Table 3 Results of gastric cancer screening

Sex	Total number of participants	Cancer detection rate (/1000)	Detected cancers (*n*)	Deaths from gastric cancer (*n*)	Deaths from all cancers except gastric cancer (*n*)	Screening group
All	16373	6.29	103	24	216	Endoscopy
Men	6476	11.12	72	18	154	
Women	9897	3.13	31	6	62	
All	18221	4.28	78	43	266	Regular radiography
Men	7019	6.70	47	29	173	
Women	11202	2.77	31	14	93	
All	15927	0.75	12	38	208	Photofluorography
Men	5188	1.93	10	31	130	
Women	10739	0.19	2	7	78	

Table 4 Comparison of standardized mortality ratio among the screening groups

Reference population	Group		Gastric cancer deaths			All cancer deaths except gastric cancer deaths		
			Observed number	Expected number	SMR (95%CI)	Observed number	Expected number	SMR (95%CI)
Niigata city	Endoscopy	Total	24	56	0.43 (0.30-0.57)	216	349	0.62 (0.57-0.67)
		Men	18	37	0.49 (0.32-0.66)	154	220	0.7 (0.64-0.76)
		Women	6	20	0.31 (0.12-0.54)	62	129	0.48 (0.39-0.57)
	Regular radiography	Total	43	63	0.68 (0.55-0.79)	266	393	0.68 (0.63-0.73)
		Men	29	40	0.72 (0.56-0.85)	173	244	0.71 (0.65-0.77)
		Women	14	23	0.62 (0.39-0.80)	93	149	0.62 (0.53-0.70)
	Photofluorography	Total	38	45	0.85 (0.71-0.94)	208	281	0.74 (0.68-0.79)
		Men	31	27	1.13 (1.04-1.43)	130	169	0.77 (0.70-0.83)
		Women	7	17	0.41 (0.18-0.67)	78	112	0.69 (0.59-0.77)
Niigata prefecture	Endoscopy	Total	24	58	0.41 (0.29-0.55)	216	329	0.66 (0.61-0.71)
		Men	18	39	0.47 (0.30-0.63)	154	204	0.75(0.68-0.81)
		Women	6	20	0.3 (0.12-0.54)	62	125	0.5 (0.41-0.59)
	Regular radiography	Total	43	66	0.66 (0.52-0.76)	266	371	0.72 (0.67-0.76)
		Men	29	43	0.68 (0.44-0.75)	173	227	0.76 (0.70-0.82)
		Women	14	23	0.61 (0.39-0.80)	93	144	0.64 (0.56-0.72)
	Photofluorography	Total	38	46	0.83 (0.69-0.92)	208	264	0.79 (0.74-0.84)
		Men	31	29	1.08 (1.01-1.27)	130	157	0.83 (0.76-0.88)
		Women	7	17	0.41 (0.18-0.67)	78	108	0.72 (0.63-0.80)
Japan	Endoscopy	Total	24	54	0.45 (0.31-0.59)	216	357	0.6 (0.55-0.65)
		Men	18	36	0.5 (0.33-0.67)	154	214	0.72 (0.65-0.78)
		Women	6	18	0.34 (0.13-0.59)	62	143	0.43 (0.34-0.51)
	Regular radiography	Total	43	60	0.71 (0.59-0.83)	266	403	0.66 (0.61-0.71)
		Men	29	40	0.73 (0.56-0.85)	173	238	0.73 (0.67-0.79)
		Women	14	21	0.68 (0.43-0.85)	93	165	0.56 (0.48-0.63)
	Photofluorography	Total	38	42	0.9 (0.77-0.97)	208	287	0.73 (0.68-0.78)
		Men	31	27	1.15 (1.04-1.43)	130	164	0.79 (0.72-0.85)
		Women	7	15	0.46 (0.21-0.73)	78	123	0.64 (0.53-0.71)

SMR: Standardized mortality ratio.

screening group than in the regular radiographic screening group.

Several studies have reported the possibility of reducing mortality from gastric cancer by endoscopic screening[7-10]. In particular, Matsumoto *et al*[8] showed that the SMRs of gastric cancer death decreased after the introduction of endoscopic screening in a small island as follows: 0.71 (95%CI: 0.33-1.10) for men and 0.62 (95%CI: 0.19-1.05) for women. However, an immediate decrease might be dependent on the long-term effects of radiographic screening. Since these previous reports were all observational studies and that their qualities were insufficient, the effectiveness of endoscopic screening for gastric cancer has remained unclear. Recently, 2 case-control studies have shown mortality reduction from gastric cancer by endoscopic screening[15,16]. A larger case-control study has suggested a 30% mortality reduction from gastric cancer by endoscopic screening compared with no screening, but a significant mortality reduction could not be obtained by radiographic screening[16]. Compared with previous studies, the present study showed the huge impact of endoscopic screening on mortality reduction from gastric cancer.

SMRs are commonly used for evaluating the effectiveness of cancer screening[8,17-20]. The resulting SMRs readily demonstrate the impact of cancer screening in communities. However, it is also possible to overestimate the impact of cancer screening on mortality reduction from cancers. Since the reference population included patients who could not participate in cancer screening, the mortality rate was higher than the healthy general population. Death cases from the general population included individuals whose diagnosis was made before the index date of the screening in 2005. Although the obtained impact of endoscopic screening on mortality reduction from gastric cancer in this study was considerably high at approximately 57%, careful interpretation of this result is also needed.

This study has several limitations which may result in an overestimation of the impact of gastric cancer screening on mortality reduction. First, there is possible self-selection bias in the screening groups. The participants in the screening groups were healthier than the general population and they could continue undergoing the screening. The backgrounds of the screening groups were not similar to those of the general population. Since details of the background information, including the smoking and family history, were not obtained, no adjustments could be made for the background differences. Fukao *et al*[21] reported differences in the smoking and family history between the participants and non-participants of gastric cancer screening.

Second, there were background differences even in the screening groups. Individuals can choose any screening method based on their preference. The age distribution of the participants was also different among the 3 screening groups. Since most of the older people have their own primary care doctor, screening could be offered easily at their clinic. The participants of the photofluorography screening program were younger than those of the other screening programs. This was because photofluorography screening was mainly provided as a mass screening program which was often participated in by individuals who had no primary care doctor.

Third, the screening history before the index date of the screening in 2005 was ignored. Radiographic screening was performed before the introduction of endoscopic screening. Some participants changed their subsequent screening program from radiographic screening to endoscopic screening. The rate of participants who had no screening history within 2 years from the index date of the screening in 2005 was 15.5% for the endoscopic screening and 5.7% for the regular radiographic screening.

Fourth, the sample size was small because of the low participation rate in gastric cancer screening. Although the participation rate in gastric cancer screening has increased since the introduction of endoscopic screening, the screening rate has remained at approximately 25%[10].

Finally, the follow-up period was limited to 5 years. Thus, the full impact of the screening program may not have been realized as the screening effect cannot be expected within a short period of time but within several years after the introduction of a new screening program[22]. Since more early-stage cancer was detected by endoscopic screening than by radiographic screening, there may be a difference in the preclinical phase between endoscopic screening and radiographic screening. A longer preclinical phase should be assessed, because most cancers detected by endoscopy were early-stage and slow-growing cancers. A longer follow-up is needed to comprehensively evaluate the effectiveness of endoscopic screening.

In conclusion, the present findings suggest that endoscopic screening might maximally reduce mortality from gastric cancer by 57%. Although such reduction rate suggests the effectiveness of endoscopic screening for gastric cancer, prudent interpretation of this result is needed considering the above-mentioned limitations of the present study. Additional evidence supporting mortality reduction from gastric cancer by endoscopic screening is desired to realize the introduction of endoscopic screening in communities.

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COMMENTS

Background

The burden of gastric cancer still remains in Asia and East European countries. Endoscopy, which is commonly used in clinical practice, is anticipated to be a promising screening method for gastric cancer. Although several studies have reported the possibility of reducing mortality by endoscopic screening, definitive evidence remains to be established.

Research frontiers

Authors investigated mortality reduction from gastric cancer on the basis of the results of endoscopic screening. The standardized mortality ratio (SMR) of gastric cancer and other cancer deaths in each screening group was calculated by applying the mortality rate of the reference population.

Innovations and breakthroughs

The 57% mortality reduction from gastric cancer might indicate the effectiveness of endoscopic screening for gastric cancer. The mortality reduction from gastric cancer was higher in the endoscopic screening group than in the regular radiographic screening group despite the nearly equal mortality rates of all cancers except gastric cancer.

Applications

The results suggest mortality reduction from gastric cancer by endoscopic screening. This can serve as supporting evidence regarding the effectiveness of this screening method for gastric cancer and its possible introduction in communities.

Terminology

The SMRs of cancer death were the ratios in which the numerator represented the number of observed cancer and the denominator indicated the number of expected cancer in a reference population.

Peer-review

The authors investigated the effectiveness of endoscopic screening by calculating the mortality reduction from gastric cancer. Although many endoscopists believe that endoscopic screening is the most effective method for gastric cancer screening, there have been scarce data on the mortality reduction effect by endoscopic screening, thus radiographic screening for gastric cancer is presently recommended for the public in Japan. Therefore, this study is very valuable as it provides supporting evidence regarding the effectiveness of endoscopic screening in reducing mortality from gastric cancer.

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MINI-REVIEW

Why Screening Rates Vary between Korea and Japan-Differences between Two National Healthcare Systems

Rei Goto[1]*, Chisato Hamashima[2], Sunghyun Mun[3], Won-Chul Lee[4]

Abstract

Both Japan and Korea provide population-based screening programs. However, screening rates are much higher in Korea than in Japan. To clarify the possible factors explaining the differences between these two countries, we analyzed the current status of the cancer screening and background healthcare systems. Population-based cancer screening in Korea is coordinated well with social health insurance under a unified insurer system. In Japan, there are over 3,000 insurers and coordinating a comprehensive strategy for cancer screening promotion has been very difficult. The public healthcare system also has influence over cancer screening. In Korea, public healthcare does not cover a wide range of services. Almost free cancer screening and subsidization for medical cost for cancers detected in population-screening provides high incentive to participation. In Japan, on the other hand, a larger coverage of medical services, low co-payment, and a lenient medical audit enables people to have cancer screening under public health insurance as well as the broad range of cancer screening. The implementation of evidence-based cancer screening programs may be largely dependent on the background healthcare system. It is important to understand the impacts of each healthcare system as a whole and to match the characteristics of a particular health system when designing an efficient cancer screening system.

Keywords: cancer screening - screening rate - Japan - Korea - health insurance

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Introduction

In many countries, population-based screening programs are implemented to reduce cancer incidence and mortality at the community level. Population-based screening is primarily differentiated from opportunistic screening in that invitations to target populations are issued from population registers (Miles et al., 2004). Moreover, governments have a certain responsibility for components of the screening, such as decisions about type of cancer and screening methods, eligibility decisions for the target population and providers, construction of a call-recall system, quality assurance, and budget.

In order to maximize the impact of cancer screening programs on population health, high screening rate is essential (Parkin et al., 2008). Both Japan and Korea provide population-based screening programs. However, there are many differences between the programs in these two countries. In 2010, the percentage of females screened for breast cancer among those aged 50 to 69 years was 36.4% in Japan and 63.6% in Korea, and for cervical cancer, the numbers were 37.7% in Japan and 63.8% in Korea. The difference in screening rates for cervical cancer has remained stable since 2004 when Korea began to provide comparable data to the Organization for Economic Co-operation and Development (OECD) (Organization for Economic Co-operation and Development(OECD) 2013). It is very important to understand why these differences exist.

There are many possible measures to increase screening rates. Review articles showed that interventions such as more personalized invitation methods, general practitioner involvement, and reduction of financial barriers (e.g., out of pocket payment and transportation) are effective at increasing screening rates (Vernon, 1997; Jepson and Martin-Hirsch 2002; Jepson et al., 2000; Everett et al., 2011; Forbes, Khalid-de Bakker et al., 2011). Differences in the implementation of these measures might explain large disparities in screening participation rates. However, to see the origins of these differences, it is also important to note that the underlying features of the healthcare system can be influential (International Agency for Research on Cancer 2002; Sabatino et al., 2012). Though both Japan and Korea have universal social health insurance systems, there are differences in the details of their health systems. These include the organization of insurers, the extent of centralization of different tiers of the government, coverage, and cost-containment mechanisms.

*[1]The Hakubi Center of Advanced Research, Graduate School of Economic, Kyoto University, Kyoto, [2]Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan, [3]Department of Business, Baekseok University, Cheonan, [4]Department of Preventive Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea *For correspondence: goto.rei.7w@kyoto-u.ac.jp*

This paper aimed to analyze the current status of the cancer screening and background healthcare systems in Japan and Korea and to elucidate the possible factors explaining the differences in screening rates between these two countries.

Connections between Population-based Cancer Screening Health Insurance

Table 1 shows an historical overview of population-based screening systems in the two countries. In Japan, population-based cancer screening for gastric and cervical cancer started in 1983, 21 years after the realization of universal health insurance coverage. Lung, breast, and colorectal cancer screening were added to this program in 1998. Also in 1988, the budgetary responsibility of population-based screening was transferred from the central to local government during the process of decentralization.

There are about 3500 health insurance plans: roughly half are employee-based and half are community-based (Ikegami et al., 2011). Each local municipal government is the insurer for Citizens' Health Insurance, which is one of the community-based insurance plans. Under these plans, local governments simultaneously control cancer screening and health insurance. The National Health Insurance Association is a unified community-based insurance, which is a plan for employees and family members of small to medium-sized companies.

Employee-based insurance comprises society-managed health insurance for large companies and Mutual Aid Associations for public sectors. For these plans, the governance of cancer screening and health insurance are separated.

In Korea, there were multiple insurers, both community- and employee-based, when universal coverage was established in 1989. These insurers were integrated into the National Health Insurance Corporation (NHIC) in 2000. The process of integration lasted until 2003, when the accounting system and premium collection integrated. The cancer screening program was expanded during the same time as detailed below (ref).

Screening Delivery System

In Japan, each insurer can provide their own cancer screening program for their beneficiaries under the Health Insurance Act. However, these screening programs cannot be categorized into population-based screening because the insurer (not the government) is the responsible party for the screening provision. The screening budget is the collective fund from the insured. Thus, there are at least two types of opportunistic screening in Japan: individual opportunistic screening, in which the person undergoing screening pays the whole cost; and collective opportunistic screening, in which health insurers provide a subsidy for their beneficiaries.

In Korea, the public cancer screening program was started only for public sector employees. In 1999, the National Cancer Screening Program (NCSP) was launched for the low-income population as a welfare policy. It is important to note that the unification of social health insurers was taking place concurrently. Prior to that, employee-based and community-based health insurance were operating independently and covered the entire population, like in Japan. Each insurer had its own independent screening program. During the unification, cancer screenings provided by different insurers were

Table 1. Historical Overview of Population-based Cancer Screening Systems

Japan	Year	Korea
Universal social health insurance coverage established	1961	
Population-based cancer screening governed and sponsored by the central government launched: gastric and cervical cancer screening	1983	
Expanded to include lung and breast cancer screening	1987	
	1989	Universal social health insurance coverage established
	1990	Cancer screening governed and sponsored by the central government launched: only for public servants and teachers
Expanded to include colorectal cancer screening	1992	
Responsibility for the provision of cancer screening was transferred from central to local government (municipal level)	1998	
	1999	The National Cancer Screening Program (NCSP) launched for people with low income: gastric, breast, and cervical cancer
	2000	Unification of public health insurers to single insurer, the National Health Insurance Corporation (NHIC)
	2002	NCSP: target expanded to NHIC insured (whose insurance premium is less than the 20th percentile)
	2003	Integration of an accounting system for insurers established Target expanded to people whose insurance premium is less than the 30th percentile Expanded to include hepatic cancer screening
	2004	Expanded to include colorectal cancer screening Financial support program for cancer patients started
	2005	Target expanded to people whose insurance premium is less than the 50th percentile

integrated into programs provided by the single insurer, the National Health Insurance Service (NHIC).

Currently, the NHIC provides the same cancer screening as the NCSP for those who are not eligible to be insured by the NCSP. The cancer screening provided by the NCSP and the NHIC is all the same program with tiny differences around available financial resources as described later. Thus, these two programs are operated as a single population-based program. Figure 1 shows a brief sketch of the Korean population-based screening system.

In Korea, large companies also provide an independent cancer-screening program using funds collected from the insured. Individuals can have free screening services paying total expenses. Thus, there are three types of cancer screening in Korea as well. Table 2 shows the different tiers of cancer screening in the two countries.

Screening Program

Table 3 shows the type of cancer, screening method, and screening interval. In Japan, the type, method, and interval have been recommended by a research group funded by a grant supported by the Ministry of Health, Labor, and Welfare (MHLW). This research group published evidence-based screening guidelines for each cancer type (Hamashima et al., 2008). These guidelines were not formulated by the Ministry and therefore are not mandatory. Thus, each municipality has final approval about these issues and the autonomy to decide whether or not to adhere to the guidelines.

In Korea, the board governing the NCSP is within the National Cancer Center and this board issues evidence-based recommendations. The expansion of the NCSP has been gradually expanded as the budget has grown to cover the cost of screening. Each provider must adhere to the government recommendations for financial support of cancer screening. Also, the National Cancer Center created its own guideline for cancer screening methods for opportunistic screening.

Quality Assurance

In Korea, a unique ID number is used within the health

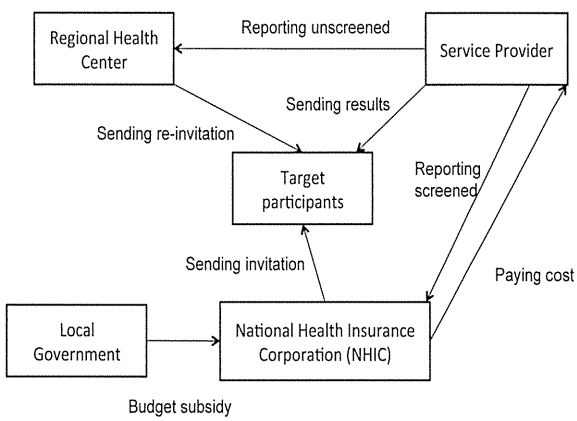

Figure 1. Delivery System of Population-based Screening in Korea

Table 2. Three Types of Cancer Screening in Japan and Korea

Japan	Type of cancer screening	Korea
*Municipal cancer screening program	Population-based screening	*National Cancer Screening Program (NCSP) *National Health Insurance Corporation (NHIC) cancer screening program
*Cancer screening subsidized by insurers *Optional cancer screening added to basic health check-up for the employed	Collective opportunistic screening	*Cancer screening subsidized by companies
*Cancer screening demanded by individuals with full out-of-pocket *Cancer screening provided under health insurance	Individual opportunistic screening	*Cancer screening demanded by individuals with full out-of-pocket

Table 3. Type of Cancer, Screening Method, and Screening Interval

Japan				Korea		
Target Age	Screening Method	Screening Interval		Target Age	Screening Method	Screening Interval
40 and over	Barium enema	1 year	Gastric caner	40 and over	Barium enema or upper endoscopy	2 years
20 and over	Pap smear	2 years	Cervical cancer	30 and over	Pap smear	2 years
40 and over	Chest X-ray and sputum cytology	1 year	Lung cancer	Not Available		
40 and over	Breast examination and mammography	2 years	Breast cancer	40 and over	Mammography	2 years
40 and over	Fecal occult blood test (FOBT)	1 year	Colorectal cancer	50 and over	Fecal occult blood test (FOBT)	1 year
Not Available			Hepatic cancer	40 and over (only for those with liver cirrhosis, HBV/HCV positive hepatitis)	Abdominal ultrasonography and α fetal-protein	1 year

Table 4. Financial Resources for Population-based Cancer Screening in Korea

	Target	Type of Cancer	Financial Resources			
			Central Government	Local Government	NHIC	Out-of-pocket
NCSP	Low income (those exempted from premium payment)	Gastric, colorectal, breast and cervical cancer	50% (30% in Seoul)	50% (30% in Seoul)	0%	0%
	Those whose insurance premium is less than the 50th percentile	Gastric, colorectal, and breast cancer	50% (30% in Seoul)	50% (30% in Seoul)	90%	0%
		Cervical cancer	0%	0%	100%	0%
NHIC Cancer Screening	Those whose insurance premium is more than the 50th percentile	Gastric, colorectal, and breast cancer	0%	0%	90%	10%
		Cervical cancer	0%	0%	100%	0%

care system. The NHIC created a list of objectives for the NCSP and the NHIC screening programs based on premium amounts for each individual. The NHIC sent invitation letters to participate in screening to all eligible residents. The demographic information of objective persons is stored in a database that can be accessed by the NHIC, regional health centers, and screening providers. This database is administered by the National Cancer Center. Regional health centers use this database to call people who were sent invitation letters and did not participate in screening to encourage them to do so.

The authentication of screening providers and quality management are mainly conducted by the National Cancer Center. The role of hospitals in providing screening services is larger than that of small clinics. Recently however, screening services have been expanded to include clinics in order to increase screening capacity.

In Japan, the ministry provides guidelines for evaluation of the municipal cancer screening program (Cancer screening committee Ministry of Health Labour and Welfare, 2007). The local municipalities contract with providers including hospitals, outpatient clinics, and both for- and non-profit organizations specializing in screening services. It is up to the local municipalities to monitor and maintain the quality of the screening performed by these various providers. However, the local municipalities only report macro-level data to the central government such as the number of participants screened, given a secondary examination, those with cancer detected, and the computed positive predictive value. The local municipalities do not monitor each provider at the micro-level.

Available Financial Resources for Screening

Table 4 depicts the payment allocation of population-based cancer screening in Korea. Under the NCSP, the central or local governments assume the total screening cost for those with low income. For the other participants, the NHIC pays most of the cost as for the NHIC Cancer Screening. Eventually, there is no out-of-pocket payment for NCSP participants. Those with higher income have 10% out-of-pocket payment for gastric, colorectal, and breast cancer screening. This out-of-pocket payment is covered by central and local governments in the NCSP. The difference between the NCSP and NHIC Cancer Screening lies only in this payment allocation. Secondary examination after a positive screening result is also provided for free. Thus, population-based cancer screening is provided almost for free in Korea.

In Japan, each local municipal government can set the amount of out-of-pocket payment independently. The MHLW collected data on the content of examinations, strategies, and out-of-pocket costs for cancer screening among the different municipalities. According to this survey, the percentage of municipalities providing a free screening program is 8.3% for gastric cancer, 22.5% for lung cancer, 9.7% for colorectal cancer, 9.4% for cervical cancer, and 7.0% for breast cancer (Sano, Goto and Hamashima, 2014). Thus, most population-based screenings in Japan incur a financial burden on the participant being screened, which is rare in Korea.

Available Financial Resources for Cancer Treatment

According to the OECD health data, the percentage of gross domestic product (GDP) spent on healthcare in 2010 was 9.6% in Japan and 7.3% in Korea. In Japan, the government put a concerted effort toward cost containment via price control. The cost to payers is determined by a single-fee schedule. This single payment system has allowed total health care spending to be controlled despite a fee-for-service system with broad coverage of services and incentives to increase the volume of services (Ikegami and Anderson, 2012). The copayment rate is almost the same among different tiers of health care services. Generally, copayment rate is 30%, and this is reduced to 10% for the elderly over 70 years old. In Korea, the government adopted a policy of limited benefit coverage under the NHI scheme with a high copayment for patients (Chun et al., 2009). The copayment rate ranges from 20% for inpatient care to 50% for outpatient care in general hospitals. In Korea, people often have to pay by themselves for services that are not covered by the NHI. In Japan, one cannot receive covered services and uncovered services at the same time in principle. Once a patient wants to have an uncovered service, they must pay the total cost of covered service as well as that of uncovered services. Private insurance benefits for uncovered services are not as common in Korea as in Japan. As a result, the percentage of out-of-pocket payment in the total health expenditure in 2010 was 34.2%, which is much higher than in Japan (14.1%).

Another important feature in Korean cancer screening

is that there is a financial subsidy to medical treatment for those who are diagnosed with cancer in the NCSP. The subsidy is for out-of-pocket costs associated with cancer treatment covered by the NHIC, for a maximum of 3 years and a limit of 2 million won (=2,000 USD if 1 USD=1,000 won) per year. Those with high income are not eligible for the subsidy. Participants in the NCSP whose cancer is diagnosed by opportunistic cancer screening cannot have access to this subsidy program. The subsidy can provide a large incentive for those with lower income to participate in population-based screening as opposed to opportunistic screening where there is danger of a large financial burden for the individual.

Coverage of Social Health Insurance

In Japan, coverage of healthcare by public health insurance is broader than in Korea and physicians' autonomy for treatment choice is highly valued. Basically, preventive care for asymptomatic people is not covered in Japan. However, screening can be performed under public health insurance with low out-of-pocket cost, if the physician states a suspicion that the individual may have cancer even if the probability is about the same as the general population. Under the Japanese health insurance system, it is easy for asymptomatic individuals to receive healthcare services in an outpatient clinic identical to those provided in screening programs (Leung et al., 2008). An individual pays no more than 30% of the costs associated with such an examination and government insurance covers the rest. These patients usually see physicians regularly so additional transportation and time required are minimum.

In Korea, the Health Insurance Review and Assessment Service (HIRA), together with the NHIC, was founded to monitor medical claim data and provide quality assurance of NHIC health services (Park et al., 2012). Physicians generally hesitate to take risks to provide uncovered services because of this central audit system of medical claim data.

Discussion

In Japan and Korea, population-based cancer screening is provided for similar types of cancer and healthcare is managed under social health insurance. However, population-based cancer screening is managed differently in the two countries, which may explain the variance in screening rates between Japan and Korea.

Population-based cancer screening in Korea is coordinated well with social health insurance due to the centralized information system under the unified insurer. It is also operated along with the insurer's cancer screening program and together they cover the whole population. Unification of insurers drastically decreased the coordination cost between them. As a result, cancer screenings follow the country's cancer-control measures. In contrast, there are over 3000 insurers in Japan. The cost to coordinate cancer screening promotions between insurers can be very large.

One of the impacts that insurer unification can have on cancer screenings is clarification of the purpose of population-based screening. In Japan, many cancer screening programs are provided using a collective budget. Insurers can provide cancer screening programs independently and companies can add cancer screening to their basic health check-up items required for employees based on the Industrial Safety and Health Act. These are additional benefits for individuals and can be categorized as opportunistic cancer screening. These cancer screenings lack clear purpose, evidence-based management, and quality assurance. They do, however, use collective budgets unlike cancer screening with complete out-of-pocket payment. The decentralized nature of the Japanese healthcare system allows multiple opportunities for cancer screening. In Korea, companies independently provide financial support for cancer screening; but this is limited to employees of large companies.

The public healthcare system also has influence over cancer screenings. In Korea, public healthcare does not cover a wide range of services and it is common to have medical services that are only partially covered by public insurance. Low income households can get cancer screenings for free and their treatments will also be subsidized in case of cancer detection. This shows that cancer screenings are of the most social benefit to low income households. This reflects the fact that cancer screening services began by only covering low income households, and then expanded the eligible population based on impact on the budget. In Japan, on the other hand, a larger coverage of medical services, low co-payment, and a lenient medical audit enables people to have cancer screening under public health insurance as well as the broad range of cancer screening described above. For most people, screenings provided by insurance and population-based screenings are the same.

Access to opportunistic screening is widely varied. In both countries, there are three types of cancer screening: population-based screening, collective opportunistic screening and individual opportunistic screening. In Korea, access to opportunistic screening is more limited than in Japan. Although some companies provide screening for their employees, Korean workers are facing greater instability of employment after the economic crisis in the 1990s and the average retirement age is younger than in Japan (Jung and Cheon, 2006). Even employees of large companies have to rely on one of two population-based screenings after retirement. For lower income Koreans, the NCSP is the only opportunity for affordable cancer screening. Meanwhile, there are many opportunities for cancer screening for all income levels in Japan. Both employee- and community-based insurers provide additional screening opportunities; municipal cancer screening is only one of them.

If we only examine cancer screenings, Korea seems more likely to provide well-managed service owing to the unified population-based screening. However, population-based cancer screening plays a role to complement public health insurance with comparatively narrow coverage. On the other hand, Japan provides broad opportunities for cancer screenings. From the perspective of consumer sovereignty, it is reasonable if costs and benefits of

each individual screening are considered. However, it is inappropriate and inefficient resource allocation if screenings are performed with little scientific evidence of their necessity. There is only a few economic evaluations of cancer screenings for both countries (Sekiguchi et al. 2012; Shin et al. 2014). It needs more discussions about cost-effectiveness to realize the delivery of cancer screening efficiently

In Korea, most people choose population-based screening rather than opportunistic screening. Lee et al., estimated the gastric cancer screening rate from a sample survey by the National Cancer Center (Lee et al., 2010). The population-based screening rate for the bottom quartile of households in income increased from 23.9% in 2005 to 33.7% in 2009, but the opportunistic screening rate decreased from 18.4% to 8.6% during the same time period. It is easy to infer that low income people switch from opportunistic screening to population-based screening because of large financial incentives. Moreover, the population-based screening rate for the top quartile households in income increased from 15.5% to 35.8% during the same period, but there was no significant change in the opportunistic screening rate (23.9% to 24.8%). This suggests that the overall increase in the population-based screening rate in Korea came from the shift of low-income households from opportunistic screening to population-based screening as well as the overall increasing trend of participation to population-based screening.

In Japan, many measures have been taken to try to raise the screening rate. However, broad opportunities for cancer screening may lessen the impact of these measures targeted for population-based screening. The Japanese government began to send free vouchers to certain age groups. This policy might encourage these targeted populations to participate in population-based programs by publicizing the importance of cancer screening (Kuroki, 2012). However, if the screening service was already performed by the insurer, they may be reluctant to switch to population-based screening. It is important to formulate connections between population-based screening and screening programs provided by the insurer and to share information regarding evidence-based screening programs in the same fashion.

The implementation of evidence-based cancer screening programs may be largely dependent on the background healthcare system. A method that has shown to be successful in increasing the participation rate may not be effective in countries or regions with different health systems. It is important to understand the impacts of each healthcare system as a whole and to match the characteristics of a particular health system when designing an efficient cancer screening system.

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Implementation of gastric cancer screening – The global experience

Mārcis Leja, MD, PhD, Professor [a, *],
Weicheng You, MD, Professor [b, 1],
M. Constanza Camargo, PhD, MSc [c, 2],
Hiroshi Saito, MD, PhD, Professor [d, 3]

[a] *Faculty of Medicine, University of Latvia, 6 Linezera iela, LV1006 Riga, Latvia*
[b] *Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Cancer Epidemiology, Peking University Cancer Hospital & Institute, Beijing 100142, PR China*
[c] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA*
[d] *Cancer Screening Assessment & Management Division, Research Center for Cancer Prevention & Detection, National Cancer Center, Tokyo 104-0045, Japan*

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A B S T R A C T

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.

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* Corresponding author. Tel.: +371 29497500; fax: +371 67040248.
E-mail addresses: cei@latnet.lv (M. Leja), weichengyou@yahoo.com (W. You), camargomc@mail.nih.gov (M.C. Camargo), hrsaito@ncc.go.jp (H. Saito).
[1] Tel.: +86 01 88130266; fax: +86 01 88196669.
[2] Tel.: +1 240 2767175; fax: +1 240 2767806.
[3] Tel.: +81 3 35422511x1712; fax: +81 3 35478581.

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Introduction

Although declining in incidence globally, gastric cancer (GC) is still the 3rd leading cause of cancer-related deaths [1], and the 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 five-year survival rate for patients with GC is poor. In Western populations, including Europe and the United States, five-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 *Helicobacter 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

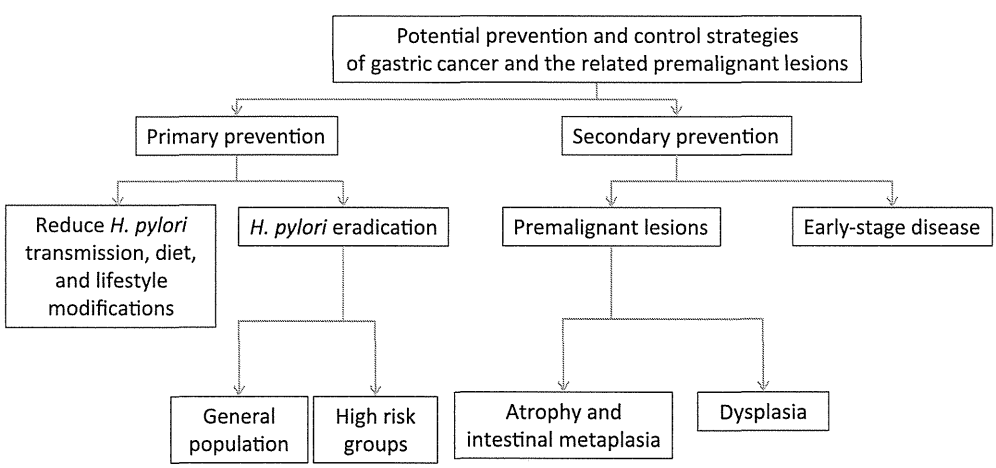

Fig. 1. Potential prevention and control strategies of gastric cancer and the related premalignant lesions.

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 120 ml 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 two specimens from the corpus, and two 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, five biopsies (two from antrum, two from corpus and one 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 extensive 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 four 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, HyuA, 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

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 *H. pylori* eradication pilot	Matsu island, Lienchiang county	Changhua county		
Targeted condition	Cancer	Cancer	Cancer	*H. pylori*	*H. pylori*	*H. pylori*	Cancer	Cancer
Type of program	Organized	Organized	Pilot	Pilot	Pilot	Pilot	Opportunistic	Opportunistic
Coverage	Nation-wide	Nation-wide	Regional (112 counties)	Regional	Regional	Regional	Regional (most regions of the country covered by 2014)	Local (Cartago and los Santos)
Initiation	1983	1999	2008	2011	2004	2012	2013	1996
Current status	Ongoing	Ongoing	Enrolling	Enrolment completed in 2013	Ongoing	Enrolling	Enrolling	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	50–74, both genders
Frequency	Annual	Biennial	Annual	Single-time	Single-time	Single-time	Biennial	Single-time
Primary screening method	X-ray	(1) Upper endoscopy (2) X-ray	Upper endoscopy	^{13}C-UBT	^{13}C-UBT	Faecal *H. pylori* antigen	Upper endoscopy	X-ray
Confirmatory method	Upper endoscopy	Upper endoscopy if screened by X-ray	N.A.	N.A.	Upper endoscopy if *H. pylori* positive	Upper endoscopy if *H. pylori* positive	N.A.	Upper endoscopy
Photo-documentation required at endoscopy	No, but routine	No, but routine	Yes	N.A.	Yes	Yes	No	No, but routine
Standard biopsy protocol required at endoscopy	No	No	No	N.A.	Yes	No	No	No
Defined strategy of management *H. pylori*	No	No	No	Yes (test-and-treat)	Yes (test-treat-retest-retreat)	Yes (test-treat-retest-retreat)	No	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	Yes

(*continued on next page*)

Table 1 (*continued*)

	Japan	Korea	China		Taiwan		Kazakhstan	Costa Rica
			General screening program	Linqu *H. pylori* eradication pilot	Matsu island, Lienchiang county	Changhua county		
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	Regular within organized screening settings
Number of individuals screened to date	~4 million a year	~5.8 million in 2011; (2002–2008 – 6.1 million in total screened at least once)	400,000	~200,000	~5,000	Approximate 12,000	306,480/18 months (Jan.2013-June, 2014)	43,255
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).

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-trea't* 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 five-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 two 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. ^{13}C-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 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 the 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 50–60% reduction in GC mortality, with consistent results across studies [13,74–77]. It is important to mention that improvement in five-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 programs 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 the 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 Linqu 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 2290 residents of Linqu 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, 3018 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 3040 (1.61%) oesophageal cancer and GC were detected, of which 2201 (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 seven years and the difference in the incidence rate between the groups is to be 20–40% [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) 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) 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 six 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 ageing 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.

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 of 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

Conflict of interest

Nothing to declare.

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