Lynch syndrome caused by dysfunction of the mismatch repair system, familial nonpolyposis coli (FAP) caused by *APC* mutations, and hereditary nonpolyposis coli (HNPCC) due to mutations of mismatch repair (MMR) genes (Kory 2010). HNPCC is a genetic disease with autosomal dominant inheritance and accounts for 2–4% of CRC (Kory 2010). It arises as a result of mutations in the DNA mismatch repair gene (MMR) encompassing MLH1, MSH2, MSH6, and PMS2 (Markowitz and Bertagnolli 2009). HNPCC affects approximately 1 in 300 individuals in the West (Win et al. 2017) and is complicated by MSI-high CRC primarily in the proximal colon (Lynch and De la Chapelle 2003) which starts with the occurrence of a few polyps which undergo an accelerated carcinoma sequence and progress to CRC within 2 to 3 years in contrast to 8 to 10 years in the general population (Jass et al. 1994). There is a 60% lifetime risk of development of CRC in HNPCC (Winawer et al. 1997), however it only accounts for <1% of CRC (Patel and Ahnen 2012). It is recommended that patients who have MLH1 and MSH2 mutations undergo screening colonoscopy starting at the age of 25 and subsequently yearly until the age of 75. Meanwhile, patients with MSH6 and PMS2 mutations should undergo a screening colonoscopy starting at the age of 35 and subsequently 2-yearly until the age of 75 (Monahan et al. 2020; van Leerdam et al. 2019).

Familial adenomatous polyposis (FAP) is a result of an inherited germline *APC* mutation (Patel and Ahnen 2012). It has a prevalence of 1 in 10,000 and results in approximately 2 to 5% CRC (Kory 2010). The risk of CRC is almost 100% by the age of 40 without prophylactic panproctocolectomy (Winawer et al. 1997). APC plays a role as tumor suppressor gene of the Wnt/β-catenin signaling pathway via APC/AXIN/GSK3 β-catenin inactivation (X. Yang et al. 2021b). Mutations in APC are characterized by the stabilization of β-catenin, entry of β-catenin into the nucleus, and a surge in cellular proliferation (Stefanski and Prosperi 2020). Phenotypically, this is expressed by the development of 100 polyps and above throughout the colon which starts in puberty (Patel and Ahnen 2012). Polyps also develop in the duodenum in nearly all patients (88 to 98%) and eventually two thirds of patients develop duodenal adenomas (Burke et al. 1999). The risk of developing duodenal malignancy is 4% by the age of 70 (Kanth et al. 2017) and the risk of ampullary malignancy is 18% by 75 years of age (Björk et al. 2001). In view of the elevated risk of CRC in those with FAP, screening colonoscopy is recommended to commence at 12 to 14 years and every 1 to 2 years thereafter (Monahan et al. 2020; van Leerdam et al. 2019). Colonoscopy surveillance for FAP has been shown to reduce the incidence of CRC. FAP patients who were under surveillance colonoscopy had a CRC incidence of 3.8 to 9.4% compared to those presenting symptomatically at 33.6 to 66.2%. There was also a mean delay in the occurrence of CRC by up to 16 years with a better survival of up to 12 years (Barrow et al. 2013).

Peutz-Jeghers syndrome (PJS) is due to a mutation in the serine threonine kinase 11 tumor suppressor gene (STK11/LKB1 gene) and is inherited in an autosomal dominant manner. This is manifested by the formation of gastrointestinal tract polyposis which occurs most often in the small bowel (60 to 90%) in particular the jejunum (Latchford et al. 2011). Complications of this include anemia, bleeding and bowel intussusception (Latchford et al. 2011). The cumulative risk of colorectal malignancy was 39% at 15 to 64 years of age (H.-Y. Chen et al. 2017b). It is recommended that patients with PJS undergo a baseline colonoscopy at eight years of age in subjects who are asymptomatic with subsequent surveillance intervals ranging from one to three years depending on the colonoscopic findings (van Leerdam et al. 2019).

Lifestyle and Dietary Factors

Obesity is a state of low-grade chronic inflammation which results in the release of pro-inflammatory cytokines by adipokines that mediate tumorigenesis. There has been evidence to suggest that waist circumference is a greater risk factor than BMI for CRC (Song et al. 2016). This was due to the secretion of proinflammatory adipokines, which resulted in chronic low-grade inflammation (Ouchi et al. 2011) as well as the presence of insulin resistance which creates an optimal condition for tumor development (Ouchi et al. 2011). Insulin resistance also gives rise to hyperinsulinemia which increases free insulin-like growth factor 1 (IGF-1) which promotes CRC via enhanced cell proliferation and reducing apoptosis (Calle and Kaaks 2004).

A sedentary lifestyle has been shown to be a risk factor for CRC (de Rezende et al. 2018). The American Cancer Society has recommended that adults should engage in 150–300 min of moderate-intensity physical activity per week, or 75–150 min of vigorous-intensity physical activity, or an equivalent combination, while achieving or exceeding the upper limit of 300 min is optimal (Rock et al. 2020). Alcohol is also a risk factor for CRC, whereby drinking more than 1 alcoholic drink per day was shown to increase the CRC risk (RR 1.04, 95% CI 1.01–1.06) compared to non or infrequent consumption of alcohol (Choi et al. 2018). Alcohol goes to the colonocytes via systemic circulation and is metabolized by alcohol dehydrogenase into acetaldehyde (Salaspuro 1997) which injures the mucosa causing regenerative cellular proliferation

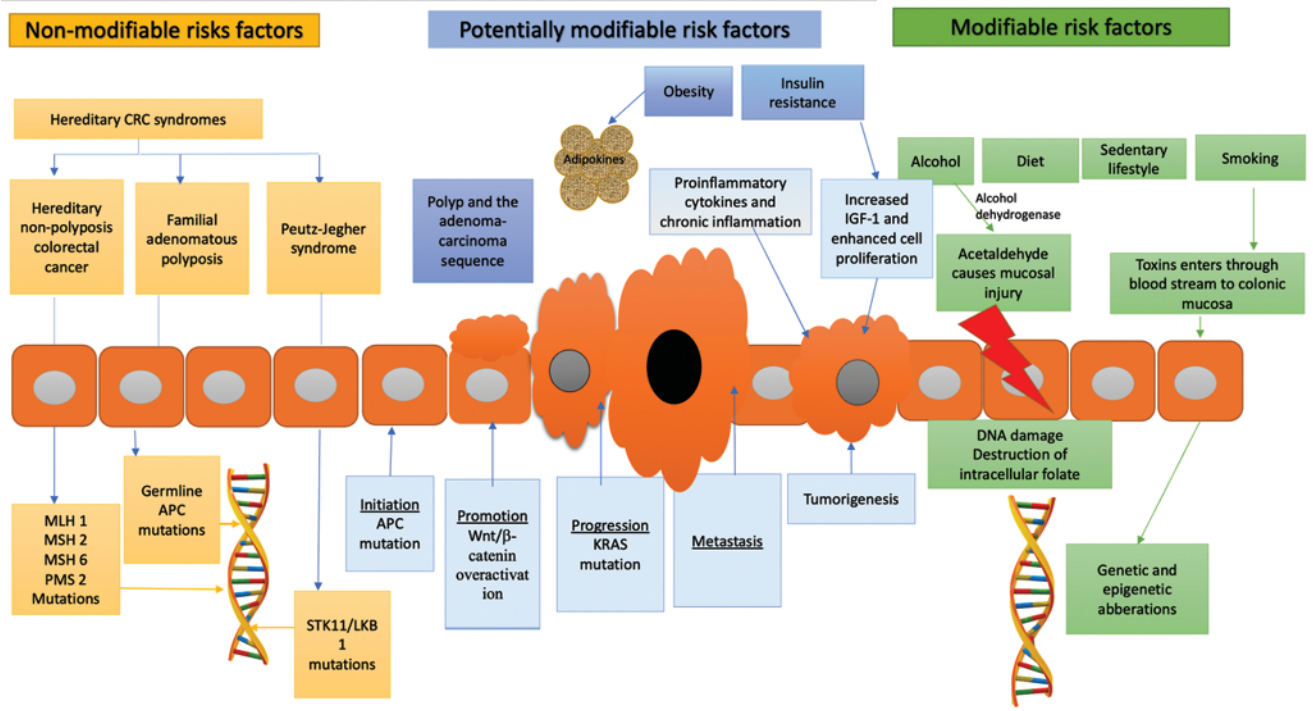

Figure 3 Pathways of colorectal carcinogenesis.

(Seitz and Stickel 2007). Intracellular acetaldehyde causes DNA damage and destroys intracellular folate which is needed for DNA production and methylation (Giovannucci and Martinez 1996; Seitz and Stickel 2007).

Smoking is another established risk factor for CRC, the risk of CRC has been found to correspond with the number of pack years, the RR for five pack years: 1.06 95% CI 1.03 – 1.08, the RR for 30 pack years 1.26, 95% CI 1.17–1.36. Smoking exerts its effects through genetic and epigenetic aberrations (Giovannucci and Martinez 1996). Other risk factors for CRC include high processed meat, low fiber, low whole grain and low calcium intake (Clinton et al. 2020). The pathogenesis of CRC is depicted in Figure 3.

Microbiome and Colorectal Cancer

Dysbiosis in Colorectal Cancer (CRC)

The composition of microbiota in CRC patients shifts as compared to those in healthy individuals. This shift includes the enrichment of *Bacteroides fragilis* (*B. fragilis*), *Escherichia coli* (*E. Coli*), *Enterococcus faecalis (E. faecalis), Streptococcus gallolyticus* (Wong and Yu 2019), as well as oral bacteria such as *Fusobacterium nucleatum (F. nucleatum), Parvimonas, Peptostreptococcus*, and *Porphyromonas* in fecal and tumor samples from patients with CRC (Feng et al. 2015; Flemer et al. 2017; Kostic et al. 2013; Nakatsu et al. 2015; Thomas et al. 2019; Wirbel et al. 2019; Yachida et al. 2019; Yu et al. 2015; Zeller et al. 2014). However, there are inter-individual differences in the CRC microbiota across geographical locations. Meta-analyses of various studies have identified enrichment of 29 species in CRC microbiota across eight geographical locations (Wirbel et al. 2019). Stage-specific analyses have shown that some bacteria such as *Fusobacterium nucleatum* and *Solobacterium moorei* are enriched progressively from early to late stages of CRC while other species such as *Atopobium parvulum* is enriched in adenoma, that is a precursor to CRC.

Apart from bacteria, viruses from the gut microbiota have also been associated with CRC. For examples, cytomegalovirus, John Cunningham (JC) virus, and human papillomavirus have been positively associated with CRC samples (Cheng et al. 1995; Harkins et al. 2002; Laghi et al. 1999). However, these associations are inconsistent as other studies have not confirmed these findings (Gornick et al. 2010; Hart et al. 1982; Knösel et al. 2004). Nonetheless, an untargeted metagenomic analysis of stool samples found that the gut DNA virome of CRC patients was altered as compared to that of healthy controls (Nakatsu et al. 2018). Of these, 22 viral taxa including cytomegalovirus and bacteriophages could differentiate CRC patients from the healthy controls (Nakatsu et al. 2018).

Another study also found that temperate bacteriophages are associated with CRC (Hannigan et al. 2018). Consistent with these human studies, our longitudinal study on a carcinogen-induced CRC mouse model identified bacteriophage genera that are associated with the CRC growth (Li et al. 2022). We found that Brunovirus and Hpunavirus are positively associated with tumor growth whereas members from Lubbockvirus show a negative correlation with tumor growth (Li et al. 2022). This suggests that bacteriophages may play a role in CRC carcinogenesis. However, further investigation is required to understand the mechanism of carcinogenesis.

Dysbiosis and the CRC Carcinogenesis

An early study has shown that germ-free rats treated with the carcinogen, 1,2-dimethylhydrazine, develop fewer colonic tumors compared to conventional rats treated with the carcinogen (Reddy et al. 1974). A later study showed that mice transplanted with fecal microbiota from patients with CRC developed more intestinal polyps than those transplanted with fecal microbiota from healthy individuals (Wong et al. 2017). These studies suggest that colorectal dysbiosis plays a crucial role in CRC carcinogenesis. Each microbe influences CRC carcinogenesis via the following mechanisms.

Genotoxicity: bacterial species such as *E. Coli* (pks^+), enterotoxigenic *B. fragilis* (ETBF) and *E. faecalis* are genotoxic. For example, colibactin produced by *E. Coli* (pks^+) induces DNA double-strand breaks, aneuploidy and improper cellular division (Cougnoux et al. 2016; Cuevas-Ramos et al. 2010) and promotes CRC carcinogenesis in an $APC^{min/+}$ CRC mouse model (Tomkovich et al. 2017). In response to the colibactin-producing *E. Coli* infection, colon epithelial cells induce the expression of DNA repair protein RAD51 which in turn induces autophagy for lowering the DNA damaged cells (Lucas et al. 2020), thus limiting the bacterium-promotion of carcinogenesis. Consistent with these *in vitro* and *in vivo* data, *E. Coli* (pks^+) induces mutation signatures in human colorectal organoids which were previously identified as the CRC-driver mutations (Pleguezuelos-Manzano et al. 2020). In addition, *B. fragilis* toxin produced by ETBF and reactive oxygen species produced by *E. faecalis* induce DNA damage and genomic instability, leading to CRC carcinogenesis (Goodwin et al. 2011; Huycke et al. 2002; Wang and Huycke 2007).

Inflammation. Chronic inflammation is the risk factor for CRC. This is evidenced by the increased risk of CRC for patients who have inflammatory bowel disease (Beaugerie and Itzkowitz 2015). The inflammation observed in sporadic CRC could be initiated by defects of the epithelial barrier in the adenoma (Grivennikov et al. 2012). Barrier defects allow the dysbiotic bacteria to translocate to the mucosa and lamina propria thus triggering pro-inflammatory responses (Grivennikov et al. 2012). For example, *F. nucleatum* stimulates the TLR4-NFkB signaling pathway and triggers myeloid cell infiltration and inflammation in the tumors, leading to the promotion of colorectal carcinogenesis in $APC^{min/+}$ mouse model (Kostic et al. 2013; Wu et al. 2018; Yang et al. 2017). On the other hand, two proteins expressed by *F. nucleatum* have been shown to promote CRC tumorigenesis via direct interactions. FadA adhesin of *F. nucleatum* binds to E-cadherin of the colorectal mucosa and stimulates b-catenin signaling to increase cell proliferation and inflammatory cytokine response, thereby promoting tumor growth in xenograft CRC models (Rubinstein et al. 2013). The other protein, Fap2 of *F. nucleatum*, interacts with TIGIT, a human NK cell inhibitory receptor, leading to the inhibition of NK cell killing of the CRC tumors (Gur et al. 2015). The second example of proinflammatory bacterium is ETBF. *B. fragilis* toxin produced by ETBF activates the T_H17 inflammatory responses and STAT3 signaling pathways thus potentiating CRC carcinogenesis (Wu et al. 2009). Similarly, *Parvimonas micra* induces T_H17 inflammatory responses, promoting CRC carcinogenesis (Zhao et al. 2022). Yet, the bacterial factor responsible for this effect remains unknown. Another example is *Peptostreptococcus anaerobius* (*P. anaerobius*). It activates TLR2 and/or TLR4 pathways to generate reactive oxidative species. This in turn enhances cholesterol synthesis and cell proliferation, leading to the promotion of tumorigenesis (Tsoi et al. 2017). *P. anaerobius* surface protein, PCWBR2, also interacts with the α2/β1 integrins that are overexpressed in human CRC to activate the PI3K-Akt pathway and NFkB, leading to the infiltration of tumor-associated macrophages and granulocytic tumor-associated neutrophils (Long et al. 2019). These inflammatory responses promote tumorigenesis in the $APC^{min/+}$ mouse model (Long et al. 2019).

Summary

GIT malignancies involve a complex interplay of environmental and genetic risk factors. While the complete pathogenesis of this interaction is not completely understood, it is clear that the rising obesity epidemic and westernization of lifestyle increase the risk of these cancers. Toxins such as alcohol and smoking also exhibit a dose-response relationship in increasing the likelihood of GIT cancers hence lifestyle modifications should be targeted at these risk factors. Screening has improved the rates of early detection thereby conferring a better prognosis for upper CI malignancies. While colonoscopy has reduced the rates of CRC, the rise of early-onset CRC highlights the fact that personalized screening strategies are needed in order to identify at-risk populations earlier. These strategies could include the classification of malignancies beyond anatomical sites or subtypes of histology to molecular classification of malignancies. This enables a more precise understanding of the prognosis and treatment outcome.

Key Take Home Messages

1 Cigarette smoking should be stopped and strategies to support cessation put in place at every opportunity on the patient's pathway.
2 Alcohol consumption should be minimised and ideally 10 units or less per week.
3 Strategies to manage excess body weight should be handled by progressive escalation and if needed referral to a medical/endocrine, surgical, nutrition, psychology MDT.
4 Dysbiosis should be managed proactively by both active prevention (diet and prebiotics) and intervention (next generation probiotic) strategies.

Areas for Further Research

1 Development of diagnostic biomarkers for personalized cancer prevention strategies.
2 Development of predictive biomarkers for optimized interventions.
3 Development of prognostic biomarkers for stratification into endoscopy surveillance.

Trusted Websites for Further Reading

https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staging/signs-and-symptoms.html
https://opa.org.uk/oesophageal-cancer-2
https://www.cancerresearchuk.org/about-cancer/stomach-cancer

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