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## Screening for and surveillance of gastric cancer

Debora Compare, Alba Rocco, Gerardo Nardone

Debora Compare, Alba Rocco, Gerardo Nardone, Department of Clinical Medicine and Surgery, Gastroenterology Unit, University Federico II of Naples, 80131 Napoli, Italy

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**Correspondence to:** Gerardo Nardone, MD, Department of Clinical Medicine and Surgery, Gastroenterology Unit, University Federico II of Naples, Via Pansini 5, 80131 Napoli, Italy. [nardone@unina.it](mailto:nardone@unina.it)

Telephone: +39-81-7462158 Fax: +39-81-7464293

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## Abstract

Although the prevalence of gastric cancer (GC) progressively decreased during the last decades, due to improved dietary habit, introduction of food refrigeration and recovered socio-economic level, it still accounts for 10% of the total cancer-related deaths. The best strategy to reduce the mortality for GC is to schedule appropriate screening and surveillance programs, that rises many relevant concerns taking into account its worldwide variability, natural history, diagnostic tools, therapeutic strategies, and cost-effectiveness. Intestinal-type, the most frequent GC histotype, develops through a multistep process triggered by *Helicobacter pylori* (*H. pylori*) and progressing from gastritis to atrophy, intestinal metaplasia (IM), and dysplasia. However, the majority of patients infected with *H. pylori* and carrying premalignant lesions do not develop GC. Therefore, it remains unclear who should be screened, when the screening should be started and how the screening should be performed. It seems reasonable that screen-

ing programs should target the general population in eastern countries, at high prevalence of GC and the high-risk subjects in western countries, at low prevalence of GC. As far as concern surveillance, currently, we are lacking of standardized international recommendations and many features have to be defined regarding the optimal diagnostic approach, the patients at higher risk, the best timing and the cost-effectiveness. Anyway, patients with corpus atrophic gastritis, extensive incomplete IM and dysplasia should enter a surveillance program. At present, screening and surveillance programs need further studies to draw worldwide reliable recommendations and evaluate the impact on mortality for GC.

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**Key words:** Screening; Surveillance; *Helicobacter pylori*; Gastric cancer; Preneoplastic lesions; Gastric atrophy; Intestinal metaplasia; Gastric dysplasia

**Core tip:** Because of expansion and aging of the world population, gastric cancer incidence is still increasing. The primary objective of World Health Organization is to arrange screening and surveillance programs for cancer prevention. However, although we know the main etiological agent and the natural history, a gastric cancer elimination project, combining appropriate screening and surveillance programs, has yet to be defined because of the lack of standardized recommendations. This review addresses the most relevant literature focusing on this topic and tries to design the hypothetical screening and surveillance programs.

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## INTRODUCTION

Gastric cancer (GC) is one of the most frequent and lethal cancer worldwide. The current 5-year survival rate of individuals diagnosed with GC is about 24%, reflecting the reality that most cases are already in an advanced stage when diagnosed<sup>[1]</sup>. The late diagnosis of the disease and the intrinsic resistance to radio- and chemo-therapy may account for the worst prognosis of this malignancy. At present, the best strategy to reduce the mortality for GC is to schedule appropriate screening and surveillance programs. This issue is further supported by the fact that, firstly, it is possible to recognize the major causative agent of GC, *i.e.*, *Helicobacter pylori* (*H. pylori*) and secondly, the well known gastric carcinogenesis process lasts few decades.

However, the submission of a screening or surveillance program for GC rises many relevant concerns taking into account that GC shows a worldwide variability and the majority of patients with *H. pylori* infection and premalignant lesions will not develop GC.

## SCREENING

Screening is a public health service that has the potential to save lives or improve quality of life through early diagnosis of serious conditions. Screening is the process of checking people who have no symptoms or signs of an unsuspected disease which can be treated more successfully than if the disease had been left until it showed itself.

The United Kingdom National Screening Committee in 2003 wrote the criteria that should be met before screening for a disease can be planned<sup>[2]</sup>. They concern the condition, the diagnostic test, the treatment, and finally the program.

### Condition

“The condition should be an important health problem, the epidemiology and the natural history should be well understood and the risk factors and the disease markers should be detectable”. Gastric cancer continues to be the 4th most frequently diagnosed cancer worldwide. In 2008, 989000 new cases, accounting for 8% of the total new cancer cases and 730000 deaths, accounting for 10% of the total cancer deaths were reported<sup>[3]</sup>. However, there is a 10-fold variation in incidence between the various countries and, sometimes, also in the same country. Low incidence rates are found in South Asia, North and East Africa, North America, Australia, and New Zealand. High-incidence areas for non-cardia GC include East Asia, Eastern Europe, and Central and South America<sup>[4]</sup>. In Japan, GC remains the most common type of cancer among both men and women with age-standardized incidence rates of 69.2 per 100000 in men and 28.6 per 100000 in women<sup>[5]</sup>.

Due to the high incidence, the economic burden of GC remains very high, significantly affecting social and economic resources. Indeed, in 2010 the national cost of GC care was estimated to be \$2.26 billion in United

States and \$11.47 billion in Japan<sup>[6,7]</sup>, with total cost of illness of the stomach cancer of approximately \$45000 per patient during the first year, and up to \$130000 per patient if the diagnosis was performed at 20-30 years of age<sup>[6]</sup>.

Gastric cancer may be classified, according to topography, in cardia and non-cardia, and, according to histology, in intestinal and diffuse type<sup>[8,9]</sup>. Each GC type is characterized by a different natural history and pathogenesis<sup>[10]</sup>.

In this review we will focus on non-cardia, intestinal type GC, due to its frequency and natural history.

During the last few years, it has become apparent that the most important single factor responsible for the development of both intestinal and diffuse type GC is *H. pylori* infection. *H. pylori* is a curved, motile, gram-negative organism that represents one of the most common infections, affecting more than 50% of the world population, with prevalence rates ranging from 30% in industrialized areas to 90% in developing countries and Eastern Asia<sup>[11]</sup>. It is acquired during childhood and colonizes the gastric epithelial cells where, in absence of appropriate treatment, it may persist along life and induce a chronic inflammatory response leading to the development of atrophy, intestinal metaplasia (IM), dysplasia and ultimately cancer.

Epidemiological investigations (retrospective, case-control and prospective studies) and several meta-analyses have demonstrated that current or previous *H. pylori* infection is associated with an increased risk of GC in respect to uninfected people (OR = 2.97; 95%CI: 2.34-3.77)<sup>[12]</sup>. However, the risk depend on *H. pylori* strain and duration of infection. *H. pylori*, indeed, is characterized by several putative virulence factors, *i.e.*, *vacA*, *iceA*, *babA*, *dupA*, *oipA* and *cagA*, with the *cag* pathogenicity island, that are variously associated with the risk of gastric diseases<sup>[13]</sup>. Pooled data have shown that *cagA* positive strains of *H. pylori* are associated with a higher risk of GC (OR = 2.01; 95%CI: 1.21-3.32) in respect to *cagA* negative strains<sup>[14]</sup>. A more recent meta-analysis including 44 studies (13 case-control and 31 cross-sectional studies), with a total of 17374 patients, showed that GC risk was higher in individuals infected with *cagA* positive *H. pylori* strains (OR = 2.09; 95%CI: 1.48-2.94) and in those infected with *vacA s1* (OR = 5.32; 95%CI 2.76-10.26), *vacA m1* (OR = 2.50; 95%CI: 1.67-3.75), *vacA s1m1* (OR = 4.36; 95%CI: 2.08-9.10) *H. pylori* strains<sup>[15]</sup>.

*CagA* protein is phosphorylated on the tyrosine residue within the phosphorylation motifs in the carboxy-terminal variable region. These motifs are defined as EPIYA (Glu-Pro-Ile-Tyr-Ala) A, B, C and D according to different flanking aminoacids. The magnitude of risk for GC increased with increasing number of EPIYA C motifs: strains with one EPIYA C motif conferred an OR of 17 (95%CI: 5.4-55), and strains with two or more EPIYA C motifs conferred an OR of 51 (95%CI: 13-198)<sup>[16]</sup>.

Age at the time of *H. pylori* infection may be another determinant of the disease outcome. Epidemiological studies have revealed a high incidence of adulthood GC

in areas with a high prevalence of *H. pylori* infection in childhood<sup>[17,18]</sup>. The younger Japanese *H. pylori*-infected generation had an increased risk for GC (OR = 13.3; 95%CI: 5.3-35.6)<sup>[19]</sup>. Diet is another important etiological factor implicated in gastric carcinogenesis. High intake of salted, pickled or smoked foods, as well as dried fish and meat and refined carbohydrates, significantly increased the risk of developing GC, while, fibers, fresh vegetables and fruit were found to be inversely associated with GC risk. A large prospective study on diet and cancer including 521457 individuals aged 35-70 years from 10 European countries (EPIC-European Prospective Investigation into Cancer and Nutrition study), followed for 6.6 average years, reported a significant increase of non-cardia GC risk associated with intake of total meat (100g/d increase HR = 3.52; 95%CI: 1.96-6.34)<sup>[20]</sup>. A recent meta-analysis, including eight epidemiological studies, with a total of 53,729 subjects, reported an increased risk of GC associated with a “western/unhealthy” diet rich in starchy foods, meat and fats in respect to a “prudent/healthy” diet rich in fruits and vegetables, (OR = 1.51, 95%CI: 1.21-1.89)<sup>[21]</sup>. In addition, dietary salt intake was directly associated with the risk of GC in a prospective population study (268718 participants, 1474 events, follow-up 6-15 years), with progressively increasing risk across consumption levels (high vs low consumption RR = 1.68, 95%CI: 1.17-2.41, *P* = 0.005, and moderately high vs low consumption RR = 1.41; 95%CI: 1.03-1.93, *P* = 0.032)<sup>[22]</sup>. Opposite, the consumption of fruit and vegetables is a protective factor for GC. A recent EPIC analysis involving 477312 subjects with 683 incident GC cases, found an inverse association between total intake of vegetable and fruit and GC risk (HR = 0.77; 95%CI: 0.57-1.04; *P* for trend 0.02)<sup>[23]</sup>. However, although calibration revealed somewhat stronger inverse associations, there was no association between total or specific vegetables intake and GC risk. The inverse association between fresh fruit and risk of GC seems to be restricted to smokers and the Northern European countries<sup>[23]</sup>. According to the recent report from International Agency for Research on Cancer (IARC), GC is considered a tobacco-related cancer<sup>[24]</sup>. Ferrari *et al*<sup>[25]</sup> studying risk factors for GC by population databases analysis found that the consumption of tobacco was associated with the highest incidences of GC, with an average of 30.03% of the population being consumers of any tobacco product, compared with an average of 14.47% among countries with incidences of cancer below the 25<sup>th</sup> percentile.

The variability of *H. pylori* infection and dietary habit may explain, at least in part, the geographical distribution of GC and the differences observed in the same country.

Genetic susceptibility also plays a role in the pathogenesis of GC. The risk of GC is increased in siblings or offspring of patients with GC of at least 1-5-times<sup>[26]</sup>. Interestingly, subjects with both a positive family history and infection with *cag A*-positive *H. pylori* strains had a 16-fold increased risk of GC<sup>[27]</sup>. On the other hand, genetic alteration of the hosts is related to the severity of

the *H. pylori*-related inflammation. Therefore, polymorphisms involved in the inflammatory response to this infection may affect susceptibility to GC. Two recent meta-analyses involving a very large number of patients found that IL-1B -511C/T polymorphism, as well as TP53 rs1042522 polymorphism might contribute to GC susceptibility<sup>[28,29]</sup>. Opposite IL-10 -819C/T polymorphism may be a protective factor for GC in Asians<sup>[30]</sup>.

### Diagnostic test

“The ideal screening test should be simple, safe, validated and acceptable to the population”. Around 1960, GC screening using photofluorography was started in Miyagi prefecture in Japan. In 2001, this approach has been adopted nationwide for GC screening, even if, no randomized controlled trial has been published. Photofluorography looks for suspicious lesions such as decreased calibrum of lumen, stenosis, deformity, rigidity, presence of a niche or a filling defect in the gastric wall, changes in gastric folds and presence of polypoid lesions. Most of the case-control studies suggested a 40%-60% decrease in GC mortality with photofluorography screening<sup>[31-33]</sup>. A meta-analysis of three case-control studies, including 4369 subjects, showed a mortality reduction from GC (male OR = 0.47; 95%CI: 0.29-0.52; female OR = 0.50; 95%CI: 0.34-0.72)<sup>[34]</sup>. Based on cancer registry data, the sensitivity of photofluorography ranged from 60% to 80%, whereas the specificity ranged from 80% to 90%<sup>[35]</sup>. However, due to the lack of data from prospective series, that defined death from GC as an endpoint, photofluorography got a low grade recommendation for population-based GC screening.

The discovery of *H. pylori* in 1982, classified after few years (1994) as first class carcinogen by the IARC<sup>[36]</sup>, has changed the approach to GC screening providing the possibility to adopt diagnostic test targeting the etiological agent. *H. pylori* is detected by serological test, <sup>13</sup>C-urea Breath test (<sup>13</sup>C-UBT) and *H. pylori* stool antigen (HpSA), but only serology got sufficient evidence to be considered as screening test, mainly in terms of health costs. Overall, studies on *H. pylori* screening concluded that serology was cost-effective, but they did not show a reduction of GC risk in the general population<sup>[37]</sup>. On the other hand, when screening occurred at age 20, treatment for *H. pylori* reduced the mean lifetime GC risk by 14.5% in men and 26.6% in women, suggesting that *H. pylori* prevention efforts should target younger age groups<sup>[38]</sup>. In spite of these positive results, currently, no clinical guidelines worldwide recommend screening for *H. pylori* in young asymptomatic individuals.

Mounting evidence suggests to perform GC screening by using the serum profile of gastric secretion as marker of gastric atrophy. Loss of gastric chief cells leads to lower pepsinogen (PG) I levels and a decreased PGI/PGII ratio in the peripheral blood<sup>[39,40]</sup>. Thus, such tests may be considered a non-invasive “serological biopsy”, to detect gastric atrophy and may be a key tool of screening programs. Di Mario *et al*<sup>[41]</sup> and Bodger *et*

*et al.*<sup>[42]</sup> independently found that PGI levels were inversely associated to atrophic body gastritis while PGII levels positively correlated with the severity of *H. pylori*-related gastric inflammation. Individuals with a strong-positive serum PG test, based on the combination of the serum pepsinogen I level and PGI/PGII ratio, had at least a 4-time higher risk of GC for up to 14 years of follow-up compared with those with a negative serum PG test<sup>[43]</sup>. The potential usefulness of serum PG tests has been documented in many countries such as Japan, China, Italy, Sweden, Finland, Portugal, Costa Rica, Mexico and others<sup>[44]</sup>. In 2004, a pooled meta-analysis of Japanese studies assessing approximately 300000 people, showed that the sensitivity and specificity of serum PG testing for GC screening were 77% and 73%, respectively<sup>[45]</sup>. Subsequently, cancer screening programs in Japan have accepted the measurement of serum PG as a noninvasive screening test of GC<sup>[46]</sup>.

The combination of *H. pylori* serology and the measurement of PG concentrations might be good for predicting GC development. In a large Japanese series, more than 9000 people were stratified according to *H. pylori* antibody status (positive *vs* negative) and serum PG concentrations (normal *vs* atrophic)<sup>[47]</sup>. PG concentrations indicative of atrophic gastritis increased the risk of developing GC in a 5-year follow-up of 6-8-times in respect to normal PG concentrations. In addition, individuals with both negative *H. pylori* serology and reduced PGI/PGII ratio, had a higher risk than those with positive serology, presumably due to loss of *H. pylori* in advanced gastric atrophy. Similarly, men who were older than 60 years and who had negative *H. pylori* serology had the highest (1%-8%) annual GC incidence<sup>[47]</sup>.

Gastrin-17 has been proposed for the identification of patients with gastric atrophy<sup>[46]</sup>. Serum or plasma gastrin-17 concentrations depend on intragastric acidity and on the number of G cells in the antrum. Fasting gastrin-17 concentration is low in people with high acid production or atrophic antrum gastritis. Therefore, the use of serum gastrin-17 measurement alone cannot be used as a single serum marker for GC. The combination of serum PG concentrations and serum gastrin-17 can diagnose atrophic gastritis that is limited to the antrum (*i.e.*, low gastrin-17 concentration) or corpus (*i.e.*, high gastrin-17 concentration)<sup>[48,49]</sup>.

Gastropanel is a diagnostic tool based on the combined serological detection of PGI, PGII, gastrin-17 and antibodies anti-*H. pylori*<sup>[50]</sup>. Even if gastropanel seems to be a promising diagnostic tool to identify patients at increased risk of GC, currently the lack of scientific evidence and the cost-benefit concerns do not allow to propose gastropanel as a reliable screening tool.

The last test potentially useful for GC screening is endoscopy. This invasive technique identifies superficial flat and non-ulcerative lesions that conventional barium examination can miss. A study from Japan, showed a detection rate of GC by endoscopy 3-5 folds higher than radiographic studies<sup>[51]</sup>. Screening by endoscopy conducted

in Linqu County, China on 4394 residents identified 85 GCs, of which 29 cases were early cancers<sup>[52]</sup>. The overall sensitivity of endoscopy for GC screening ranges from 78% to 84%<sup>[35]</sup>. However, in spite of these promising data, the technique depends heavily on the skills of the endoscopist, the compliance of patients to endoscopy is poor, the adverse events may occur and the costs are high. Therefore, mass screening by endoscopy is likely to be unfeasible. The introduction of various new endoscopic techniques such as chromoendoscopy, narrow band imaging, confocal endomicroscopy, and autofluorescence, might increase the sensitivity and detection of GC, but this issue still remains controversial.

### Treatment

“The available treatments should be effective in modifying the natural history of the disease”. Due to the strong causal relationship between *H. pylori* infection and GC, the eradication of the infection would eliminate or reduce the cancer risk. However, only a very small proportion of infected subjects develop GC and massive eradication therapy may lead to the selection of antibiotic-resistant strains of *H. pylori* in the general population along with the over consumption of medical resources and high health costs. Therefore, the benefit of eradication of *H. pylori* to prevent GC remains unsubstantiated.

The first trial aimed to investigate whether eradication of *H. pylori* would be applicable for GC prevention was performed in 1991 by Correa *et al.*<sup>[53]</sup> on individuals at high risk for GC in Colombia. After six years of follow-up, GC incidence was similar in both treated and untreated groups, even if a significant increase in the rates of regression of precancerous lesions was reported. A meta-analysis by Fuccio *et al.*<sup>[54]</sup> including six randomized trials, showed that 27 out of 3388 patients in the *H. pylori* antibiotic treated group developed GC compared to 56 out of 3307 in those subjects who did not undergo treatment in a follow-up period ranging from 4 to 10 years (RR = 0.65; 95%CI: 0.43-0.98). A Chinese study by Wong *et al.*<sup>[55]</sup> in 2004, including 1630 *H. pylori*-infected subjects randomized to receive eradication treatment or not, did not show a significant difference in the development of GC between the two groups in a follow-up period of 7.5 years. However, the difference became significant when only subjects without precancerous lesions were considered. More recently Yanaoka *et al.*<sup>[56]</sup> by following 473 successful eradicated subjects up to 10 years, confirmed that *H. pylori* eradication did not halt the gastric carcinogenesis process when chronic atrophic gastritis was detected at the time of eradication. Finally, Wu *et al.*<sup>[57]</sup> in a large cohort study including 80255 patients, found that, patients receiving early *H. pylori* eradication had a risk to develop GC similar to that of the general population. Overall these large prospective interventional studies suggest that eradication of *H. pylori* is useful if performed in younger subjects without precancerous lesions at baseline.

The molecular alterations underlying gastric carcinogenesis are mainly driven by the up-regulation of cy-

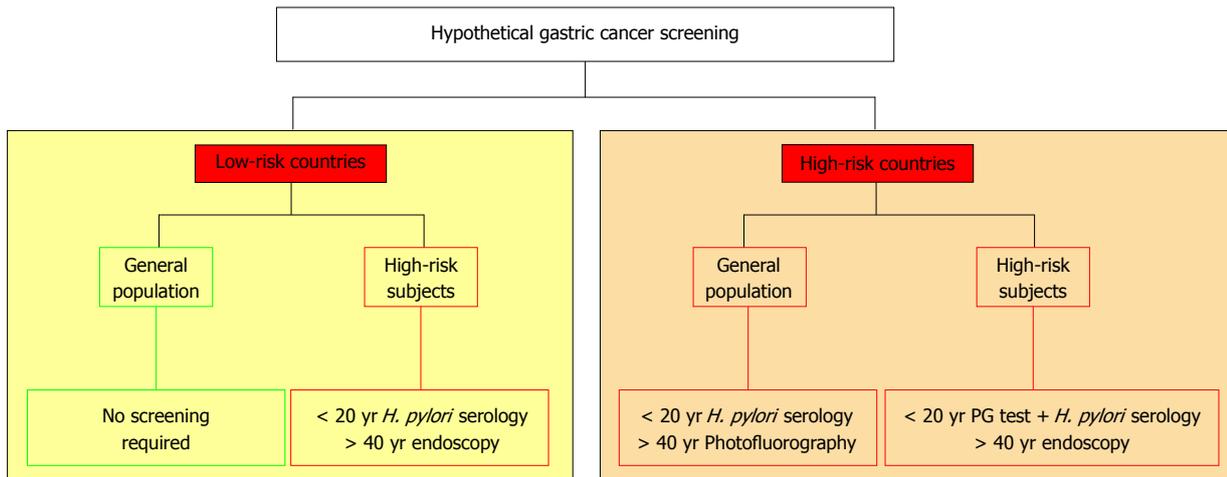


Figure 1 “Hypothetical” screening program for gastric cancer according to geographic area and individual risk. *H. pylori*: *Helicobacter pylori*; PG: Pepsinogen.

cloxygenase (COX)-2<sup>[58]</sup>, thus, the inhibition of COX-2 could be a potential target for GC prevention and treatment. In 2002, in a large cohort study (635,031 subjects followed over 6 years), supported by the American Cancer Society, aspirin users ( $\geq 16$  times/mo) were found to have a decreased risk of GC compared with non-users (OR = 0.53; 95%CI: 0.34-0.81)<sup>[59]</sup>. In 2012, a meta-analysis by Bosetti *et al*<sup>[60]</sup> including seven case-control and six cohort studies, with a total of 4519 GC cases, reported an overall risk reduction for GC for regular aspirin use (RR = 0.67; 95%CI: 0.54-0.83,  $P < 0.001$ ). The risk reduction was greater for longer aspirin use (RR = 0.80; 95%CI: 0.66-0.98, for  $< 5$  years and RR = 0.62; 95%CI: 0.50-0.77, for  $\geq 5$  years). However, the lack of prospective randomized controlled trials on one side, and the occurrence of adverse events (gastrointestinal and renal toxicity) on the other side, currently, do not allow to recommend NSAIDs to reduce GC risk. Selective COX-2 inhibitors (celecoxib and rofecoxib), could have been useful to overcome the gastrointestinal side effects of NSAIDs. However, selective coxibs were approved for use in 1999, but just in 2004 rofecoxib (Vioxx) was withdrawn from the marketplace due to a five-fold increase in cardiovascular risk. Nevertheless, even in the short window of exposure to these compounds, intake of selective coxibs produced significant reductions in the risk of the major human cancers, the magnitude of which, was slightly higher than that of aspirin<sup>[61]</sup>.

### Program

“The screening program should be cost-effective, that is successful in reducing mortality and morbidity and, in the same time, watchful in controlling health costs”. From a scientific perspective, there is insufficient evidence to conclude that benefits of GC screening are greater than possible harms in the general population. It remains still unclear who should be screened, when the screening should be started and how the screening should be performed. It is suggested that the screening strategy for GC should be based on incidence of the population and

individual risk. Based on the available data in high-risk countries, male subjects younger than 20 years should be screened for *H. pylori* infection by serology, while individuals older than 40 years should be screened for precancerous lesions by PG test plus *H. pylori* serology or photofluorography. In low-risk countries, screening programs should be addressed to individuals at high risk of GC, that is, those with a positive familial history (Figure 1).

Japan since 1960, and subsequently South Korea, Singapore and Taiwan have started national screening programs. In China, where GC remains the second most common cancer, no systematic screening program is started until now. Currently, even in the majority of the countries at high-risk of GC, except for Japan, defined guidelines for GC screening are largely lacking. The incidence of GC appears to have declined substantially in several Asian countries during the past 3 decades, but whether this is the effect of successful screening programs remains elusive<sup>[62]</sup>.

### SURVEILLANCE

The intestinal type GC develops through a multistep process triggered by *H. pylori* and progressing from superficial gastritis to atrophic gastritis, IM, and dysplasia<sup>[63]</sup>. Atrophy, IM and dysplasia are considered precancerous lesions and require accurate surveillance programs. However, such lesions, may show a different rate of progression: some lesions remain stable, other may progress and other may show even regression<sup>[64,65]</sup>. In a large cohort study, the risk of progression to cancer within 10 years was 0.8% for atrophic gastritis, 1.8% for IM and 3.9% for low-grade dysplasia<sup>[66]</sup>. In another study from western populations the annual incidence of GC within 5 years after diagnosis, was 0.1%, 0.25%, 0.6%, 6% for atrophic gastritis, IM, mild-to-moderate dysplasia, and severe dysplasia, respectively<sup>[67]</sup>. The severity of premalignant gastric lesions at initial diagnosis (*i.e.*, severe dysplasia, HR = 40.14; 95%CI: 32.2-50.1), together with old age (*i.e.*, 75-84 years, HR = 3.75; 95%CI: 2.8-5.1) and male gender (HR = 1.50; 95%CI: 1.3-1.7) remain the main risk

factors for GC development<sup>[67]</sup>.

Currently, there are no international recommendations for the surveillance of preneoplastic lesions. Here, we will try to address this issue focusing on: (1) Which is the optimal diagnostic approach? (2) Which patients are at higher risk? (3) Which is the best timing of surveillance? and (4) Is surveillance of preneoplastic lesions cost-effective?

### Which is the optimal diagnostic approach?

Conventional white light endoscopy cannot accurately differentiate, diagnose and allow the surveillance of gastric preneoplastic lesions. Magnification, chromoendoscopy and narrow band imaging (NBI) improve the ability to follow the progression of these lesions and the probability to detect early GC. Magnification chromoendoscopy using methylene blue, indigo carmine, acetic acid, or hematoxylin, showed a high accuracy to diagnose these lesions and in particular dysplasia<sup>[68-70]</sup>. The recent technology of NBI, based on the irradiation with two narrow wave band of light, blue and green, easily absorbed by the hemoglobin in the mucosa blood vessels, may also be useful to diagnose gastric lesions<sup>[71-73]</sup>. However, the length of the endoscopic procedure, the workload of endoscopy team, the reduced patient compliance, the limited expertise, the additional costs, and, for NBI, the lack of agreement on the patterns associated with precancerous lesions, do not allow to recommend routine performance of these techniques. In spite of the undoubted advantage of endoscopic techniques in identifying the potential precancerous lesions, the diagnosis needs biopsy sampling and histological evaluation.

The Updated Sydney System<sup>[74]</sup>, including five biopsy samples (2 antrum, 1 incisura, 2 corpus, with 1 from the greater and 1 from the lesser curvature) is the most widely accepted protocol for classification and grading of gastritis, even if el-Zimaity and Graham concluded that it underestimated the presence of IM and identified corpus atrophy only when it was extensive<sup>[75]</sup>. A biopsy protocol consisting of seven non-targeted biopsies (3 antrum, 1 incisura, 3 corpus, with 1 from the greater and 2 from the lesser curvature) diagnosed IM in 97% of cases and all cases of dysplasia or cancer<sup>[76]</sup>.

Mounting evidence suggests the use of non invasive tests for the surveillance of precancerous lesions<sup>[40,77-81]</sup>. A low PGI level, a low PGI/II ratio, or both are good indicators of atrophic changes in the gastric mucosa. Many studies from different countries, comparing the levels of the serum PGs with histology, based on different cutoff values, showed conflicting results<sup>[77-81]</sup>. A meta-analysis by Dinis-Ribeiro *et al*<sup>[82]</sup> including 27 population studies (296553 patients) and 15 selected-population studies (4385 patients) found that a combination of PGI < 50 ng/mL and a PG I /PG II ratio 3.0 provided the best results, with a sensitivity of 65%, a specificity of 74%-85%, and a negative predictive value > 95%.

### Which patients are at higher risk?

Only few patients with atrophy and IM develop GC. The risk is closely related to the location, severity, and extension of precancerous lesions. There is a wide variability concerning the prevalence and the pattern of chronic atrophic gastritis worldwide. In countries at higher incidence of GC, chronic atrophic gastritis is prevalently diagnosed as pangastritis or corpus gastritis, while in western countries, at lower incidence of GC, it is diagnosed more often in the antrum than in the corpus, and the lesser curvature is more often affected than the greater curvature<sup>[65]</sup>.

Intestinal metaplasia is classified as complete (“small-intestinal” or type I, showing goblet and absorptive cells and decreased expression of gastric mucins), or incomplete (“enterocolic” or type II A/ II B and “colonic” or type II B/ III, showing goblet and columnar non-absorptive cells, in which gastric mucins are coexpressed with MUC2)<sup>[83,84]</sup>. Incomplete metaplasia is associated with the risk of malignant progression<sup>[85]</sup>. In addition, the risk of GC is least in patients with sporadic IM, is higher in patients with more widespread IM in the antrum or along the lesser curvature, and highest in patients with diffuse IM<sup>[85]</sup>.

The application of the operative links on gastritis assessment, addressing the grade and extension of atrophy (OLGA) and IM (OLGIM), may be useful for identifying subgroups of patients with different risks of progression to GC<sup>[86,87]</sup>. Both, OLGA and OLGIM have been validated in prospective studies<sup>[89-91]</sup>.

Another pattern of metaplasia, the “spasmolytic polypeptide-expressing metaplasia” (SPEM), has been described<sup>[92]</sup>. It is characterized by the expression of the TFF2 spasmolytic polypeptide, that is associated with oxyntic atrophy<sup>[93]</sup>. SPEM, which characteristically develops in the gastric body and fundus and appears to share some characteristics with pseudopyloric metaplasia, has a strong association with chronic infection with *H. pylori* and with GC, and may represent another pathway to gastric neoplasia<sup>[94]</sup>.

Gastric dysplasia is characterized by cellular atypias reflective of abnormal differentiation and glandular architecture disorganization without evidence of tissue invasion. The reported rates of dysplasia progression vary greatly, ranging from 0% to 73% per year in different studies<sup>[67,95,96]</sup>. The difference between Japanese and European/North American pathologists in categorizing gastric dysplasia accounts for this discrepancy. In Japan, non-invasive intramucosal neoplastic lesions with high-grade cellular and architectural atypias are termed “non-invasive intramucosal carcinoma”, whereas the same lesions are diagnosed as high-grade dysplasia by most pathologists in Western countries<sup>[97]</sup>. The World Health Organization identified five diagnostic categories: (1) negative for intraepithelial neoplasia/dysplasia; (2) indefinite for intraepithelial neoplasia/dysplasia; (3) low-

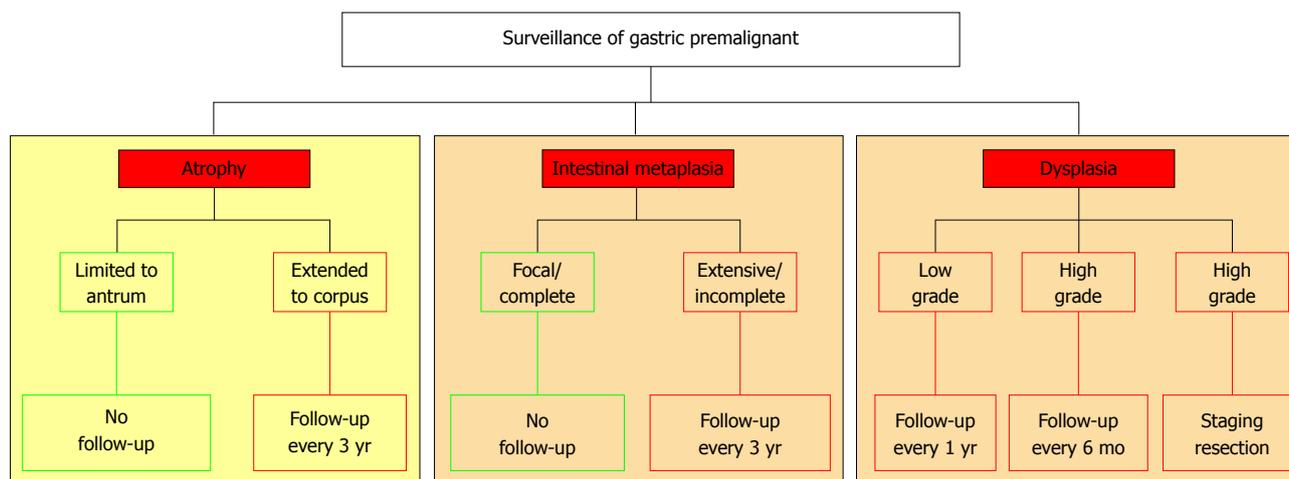


Figure 2 Surveillance protocol of gastric precancerous lesions according to the guidelines of a recent International Consensus Project<sup>[99]</sup>.

grade intraepithelial neoplasia/dysplasia; (4) high-grade intraepithelial neoplasia/dysplasia; and (5) intramucosal invasive neoplasia/intramucosal carcinoma<sup>[98]</sup>.

In a cohort of patients with premalignant gastric lesions, approximately 25% of patients with high-grade dysplasia received a diagnosis of GC within 1 year of follow-up, while only 7% of patients with low-grade dysplasia progressed to invasive carcinoma<sup>[67]</sup>.

In addition to histological findings other possible risk factors for more severe lesions at surveillance endoscopy were current or past *H. pylori* infection ( $P < 0.05$ ), BMI  $> 25 \text{ kg/m}^2$  ( $P < 0.05$ ) sex, ethnicity, family history positive for GC, alcohol consumption  $> 2$  units/d and smoking  $> 20$  pack/year<sup>[63]</sup>.

#### Which is the best timing of surveillance?

A recent International Consensus Project<sup>[99]</sup> summarizing current evidence on the management of patients with precancerous conditions and lesions proposed the following recommendations (Figure 2): (1) patients with mild-to-moderate atrophy and or IM only in antrum do not need follow-up (evidence level 4, recommendation grade D); (2) patients with extensive atrophy and/or extensive IM should be offered endoscopic surveillance (evidence level 2++, recommendation grade B) every 3 years (evidence level 4, recommendation grade D); (3) patients with low-grade dysplasia should be followed up every 12 mo while those with high-grade dysplasia should be closely followed up every 6 mo (evidence level 2+, recommendation grade C); and (4) patients with dysplasia or cancer within an endoscopically visible lesion should undergo staging and resection.

#### Is surveillance of preneoplastic lesions cost-effective?

Two studies addressing the surveillance of patients with IM concluded that endoscopic follow-up was cost-effective, with ICER (incremental cost-effectiveness ratio) values between 1868 and 72519, but below the adopted threshold<sup>[100,101]</sup>. Opposite, another study concluded that only in patients with dysplasia endoscopic surveillance

was cost-effective, with ICER values ranging from 18600 to 39800 depending on the endoscopic intervals, but all below the 50000 threshold<sup>[102]</sup>. These conflicting results might depend on many factors such as geographic area, rate for progression of conditions, and different cost of endoscopy.

## CONCLUSION

Although there is a progressive decline of GC incidence more cases occur because of expansion and aging of the world population. Gastric cancer remains a major clinical challenge due to its frequency, poor prognosis and limited treatment options. Therefore, one of the primary objective of World Health Organization and researchers is to arrange programs for GC screening and surveillance. This strategy should target general population in those countries in which GC continues to be one of the most frequent tumor disease. However, although we know the main etiological agent and the natural history, a GC elimination project, combining appropriate screening and surveillance programs, has yet to be defined because of the lack of standardized recommendations based on a rigorous process of guideline development. At present, screening and surveillance programs appear sufficiently sensitive but further studies are needed to evaluate the mortality reduction and cost-effectiveness.

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