Gastric cancer: Etiology, diagnosis and incidence among patients with precancerous lesions

Edite Sadiku¹, Stela Taci¹, Ergita Nela², Adriana Babameto¹

¹Gastro-Hepatology Service, University Hospital Center “Mother Teresa”, Tirana, Albania; ²Internal Medicine Service, University Hospital Center “Mother Teresa”, Tirana, Albania.

Corresponding author: Edite Sadiku, MD; Address: Rr. “Dibres”, No. 371, Tirana, Albania; Telephone: +355682020275; E-mail: editesadiku@gmail.com

Abstract

Gastric cancer is the fourth most common cancer in the world and the second most frequent cause of death from cancer. The proportional mortality of gastric cancer is estimated at 10% of all deaths from cancer. The distribution of gastric cancer is related to specific geographical regions.

Gastric adenocarcinoma is divided into the diffuse subtype and the intestinal subtype. These two morphological subtypes display different clinical and epidemiological features. Furthermore, these two subtypes of gastric cancer have different risk factors. The intestinal subtype is more related to the known risk factors such as Helicobacter Pylori, smoking, or other dietary factors. On the contrary, the diffuse subtype is less related to the known risk factors, and is more “mysterious” in its pathogenesis.

Gastric cancer is a pathology that starts silently, and rarely gives symptoms at the beginning. If diagnosed at an early stage (early gastric cancer), its survival rates can be very high, but there are numerous factors that delay the diagnosis for months, or even for years. In countries where gastric cancer has a greater prevalence, like Japan, rigorous screening and early diagnosis procedures have made the early detection quite possible. This way, in these countries even the survival rates are higher.

A screening program and further cost-benefit deliberations are needed to guide policy making for the long-term endoscopic surveillance of premalignant gastric lesions in Albania and also in other transitional populations.

Keywords: gastric cancer, screening program.
Introduction
Gastric cancer is the fourth most common cancer in the world and the second most frequent cause of death from cancer. The proportional mortality of this type of cancer is estimated at 10% of all deaths from cancer. The distribution of gastric cancer is related to specific geographical regions (1).
The successive progression from chronic non-atrophic gastritis, by way of atrophic gastritis and intestinal metaplasia, to dysplasia, known as Correa’s cascade (2,3) is widely recognized as a common route to the intestinal type of non-cardia gastric cancer (4). *Helicobacter pylori* infection has been generally accepted as the initiator of this cascade (5,6) and epidemiological data support its role as the most important risk factor for gastric cancer (7,8).
It is important then to accurately measure the incidence of gastric cancer among patients with minor changes, chronic non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia at baseline. This was the aim of the largest follow-up observational cohort study in a low risk Western population.

Etiology and pathogenesis
According to Lauren et al., gastric adenocarcinoma is divided into the diffuse subtype and the intestinal subtype. These two morphological subtypes appear to have different clinical and epidemiological features. Furthermore, these two subtypes of gastric cancer display different risk factors. The intestinal subtype is more related to the known risk factors such as *Helicobacter Pylori*, smoking, or other dietary factors. On the contrary, the diffuse subtype is less related to the known risk factors, and is more "mysterious" in its pathogenesis (9).

Diet
One of the most important dietary factors is the quantity of salt in food. Different studies have found a relation between geographic variation of gastric cancer, and the geographic variation of salt use in the diet. Salt intake was first reported as a possible risk factor for gastric cancer in 1959. Scientists found correlations between the use of refrigerators and the lowering of the incidence of the disease. The explanation given by them was that, before the use of refrigerators, food was conserved in high amounts of salt. The most published epidemiological studies provide positive evidence for an association between salt consumption and stomach cancer risk, which is also supported by experimental studies (10).
The N-Nitroso Compounds, also called NOC or Nitrosamines, are also among the suspected risk factors for gastric cancer. These compounds are potential carcinogens in humans and animals. Humans are exposed to N-nitroso compounds (NOCs) from diet, smoking, work place and drinking water, which are the major sources of exposure in the general population. Exogenous forms of nitrosamines are often found in treated meat, like sausages, beef, and the like. They are also found in smoked, salty or pickled foods, and alcoholic drinks such as beer and whiskey. Nitrosamines are also formed endogenously from nitrate and nitrite. Nitrites are still widely used as food preservatives in cured meats. Nitrite is also formed in the human body from oral reduction of salivary nitrate. In the last 20 years, the use of nitrites is lowered, but they nevertheless remain important meat preservatives. On the other hand, nitrates enter the body mainly by means of vegetables and water intake. Nitrates are reduced to nitrites, and nitrites are transformed into nitric oxide by gastric acid-catalysed formation, which acts as a nitrosating agent of amines and amides, as consequence of N-nitroso compounds. A review of 75 articles about N-nitroso compounds as risk factors for cancer indicated a positive association between the intake of NOCs and the gastric cancer. There was consistent evidence about the positive association between meat and processed meat intake with gastric cancer risk. Furthermore, there was quite consistent evidence from case-control studies about the positive association between preserved fish and preserved vegetable...
intake and gastric cancer risk. However, more detailed cohort studies are needed to scientifically define the relation between NOCs and gastric cancer (11).

Diet low in fat or protein, diets high in complex carbohydrates, poor food preparation, use of water from wells, and alcohol consumption are also studied as potential risk factors, but epidemiological studies have not found yet consistent evidence on the relationship between these factors and gastric cancer.

Helicobacter pylori and atrophic gastritis

Helicobacter pylori (H. Pylori) is a family of bacteria that colonizes the stomachs of humans for years. However, unlike other microorganisms which can stay in hosts for decades but exist mainly in a latent state, H. pylori causes continuous inflammation. A large number of people are infected by H. Pylori, but only a small percentage develops gastric cancer in the course of their life. The inflammatory response induced by the infection consists of neutrophils, lymphocytes, plasma cells, and macrophages, and is followed by varying degrees of epithelial injury. A sequential degeneration of the gastric mucosa is found, which goes from superficial gastritis, to atrophic gastritis, and can be the initial process of gastric cancerogenesis. This is called the Correa pathway, and consists of the following steps: normal mucosa, superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and gastric cancer (12). In fact, the association between chronic inflammation and cancer is now very well-established. In the first studies that linked gastritis with cancer, observing the surgical pieces, it was seen that often the gastric adenocarcinoma was found in mucosal areas that were previously chronically inflamed.

The natural course of infection with H. pylori is extremely variable. The majority of infected individuals remain asymptomatic, and infection with H. pylori is not sufficient to induce gastric cancer. Therefore, studies aim to find the other cofactors that help in the pathogenesis. Bacterial and host cofactors, and perhaps other unknown cofactors are targeted in the latest researches. It is found that bacterial strains containing in their DNA the cag locus, are more likely to cause gastric cancer. This is only true considering the intestinal type gastric cancer, while for the diffuse type, the risk is the same as with other strains not containing the cag locus. On the other hand, host factors are very important in causing the inflammation. The risk of developing gastric cancer in an individual after H. Pylori infection is increased up to three times when the individual has a close relative with gastric cancer after H. Pylori infection, and 10% of cases show familial history of gastric cancer. This means that there is a genetic cofactor helping the infection in its pathogenesis. One of the most studied cofactors is the IL-1β, a pro-inflammatory cytokine. An increased risk for gastric cancer associated with pro-inflammatory IL-1β polymorphisms has now been confirmed in many populations throughout the world. Other genetic factors closely related with the pathogenesis of H. Pylori are TNF-α and IL-10 polymorphisms. When these factors are associated with IL-1β polymorphisms, the risk of gastric cancer following H. Pylori increases 27 times.

Antibiotic eradication of H. Pylori is an optimal strategy in the prevention of atrophic gastritis and its neoplastic risks. Other more modern therapeutical strategies aim at stopping specific immune pathways that can lead to gastritis and cancer when chronic (13).

Smoking

Cigarette smoking is listed as one of the most important behavioral risk factors for gastric cancer. A recent cohort study analyzed the data of 215,000 men and women, representing five different ethnic groups. After 7.3 years of follow-up, a total of 696 individuals were diagnosed with gastric cancer, 454 men and 242 women. After analyzing the data with
the appropriate statistical methods, it was found that there is a strong association of cigarette smoking with gastric cancer in both sexes. It was observed consistent effect across five ethnic groups, evidence for a dose–response effect of smoking in both sexes, a stronger effect for cardia than for non-cardia gastric cancer, and a stronger association for intestinal than for diffuse gastric cancer (14).

**Gastric polyps**

Gastric polyps are lesions in the lumen of the stomach projecting above the plane of the mucosal surface. They are frequently found in routine diagnostic procedures, especially gastric endoscopy. These lesions have different risks for transformation to adenocarcinoma, related to their type, size, histology, and other factors. Various subtypes of gastric polyps are recognized and generally divided into non-neoplastic and neoplastic. This form of classification is used to describe the biologic origin of the cells found in the polyp, and not their final destination. This means that the fact that a polyp is non-neoplastic in origin does not exclude the risk that it has for turning neoplastic, even into an aggressive adenocarcinoma.

The most frequent type of non-neoplastic polyps includes the hyperplasic polyps. These benign lesions can be sessile or pedunculated and composed of elongated and distorted pits lined by foveolar epithelium. The stimuli responsible for the development of hyperplastic polyps are not known. They are generally thought to result from excessive regeneration following mucosal damage and, consequently, commonly occur in chronic H. Pylori–associated gastritis (25% of the cases), in pernicious anemia, adjacent to ulcers and erosions, or at gastroenterostomy sites. Malignant transformation, although rare, is well-documented. A small proportion (1.5%–3.0% of the cases), usually those measuring greater than 2 cm, show dysplasia or even intramucosal carcinoma. In these cases, the polyps should be completely excised and sent for histological evaluation, and the whole stomach should be carefully evaluated, because of the risk of compression of adenocarcinoma in a site near the polyp. The neoplastic polyps are slightly more frequent. Two well-documented subtypes are the fundic gland polyps and the adenomatous polyps. Fundic gland polyps are small lesions that are found uniquely in the fundus and in the upper body of the stomach. No malignant transformation is documented, and endoscopic surveillance is not needed. However, in individuals with familial polyposis syndromes, if fundic gland polyps are found, they have a strong risk of having dysplasia, and should be studied. On the other hand, adenomatous polyps are considered premalignant conditions, with a high risk of malignant transformation. The risk is proportional with the size, the villosity and the degree of dysplasia, with the incidence of adenocarcinoma reaching 50% in polyps over 2 cm in size. These lesions should be carefully studied, and if dysplasia is found, they should be completely removed (15).

**Family history**

A positive family history is a strong risk factor for gastric cancer. Unfortunately, the exact molecular and genetic mechanism that causes the familial aggregation is still unknown (with the exception of hereditary diffuse gastric cancer, a genetic condition whose etiology is well-defined) (1). In general, the risk for developing gastric cancer among relatives of gastric cancer patients is estimated to be 2-3 times higher than in persons with no familiar history of the disease. This is a fact that, however, should be carefully interpreted because, besides the common genetic background, environmental and cultural factors (H. pylori, diet and other lifestyle factors) may be similarly shared among the family members and in some cases are difficult to differentiate (16). A large number of studies have indicated a relationship between family history and gastric cancer, adjusting for age, gender, smoking, alcohol intake, BMI and household income. In 2001, Dhillon et al. published a large case-control study, based in patients with gastric cancer in USA. The
study estimated a relative risk of gastric cancer as 2.2 for a positive family history of this condition. Other studies in Europe and Asia have found slightly different estimates ranging from 1.8 in Italy (Palli et al.) to 3.4 in Spain (Garcia-Gonzalez et al. 2007). Overall, the main conclusion of these studies is that positive family history is a consistent risk factor for gastric cancer (1).

Other factors
Updated epidemiological studies indicate a relationship between some other factors and the gastric cancer. Some of these factors include the following (17):
- Low fat or protein consumption
- Poor food preparation
- Poor drinking water
- Low social class
- Prior gastric surgery
- Male gender

Protective factors
Epidemiological studies suggest an inverse association between intake of foods rich in antioxidant substances, and risk of gastric cancer, especially for raw vegetables and citrus fruits rich in vitamin C and polyphenols. When clinical trials started to examine this association, debated results came out. Some of the trials found no statistically significant data, particularly those trials which studied the association of antioxidants and the risk of gastric cancer using synthetic antioxidants (β-carotene, vitamin A, vitamin C, vitamin E and selenium). However, one of the largest prospective studies in Europe (European prospective investigation into cancer and nutrition, EPIC), has clearly indicated an inverse association between intake of foods high in antioxidants and the risk of gastric cancer. EPIC found that statistically significant trends of risk reduction are observed in individuals who consume a large amount of foods rich in antioxidants. This is true for both cardia and non-cardia cancers. The inverse association is stronger in smokers, meaning that antioxidants help more the smokers than the non-smokers, or former smokers. It is hypothesized that there is a threshold for the quantity of antioxidants needed, but this threshold remains undefined yet. This explains the fact that in studies where artificial antioxidants are used, maybe an overload of antioxidants has caused the loss of the protective properties. The threshold hypothesis can explain also the fact that foods high in antioxidants help more the smokers, where free radicals are more abundant and more antioxidants are needed, thus moving the threshold to a higher level (18).

Diagnostic approach
Gastric cancer is a pathology that starts silently, and rarely gives symptoms at the beginning. If found at the early stages (early gastric cancer, EGC), its survival rates can be very high, but there are numerous factors that delay the diagnosis for months, or even for years. In countries where gastric cancer has a greater prevalence, like Japan, rigorous screening and early diagnosis procedures have made the early detection more possible. This way, in these countries, even the survival rates are higher.

In almost 80% of the patients, gastric cancer is asymptomatic at the beginning, or presents with non-specific symptoms which are a strong factor in the delaying of the diagnosis. Often when the patients feel the epigastric discomfort, they take antacids or proton pump inhibitors to relieve these symptoms, thinking of their problem as a simple gastritis or a peptic ulcer. While the symptoms are relieved, the cancer continues its development and enters a phase in which the symptomatic drugs are less effective and cannot control the symptoms. This phase is generally the time when the patients decide to make a visit to their physician and make further investigations (19,20).

As the tumor grows and infiltrates the stomach’s
wall and the surrounding structures (advanced gastric cancer, AGC), more specific signs and symptoms appear. The epigastric discomfort becomes more evident, going up to severe and steady pain (21). This abdominal pain and a strong weight loss are found to be the most frequent symptoms, present in more than half of the patients at the time of diagnosis. Nausea, anorexia and dysphagia are found in one third of the patients, and melena in 20% of the patients. Less frequent symptoms include early satiety, ulcer type pain and swelling of the lower extremities. If the tumor invades the pylorus, vomiting can be frequent, whereas if the tumor invades the cardia, dysphagia may be the main symptom (22).

Gastric carcinomas spread mainly by direct extension to the perigastric tissue, and can also invade other tissues and organs next to the stomach (pancreas, colon, and the liver). When entering the lymphatic system, the tumoral cells can spread in different directions, going even as far as the extra-regional lymph nodes. Two specific signs related to the lymphatic extension of the gastric cancer are as follows:

- **The Virchow's node**: a lymph node in the left supraclavicular fossa, which takes its lymphatic supply from the abdominal organs. If swollen, it can be a specific sign of an abdominal neoplasm, especially gastric cancer. It is also called Troisier’s sign.

- **The Sister Mary Joseph nodule**: a palpable nodule bulging into the umbilicus as a result of metastasis from a malignant cancer in the pelvis or abdomen (21).

In females, the Krukenberg tumor is a frequent finding. This is a metastasis in the ovaries, generally from the gastrointestinal tract. The stomach cancer is the main cause of the Krukenberg tumor, being responsible for almost 70% of the cases. The way of diffusion is debated, from the existence of two theories, either the direct passage of neoplastic cells through the peritoneal cavity, or the transport by the lymphatic vessels. The lymphatic extension is more supported in the literature. The prognosis is generally very poor (23).

Less frequently, patients with gastric carcinoma present with paraneoplastic syndromes, such as:

- **Microangiopathic hemolytic anemia**: A destruction of the red blood cells deriving from damaged endothelium. Destroyed pieces of the red blood cells remain in the blood stream, called schistocytes.

- **Membranous nephropathy**

- **The Leser-Trelat sign**: defined as the sudden appearance and rapid increase in size and number of freckles and seborrheic kératoses, accompanied by pruritus.

- **Acanthosis nigricans**: a skin disorder in which the skin is darker, thicker and papular, at the mucous membranes and the skin folds.

- **Trousseau’s syndrome**

- **Dermatomyositis** (21).

**Screening**

Screening programs are active in Japan, where the gastric cancer has been for years a public health problem. For over 40 years, the double-contrast barium meal study has been used as the principal test for screening the population. Different authors have studied the mortality rates in times before and after the mass screening programs took place, and found great results, with evident decline in the mortality rates, after the full implementation of these programs (24).

In the recent years, four other procedures are standardized for screening. Photofluorography, endoscopy, serum pepsinogen testing and H. Pylori antibody testing have become the new techniques leading the battle for an earlier diagnosis. Serum pepsinogen testing is a simple procedure used for finding patients with atrophic gastritis, which is one of the most important risk factors of gastric cancer. New studies suggest combining the serum pepsinogen testing with the H. Pylori antibody testing. This combination is considered to be a good predictive marker for the development of gastric cancer (25).
**Radiology**

Often an upper gastrointestinal series is the first test performed to diagnose gastrointestinal problems. This test is able to find and diagnose both anatomical and functional disorders of the esophagus, stomach and the duodenum. There are used two contrast agents, air and barium and, after the correct procedures of administration of the contrasts are undertaken, the radiologist makes a series of x-rays. The upper gastrointestinal series can allow the detection of erosions, ulcers (an ulcer is a focal area of mucosal disruption that penetrates through the muscularis mucosae into the deeper layers of the gastric wall), and other defects in the gastric wall. The most important duty of the radiologist is to determine the risk of an ulcer, because of the fact that gastric ulcers can be simply peptic ulcers (benign ulcer), or ulcers in a tumoral site (malignant ulcer).

In malignant ulcers, the ulcer crater represents an area of necrosis and excavation within a malignant tumor, usually gastric carcinoma or lymphoma. The surface of the ulcer and of the surrounding mucosa is composed of nodules, irregular elevations, or irregular depressions of varying size within the tumor. The folds adjoining a malignant ulcer may have a coarse, lobulated, clubbed, or penciled shape due to infiltration of the folds by the tumor.

**Endoscopy**

The strong advantage of endoscopy related to other diagnostic procedures is that the physician can take material for biopsy in areas of the stomach he/she finds suspicious. Endoscopy and biopsy have a diagnostic accuracy of 95% (21,26). The number of biopsies needed for a correct diagnosis is reduced with the modernization of the equipment. In the past, a large number of biopsies was needed, going from four to ten, but numerous complications were reported, especially gastric bleeding. Recent studies have found that going from one biopsy to three, the diagnostic accuracy increases, but passing to more than three does not change the accuracy anymore, thus only increasing the risk of complications and the work of the endoscopist. A larger number of biopsies and a more detailed study of these biopsies is indicated in patients where the first biopsies result negative, while other radiologic studies indicate the presence of suspicious masses in the gastric mucosa or submucosa (27).

For detecting early gastric cancer, which, depending on different factors, can be difficult to see, the endoscopic studies have been further modified. Several advanced techniques were introduced, such as the Chromoendoscopy, and the Magnifying endoscopy. Chromoendoscopy is performed by applying different staining agents on the gastric mucosa during or before the endoscopy, and then studying the coloration patterns. Different staining methods are developed, according to the way the staining agent acts on the mucosa:

- Contrast staining that colors the mucous depressions. Indigo carmine is a blue pigment used in this type of staining. The mucosa is studied directly after the administration of the stain. Early gastric cancer can be found using this method.
- Absorptive staining when the stain is absorbed by certain types of cells. This type of staining is used more for esophageal and intestinal lesions, and less for gastric cancer.
- Reactive staining which allows identifying of altered pH, used mainly for finding differences in pH created from the presence of Helicobacter Pylori in the gastric mucosa.
- Tattoo staining - permanent staining, used to study the precancerous lesions in time. The stain primarily colors the site of the precancerous lesion and, next, any difference in this zone during months or years, serves as an alarm sign that the lesion is progressing to another phase.

Magnifying endoscopy uses optic zoom composed of movable motor-driven lens. Changing the focus of the lens provides considerable magnification of the area observed by circa 80, even 200 times. It is used for the diagnosis of subtle mucosal abnormalities 1-2 mm in diameter. Magnifying
endoscopy is used to detect early cancerous changes and to precisely observe pathological changes in the biopsy (28).

**Endoscopic ultrasonography**
Endoscopy is also used to make possible the ultrasound examination of the gastric wall. In fact, endoscopic ultrasonography (EUS) was developed more than 30 years ago, and since then different studies have found it very effective for determining both the locoregional staging (especially the N-parameter) and the depth of invasion of gastric cancers (the T-parameter) (29). Endoscopic ultrasonography is unique as a diagnostic tool, because it brings the possibility of imaging five layers in the gastric wall, which correspond to the actual histological layers (30). If there is a metastasis present in a regional lymph node, specific signs can be seen in the EUS. They include a rounded shape, hypoechoic patterns and a size more than 1 cm. A study comparing preoperative findings from EUS with pathological findings at operation, found that EUS was 100% sensitive for N0 disease, and 66.7% sensitive for N1 disease (31).

**Computed tomography**
Computed tomography (CT) scans of the abdomen can delineate the extent of the primary tumor, as well as the presence of nodal or distant metastases. The CT scan has lower sensitivity compared to the EUS, when used to study the gastric wall and the regional lymph nodes, but is more accurate for staging purposes because it can reach other parts of the abdomen where the EUS is totally ineffective. For this reason, CT scan is frequently used to search for distant metastases in the abdomen (21).

**Laparoscopy**
The majority of patients diagnosed with gastric cancer are found to have an advanced disease and, hence, an accurate study of the metastasis should be performed. Current imaging technologies have a low sensitivity for the abdominal metastasis, and therefore the largest part of them is found during laparotomy. If present, the metastasis can be very predictive for the survival time of the patient. To prevent the open exploration without resection, and spare the patient from an imperfect surgery, laparoscopy is an optimal examination. In a study from Burke EC et al., 111 patients were studied, all being newly diagnosed with gastric cancer. Of these, 94% of the patients were accurately staged, with a sensitivity of 84% and a specificity of 100%. In addition, 37% of the patients had a subclinical metastatic disease.

**Tumor markers**
Tumor markers are substances found in blood, urine and human tissues, used as specific signs of tumor when found in excess. Differently from what happens with other tumors, where these markers are very useful, they play only a modest role in the early detection of gastric cancer. In fact, elevated quantities of the carcinoembryonic antigen (CEA) are found only in 40% to 50% of the patients diagnosed with gastric carcinoma, and only in 10% to 20% of the patients with surgically resectable disease. The alpha-fetoprotein level, a marker more commonly used for germ-cell and hepatocellular tumors, and the CA 19-9 level, a marker often associated with pancreatic cancer, are elevated in 30% of the patients with gastric carcinoma. These data exclude all three markers from the early diagnostic protocol (32).

On the other hand, different studies have found statistically accurate data that links these three markers (and others such as CA72-4, and the like) with two other clinical processes: the follow-up after radical surgical resections, and a clear view on the prognosis, especially in advanced gastric cancer. In a study conducted in Beijing, China, a total of 142 patients were involved, each of them undergoing radical gastrectomy. After the follow-up, it was found that in 71 of these patients the cancer
reappeared, as confirmed with imaging studies. The levels of CEA, CA19-9 and CA72-4 were measured in these patients and in those without recurrences. When combined, the three markers had 62.0% sensitivity in the diagnosis of recurrence after radical surgery. Thus, patients whose tumor markers continue to increase should be highly suspected for relapse (33).

Tumor markers can also help in defining the resectability and the prognosis of the disease. Elevated serum CEA and CA19-9 levels correlate well with lymph node metastasis, lymphatic invasion, vessel invasion, stage grouping, depth of invasion, and curability. Patients with elevated serum CEA levels are at a significantly higher risk of having all recurrence factors than are those with normal serum CEA levels. Patients with elevated serum CA19-9 levels are at a significantly higher risk of having peritoneal metastases and distant metastases than those with normal serum CA19-9 levels. Such findings make these two markers useful when trying to define the prognosis. Elevated levels of CEA and 19-9 correlate to a poorer prognosis, with a lower survival rate and lower treatment options for the patients (34).

**Gastric cancer incidence among patients with precancerous lesions**

Findings on atrophic gastritis and intestinal metaplasia have been reported from a large follow-up study conducted in the general Swedish population and in another similar large scale follow-up study from Holland (35). Therefore, such findings should be generalizable at least to the patients undergoing endoscopy in northwestern Europe. The incidence that was observed among patients with dysplasia in Sweden, however, was only a fraction of that reported in the Dutch study.

Nonetheless, throughout the 15-20 years of follow-up, during which they had sufficient power to monitor the long term progression, patients with dysplasia remained at substantially increased risk - as reported in the Dutch study (35).

Thus, dysplasia, and particularly severe dysplasia (35) is a powerful signal that a gastric cancer may be present (and should heighten clinical observation and prompt repeated endoscopy (35,36).

Consistent with previous investigations, benign tumours (37), non-intestinal metaplasia, polyps (38,39) and hyperplasia (40) were all associated with an increased risk of gastric cancer, although the excesses were moderate. Conversely, for reactive gastropathy (an abnormality in the stomach caused by chemical injury), no excess risk for gastric cancer was noted (41).

**Conclusion**

The results in a low-risk Western patient population show that all stages of Correa’s cascade predict an incidence of gastric cancer above that of the general population. These data predict that about 1 in 256 people with normal mucosa, 1 in 85 with gastritis, 1 in 50 with atrophic gastritis, 1 in 39 with intestinal metaplasia, and 1 in 19 with dysplasia will develop gastric cancer within 20 years after gastroscopy. If repeated biopsy showed a change-upward or (more noteworthy) downward in the Correa’s cascade-compared with the initial grouping, this seemed to have prognostic significance.

A screening program and further cost-benefit deliberations are needed to guide policy making for the long-term endoscopic surveillance of premalignant gastric lesions in Albania and also in other transitional populations.

**Conflicts of interest:** None declared.
References


