A study protocol for expanding the screening interval of endoscopic screening for gastric cancer based on individual risks: prospective cohort study of gastric cancer screening

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Background: The Japanese government has recommended a 2-year endoscopic screening interval for gastric cancer. However, insufficient resources have constrained participation in endoscopic screening for gastric cancer. One way to avoid endoscopic screening harms and provide equal access is to define the appropriate screening interval.

Methods: To expand screening interval from more than 2 years for low-risk group, a single-arm cohort of endoscopic screening started. At the baseline screening, the participants underwent endoscopic screening for gastric cancer, Helicobacter pylori (H. pylori) antibody test, and serum pepsinogen test (first year), and followed after 2 and 4 years (within the first 5 years). We also assessed H. pylori infection and atrophy status on images of upper gastrointestinal endoscopy at the baseline. A new screening model will be developed by dividing the participants into high-risk and low-risk groups based on demographics, history of H. pylori eradication, serological testing, and endoscopic diagnosis. The cumulative gastric cancer incidence after negative results at baseline are compared between the low-risk group on the 3rd screening round after 4 years from baseline and the total screening group on the 2nd screening round after 2 years. If the cumulative gastric cancer incidence in the low-risk group on the 3rd screening round is lower than that in the total screening group on the 2nd screening round, the screening interval can be expanded to 4 years in the low-risk group.

Discussion: To reduce mortality from gastric cancer, a high participation rate of the target population is required. The screening interval of endoscopic screening can be changed if the individual risks for H. pylori infection are clarified. Our goal in this study is to obtain relevant data that can be used to improve the efficient use of endoscopic screening for gastric cancer by referring to individual risks in Japan.

Trial registration: UMIN000025839 (University Hospital Medical Information Network, Japan)

Keywords: Gastric cancer; cancer screening; endoscopic screening; screening interval; atrophic gastritis; Helicobacter pylori

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Introduction

Although gastric cancer mortality in Japan has decreased over the last 3 decades, its burden remains. Gastric cancer is the second and the fourth leading cause of cancer death in men and women, respectively (1). It accounts for about 10% of all cancer deaths in Japan. Upper gastrointestinal series (UGI) for gastric cancer screening was originally developed in Japan and it subsequently became a standard screening method (2). UGI for gastric cancer screening has been conducted as a national program across Japan since 1983 under the law for cancer screening (3). However, the participation rates in gastric cancer screening in Japan has decreased over the last 2 decades, and it has remained at approximately 10% (4). On the other hand, the upper gastrointestinal endoscopic technique has become more commonly used among general physicians nationwide, with the number of endoscopic examinations increasing among medical offices (5). Thus, the introduction of endoscopic screening for gastric cancer has been expected. In 2016, the Japanese government introduced endoscopic screening as a national program based on the gastric cancer screening guidelines developed by the National Cancer Center of Japan (3).

Despite the rapid introduction of endoscopic screening in most urban cities, there has been some hesitation in regional municipalities because of the insufficient human resources. In these areas, endoscopic screening is mainly performed by general physicians. There are no dedicated rooms for endoscopic screening in regional areas, and this situation is aggravated by the insufficient number of physicians who can provide medical services (6). Therefore, to spread the use of endoscopic screening in Japan, the expansion of endoscopic capacity has become an urgent issue.

Although the screening interval of endoscopic screening was equally defined every 2 years for the target population, a different screening interval might be defined and considered depending on its relation to the individual’s background and gastric cancer risk. Gastric cancer incidence differs according to individual risks and is mainly defined by H. pylori infection and atrophic gastritis (7,8). If individuals with a low risk of gastric cancer could be identified and adopted to the programs, their screening interval can be expanded. This information would be useful in both avoiding the harms of screening and providing equal access to endoscopic screening nationwide in Japan. The purpose of this cohort study is to clarify the appropriate individual risks for endoscopic screening and then expand the screening interval for gastric cancer in the low-risk group.

Methods

Study setting

The proposed cohort involves multi-municipalities which have endoscopic screening program for gastric cancer. For implementation of endoscopic screening as national program, a quality assurance manual was developed (9) and it has been used in gastric cancer screening programs in regional areas. The ideal study areas that regularly follow the above-mentioned manual will be selected. Until 2019, the following municipalities in Japan that meet our requirements were recruited as study areas: Niigata, Kanazawa, Maebashi, Tottori, Yonago, Yuri-Honjyo, and Morioka. Also, Sendai, Setagaya-Tokyo, Yazu, and Fukuoka will be included in this study in 2020.

Study population

The main target of gastric cancer screening is individuals aged from 50 to 60 years. Their incidence rate of those aged from 50–69 years is estimated to be 121.8 (/100,000) (1). The subjects aged 50–69 years are recruited from the study areas. The eligibility criteria for participants in this study were as follows: (I) subjects aged 50–69 years at the year of recruitment, (II) inhabitants of the study area, (III) subjects who can participate in endoscopic screening for gastric cancer in local programs, and (IV) subjects who provide written informed consent to participate in this study. The exclusion criteria were as follows: (I) individuals who have cancer, (II) individuals with severe health conditions and unable to participate in endoscopic screening for gastric cancer, and (III) individuals who underwent gastric resection.

Study design

We performed a single-arm cohort study to assess the most appropriate endoscopic screening interval for gastric cancer in the low-risk group. The trial was registered at University Hospital Medical Information Network, Japan (UMIN000025839). The study was approved by the Ethics Committee of the Miyagi Cancer Association (No.1612, Date of approval 21st March 2017). Each participant provided written informed consent before inclusion in the
study.

If individuals with a low risk of gastric cancer can be divided from individuals with a high risk of gastric cancer, the screening interval can be expanded. At this stage, the discrimination of individual risks for gastric cancer has not yet been strategically used in a gastric cancer screening program. Importantly, a new screening model can be developed regarding demographic information covering the history of *H. pylori* eradication, serological testing, and endoscopic diagnosis. The new screening model is expected to become more clearly delineated than serological testing alone. Participants without gastric cancer will continue to have endoscopic screening every 2 years. If the cumulative incidence in the low-risk group on the 3rd assessment round (P2) becomes lower than the cumulative incidence of gastric cancer in the total screening group on the 2nd assessment round (P1), the screening interval can be expanded from 2 to 4 years in the low-risk group.

Figure 1 Basic concept of screening interval expansion. A new model that divides the participations into high-risk and low-risk groups will be developed by referring to the participants’ demographic information with reference to their history of *H. pylori* eradication, serological testing, and endoscopic diagnosis. If the cumulative incidence of gastric cancer in the low-risk group on the 3rd assessment round (P2) becomes lower than the cumulative incidence of gastric cancer in the total screening group on the 2nd assessment round (P1), the screening interval can be expanded from 2 to 4 years in the low-risk group.

Data management and monitoring

All study data is collected and maintained in regional management office which are mainly located in regional medical associations. The data includes informed consent forms, screening results, questionnaire survey and follow-up results. The regional management office revises them annually and submits the anonymous data to the central database. The principal investigators at the participating municipalities are responsible for collecting the medical research records from the screening database and population registries in their municipalities as well as reviewing and storing them. The central database maintains all data submitted from study areas. To maintain the quality of the database, regular checks are performed to identify missing or contradictory in their data.

Sample size calculation

Individuals who participate in endoscopic screening are divided into a high-risk group and a low-risk group for gastric cancer. Grading of atrophic gastritis was by the classification of Kimura and Takemoto (11). Borderline atrophic gastritis is defined as extending from the antrum toward the lesser curvature of the body and to the greater curvature. If the borderline atrophic gastritis does not reach the cardia, the atrophy grade is classified as a close type (C).
If the borderline atrophic gastritis extends over the cardia, the atrophy is classified as an open type (O). Each group is further classified into 3 groups based on the atrophic areas: C-I, C-II, and C-III; O-I, O-II, and O-III. The distributions of atrophic gastritis in subjects undergoing endoscopic screening for gastric cancer have been reported in Kanazawa and Niigata, Japan. These places have conducted endoscopic screening for over 10 years (12,13). Based on these previous studies, 2 cut-off values were assumed at C-II and O-I (Table 1). The distribution and cumulative incidence were defined for low and high groups in each scenario, respectively. The sample size was calculated to achieve 5% on both sides with an 80% power. In the first scenario, 19,844 subjects were needed. In the second scenario, 10,372 subjects were needed. If the follow-up rate is assumed as 80%, 12,965 subjects are required for the second scenario.

Statistical analysis plan

We compared baseline characteristics of the high-risk and low-risk group by the Chi-square test, including sex, age, H. pylori infection, history of H. pylori eradication, history of gastric cancer screening and other demographic information which is obtained by a questionnaire survey. We examined the cumulative incidence of gastric cancer for 10 years. Cox-proportional hazards model will be used to calculate hazard ratios (HRs) with 95% confidence interval. The HR of the cumulative incidence of the low-risk group on the 3rd assessment round (P2) will be calculated referred to total screening group on the 2nd assessment round (P1) (Figure 1). The HR of the cumulative gastric cancer incidence in the low-risk group will be also calculated referred to the high-risk screening group at 3, 5 and 10 years.
of being free from cervical cancer than cytology-negative and that HPV-negative results indicate a longer period adequately the development of cervical cancer than cytology results suggest that the HPV test could predict more negative women on the 3rd screening round (20,21). These 2nd screening round was similar to that among cytology-negative cervical cancer among HPV-negative women on the of cervical cancer has been compared between women with negative human papillomavirus (HPV) test results and cervical cancer has been considered to play the main role in cancer prevention (2,3). Although endoscopic screening has gradually been disseminated nationwide, there is a huge disparity in endoscopic screening access between urban and regional areas, and rapid dissemination is difficult (6). To achieve the goal for mortality reduction from gastric cancer, equal access to endoscopic screening should be provided.

Recently, the HPV test has been adopted to cervical cancer screening in the U.S. and some countries (18-20). This screening interval of the HPV test can be expanded by as much as twice that of cytological screening. This screening interval expansion has been suggested by cohort studies conducted in the U.S. and the Netherlands (20,21). In cervical cancer screening, the cumulative incidence of cervical cancer has been compared between women with negative human papillomavirus (HPV) test results and women with negative cytological test results. Particularly in Dutch and the U.S. studies, the cumulative incidence of cervical cancer among HPV-negative women on the 2nd screening round was similar to that among cytology-negative women on the 3rd screening round (20,21). These results suggest that the HPV test could predict more adequately the development of cervical cancer than cytology and that HPV-negative results indicate a longer period of being free from cervical cancer than cytology-negative results. Thus, if the HPV test is adopted for cervical cancer screening, the screening interval can be expanded by as much as twice the regular screening interval. In essence, the same theory can be adapted to enable risk stratification for gastric cancer and expand the endoscopic screening interval for gastric cancer.

Gastric cancer remains a heavy public health burden in Japan. Thus, there is a continuing need for gastric cancer screening. In such screening, a high participation rate of the target population is required to reduce mortality from gastric cancer. The recent introduction of endoscopic screening for gastric cancer as a national program is aimed at helping to improve the participation rate. However, a greater increase in participation should be required to achieve this goal. Then, in order to help build capacity for endoscopic screening, one of the potential solutions could be expand the screening interval for the low-risk group. The advantage to expanding the screening interval can be seen from the two perspective. First, from an individual perspective, there is a possibility of developing complications and the potential for overdiagnosis when they participate in endoscopic screening (22,23). Decreasing the screening frequency can help to protect people from being exposed to these harms. From a population perspective, equal assess has been provided to all within the target population regardless of their living areas thus assisting efficient use of limited resources. As human resources remain insufficient, disparities in the use of endoscopic screening persist. To address these issues, a possible solution is to divide the intensive target group from low-risk group for gastric cancer and increase the endoscopic screening interval.

Endoscopic screening has been expected to reduce mortality from gastric cancer in East Asian countries which continues to bear a heavy burden of gastric cancer (14). Distinctively, Korea and Japan have national cancer screening programs whereas some countries have opportunistic or research-based screening programs (2,3,15-17). In Japan, gastric cancer screening has been considered to play the main role in cancer prevention (2,3). Although endoscopic screening has gradually been disseminated nationwide, there is a huge disparity in endoscopic screening access between urban and regional areas, and rapid dissemination is difficult (6). To achieve the goal for mortality reduction from gastric cancer, equal access to endoscopic screening should be provided.

Discussion

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| Scenario | 1 | 2 |
| --- | --- | --- |
| Cut-off value* | C-II | O-I |
| Ratio, high-risk group: low-risk group | 50:50 | 30:70 |
| Cumulative incidence in the high-risk group at P3 in Figure 1 (%) | 0.50% | 0.70% |
| Cumulative incidence in the low-risk group at P2 in Figure 1 (%) | 0.25% | 0.30% |
| Sample size | 19,844 | 10,372 |

* the cut-off value was defined by grading of atrophic gastritis using the classification of Kumara and Takemoto (11). C2: close type 2; O1: open type 1.
specificity is still not sufficiently high (27,28). Besides, the International Agency of Research on Cancer recommended \textit{H. pylori} screening to eradicate \textit{H. pylori} for gastric cancer prevention based on expert opinions (29). Although the efficacy of \textit{H. pylori} eradication has been evaluated, long-term effects remains unclear (30,31). However, gastric cancer incidence after \textit{H. pylori} eradication has been reported and these cannot be ignored (32). Although \textit{H. pylori} eradication is covered by national health insurance in Japan, surveillance following the treatment has not been established (33). Afterwards, person following \textit{H. pylori} eradication often return to cancer screening program individually. Then, participants in endoscopic screening include individuals with various risks of gastric cancer regardless of \textit{H. pylori} eradication. Therefore, a new risk stratification is needed for the efficient use of endoscopic screening. To address disparities in the use of endoscopic screening, the endoscopic screening interval may be expanded, and the target age group defined. This can be achieved by applying the basic concept of \textit{H. pylori} screening to the current endoscopic screening program. The overall of this study is to obtain relevant data that can be used to improve the efficient use of endoscopic screening for gastric cancer by referring to individual risks in Japan.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5949). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of the Miyagi Cancer Association (No.1612, Date of approval 21th March 2017).

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