Optimal Screening Interval for Gastric Cancer in Japan

Akira Babazono, Toshihide Tsuda, Yoshio Mino, Takanori Ogawa, and Hideyasu Aoyama

Annual gastric cancer screening has been recommended for residents over the age of 40 in Japan. We conducted a cost-effectiveness study in order to determine an optimal screening interval in both genders using a cohort model. Hypothetical cohorts of 100,000 asymptomatic individuals aged 40 were assumed to have taken part in each strategy with a follow-up period of 20 years. In order to evaluate both the cost and effectiveness of the gastric cancer screening, a Markov modeling process was used. The incremental cost per year-of-life saved in gastric cancer screening, compared to no screening, illustrates a tendency toward a higher cost per year-of-life saved in both, shorter than and longer than 3-year screening intervals. Our results indicate that the recommended method of annual screening represents the least cost-effective option regarding both genders. The incremental cost per year-of-life saved of annual screening strategy was 2,764,000 yen ($25,127) for males and 3,753,000 yen ($34,118) for females, compared to no screening. The figures of the incremental cost per year-of-life saved in the three year screening interval at 1,670,000 yen ($15,182) for males and 2,431,000 yen ($22,100) for females clearly show this strategy as the most efficient solution in both genders, compared to no screening. However, the screening program on annual basis is not considered to be less efficient than other screening programs so far. The cost-effectiveness of gastric cancer is decreasing as its incidence decreases. It is very important for policy makers to pay attention to the incidence of diseases targeted by screening programs and to evaluate screening interval. J Epidemiol, 1995; 5: 67-74.

A significant factor in early detection of gastric cancer should be the determination of optimal screening interval, since test frequency directly affects the overall efficiency of screening programs. Shorter screening intervals, however, would not only result in detection of more cases but would also produce more false positive results. Nevertheless, there are few studies evaluating screening efficiency in relation to frequency.

Gastric cancer is one of the most common malignancies worldwide. Globally, Japan tops the list with the highest age-adjusted mortality rate in gastric cancer. Mass screening for early detection and treatment of gastric cancer in Japan has been conducted nationwide by the municipalities since 1960, although in the absence of clearly defined legal obligations. In 1983, enhanced government legislation (The Health Services Scheme for the Aged) recommended annual screening of all residents over the age of 40. The task of implementing this policy was assigned to municipalities, without any valid scientific evidence that would support the decision to conduct the screening annually. In Japan, the screening by the indirect X-ray (photofluoroscope method) is usually performed using mobile equipment. A barium meal photofluoroscopy rather than standard X-ray is used during this procedure in stomach imaging.

Numerous studies have evaluated the effectiveness of gastric cancer screening in Japan, although these were not randomized controlled studies. Several others aimed at cost-effectiveness. However, there is an absence of specific study concentrating on how the intervals affect the entire screening program in Japan. Most cost-effectiveness studies in Japan have been based on cross-sectional designs where screening intervals cannot be evaluated. In addition, due to a decrease in gastric cancer incidence in Japan this would have a negative influence on determining the efficiency of screening programs in relation to screening intervals.
The specific aim of our cost-effectiveness study was to determine an optimal screening interval in both genders using a cohort model.

**METHODS**

**Screening Model**

Four screening strategies were compared with a no intervention alternative. The screening intervals ranged one to four years inclusive. Hypothetical cohorts of 100,000 asymptomatic individuals aged 40 were assumed to have taken part in each strategy and followed for 20 years, commencing in 1990, given the eligibility of those in the age bracket of 40 years and older for the government screening program.

A decision tree chart developed by us is based on sequential procedures follow-up through the entire screening process (Figure 1). In order to detect and monitor the health transition of each subject, a Markov modeling process was employed to evaluate the cost and effectiveness of each screening strategy. The natural history of the disease was defined by five different states: (1) disease-free; (2) preclinical cancer; (3) clinical cancer; (4) follow-up care; and (5) death. The probability of patients' transition from one state to another was obtained from published clinical studies.

All those who were never diagnosed as suffering from gastric cancer were assumed to participate in individually assigned screening scheme. To address the variable of patients compliance with the recommendation for further evaluation (whenever necessitated during their first screening), we have used different compliance rates to distinguish the two genders, since the female patients are represented in higher compliance rate. The patients suspected by endoscopy as having cancer had undergone biopsy to confirm the diagnosis. Those confirmed through the biopsy as positive were assumed to undergo treatment and were excluded from all further screening. Furthermore, all patients diagnosed as inoperable advanced cancer or recurrence case were assumed to have died within the same year in which they were in terminal care. The non-compliant cases (those who could not be evaluated further), including individuals with false negative screening results, were assumed to have been diagnosed after the lead time has elapsed and present with less early cases than would have been the case had the tumor been discovered at screening. Early cancer of the stomach is defined as a neoplasma in which depth of invasion at histologic examinations is limited to the submucosal layer of the stomach.

The age-adjusted mortality rate of gastric cancer in Japan has been decreasing exponentially since the 1970s. The mortality rate of gastric cancer stratified by sex and age, covering a period from 1990 to 2009 was estimated by log linear regression based on all available data from 1970 to 1990. All correlation coefficients were higher than 0.97. The incidence of gastric cancer was assumed to be 1.38 times mortality of gastric cancer, based on a study covering

![Figure 1. A decision tree for gastric cancer screening.](image)
39.2% of the Japanese population from 1981 to 1983\textsuperscript{14). The number of deaths of other than gastric cancer causes was deduced from statistical information using vital statistics of Japan in 1990 which lists the overall mortality rate itemized by causes\textsuperscript{15).}

### Data Collection

All epidemiological data\textsuperscript{6,16–20} were obtained from published articles including official Japanese government statistics (Table 1). Since medical care costs are regulated by the National Government in Japan, costs of endoscopy and biopsy, including pathology were gathered from the uniform fee schedules in 1990\textsuperscript{21). Costs for indirect

| Table 1. Epidemiological data used in the model. |
|-------------------|-----------|----------------|
|                      | Data      | Value          |
| 1. Lead time        | 2.5 years | 16             |
| 2. Sensitivity and specificity |          |                |
| Indirect X-ray      | sensitivity | 69.4%         |
|                     | specificity | 83.8%         |
| Endoscopy           | sensitivity | 80.1%         |
|                     | specificity | 91.9%         |
| 3. Compliance rate for further evaluation |          |                |
| male                | 66.8%      | 19             |
| female              | 79.2%      |                |
| 4. Complication by endoscopy |          |                |
| Direct complication rate | 0.009%     |                |
| Death rate          | 0.0005%    |                |
| 5. Complication by biopsy |          |                |
| Direct complication rate | 0.008%     |                |
| Death rate          | 0.0003%    |                |
| 6. Stage distribution |          |                |
| Screening detection | 19         |                |
| Annual screening    |            |                |
| Early stage         | 68.7%      |                |
| Advanced stage      | 31.3%      |                |
| [inoperable stage]  | 3.6%*      |                |
| Screening with two year interval |          |                |
| Early stage         | 68.1%      |                |
| Advanced stage      | 31.9%      |                |
| [inoperable stage]  | 3.7%*      |                |
| Screening with three year interval |        |                |
| Early stage         | 61.0%      |                |
| Advanced stage      | 39.0%      |                |
| [inoperable stage]  | 4.5%*      |                |
| Screening with four year interval |        |                |
| Early stage         | 59.2%      |                |
| Advanced stage      | 40.8%      |                |
| [inoperable stage]  | 4.7%*      |                |
| Clinical detection  |            |                |
| Early stage         | 23.4%      |                |
| Advanced stage      | 76.6%      |                |
| [inoperable stage]  | 24.9%      |                |
| 7. Ten year's survival rate |      |                |
| Screening detection |            |                |
| Early stage         | 91.0%      | 5              |
| Advanced stage      | 61.8%      |                |
| Clinical detection  |            |                |
| Early stage         | 85.6%      |                |
| Advanced stage      | 35.1%      |                |

*Distribution of inoperable cancer by screening interval was estimated by report 5
screening program, work-up, initial treatment and a follow-up in 1990 were collected from published articles\textsuperscript{10,22}. Terminal care costs for the 1982-1984 period were brought to the 1990 levels, given the prevailing inflationary prices for the medical services in Japan\textsuperscript{23}. Thus, all cost-related data were obtained from published works on the topic and the official Japanese governmental statistics, with the exception of treatment cost of endoscopy related complications, the data of which were obtained directly from the specialists in the field (Table 2).

\textbf{Costs}

Only direct medical costs involved were estimated, taking the viewpoint of the payer into consideration. Other costs, including non-medical direct costs, indirect costs as well as intangible costs were excluded. The direct medical costs taken into account were screening costs, work-up costs, initial treatment costs, follow-up treatment costs, and terminal care costs. These were discounted at an annual rate of 5\% during the period of screening, treatment, and the follow-up. The mentioned costs were listed in both currencies at the exchange rate of a Japanese yen toward a U.S. dollar, assumed to be U.S. $/110 yen.

\textbf{Effectiveness}

The number of years-of-life saved was adopted as an indicator of the overall effectiveness of gastric cancer screening, since early detection leads to intervention, increasing the patients chances for recovery and thus, survival. The number of years-of-life lost was calculated based on a life expectancy, given the subjects age at the point of entry into the model.

\textbf{Sensitivity Analysis}

We performed sensitivity analysis to assess the effects of changes in our assumptions on incidence, sensitivity, specificity and discount rate of effectiveness. In this analysis, we allowed a $+/-30\%$ margin for incidence, as an important factor of the screening cost-effectiveness study. With a current pace of technology development in mind, 10 \% of improvement in sensitivity and specificity were taken into account. Discounting years-of-life saved was considered in sensitivity analysis since discounting of non-monetary outcomes is a highly controversial issue.

\textbf{RESULTS}

\textbf{Optimal Screening Interval}

In order to compare the relevant data to no screening option, our calculation results referring to the incremental cost, total numbers of years-of-life saved, and incremental cost-effectiveness ratios of each strategy were used (Table 3). Both, the cost and the number of years of life saved proved the highest and the largest (respectively), in the annual screening strategy, while the four-year screening interval indicated the cost as the highest with the number of years of life saved being the smallest. However, our graphical illustration of incremental costs shows a U-shaped curve as the screening interval lengthens (Figure 2). Our results indicate that the recommended method of annual screening represents the least cost-effective option regarding both genders. The incremental cost per year-of-life saved in the annual screening strategy was 2,764,000 yen ($25,127) for males and 3,753,000 yen ($34,118) for females compared to no screening. The figures of the incremental cost per year-of-life saved in the three year screening interval at $1,670,000 yen ($15,182) for males and 2,431,000 yen ($22,100) for females clearly favor this strategy as the most efficient option to adopt for both genders screening, compared to no screening and other strategies alike.

\textbf{Sensitivity Analysis}

The results of sensitivity analysis are shown as in Table 4, Figure 3 and 4. As these figures indicate, the incidence of gastric cancer being estimated with a margin of $+30\%$ also increases the cost effectiveness of screening program, whereas using the margin of $-30\%$ has a decreasing effect compared to our estimate. Notwithstanding, even if the

| Table 2. Cost data used in the model. |
|---------------------------------------|
| Data | Value | Source |
|------|-------|--------|
| 1. Screening cost | | |
| Indirect X-p | 3,610 Yen | ($33) | 10 |
| Endoscopy | 10,000 Yen | ($73) | 21 |
| Biopsy & pathology | 8,600 Yen | ($78) | 21 |
| 2. Treatment cost for complication by endoscopy | 500,000 Yen | ($4,545) | specialist opinion |
| 3. Work-up cost | 26,035 Yen | ($239) | 10 |
| 4. Initial treatment cost | | |
| Early stage | 1,146,210 Yen | ($10,420) | 10 |
| Advanced stage | 2,107,060 Yen | ($19,155) | 10 |
| 5. Follow-up cost for gastric cancer | 21,956 Yen | ($200) | 22 |
| 6. Terminal care cost for gastric cancer | 2,602,547 Yen | ($23,660) | 23 |
Table 3. Results of incremental cost-effectiveness analysis for gastric cancer screening compared to no screening.

| Gender | Screening interval | Incremental cost per cohort | Years of life saved per cohort | Incremental cost per year of life saved |
|--------|-------------------|-----------------------------|-------------------------------|----------------------------------------|
| Male   | one year          | 8,838,873,000 Yen ($80,353,391) | 3,198                         | 2,764,000 Yen ($25,127)               |
|        | two years         | 4,308,932,000 Yen ($39,172,109) | 2,383                         | 1,808,000 Yen ($16,436)               |
|        | three years       | 2,505,600,000 Yen ($22,778,182) | 1,500                         | 1,670,000 Yen ($15,182)               |
|        | four years        | 2,130,082,000 Yen ($19,364,382) | 1,058                         | 2,013,000 Yen ($18,300)               |
| Female | one year          | 9,304,258,000 Yen ($84,584,164) | 2,479                         | 3,753,000 Yen ($34,118)               |
|        | two years         | 4,576,928,000 Yen ($41,608,436) | 1,853                         | 2,471,000 Yen ($22,464)               |
|        | three years       | 2,719,644,000 Yen ($24,724,218) | 1,119                         | 2,431,000 Yen ($22,100)               |
|        | four years        | 2,273,952,000 Yen ($20,672,291) | 745                           | 3,051,000 Yen ($27,736)               |

*Total cost per cohort of no screening option for males is 1,798,223,000 Yen. Total cost per cohort of no screening option for females is 1,014,182,000 Yen. Years of life lost per cohort of no screening option for males is 223,976. Years of life lost per cohort of no screening option for females is 130,749.

Any improvement in sensitivity and specificity will reduce the cost per year-life-saved, but it would not change the order of cost-effectiveness among the strategies. In addition, there is no substantial difference between the cost-effectiveness and its base model.

As expected, discounting years-of-life saved reduces the estimate of efficiency. The incremental cost per year of life saved of screening in the 3-year interval increases to 28,540,000 yen ($25,945) and 46,800,000 yen ($37,440) for males and for females, respectively. This, however, does not change its ranking in the cost-effectiveness hierarchy.
### Table 4. Incremental cost per year of life saved by sensitivity analysis of incidence, sensitivity, specificity and discounting years of life saved.

| Gender | Screening interval | Incidence -30% | Incidence +30% | Sensitivity | Specificity | Discounting life saved |
|--------|--------------------|-----------------|----------------|--------------|-------------|------------------------|
| Male   | one year           | 3,956,000 Yen ($35,964) | 2,127,000 Yen ($19,336) | 2,555,000 Yen ($23,227) | 2,336,000 Yen ($21,236) | 4,738,000 Yen ($43,072) |
|        | two years          | 2,594,000 Yen ($23,582) | 1,386,000 Yen ($12,600) | 1,641,000 Yen ($14,918) | 1,525,000 Yen ($13,864) | 3,099,000 Yen ($28,172) |
|        | three years        | 2,415,000 Yen ($21,555) | 1,270,000 Yen ($11,545) | 1,491,000 Yen ($13,555) | 1,400,000 Yen ($12,727) | 2,854,000 Yen ($25,945) |
|        | four years         | 2,883,000 Yen ($26,209) | 1,546,000 Yen ($14,055) | 1,875,000 Yen ($17,045) | 1,695,000 Yen ($15,409) | 3,468,000 Yen ($31,527) |
| Female | one year           | 5,403,000 Yen ($49,118) | 2,875,000 Yen ($26,136) | 3,476,000 Yen ($31,600) | 3,076,000 Yen ($27,964) | 7,229,000 Yen ($65,718) |
|        | two years          | 3,555,000 Yen ($32,318) | 1,891,000 Yen ($17,190) | 2,215,000 Yen ($20,136) | 2,027,000 Yen ($18,427) | 4,759,000 Yen ($43,264) |
|        | three years        | 3,500,000 Yen ($31,818) | 1,859,000 Yen ($16,900) | 2,111,000 Yen ($19,190) | 1,989,000 Yen ($18,082) | 4,680,000 Yen ($42,545) |
|        | four years         | 4,383,000 Yen ($39,845) | 2,341,000 Yen ($21,282) | 2,652,000 Yen ($24,109) | 2,497,000 Yen ($22,700) | 5,890,000 Yen ($53,545) |

Costs per year-of-life saved

Unit: 1,000 Yen

![Figure 3. Sensitivity analysis for males.](image_url)

**DISCUSSION**

Japan is the only country in which a mass screening program to detect gastric cancer has been initiated. The efficiency of annual screening rapidly decreases with a drop in its incidence. It is conceivable to improve the screening programs efficiency, provided that the screening interval longer than one year adopted. On the other hand, setting excessively long intervals would inevitably result in adverse effect on our effort to save lives, lowering the overall efficiency. Thus, deciding on the optimal screening frequency is of utmost importance.

Per year-of-life saved costs as demonstrated previously, show the interrelated differences between various interval lengths, with the annual screening sessions being least efficient option. Even as the screening intervals gain in length, there are reduced chances to save lives, for in the 4-year period, it is usually too late to intervene in gastric cancer cases. Based on attained results, we therefore
concluded that the most cost-effective screening interval is three years. The reason why the male gender shows no better rating in cost-effectiveness is that the male group displays a higher incidence in gastric cancer than their counterpart. Nevertheless, we arrived at the same conclusion regarding the most efficient screening interval applicable to both genders. However, efficiency is not only determinant for deciding screening interval. The effectiveness was a half of that of annual screening model and the cost-effectiveness of annual gastric cancer screening was not seemed to be so bad. Okubo, et al.\textsuperscript{24) reported that the cost-effectiveness study of annual breast cancer screening for a cohort aged 30 followed for 50 years, using mammography, stud at $2,728,000 per year-of-life saved in Japan. Tsuji, et al.\textsuperscript{25) estimated that the cost per year-of-life saved by annual colorectal cancer screening for a cohort aged 40 followed for 40 years was 3,308,500 yen for males and 4,130,300 yen for females. They were not more cost-effective than annual gastric cancer screening although their models were different from ours.

It was reported that the total cost of one gastric cancer screening was 873,215,860 yen and that of no screening option was 152,741,329 yen for hundred thousands of male fifties\textsuperscript{10). Our study showed the total cost per cohort of males was 10,637,096,000 yen for annual screening program. and 1,798,223,000 yen for no screening option. Their incremental cost-effectiveness per life year saved for male fifties was 980,000 yen, while ours for male cohort was 2,764,000. Two studies were compatible, considering that our study was assumed to be followed for twenty years and that the incidence of gastric cancer in our model was lower than in theirs. Although there are other studies referring to cost-effectiveness of gastric cancer screening in Japan, their and our results are not compatible because of a substantial difference in the study models and epidemiological data used.

In our case, life expectancy was used as the outcome measure for it relates to productivity and reflects the patients preferences. In addition, it is determined by a complex sequence of events in patients life. Given the fact that the probabilities of a patient transition among the different state-of-health categories are known, the life expectancy can be estimated using a Markov model\textsuperscript{26,27). Nevertheless, there seems to be a problem in the estimation. The survival rates we used in the study were based on observational studies. The rates are easy to be overestimated by biases\textsuperscript{28,29). Therefore, in our model, we took two and half years of lead time into consideration and chose to use a 10-year survival rate rather than 5-year, which would have reduced lead time bias\textsuperscript{30). Moreover, we applied the same stage specific 10-year survival rates to all other screening alternatives, although stage distributions are different within these categories. Thus, biases in survival rates would not change the efficiency order of the screening strategies.

This study has other several limitations. First of all, it is not based on a randomized controlled study but on a computer simulation, requiring numerous assumptions and
estimates. Second, lead time was estimated from observed difference in survival curves of patients who died of gastric cancer between screening detection and clinic detection. It might vary from the age of 40 to 60. Third, the risk of inducing cancer by X-ray was not considered. However, the radiation dosage associated with the exposure to indirect X-ray method is estimated to be low9). In summary, the most cost-effective screening interval is three years, although the screening program on an annual basis is not considered to be less efficient than other screening programs. However, the cost-effectiveness of gastric cancer is decreasing as its incidence decreases. It is very important for policy makers to pay attention to the incidence of diseases targeted by screening programs and to evaluate screening recommendations.

ACKNOWLEDGMENTS

We wish to thank Dr. Alan Hillman (University of Pennsylvania) for his kind advice on our modeling, Dr. Susumu Kanazawa (Department of Radiology, Okayama University Medical School) and Dr. Tsuneo Kato (Kato Clinic) for specialist opinions.

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