

## Gastric Cancer: An Epidemiological Overview

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### Abstract

Gastric cancer constitutes one of the leading causes of cancer incidence and mortality in the worldwide despite its decline over the past century. In this article we will first review descriptive epidemiology of gastric cancer. Next we will discuss its precursors and risk factors; the principal risk factors of stomach cancer are HP Infection, smoking, high salt intake and genetic factors. Finally we will discuss screening strategies and prevention of gastric cancer.

### Key words:

Stomach; Cancer; Epidemiology; *Helicobacter pylori*

### Introduction

The first statistical analysis of stomach cancer incidence and mortality was in Italy, in the 18s century. This analysis has shown that gastric cancer was the most common and lethal cancer [1]. Since then, stomach cancer remains one of the leadings causes of cancer incidence and mortality.

Epidemiology of stomach cancer varies depending on several parameters including demographic, histological and geographic features. On the other hand, the measures of the associations of gastric cancer with putative risk factors are relatively robust with regard to these variations.

### Descriptive Epidemiology of Gastric Cancer

#### Incidence

Stomach cancer represents the fifth most common malignancy in the world, after lung, breast, colorectal and prostate cancers. In 2012, almost 952,000 cases new cases of gastric cancer were estimated to have occurred in the world (6.8% of all cancer localizations) [2].

In the USA, according to the 2011 SEER data, the prevalence of gastric cancer was estimated at 74,035 cases. The number of new patients diagnosed with stomach cancer was 7.5 per 100,000 men and women per year. Thus, stomach cancer represents 1.3% of all new cancer cases in the U.S [3].

**Lifetime risk of developing stomach cancer:** About 0.9 % of men and women in USA will be diagnosed with gastric cancer at some point of their lifetime [3].

#### Mortality

Stomach cancer represents the third cause of cancer death in the world (723,000 deaths). It accounts for 8.8% of all cancer deaths [2]. In

the USA, according to the SEER data, the number of deaths was 3.5 per 100,000 men and women per year [3].

#### Secular trends

Incidence of gastric cancer has declined over the recent decades worldwide (49,510). This is may be due to the recognition of the HP infection role in the carcinogenesis of gastric cancer and the importance of its eradication [1,4].

In the USA, incidence rates have been falling on average 1.5% each year over the last 10 years. Death rates have been falling on average 3.0% each year over 2002-2011 [3].

Regarding gastric cancer mortality rate, a study concluded to an annual percent change in gastric mortality rate around 3%-4% [5].

#### Geographical variations and ethnicity

More than 70% of gastric cancer cases occur in developing countries (677,000 cases), and half the world total occurs in Eastern Asia (mainly in China) [2]. A difference in incidence and mortality from north to south has been observed in several countries, with the northern areas having a higher mortality risk than those in the south [1,6]. In Japan for instance, gastric cancer mortality and incidence are higher in the northeastern prefectures [7].

In the United States, gastric cancer incidence is increased in Black, Hispanic and Asian than in non-Hispanic whites [3].

#### Demographical variations

**Age:** Based on the GLOBOCAN data base, the age-standardised gastric cancer incidence rates per 100,000 persons increases from 49.6 in the 60-64 rank to 87.9 in the 70-74 rank [2].

According to the SEER data base, the majority of patients are diagnosed between 65 and 74 years old. The median age at diagnostic is 69 years old [3].

**Gender:** The incidence rates of stomach cancer are about twice as high in men as in women. According to GLOBOCAN database, the

age standardized incidence rates ranges from 3.3 in Western Africa to 35.4 in Eastern Asia for men and from 2.6 in Western Africa to 13.8 in Eastern Asia for women [2].

In the USA, the age standardized incidence rates ranges from 10.3 in men to 5.3 cases per 100000 persons in women [3].

### Distribution of histologic types

The Intestinal gastric cancer occurs more frequently in males and older age groups. It is more prevalent in high-risk areas and is probably associated to environmental factors.

The diffuse or infiltrative type is equally frequent in both sexes. It occurs mainly in younger age groups, and is correlated to the worse prognosis [1].

The incidence of the intestinal type was declining worldwide in recent few decades. On the other hand, the decline in the diffuse type has been more gradual. Consequently, the diffuse type represents about 30 percent of gastric carcinoma [8].

### Distribution by stage

In the USA, 25.7% of gastric cancers are diagnosed at the local stage whereas 29% and 35% are diagnosed at the regional and distal stages respectively [3].

### Precursor Lesions for Gastric Cancers (Mainly Intestinal Gastric Cancers)

The typical model of gastric cancer carcinogenesis describes a progression from chronic gastritis to chronic atrophic gastritis, to intestinal metaplasia, dysplasia, then adenocarcinoma [9,10].

### Atrophic gastritis

Atrophic gastritis is associated with an increased risk of gastric adenocarcinomas with a magnitude of the relative risk ranging from 3 to 18.

### Intestinal metaplasia

It occurs as a result of *Helicobacter pylori* infection, and is more frequent in countries with a higher incidence of gastric carcinoma.

### Dysplasia

Rates of progression from dysplasia to gastric cancer have been estimated at 21, 33, and 57 percent of cases of mild, moderate, and severe dysplasia, respectively.

### Risk Factors for Gastric Cancers

#### Environmental risk factors

Environmental factors represent an important etiology of Gastric cancer. This finding is suggested by the decreased incidence of gastric carcinoma in Emigrants from high to low incidence countries.

#### *Helicobacter pylori* (HP)

Since 1994 HP has been classified as a class I carcinogen by the World Health Organization (WHO) [11]. Chronic infection with HP

may cause atrophic gastritis and pre-cancerous modifications of the gastric mucosis.

The risk of gastric adenocarcinoma and MALT lymphoma increases by 3 to 6 folds in HP infected patients than in those who are uninfected [12]. This association is mainly observed in distal and intestinal-type of gastric cancer.

These findings are supported by the results of a Meta-analysis stating the relative risk of cancer of stomach to be 0.65 after HP eradication [12].

### Epstein-Barr virus

It has been estimated that EBV is associated with stomach cancer in 5 to 10 percent of cases [13].

### Diet

**Salt and salt-preserved foods:** High salt intake is strongly associated with the risk of gastric cancer in a Japanese prospective study [9,14].

**Nitroso compounds:** The association of gastric cancer and dietary intake of Nitroso compounds was investigated in the European Prospective Investigation into Cancer and Nutrition study [9,15]. The study concluded to no association between intake of nitrites and risk of gastric cancer. Nevertheless, endogenous production of N-nitroso compounds was significantly associated with non-cardia cancer risk (hazard ratio 1.42, 95% CI 1.14-1.78).

**Fruits, vegetables, and fiber:** Consumption of fruits protects probably against gastric cancer with a summary relative risk of 0.9 (95% CI 0.83-0.98) according to a meta-analysis of 17 studies [16]. However, there was no distinguishable effect from vegetables (summary relative risk: 0.96 (95% CI 0.88-1.06)) [9,16].

Regarding dietary fiber the summary odds ratio for the highest versus lowest intake of dietary fiber was 0.58 (95% CI 0.49-0.67) [17].

### Tea and coffee

**Tea:** Among seven prospective studies, only one concluded to an inverse association which was confined to distal stomach cancer among women [18].

**Coffee:** its consumption has been unrelated to stomach cancer risk in most studies [19].

### Folate

A meta-analysis found an inconsistent association between dietary folate and gastric cancer risk [20].

### Obesity

Excess body weight defined as a body mass index superior to 25 kg/m<sup>2</sup> was associated with a higher risk of gastric cancer with an odds ratio of 1.22 (95% CI 1.06-1.41) according to a meta-analysis of cohort studies [9,21].

### Smoking

The European Prospective Investigation into Cancer and Nutrition (EPIC) examined the association between smoking and gastric cancer and concluded to a HR of smoking of 1.87 (95% CI=1.12-3.12) in

females and 1.73 (95% CI=1.06-2.83) in males. The magnitude of this association increases with duration and intensity of smoking [22].

### Alcohol

Data are inconsistent regarding the role of alcohol as a risk factor of gastric cancer [23].

### Occupational exposures

Working in the coal, metal, and rubber industries increases the risk of gastric cancer [9,24].

### Socioeconomic status

Data from epidemiology studies suggest an increased distal gastric cancer in low socioeconomic population whereas risk of proximal gastric cancers was higher in higher socioeconomic population [25].

### Gastric surgery

The association between gastric cancer and gastric surgery was suggested by 2 meta-analyses concluding to an estimated relative risk ranging from 1.5 to 3.0 [26,27].

### Abdominal irradiation

A strong association between cancer of stomach and abdominal radiotherapy was reported in cancer survivors who underwent abdominal irradiation [9,28].

### Host-related factors

**Blood group:** Individuals of blood group A have a 20 percent excess of gastric cancer than those of group O, B, or AB [29].

**Familial predisposition:** A familial history of gastric cancer increases the risk of this disease. This association was independent from HP infection [30,31].

Gastric cancer has been described in association with certain cancer syndromes including:

Hereditary diffuse gastric cancer with a lifetime cumulative risk varying between 40 and 67 percent in men, and 60 to 83 percent in women. This condition is caused by mutations in the *CDH1* gene.

Hereditary non polyposis colorectal cancer, Familial adenomatous polyposis, Li-Fraumeni syndrome, Peutz Jeghers syndrome. The association between a genetic predisposition for chronic atrophic gastritis and gastric cancer was described in some cases of familial gastric cancer [9,32].

**Genetic polymorphisms:** Polymorphisms found in the literature to be associated with gastric cancer are:

The human interleukin 1 beta gene.

The Interferon gamma IFNGR1.

Polymorphisms of methylenetetrahydrofolate (MTHF) mainly in East Asians [9].

### Gastric polyps

Gastric polyps may have malignant potential and might be transformed into gastric cancer.

### Ménétrier's disease

It's thought to be linked with gastric cancer. Nevertheless, the strength of this association has not been determined [9].

### Gastric ulcer

An association between benign gastric ulcers and gastric cancers probably reflects common risk factors (HP infection) [9]. The largest cohort study examining the role of gastric ulcer in gastric cancer concluded that the risk of gastric cancer was higher among patients with benign gastric ulcers (incidence ratio 1.8) and decreased among those with benign duodenal ulcers (incidence ratio 0.6) [33].

### Pernicious anemia

Pernicious anemia represents a two to six fold higher risk of gastric cancer [9,34]. The magnitude of this association varies according to the duration of disease and geographic location. Pernicious anemia increases also the risk of gastric carcinoid tumors, probably because of prolonged achlorhydria and the consequent hypergastrinemia and cell hyperplasia [34].

### Reproductive hormones

Some data from epidemiology studies support the hypothesis suggesting a protective role of reproductive hormones in women Gastric cancer. For example, the hazard ratio of the association between a five year increase in age of menopause and stomach cancer was 0.80 (95% CI: 0.66-0.97) [35].

### Prevention and Screening

#### Prevention

**Diet, smoking, and physical activity:** To help reduce the risk of stomach cancer, people should avoid smoking and salted meats and fish and promote a diet high in fresh vegetables, fruits, whole-grain breads cereals.

Studies that have looked at using dietary supplements (vitamins A, C, E and the mineral selenium) to lower stomach cancer risk have had inconsistent results.

Some small studies suggested that drinking green tea may help protect against stomach cancer, however this was not confirmed in large studies.

Maintaining a healthy weight throughout life by balancing calorie intake with physical activity may reduce the stomach cancer risk [36].

**Treating *H. pylori* infection:** Eradication of HP reduces the burden of gastric cancer. Thereby, a suspicion of HP infection has to be confirmed through a blood test that looks for antibodies to HP or an endoscopy with biopsy to identify HP by culture or direct exams or through a special breath test for the bacteria [36].

**Aspirin use:** Studies investigating the role of regular use of aspirin concluded to a protective effect especially in distal stomach. The magnitude of this association was higher in patients beforehand infected by HP [37]. However it is not routinely recommended to take aspirin specifically to prevent stomach cancer.

**For people at greatly increased risk:** A personal history of invasive lobular breast cancer before age 50 as well as having close family

members who have had stomach cancer suggests that they might be at risk for having hereditary diffuse gastric cancer syndrome.

If the genetic testing in these cases shows the person has a CDH1 gene mutation total gastrectomy may reduce the risk of gastric cancer [36].

## Screening

The American guidelines do not recommend a routine screening for gastric cancer. However, in some countries with a high gastric cancer burden, screening programs are already implemented.

Screening recommendations for specific groups of patients

**Gastric epithelial polyps:** Polyps have to be endoscopically excised whenever feasible. When the endoscopic polypectomy is not possible, a biopsy should be performed to refer patients to surgical resection if adenomatous or dysplastic tissue is detected.

**Gastric metaplasia and dysplasia:** Endoscopic surveillance for gastric intestinal metaplasia cannot be uniformly recommended.

**Pernicious anemia:** A single endoscopy should be considered to identify prevalent lesions.

**Familial adenomatous polyposis:** Patients should undergo upper endoscopy early in the third decade of life. If no adenomas are detected, it should be repeated five years later.

## Summary and Conclusion

Gastric cancer constitutes one of the leading causes of cancer incidence and mortality in the worldwide. The principal risk factors of stomach cancer are HP Infection, smoking and high salt intake. Several advances have been made in the diagnostic and therapeutic approaches however gastric cancer is still rampant in several countries in the world. Therefore, other interventions should be developed.

A deeper understanding of effect modifying factors of the HP-gastric cancer association may help to design large studies to identify the targeted populations of mass screening of HP.

Further research is needed also to confirm or refute the hypothesis of the preventive role of green tea intake and dietary supplements.

Wider companions awareness against smoking should be conducted.

For the aspirin use, large scale studies have to be designed to determine for which patients the benefits of lowering cancer risk would outweigh the risks of bleeding complications.

More specific tests for the early diagnosis (new techniques of endoscopy, serum markers) should be developed.

Several molecular abnormalities were identified in gastric cancer. Besides, as seen earlier, more than one third of gastric cancers are diagnosed in distal stages. This emphasis the need of conducting more clinical trials to develop targeted therapies and improve quality of life and survival of the patients. To achieve these goals, epidemiologists, gastroenterologists, biologists, geneticists and oncologists should collaborate to fight against gastric cancer.

## Competing Interests

There are no competing interests.

## Author's Contribution

The work presented here was carried out in collaboration between all authors. ZB, AE and NL wrote the manuscript. SA and ZI participated in reviewing the scientific literature and contributed to the final version of the manuscript. All authors read and approved the final manuscript.

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