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IMPLEMENTATION OF GASTRIC CANCER SCREENING – THE GLOBAL EXPERIENCE

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Abstract

Gastric cancer (GC) is still an important global healthcare problem, and in absolute figures it is going to remain at the present level in foreseeable future. In general, survival of patients with GC is poor mainly due to advanced-stage diagnosis. Early-stage GC can be cured by endoscopic resection or less invasive surgical treatment. Unfortunately, there is no appropriate screening strategy available for global application. This article provides a description of established national and regional GC screening programs and the screening modalities used. This review also summarizes current approaches to develop cancer-screening biomarkers. Although candidates with initial promising results have been suggested, moving discovery into clinical practice is still a major challenge. Well-designed biomarker studies, with systematic validation steps, are needed to decrease the burden of this fatal disease.

Keywords

biomarkers; gastric cancer; *H. pylori*; precancerous lesions; screening

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CONFLICT OF INTEREST

Nothing to declare

INTRODUCTION

Although declining in incidence globally, gastric cancer (GC) is still the 3rd leading cause of cancer-related deaths [1], and absolute number of cases is not going to decline in the near future [2]. Most of GC cases are originating in Eastern Asia (58.1%), Europe (14.7%) and part of Central and Latin America (7.8%) [1]. The development of GC is characterized by a multistage process that hypothetically provides ample opportunity for intervention.

With the exception of Japan [3], the 5-year survival rate for patients with GC is poor. In Western populations, including Europe and the United States, 5-year survival rates do not exceed 25–30% [4, 5]. This is mainly related to late detection of the disease at symptomatic stages. Therefore, there is a need for improvement in the detection of early-stage GC, and screening is one of the tools to reach this objective.

The current review provides insight on potential GC prevention approaches, and describes major programs and methods used in GC screening.

Approaches to reduce GC incidence and mortality

Primary and secondary prevention strategies may have an effect in decreasing GC-related mortality (Fig.1). Primary prevention includes lifestyle (i.e., smoking cessation) and diet (i.e., reduce salt intake) modifications as well as preventing or eradicating *H. pylori* infection. On the other hand, secondary prevention focuses on detection of precancerous lesions (atrophy, intestinal metaplasia, dysplasia) and early-stage cancer [6]. Thus, screening approaches may have different targets. The primary goal of screening for early-stage GC is to decrease mortality. Detection, surveillance and management of precancerous lesions aim to reduce both mortality and incidence. Finally, *H. pylori* eradication (including a “*screen-and-treat*” strategy) aims to decrease GC incidence [6].

Although subjects with atrophic gastritis or intestinal metaplasia (IM) are at higher risk for GC, the majority of these patients will never develop cancer; however surveillance of the patients is recommended [7, 8]. Dysplasia is considered an advanced precancerous gastric lesion and those with high-grade dysplasia should be under strict endoscopic surveillance [9]. According to the results from a nation-wide study in the Netherlands, the annual incidence of GC is 0.1% for patients with atrophic gastritis, 0.25% for IM, 0.6% for mild-to-moderate grade dysplasia, and 6% for severe dysplasia [10].

GC screening may be considered as a two-stage approach with a primary screening test (e.g. X-ray, pepsinogens or other blood-based test) to identify individuals at high GC risk, who then would be referred to upper endoscopy as a confirmatory method. When endoscopy is used as the primary screening tool, this would be a one-stage screening modality.

An organized population-based screening program is substantially more effective in decreasing the mortality than disarticulated control and prevention activities. The International Agency for Research on Cancer has defined the characteristic features of an organized screening program [11]. Such a program should correspond to the following features: 1) an explicit policy with specified age categories, defined screening method and

intervals; 2) a defined screening target population; 3) management team responsible for the implementation; 4) health-care team involvement in decisions and care; 5) structure for quality assurance; 6) method for identifying cancer occurrence and death in the population [11]. As described below, organized GC screening is only implemented in a few Asian countries.

Methodological approaches for GC screening

Upper gastrointestinal X-ray series (photofluorography)—Gastric photofluoroscopy has been the screening test for GC in Japan over the past several decades [12]. During the 1950's, a GC screening model was studied by using indirect radiography. After that, fluoroscopy was further developed by employing the double-contrast method in 1958, combination of a barium meal and air that was found to provide fine contrast shadow of early cancer lesions in the stomach. Therefore, a 120ml barium meal is combined with a foaming agent to obtain double contrast images of gastric mucosal surface. Commonly, eight X-ray pictures are taken by changing posture to cover the whole part of the stomach; the reading of the films is done by two reviewers, who are gastroenterologists or radiologists. Reported sensitivity and specificity of the test are 57-89% and 81-92%, respectively [13].

Photofluoroscopy has been widely used as a standard diagnostic test as well as a mass screening test until very recently. After introduction of the method as a diagnostic test, curative resection rate of GC improved as compared to before intervention [12]. In screening settings outside Japan the method has been evaluated or introduced in South Korea and some Latin American countries.

Endoscopy—Upper endoscopy is the best method for detecting either GC or related precancerous lesions; both by visual evaluation of the stomach mucosa as well as by biopsy sampling for further histological evaluation. When a non-invasive method is used as a screening tool, endoscopy is the gold standard for confirmation.

There are differences in clinical approaches in Eastern and Western countries: while detailed visual evaluation with wide use of chromoendoscopy following a mucolytic preparation of the stomach and taking multiple endoscopic images is a widely accepted standard in Asia, routine non-targeted (random) biopsies from all the parts of the stomach is recommended in the West, e.g. Europe [7]. The minimum set of biopsies according to the European (MAPS – Management of precancerous conditions and lesions in the stomach) guidelines include 2 specimens from the corpus, and 2 from the antral area, while the need for an incisura biopsy has been left open [7]. At the same time, OLGA (Operative Link on Gastritis Assessment) and OLGIM (Operative Link on Gastric Intestinal Metaplasia) grading systems of mucosal lesion severity require evaluation of an incisura biopsy [9]. A recent study has demonstrated substantial downstaging of lesions if the incisura biopsy is not considered [14]. Therefore, 5 biopsies (2 from antrum, 2 from corpus and 1 from incisura) as recommended by the updated Sydney system, should be considered as a standard [15].

Although novel methods allowing better visualization of lesions of the gastric mucosa are available (e.g., NBI, FICE, magnifying endoscopy), so far in routine clinical settings outside Asia they do not allow the endoscopist to limit biopsy sampling to targeted biopsies from the

mucosal areas suspected for lesions [7], while in Japan and Korea only suspected cancer lesions are biopsied.

Commonly used non-invasive methods—Blood-based biomarker detection can potentially be used to screen either for GC, precancerous lesions and *H. pylori* infection. In the following paragraphs, we described the markers commonly used for detection of gastric precancerous lesions. In the “Emerging methods” Section, new potential biomarkers for GC are briefly discussed.

Pepsinogen testing is the most extensively studied and probably the best widely available non-invasive method to screen for “serological” atrophy. Decreased pepsinogen I levels and the pepsinogen I to II ratio (PgI/II) are reflecting mucosal atrophy in the gastric corpus, with a sensitivity of 66.7-84.6% and a specificity of 73.5-87.1% [16–19]. Although an increased GC risk has been demonstrated in subjects with decreased pepsinogens levels [20–23], accuracy of pepsinogen testing to detect GC is low, with sensitivity estimates ranging from 36.8% to 62.3% [24–26].

Pepsinogens can be detected by different methods. Variation in testing systems has been reported in Asia using latex agglutination and Europe using ELISA, and there had been limited efforts to adjust cut-off values [27]. Caution should therefore be exercised in interpreting results from different populations. In addition, it should be emphasized that pepsinogen testing assesses the presence of atrophy, not GC itself.

Combination of serum or plasma pepsinogen levels with serological testing for anti- *H. pylori* IgG, also known as the “**ABC**” method has been proposed by Japanese investigators [22, 28]. According to these markers, subjects are grouped into 4 groups: A) normal pepsinogens and negative for *H. pylori*; B) normal pepsinogens and positive for *H. pylori*; C) decreased pepsinogens and positive for *H. pylori*; and D) decreased pepsinogens and negative for *H. pylori*. Group “D” is the group with highest risk (the Hazard ratio for developing GC 8.2; 95% CI 3.2-21.5), since the bacterial infection could have disappeared because of the very advanced atrophy [22].

The two major limitations of the “ABC” method are: 1) inability to apply to subjects following eradication since successful eradication otherwise will move the subject into a higher risk group; and 2) serology is not recommended as the method for therapy decision except in special circumstances [8].

Emerging methods

Risk stratification according to *H. pylori* strain virulence—Although differences in the risk for GC associated with different *H. pylori* strains are well established, current strategies of managing *H. pylori*-related disease do not consider this information [8].

Anti-*H. pylori* seropositivity, and particularly anti-CagA have been consistently associated with GC risk. However, these findings are not widely used for screening purposes as CagA negative strains may lead to GC development. Novel serology methods evaluating multiple *H. pylori* antigens are now available [29, 30] and have been applied to studies of

preneoplastic [31, 32] and neoplastic lesions [33, 34]. Of interest, a prospective case-control study in Chinese individuals by Epplein *et al.* [33] found that along with the known virulence factors, *cagA* and *vacA*, four additional antigens, *Omp*, *HP0305*, *HyaA*, and *HpaA* may be markers of disease. Additional studies on bacterial factors may lead to novel strategies for screening and better understanding of GC risk variation across populations.

Novel methods for detecting cancer and/or premalignant lesions—In addition to pepsinogen testing, gastrin-17 has been proposed as a marker for antral atrophy [35]. However, its performance has been disappointing since the blood levels of the marker are influenced by various factors [36]. Low ghrelin concentrations are associated with GC development (OR 1.75; 95% CI 1.49-2.01) [37]. Also, trefoil factor 3 (TFF3) has been suggested as a marker for both atrophy and GC, with better performance for GC detection than pepsinogens [38, 39]. Antibodies against gastric parietal cells have been suggested as independent markers for atrophy that could complement pepsinogens and *H. pylori* antibodies detection [40].

During recent years, many biomarkers for the detection of GC and its related precancerous lesions have been identified, and additional discovery studies are on the way. However, the transfer of biomarkers from a discovery phase to clinical practice is still a major challenge, mostly due to the lack of a systematic evaluation process [41, 42]. Biomarkers with potential clinical relevance have been identified by several approaches, including proteomics [43–47], metabolomics [48], genomics [49], epigenomics [50], and microRNA assessment [51]. Risk stratification according to the host genetics has been suggested [49]; however candidate polymorphisms appear to be highly variable across populations [52–55].

The recent comprehensive molecular characterization of GC by the Cancer Genome Atlas Research Network has suggested four subtypes of GC: Epstein–Barr virus related, microsatellite instable tumours, genomically stable tumours, which are enriched for the diffuse histological variant, and tumours with chromosomal instability [56]. These findings may have importance not only in prognostic settings for targeting therapies, but also in early detection, including screening.

Among other markers with initial promising results for GC detection, we can list circulating GC-associated antigen (MG7-Ag) [57], GC autoantibody panel [58] and volatile markers as detected by gold nanoparticle-based gas-sensor technology [59]. However, these studies require replication and proper validation.

***H. pylori* “Screen-and-treat” (mass eradication) strategy**

It is well-accepted that only 1-2% of *H. pylori*-infected individuals will develop GC during their lifetime [60]. A recent meta-analysis [61] combining results of eradication trials suggested that these data provide limited evidence that searching for and eradicating of *H. pylori* can reduce the incidence of GC in healthy asymptomatic infected individuals. Several recent systematic analyses have suggested “*screen-and-treat*” strategy to be cost-effective approach for reducing GC burden in general population [62–64]. Nevertheless, it has not been introduced into any organized screening program.

A pre- and post-intervention study in Matsu, an island in Taiwan with high incidence of GC, has demonstrated decrease in GC incidence by 25% and in atrophy by 77.2%, when compared to the 5-year period prior to the intervention [65]. As an extension of this work and based on the recently published experience of a community-based validation study [66], two additional counties in Taiwan (Changhua County and Yi-Lan County) have implemented simultaneous colorectal and GC screening programs using 2 faecal samples, after feasibility studies. These activities are funded by the two local governments, and the decision on whether this approach could become a nationwide screening program is still uncertain.

If “*screen-and-treat*” is being applied in general population, the detection method of *H. pylori* infection should be discussed as part of the program implementation. In general, serology is not recommended for the purpose of treatment decision [8] because a positive serological test result is commonly observed for a substantial time period following successful eradication. ¹³C-urea breath test or faecal antigen tests would be the methods of choice or tests to confirm a positive serology test; however this would substantially increase the costs for a screening program. Different acceptance for a serological and faecal test in different parts of the world is expected.

Further research is needed on whether and how to implement population-based “*screen-and-treat*” programs including studies on adverse events of antibiotic use and changes in microbiota [67, 68].

Global experience with gastric cancer screening

A description of existing major screening programs and initiatives for *H. pylori* eradication is presented below, and their main characteristics were summarized in the Table 1.

Japan—Mass GC screening was started in Miyagi Prefecture in 1960 by using a special mobile unit with a photofluorographic device. Government subsidy began in 1966, and expansion to a nation-wide screening program under the regulation of the Health and Medical Services Law for the Aged started in 1983. Japanese men and women aged 40 years or older are recommended to participate annually in screening programs with photofluorography using X-ray devices. Although the Japanese government set an initial goal of an annual participation rate of 30% among the target population, the participation rate had remained as low as less than 20% [69–71]. The participation rate has been declining to 9% in 2011 [72] partially due to insufficient diagnostic capacities. However, these figures might be underestimates as individuals who attend screening at their workplaces are not recorded as participants in the National Program. The overall screening rate, including opportunistic screening, is estimated to be 34% in 2013 [73]. In addition to the screening program by fluoroscopy, endoscopy-based screening is available to a proportion of population outside organized screening program settings (e.g. at workplaces) and acceptability rates are constantly increasing.

Several case-control and cohort studies have evaluated the efficacy of the fluoroscopy screening program, and found a 50 to 60 % reduction in GC mortality, with consistent results across studies [13, 74–77]. It is important to mention that improvement in 5-year

survival rates in Japan cannot be entirely attributed to the benefits of the screening program; a study conducted in National Cancer Center Hospital, Tokyo (a specialized institution not reflecting the general population of the country) revealed that only 12.3% of the patients with asymptomatic early stage GC were screen-detected cancers [78]. This data suggest that the main contributor to detection of early GC was frequent endoscopy performed outside screening program due to low cost of and easy access.

Starting from 2013, a new initiative for eliminating GC in Japan has been promoted by several professional Societies in Japan. In the age group below 20 years “*test-and-treat*” strategy for *H. pylori* is now recommended, while in the age group of 50 year and above *H. pylori* eradication is combined to secondary prevention by upper endoscopy [79–81]. The Ministry of Health, Labour and Welfare approved eradication as a usual care for patients with gastritis, but do not consider it as a general prevention (*screen-and-treat*) strategy. Among the limitations is the fact that the diagnosis of chronic gastritis has to be set to have the reimbursement for eradication medication, i.e. endoscopy is required for the reimbursement purpose. In addition, the initiative is applied by gastroenterologists mainly to symptomatic patients instead of general asymptomatic population. So far, there is no *H. pylori* mass eradication strategy approved by the national government in Japan to prevent GC.

Korea—Screening for GC in Korea has been part of the National Cancer Screening Program since 1999. Screening is offered every second year for men and women starting at the age 40 years with either upper endoscopy or upper gastrointestinal X-ray series. The participation rate of the target population has been reported as 29.1% for 2008 [82], 34.9% for 2009 [83], and 44.5% for 2011 [84], exceeding participation rates in Japan. If including opportunistic screening, the participation rates would be even higher. Importantly, higher participation rates have been observed for endoscopy than for X-ray. The screening program has demonstrated to identify GC at earlier stage [85] and to be cost-effective [86] in this country. Endoscopy-based screening was estimated to have the highest cost-efficacy in both the genders. Putting an upper age limit of 75-80 years for screening males is also being considered [86].

China—Two population-based pilot studies were conducted In Linq County to compare endoscopic evaluation to pepsinogen testing from 1989 to 1990. A total of 3,433 residents aged 35-64 years were selected at random and enrolled, representing 83% of eligible population in 14 villages. The subjects underwent upper endoscopy with biopsy specimens taken from seven anatomical locations. A total of 13 GCs (0.38%) were detected, of which 8 (62%) were in stage I or II [87]. The pepsinogen testing was not found to be sensitive or specific for detecting advanced preneoplastic lesions or GC [88].

Another pilot study including 2,290 residents of Linq County aged 40-69 years was conducted from 2008 to 2011 to compare the efficacy of pepsinogen detection to endoscopy for early detection of GC. Overall, 11 GCs (0.48%) and 10 cases (0.44%) with high-grade intraepithelial neoplasia (dysplasia) were detected by pepsinogen testing, of which 7 (0.31%) cases were early-stage GC. Simultaneously, 19 (0.83%) cases of GC and 10 (0.44%) cases with high-grade intraepithelial neoplasia were detected by direct endoscopy,

of which 12 (0.52%) were cases of early-stage GC. Endoscopy had a higher detection rates of GC (OR=2.83, 95% CI 1.34-5.98), and early GC/high grade intraepithelial neoplasia (OR=2.12, 95% CI 1.12-4.02) than Pg I/II testing. The sensitivity and specificity of Pg I/II for detection of GC were 76.5% and 41.9%, respectively [89].

Since the above studies revealed that direct endoscopy scheme is more effective in detection of early-stage GC than pepsinogen testing, 3,018 residents aged 40-69 of Linqu County were screened by endoscopy in 2013, and 38 (1.26%) cases of GC were detected. Among those cases, 30 cases of GC (79%) correspond to early stages. Within an early GC detection program in China, annually 3000 residents aged 40-69 years are selected in 990 villages by a cluster randomization for an endoscopic examination. Currently, a nationwide oesophageal cancer and GC screening program by endoscopy has been going on in China supported by the Chinese Ministry of Health since 2008. A guideline of screening and early detection/treatment of oesophageal and GC was developed by a panel of experts in 2005 and revised in 2011, and 2014 [90]. The guideline consists of detailed information on population eligibility, informed consent, procedures of screening, endoscopy and pathology diagnosis, principle treatment, algorithms, a manual for follow-up and quality control for the screening program. Training courses for endoscopists, gastroenterologists, pathologists and epidemiologists have been organized periodically. A total of 110 counties in 26 provinces of China are enrolled so far in this project, in the majority of those counties being high-risk areas for oesophageal and GC. In 2013, a total of 189,329 residents aged 40-69 years were screened by endoscopy, and 3,040 (1.61%) oesophageal cancer and GC were detected, of which 2,201 (72.40%) cases were in early stages [91].

In addition, the globally largest randomised intervention trial has been started in Linqu County; as per the end of 2013, altogether close to 200,000 residents aged 24-54 years in 980 villages were enrolled. Subjects with *H. pylori* infection received either *H. pylori* eradication therapy or a look-alike placebo. The participants will be followed for at least 7 years and the difference in the incidence rate between the groups is to be 20 to 40% [92].

Latin America—There is geographic variation in the risk of GC in Central and South America, with high incidence rates in communities residing in the mountains (i.e., Sierra Madre and Andes Ranges) as compared to those in coastal areas [93]. Population-based interventions for malignant and premalignant gastric lesions or *H. pylori* infection have not been widely implemented in Latin American countries. However, two demonstration projects, with contradictory results, have been conducted. A case-control study of the efficacy of photofluorography in Venezuela during the period 1981-1989 suggested that screening did not reduce GC mortality [94]. In contrast, a study in Costa Rica between 1996 and 2000 found that photofluorography screening may reduce GC mortality but high costs limited the wide application of this intervention [95]. A modified opportunistic screening approach is currently active in the same high-risk area where the demonstration project was performed.

Europe and bordering areas—The risk of GC in Europe varies, with the highest rates reported in Albania, Belarus, Macedonia, Russia, Ukraine, the Baltic States and Portugal; also Asian countries bordering to Europe, e.g. Kazakhstan have high incidence of the disease

[1]. Currently the European Commission has not included screening for GC in the recommended cancer screening programs; however the re-evaluation of the available evidence is being planned.

Several pilot-initiatives and screening investigations have been conducted and are currently on the way in Europe; two GC screening / prevention trials are currently recruiting middle-aged population.

Gastric cancer screening in conjunction with colorectal cancer screening in Europe

(GACSE): Gastric cancer screening in conjunction with colorectal cancer screening in Europe (GACSE) is a multi-centre study in >50 years aged subjects undergoing screening colonoscopy who are offered serological testing for gastric premalignant lesions (i.e. pepsinogen I, pepsinogen II, gastrin-17 and *H. pylori* antibody detection). The individuals with confirmed presence of *H. pylori* infection will be offered eradication therapy. Subjects with decreased pepsinogen levels will be referred for upper endoscopy with appropriate biopsy sampling, and follow-up if mucosal atrophy is confirmed. Recruitment of 4300 subjects is expected to prove the expected 75% sensitivity of the biomarker test to detect atrophy [96]. The study has been initiated in Magdeburg, Germany; other involved countries are Italy, Hungary, Serbia, France, Croatia, Poland, Slovenia, Israel, Russia [97].

Multicentric randomized study of *H. pylori* eradication and pepsinogen testing for prevention of GC mortality (GISTAR)

(GISTAR): Multicentric randomized study of *H. pylori* eradication and pepsinogen testing for prevention of GC mortality (GISTAR) is a randomised population-based study in 40-64 years old individuals at the time of enrolment to evaluate the rationale for mass *H. pylori* eradication as well as the potential of risk-markers and follow-up strategies following the identification of premalignant lesions. The end-point is the difference in GC-caused mortality that is expected to be reached in 15 years after recruiting 30,000 individuals; currently the study is recruiting in the pilot phase in Latvia [98].

Kazakhstan has declared the intention to introduce biennial screening with upper endoscopy for oesophageal cancer and GC in the age group between 50 and 60 years [99]. From the beginning of 2013 the attempt has been started in 6 out of 16 regions of the country with the intention to expand to the entire country. In 2014, 11 regions were involved. So far there are no data on the participation rate available. There are concerns on the organization and quality assurance issues that are pre-requisites of an organized screening program. In addition, the strategy for managing the revealed lesions and *H. pylori* infection are not clearly defined [97].

SUMMARY

Due to increasing and aging of high-risk populations, GC is going to remain an important global healthcare problem for the upcoming decades. Mortality rates of GC are high in most parts of the world, and mainly related to late detection of the disease. Screening for GC could have a potential for increasing survival, however there is no appropriate universal screening method available. Currently, nationwide organized screening programs are

running only in Japan and Korea. A few other countries, including China and Kazakhstan are attempting to implement screening. However endoscopic- or photofluorography-based programs would be hardly feasible outside the high GC risk areas of Asia, therefore there is an unmet need for an appropriate non-invasive screening tool to detect GC or the related precancerous lesions.

Screening modalities in GC should be clearly differentiated, and performance indicators should be used depending on the targeted condition: 1) screening for early-stage GC to improve the outcome of endoscopic or surgical management; 2) screening for precancerous lesions to enable follow-up of the individuals at increased risk; 3) screening for *H. pylori* infection with the intention to implement mass eradication strategies (“screen-and-treat” strategy) in high GC risk areas. The latter is considered cost-effective; however, additional well-designed studies addressing potential short and long-time adverse events, including changes of the microbiota and the antibiotic resistance, are needed prior to implementing mass eradication in high GC risk populations.

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PRACTICE POINTS

- GC related mortality is going to remain an important cancer-related cause of death in the decades to come
- Control and prevention strategies to decrease GC mortality should be clearly divided into screening for: a) early-stage cancer; b) precancerous lesions; c) *H. pylori* infection
- Screening with upper endoscopy and/or photofluorography have demonstrated the potential to decrease GC mortality in East Asia, however these methods could be hardly feasible outside Asia
- Pepsinogen screening is the best available option for detection of extensive atrophic gastritis, but still imperfect for GC diagnosis
- Attention should be paid to the diagnostic cut-off values when results of different pepsinogen detection test systems are compared
- There is no non-invasive screening tool available that could be recommended for implementation in organized population-based screening settings
- A number of new and non-invasive tests for detecting either GC or precancerous lesions have promising results but need replication and proper validation before being added to organized screening programs

RESEARCH AGENDA

- Screen-and-treat strategy for *H. pylori* infection (i.e. mass eradication) should be further evaluated by well-designed implementation studies in high-risk areas, in particular outside Asia for proving the feasibility and cost-efficacy data on this approach in real population-based screening settings
- Risk stratification studies evaluating the combined role of host and bacterial characteristics should be considered as an alternative to mass eradication strategies
- Well-designed discovery studies of biomarkers for detection of GC and precancerous lesions should include strict and systematic validation steps to accelerate transfer to clinical practice

Figure 1.

Potential prevention and control strategies of gastric cancer and the related premalignant lesions

Table 1

Summary of the existing screening programs and pilot *H. pylori* eradication initiatives worldwide

	Japan	Korea	China			Taiwan			Kazakhstan	Costa Rica
			General screening program	Linqu <i>H.pylori</i> eradication pilot	Matsu Island, Lienchia ng County	Changhua County				
Targeted condition	Cancer	Cancer	Cancer	<i>H. pylori</i>	<i>H. pylori</i>	<i>H. pylori</i>	Cancer	Cancer	Cancer	Cancer
Type of program	Organized	Organized	Pilot	Pilot	Pilot	Pilot	Opportunistic	Opportunistic	Opportunistic	Opportunistic
Coverage	Nation-wide	Nation-wide	Regional (112 counties)	Regional	Regional	Regional	Regional (most regions of the country covered by 2014)	Regional (most regions of the country covered by 2014)	Local (Cartago and los Santos)	Local (Cartago and los Santos)
Initiation	1983	1999	2008	2011	2004	2012	2013	2013	1996	1996
Current status	Ongoing	Ongoing	Enrolling	Enrolment completed in 2013	Ongoing	Enrolling	Enrolling	Enrolling	Ongoing	Ongoing
Target population	40 years, both genders	40 years, both genders	40-69, both genders	24-58, both genders	30, both genders	50-69, both genders	50-60, both genders	50-60, both genders	50-74, both genders	50-74, both genders
Frequency	Annual	Biennial	Annual	Single-time	Single-time	Single-time	Biennial	Biennial	Single-time	Single-time
Primary screening method	X-ray	1) Upper endoscopy 2) X-ray	Upper endoscopy	¹³ C-UBT	¹³ C-UBT	Faecal <i>H. pylori</i> antigen	Upper endoscopy	Upper endoscopy	X-ray	X-ray
Confirmatory method	Upper endoscopy	Upper endoscopy if screened by X-ray	N.A.	N.A.	Upper endoscopy if <i>H. pylori</i> positive	Upper endoscopy if <i>H. pylori</i> positive	N.A.	N.A.	Upper endoscopy	Upper endoscopy
Photo-documentation required at endoscopy	No, but routine	No, but routine	Yes	N.A.	Yes	Yes	No	No	No, but routine	No, but routine
Standard biopsy protocol required at endoscopy	No	No	No	N.A.	Yes	No	No	No	No	No
Defined strategy of management <i>H. pylori</i>	No	No	No	Yes (test-and-treat)	Yes (test-treat-retest-retreat)	Yes (test-treat-retest-retreat)	No	No	Yes, when is required	Yes, when is required
Defined strategy for management premalignant lesions. i.e. different from the consecutive next round investigation	Yes	No	Yes	N.A.	Yes	Yes	No	No	Yes	Yes
Quality assurance	Regular within organized screening settings	Regular within organized screening settings	Regular within organized screening settings	Regular within study settings	Regular within study settings	Regular within study settings	No	No	Regular within organized screening settings	Regular within organized screening settings
Number of individuals screened to date	~ 4 million a year	~ 5.8 million in 2011; (2002-2008 – 6.1	400,000	~200,000	~ 5,000	Approximate 12,000	306,480 / 18 months (Jan. 2013-June, 2014)	306,480 / 18 months (Jan. 2013-June, 2014)	43,255	43,255

	Japan	Korea	China		Taiwan			Kazakhstan	Costa Rica
			General screening program	Linqu <i>H.pylori</i> eradication pilot	Matsu Island, Lienchia ng County	Changhua County			
		million in total screened at least once)							
Participation rate	9-20%	29.1% (2008), 34.9% (2009), 44.5% (2011)	60-80%	55%	~80%	~30%	N.D.	~80%	
Outcome / Comments	Mortality. Case-control and cohort studies have consistently suggested mortality reduction. [13, 74–77]	Acceptability/adherence. Better participation for endoscopy than X-ray. [82–85]	70-80% cancers detected at early stage [91]	Randomised controlled trial. [92]	Interventional cohort study, with significant reduction of 77% on atrophic gastritis but 25% non-significant reduction of GC incidence until 2008 [65, 100]	Feasibility rounds followed by a randomised study [66]	Organizational issues, insufficiently defined management strategies and quality assurance issues are the limitations. [97, 99]	Mortality. A community controlled trial suggested mortality reduction. [95]	

N.A. – not applicable

N.D. – no data

Participation rate is estimated as the proportion of individuals from the total target group that have undergone the primary screening test within the particular program (at least within one screening round)