

Microbial Etiopathogenesis of Gastric Malignancy

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Abstract

Gastric cancer (GC) is one of the most common disease and fifth most common cancer among male and seventh most common cancer among female in India. It is the most frequent causes of majority of deaths among non-communicable diseases in the world. The incidence of GC is higher in developed Asian countries like Republic of Korea, China, India and Japan. This review summarizes the newer concepts of microbial etiopathogenesis and molecular or recent diagnostic tools of GC and the new important recommendations for the management of patient with GC.

The etiological factors and pathogenesis of GC are not yet fully understood but it is affected by several other factors like; strain diversity, genetics, environmental, immunological response of host, exposure to N-nitroso compounds from diet or smoking, alcohol, low socioeconomic status, BMI, age, previous gastric surgery and geographical distribution. To understand the pathogenesis of GC, several researchers mentioned the incidence, etiology, diagnostic tools and the different therapeutic options have also undergone important changes in recent years. *Helicobacter pylori* is a well recognized risk factor, which can modulate the acidity of the stomach to alter the gastric microbiome, causing *H. pylori*-associated diseases. Moreover, there is increasing evidence that bacteria other than *H. pylori* and their metabolites also contribute to gastric carcinogenesis. Therefore, the development and progression of GC can lead to improvements in prevention, diagnosis, and treatment. In this review, we discuss the carcinogenic effects of *H. pylori* and non-*H. pylori* microorganism in GC, as well as the potential therapeutic role for GC.

Keywords: Gastric Cancer; Mucosa-associated Lymphoid Tissue (MALT); *H. pylori*; Microbial Pathogenesis of Gastric Carcinoma; Gastric Malignancy

Abbreviations

GC: Gastric Cancer; MALT: Mucosa-associated Lymphoid Tissue; NARC: National Cancer Registry Programme; AAR: Age Adjusted Rate; LPS: Lipopolysaccharides; IHC: Immunohistochemistry; MMP: Matrix Metalloproteinases; EAID: Enzyme Activation Induced Deaminase; EGFR: Epidermal Growth Factor Receptor

Introduction

Cancer is a second most common disease for majority of deaths among non-communicable diseases in the world. In human, gastric cancer is the only malignant neoplasia caused by a bacterium [1]. Incidence of carcinoma stomach and gastric cancer varies

in different parts of the world and still it is a fifth most common cancer among male and seventh most common cancer among females in India [2]. The worldwide distribution of gastric cancer varies substantially across geographical regions which illustrate the multitude of factors that are associated with the incidence, survival and mortality of the disease. The Asian countries account for the majority of the world's cases while Europe and the America combined makeup less than a quarter of the world disease burden [3]. Even within the highly affected areas, certain populations are more commonly affected; especially the lower socioeconomic class, and within the United States especially the African American population [4]. Gastric carcinoma occurs in several steps with the predisposition of multiple factors but the intestinal type of gastric cancer is often related to *Helicobacter pylori* infection [5]. The sufficient evidences found in humans for the carcinogenicity of infection through *H. pylori*, which was reported and concluded by the International Agency for Research on Cancer (IARC) in 1994 [6]. *H. pylori* is associated with causation of gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma and account for more than 90% of all gastric malignancies [7].

In 2010 National Cancer Registry Programme (NARC) reported that in India the mean age adjusted rate (AAR) of gastric cancer among urban registries in India varied from 3.0 to 13.2 and Manipur was the high prevalence state for gastric cancer [2]. Over the last few years it is reported that incidence of gastric carcinoma has declined due to improved nutrition, food preservation, better prevention, earlier clinical diagnosis and better treatment facilities but prognosis of this disease still remains poor [8].

The types of gastric cancer can be classified into the distal portion of the stomach (non-cardia) and cancers arising from the proximal cardia according to its location within the stomach [9]. It is very important to differentiate between cardia and non-cardia disease because there is evidence that they have different etiologies and it is supported by in several reports that gastric cardia cancer and gastro-esophageal junction tumor are increasing in incidence and there is a parallel increased incidence in non-cardia cases in the young western populations [10].

Geographic variation of *h. pylori* in gastric cancer

The incidence of gastric cancer due to *H. pylori* varies in different parts of the world with highest incidence reported in East Asia, Eastern Europe, and South America. China is known to have one of the highest rates of gastric cardia cancer [11]. Most *H. pylori* isolates from East Asia constitute a distinct group based on

multilocus inherent house-keeping genes under positive selection (including *cagA* and *vacA*) are highly divergent in East Asian strains as compared to strains, isolated elsewhere in the world [12]. Conversely, *cagA*-negative strains containing type s2 *vacA* alleles and lacking *babA* are commonly found in the United States and Western Europe but are rarely isolated in East Asia.

The observed patterns of geographic diversity suggest that *H. pylori* has been present in humans for at least 100,000 years that *H. pylori* accompanied humans out of Africa in multiple waves of migration beginning about 60,000 years ago [13].

Pathogenesis of gastric cancer

The incidence of gastric cancer is higher in developed East Asian and other Asian countries like Republic of Korea, China, India and Japan. However, the frequency of gastric cancer among other cancer is very low in India. The host's genetic composition and the dietary and environmental factors might play an important role to solve this mystery [14].

There are many factors which resulted in the causation of gastric cancer, like other cancers due to the interaction between harmful and defensive factors. The etiology of gastric cancer also depends and influenced by several other factors like; strain diversity, genetics, environmental, immunological response of host, exposure to N-nitroso compounds from diet or smoking, alcohol consumption, low socioeconomic status, high BMI, old age, previous gastric surgery and geographical factors as shown in figure 1 [15,16].

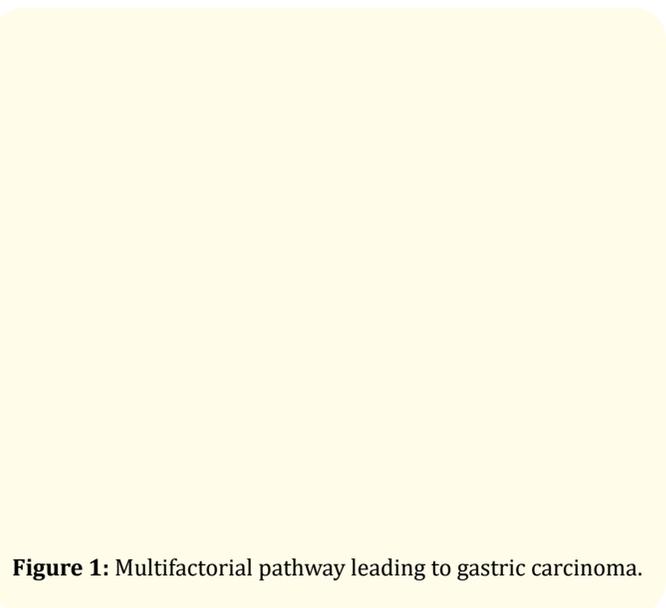


Figure 1: Multifactorial pathway leading to gastric carcinoma.

Many studies revealed that gastric carcinoma develops sequentially, in order to develop chronic gastritis; atrophy; intestinal metaplasia; and dysplasia. *H. pylori* play an important role in gastric carcinogenesis may be due to different natural factors, improper intake (excessive salt based food) and infection. Colonization of *H. pylori* leads to chronic gastritis and even some cases patients may develop recurrent gastric cancer within 5 years. Genetic constituents also assumed as a significant cause in gastric carcinogenesis; might be due to alteration in the expression of normal genes, resulted in phenotypic malignancy [17,18]. Hence, the time to time studies on *H. pylori* in relation to genetic and environmental risk factors are required to uncoil the complexity of this disease.

Host

Host can be a key in the inclination of *H. pylori* induced diseases and sensitivity towards a severe clinical or pathological outcome. Gastric carcinogenesis and the interrelation between chronic inflammation and cancer are naturally occurring due to the infiltration of inflammatory cells. Injury of mucosal lining leads in the development of gastric cancer may be due to the prolonged inflammatory response against *H. pylori*. Factors specific to the host, such as genetic background might influence the nature and intensity of the immune response to *H. pylori* [19].

Infectious agents

H. pylori

It is a Gram negative aerobic, flagellated microorganism, urease, catalase, and oxidase positive which appear spiral shaped and mostly lies in the extracellular region of gastric lumen. Earlier it was known as *Campylobacter pyloridis*. Most of the *H. pylori* strains express various virulence factors that influence to affect host cell signaling pathways. *H. pylori* is highly adapted to form microcolonies in human gastro-intestinal tract and found approximate in 50-60% of human population [20]. The presence of lipopolysaccharide (LPS) that reduces the intensity of the host immune response and the expression of adhesions also facilitate the persistence of the microorganism in the stomach. It has capability to hydrolyze urea in lumen, which form protective layer of ammonia around the bacteria to prevent them from acidic pH of stomach because amino acids and urea are the two major sources of nitrogen in the gastric lumen [20].

However, high risk of developing site-specific infection is due to the long-term existence of *H. pylori*. It was reported in several studies that among infected individuals, approximately 10% develop peptic ulcer disease, 1 to 3% develop gastric adenocarcinoma, and 0.1% develop mucosa associated lymphoid tissue (MALT) lymphoma [16]. In spite of the fact that both gastric and duodenal peptic ulcers are linked to *H. pylori* infection, it has been perceived that the gastric peptic ulcer is associated with a high risk of developing gastric cancer, whereas duodenal ulcer with a low risk, as demonstrated in table 1, individuals with duodenal ulcers only have antrum-predominant gastritis without atrophic alterations, while patients with gastric ulcers often have multifocal atrophic gastritis [1,20].

Species	Affected organ	Host	Pathophysiology
<i>H. pylori</i>	Stomach	Human and primitive	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma
<i>H. felis</i>	Stomach	Mouse, cat and dog	Gastritis in natural host; may cause peptic ulcers or gastric adenocarcinoma in mouse
<i>H. acinonychis</i>	Stomach	Tiger, cheetah and cats	Gastritis, peptic ulcer disease
<i>H. mustelae</i>	Stomach	European polecat	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma
<i>H. heilmannii</i>	Stomach	Human and other mammals	Gastritis, dyspeptic symptoms, MALT lymphoma
<i>H. hepaticus</i>	Liver	Rodents	Proliferative typhlo-colitis, hepatitis, hepatocellular carcinoma

Table 1: Different species of *Helicobacter* and their pathophysiological role.

H. heilmannii

It's infection may cause gastritis, dyspepsia, and ulceritis, but found sporadically in few human populations. It is difficult to characterize *H. heilmannii* because it has not been cultured successfully *in vivo* till date and inflammation is comparatively low as *H. pylori* [20].

Epstein-Barr virus (EBV)

Several studies also evaluated the etiology of gastric cancers and found the some evidences regarding association of EBV. It is an icosahedral double stranded DNA (deoxy-ribose nucleic acid) herpes virus. It is present in all human population. Gastric carcinoma has been reported from several region of the world due to EBV including Korea, Germany, France, China and Japan. It can cause infection of intestine and diffuse type of gastric carcinoma and it has been estimated that the EBV-associated adenocarcinoma are more common in males than females, accounting for 8.7% of its overall positivity among cases of gastric cancer [21].

Mycoplasma hyorhinis

Mycoplasma is one of the smallest living organism present widely in nature and some mycoplasmas cause chromosomal changes and cell transformations *in vitro* through progressive chromosomal loss and translocations. Hua Yang, *et al.* (2010) demonstrated high infection rate of *M. hyorhinis* in gastric cancer tissues by immunohistochemistry (IHC) with PD4 monoclonal antibody against P37 protein of *M. hyorhinis* but the association between mycoplasmas and gastric cancer remains unclear. Nested PCR and IHC staining is used to identify the presence of *M. hyorhinis* as shown in figure 2 [22,23].

Figure 2: Demonstration of *Mycoplasma* infection in gastric cancer tissues by using IHC staining.

Rhizopus microspores

The role of fungus causing gastric carcinoma is not well understood. Christian, *et al.* in 1999 mentioned that small piece of biopsies might be not enough to diagnose fungal infection. Collection of multiple samples of biopsy should be taken not only for histopathology but for tissue culture also, which help in the identification of fungus as well as in the determination of fungal colonization in gastric cancer tissues. However, isolation of *Rhizopus microspores var. rhizopodiformis* was reported in a study done by Kimura, *et al.* in 1995 from gastric cancer tissue biopsies [24].

Parasites

Histopathological examination of polyadenomas revealed that nematode; *Anisakis simplex* may be a factor for certain form of gastric cancer. The infection rate of *A. simplex* increasing throughout the world, due to intake of Japanese traditional foods. Most of the cases found in Japan but USA and England are also affected with anisakiasis infection [21].

Environmental

Diet

Diet plays an important role to reduce the risk of gastric carcinoma by intake of fruits and vegetables or healthy foods while, the risk of stomach cancer is increased by excessive salt consumption and salty diet. Cooked food may include carcinogens, or dietary components may interact to synthesize them. Consuming too much salt damages the mucosal barrier because it directly affects the stomach lining and increases epithelial cells proliferation. Risk of gastric cancer can be overcome by in taking balance diet [21,25].

Smoking

Smoking and chewing tobacco are two risk factors that affect a significant portion of the population worldwide and are directly linked to stomach cancer incidence. Although the mechanisms by which smoking increases the risk of gastric cancer are not fully understood, it is possible that the numerous well-known chemical carcinogens in tobacco smoke affect the risk of gastric cancer either directly through contact with the stomach mucosa or indirectly through the blood circulation [1].

Chemical

Non-steroidal anti-inflammatory drugs

Different observational studies have demonstrated a beneficial effect on risk of gastric cancer by frequent use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin. According to a meta-analysis done in 2009, showed that regular users of NSAID had an 18%–20%, 32%–36% reduced risk of gastric cardia adenocarcinoma and distal gastric adenocarcinoma respectively. So, now NSAIDs are seen as chemo-preventive agents as they suppress the production of enzymes cyclooxygenase, which is involved in prostaglandin biosynthesis.

Socio-economic status

Poor population that belongs to lower socioeconomic status, whether measured by literacy and earning, they are consistently living under high risk of gastric cancer. Factors likewise; poor sanitation, malnutrition or poor diet, habit of open defecation, over-crowding and poor availability of medical health facility) creating risk of gastric carcinoma are associated with low socioeconomic status. In high socioeconomic countries it is not completely understood but prevalence of highly virulence strain of *H. pylori* and excess intake of alcohol or smoking which has carcinogenic properties may be the cause because now a days, these are the few things which participating to maintain the status of an individual [1].

Agent-host interaction

The development of gastric cancer depends on the intricate interaction between the environmental with agent(s) and host factors, and it can be used to understand the etio-pathogenesis of gastric cancer. There are clearly two strong mechanisms that affect the cancer risk:

Indirect effects

Infection of *H. pylori* leads to an inflammatory response resulted in activation of oncogenes or inactivation of tumor suppressor genes and mitotic errors. Rise in pH and hypochlorhydria or achlorhydria is due to the atrophic gastritis, which facilitates the colonization and proliferation of gastric cancer. Initially *H. pylori* associated with antral gastritis, but later on due to the persistent infection it develops into hypochlorhydria, which allow bacteria to migrate proximally and resulted in adenocarcinoma [15]. Polymorphisms in cytokine genes IL1B and IL1RN genes have been shown to be

related with hypochlorhydria and gastric cancer in subjects with *H. pylori* infection. Other cytokines genes like; IL1B-511T, IL1RN*2 and tumor necrosis factor alpha and IL-10 also been linked to an increased risk of gastric cancer [15].

Direct effects

Mutations of cell-cycle regulating genes CagA and VacA associated with precancerous gastric lesions and progression of phenotypic malignancy. Cag PAI positive strains may directly induce gene mutations in gastric mucosal cells by enhancing the expression of the enzyme activation induced deaminase (EAID). VacA increases the life span of *H. pylori* infection by disrupting the epithelial cell barrier and suppressing the T-cell response. Other virulence factors, such as adhesions and outer membrane proteins including: BabA, DupA, FlaA, SabA and OipA have been associated with an early *H. pylori* infection [26].

Transmission routes of *H. pylori*

It is still unclear how *H. pylori* spread; too far, no single pathway has been conclusively shown. According to van Duynhoven, *et al.* (2001) a housefly can possibly transmit *H. pylori* infection mechanically and therefore, fly excreta may hypothetically responsible for the contaminating food. Among the populations with inadequate sanitation all over the world, this theory might be the most significant. Three potential causes of transmission from one person's stomach to another have been illustrated and explained [25].

Iatrogenic

This type of transmission occurs most frequently when tubes or endoscopes that have come into touch with the gastric mucosa of one patient are inserted into another patient. Iatrogenic diseases afflict large populations, are spreading quickly, and contribute significantly to hospital acquired infections.

Oro-faecal

H. pylori have been isolated from the faeces of infected children but in adult, due to the lack of standard procedure and toxicity present in faeces may leads to failure of isolation. Several studies have already proven that the modes of transmission of *H. pylori* and hepatitis-A virus were similar ie. faeco-oral. The children who used the common supply/municipal water supply had a higher prevalence of *H. pylori* infection than the others who used private

water supply. In one study conducted by van Duynhoven., *et al.* (2001) suggested that, the transmission may occur via water and food in developing countries due to unhygienic water and poor sanitation.

Oral-oral

There are no reliable evidences for transmission method of *H. pylori*, but possible transmission through oral to oral contact has been suggested indirectly by the fact that spouses and children of infected individuals with *H. pylori* having more seropositivity than spouses and children of non-infected individuals. A significant association was found in between samples from tooth surfaces with plaque and positive test results for *H. pylori* [25].

Microbiology of *H. pylori*

H. pylori is genotypically heterogeneous and its genome is approximately 1.7 Mbp size and contains 16S, 23S, and 5S rRNA genes. There is known genetic change in genome is due to the adaptation against host body environment and marked pattern of host-mediated immune response to *H. pylori*. Diversity in *H. pylori* is also seen at the nucleotide level, which includes transcriptional, translational and mutation due to shift in translation of the affected gene. *H. pylori* is a fastidious microorganism and require complex growth media like horse or sheep blood. The cell envelop composition is similar with other Gram negative bacilli. The inner membrane is made up of peptidoglycan and external membrane is composed with phospholipid with lipopolysaccharides (LPS). Rapid responses of *H. pylori* to stressful changes according to environmental conditions are often mediated by alteration in transcription of sets of genes that help in the encoding of operon and the transcription is regulated by one or two regulatory proteins [20].

Clinical manifestations

The sign and symptoms of gastric carcinoma are often nonspecific and are frequently diagnosed at an advanced stage in most of the cases. This is mainly due to the fact that both the stomach and the abdominal cavity are large and bear distention. In the early stage common clinical symptoms such as vague gastrointestinal distress, episodic nausea, vomiting, and anorexia even found in patients without cancer. They are usually not taken seriously by the patient and the physician initially, unless they are persistent or progressive over a period of time.

According to Kufe., *et al.* in 2003; the most common symptoms at diagnosis of gastric carcinoma are abdominal pain (50% to 65%) and weight loss (40%). Although anemia is a frequent finding among patients with gastric cancer, overt upper gastrointestinal bleeding is less common and occurs in 16% to 17% of patients. The symptom of gastric cancer depends upon the location of the primary lesion. Dysphagia occurs predominantly among patients with proximal cancer localization. Nausea and vomiting are more common among patients with non-proximal cancer. Early satiety can be especially prominent among patients with *linitis plastica* type of disease [27].

Diagnosis of gastric carcinoma and concerned microbes

There are different methods to diagnose *H. pylori* and other etiological agents causing gastric carcinoma; each with their advantages and disadvantages. The available diagnostic methods are invasive and non-invasive based on kind of sample obtained. Tumors of the stomach classified on the basis of morphological and histo-pathological features as shown in table 2 [20,28-34]. It allows the clinician to characterize gastric cancer and to make prognosis of the relevant disease. To diagnose gastric cancer specimen divided in three categories; fundus, pylorus and cardia [21].

Diagnostic method		Application	Sensitivity
Invasive methods	Histology	<i>H. pylori</i> -Gold standard” in routine hospital diagnostics	>95%
		EBV-lymphoepithelioma- like gastric carcinoma	>90%
		Fungal Stains-Periodic acid-Schiff , Grocott- Gomori methenamine silver [GMS], Haematoxylin and eosin or other stains used	~50-80%
	Culture biopsy	<i>H. pylori</i> -Alternative gold standard	>95%
		EBV-Cell line; Immortalized B cell lines, Human embryonic lung fibroblast, Chinese hamster ovary cells, Human laryngeal carcinoma etc	--
		Fungal- Sabouraud dextrose agar etc	~50-80%
Rapid urease test	<i>H. pylori</i> -Cost-effective and rapid test	>90%	

Non-invasive methods	Urea breath test	<i>H. pylori</i> -Alternative gold standard	>95%
	Fecal antigen (Ag) test	<i>H. pylori</i> -Not widely used yet	>90%
	Serology	<i>H. pylori</i> -Mainly used for epidemiological studies	80-90%
		EBV-Viral capsid antigen IgG, VCA IgM and EBV nuclear antigen (EBNA)-1 IgG etc	~35-50%
	Molecular	<i>H. pylori</i> -studies Mainly used for epidemiological	>95%
		EBV-for diagnosis using Real time PCR	>96%
Radiological methods	Endoscopic ultrasound	To see the inside of the body with a thin, lighted, flexible tube called a gastroscope or endoscope and removes a sample of tissue as a biopsy during an endoscopy	--
	X-ray	To create a picture of the structures inside of the body using a small amount of radiation.	--
	Barium swallow	Barium coats the lining of the esophagus, stomach, and intestines after taking barium orally and series of x-rays are taken	--
	Computed tomography (CT or CAT) scan	3-dimensional image that shows any abnormalities or tumors. A CT scan can be used to measure the tumor's size. Sometimes, a special dye called a contrast medium is given before the scan to provide better detail on the image.	--
	Magnetic resonance imaging (MRI)	Used to measure the tumor's size. A special dye called a contrast medium is given before the scan to create a clearer picture	--
	Positron emission tomography (PET) or PET-CT scan	Way to create pictures of organs and tissues inside the body. A small amount of a radioactive sugar substance is injected into the patient's body. This sugar substance is taken up by cells that use the most energy A scanner then detects this substance to produce images of the inside of the body	--
	Endoscopic ultrasound	To see the inside of the body with a thin, lighted, flexible tube called a gastroscope or endoscope and removes a sample of tissue as a biopsy during an endoscopy	--
	Laparoscopy	To find out if the cancer has spread to the lining of the abdominal cavity or liver.	--

Table 2: Diagnostic methods for different causative agents.

Treatment and outcome of gastric carcinoma

Surgery is the only significant treatment for localized gastric cancer, in which the complete surgical resection of the carcinogenic part done. Dissection of enbloc lymph and total or partial gastrectomy are the standard treatment but the prognosis

remains self-conscious in the western world. However, relapse and regrowth of the lymphoma occur due to reinfection with the same strain of *H. pylori* [35].

Adjuvant and neoadjuvant therapies adoption of chemo-radiation become a standard adjuvant therapy in North America

because administration of postoperative chemo-radiation to patients regardless of whether adequate or inadequate lymph node dissection has been resulted in the survival benefits. It was suggested by Farhat., *et al.* in 2019; that the theoretical advantages of this method helps in the earlier treatment of metastasis and also avoiding postoperative delays in chemotherapy in addition to down-staging of tumors [17].

Clinical and pathophysiology of *H. pylori* makes them a perfectly appropriate tumor population for novel targeted therapies. Among various therapeutic agents include epidermal growth factor

receptor (EGFR) inhibitors, apoptosis promoters, anti-angiogenic agents, cell cycle inhibitors, matrix metalloproteinases (MMP) inhibitors and targets for immunotherapy and gene therapy. Only MMP inhibitor agent showed its advance clinical value in clear survival benefit in patients with advanced gastric cancer. Consequently, patients with advanced gastric cancers should be considered for inclusion in clinical trial of targeted therapies in several studies shown in table 3, it has the potential to serve as a useful prognostic marker in search for more effective treatment [36].

Authors	Year	Reference no.	Result/conclusion
Barad et al.	2014	2	<ul style="list-style-type: none"> Most common site of gastric cancer in this study was antrum (50.6%) followed by cardia (17.1%), body (13.9%), pylorus (13.3%) and fundus (2.5%). Symptoms of weight loss and abdominal pain in elderly population may be the possibility of gastric cancer.
Carcas PL	2014	8	<ul style="list-style-type: none"> All high-risk areas should undergo routine screening and treatment of the infectious and carcinogenic organism, <i>H. pylori</i>. Patients who have atrophic or dysplastic changes in the gastric mucosa are at an increased risk of developing invasive cancer.
Cover TL	2016	12	<ul style="list-style-type: none"> <i>H. pylori</i> has been established the strongest known risk factor for gastric cancer. The risk of gastric cancer or premalignant lesions is higher in persons infected with <i>cagA</i>-positive <i>H. pylori</i> strains.
Kim et al.	2015	14	<ul style="list-style-type: none"> The incidence of stomach cancer in the Philippines was the lowest among all of the Asian countries, despite their tendency to consume a high-salt diet. The incidence rates of males were approximately 2 times higher than those among females in Asian countries.
Sato et al	2019	18	<ul style="list-style-type: none"> Endoscopic resection has been established as a proper technique to treat early gastric cancer. Dominance of T helper 2 (Th2) immunity controlled by IL-10 cytokine may be associated with <i>H. pylori</i>-associated gastric cancer recurrence.
Elsalem et al.	2020	35	<ul style="list-style-type: none"> <i>H. pylori</i> were highly correlated with the development of gastric adenocarcinoma and MALT lymphoma. Positive effects of probiotics use, including enhancement of bacterial eradication, prevention of cancer development, and/or reduction of chemotherapy associated toxicities.
Yang et al.	2021	36	<ul style="list-style-type: none"> Possible carcinogenic roles of non-<i>H. pylori</i> and their metabolites, includes induction of inflammatory response, modulation of immune response, induction of DNA damage, and promotion of EMT. More than half of the global population is infected with <i>H. pylori</i>, which can modulate the acidity of the stomach to alter the gastric microbiome profile, leading to <i>H. pylori</i>-associated diseases

Table 3: Previous studies based on microbial etiopathogenesis of Gastric cancer

Advanced/metastatic disease

The prognosis of patients with advanced gastric cancer is poor as per recent literature with a median survival of 3-5 months with best supportive care. Different chemotherapy combinations have been advised and tried in gastric cancer patients with

variable outcome, eventually resulting in the development of ECF (epirubicin, cisplatin and continuous 5FU infusion) as a current standard treatment resulting in median survival of 8-9 months. One new agent, which has found an important place in gastric cancer, is capecitabine- an oral pro-drug form of 5FU. The advantages of

this drug over 5FU include easy administration and equivalent activity to infused 5FU. The currently accruing UK National Cancer Research Institute (NCRI) trial REAL2 has a 2x2 factorial design testing the substitution of oxaliplatin, for cisplatin and capecitabine for 5FU, against ECF in patients with advanced oesophago-gastric adenocarcinoma. This trial was conducted on 1000 patients and has concluded that there is define the role of oxaliplatin and capecitabine in gastric cancer patients [17].

Conclusion

The role of micro-organism in gastric cancer has become firmly established by investigators with different background and expertise. Disease outcome is the result of the complex, ongoing interplay between three important pillars of infectious diseases like environmental, bacterial and host factors. Strain-to-strain genetic variability in virulence factors such as *vacA* and *cagA* not only affects the ability to colonize and cause disease but also affects the extent of inflammation and gastric acid synthesis. It is clear that gastric cancer is a disease of multiple etiologies involving many risk factors including dietary, infectious, occupational and genetic factors. A planned prevention programme helps to compress the risk factors or to reduce the duration and intensity of development of gastric cancer.

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Conflict of Interest

None.

Author Contributions

Dr. Amresh Kumar Singh was responsible for the whole manuscript, contributed to the editing/corrective actions and provided the final version of the review. Mr. Vivek Gaur designed and contributed to the writing of the manuscript. Dr. Yogendra Singh was responsible for proof reading.

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