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

Asian Pac J Cancer Prev, **16 (2)**, 395-400

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.

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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

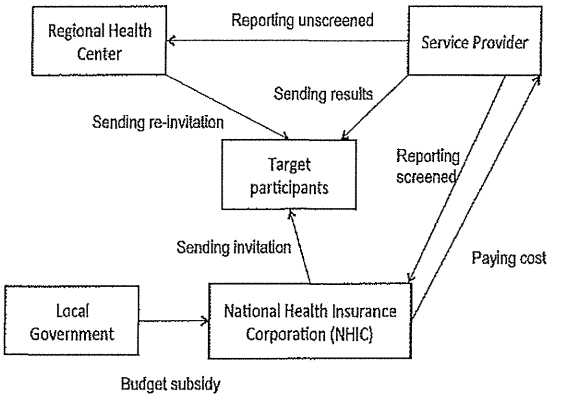

Figure 1. Delivery System of Population-based Screening in Korea

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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投稿

内視鏡胃がん検診プログラムへの参加要因

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目的　がん検診受診者が近くのかかりつけ医で検診を受けられることは，利便性が高いといえるだろう。そこで，診療所での検診プログラムの普及についての探索的な研究を行う。具体的には，診療所が，内視鏡胃がん検診プログラムへの参加を決定する要因を明らかにした。

方法　内視鏡胃がん検診を診療所で実施している米子市において，内科か外科を標ぼうしているすべての診療所を対象とした郵送自記式の質問票調査を実施した。この質問票では，医師のプロファイル情報や診療所の状況についての変数が含まれている。全体で90施設に質問票を送付した。

結果　56施設から質問票の返信を得た（回答率62.2%）。検診参加・不参加別の無回答バイアスは存在しなかった。過去に内視鏡の経験があること，院長の年齢が若いこと，鳥取大学消化器内科（第二内科）医局出身であること，診療所の継承予定があることの4点が，プログラムへの参加に影響していた。

結論　内視鏡経験以外にも，人的ネットワークや診療所の存続可能性が検診プログラムの普及と関連することが示唆された。

キーワード　内視鏡，胃がん検診，質問票調査

I 緒　言

胃がんは，2011年の死亡者数が男性では肺がんに続いて第2位，女性では大腸がん，肺がんについで第3位である[1]。死亡率の低下を目的として市町村事業としての対策型検診が行われているが，胃がんについてはX線検診が推奨されている[2]。一方，任意型検診として内視鏡胃がん検診が行われており，自治体の中には独自の試みとして検診費用に対して補助を行っている自治体もある。対策型検診としてがん検診を行うためには，死亡率の減少に関する科学的な知見が不可欠であり，実際に内視鏡胃がん検診受診と胃がん死亡率減少との関連を示唆する研究が蓄積されつつある[3)-5)]。今後，科学的な根拠が蓄積されていけば対策型検診として推奨されることもあり得る。

しかし，内視鏡胃がん検診は，大腸がんの便潜血検査のように人的・物的資源が比較的少なくても実施可能な検診とは異なり，内視鏡関連機器や検査室，洗浄装置といった物的資源だけでなく，内視鏡の行える医師や準備・介助・片付けを行う看護師といった人的資源も必要とする。したがって，死亡率減少効果に関する疫学的な検討や，受診率を向上させる施策に関する検討に加え，供給能力の決定要因に関する検討

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が必要となる。また，受診者の利便性の観点からは，かかりつけ医を含めた診療所での検診供給が重要性を増している。診療所は，人的・物的資源への大規模な投資が病院に比べ難しいため，供給能力に影響する人的・物的資源の制約を明らかにすることが重要となる。

診療所の内視鏡胃がん検診の供給能力についての検討は，後藤らが自治体補助の内視鏡検診に参加している診療所を対象に，検診件数を決定する要因を分析している。その結果，内視鏡の本数，全自動洗浄機の保有，専用内視鏡室の有無といった物的資源と消化器内視鏡学会専門医資格の有無，若年の医師であることが検診件数増加と関連していた[6]。一方，そもそも内視鏡胃がん検診プログラムに参加するかどうかに影響を与える要因に関する研究は行われていない。本稿では，診療所が内視鏡胃がん検診プログラムへの参加を決定する要因を明らかにした。

Ⅱ 方　法

研究方法は，施設長を対象とした自記式の郵送質問票調査とした。この研究方法を選択した理由は，診療所固有の要因を測定し，それら要因の統計的な影響力を検証する上で有効だからである。郵送質問票調査の対象地域については，①公的補助を受けた診療所での内視鏡胃がん検診プログラムが開始してから一定年数経過し検診への参加の有無が確定している状況であること，②統計的な検定のため一定数以上の診療所が存在していること，③地域性などの影響を減ずるため特定の地域からデータを収集すること，などが考慮された。結果として，鳥取県米子市を研究対象として選択した。鳥取県米子市は，2000年から自治体が内視鏡胃がん検診に費用補助を行っており，十分に時間が経過しているといえる。また，外科や内科を標ぼうしている診療所が調査時点（2010年）で90施設ほどあるため，統計的な検証が可能であると判断された。米子市は，7月から12月までの半年間に内視鏡検診を集中させる方式を採用しており，検診の対象年齢は40歳以上で，受診者の自己負担金は3,300円（70歳以上は1,100円）である。2007年での総胃がん検診数に対する内視鏡検診の割合は77.0%であった[7]。また，精度管理のための検診担当医と読影委員会でのダブルチェックを義務化している。

米子市における調査票配布先の医療機関には，2010年8月時点で鳥取県西部医師会のWebに公開されている診療所（全157施設）のうち，内科あるいは外科を標ぼうしている90診療所を選択した。2010年10月に調査票を送付した。質問票の作成にあたり，2010年8月に米子市において2人の検診施行医に対して予備的なインタビュー調査を行い，内視鏡検診プログラムへの参加に影響を与える可能性がある要素の探索を行った。診療所でのがん検診の供給は通常の外来診療に追加して行わるため，診療所の人的資源の状況（医師数，看護師数，事務員数など）が重要であると考えられた。また，検診プログラム開始前の胃内視鏡に対する経験，医師の年齢，出身医局，消化器科標ぼうといった医師の特性も重要であると考えられた。

質問票には上記の項目に加え，外来患者数など診療状況に関する質問も加えた。被説明変数である内視鏡胃がん検診プログラムへの参加の有無については，鳥取県西部医師会より情報提供を受けた。

これら調査の実施に際して，国立がん研究センター倫理委員会の承認（承認番号19-30）を受けた。統計分析においては，記述統計量の差の検定についてはt検定とウィルコクスンの順位和検定を用い，探索的な影響要因の確認においては参加と不参加を被説明変数とするロジスティック回帰分析を実施した。そして，これらの分析には統計解析ソフトウェアのR（Ver.3.0.2）を用いた。

Ⅲ 結　果

サンプルの記述統計量は，表1にまとめられている。最終的な回収数は56施設となった（回答率62.2%）。医師数が1人という診療所がほとんどであるが（平均値1.60人，中央値1人），

実際には5人以上の医師を持つ病院もサンプルに含まれている。看護師数については0人というサンプルから28人というサンプルまで，十分に分散を有している（平均値4.23人，中央値3人）。また，事務職員数は平均2.70人，中央値2.5人となった。院長の平均年齢は61.8歳，診療所における1週間の外来患者数の平均値は267.8人となった。

また，サンプルの85.7%が鳥取大学医局出身で，33.4%が消化器科を標ぼうしており，80.0%が開業前に胃内視鏡の経験を有していた。そして，診療所の継承予定があると答えたサンプルは25.9%であった。なお，鳥取大学医局のうち，鳥取大学消化器内科（第二内科）医局出身者は，28.6%を占めていた。

表1　分析対象診療所の記述統計量

	平均値	標準偏差	最小値	第1四分位	中央値	第3四分位	最大値
医師数（人）	1.60	1.64	1	1	1	1	11
うち，常勤医師数（人）	1.36	1.00	1	1	1	1	6
看護師数（人）	4.23	5.32	0	2	3	4	28
うち，常勤看護師数（人）	3.23	4.26	0	1	2	3	23
事務職員数（人）	2.70	1.50	0	2	2.5	3	10
うち，常勤事務員数（人）	2.23	1.36	0	1	2	3	8
開院年（西暦）	1980	18.4	1931	1965	1979	1996	2006
院長就任年（西暦）	1989	15.4	1946	1978	1992	2002	2010
院長年齢（歳）	61.8	11.6	40	53.75	60	73	85
院長医学部卒業年（西暦）	1974	12.2	1949	1962	1976	1983	1995
1週間外来者数（人）	267.8	162.0	18	182	238	324	834
午前の外来者数平均（人）	32.8	22.1	2.5	21.7	27.0	41.5	119.1
午後の外来者数平均（人）	17.5	12.4	10.1	10.1	15.8	22.7	69.6
米子市胃がん検診参加先（%）	69.6						
鳥取大学医局出身の院長（%）	85.7						
鳥取大学消化器内科(第二内科)医局出身の院長（%）	28.6						
消化器科を標ぼう（%）	33.4						
開業前の胃内視鏡の経験（%）	80.0						
診療所の継承予定有（%）	25.9						

表2　参加・不参加診療所ごとの記述統計量

	参加先平均値	不参加先平均値	t検定（t）	ウィルコクスンの順位和検定（W）
医師数（人）	1.71	1.35	0.86	270
うち，常勤医師数（人）	1.44	1.18	0.89	256*
看護師数（人）	4.33	4.00	0.20	260
うち，常勤看護師数(人)	3.46	2.71	0.52	194**
事務職員数（人）	2.79	2.47	0.58	235*
うち，常勤事務員数(人)	2.36	1.94	0.88	228*
開院年（西暦）	1981	1977	0.67	305
院長就任年（西暦）	1992	1982	2.43**	190**
院長年齢（歳）	57.9	70.8	4.27***	538***
院長医学部卒業年（西暦）	1978	1962	4.28***	114***
1週間外来者数（人）	283.8	227.5	0.95	199*
午前の外来者数平均（人）	34.2	29.4	0.55	192*
午後の外来者数平均（人）	19.4	11.9	2.46**	130*

注　$*p<0.1$，$**p<0.05$，$***p<0.01$

	参加先平均値（%）	不参加先平均値（%）	フィッシャーの正確確率検定（オッズ比）
鳥取大学医局出身の院長	82.0	94.1	0.291
鳥取大学消化器内科(第二内科)医局出身の院長	33.3	17.6	2.301
消化器科を標ぼう	41.0	17.7	3.183
開業前の胃内視鏡の経験有	97.4	41.2	47.436***
診療所の継承予定有	0.263	0.250	1.070

注　$*p<0.1$，$**p<0.05$，$***p<0.01$

表2は，胃がん検診プログラムに参加している診療所（以下，参加先），参加していない診療所（以下，不参加先）の両者の統計量を比較したものである。数量データについては差の検定を，（t検定およびウィルコクスンの順位和検定），比率データについては独立性についてのフィッシャーの正確確率検定を実施した。主たる結果は次の6点である。1点目は，医師数，看護師数などの人的資源の量はプログラムへの参加における要因である可能性が低いということである。2点目として，院長が若いほどプログラムへ参加しているということである。さらに，年齢と高い相関を持つ院長就任年や医学部卒業年も同様の結果にあることがみてとれる。3点目は，外来者数，特に午後における外来者が多い診療所はプログラムへ参加している割合が高いということである。これは参加したために外来者数が増加したという可能性も含んでいるため，解釈には注意が必要となる。4点目は，鳥取大学消化器内科（第二内科）医局出身であったり，消化器科を標ぼうしていたりしても，必ずしもプログラムへ参加しているとはいい切れないことである。しかし

ながら，5点目として，胃内視鏡の経験とプログラムへの参加には有意な関連が存在することが示された。なお，開業前に胃内視鏡の経験はないがプログラムに参加している診療所が1つ存在し，これは経験がない病院・診療所の9.1%となる。また，経験がある場合でも，そのうち15.9%の診療所はプログラムに参加していなかった。6点目として，診療所の継承予定は両者の間でそれほど変わらない点が示された。

表2における差や比率の検定を繰り返す場合，変数間の影響をコントロール出来ていないという問題がある。そこで，プログラムに参加している場合は1をとるダミー変数を被説明変数としたロジスティック回帰分析を実施した。結果は表3のとおりである。ただし，回帰分析であるために，変数間に強い相関がある場合は，多重共線性の問題が起きてしまう。そのため，院長年齢と相関の強い院長就任年などの変数は分析から除外している。同様に，鳥取大学医局出身ダミー変数，外来患者数（午前），外来患者数（午後）などの変数も除外している。さらに，開業前の胃内視鏡の経験という変数も，経験がなければ参加しないという結果をほぼ予測してしまうため分析から除外している。少数サンプルであり，探索的な分析であるという本研究の特徴を考慮して，10%の有意水準を基準として結果の解釈を行うと次の3点が明らかになった。

1点目として，院長年齢が若いことが参加の決定において重要な役割を果たしている可能性である。オッズ比から，1歳年齢が上昇すると参加の確率が0.84倍になることが読み取れる。2点目として，鳥取大学消化器内科（第二内科）医局出身であるかどうかも有意な変数であり，オッズ比は7.98と高い値を示した。3点目として，診療所の継承予定がある場合，オッズ比は6.95とやはり高い値となった。なお，表4はAIC（赤池情報量基準）を用いたステップワイズな変数選択を行った上でのロジスティック回帰分析の結果である。変数選択を行った上でも表3の結果と基本的には大差ないため，これらの結果は頑健であるといえる。

表3　参加選択のロジスティック回帰分析（n=54）

	係数	オッズ比	z値
（定数項）	10.473	-	2.08**
医師数（人）	1.264	3.54	0.93
看護師数（人）	-0.021	0.98	-0.08
事務職員数（人）	-0.446	0.64	-0.54
院長年齢（歳）	-0.173	0.84	-2.76***
1週間外来者数（人）	-0.000	0.99	-0.13
鳥取大学消化器内科（第二内科）医局出身の院長（出身ならば1をとるダミー変数）	2.077	7.98	1.70*
消化器科を標ぼう（標ぼうならば1をとるダミー変数）	0.818	2.27	0.79
診療所の継承予定有（予定があれば1をとるダミー変数）	1.939	6.95	1.67*
AIC（赤池情報量基準）		52.90	
McFadden's Pseudo R^2		0.447	

注　1）$*p<0.1$，$**p<0.05$，$***p<0.01$
　　2）被説明変数は，参加先ならば1をとるダミー変数。

表4　参加選択のロジスティック回帰分析（AICによるステップワイズ後）（n=54）

	係数	オッズ比	z値
（定数項）	8.08	-	2.41**
医師数（人）	1.19	3.27	0.99
院長年齢（歳）	-0.15	0.86	-3.07***
鳥取大学消化器内科（第二内科）医局出身の院長（出身ならば1をとるダミー変数）	1.97	7.18	1.72*
診療所の継承予定有（予定があれば1をとるダミー変数）	2.06	7.87	1.78*
AIC（赤池情報量基準）		46.08	
McFadden's Pseudo R^2		0.429	

注　1）$*p<0.1$，$**p<0.05$，$***p<0.01$
　　2）被説明変数は，参加先ならば1をとるダミー変数。

Ⅳ 考　察

本稿では，自治体の内視鏡胃がん検診プログラムに参加するかどうかの意思決定に与える影響を分析するために，10年以上にわたり継続しているプログラムのある鳥取県米子市の診療所に対して郵送自記式の質問紙調査を行った。

少数サンプルの分析となったため，差・比率検定に追加してロジスティック回帰分析を行うなど，頑健な結果を得るために複数の統計解析を実施した。また，56施設という比較的少数のサンプルサイズに基づいて議論を行うため，これらサンプルが母集

団を適切に代表しているのかは慎重になる必要があるだろう。そこで，表5にまとめられているとおり，無回答バイアスの影響を確認するために検診プログラムへの参加の有無，消化器科の標ぼうの有無で回答率に差がないのかを検証した。本調査は内視鏡胃がん検診の調査であるために，この調査結果に対する関心の差から回答率に影響が出た場合，結果の内的妥当性に疑義が生じかねない。しかしながら，委託の有無と標ぼうの有無のいずれにおいても有意な回答率の差は確認されなかったため，本研究では無回答バイアスは存在しないものと判断できる。

表5　回答の状況

	全体サンプル	米子市内視鏡胃がん検診プログラムへの参加先サンプル		「消化器科」を標ぼうしているサンプル	
		参加先	不参加先	標ぼう	標ぼうせず
送付数(施設)	90	55	35	28	62
回答数(〃)	56	39	17	19	37
回答率(%)	62.2	70.9	48.6	67.9	59.7

注　参加先・不参加先からの回答率は，参加先のほうがやや多いが，これは統計的に有意であるほど大きな差とはいえなかった（一様性検定：カイ二乗値＝1.72，$p=0.19$）。そして，「消化器科」の標ぼう別についても同様に，回答率に有意な差はなかった（一様性検定：カイ二乗値＝0.21，$p=0.65$）。

本研究の主要な結果は次の3点である。1点目は，参加の意思決定においては人的資源の量的な制約は限定的であるという点である。特に医師・看護師不足が指摘されている地域においても検診プログラムを実施する時に人的資源の量が障害にならないことを示唆している。しかし，実際に内視鏡検診プログラムに参加している診療所で検診のタイムスタディを行ったところ，準備・介助・片付けに関与する看護師の時間資源が重要であることが指摘されている[8]。検診プログラム参加後に内視鏡検査が増加した場合，特に看護師への労働負担が高まる可能性がある。

2点目は，医師の質的特性の影響である。例えば，院長の過去の内視鏡医経験とプログラムへの参加には強い関連がある。特に，経験がない場合は9.1%の診療所がプログラムに参加するのみとなり，明らかに最も影響力のある変数であったといえる。とはいえ，経験がある場合でも15.6%の病院・診療所は参加を見送っており，その理由を明らかにするためにも他の変数の影響の探究にも意義があるといえるだろう。実際に，院長の年齢は一貫して影響力を有していた変数である。さらに，地元の大学の消化器内科を専門とする医局の出身であることが参加に有意な影響を与えることも，ロジスティック回帰分析では明らかにされている。このような過去の経験や出身医局，あるいは年齢といった医師の特性は，技術の習得上有利な条件であるといえる。米子市では，歴史的に精度管理やプログラム内容の整備について鳥取大学消化器内科（第二内科）出身の診療所医師や病院医師が中心となり医師会などを通じて協働で行っている。結果として，出身医局が同じであることが，より適切な検診の実施に影響すると医師に自覚させ，プログラムへの参加に影響するものと考えられる。加えて，出身医局が違う医師に対しては，医師会などが検診プログラムの詳細と，精度管理などのサポート体制について十分な情報提供を行うことが，プログラム参加者を広げることに重要であろう[3]。

3点目として，診療所の存続可能性が影響するという事実である。例えば，先ほども指摘した年齢は，技術習得における有利性という面だけでなく，診療所の維持にも影響する変数である。診療所の存続可能性が高い場合，検診プログラムへの参加など新しい試みに参加する，または参加するための投資を行うことが促される。今回の質問票では，継承予定者が家族であるかどうかは聞いていないが，非家族も含めた診療所のスムーズな継承が地域の予防医療供給体制の持続可能性にも影響を与えることが示唆される。

本稿では，10年以上にわたり公的な補助を伴う内視鏡胃がん検診プログラムを行っている一つの自治体で調査を行った。結果として特定の大学医局の影響といった地域特性に左右される変数の重要性が指摘された。今後も他地域における同様の調査を行う必要があろう。

V 結　　語

本研究は，内視鏡胃がん検診プログラムへの参加要因を探索的に調査した。結果として，量的な人的資源の影響よりも，院長の質的な特性や，診療所の存続可能性が影響する可能性が示された。今後，同種の検診を普及させようと試みる場合，量的な支援ではなく，医師への技術的な支援体制を構築することが効果的であるといえる。また，地域が高齢化などの問題に直面しているため存続可能性がそれほど高くない診療所が多い場合，プログラムの普及には困難が伴うことも想定される。

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Prediction of Gastric Cancer Development by Serum Pepsinogen Test and *Helicobacter pylori* Seropositivity in Eastern Asians: A Systematic Review and Meta-Analysis

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Abstract

Background: To identify high-risk groups for gastric cancer in presumptively healthy populations, several studies have investigated the predictive ability of the pepsinogen test, *H. Pylori* antibodies, and a risk-prediction model based on these two tests. To investigate whether these tests accurately predict gastric cancer development, we conducted a systematic review and meta-analysis.

Methods: PubMed and other electronic databases were searched for cohort studies published in English or Japanese from January 1985 through December 2013. Six reviewers identified eligible studies, and at least two investigators extracted data on population and study-design characteristics, quality items, and outcomes of interest. Meta-analyses were performed on non-overlapping studies.

Results: Nine prospective cohorts from Eastern Asia reported in 12 publications, including 33,741 asymptomatic middle-aged participants of gastric cancer screening, were eligible. For discriminating between asymptomatic adults at high and low risk of gastric cancer, the pepsinogen test (summary hazard ratio [HR], 3.5; 95% confidence interval [CI], 2.7–4.7; $I^2 = 0\%$) and *H. pylori* antibodies (summary HR, 3.2; 95% CI, 2.0–5.2; $I^2 = 0\%$) were statistically significant predictors as standalone tests. Although the risk-prediction model was in general moderately accurate in separating asymptomatic adults into four risk groups (summary *c*-statistic, 0.71; 95% CI: 0.68–0.73; $I^2 = 7\%$), calibration seemed to be poor. The study validity was generally limited.

Conclusions: The serum pepsinogen test, *H. pylori* antibodies, and the four-risk-group model for predicting gastric cancer development seem to have the potential to stratify middle-aged presumptively healthy adults. Future research needs to focus on comparative studies to evaluate the impact of screening programs adopting these tests. Also, validation, preferably with model updating, is necessary to see whether the current model performance is transferable to different populations.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files except for the exact search strategies for the original health technology assessment, which are described in detail in Ref #3. The pertinent data (the interim results of a health technology assessment conducted by the literature review committee for the Japanese Guidelines for Gastric Cancer Screening) has already been published online as Draft, the Japanese Guidelines for Gastric Cancer Screening 2013, available at http://canscreen.ncc.go.jp.

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Introduction

Gastric cancer is the fourth most common cause of cancer death worldwide [1], and is the most prevalent cancer in Eastern Asia [2]. Because high cure rates can be expected for early stages of gastric cancer, and non-randomized evidence suggests that radiographic screening can decrease gastric-cancer-specific mortality [3], several Asian countries have initiated cancer-screening programs using upper gastrointestinal tract photofluorography or gastric endoscopy [4]. However, recent nationwide gastric cancer screening rates for the general population in Japan have been unsatisfactorily low [5]; therefore, a major current focus is on developing a risk-stratified screening program by efficiently identifying high-risk populations.

Infection with *Helicobacter pylori* and its associated chronic atrophic gastritis (CAG) are two major risk factors for gastric cancer [6,7]. In addition to several candidate oncogenic mechanisms [7,8], epidemiologic studies [9–12], have shown the associations between these factors and gastric cancer. To predict gastric cancer development in healthy populations, several cohort studies have assessed the serum pepsinogen test and *H. pylori* seropositivity, respectively, as surrogate markers for CAG and *H. pylori* infection, and a risk-prediction model based on the two tests. However, these studies have small sample sizes and use heterogeneous designs, making it difficult to interpret the published data. Also, those studies that have assessed the prediction model typically focus on relative risk estimates and fail to assess the performance of the model [13]. Therefore, we performed a systematic review to provide a comprehensive summary of the predictive ability of these tests in presumptively healthy adults. We also aimed to quantitatively explore the calibration and discrimination of the prediction model based on the reported data.

Materials and Methods

This work is an updated, in-depth systematic review and meta-analysis based on a broad health technology assessment conducted by the literature review committee for the Japanese Guidelines for Gastric Cancer Screening [3], using a set of standardized systematic review methods [14] and following a prespecified protocol. There is no specific protocol for this focused, updated review. The aim of the health technology assessment was twofold: in an asymptomatic healthy population, to evaluate the existing evidence on benefits and harms of conventional screening strategies using photofluorography or gastrointestinal endoscopy, and to evaluate "risk-stratified" screening strategies incorporating the serum pepsinogen test, *H. pylori* antibodies, or a risk-prediction model based on the two tests as the primary screening modality before performing photofluorography or endoscopy. In this paper, we focus on the predictive ability of the serum pepsinogen test, *H. pylori* serology, and the prediction model to predict gastric cancer development in asymptomatic populations.

Literature search

We searched PubMed, Web of Science, Cochrane Central, and the Japanese Medical Research Database (Igaku-Chuo-Zasshi) using search terms like "stomach neoplasms", "gastric cancer", "endoscopy", "*Helicobacter pylori*", "pepsinogens", "atrophy", "diagnosis", "mass screening" and their synonyms. The searches were limited to English- or Japanese-language publications, and citations from Jan 1 1985 to July 10 2013. The exact search strategy is reported in the guidelines [3]. The search was updated to December 31 2013 to include only studies assessing the serum pepsinogen test and/or *H. pylori* serology. The updated search was then supplemented by examining the title and abstract of all articles that cited at least one of the already included publications found through the citation-tracking function of the ISI Web of Knowledge database, Scopus, and Google Scholar. We also perused the reference list of eligible studies and relevant review articles, and consulted with experts in gastric cancer screening.

Study eligibility

Six reviewers in three pairs independently screened non-overlapping sets of abstracts and independently examined the full text of each potentially eligible study. Studies that assessed the serum pepsinogen test and/or *H. pylori* seropositivity at enrollment as predictors of gastric cancer development in asymptomatic participants of gastric cancer screening programs were considered eligible. We included both prospective cohort studies and retrospective analyses of prospective cohorts of any sample size that followed up all participants. We did not prespecify a minimum follow-up period, how the studies followed up participants, or how they verified gastric cancer development. We accepted studies regardless of whether they included or excluded participants with gastric cancer diagnosed at enrollment or shortly after positive screening results for pepsinogen test and/or *H. pylori* antibodies (endoscopy and biopsy were typically performed). We excluded case-control studies and nested case-control or case-cohort studies. We also excluded studies that assessed the detection rates of gastric cancer based on the pepsinogen test and/or *H. pylori* antibodies without follow-up. Discrepancies regarding inclusion were resolved by consensus between the assessors including a third reviewer.

We took particular care to identify publications with at least partially overlapping populations by comparing authors, centers, recruitment periods, and patient demographic characteristics. In the case of multiple publications from one study, we included only the publication with the longest follow-up.

Table 1. Gastric cancer risk groups defined by the pepsinogen test and *H. pylori* antibody.

Pepsinogen test	*Negative*	*Negative*	*Positive*	*Positive*
H. pylori **serology**	**Negative**	**Positive**	**Positive**	**Negative**
4-risk group model[a]	Group A	Group B	Group C	Group D
3-risk group model[b]	Group A	Group B	Group C + Group D	

[a]The original model adopted in the primary studies.
[b]An alternative model used in our *post-hoc* sensitivity analysis.
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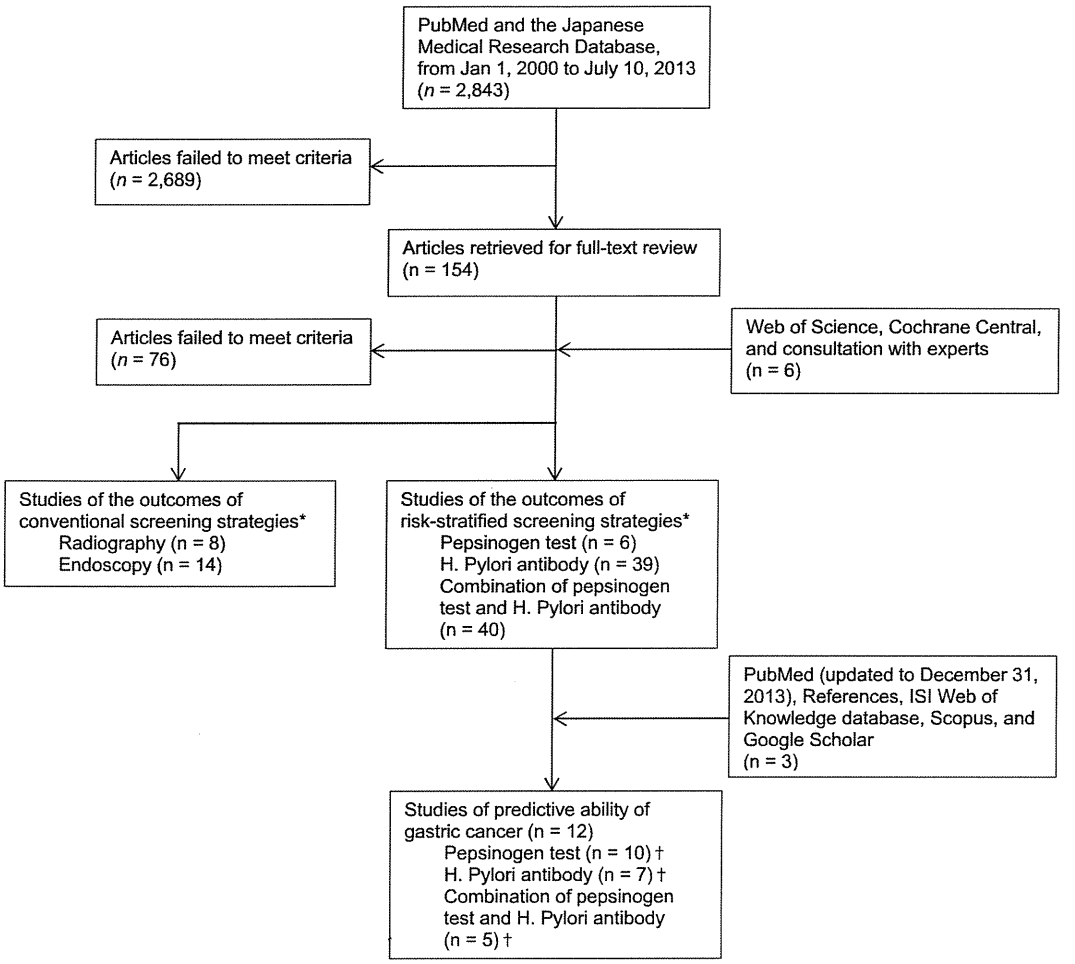

Figure 1. Study flow diagram. *, † These studies are not necessarily mutually exclusive; some met more than two research questions in the original health technology assessment.
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Data extraction

One reviewer extracted descriptive data from each eligible paper, which were confirmed by at least one other reviewer. We extracted the following information: first author, year of publication, study location, study design and setting, inclusion and exclusion criteria, baseline participant demographic characteristics, follow-up period, methods used to ascertain gastric cancer development, and technical specification of the pepsinogen test and *H. pylori* antibodies. We also recorded the reported performance of each test for diagnosing respective target clinical conditions and their reference standard, if any, in the literature (i.e., CAG by pepsinogen test and *H. pylori* infection status by seropositivity).

One reviewer extracted numerical data regarding test results and gastric cancer development from each study, which were confirmed by at least one other reviewer. Specifically, for each risk group defined we recorded the cumulative number of gastric cancer cases identified through follow-up, the total number at risk, and the hazard ratio (HR) estimates from the full statistical model that adjusted for the largest number of potential confounders. Two out of 150 (1%) extractions by the second reviewer for the numerical data were inconsistent.

Any disagreements were resolved by consensus. A third investigator adjudicated any unresolved discrepancies. We contacted by email authors of studies for additional information when it was not possible to extract numerical data from the publication.

Quality assessment

We abstracted information on aspects of the design and conduct of individual studies using a checklist specifically designed for assessing studies of prognostic tests [15]. Items included study design, selection of study participants, description of tested population, inclusion and exclusion criteria, start point of follow-up, description of test characteristics (assay methods and blinding of test assessors to clinical outcomes and *vice versa*), description of ascertainment of gastric cancer development, follow-up period, and methods of data analysis (internal and external validation, and whether appropriate statistical analyses including multivariable adjustment taking account of other established risk factors had been performed). We then judged the risk of bias for studies that assessed the pepsinogen test or *H. pylori* antibodies as a standalone test, using the Quality In Prognosis Studies (QUIPS-2) [16], and rated the risk of bias and concerns about applicability for studies of a risk-prediction model based on the two tests, using the Prediction