89180_Auto_Edited.docx

Name of Journal: *World Journal of Clinical Oncology*

Manuscript NO: 89180

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Population-based X-ray gastric cancer screening in Hiroshima Prefecture: trends of the last four decades and the future challenges

X-ray gastric cancer screening in Japan

Nhu Thi Hanh Vu, Yuji Urabe, Duc Trong Quach, Shiro Oka, Toru Hiyama

Abstract

BACKGROUND

X-ray gastric cancer (GC) screening has been shown to decrease mortality.

AIM

This study evaluated the time trends and the efficacy of population-based X-ray GC screening in Hiroshima Prefecture, Japan, for the last 39 years, from 1983 to 2021, and identified the challenges and suggested solutions for the future.

METHODS

This is a *population*-based *retrospective study*. The data was derived from aggregated data of the Hiroshima Regional Health Medical Promotion Organization, including the number and rate of participants and those esophagogastroduodenoscopies (EGDs) were required, the number and rate of participants diagnosed with GC, and the positive predictive value of the abnormal findings detected by X-ray and confirmed by EGDs. The number and rate of esophageal cancer were also collected. Further, the cost of detecting one GC was evaluated.

RESULTS

The number of participants has decreased during the last four decades, from 39,925 in 1983 to 12,923 in 2021. The rate of those EGDs required decreased significantly in recent years. The number of participants diagnosed with GC has also declined, from 76 to 10 cases. However, the rate of cases diagnosed as GC among the participants remained around 0.1%. The positive predictive value increased significantly in recent years except for the first period. The number and rate of accidentally detected esophageal cancers have risen recently, from 0% in 2008 to 0.02% in 2021, one-fifth of the diagnosis rate of GC. One GC diagnosis cost approximately 4,200,000 JPY (30,000 USD) for the X-ray screenings and EGDs.

CONCLUSION
X-ray GC screening in Hiroshima has been efficient. One of the challenges is the cost. Esophageal cancers may also be considered.

Key Words: Population; Retrospective Studies; X-ray; Gastric Cancer; Screening

Vu NTH, Urabe Y, Quach DT, Oka S, Hiyama T. Population-based X-ray gastric cancer screening in Hiroshima Prefecture: trends of the last four decades and the future challenges. *World J Clin Oncol* 2023; In press

Core Tip: This is a *population*-based *retrospective study* to evaluate the time trends and the efficacy of population-based X-ray gastric cancer screening in Hiroshima for the last four decades. The number of participants and those EGDs required has decreased significantly. The number of participants diagnosed with gastric cancer has also declined. However, the rate of cases diagnosed as gastric cancer among the participants remained around 0.1%. The positive predictive value also increased significantly. The number and rate of accidentally detected esophageal cancers have risen recently. One gastric cancer diagnosis cost approximately 4,200,000 JPY (30,000 USD) for the X-ray screenings and EGDs.

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide, with the fourth highest mortality rate [1]. Notably, the survival rate for GC has improved globally over the years due to advancements in both diagnosis and treatment [2, 3]. In Japan, there has also been a decline in the adjusted incidence and mortality rates of GC over the last few decades [4]. *Helicobacter pylori* (*H. pylori*) infection is considered the leading cause of GC [5]. Therefore, this decrease in GC is mainly attributed to reducing *H. pylori* infection rates due to hygiene improvement and the efficacy of the *H. pylori* eradication therapy [6, 7]. Despite this reduction, GC still has the third-highest incidence and mortality rates in

Japan [8]. Consequently, the burden of GC remains substantial and makes it a critical public health issue.

In addition to the *H. pylori* eradication regimen, it is crucial to implement the GC screening program to lower GC mortality. In East Asian countries, only Japan and Korea have a national program for GC screening [9]. GC screening has extensively contributed to declining GC mortality in both countries [10, 11].

In Japan, GC screening has been conducted in local areas for a long time since the 1960s. Until 1983, it has expanded nationwide in accordance with the Health Law for the Aged [12]. Cancer screening in Japan can be categorized into population-based screening, which attempts to reduce overall mortality rates in target populations, and opportunistic screening, which aims to minimize individual risk. Effective population-based screening is a cornerstone of cancer control in Japan.

Although there are complications such as intestinal obstruction due to barium, aspiration pneumonia, and anaphylactic shock, radiographic screening has been the main approach for GC screening in Japan. Currently, the government of Japan has suggested either radiography or endoscopy examination for GC screening [12]. The updated version of the Japanese Guidelines for GC Screening in 2018 recommended radiographic screening for population-based and opportunistic screenings since its advantages outweigh its risks. Endoscopic screening is also recommended for population-based and opportunistic screenings because its benefits outweigh its harms. Although endoscopic screening detected more cases of GC than radiographic screening, there was a report that the reduction in GC mortality was not significantly different between the two screening methods [13]. GC screening using radiographic examination has been shown to be safe, cost-effective, accurate, and has a remarkable capacity for mass processing [14]. Besides, the GC risk stratification method, named ABC method, using *H. pylori* antibody and pepsinogen I and II, has been applied in some areas in Japan (15).

Hiroshima Prefecture is located in the southwestern part of Japan's main island of Honshu and the center of the Chugoku region, with a total land area of 8,480 km^2 and a population of 2.8 million people [15]. Hiroshima Regional Health Medical Promotion Organization is in charge of GC screening in Hiroshima Prefecture. The radiographic screening has been chosen for population-based GC screening in Hiroshima Prefecture. The ABC method has not been applied in the Prefecture. It is essential to assess the trends of X-ray GC screening from the past and investigate future perspectives. Hence, this study aims to evaluate the trends and the efficacy of population-based X-ray GC screening in Hiroshima Prefecture for the last 39 years, from 1983 to 2021. This can lead to identifying the challenges and developing future solutions.

MATERIALS AND METHODS

This is a *population*-based *retrospective study*. Hiyama T, Vu NTH contributed to the study's conception, design, and execution of the research. The data was derived from the aggregated data of the Hiroshima Regional Health Medical Promotion Organization, Hiroshima, Japan. Vu NTH, Hiyama T, and Urabe Y conducted data collection and curation with the staff in this institution. Data obtained from this organization may represent the majority of residents living in Hiroshima Prefecture. In Hiroshima Prefecture, residents aged 40 years and older were qualified to participate in an annual population-based X-ray GC screening. Each year, the coupons were issued to eligible residents by the health center of each local city and town in Hiroshima Prefecture. Even if residents were under 40, they could take the screening if they desired.

High-resolution, double-contrast agents for the upper gastrointestinal tract were utilized for the X-ray examination in Hiroshima Prefecture. Consequently, the capability of gastric radiography examination to detect lesions has been significantly enhanced. The citizens were ineligible for barium X-ray screening if they had one or more of the following conditions: past medical history of total gastrectomy, hypersensitive to barium sulfate products, pregnant (or possibly pregnant) women. Radiographic examination was performed using the standard imaging method (8-image method). The screening report has been double-reading (double-checked) by two radiologists on two separate occasions.

We collected the number of participants who underwent X-ray GC screening during the last 39 years, from 1983 to 2021, and examined the age distribution of participants from 2002 to 2021. Participants with a suspicious X-ray abnormality (cancers or other gastric lesions such as ulcers) were recommended detailed examination with esophagogastroduodenoscopy (EGD). We also gathered the number of participants and the rate for those EGD required during the study period. Participants who were ineligible to take X-ray gastric screening were not included in those for whom EGDs were required. Moreover, the number, the rate of participants diagnosed with GC, and the invasion depth of each cancer were recorded. The invasion depth of each cancer was divided into two: early stage, *i.e.*, invasion depth is the lamina propria or the submucosa, and advanced stage, *i.e.*, invasion depth is the muscularis propria or deeper. We derived the positive predictive value detected by X-ray and confirmed by EGDs. We also obtained data about the number, clinical stages (early or advanced), and the rate of esophageal cancer detected in the screening from 2008 to 2021. Additionally, reported complications of X-ray GC screenings from 2007 to 2021 were evaluated.

To examine the time trend of each rate, the 39 years were divided into four periods: first nine years (1983-1991), second ten years (1992-2001), third ten years (2002-2011), and fourth years (2012-2021). Each rate was compared among the four periods.

One case of X-ray GC screening in Hiroshima Prefecture costs approximately 3,000 JPY (21 USD). The patient will pay 30% of the total cost, with the remaining covered by the government. One case of EGD costs approximately 15,000 JPY (110 USD). The cost of detecting one GC was calculated based on the detection rate of GC.

Hiyama T, Vu NTH, Oka S, Quach DT, and Urabe Y performed data analysis. The collected data were organized in an Excel spreadsheet (Microsoft *et al*, USA). All statistical analyses were performed using MedCalc® Statistical Software version 19.6.1 (MedCalc Software Ltd, Ostend, Belgium). Categorical variables are presented as numbers and percentages. The difference between the two proportions was compared with the chi-squared test. A p-value of less than 0.05 was considered statistically significant. A Bonferroni correction (a p-value of less than 0.0083) was used to compare each rate among the four periods. During the study period, Oka S, Hiyama T, and Quach DT provided supervision and ensured the overall integrity of the research. NTH drafted the initial manuscript; Hiyama T, Quach DT, Urabe Y, and Oka S reviewed and edited the manuscript.

Ethical approval was obtained from the Ethical Committee of Hiroshima University (ethical number: E2023-0018) for this study.

RESULTS

Figure 1 shows annual trends in the number of Hiroshima Prefecture residents participating in population-based X-ray GC screening. In 1983, there were 39,925 participants in the screening. This number gradually increased to 55,406 people in 1991. After that, there was a decrease in the number of participants. There were 12,923 participants remaining until 2021. During the period between 2015 and 2020, the rate of the eligible population in Hiroshima Prefecture taking part in GC screening ranged from 5.3% to 7.3%, which was average compared to other prefectures in Japan [16, 17].

Figure 2 indicates the age distribution of the participants from 2002 and 2021. The rate of participants less than 50 among all participants was 20.6% in 2002. The rate gradually increased over the years to 30.0% in 2021.

During the ten years between 1983 and 1992, the number of screening participants who required detailed examination by subsequent EGD ranged from 6,000 to 9,000. After 1992, this number also declined annually. From 2012 to 2021, only 500 to 1,500 participants needed EGDs (**Figure 3**). The rate of participants who required EGDs also decreased significantly in recent years ($p < 0.001$, first period: 13.0%, second: 12.0%, third: 10.4, and fourth: 5.1%).

The number of participants with a confirmed diagnosis of GC also dropped over the last 39 years. In 1993, 76 cases of GC were the most ever recorded. Until 2020 and 2021, the number of participants diagnosed with GC was only 10 (**Figure 4**). On the other hand, the rate of cases diagnosed as GC remained around 0.1% during the study period, with no significant differences among the four periods.

The rates of early-stage GC among all the GC detected in the screening from 1994 to 2021 are shown in **Figure 5**. This rate remained around 55% during the research period.

Figure 6 illustrates a gradual increase in the positive predictive value of the GC screening program, from 0.8% in 1983 to 2-3% over the last five years. The positive predictive value increased significantly in recent years except for the first period ($p < 0.001$, first period: 0.8%, second: 0.8%, third: 1.3%, and fourth 2.5%). **Figure 7** demonstrates an example of GC detected during the screening program.

The number and rate of esophageal cancer among the participants in GC screening also raised steadily from 2008 to 2021. In 2008, the diagnosis rate was 0% (0 cases); this rate grew to 0.02%, one-fifth of the diagnosis rate of GC, between 2017 and 2021 (3-4 cases/year). During the observation period, a total of 28 esophageal cancers were detected. Among them, 9 (32%) were in the early stages, 17 (61%) were in advanced stages, and the remaining 2 (7%) were in unknown clinical stages. The rate of early-stage esophageal cancers among all the esophageal cancers fluctuated, and no consistent trend was observed during the period due to the limited number of patients per year (data not shown).

As for complications of X-ray GC screenings from 2007 to 2021, a total of 9 cases were reported: 4 cases with intestinal obstruction due to barium, 2 cases with barium aspiration, 2 cases with rib fracture due to compression, and 1 case of barium reflux into the common bile duct. The complication rate was 0.003% among 335,873 applicants who took X-ray GC screenings during the period.

The detection rate of GC was approximately 0.1%. In other words, to detect one GC, approximately 1,000 gastric X-ray screening was needed. Regarding the cost aspect, detecting one GC cost approximately 3,000,000 JPY (21,400 USD) for gastric X-ray screenings (approximately 3,000 JPY (21.4 USD)/X-ray screening). The cost of EGDs should be considered. Approximately 8% of the applicants required EGDs; thus, 80 EGDs were needed to detect one GC. The cost of 80 EGDs was approximately 1,200,000

JPY (8,600 USD) (approximately 15,000 JPY (107 USD)/EGD). The total cost of one GC diagnosis using X-ray screenings and EGDs was approximately 4,200,000 JPY (30,000 USD).

DISCUSSION

GC development is an interactive, multistep, and multifactor process [18, 19]. A variety of factors influence the development of GC. Previous research demonstrated that more than 90% of GC cases in Japan have been associated with *Helicobacter pylori* infection [20]. Other factors, including family history, diet, lifestyle choices, genetics, socioeconomic status, and other environmental factors, also contribute to the formation of GC [21]. The development of GC is a gradual process, including the formation of precancerous lesions. This involves sequential histopathological changes in the gastric mucosa, with atrophic gastritis and the loss of the parietal cell mass, followed by intestinal metaplasia, dysplasia, and, ultimately, carcinoma [22]. The primary prevention strategies for GC include the intervention of GC etiology by improving dietary habits and reducing the incidence of *H. pylori* infection. Consuming more fresh fruit and vegetables and limiting salt and salt-preserved foods may reduce the risk of GC. Further, lifestyle modifications, such as increasing physical activity and restricting smoking, may also decrease the risk of GC [21]. Secondary prevention efforts should focus on early detection and treatment of GC.

There is a considerable regional variation in GC mortality and incidence, with Eastern Asia and Eastern Europe having the highest age-standardized incidence rates [23]. GC screening was initiated in countries with a high prevalence of GC, such as Japan and Korea [24]. The implementation of GC screening in Asia increased the diagnosis of early GC, reduced mortality, and improved 5-year survival [11] [25]. Previous studies have also indicated a reduced risk of GC mortality in patients undergoing X-ray GC screening [14] [26]. In a population-based X-ray GC screening study, with a 13-year follow-up in Japan., Lee *et al* concluded that the screened participants had a 48% reduced risk of mortality from GC compared to the unscreened participants [27]. Additionally, X-ray GC screening has been shown to be equally effective as endoscopic screening in reducing GC mortality [13] [28].

This study indicated that, although the number of participants in population-based X-ray GC screening in Hiroshima Prefecture had fallen during the last 39 years, the screening program has still been efficient. Our findings were consistent with the fiscal 2015-2018 nationwide aggregate surveys of the Japanese Society of Gastrointestinal Cancer Screening. The rate of GC in these surveys ranged from 0.13 to 0.16% [16].

The downtrend of participants may be due to the fact that the residents have had the option to participate in GC screening programs at private facilities rather than those offered by the Hiroshima Regional Health Medical Promotion Organization. Additionally, endoscopic GC screening has become widespread recently. Another reason was that the incidence and mortality from GC in Japan also reduced annually. As a result, residents' awareness of GC also decreased, leading them to believe that attending the screening may be unnecessary. This downtrend may also be attributable to the annual decline of Hiroshima Prefecture's population. The population peaked at 2.89 million in 1998 and gradually declined by 2.77 million in 2022 [15].

During our study period, the positive predictive value of GC screening also grew gradually. Annual radiographic screening for all adults over 40 was established in the 1960s as a secondary preventive measure for GC in Japan [12]. Using high-concentration, low-viscosity barium preparations, double-contrast radiography, and the introduction of digital X-ray devices have substantially enhanced the visibility of lesions on gastric radiographic examination. The utilization of high-concentration thin barium sulfate has become prevalent in Japan since the 2000s. The Japanese Society of Gastrointestinal Cancer Screening published new guidelines on imaging methods to recommend this use for GC screening in 2005 [29]. Furthermore, the transition from traditional film to digital images occurred during the 2000s and 2010s [30]. These modifications have the potential to enhance the detection rate of minor lesions. This Japanese radiographic screening technology has been highly regarded internationally [31] and has been demonstrated in two case–control studies to reduce GC mortality [14, 26]. It was also mentioned in the Japanese Guidelines for GC Screening in 2005 as a modality associated with reduced GC mortality [11].

In our study, the number of participants with confirmed diagnosis of GC has reduced, while the rate of cases diagnosed as GC remained around 0.1% among all the participants. The prevalence of *H. pylori* infection has decreased in Japanese populations year by year. *H. pylori* infection is a definite carcinogen; therefore, thinking simply, the number of GC patients is expected to decrease year by year. However, our data did not indicate a decrease but was stable at around 0.1% among all the participants. There are two possible reasons for this. The first reason may be improvements in X-ray imaging and diagnostic skills. The second reason may be the changes in the participants. It is conceivable that the number of participants infected with *H. pylori* and/or gastrointestinal symptoms, who are at high risk of GC, might have increased.

On the other hand, one of the challenges for the future is whether X-ray screening should be replaced by endoscopic screening. The revised 2018 Japanese Guidelines have also approved endoscopic examinations for GC screening [32]. Even though endoscopic screening detected more cases of GC than radiographic screening, there was no significant difference in the reduction of GC mortality between the two screening modalities [13]. Another study reported that radiographic screening is as effective as endoscopic screening in reducing GC mortality [28]. Further, it is impossible to replace all conventional radiography with endoscopic examinations because of issues with the endoscopy capacity, budget, and high human resources of endoscopists [12, 33, 34]. In the Japanese medical system, upper endoscopic screening is 5-fold more expensive than gastric X-ray screening (approximately 15,000 JPY (110 USD) vs. 3,000 JPY (21 USD) per applicant). There is also a need to establish a certification system for screening endoscopists as well as physician education on endoscopic screening and image interpretation. Endoscopic screening, on the other hand, also has some limitations, including complications and overdiagnosis. Serious complications may even lead to death. Infection control is also essential, so the endoscope needs to be appropriately cleaned [32]. X-ray GC screening has recently utilized imaging and artificial intelligence

(AI) to detect *H. pylori*-infected gastritis and gastric mucosal atrophy [35]. This will enhance the diagnostic efficiency of X-ray GC screening. Therefore, it may be necessary to continue using radiographic examinations with a high processing capacity for population-based GC screening.

The risk of developing GC depends on the background condition, particularly *H. pylori* infection and gastric mucosal atrophy [36]. Because of the sharp drop in *H. pylori* infection rates, the background of GC risk has changed compared to the past [6, 7, 37-39]. Recently, the prevalence of *H. pylori* infection in Japan has been shown to vary by birth year, with those born in the 1970s or later having a low prevalence [37]. According to recent Japanese research, the risk of cumulative incidence of GC in the *H. pylori*-infected population was 17.0% in men, 7.7% in women, and < 1% in the non-infected population [40]. As a result, identifying patients as *H. pylori*-infected should be required for effective GC screening [38, 41, 42]. GC screening targeting all populations of a certain age every year may become inefficient, and there may be a cost-effectiveness issue.

Currently, one case of X-ray GC screening in Japan costs approximately 3,000 JPY (21 USD). Compared to the other cancer screening programs in Hiroshima Prefecture, the cost of GC screening is equivalent to that of cervical cancer screening. Nevertheless, the expenses of GC screening are higher than lung and colon cancer screening and lower than breast cancer screening. Lung and colon cancer screenings cost around 1,100 JPY (8 USD), whereas breast cancer screening costs nearly 4,300 JPY (31 USD).

Another finding in our study is that the number and rate of esophageal cancer among the participants in GC screening have increased recently. The incidence of esophageal cancer varies across regions and populations. The regions of Eastern Asia, Southern Africa, and Eastern Africa exhibited the highest incidence rates. Specific risk factors, including tobacco use, alcohol consumption, and hot beverage consumption, are probable contributors to the high incidence rates in these regions [43]. In Japan, an estimated 26,600 individuals were newly diagnosed with esophageal cancer, and 11,100 deaths were attributed to this cancer in 2021 [8]. The best outcomes for esophageal cancer are associated with early diagnosis, commonly known as "early stages" [44].

Therefore, screening and early detection are critical for esophageal cancer control in high-risk populations [43]. Unfortunately, there are currently no established guidelines for esophageal cancer screening in Japan. Hence, individuals with esophageal cancer risk factors, such as high consumption of tobacco, alcohol, or hot beverages, may be encouraged to have additional esophageal X-rays during GC screening.

Our result showed that the detection rate of GC was approximately 0.1%; as a result, the cost for one case of GC diagnosed was approximately 4,200,000 JPY (30,000 USD), including X-rays and EGDs, not a small amount. According to the National Cancer Center Japan report, the estimated 5-year survival rate of all GC patients in Japan, including early and advanced stages, is 65% (8). If this percentage were to hold in the present study, 65% of diagnosed GC patients would survive after five years of the screening. In that case, it costs about 6,500,000 JPY (46,400 USD) to diagnose one GC patient alive five years after the screening. Therefore, in the future, it may be necessary to stratify individuals based on their GC risk by identifying risk factors, such as a history of *H. pylori* infection and gastric mucosal atrophy, and determining the screening interval. For those with a low risk of GC, such as *H. pylori*-never infection and no gastric mucosal atrophy, their screening interval could be expanded or eliminated from the population-based GC screening. This may lead to major cost savings for the government and participants. The GC risk stratification method, named the ABC method, has been applied in some areas in Japan. However, *H. pylori* eradicated cases are classified as low risk of GC by the ABC method [45]. The number of *H. pylori* eradicated cases has increased, and even after the eradication, the risk of GC remains relatively high if the grade of atrophy of the gastric mucosa is high [46]. It is desired to develop a simple and low-cost method for determining GC risk.

There are several future challenges of X-ray GC screening in Japan. Improving the sensitivity and specificity of the imaging technology to detect early-stage GC is essential to enhance the screening quality. Improvements to the quality of machine learning algorithms and artificial intelligence can potentially increase the accuracy of X-ray interpretation for GC detection. In addition, reducing the radiation exposure associated with X-ray screening is an important consideration for patient safety. Furthermore, one of the upcoming challenges is to enhance the engagement of the citizens in the screening programs. Moreover, it is critical to prioritize the resolution of financial obstacles in order to establish an effective population screening program.

There are several limitations in our study. First, the ultimate purpose of GC screening is to reduce the mortality rate of GCs in the target populations. In the present study, however, the mortality rate of GCs was not assessed. To examine the mortality rate, different approaches, such as examining the cancer registries, are needed. This issue will be the next research topic. Second, in a few applicants, it was unknown whether or not they had undergone EGDs and the results thereof. Because it was a small number, it may be considered to be a very small bias. Third, we still need to get detailed data, such as the location of cancers, for this study. However, the purpose of this study is mainly to examine the major trends over the last four decades. The details are for future studies. Fourth, the cost to detect one gc should include not only the cost of X-ray gastric screenings and EGDs but also the cost of treatments for complications. We did not have data on the cost. However, the cost may be ignored because our study's rate of complications for X-ray gc screening was quite low, 0.003%.

CONCLUSION

In conclusion, GC screening in Hiroshima Prefecture has still been efficient. However, one of the challenges is the cost. Therefore, risk stratification may be needed, such as eliminating participants with *H. pylori*-never-infected and no gastric mucosal atrophy. Esophageal cancers may also be considered because there has been a gradual increase in recent years.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is the fifth most common cancer worldwide, with the fourth highest mortality rate [1]. Notably, the survival rate for GC has improved globally over the years due to advancements in both diagnosis and treatment [2, 3]. In Japan, there has also been a decline in the adjusted incidence and mortality rates of GC over the last few decades [4]. *Helicobacter pylori* (*H. pylori*) infection is considered the leading cause of GC [5]. Therefore, this decrease in GC is mainly attributed to reducing *H. pylori* infection rates due to hygiene improvement and the efficacy of the *H. pylori* eradication therapy [6, 7]. Despite this reduction, GC still has the third-highest incidence and mortality rates in Japan [8]. Consequently, the burden of GC remains substantial and makes it a critical public health issue.

In addition to the *H. pylori* eradication regimen, it is crucial to implement the GC screening program to lower GC mortality. In East Asian countries, only Japan and Korea have a national program for GC screening [9]. GC screening has extensively contributed to declining GC mortality in both countries [10, 11].

In Japan, GC screening has been conducted in local areas for a long time since the 1960s. Until 1983, it has expanded nationwide in accordance with the Health Law for the Aged [12]. Cancer screening in Japan can be categorized into population-based screening, which attempts to reduce overall mortality rates in target populations, and opportunistic screening, which aims to minimize individual risk. Effective population-based screening is a cornerstone of cancer control in Japan.

Although there are complications such as intestinal obstruction due to barium, aspiration pneumonia, and anaphylactic shock, radiographic screening has been the main approach for GC screening in Japan. Currently, the government of Japan has suggested either radiography or endoscopy examination for GC screening [12]. The updated version of the Japanese Guidelines for GC Screening in 2018 recommended radiographic screening for population-based and opportunistic screenings since its advantages outweigh its risks. Endoscopic screening is also recommended for population-based and opportunistic screenings because its benefits outweigh its harms. Although endoscopic screening detected more cases of GC than radiographic screening, there was a report that the reduction in GC mortality was not significantly different between the two screening methods [13]. GC screening using radiographic examination has been shown to be safe, cost-effective, accurate, and has a remarkable capacity for mass processing [14]. Besides, the GC risk stratification method, named ABC method, using *H. pylori* antibody and pepsinogen I and II, has been applied in some areas in Japan (15).

Hiroshima Prefecture is located in the southwestern part of Japan's main island of Honshu and the center of the Chugoku region, with a total land area of 8,480 km^2 and a population of 2.8 million people [15]. Hiroshima Regional Health Medical Promotion Organization is in charge of GC screening in Hiroshima Prefecture. The radiographic screening has been chosen for population-based GC screening in Hiroshima Prefecture. The ABC method has not been applied in the Prefecture. It is essential to assess the trends of X-ray GC screening from the past and investigate future perspectives. Hence, this study aims to evaluate the trends and the efficacy of population-based X-ray GC screening in Hiroshima Prefecture for the last 39 years, from 1983 to 2021. This can lead to identifying the challenges and developing future solutions.

Research motivation

GC screening in Hiroshima Prefecture has still been efficient. However, one of the challenges is the cost. Therefore, risk stratification may be needed, such as eliminating participants with *H. pylori*-never-infected and no gastric mucosal atrophy. Esophageal cancers may also be considered because there has been a gradual increase in recent years.

Research objectives

GC screening in Hiroshima Prefecture has still been efficient. However, one of the challenges is the cost. Therefore, risk stratification may be needed, such as eliminating participants with *H. pylori*-never-infected and no gastric mucosal atrophy. Esophageal cancers may also be considered because there has been a gradual increase in recent years.

Research methods

Figure 1 shows annual trends in the number of Hiroshima Prefecture residents participating in population-based X-ray GC screening. In 1983, there were 39,925 participants in the screening. This number gradually increased to 55,406 people in 1991. After that, there was a decrease in the number of participants. There were 12,923 participants remaining until 2021. During the period between 2015 and 2020, the rate of the eligible population in Hiroshima Prefecture taking part in GC screening ranged from 5.3% to 7.3%, which was average compared to other prefectures in Japan [16, 17].

Figure 2 indicates the age distribution of the participants from 2002 and 2021. The rate of participants less than 50 among all participants was 20.6% in 2002. The rate gradually increased over the years to 30.0% in 2021.

During the ten years between 1983 and 1992, the number of screening participants who required detailed examination by subsequent EGD ranged from 6,000 to 9,000. After 1992, this number also declined annually. From 2012 to 2021, only 500 to 1,500 participants needed EGDs (**Figure 3**). The rate of participants who required EGDs also decreased significantly in recent years ($p < 0.001$, first period: 13.0%, second: 12.0%, third: 10.4, and fourth: 5.1%).

The number of participants with a confirmed diagnosis of GC also dropped over the last 39 years. In 1993, 76 cases of GC were the most ever recorded. Until 2020 and 2021, the number of participants diagnosed with GC was only 10 (**Figure 4**). On the other hand, the rate of cases diagnosed as GC remained around 0.1% during the study period, with no significant differences among the four periods.

The rates of early-stage GC among all the GC detected in the screening from 1994 to 2021 are shown in **Figure 5**. This rate remained around 55% during the research period.

Figure 6 illustrates a gradual increase in the positive predictive value of the GC screening program, from 0.8% in 1983 to 2-3% over the last five years. The positive predictive value increased significantly in recent years except for the first period ($p < 0.001$, first period: 0.8%, second: 0.8%, third: 1.3%, and fourth 2.5%). **Figure 7** demonstrates an example of GC detected during the screening program.

The number and rate of esophageal cancer among the participants in GC screening also raised steadily from 2008 to 2021. In 2008, the diagnosis rate was 0% (0 cases); this rate grew to 0.02%, one-fifth of the diagnosis rate of GC, between 2017 and 2021 (3-4 cases/year). During the observation period, a total of 28 esophageal cancers were detected. Among them, 9 (32%) were in the early stages, 17 (61%) were in advanced stages, and the remaining 2 (7%) were in unknown clinical stages. The rate of early-stage esophageal cancers among all the esophageal cancers fluctuated, and no consistent trend was observed during the period due to the limited number of patients per year (data not shown).

As for complications of X-ray GC screenings from 2007 to 2021, a total of 9 cases were reported: 4 cases with intestinal obstruction due to barium, 2 cases with barium aspiration, 2 cases with rib fracture due to compression, and 1 case of barium reflux into the common bile duct. The complication rate was 0.003% among 335,873 applicants who took X-ray GC screenings during the period.

The detection rate of GC was approximately 0.1%. In other words, to detect one GC, approximately 1,000 gastric X-ray screening was needed. Regarding the cost aspect, detecting one GC cost approximately 3,000,000 JPY (21,400 USD) for gastric X-ray screenings (approximately 3,000 JPY (21.4 USD)/X-ray screening). The cost of EGDs should be considered. Approximately 8% of the applicants required EGDs; thus, 80 EGDs were needed to detect one GC. The cost of 80 EGDs was approximately 1,200,000 JPY (8,600 USD) (approximately 15,000 JPY (107 USD)/EGD). The total cost of one GC diagnosis using X-ray screenings and EGDs was approximately 4,200,000 JPY (30,000 USD).

Research results

This is a *population*-based *retrospective study*. Hiyama T, Vu NTH contributed to the study's conception, design, and execution of the research. The data was derived from the aggregated data of the Hiroshima Regional Health Medical Promotion Organization, Hiroshima, Japan. Vu NTH, Hiyama T, and Urabe Y conducted data collection and curation with the staff in this institution. Data obtained from this organization may represent the majority of residents living in Hiroshima Prefecture. In Hiroshima Prefecture, residents aged 40 years and older were qualified to participate in an annual population-based X-ray GC screening. Each year, the coupons were issued to eligible residents by the health center of each local city and town in Hiroshima Prefecture. Even if residents were under 40, they could take the screening if they desired.

High-resolution, double-contrast agents for the upper gastrointestinal tract were utilized for the X-ray examination in Hiroshima Prefecture. Consequently, the capability of gastric radiography examination to detect lesions has been significantly enhanced. The citizens were ineligible for barium X-ray screening if they had one or more of the following conditions: past medical history of total gastrectomy, hypersensitive to barium sulfate products, pregnant (or possibly pregnant) women. Radiographic examination was performed using the standard imaging method (8-image method). The screening report has been double-reading (double-checked) by two radiologists on two separate occasions.

We collected the number of participants who underwent X-ray GC screening during the last 39 years, from 1983 to 2021, and examined the age distribution of participants from 2002 to 2021. Participants with a suspicious X-ray abnormality (cancers or other gastric lesions such as ulcers) were recommended detailed examination with esophagogastroduodenoscopy (EGD). We also gathered the number of participants and the rate for those EGD required during the study period. Participants who were ineligible to take X-ray gastric screening were not included in those for whom EGDs were required. Moreover, the number, the rate of participants diagnosed with GC, and the invasion depth of each cancer were recorded. The invasion depth of each cancer was divided into two: early stage, *i.e.*, invasion depth is the lamina propria or the submucosa, and advanced stage, *i.e.*, invasion depth is the muscularis propria or deeper. We derived the positive predictive value detected by X-ray and confirmed by EGDs. We also obtained data about the number, clinical stages (early or advanced), and the rate of esophageal cancer detected in the screening from 2008 to 2021. Additionally, reported complications of X-ray GC screenings from 2007 to 2021 were evaluated.

To examine the time trend of each rate, the 39 years were divided into four periods: first nine years (1983-1991), second ten years (1992-2001), third ten years (2002-2011), and fourth years (2012-2021). Each rate was compared among the four periods.

One case of X-ray GC screening in Hiroshima Prefecture costs approximately 3,000 JPY (21 USD). The patient will pay 30% of the total cost, with the remaining covered by the government. One case of EGD costs approximately 15,000 JPY (110 USD). The cost of detecting one GC was calculated based on the detection rate of GC.

Hiyama T, Vu NTH, Oka S, Quach DT, and Urabe Y performed data analysis. The collected data were organized in an Excel spreadsheet (Microsoft *et al*, USA). All statistical analyses were performed using MedCalc® Statistical Software version 19.6.1 (MedCalc Software Ltd, Ostend, Belgium). Categorical variables are presented as numbers and percentages. The difference between the two proportions was compared with the chi-squared test. A p-value of less than 0.05 was considered statistically significant. A Bonferroni correction (a p-value of less than 0.0083) was used to compare each rate among the four periods. During the study period, Oka S, Hiyama T, and Quach DT provided supervision and ensured the overall integrity of the research. NTH drafted the initial manuscript; Hiyama T, Quach DT, Urabe Y, and Oka S reviewed and edited the manuscript.

Ethical approval was obtained from the Ethical Committee of Hiroshima University (ethical number: E2023-0018) for this study.

Research conclusions

This study aims to evaluate the trends and the efficacy of population-based X-ray GC screening in Hiroshima Prefecture for the last 39 years, from 1983 to 2021. This can lead to identifying the challenges and developing future solutions.

Research perspectives

It is essential to assess the trends of X-ray GC screening from the past and investigate future perspectives.

ACKNOWLEDGEMENTS

The authors thank *Shinji Tanaka*, Honorary Professor, Hiroshima University and President of Japan Gastroenterological Endoscopy Society, Masaharu Yoshihara, Honorary Professor, Hiroshima University, Kenji Nakagaki, Takayuki Harakawa, and Hiroya Matsuoka, Hiroshima Regional Health Medical Promotion Organization for their support.

89180_Auto_Edited.docx

ORIGINALITY REPORT

11%
SIMILARITY INDEX

PRIMARY SOURCES

1	"International Poster Session", Nihon Shoukaki Gan Kenshin Gakkai zasshi, 2023 Publications	267 words — 4%
2	mdpi-res.com Internet	158 words — 2%
3	academic.oup.com Internet	102 words — 2%
4	0-www-mdpi-com.brum.beds.ac.uk Internet	83 words — 1%
5	Takahisa Matsuda. "Expectations for and challenges in population-based endoscopic gastric and colorectal cancer screening", Digestive Endoscopy, 2021 Crossref	74 words — 1%
6	www.researchsquare.com Internet	47 words — 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 1%
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 10 WORDS