Gastric cancer: epidemiology, biology, and prevention: a mini review

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Gastric cancer is one of the most common causes of cancer-related mortality worldwide. The objective of this article is to review the epidemiology and biology of gastric cancer risk. This literature review explores the biological, clinical, and environmental factors that influence the rates of this disease and discuss the different intervention methods that may not only increase the awareness of gastric cancer but also increase screening in efforts to reduce the risk of gastric cancer. *Helicobacter pylori* infection is the primary risk factor for gastric cancer. Additional risk factors include geographical location, age, sex, smoking, socioeconomic status, dietary intake, and genetics. Primary and secondary prevention strategies such as dietary modifications and screenings are important measures for reducing the risk of gastric cancer. Interventions, such as *H. pylori* eradication through chemoprevention trials, have shown some potential as a preventative strategy. Although knowledge about gastric cancer risk has greatly increased, future research is warranted on the differentiation of gastric cancer epidemiology by subsite and exploring the interactions between *H. pylori* infection, genetics, and environmental factors. Better understanding of these relationships can help researchers determine the most effective intervention strategies for reducing the risk of this disease. *European Journal of Cancer Prevention* 28: 397–412 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Overview

During the 1930s, gastric cancer was the most common cause of cancer-related death in the USA and in Europe (American Cancer Society, 2016). Today, gastric cancer remains a global health burden as it is one of the most common causes of cancer-related mortality (Catalano *et al.*, 2009; Piazuelo and Correa, 2013; Saghier *et al.*, 2013; Karimi *et al.*, 2014; American Cancer Society, 2016; Yang *et al.*, 2017). Despite the declining trends in incidence and mortality, gastric cancer is still one of the most common cancers globally (Piazuelo and Correa, 2013; Saghier *et al.*, 2013; Fock, 2014; Karimi *et al.*, 2014; Cancer.Net, 2015; Yang *et al.*, 2017). In 2008, among all cancers worldwide, gastric cancer ranks fourth in incidence, behind lung, breast, and colorectal cancers, and second in mortality, after lung cancer (Liu and Russell, 2008; Park *et al.*, 2011; Suzuki *et al.*, 2012; Piazuelo and Correa, 2013; Fock, 2014; Karimi *et al.*, 2014; Lee *et al.*, 2014; Subhash *et al.*, 2015). As of 2012, gastric cancer is ranked fifth worldwide in cancer incidence and third in cancer-related death (Globocan IARC, 2012; Fock, 2014). The incidence and mortality of gastric cancer globally account for 8% and 10%, respectively (Ward *et al.*, 2011). More importantly, the majority of incidence and mortality (i.e. 70%) occurred in developing countries (Jemal *et al.*, 2011; Ward *et al.*, 2011; Piazuelo and Correa, 2013; Fock, 2014; American Cancer Society, 2016).

The primary risk factor for gastric cancer is *H. pylori* infection. Other risk factors include geographical location, age, sex, socioeconomic status, tobacco smoking, consuming salty meats, and genetics. Gastric cancer is usually differentiated into two types; cardia and noncardia gastric cancer. Cardia gastric cancer occurs near the gastroesophageal junction, whereas noncardia gastric cancer occurs in the lower portion of the stomach. Globally, noncardia gastric

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cancer is more prevalent, especially within the East Asian region. Noncardia gastric cancers are either intestinal or diffuse with intestinal types occurring more in males and older adults and diffuse types occurring among males and females and in all age groups. When compared with intestinal noncardia gastric cancer, diffuse noncardia gastric cancer has a more rapid progression and poorer prognosis. For noncardia gastric cancer, men generally have rates twice as high than women (Jemal *et al.*, 2011; Ward *et al.*, 2011; Nagini, 2012; Piazuelo and Correa, 2013; Fock, 2014; Karimi *et al.*, 2014; World Cancer Research Fund International, 2015). The incidence and mortality rates of gastric cancer progressively increase with age (Piazuelo and Correa, 2013; Karimi *et al.*, 2014; National Cancer Institute, 2016). Ethnicity is also a risk factor where living in the same country has significant variations in the overall incidence of gastric cancer (Piazuelo and Correa, 2013; Fock, 2014).

Diagnosis

There are multiple screening tests that can be used to screen for stomach cancer; however, there is no routine or standard screening for diagnosis (National Cancer Institute, 2016). As ~80% of patients are asymptomatic during the early stages of gastric cancer, the initial diagnosis is often delayed. It is only after the local invasion has advanced that diagnosis most often occurs (Park *et al.*, 2014; Ronning, 2014). The two most common types of gastric cancer screening tests are endoscopic and radiological examinations (Catalano *et al.*, 2009; Ronning, 2014; Cancer.Net, 2015; Setia *et al.*, 2015). Esophagogastroduodenoscopy (or upper gastrointestinal scope) is the endoscopic examination of the esophagus, stomach, and duodenum and can involve the *CDH1* gene. This test is the most accurate for diagnosing cases (Park *et al.*, 2014; Ronning, 2014; National Cancer Institute, 2016). Endoscopic ultrasonography is the best screening method for determining infiltration into the stomach and metastasis to local lymph nodes (Park *et al.*, 2014; Ronning, 2014). Radiological exams include spiral computed tomography (CT) scans, ultrasound-guided liver biopsy, ultrasound of liver with contrast, PET scan, and MRI. Spiral CT scans of the thorax and upper abdomen are sensitive toward detecting tumors smaller than 5 mm in the liver. Ultrasound-guided liver biopsy and ultrasound of the liver with contrast are used when the diagnosis is uncertain. The liver can be examined with an MRI, but a PET scan has higher sensitivity toward distant metastases than the CT or MRI scans (Ronning, 2014). These are the most commonly used screening tests today (Park *et al.*, 2014; Ronning, 2014; National Cancer Institute, 2016).

Treatment

Treatment of gastric cancer depends on the stage of the disease (Jackson *et al.*, 2009; Saghier *et al.*, 2013). If the tumor is detected at an early stage, specifically stage II, gastric cancer can be cured with surgery (Saghier *et al.*, 2013; Ronning, 2014). Laparoscopy-assisted distal gastrectomy (*LADG*) is the most common surgical procedures for gastric cancer (Saghier *et al.*, 2013). Unfortunately, because gastric cancer is usually diagnosed at an advanced stage (Catalano *et al.*, 2009; Park *et al.*, 2014; Ronning, 2014), performing a LADG can be difficult. Two other common treatment methods are radiotherapy and chemotherapy. Radiotherapy includes treatments given over a set period of time. Patients with gastric cancer typically receive external-beam radiation therapy given outside the body (Cancer.Net, 2015). Radiation dosage is 50 Gy and combined with chemotherapy (Park *et al.*, 2014; Ronning, 2014). Chemotherapy is effective in downstaging stomach cancer, sometimes with a chance of a later resection with a curative intention (Ronning, 2014; Cancer.Net, 2015). Toxicity of dose-limiting structures surrounding the stomach and tumor recurrence may occur with stomach cancer treatment (Park *et al.*, 2014; Cancer.Net, 2015).

Survival

With improved technological advances, the survival rate has increased within the last few decades (Saghier *et al.*, 2013; National Institute of Health NIH, 2015; American Cancer Society, 2016; Yang *et al.*, 2017); however this disease remains difficult to manage (Saghier *et al.*, 2013). As the staging of gastric cancer increases, the survival rate significantly decreases (Saghier *et al.*, 2013; Karimi *et al.*, 2014; Park *et al.*, 2014; American Cancer Society, 2016; National Cancer Institute, 2016; Yang *et al.*, 2017). In the USA, the overall 5-year survival rate for all people with stomach cancer is ~65% without metastases (Cancer.Net, 2015). With most diagnoses occurring in advanced stages, the overall 5-year survival rate for all people drops to as low as 30% (Cancer.Net, 2015; National Institute of Health NIH, 2015; American Cancer Society, 2016; National Cancer Institute, 2016).

Epidemiology

Gastric cancer statistics

In 2008, the number of annual new cases and deaths from gastric cancer worldwide was 989 600 and 738 000, respectively (Ward *et al.*, 2011; Piazuelo and Correa, 2013; Saghier *et al.*, 2013; Karimi *et al.*, 2014). Incidence rates of gastric cancer vary significantly in different parts of the world (Nagini, 2012; Saghier *et al.*, 2013; Fock, 2014; Cancer.Net, 2015). When comparing international stomach cancer incidence rates, East Asia (40–60 per 100 000), South America (20–30 per 100 000), and East Europe (35 per 100 000) have the highest rates while North America (~6 per 100 000) and most of Africa (less than 3 per 100 000) have the lowest incidence rates observed (Ward *et al.*, 2011; Nagini, 2012; Piazuelo and Correa, 2013; Saghier *et al.*, 2013; Karimi *et al.*, 2014). For example, China itself accounts for over 40% of incident stomach cancer cases worldwide, which could also be because of its population size (Saghier *et al.*, 2013). Globocan 2008 ranks gastric cancer as the third most frequently diagnosed cancer and

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second leading cause of cancer-related deaths in Japan. Japan's 2008 estimated incidence and mortality were ~100 000 and 50 000, respectively (Saghier *et al.*, 2013). Stomach cancer incidence ranks fourth, whereas stomach cancer mortality ranks second in Colombia (Piazuelo and Correa, 2013). Globocan, in 2012, reported that there were over 950 000 new cases of stomach cancer in the world, accounting for 6.8% of all cancers. This placed gastric cancer at the fifth most common malignancy globally after lung, breast, colorectal, and prostate cancer. Over 70% of cases occurred in developing countries (Globocan IARC, 2012; Fock, 2014). Sixty percent of all gastric cancer cases occurred in Japan, China, and Korea (Fock, 2014).

In the USA, the gastric cancer rates are among the lowest compared with other countries worldwide (Ward *et al.*, 2011; Nagini, 2012; Saghier *et al.*, 2013; Ferro *et al.*, 2014; Fock, 2014; Karimi *et al.*, 2014). It represents only about 1.6% of all the new cancer cases in the USA (Siegel *et al.*, 2014; National Institute of Health NIH, 2015; National Cancer Institute, 2016). Stomach cancer is actually ranked as the 15th leading cause of death within the USA. In 2013, there were ~80 000 people living with stomach cancer in the USA (National Cancer Institute, 2016). According to the American Cancer Society, it is estimated that for the year of 2016, gastric cancer in the USA will have about 26 400 cases and about 10 700 deaths (American Cancer Society, 2016).

Geographic differences

Temporal trends

During the 1930s, stomach cancer was the most common cause of cancer-related death in the USA and in Europe (American Cancer Society, 2016). However, death rates have steadily decreased over the last 50–70 years in all developed countries (Catalano *et al.*, 2009; Nagini, 2012; Patru *et al.*, 2013; Ferro *et al.*, 2014; American Cancer Society, 2016) and is no longer among the top causes of death due to cancer in the USA and other countries across the world (Ferro *et al.*, 2014; Siegel *et al.*, 2014; American Cancer Society, 2016). Despite an overall reduction in gastric cancer rates, the incidence of gastric cardia adenocarcinoma increased significantly in developed countries (Catalano *et al.*, 2009; Karimi *et al.*, 2014). It is important to note that the patterns in gastric cancer trends vary across geographical regions. This variation reflects a heterogeneous distribution of the factors associated with gastric cancer incidence, survival, and mortality rates (Ferro *et al.*, 2014).

Sex

Males have a higher risk of gastric cancer compared with females for both cardia and noncardia gastric cancer (Karimi *et al.*, 2014; Cancer.Net, 2015; American Cancer Society, 2016). There is a five-fold difference in risk for cardia gastric cancer. Although the reason for this difference is not really known, environmental, and occupational exposures could play a role. For example, sex differences reflect different physiologic differences. Women have estrogen that may protect them against the development of the disease. A delayed menopause or increased fertility could lower the risk of gastric cancer while antiestrogen drugs like tamoxifen may increase the risk. These physiological characteristics can help to create a 10–15-year lag for women to develop stomach cancer compared with men (Karimi *et al.*, 2014).

When looking at the difference in noncardia gastric cancer rates between men and women, men generally have rates twice as high than women (Ward *et al.*, 2011; Nagini, 2012; Piazuelo and Correa, 2013; Karimi *et al.*, 2014); however, the incidence rates for gastric cancer can vary wildly between men and women (Karimi *et al.*, 2014). For example, in Brazil, gastric cancer is the fourth and sixth most common cancer among men and women, respectively (Saghier *et al.*, 2013). In Colombia, men have a gastric cancer incidence rate of 23.4 per 100 000 population, whereas women have a rate of 12.5 per 100 000 population (Piazuelo and Correa, 2013). In Japan, gastric cancer remains the most common type of cancer for both men and women. Although the incidence of proximal tumors in the West is increasing, the distal tumors in Japan continue to prevail (Patru *et al.*, 2013). In the USA, incidence rates for gastric cancer among males have decreased by 1.7%, whereas incidence rates among females have decreased by 0.8% annually from 1992 to 2010 (Karimi *et al.*, 2014). On the basis of the 2010–2012 data, ~0.9% of men and women will be diagnosed with gastric cancer at some point in their lives (National Cancer Institute, 2016). On the basis of the age-adjusted 2009–2013 cases and deaths, the number of new cases and deaths for men and women in the USA, per year, were 7.4 per 100 000 and 3.3 per 100 000, respectively. Of the estimated 26 400 gastric cancer diagnoses for the USA in 2016, ~16 500 were male, whereas 9900 were female. Of the estimated 10 700 gastric cancer deaths, ~6500 were male, whereas 4200 were female (Cancer.Net, 2015).

Age

Age plays an important role in the increased risk for gastric cancer (Karimi *et al.*, 2014; Cancer.Net, 2015; Cancer Research UK, 2015; American Cancer Society, 2016). The older population is mostly affected by gastric cancer (Nagini, 2012; Fock, 2014; World Cancer Research Fund International, 2015; American Cancer Society, 2016; National Cancer Institute, 2016). The incidence and mortality rates of gastric cancer progressively increase with age (Piazuelo and Correa, 2013; Fock, 2014; Karimi *et al.*, 2014; National Cancer Institute, 2016). Most new cases are in older adults between the age of 50 and 70 years (Nagini, 2012; Fock, 2014; Cancer.Net, 2015), with the average age of diagnosis being 69 years of age (American Cancer Society, 2016). Between 2005 and 2009, of the

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cases diagnosed in the USA, only about one percent occurred between the ages of 20 and 34 years. However, 29% occurred between the ages of 75 and 84 years. Each year approximately six out of 10 people diagnosed with gastric cancer are 65 years or older. People aged 75–84 years have the highest percentage of gastric cancer deaths (National Cancer Institute, 2016). Gastric cancer cases in people 30 years old or younger are very rare (Piazuelo and Correa, 2013; Fock, 2014).

Ethnicity

Certain ethnic groups living in the same geographic region have significant variations in the overall incidence of gastric cancer (Patru *et al*., 2013; Piazuelo and Correa, 2013; Fock, 2014). For example, African–Americans, Hispanics, and Native Indians in the USA are more affected by noncardia gastric cancer than Whites (Piazuelo and Correa, 2013). The SEER age-adjusted 2009–2013 ethnic incidence rates for all races, in the USA, were 10.0 and 5.3 per 100 000 for males and females, respectively. For White, Black, Asian/Pacific Islander, American Indian/Alaskan Native, Hispanic, and Non-Hispanic males, the incidence rates per 100 000 were 9.1, 14.0, 14.3, 13.5, 13.5, and 9.5, respectively. The same rates for females per 100 000 were 4.5, 8.1, 8.5, 8.0, 8.5, and 4.8, respectively. The mortality rate of gastric cancer for all races was 4.5 and 2.4 for males and females, respectively. For White, Black, Asian/Pacific Islander, American Indian/Alaskan Native, Hispanic, and Non-Hispanic males, mortality rates per 100 000 were 3.9, 8.8, 7.5, 7.4, 7.1, and 4.2, respectively. For females per 100 000, the rates were 2.1, 4.2, 4.4, 3.8, 4.1, and 2.2, respectively (National Cancer Institute, 2016). The ethnic distribution of cardia gastric cancer is not the same. Whites in the USA have higher rates than Blacks (Patru *et al*., 2013; Karimi *et al*., 2014). This is also true for the non-Maori population compared with the Maoris population in New Zealand (Nagini, 2012; Karimi *et al*., 2014). These statistics express the importance of understanding which factors influence these gastric cancer ethnic distributions.

Risk factors

Gastric cancer is a multifactorial disease (Nagini, 2012; Zabaleta, 2012; Piazuelo and Correa, 2013; Sala *et al*., 2013; Karimi *et al*., 2014; Park *et al*., 2014; Rota *et al*., 2017). Some of the factors associated with gastric cancer are modifiable, such as smoking and potentially *H. pylori* infection, while others are nonmodifiable, such as age and sex. The risk factors for cardia and noncardia gastric cancer (Karimi *et al*., 2014; Lee *et al*., 2014) may vary but there are some factors that they both have in common including older age, male sex, tobacco smoking, and family history. Factors like race affect both cardia and noncardia gastric cancer, but the direction of the association differs by site. For example, in the USA, Whites are more likely to have cardia gastric cancer, whereas Hispanics are more likely to be diagnosed with noncardia gastric cancer (Karimi *et al*., 2014). There are risk factors that increase the chances of getting gastric cancer and there are others that reduce the chances of getting the disease. Likewise, there are some factors that only increase the risk of cardia gastric cancer and some factors that only increase the risk of noncardia gastric cancer.

Helicobacter pylori infection

H. pylori is considered one of the primary risk factors for gastric cancer (Park *et al*., 2011; González and Agudo, 2012; Nagini, 2012; Zabaleta, 2012; Ferro *et al*., 2014; Fock, 2014; Karimi *et al*., 2014; World Cancer Research Fund International, 2015; American Cancer Society, 2016; Ronning, 2014; Cancer.Net, 2015; Cheng *et al*., 2016; Vyas *et al*., 2016; Rota *et al*., 2017; Mahendra *et al*., 2018). It accounts for 50% of gastric cancer cases (Fock and Ang, 2010; Kim *et al*., 2011; Lee *et al*., 2014; Noto and Peek, 2017). *H. pylori* has also been linked to other severe gastric diseases such as peptic ulcer (Suzuki *et al*., 2012). *H. pylori* bacteria is a gram-negative, spiral-shaped, microaerophilic urease-positive bacillus (Shanks and El-Omar, 2009; Fock and Ang, 2010; Kim *et al*., 2011; Cheng *et al*., 2016) acquired during childhood via fecal-oral transmission (Shanks and El-Omar, 2009; Kim *et al*., 2011; Suzuki *et al*., 2012; Leja *et al*., 2016). These bacteria reside on the surface mucus gel layer, with a little invasion of the gastric glands, and most infections occur chronically (Shanks and El-Omar, 2009). The prevalence of *H. pylori* infection has generally declined globally; however, many subpopulations and geographical regions continue to experience a high prevalence rate of gastric cancer. These subpopulations include men, older age groups, and developing regions (Suzuki *et al*., 2012; Leja *et al*., 2016). One study found that ~90% of the gastric cancer cases occur among those aged 70 or older. There was only a 5% prevalence for children 2 years of age or younger. The explanation for the general decline was due to the improvements of living circumstances and changes made by populations such as increased availability of indoor toilets, bathrooms, and electricity within the homes (Leja *et al*., 2016). The association has been strongly linked to the distal, noncardia part of the stomach versus the cardia (González and Agudo, 2012; Karimi *et al*., 2014; American Cancer Society, 2016). It is also estimated that 89% of noncardia gastric cancer cases are due to this infection.

H. pylori transmission has been recently linked to specific water sources. A study carried out by Krueger and colleagues (Leja *et al*., 2016) examined the environmental exposure of well water usage and occupational contact with soil played a role in *H. pylori* transmission. The odds ratio (OR) of seropositivity of those exposed compared with those unexposed was 2.7 [95% confidence interval (CI): 1.3–5.6]. A case–control study conducted in Golestan Province, Iran found that chlorinated well water had a reduced risk of *H. pylori* seropositivity compared

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with an increased risk due to nonchlorinated well water and surface water with ORs of 0.23, 4.58, and 4.26, respectively. Even water from cisterns and nonpiped sources were shown to increase *H. pylori* seropositivity (Leja *et al.*, 2016).

How the *H. pylori* infection actually causes gastric cancer is unclear, but there are two possible pathways that are considered: the first is indirect action of *H. pylori* on gastric epithelial cells and the second is directly modulating epithelial cell function through bacterial agents like CagA (Kim *et al.*, 2011; Yamashita *et al.*, 2011; Karimi *et al.*, 2014). Many epidemiological studies documented the link between this bacterium and gastric cancer, most recently with both meta-analysis and experimental models in Japanese and Chinese populations. Four prospective studies showed a positive association and relative risks (RR) ranging from 1.0 to 5.1 for *H. pylori* and gastric cancer. The largest study of Sasazuki and colleagues showed that the OR for this association was 5.1, which was similar to a combined analysis of 12 case–control studies nested within prospective cohorts with an OR of 5.9 for noncardia gastric cancer. Another study conducted on a Chinese population showed that *H. pylori* seropositivity resulted in an increased risk of gastric cancer by approximately two-fold, which was also found in another case-cohort study (Saghier *et al.*, 2013). It is estimated that *H. pylori* causes two-thirds to three-quarters of all gastric cancer cases annually (González and Agudo, 2012; Karimi *et al.*, 2014). Increased sanitation and extensive use of antibiotics may be important methods to reduce the incidence of noncardia gastric cancer caused by *H. pylori* infection (Karimi *et al.*, 2014; Cancer.Net, 2015; American Cancer Society, 2016).

Table 1 Gastric cancer in five continents (age-standardized rates per 100 000 population)

Continents	Male (ASR)	Female (ASR)
North America		
USA	7.2	[b]
Canada[a]	7.8	[b]
Latin America		
Ecuador[a]	22.0	14.7
Argentina[a]	12.9	[b]
Brazil[a]	20.0	9.3
Chile[a]	33.4	12.5
Colombia[a]	26.1	12.5
Uruguay	14.3	[b]
Europe		
UK[a]	9.2[c]	[b]
France[a]	8.4[c]	[b]
Italy[a]	14.6	7.3[c]
Germany[a]	12.7	[b]
Ireland	10.5	[b]
Spain[a]	11.9	5.2[c]
Sweden	[b]	[b]
Switzerland[a]	7.7[c]	[b]
Asia		
China[a]	38.8	16.5
Japan[a]	59.5	22.4
Republic of Korea[a]	63.3	25.5
India[a]	10.3	4.9[c]
Israel	10.1	[b]
Africa		
Uganda	8.0	5.9
Zimbabwe	11.7	14.2
South Africa	[b]	[b]
Tunisia	5.8	[b]
Malawi	[b]	[b]
Libya	[b]	[b]
Egypt	[b]	[b]
Algeria	5.7	3.4

ASR, age-standardized rate.
[a]There were multiple areas in particular country that reported rates so the average of IARC reported rates for country was provided.
[b]Average reported rates are lower than the listed top 10 major cancers for geographical area.
[c]Average includes some reported rates that were not in the top 10 major cancers.
Source: *http://www.iarc.fr/en/publications/pdfs-online/epi/sp164/CI5volX_Full.pdf.*

Non-H. pylori factors

Geographic location

As mentioned previously, the incidence and mortality rates vary significantly across the world (Nagini, 2012; Saghier *et al.*, 2013; Fock, 2014; Cancer.Net, 2015). This is also true for a person's risk of getting the disease. For example, in countries like Japan, Korea, China, Eastern Europe, and South and Central America, gastric cancer risk is higher than in countries like Northern and Western Africa, South Central Asia, and North America (Jemal *et al.*, 2011; Ronning, 2014; American Cancer Society, 2016). The countries with the greatest risk are Japan, Korea, and China (Park *et al.*, 2011; Ferro *et al.*, 2014; Ronning, 2014). Different geographic areas can also bring about different risk factors (Saghier *et al.*, 2013). Migration also influences the risk of getting the disease (Kim *et al.*, 2011; Nagini, 2012; Zabaleta, 2012; Karimi *et al.*, 2014). Studies show that after migration, there are two patterns of risk change. The first is that it takes two generations to reach the level of risk of the adopted country. An example would be the *H. pylori* infection. The second is that place of birth is a stronger predictor than the current place of residence of gastric cancer risk (Karimi *et al.*, 2014). Migrant populations from high-risk areas showed a reduction in risk moving to a low-incidence area like the USA. Succeeding generations acquire risk levels similar to those of their host country (Nagini, 2012), showing the important impact the geographical environment (Table 1).

Race and low socioeconomic status

Gastric cancer rates vary across different races worldwide. In the USA, for example, gastric cancer rates are higher in Latinos than in non-Hispanic White populations with rates for Latino men and women being 13.9 per 100 000 and 8.2 per 100 000, respectively (Karimi *et al.*, 2014). With regard to noncardia gastric cancer, minority populations have higher rates of stomach cancer. For cardia gastric cancer; however, Whites tend to have higher rates than minority populations (Piazuelo and Correa, 2013; Cancer.Net, 2015; American Cancer Society, 2016). Some studies show rates of cardia gastric cancer in Whites double the rates in minority populations such as Hispanics and Blacks. The risk of noncardia gastric cancer in the USA is

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highest among Asians/Pacific Islanders, with Blacks and Hispanics following. Whites have the lowest risk. The association between race and gastric cancer may be more influenced by the environment than genetics. This is best demonstrated in the Japanese. Japan has the highest incidence of gastric cancer; however, after the Japanese migrate to the USA, where the incidence is much lower, the first generation still has a very high rate. Following generations, however, experience lower rates and resemble those of Americans or European lineage.

Scientists have also known for many years that low socioeconomic status is associated with higher risk of total and cause-specific mortality from noncardia gastric cancer. Lower levels of education and income are two specific socioeconomic markers associated with gastric cancer precursor lesions. The intake of starchy food and limited access to fresh fruit and vegetables may be responsible for the association between socioeconomic status and increased risk of gastric cancer (Karimi *et al.*, 2014).

Tobacco smoking and alcohol consumption

Although early studies examining the associations between smoking and gastric cancer were not consistent enough to classify smoking as a risk factor for gastric cancer, the International Agency for Research on Cancer concluded in 2002 that enough evidence supported the notion that smoking was a risk factor for the disease (Karimi *et al.*, 2014). Eighteen percent of gastric cancer cases in the USA were attributed to tobacco use (González and Agudo, 2012; Piazuelo and Correa, 2013). A meta-analysis of cohort studies also showed a significantly increased risk of gastric cancer due to smoking. In males, the risk is increased by ~60% in smokers compared with males who never smoked and ~20% in female smokers compared with females who never smoked. The studies also showed that smoking is a risk factor for both cardia and noncardia gastric cancer. Gastric cancer risk was not higher in ex-smokers compared with never-smokers (Karimi *et al.*, 2014; Cancer Research UK, 2015). The Hisayama study in 2006 concluded that smoking increased the risk of gastric cancer in the Japanese population with a summary relative risk of 1.8 for men and 1.2 for women (Saghier *et al.*, 2013). These studies show a significant relationship between smoking and developing gastric cancer when comparing smokers to nonsmokers; however, in 2009, a retrospective study that analyzed the dose-dependent relationship between gastric cancer and smoking was unable to find a significant dose–response effect between the two (Smyth *et al.*, 2012).

Although moderate alcohol consumption was not found to be an associated risk factor for gastric cancer, excessive alcohol consumption was in some studies. The risk of gastric cancer is 20% higher per 50 g + per day of alcohol consumed compared with nondrinking or moderate drinking (Cancer Research UK, 2015). A case–control study in Poland found an association between vodka consumption and gastric cancer. Those drinking vodka at least once a week had three times the risk of gastric cancer than nondrinkers (Saghier *et al.*, 2013). Although there are other sources that support this conclusion (Selgrad *et al.*, 2011; Piazuelo and Correa, 2013; Park *et al.*, 2014; Cancer.Net, 2015; American Cancer Society, 2016), there are some experimental studies that were unable to support this claim (Saghier *et al.*, 2013). A European prospective nutrition cohort study found that heavy alcohol consumption at baseline was positively associated with gastric cancer risk (hazard ratio = 1.65, 95% CI: 1.06–2.58), whereas lower consumption (< 60 g/day) was not (Cheng *et al.*, 2016).

Researchers, who participated in the Stomach cancer Pooling Project (StoP), carried out studies on the association between cigarette smoking and alcohol consumption and gastric cancer risk. StoP carried out "an individual participant data meta-analysis of studies participating in the 'Stomach cancer Pooling (StoP) Project' a recently established consortium of epidemiological studies on risk factors for gastric cancer." StoP utilized data from a large dataset of studies that included 10 290 cases and 26 145 controls from different countries such as Germany, Russia, China, and Japan (Rota *et al.*, 2017; Praud *et al.*, 2018).

In one study where they analyzed the relationship between cigarette smoking and gastric cancer, StoP researchers found that the ORs among those who ever smoked, were former smokers, and current smokers were 1.20 (95% CI: 1.09–1.32), 1.12 (95% CI: 0.99–1.27), and 1.25 (95% CI: 1.11–1.40) compared with those who never smoked, respectively. If current smokers smoked over 20 cigarettes a day, the OR would increase to 1.32 (95% CI: 1.10–1.58). Duration of smoking also increased the risk of gastric cancer, meaning the longer a person smoked increased their risk significantly and the more time after a person quit smoking decreased their risk of gastric cancer. This particular study showed not only that there was a relationship between cigarette smoking and gastric cancer risk, but it also showed how dosage and duration of smoking played an important role as well (Praud *et al.*, 2018).

StoP's analysis on the relationship between alcohol consumption and gastric cancer risk found that those who consumed alcohol had an OR of 1.10 (95% CI: 0.99–1.21) compared with those who never drank. Drinking intensity was significantly associated with gastric cancer risk. Compared with never drinkers, the ORs for those consuming between 4 and 6 drinks/day and more than 6 drinks/day were 1.26 (95% CI: 1.08–1.48) and 1.48 (95% CI: 1.29–1.70), respectively. There was also a significant trend in gastric cancer risk ($P < 0.01$). Among drinkers who only consumed one type of beverage, researchers found a significant risk for spirits-only drinkers of more than 1 drink/day (pooled OR: 1.66, 95% CI: 1.23–2.22), wine-only drinkers of more than three 3 drinks/day (pooled OR: 1.44, 95% CI 0.98–2.11), and beer-only drinkers of

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more than 1 drink/day (OR: 1.27, 95% CI: 0.89–1.82). Similar to tobacco, the duration of alcohol consumption also had a significant impact on the risk of gastric cancer. However, increased duration of drinking did not show the same trend as smoking. Those who have been drinking between 20 and 40 years had an OR of 1.28 (95% CI: 1.08–1.51), but those drinking for more than 40 years had a slightly lower OR of 1.13 (95% CI: 0.97–1.33). Those who have quit drinking for less than 5 years had a significantly decreased risk for gastric cancer (pooled OR: 1.93, 95% CI: 1.39–2.68) (Rota *et al.*, 2017).

Diet

Preserved and/or processed food: Smoked meats and salt-preserved foods are potentially carcinogenic and large intakes can increase the risk of *H. pylori* infection (González and Agudo, 2012; Nagini, 2012; Saghier *et al.*, 2013; Fock, 2014; American Cancer Society, 2016; Cheng *et al.*, 2016). The World Cancer Research Fund/American Institute for Cancer Research concluded that salt and salt-preserved foods are probable causes of noncardia gastric cancer (Karimi *et al.*, 2014). Studies show smoked meat creates the formation of *N*-nitroso compounds that are linked to gastric cancer (Nagini, 2012; Saghier *et al.*, 2013; Karimi *et al.*, 2014; Cancer Research UK, 2015; American Cancer Society, 2016; Cheng *et al.*, 2016). Many other epidemiological and experimental studies supported this hypothesis (Selgrad *et al.*, 2011; González and Agudo, 2012; Piazuelo and Correa, 2013; Sala *et al.*, 2013; Park *et al.*, 2014; Ronning, 2014; Cancer.Net, 2015). This association between smoked foods and gastric cancer was suggested in the 1960s because high rates of gastric cancer were found in areas where consumption of smoked meat was very high. Large cohort studies in Korea showed that people who consume more salty food have a higher risk of noncardia gastric cancer due to the direct damage to the gastric mucosa resulting in gastritis. A meta-analysis of 11 studies showed smoked meat increased the risk by 22%. Studies in Europe also support these conclusions (Karimi *et al.*, 2014). Another meta-analysis of cohort studies found that 'high' and 'moderately high' salt intake were associated with an increased risk of gastric cancer (RR = 1.68,95% CI: 1.17–2.41, $P = 0.005$ and RR = 1.41, 95% CI: 1.03–1.93, $P = 0.032$, respectively) compared with low salt intake (D'Elia *et al.*, 2012). A study in Portugal analyzed the relationship between salt intake and further risk factors like *H. pylori* and tobacco. Results showed an increased risk of gastric cancer for the group with the highest salt intake compared with the group with the lowest salt consumption (salt intake: OR: 2.01, 95% CI: 1.16–3.46; food with high salt contribution: OR: 2.54, 95% CI: 1.56–4.14) (Selgrad *et al.*, 2011). Ge *et al.* (2012) carried out a systematic review of dietary salt intake and noncardia gastric cancer risk in different geographic locations from studies carried out between 1992 and 2012. Of the 11 studies included, there was a positive association between high salt intake and gastric cancer. The OR was 2.05, meaning higher salt consumption increased one's risk of developing gastric cancer (Saghier *et al.*, 2013). The decline in gastric cancer may be due to refrigeration of foods and a decreased use of salt to preserve food (Jemal *et al.*, 2011; Park *et al.*, 2011; Selgrad *et al.*, 2011; Ward *et al.*, 2011; Nagini, 2012; Piazuelo and Correa, 2013; Siegel *et al.*, 2014; American Cancer Society, 2016). A study's results show an OR of 0.28, which means that refrigeration of foods and a decreased use of salt lowered a person's risk of developing gastric cancer (Selgrad *et al.*, 2011).

Intake of fruits and vegetables: High intake of fruits and vegetables are considered a protective measure in gastric cancer risk (Fock, 2014; Park *et al.*, 2014; Cancer Research UK, 2015; Cheng *et al.*, 2016). Consumption of fruits and vegetables appears to lower the risk of noncardia gastric cancer (Liu and Russell, 2008; Selgrad *et al.*, 2011; Gonzalez *et al.*, 2012; Sala *et al.*, 2013; Park *et al.*, 2014; Cancer.Net, 2015; American Cancer Society, 2016; Leja *et al.*, 2016). Most studies suggest an inverse association between vegetables and citrus fruits and gastric cancer risk (Liu and Russell, 2008; Gonzalez *et al.*, 2012; Navarro Silvera *et al.*, 2014); however, meta-analyses have shown that this inverse association is stronger for fruits than for vegetables (Liu and Russell, 2008). The World Cancer Research Fund recommended a vegetable/fruit intake per day of more than 400 g for cancer prevention (Park *et al.*, 2011). Prospective studies have reported this significant association, mainly in case–control studies (Nagini, 2012; Saghier *et al.*, 2013; Sala *et al.*, 2013). Case–control studies in Europe, Asia, and North America found that intake of fruits and vegetables reduce the risk of gastric cancer by 40 and 30%, respectively. The findings from this study are similar to a study carried out in Japan, which concluded that even in low amounts, fruits and vegetables could lower the risk of gastric cancer (Saghier *et al.*, 2013). A Korean study of 552 participants, that incorporated the Korean National Health and Nutrition Examination Survey and Korean Statistical Information Service, looked at the association between the increase in refrigeration of fruits and vegetables and the risk of gastric cancer. Results showed a strong negative correlation between refrigerator use and fruit consumption and gastric cancer mortality in the Korean population. The association between refrigeration of vegetables and gastric cancer risk was not found to be significant (Park *et al.*, 2011).

Vitamin D and dietary fiber: Recent studies have researched the association of other dietary factors, such as vitamin D and dietary fiber. Vitamin D is a fat-soluble secosteroid that has been known to affect the intestinal, skeletal, and biologic pathways such as immune cells and tumor microenvironment (Vyas *et al.*, 2016; Mahendra *et al.*, 2018). A vitamin D deficiency (VDd), has been associated

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with gastrointestinal malignancies that are mediated by vitamin D receptors. VDd is defined as 25(OH)D of less than 15–20 mg/dl and sufficient range greater than 30 mg/dl. And although VDd has been associated with cancers, there are limited studies on its association with gastric cancer (Vyas *et al.*, 2016). However, some studies have found that an increase in vitamin D levels was linked to a decreased risk of gastric cancer (Vyas *et al.*, 2016; Mahendra *et al.*, 2018).

A retrospective case–control study that reviewed 304 patients with gastric adenocarcinoma diagnosed between 2005 and 2015. Of those patients, 49 of them had recorded vitamin D levels. Results showed that the average age and vitamin D level of patients were 64 years old (95% CI: 27–86) and 20.8 (95% CI: 4–44), respectively. VDd was significantly higher among patients who had gastric adenocarcinoma compared with the matched controls (83.7 vs. 63.27%). Approximately 84% of patients with gastric adenocarcinoma had a VDd compared with 37% of patients without a VDd or gastric adenocarcinoma (OR: 8.8, 95% CI: 5–22, $P < 0.0001$). This study supports the suggestion that gastric cancer risk is significantly higher among those with a VDd (Vyas *et al.*, 2016).

Dietary fiber has also been studied as a preventative factor for gastric cancer, although studies examining the association between dietary fiber and gastric cancer have provided indeterminate results. Dietary fiber is thought to act as a countering component to the carcinogenic effects of *N*-nitroso compounds. In a meta-analysis, 21 articles, that included over 580 000 patients, were analyzed. The summary OR of gastric cancer for dietary fiber intake was 0.58 (95% CI: 0.49–0.67) with significant heterogeneity among studies ($P < 0.001$, $I^2 = 62.2\%$). A dose–response analysis also showed that a 10-g/day increment in fiber intake had a 44% reduction in the risk of gastric cancer. This analysis found dietary fiber intake to be inversely associated with gastric cancer risk, although the magnitude was not as consistent between studies (Zhang *et al.*, 2013).

Obesity and gastroesophageal reflux disease: The risk of cardia gastric cancer has been linked to obesity and gastroesophageal reflux disease (GERD) (Nagini, 2012; Saghier *et al.*, 2013; Sala *et al.*, 2013; Karimi *et al.*, 2014; Navarro Silvera *et al.*, 2014; American Cancer Society, 2016). However, the evidence does not show an association between these risk factors and noncardia gastric cancer (Abnet *et al.*, 2008; Saghier *et al.*, 2013; Sala *et al.*, 2013; Karimi *et al.*, 2014; American Cancer Society, 2016). A study analyzed the association of BMI scores and one's risk of gastric cancer. Those with a BMI 30–35 kg/m^2 had a two-fold, whereas those with a BMI greater than 40 kg/m^2 had a three-fold risk of cardia gastric cancer (Karimi *et al.*, 2014). Another study and meta-analysis had similar significant results for BMI greater than 30 kg/m^2 increasing the risk of cardia gastric cancer (Abnet *et al.*, 2008; Lin *et al.*, 2014). A systematic review of four studies that assessed the association between BMI and the risk of cardia gastric cancer reported that overweight or obesity was significantly associated with a 1.5-fold increase in the risk of cardia gastric cancer (Liu and Russell, 2008). GERD has shown to be significantly associated with cardia gastric cancer and some study results show a 2–4-fold increased risk (Saghier *et al.*, 2013). Obesity can promote GERD and increase the risk of gastric cancer as well (Saghier *et al.*, 2013; Herbella *et al.*, 2015). Some researchers have shown that for every five-point increase in BMI, the DeMeester GERD score increases by three units (Herbella *et al.*, 2015). This supports the notion that obesity and GERD are linked to gastric cancer.

Other factors

Other factors were shown to increase the risk of gastric cancer but are less common include previous stomach surgery (American Cancer Society, 2016), occupational exposures such as dust and fumes, radiation, having type A blood (Nagini, 2012; American Cancer Society, 2016) and pernicious anemia (American Cancer Society, 2016). According to the American Cancer Society (2016), gastric cancer is more likely to develop in persons that have had part of their stomach removed to treat noncancerous diseases such as ulcers. With part of the stomach removed, less acid is being produced that increases the chances of more nitrite-producing bacteria to be present. Occupations that include mining, farming, and working with a material such as timber or asbestos have shown a positive correlation for gastric cancer risk (Nagini, 2012). Although the specific reasons are unknown, persons with type A blood appear to have a higher risk of developing gastric cancer compared with those with a different blood type group (Nagini, 2012; American Cancer Society, 2016). With regard to pernicious anemia, there are some cells in the lining of the stomach that make what is called an intrinsic factor. This intrinsic factor is needed to absorb vitamin B12 from food and those that do not have enough vitamin B12 in their body are unable to make new red blood cells, hence they develop pernicious anemia. This condition increases an individual's risk of gastric cancer (American Cancer Society, 2016).

Other factors shown to reduce the risk of gastric cancer, although there are limited detailed studies available on them, include physical activity, NSAIDs, statins, and antioxidants (Selgrad *et al.*, 2011; Sala *et al.*, 2013; Karimi *et al.*, 2014). Figure 1 illustrates the relationship between the *H. pylori* and non-*H. pylori* risk factors and the risk of developing gastric cancer.

Histology and biology

Histology and staging

The histology of gastric cancer is classified by using a classification criteria method known as Lauren's criteria. The Lauren's criteria classifies gastric cancer into two major subtypes, the intestinal-type (~54%) and diffuse-type

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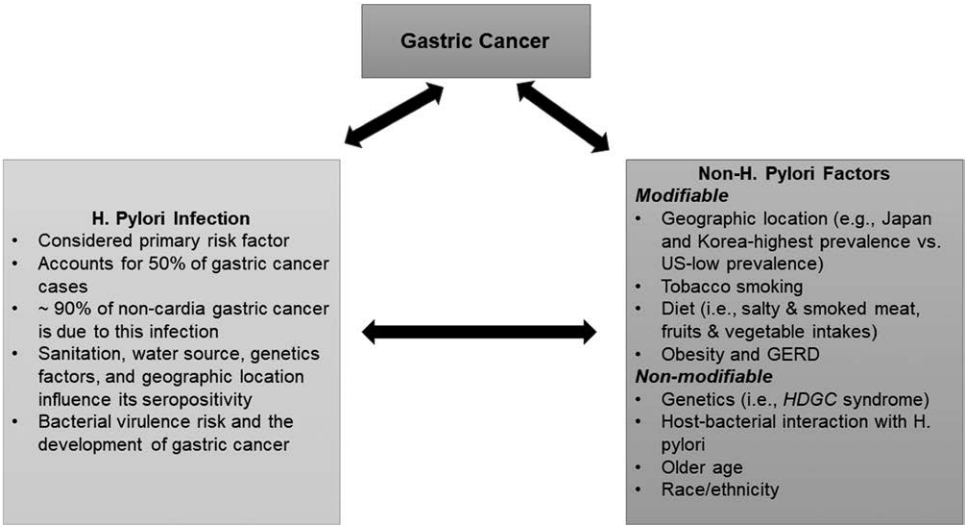
Fig. 1



Risk factors for gastric cancer. GERD, gastroesophageal reflux disease; HDGC, hereditary diffuse gastric cancer.

(~32%) adenocarcinomas (Catalano *et al.*, 2009; Kim *et al.*, 2011; Yamashita *et al.*, 2011; Hudler, 2012; Nagini, 2012; Sittler *et al.*, 2012; Patru *et al.*, 2013), plus an indeterminate type (<15%) (Catalano *et al.*, 2009; Nagini, 2012; Sittler *et al.*, 2012). Diffuse gastric carcinoma is seen more in females and young individuals while intestinal adenocarcinoma is often associated with intestinal metaplasia and *H. pylori* infection (Nagini, 2012; Sittler *et al.*, 2012). In 2010, the WHO recognized four major histologic patterns of gastric cancers as variants of adenocarcinomas. They are tubular, papillary, mucinous, and poorly cohesive (signet ring cell carcinoma) (Catalano *et al.*, 2009; Sittler *et al.*, 2012; Ronning, 2014). Tubular adenocarcinoma is the most common. It tends to form polypoid masses and has various sizes of irregularly distended, fused, or branching tubules, often with intraluminal mucus, nuclear, and inflammatory debris. Papillary adenocarcinoma is found in early gastric carcinoma and usually affects the elderly and occurs in the proximal stomach. Liver metastasis and a higher rate of lymph node involvement are associated with papillary adenocarcinoma. Ten percent of the gastric carcinoma is mucinous adenocarcinoma, which is characterized by extracellular mucinous pools accounting for at least 50% of tumor volume. Poorly cohesive carcinomas, like signet ring cell carcinoma, are often composed of a mixture of signet ring cells and nonsignet ring cells (Catalano *et al.*, 2009; Sittler *et al.*, 2012). The adenocarcinoma distinction is necessary because of the different epidemiologic patterns and causes. These adenocarcinomas arise from two anatomical subsites that are used to classify gastric cancer cases; cardia and noncardia of the stomach. Cardia gastric cancer refers to cancer that is roughly around the top inch of the stomach, whereas noncardia refers to the other parts of the stomach. When reporting the increase and prevalence rates of gastric cancer, cardia and noncardia classification is used (Karimi *et al.*, 2014). Staging is based on how far cancer has spread and is important for determining treatment methods (Cancer.Net, 2015; American Cancer Society, 2016). There are two different types of stages for gastric cancer. The clinical stage is the clinicians' best estimate of the extent of cancer while the pathologic stage more accurately predicts patient's outcome because it is based on what is found during surgery (American Cancer Society, 2016). In the USA, the American Joint Commission on Cancer TNM (i.e. tumor, nodes, and metastasis) system is currently used (Selgrad *et al.*, 2011; Park *et al.*, 2014; Ronning, 2014; Cancer.Net, 2015; American Cancer Society, 2016). Each of these three categories has numbers that range from 0 to 4 defining the severity and spread of each category. The T category ranges from 0 to 4 and describes how far through the stomach's five layers the primary tumor has spread. The T classification means the tumor is *in situ* or its original position. The N category ranges from 0 to 3 and describes the regional lymph nodes cancer has spread to. The M category ranges from 0 to 1 and describes the distant body parts cancer has invaded. There is also an 'X' classification for each category that means it cannot be assessed because of a lack of information (Ronning, 2014; Cancer.Net, 2015; American Cancer Society, 2016). Stage grouping is a classification assignment of the combined TNM classification categories. Stage 0 is the earliest stage and includes T, N0, and M0. Stage IA, spreading of the inner layer, includes T1, N0, and M0. Stage IB includes T1, N1, M0 or T2, N0, M0. Stage IIA is T1, N2, M0 or T2, N1, M0 or T3, N0, M0. Stage IIB includes T1, N3, M0 or T2, N2, M0 or T3, N1, M0 or T4a, N0, M0. Stage IIIA is T2, N3, M0 or T3,

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N2, M0 or T4a, N1, M0. Stage IIIB is T3, N3, M0 or T4a, N2, M0 or T4b, N0 or N1, M0. Stage IIIC is T4a, N3, M0 or T4b, N2 or N3, M0. Stage IV is the spread to distant organs and includes any T, any N, and M1 (Catalano *et al.*, 2009; Cancer.Net, 2015; American Cancer Society, 2016).

Immune response

The immune system is vital in controlling tumor growth and progression (Zabaleta, 2012). When the immune system has the ability to detect tumor cells as nonself and eliminate them before developing into clinical malignancy, this phenomenon is called immune surveillance. Gastric cancer cells, however, have an ability to modulate the immune system and avoid detection (Subhash *et al.*, 2015). Because diagnosis often occurs late in the disease, it is suggested that gastric tumor-specific T cells are either not sufficiently induced or suppressed by the induction of tolerance (Lee *et al.*, 2014).

There are two types of immune responses associated with tumor development: innate and adaptive immune responses. An example of an innate immune response would be tumor-associated macrophages. Studies show that treatment with a nitric oxide-specific inhibitor can actually reverse *H. pylori*-induced methylation of the stomach epithelium, providing a mechanism in which *H. pylori* causes epigenetic changes that are associated with gastric cancer malignancy through inflammation. Adaptive immune responses are, for example, effector versus regulatory T cells. Although it is unclear as to how the infection of *H. pylori* evokes adaptive immunity or how it evades immune surveillance, T-cell responses are important in clearance of chronic bacterial infection. With infection clearance, immature T cells differentiate into effector T-cell subsets, helper type 1 cells for intracellular viruses and tumors, type 2 cells for helminthic worms, and type 17 cells for extracellular bacteria (Lee *et al.*, 2014). Some studies showed that therapeutic efficacy of tumor-specific T cells depends on the generation of a type 1 response. *H. pylori* restricts an immune response toward type 1 cytokine and tumor-specific type 1 cytokine responses are associated with protection from tumors and T-cell-mediated tumor regression. Regulatory T cells, or T_{reg} cells, help with peripheral tolerance. Balancing effector T cells and T_{reg} cells is important for resolving chronic inflammation (Lee *et al.*, 2014).

Immunotherapy is an approach to gastric cancer treatment, receiving more attention because of documented clinical responses for different types of tumors and provides promising outcomes. This treatment evolved from immunotherapy strategies in melanoma, which showed impressive outcomes and gained interest in the treatment of other cancers including gastric cancer. This field focuses on creating therapeutic strategies, enabling one's immune system to achieve cancer control. Cancer immunotherapy needs an immune-based strategy that induces effective tumor-specific immunity and eliminates tumor tolerance. An antitumor response should be mounted when specific cytotoxic cells are induced to recognize and attack tumor cells. Significant results in several studies that specific immune suppressive mechanisms can act as part of the tumor or the immune system to suppress antitumor responses. Because this treatment strategy is fairly new, there are currently studies being conducted to further explore this area and its impact on gastric cancer treatment (Subhash *et al.*, 2015).

Host–bacteria interaction

An ongoing area of research is the host–bacterial relationship of *H. pylori* infection and gastric cancer risk (McNamara and El-Omar, 2008; Kim *et al.*, 2011; Brawner *et al.*, 2014). Clinical outcomes of *H. pylori* infection are highly variable as only a small fraction of infected person's progress to gastric premalignant lesions (Kim *et al.*, 2011). *H. pylori* infection in the stomach causes a complex reaction in the gastric mucosa; however, this immune response does not eliminate the bacteria, leaving the host susceptible to complications from chronic inflammation including gastric premalignant conditions (Kim *et al.*, 2011). Researchers analyzed the interaction between host *IL-8* polymorphisms and *H. pylori* CagA genotypes with regard to gastric precancerous lesions and one study found evidence that the effects of host genetic polymorphisms are context-dependent and that the *IL-8* genotype actually did not have any effect without the *H. pylori* CagA. Another study showed that CagA transgenic mice had gastric epithelial hyperplasia and some developed gastric polyps and adenocarcinomas of the gastric (Suzuki *et al.*, 2012). This suggests that host–bacterial interactions are influential in the development of gastric precancerous lesions (Kim *et al.*, 2011).

With more research focusing on this host–bacterial relationship in the development of gastric cancer, more studies are showing the key to understanding the molecular and cellular pathways associated with increased gastric cancer risk lies within the *H. pylori* bacterial virulence factors and the host genetic factors. Additional research supports the notion that host–bacterial interactions play an important role in gastric cancer risk. Research has highlighted the role of chronic sustained inflammation associated with gastric cancer and evidence has shown that those with a combination of bacterial and host high-risk genotype significantly increase the odds of having gastric carcinoma. When addressing the role of *IL-1* markers, two different meta-analyses concluded *IL-1* proinflammatory genotypes increase a person's risk of developing gastric cancer. These meta-analyses looked at *IL-1* as a cytokine that strongly impacts the pathogenesis of *H. pylori*-induced gastric cancer. *IL-8* is a powerful chemotactic and activating factor for neutrophils. Proinflammatory *IL-1* gene cluster polymorphisms increase gastric cancer risk

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in the presence of *H. pylori*. *IL-1* has proinflammatory actions and is also a powerful acid inhibitor. Those with, for example, *IL-1B*-31*C and *IL-1RN*2/*2* genotypes are at increased risk of developing conditions like gastric atrophy and a 2–3-fold increased risk of developing gastric cancer when compared with those without these genotypes. *IL-1* genotypes increased the risk of intestinal and diffuse types of gastric cancer although it only affects the noncardia area (McNamara and El-Omar, 2008). Therefore, a high level of *IL-1* genotype increases the risk of noncardia gastric cancer (McNamara and El-Omar, 2008; Yamashita *et al*., 2011).

The microbiome interaction with *H. pylori* is another relationship researchers have tried to better understand with regard to gastric cancer risk (Yang and Sheu, 2016; Noto and Peek, 2017). Susceptibility to gastric carcinogenesis is influenced by *H. pylori* strain-specific virulence determinants, host constituents, and environmental factors (Noto and Peek, 2017). There are a large number of microorganisms, that host microbiota, reside in the human gut (Yang and Sheu, 2016). Researchers have demonstrated that gut microbiota regulates the host immune homeostasis and are associated with many human metabolic disorders, including gastric malignancies (Yang and Sheu, 2016; Noto and Peek, 2017). The issue, however, is that this microbiota is delicate and if altered, becomes dysbiotic and contributes to aberrant proinflammatory immune responses, increasing susceptibility to cancer-causing pathogens. Dysbiosis contributes to the pathogenesis of gastrointestinal carcinomas in the esophagus and colon, and certain bacterial species are associated with the development of different cancers, including gastric and colorectal (Noto and Peek, 2017). These metabolic disorders have been reportedly caused by the *H. pylori* infection changing the microbial-origin fatty acid and lipid profiles in host blood that results in an imbalance between gut microbiota and the host (Yang and Sheu, 2016).

The stomach is an acidic environment in which most bacteria cannot survive. However, studies have continuously proven that *H. pylori* infection leads to achlorhydria and decreased acid secretion in a subset of colonized persons. This means that long-term *H. pylori* colonization and neutralization of the gastric environment may directly contribute to alterations in the gastric microbiota. Although further evidence is needed, these findings were supported by clinical studies that found that patients treated with acid-suppressive drugs, such as proton pump inhibitors, exhibit a significant increase in the burden of non-*H. pylori* bacteria within the stomach. That increase in non-*H. pylori* bacteria correlated with increased inflammatory responses, suggesting that non-*H. pylori* bacteria that colonize an achlorhydric stomach could facilitate the progression of cancer (Noto and Peek, 2017).

The advancement of sequencing technology has significantly enhanced scientists' ability to identify microbial species that may be associated with cancer but establishing a direct cause and effect relationship is difficult due to many studies focusing on microbiota-*H. pylori* interaction and gastric cancer development being cross-sectional (Noto and Peek, 2017).

Genetics

Susceptibility to gastric cancer

H. pylori infection is a known factor of noncardia gastric cancer and its prevalence in human is from 40 to 80%, there are only a small proportion of infected people that actually develop this disease (Peek and Blaser, 2012). This suggests that genetics may play an important role in gastric carcinogenesis. The genome-wide association study approach has been used to determine the role of genetics in the development of gastric cancer. An example of this was in a study, carried out by Shi *et al.* (2011), that found two susceptibility loci for noncardia gastric cancer at 5p13.1 (rs13361707 in the region including *PTGER4* and *PRKAA1*) and 3q13.31 (rs9841504 in *ZBTB20*) in the Chinese population. In another study, Abnet *et al.* (2010) found susceptibility loci at 10q23 (rs22744223 in *PLCE1*) in the Chinese population for gastric adenocarcinoma. Recently, the same group also found three other susceptibility loci for total gastric cancer at 5p13.1 (rs10074991 in *PRKAA1*), 6p21.1 (rs2294693 near *UNC5CL*), and 1q22 (rs4072037 in *MUC1*) (Hu *et al*., 2016). Sakamoto *et al.* (2008) also found a significant association for single nucleotide polymorphism (SNP) at 8q24.3 (rs2976392 in *PSCA*) for gastric adenocarcinoma in Japan population. Genome-wide association study studies have revealed different alcohol-dependent loci. For example, a recent study found four SNPs at 4q23 (rs2066702, rs1229984, rs1799876, and rs2309169 in *ADH1B*) for alcohol dependency (Zabaleta, 2012; Xu *et al*., 2015). Table 2 below provides a list of genetic loci markers that have been found to be associated.

Other genetic factors

The percentage of gastric cancer cases that arise from a genetic predisposition is low at ~1–3% (Saghier *et al*., 2013; Karimi *et al*., 2014; Cancer Research UK, 2015; Noto and Peek, 2017). First-degree relatives, such as parents, siblings, and children, with gastric cancer, increase a person's risk of the disease (Catalano *et al*., 2009; Piazuelo and Correa, 2013; Saghier *et al*., 2013; Cancer.Net, 2015; American Cancer Society, 2016), as much as 2–10 times an increased risk (Saghier *et al*., 2013). A positive family history could be a risk factor because of a shared environment. An example would be passing *H. pylori* from a parent to a child (Saghier *et al*., 2013). Certain genetic and familial syndromes are reported as definite risk factors (Park *et al*., 2014). The familial gastric cancer is comprised of three syndromes. They are hereditary diffuse gastric cancer (*HDGC*), gastric adenocarcinoma and

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Table 2 Genetic locus and gastric cancer risk

Locus	Gene	Outcome	References
1q11	*THBS3*	GC	Mocellin *et al.* (2015)
1q11.1	*KRTCAP2*	GC	Mocellin *et al.* (2015)
1q22	*MUC1*	GC	Sakamoto *et al.* (2008), Jia *et al.* (2010), Zhang *et al.* (2011), Sun *et al.* (2015)
1p23.3	*FCGR2A*	GC	Mayerle *et al.* (2013), Hu *et al.* (2016)
1p36	*MTOR*	GC	He *et al.* (2013)
2q33	*CASP8*	GC	Mocellin *et al.* (2015)]
3q11.1	*PPARG*	GC	Mocellin *et al.* (2015)
3q13.31	*ZBTB20*	GC	Shi *et al.* (2011), Song *et al.* (2013), Hu *et al.* (2016)
3p22	*TGFBR2*	GC	Mocellin *et al.* (2015)
4q11	*IL-8*	GC	Zabaleta (2012), Mocellin *et al.* (2015)
4p14	*TLR*	GC	Mayerle *et al.* (2013), Hu *et al.* (2016)
5p13.1	*PRKAA1*, *PTGER4*	GC	Shi *et al.* (2011), Song *et al.* (2013)
5p15	*TERT*	GC	Du *et al.* (2013)
6p21.1	*LRFN2*	GC	Jin *et al.* (2012), Hu *et al.* (2016)
6q21.3	*TNF*	GC	Mocellin *et al.* (2015)
7q13	*IGFBP3*	GC	Mocellin *et al.* (2015)
7p15.3	*DNAH11*	GC	Jin *et al.* (2012), Hu *et al.* (2016)
8q24.3	*PSCA*	GC	Sakamoto *et al.* (2008), Lu *et al.* (2010), Shi *et al.* (2011), Ye *et al.* (2013), Hu *et al.* (2016)
9q11	*TLR4*	GC	Mocellin *et al.* (2015)
10q23	*PLCE1*	GC	Abnet *et al.* (2010), Wang *et al.* (2010)
11q13	*GSTP1*	GC	Mocellin *et al.* (2015)
13q22	*MIPEP-TNFRSF19*	GC	Dong *et al.* (2015)
17q10	*TP53*	GC	Mocellin *et al.* (2015)
20p13	*SLC52A3*	GC	Wang *et al.* (2010)

GC, gastric cancer.

proximal polyposis of the stomach (*GAPPS*), and familial intestinal gastric cancer (*FIGC*) (Oliveira *et al.*, 2015; Setia *et al.*, 2015).

Of these three syndromes, it is only the *HDGC* that can be explained genetically (Oliveira *et al.*, 2015; Setia *et al.*, 2015). *HDGC* is a diffuse gastric cancer, also known as signet ring cell gastric cancer or linitis plastica. Rather than affecting only one specific area of the stomach, it affects much of the stomach. *HDGC* is caused by the mutation of the E-cadherin gene *CDH1* (Barber *et al.*, 2008; Yamashita *et al.*, 2011; Yuan, 2013; Cancer.Net, 2015; Oliveira *et al.*, 2015; Setia *et al.*, 2015; American Cancer Society, 2016). Other gene mutations, such as *CTNNA1*, also increase the risk of *HDGC* (Cancer.Net, 2015; Oliveira *et al.*, 2015; Setia *et al.*, 2015). The average age for the onset of *HDGC* is 38 years with most of the cancers in those with *CDH1* occurring before the age of 40 (Cancer.Net, 2015; Setia *et al.*, 2015). Lifetime risk for diffuse gastric cancer in those with the *CDH1* gene mutation ranges from 70 to 80% for men and 56 to 83% for women by the age of 80 (Cancer.Net, 2015; American Cancer Society, 2016). *GAPPS* is a fundic gland polyposis of the proximal stomach with no evidence of colorectal or duodenal polyposis. It has an autosomal dominant pattern of inheritance (Worthley *et al.*, 2012; Oliveira *et al.*, 2015). This syndrome was identified in 2012 as a risk factor for gastric cancer (Oliveira *et al.*, 2015). *FIGC* is characterized as an autosomal dominant inheritance pattern that is in many families with intestinal-type gastric cancer (Oliveira *et al.*, 2015; Setia *et al.*, 2015). This syndrome is within families without gastric polyposis (Oliveira *et al.*, 2015). Criteria used to diagnose *FIGC* include (i) at least three relatives having intestinal gastric cancer and one being a first-degree relative of the other two, (ii) at least two successive generations should be affected, and (iii) gastric cancer should be diagnosed before the age of 50 in one of the relatives (Setia *et al.*, 2015).

There are other genetic factors associated with the increased risk of gastric cancer, including Peutz–Jeghers syndrome (Jackson *et al.*, 2009; González and Agudo, 2012; Cancer Research UK, 2015; Oliveira *et al.*, 2015; Setia *et al.*, 2015; American Cancer Society, 2016), Li-Fraumeni syndrome (Nagini, 2012; Cancer Research UK, 2015; Oliveira *et al.*, 2015; Setia *et al.*, 2015; American Cancer Society, 2016), Lynch syndrome (Capelle *et al.*, 2010; Oliveira *et al.*, 2015; Setia *et al.*, 2015; Cancer.Net, 2015; American Cancer Society, 2016), familial adenomatous polyposis (*FAP*) (Worthley *et al.*, 2012; Oliveira *et al.*, 2015; Setia *et al.*, 2015), and other SNPs (American Cancer Society, 2016). Peutz–Jeghers syndrome, which is caused by the mutation of the *STK11* gene, is known to be associated with increased risk of gastrointestinal and breast cancers (Oliveira *et al.*, 2015; Setia *et al.*, 2015; American Cancer Society, 2016). A person develops polyps called hamartomas in the stomach, intestines, nose, the airways of the lungs, and/or the bladder (American Cancer Society, 2016) and develops at a young age, one meta-analysis suggested that there was a 29% cumulative risk of gastric cancer by the age of 65 years associated with this syndrome (Oliveira *et al.*, 2015). Li-Fraumeni syndrome increases the risk of someone developing gastric cancer before the age of 45 years. It is caused by the mutation of the *TP53* gene (Oliveira *et al.*, 2015; Setia *et al.*, 2015; American Cancer Society, 2016). Gastric cancer frequency in families carrying TP53 mutations ranges from 1.8 to 4.9%. Forty percent of families with TP53 mutations present with at least one gastric cancer with a mean age of 43 years. It is important to note that, Li-Fraumeni

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syndrome families without the *TP53* mutations can still develop gastric cancer, which suggests that incidence could be independent of the presence of germline TP53 mutation (Oliveira *et al.*, 2015). The highly penetrant colorectal cancer syndrome, known as Lynch syndrome, is caused by a mutation in one of the repair genes *MLH1*, *MSH2*, *MSH6*, *PMS1*, *PMS2*, or *EPCAM* (Capelle *et al.*, 2010; Oliveira *et al.*, 2015). The frequency of gastric cancer in carriers of this syndrome is estimated to be 1.6%, while the risk of developing gastric cancer is about 5% for those with the *MLH1* mutation and 9% for those with the *MSH2* mutation (Oliveira *et al.*, 2015). *FAP* is classified as the development of hundreds to thousands of adenomas in the colorectum (Vasen *et al.*, 2008; Oliveira *et al.*, 2015) and is responsible for less than 1% of all colorectal cancer cases (Vasen *et al.*, 2008), although many of the cases are not diagnosed early. This inherited syndrome is caused by the mutation of the *APC* gene (Vasen *et al.*, 2008; Oliveira *et al.*, 2015). Adenomatous polyps develop in the upper gastrointestinal tract, especially in the duodenum. *FAP* has been linked to a few gastric cancer cases in Japan and Korea, but the evidence is not substantial (Vasen *et al.*, 2008).

One hereditary condition, juvenile polyposis syndrome, is caused by *SMAD4* or *BMPR1A* mutations and is characterized by many juvenile polyps developing in the stomach or colon. It was found that 21% of patients with this syndrome developed gastric cancer. The *BRCA1* and *BRCA2* mutations, known for causing breast or ovarian cancer, also increase one's chance of getting gastric cancer (Oliveira *et al.*, 2015; Setia *et al.*, 2015). There was a meta-analysis carried out on more than 30 studies that showed the relative risk of gastric cancer among those with either of these genes is 1.69 (95% CI: 1.21–2.38). This relative risk is higher than that of pancreatic, prostate, and colorectal cancer (Oliveira *et al.*, 2015). When looking at all the genetic factors associated with the risk of gastric cancer, the magnitude of the relative risk of gastric cancer can vary depending on the country or type of study (Saghier *et al.*, 2013). The penetrance of different genetic syndromes is depicted in Table 3.

Prevention

Prevention of gastric cancer has mainly focused on primary and secondary prevention strategies (Ward *et al.*, 2011; Piazuelo and Correa, 2013; Karimi *et al.*, 2014; Park *et al.*, 2014). Primary prevention strategies that can reduce the risk of gastric cancer include dietary modification such as decreasing the intake of salty foods, increasing the intake of fruits and vegetables, avoiding smoking, and high alcohol consumption (Catalano *et al.*, 2009; Ward *et al.*, 2011; Nagini, 2012; Saghier *et al.*, 2013; Karimi *et al.*, 2014; Cheng *et al.*, 2016), improved sanitation and hygiene (Nagini, 2012; Saghier *et al.*, 2013; Siegel *et al.*, 2014), and refrigeration or chemical preservation of foods (Park *et al.*, 2011; Ward *et al.*, 2011; Nagini, 2012; Siegel *et al.*, 2014). Secondary prevention involves improved screening methods (Yuan, 2013; Karimi *et al.*, 2014; Park *et al.*, 2014). With most of the gastric cancer patients being diagnosed in advanced stages (Hudler, 2012; Ronning, 2014), it is important to implement effective endoscopic and radiological screening methods (Yuan, 2013; Ronning, 2014). Screenings like the esophagogastroduodenoscopy, PET scan, spiral CT scan, and endoscopic ultrasonography are used to determine what stage a patient is in and what treatment strategies should be taken on the basis of their diagnosis (Park *et al.*, 2014; Ronning, 2014; National Cancer Institute, 2016). Endoscopy screening methods are seen as the best approach for detecting gastric cancer and focusing on high-risk populations, such as those with premalignant gastric lesions, for aggressive screening and prevention methods may decrease gastric cancer mortality rates (Cheng *et al.*, 2016). Other prevention methods have also been implemented. Antioxidants may be protective against gastric cancer (Selgrad *et al.*, 2011; Nagini, 2012; Saghier *et al.*, 2013; Sala *et al.*, 2013; Karimi *et al.*, 2014). A randomized trial in Linxian, China and prospective study from the US Cancer Prevention Study II cohort found vitamin supplementation, such as vitamins C and E, to only play a preventative role of gastric cancer in populations with high risk (Nagini, 2012).

H. pylori eradication, as a preventative strategy, has also become a potential option but remains controversial (Kim *et al.*, 2011; Ward *et al.*, 2011; Nagini, 2012; Piazuelo and Correa, 2013; Herrero *et al.*, 2014). Chemoprevention trials involve the use of natural or synthetic chemical agents to reverse, suppress or prevent potential malignancy from progressing to invasive cancer (Saghier *et al.*, 2013; Cheng *et al.*, 2016). *H. pylori* eradication is recommended by American and European guidelines for all persons with atrophy and/or intestinal metaplasia, and first-degree relatives of those with gastric cancer (Karimi *et al.*, 2014). Meta-analysis of seven randomized trials suggests that *H. pylori* eradication reduces gastric cancer by 35% (Ward *et al.*, 2011; Karimi *et al.*, 2014; Cheng *et al.*, 2016). Correa *et al.*, 2013 analyzed the effect of anti-*H. pylori* therapy on intestinal metaplasia, dysplasia, and multifocal atrophy in a high-risk population in Colombia. Results from a 6-year follow-up showed that *H. pylori* eradication produced a significant increase for both intestinal metaplasia and atrophy rates (Saghier *et al.*, 2013). There are downsides to this preventative method. Developing antibiotic-resistant strains of *H. pylori* and other pathogens is one of the biggest concerns (Ward *et al.*, 2011; Piazuelo and Correa, 2013), along with esophageal adenocarcinoma (Piazuelo and Correa, 2013; Herrero *et al.*, 2014).

Discussion

Gastric cancer continues to be a public health burden being ranked fifth in incidences and third in mortality rates for cancer-related diseases (Globocan IARC, 2012; Fock, 2014). Geographic variations show that incidence

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Table 3 Genetic interaction with *Helicobacter pylori*

Name of syndrome	Genes/variants	Type of penetrance[a]	References
Hereditary diffuse gastric cancer	Mutation of the E-cadherin gene *CDH1*	High	Barber *et al.* (2008), Cancer.Net, (2015), Oliveira *et al.* (2015), Setia *et al.* (2015), American Cancer Society (2016)
Gastric adenocarcinoma and proximal polyposis of the stomach	Fundic gland polyposis of proximal stomach	Low	Worthley *et al.* (2012), Oliveira *et al.* (2015)
Familial intestinal gastric cancer	Autosomal dominant inheritance pattern	Low	Setia *et al.* (2015)
Peutz–Jeghers syndrome	Mutation of the *STK11* gene	Medium	Oliveira *et al.* (2015), American Cancer Society (2016)
Li-Fraumeni syndrome	Mutation of the *TP53* gene	Low	Oliveira *et al.* (2015), American Cancer Society (2016)
Lynch syndrome	Mutation in one of the repair genes *MLH1*, *MSH2*, *MSH6*, *PMS1*, *PMS2*, or *EPCAM*	Low	Capelle *et al.* (2010), Oliveira *et al.* (2015)
Familial adenomatous polyposis	Mutation of the *APC* gene	Low	Vasen *et al.* (2008), Oliveira *et al.* (2015)
Juvenile polyposis syndrome	*SMAD4* or *BMPR1A* mutations	Medium	Oliveira *et al.* (2015)
Breast and ovarian causing genes	*BRCA1* and *BRCA2*	High	Oliveira *et al.* (2015)

[a]Penetrance is defined as the proportion of individuals with a given genotype who exhibit the phenotype associated with that genotype (Griffiths *et al.*, 2000).

and mortality rates of this disease are more common in developing countries (Fock and Ang, 2010; Ward *et al.*, 2011; Nagini, 2012; Piazuelo and Correa, 2013; American Cancer Society, 2016) and while the highest rates of gastric cancer are in countries like Japan and China, the lowest rate are in countries like North America and Western Africa (Ronning, 2014; American Cancer Society, 2016). Unfortunately, most people with gastric cancer are diagnosed at an advanced stage, making management of the disease very difficult (Hudler, 2012; Park *et al.*, 2014; Ronning, 2014). There are different treatment methods, such as the LADG (Jackson *et al.*, 2009; Saghier *et al.*, 2013), chemotherapy, and radiotherapy (Jackson *et al.*, 2009; Cancer.Net, 2015). Because of most cases being diagnosed at an advanced stage, the 5-year survival rate is ~30% (Cancer.Net, 2015; American Cancer Society, 2016; National Cancer Institute, 2016). Most studies and resources have concluded that *H. pylori* is the main risk factor associated with gastric cancer (González and Agudo, 2012; Karimi *et al.*, 2014; Ronning, 2014; Cancer.Net, 2015; American Cancer Society, 2016), but other known risk factors that can increase or decrease a person's risk of gastric cancer include age, gender, intake of salty and smoked foods, consumption of fruits and vegetables, and family history. Risk factors like intake of salty and smoked foods, and consumption of fruits and vegetables are modifiable, but factors such as age, sex, and family history are nonmodifiable (Karimi *et al.*, 2014). Most prevention methods target the modifiable risk factors, although *H. pylori* eradication remains a controversial preventative method (Ward *et al.*, 2011; Piazuelo and Correa, 2013; Herrero *et al.*, 2014).

Even after decades of research and trials, there are still questions that remain about gastric cancer (Satoh and Kimura, 1997; Fitzgerald *et al.*, 2010; Katona and Rustgi, 2017). One question focuses on the classification schemes of gastric cancer subtypes in relation to *H. pylori* infection (Katona and Rustgi, 2017). In a small study of 78 Chinese gastric cancer samples, researchers divided gastric cancer into two subtypes, those with high clonality and low clonality. Results showed that developing new genomically based molecular gastric cancer classification schemes has a significant technologic advantage over the use of histologic classifications; however, the question still remains as to whether these new subtypes can be used effectively to change treatment paradigms, in efforts to improve survival rates of gastric cancer (Katona and Rustgi, 2017).

With the association of *H. pylori* and gastric cancer comes important questions about anti-*H. pylori* therapy, the strength of association, and the association with atrophic gastritis. The ORs for *H. pylori*-positive patients, in Europe and the USA, developing atrophic gastritis and gastric cancer was higher than those in Japan that suggests that the bacterium may exert a significant influence on the development of these diseases in Japan. It is known that *H. pylori* is associated with gastritis, intestinal metaplasia, and gastric cancer sequence, but questions still remain on whether it is directly associated with the development of gastric cancer. Researchers also do not know what age group should be given the anti-*H. pylori* therapy for the prevention of gastric cancer. Studies on the association of atrophy and *H. pylori* have produced conflicting results. Kuipers *et al.* (1995), from the Netherlands and the USA, showed an OR of 9 for the development of atrophy in people infected with *H. pylori*. Fontham *et al.* (1986) also demonstrated a significant OR of 6.4, but a report in Japan by Tsugane *et al.* (1993) showed an OR of 0.9. There have been conflicting results obtained by studies about the effect of *H. pylori* eradication on the improvement of atrophy and intestinal metaplasia. While some researchers found significant improvement, other researchers did not (Satoh and Kimura, 1997).

The use of chemotherapy on advanced gastric cancer patients has also been brought to question. The first and second line chemotherapy improves survival in patients with good performance status, but the selection of patients makes a difference for future trials and maximizing on the benefits of chemotherapy. Because of the

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fact that patients with advanced gastric cancer have other difficulties including nutritional deficiencies, treatment decisions have to consider more than just chemotherapy. A balance is needed between chemotherapy and minimization of toxicities (Fitzgerald *et al.*, 2010).

Future perspectives

Gastric cancer is a disease that is impacting different populations around the world. There are many different risk factors that decrease or increase gastric cancer rates. As gastric cancer continues to be a public health burden worldwide, future research methods are important to help reduce the high incidence and mortality rates. In the last 20 years, there have been important contributions shedding light on the many risk factors associated with gastric cancer. However, there is still an urgent need to better understand the underlying causes of this disease and implement effective prevention strategies (Tarazona *et al.*, 2013; Karimi *et al.*, 2014). It is suggested that future research focus on the differentiation of gastric cancer epidemiology by subsite and explore the interactions between *H. pylori* infection, genetics, and environmental factors (Tarazona *et al.*, 2013). Gastric cancer has come a long way with decreasing incidence and mortality rates. However, with all the risk factors and questions that remain about this disease, future research will play an important role in combating gastric cancer.

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Conflicts of interest

There are no conflicts of interest.

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