Simulation Models in Gastric Cancer Screening: A Systematic Review

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Abstract

Background: Together with such high-quality approaches as randomized controlled trials and large-scale cohort studies, simulation models are often employed to evaluate the effect of cancer screening methods and decide on their appropriateness. This study aimed to evaluate all effects of gastric cancer screening that have been assessed using simulation models, including cost-effectiveness, mortality reduction, and early-stage detection. Methods: We performed a systematic review using PubMed and Web of Science. We evaluated the effect of screening related to cost, such as incremental cost-effectiveness and incremental cost-effectiveness ratios; we also separately assessed effects other than cost, such as quality-adjusted life-years, number of deaths prevented, life-years saved, relative risk of mortality from gastric cancer; life expectancy, and incidence reduction. The methods targeted for evaluation were Helicobacter pylori testing or endoscopy. Results: We identified 19 studies dealing with simulation models in gastric cancer screenings: 14 examined H. pylori screening and 7 focused on endoscopy. Among those studies, two assessed both H. pylori and endoscopy screening. Most of the studies adopted a Markov model, and all the studies evaluated cost-effectiveness. Of the 14 H. pylori screening studies, 13 demonstrated cost-effectiveness and 11 also showed good results other than cost-effectiveness, such as extension of life-years and increase in early-stage detection. In three of the five endoscopy studies, the target population was patients; all five studies obtained good results for cost-effectiveness and four observed good results other than for cost-effectiveness. Conclusions: In this study, we showed that the H. pylori screening test was cost-effective in terms of simulation model investigations. However, the H. pylori screening test should not ordinarily be recommended since there is insufficient evidence that it reduces gastric cancer mortality. In Japan, simulation modeling should be employed to plan for cancer control, and the appropriate use of simulation models should be examined for future use.

Keywords: Simulation model- gastric cancer- screening- systematic review

Asian Pac J Cancer Prev, 19 (12), 3321-3334

Introduction

Gastrectomy is one of the leading causes of cancer incidence and mortality in Japan (Hori et al., 2015). Early detection is important towards reducing gastric cancer mortality, and mass screening using photofluorography has been implemented in Japan since 1982. The latest Japanese guidelines for gastric cancer screening published in 2014 by government recommends the use of endoscopy; that recommendation is based on scientific evidence, whereby gastric cancer screening by endoscopy could reduce gastric cancer mortality in a similar fashion to photofluorography (Terasawa et al., 2014). With a recommended means of cancer screening, it should be scientifically demonstrable that the screening is able to detect cancer at an early stage and also reduce cancer mortality. However, serum anti-Helicobacter pylori antibody testing and the serum pepsinogen method were not recommended in the above gastric cancer screening guidelines (Hamashima et al., 2008). Those two methods were introduced to the 2015 gastric cancer screening program among, respectively, 14.8% and 11.2% of Japan’s local governments (Ministry of Health, Labour and Welfare, 2017). The above gastric cancer screening guidelines do not recommend screening for the presence of H. pylori infection: no quality scientific research has demonstrated the effect of such screening on reducing gastric cancer mortality.

In general, randomized control trials (RCTs) are the most valuable method for evaluating health interventions, including cancer screening, prior to their...
broad population-based implementation. However, evaluating the effect of cancer screening on mortality reduction demands a long follow-up time and large groups of participants; thus, it is considerably difficult to make an evaluation in terms of such categories as sex, age, and risk factors. Accordingly, simulation models are often applied along with RCTs to ensure proper evaluation of the effects of screening (Koleva-Kolarova et al., 2015). For example, in screening for prostate, breast, and colorectal cancer, computer simulation modeling has been used to estimate the years of life lost as a result of those cancers in 50-year-old renal transplant recipients compared with subjects in the general population (Kiberda et al., 2003). In breast cancer screening, some simulation studies have been performed for mammography screening to determine an appropriate age for screening or to estimate cost-effectiveness (Koleva-Kolarova et al., 2015). In screening for gastric cancer using photofluorography, endoscopy, and H. pylori testing, several simulation studies have been undertaken, and a systematic review has reported the cost-effectiveness (Areia et al., 2013).

In the present study, we aimed to evaluate all the effects of gastric cancer screening, including cost-effectiveness, through a systematic review of all the published studies on gastric cancer screening that made an assessment using simulation models.

Materials and Methods

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist (Moher et al., 2009).

Eligibility criteria

Our inclusion criteria were studies of cancer patients in English- or Japanese-language publications and articles that described simulation studies. We excluded articles that were not original studies complete with full text, studies that were not simulation studies, and statistical studies. We hand searched the trials according to those criteria.

Information sources and search strategy

We conducted our search on July 11, 2016 in PubMed and Web of Science. The search terms were “gastric cancer,” “mass screening,” “endoscopy,” “X-ray,” and “simulation model.”

Data items and summary of results

We collected the following data: first author; publication year; country of study; population (number and age of target population [general population or patients]); type of simulation model; use of sensitivity and validation analysis; details of interventions; and sensitivity and specificity of screening and outcomes. We evaluated the effect related to cost, such as incremental cost-effectiveness and incremental cost-effectiveness ratios; we separately assessed the effect other than cost, such as quality-adjusted life-years (QALYs), number of deaths prevented, life-years saved, relative risk of mortality from gastric cancer, life expectancy, and incidence reduction.

We categorized the subjects into two groups according to the target population for the screening methods: general population and patients. The evaluated screening methods in the simulation were the H. pylori test, endoscopy, and both methods. We summarized the two groups of outcomes according to the screening methods.

Results

Study characteristics

The process of study selection appears in Figure 1. Our search resulted in 478 articles in PubMed and 2,361 articles in Web of Science. Two authors independently evaluated the titles and abstracts of all the selected articles using the inclusion criteria and excluded all non-relevant articles. Subsequently, we excluded articles that were not in English or Japanese (n=38), which resulted in 2,621 articles. Eventually, we identified 19 articles (Parsonnet et al., 1996; Harris et al., 1999; Fendrick et al., 1999; Davies et al., 2002; Mason et al., 2002; Roderick et al., 2003; Leivo et al., 2004; Dan et al., 2006; Lee et al., 2007; Xie et al., 2008; Xie et al., 2008; Shin et al., 2009; Xie et al., 2009; Yeh et al., 2009; Chang et al., 2012; Zhou et al., 2013; Yeh et al., 2016; Yeh et al., 2010; Hassan et al., 2010) that concerned simulation models on gastric cancer screenings.

The articles we found appear in Table 1. Among the 19 studies published between 1996 and 2016, eight were from Asia (China, Singapore, South Korea and, Taiwan), four from Europe (United Kingdom and Finland), six from the United States, and one from Canada. In all, 17 studies (Parsonnet et al., 1996; Harris et al., 1999; Fendrick et al., 1999; Davies et al., 2002; Mason et al., 2002; Roderick et al., 2003; Leivo et al., 2004; Dan et al., 2006; Lee et al., 2007; Xie et al., 2008; Xie et al., 2008; Shin et al., 2009; Xie et al., 2009; Yeh et al., 2009; Chang et al., 2012; Zhou et al., 2013; Yeh et al., 2016; Yeh et al., 2010; Hassan et al., 2010) that concerned simulation models on gastric cancer screenings.

![Figure 1. Flow Chart of Article-Selection Process](image-url)
| ID | Study   | Year     | Country  | Population | Model type          | Intervention and comparison                                                                 | Sensitivity of screening % (95%CI #) | Specificity of screening % (95%CI #) |
|----|---------|----------|----------|------------|---------------------|-----------------------------------------------------------------------------------------------|------------------------------------|----------------------------------|
| 1  | Parsonnet J | 1996     | United States | General population | 11,646,000 | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 2  | Harris RA | 1999     | United States | General population | 11,646,000 | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 3  | Fendrick AM | 1999     | United States | General population | NR       | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 4  | Davies R  | 2002     | United Kingdom | General population | 4,900,000 | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 5  | Mason J   | 2002     | United Kingdom | General population | 1,000,000 | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 6  | Roderick P | 2003     | United Kingdom | General population | 25,000,000 | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 7  | Leivo T   | 2004     | Finland    | General population | 5,228    | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 8  | Dan YY    | 2006     | Singapore  | General population | 600,839  | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 9  | Lee YC    | 2007     | Taiwan    | General population | ~3,700   | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| 10 | Xie F     | 2008     | Singapore  | General population | 237,900  | Sensitivity analysis [A: Markov model B: Computer simulation (unspecified)] | [497-506] | [456-460] |
| ID | Authors          | Year | Country    | Population                   | Model type          | Sensitivity analysis | Specificity analysis | Intervention and comparison                                                                 |
|----|------------------|------|------------|------------------------------|---------------------|----------------------|----------------------|-----------------------------------------------------------------------------------------------|
| 11 | Xie F            | 2008 | Singapore | General population           | A: Markov model     | Yes                  | Yes                  | (1) No screening (2) H. pylori serology screening (3) 13C-urea breath test for gastric cancer (UBT) |
| 12 | Shin DW          | 2009 | South Korea | General population           | A                    | Yes                  | NR                   | (1) Eradicate H. pylori after complete resection of EGC by endoscopy (2) Do not eradicate         |
| 13 | Xie F            | 2009 | Canada     | General population           | A                    | Yes                  | NR                   | (1) No screening (2) Serology test by enzyme-linked immunosorbent assay (ELISA) (3) Stool antigen test (SAT) (4) 13C-urea-urea breath test (UBT) |
| 14 | Yeh JM           | 2009 | China      | General population           | B                    | Yes                  | NR                   | (1) No screening (2) H. pylori screening once with a serology test and antibiotic treatment for positive test results (3) H. pylori screening once followed by rescreening individuals with negative results (4) Universal treatment (eradication) for H. pylori with antibiotics |
| 15 | Chang HS         | 2012 | South Korea | General population           | A                    | Yes                  | NR                   | (1) No screening (2) Screening using endoscopy (3) Screening using upper gastrointestinal X-ray (UGI) |
| 16 | Zhou HJ          | 2013 | Singapore | General population           | A                    | Yes                  | NR                   | (1) 2-yearly esophagogastroduodenoscopy (OGD) surveillance (2) Annual OGD surveillance (3) 2-yearly OGD screening (4) 2-yearly screening and annual surveillance |
| 17 | Yeh JM           | 2016 | United States | General population           | B                    | Yes                  | NR                   | (1) Serum pepsinogen screening (2) Endoscopic-based screening (3) H. pylori screening. |
| 18 | Yeh JM           | 2010 | United States | Patients (dysplasia/intestinal noncardia gastric adenocarcinoma (NCGA) microsimulation model) | B                    | Yes                  | Yes                  | (1) No treatment or surveillance (2) Referral for treatment and surveillance; varied by treatment for dysplastic and cancerous lesions (surgery or endoscopic mucosal resection) and surveillance frequency (none, every 1, 5, or 10 years) |
| 19 | Hassan C         | 2010 | United States | Patients (intestinal metaplasia) | B (Simple decision tree nested with a Markov model) | Yes                  | NR                   | (1) Non-surveillance (2) Surveillance EGD (upper endoscopy) every year for a 10-year period |

**Table 1.** Continued

NR, Not reported; # 95%CI: 95% Confidence interval.
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| ID | First author | Year | Country | "Target population" | Intervention | Outcomes measures | Main findings |
|----|--------------|------|---------|---------------------|--------------|------------------|--------------|
| 1  | Parsonnet J  | 1996 | United States | "Population (50 years; US population 51 years; women 52 years; men 53 years; African-Americans 54 years; Japanese-Americans 55 years; whites)" | H. pylori test, Endoscopy | Cost-effectiveness of screening and treatment (per year of life saved) | Screening and treatment program averted $221 million in discounted health-care costs for gastric cancer treatment. Preventing cases of gastric cancer, however, allowed medical costs from other illnesses to accrue. When these costs were included, only $4 million in discounted health-care expenditures were avoided by screening and treatment. With this more conservative estimate, the net cost-effectiveness of the model was $25,000 per year of life saved. |
| 2  | Harris RA    | 1999 | United States | "Population (18.039 life-years saved)" | H. pylori test, Endoscopy | Incremental cost (per life-year saved) | Screening for CagA-positive H. pylori is both more expensive and more effective than not screening, requiring $23,900 per life-year gained. More individuals are thus treated, requiring an additional expense of $16 and an additional benefit of approximately 0.001 life-years per person screened. |
| 3  | Fendrick AM  | 1999 | United States | "Population (12.1 discounted life-years saved per 1000 patients screened)" | H. pylori test, Endoscopy | Discounted cost (per life-year saved); assuming eradication eliminates excess gastric cancer risk | When gastric cancers prevented were translated into life expectancy, both screening strategies yielded more than 12 discounted life-years saved per 1000 screened when compared with not screening. Confirmatory testing and retreatment of those testing positive for H. pylori after therapy led to 2.3 additional life-years saved compared with the serology-only strategy. When the two H. pylori screening programs were compared with no screening, the resultant cost per life-year saved (serology-only strategy, $6,264 per life-year saved; serology and confirmatory testing, $11,313 per life-year saved) was considerably lower than the $50,000 per life-year saved threshold. Population-based H. pylori screening has the potential to produce important health benefits at a reasonable cost with moderate rates of excess risk reduction of cancer. |
Table 2. Continued

| ID | First author | Year | Country | Country | "Target population" | Intervention | Outcomes measures | Cost (95%CI #) | Cost (95%CI #) | Cost (95%CI #) | Main findings |
|----|--------------|------|---------|---------|----------------------|--------------|------------------|----------------|----------------|----------------|---------------|
| 4  | Davies R     | 2002 | United Kingdom | Population |● | ● (randomized to receive omeprazole, clarithromycin and tinidazole or placebos) | H. pylori screening and treatment | 1,300 | A statistically significant dyspepsia cost saving in men (£27.17 per subject), with no benefit in women (-£4.46 per subject). Modeling of these data suggested that population H. pylori screening and treatment would save over £6,000,000 and 1,300 years of life. Modeling suggests that population H. pylori screening and treatment are likely to be cost-effective and could be the first cost-neutral screening program. |
| 5  | Roderick P   | 2003 | United Kingdom | Population |● | ● (proton pump inhibitor, clarithromycin, and metronidazole) | H. pylori screening and treatment | 75 years | 16,263 | In the base case the cost-effectiveness rises with age but is under £10,000 per life-year saved for all age-groups. Lowering the discount rate for benefits in the base run significantly improves it to under £2000 per life-year saved in all groups. It is most cost-effective to screen at age 50 years under the base estimates, but increasing the lag to 20 years or assuming a higher opportunistic eradication rate considerably increases the cost per life-year saved. Deaths prevented decrease somewhat in the younger age-groups if there is re-infection and acquisition of H. pylori after age 20 years. H. pylori screening may be cost-effective in the long term. However, before screening can be recommended, further evidence is needed to resolve some of the uncertainties. |
| ID | First author | Year | Country | "Target population" | Intervention | Outcomes measures | Main findings |
|----|-------------|------|---------|---------------------|-------------|-------------------|--------------|
| 7  | Leivo T     | 2004 | Finland | Population          | H. pylori test, Endoscopy | Screening, Eradication | Incremental cost per case; no screening ($43); screening ($69) $26 The cost per case was $69 in screening. The incremental cost per case was $26 in screening compared with the no-screening alternative. The incremental cost per case was highest in the group aged 15 years and lowest in the group aged 45 years. H. pylori screening is more favorable in older age cohorts. However, there is uncertainty about the possible negative effect of eradicating H. pylori infection on gastroesophageal reflux disease and esophageal adenocarcinoma. |
| 8  | Dan YY      | 2006 | Singapore | Population          | ICER; cf. no screening | "Total population Women Men Chinese men" | "Total population Women Men Chinese men" |
|    |             |      |         |                     | $45,982 $63,298 $38,435 $26,836 | Deaths prevented Life-years saved | 1,144 369 775 743 18,273 4,139 8,336 8,234 |
|    |             |      |         |                     | "Total population Women Men Chinese men Total population Women Men Chinese men" | | |
|    |             |      |         |                     | "Primary prevention (C-urea breath test + H. pylori eradication) Secondary prevention (serum pepsinogen testing + endoscopy)" | "Primary prevention Secondary prevention Primary prevention Secondary prevention" | 0.86 0.87 71.382 71.379 |
|    |             |      |         |                     | Relative risk of mortality from gastric cancer Life expectancy | Relative risk of mortality from gastric cancer Life expectancy | |
|    |             |      |         |                     | $17,044 $29,741 | Both the primary and secondary prevention strategies led to more life-years gained than no intervention but also increased cost, yielding $17,044 and 29,741 per life-year gained, respectively. The primary prevention strategy dominated the secondary prevention strategy by achieving an average of 0.003 life-year gains (Life expectancy; primary prevention: 71.382 years, secondary prevention: 71.379 years) and lowering the cost by $6.2. The relative risk of mortality from gastric cancer was 0.86 per person in the primary prevention strategy and 0.87 per person in the secondary prevention strategy for no intervention." |
10. For eradication costs, we have not included the discounted costs of cancer prevention.

Table 2. Continued

| Year | Country | Population | Intervention | Outcome measures | Main findings |
|------|---------|------------|--------------|----------------|---------------|
| 2008 | Singapore | Serology C-urea breath test | $38,792 | $13,571 | $16,166 per life-year saved and $13,571 per QALY gained for serology screening, and $38,792 per life-year saved and $32,525 per QALY gained for the UBT. When compared with serology screening, the ICER was $477,079 per life-year saved or $390,337 per QALY gained for the UBT. The population-based serology screening for H. pylori was more cost-effective than UBT in the prevention of gastric cancer in Singapore Chinese males. |

12. Shin DW 2009 South Korea Populaton

H. pylori eradication costs less than no eradication and saves more lives (mean life expectancy from eradication: 13.60 years vs. 13.55 years). H. pylori eradication should be considered for reimbursement with the priority on preventing subsequent cancer and also reducing health-care costs.

Compared with no screening, the serology screening strategy for all Chinese people at age 40 years saved 788 life-years or gained 763 QALYs by preventing 101 gastric cancer cases at an extra cost of $20 million. UBT strategy saved 840 life-years or gained 814 QALYs by preventing 108 gastric cancer cases at an extra cost of $44 million. The ICER of serology screening versus no screening was $25,881 per QALY gained. The ICER of UBT versus serology screening was $470,000 per QALY gained. It cannot be confidently concluded that H. pylori screening was a cost-effective strategy than not screening in all Chinese at the age of 40 years. Serology screening has demonstrated much more potential as a cost-effective strategy, especially in the population with higher gastric cancer prevalence.
Cost-effectiveness ratios exceeded $2,500 per YLS.

Universal treatment prevented an increase in lifetime costs of $12. ICER was $1,340/YLS compared with no screening. Universal H. pylori treatment at age 20 reduced the lifetime risk of gastric cancer, providing an average increase in lifetime cancer risk by 14.5% (men) to 26.6% (women) and the discounted average life expectancy was 25.8015 years.

Screening once at age 20 provided a mean reduction of 14.5% in incidence ($1,560 per QALY) and the discounted average life expectancy was 26.1021 years. Rescreening individuals with negative results and targeting older ages was less cost-effective. Universal treatment prevented an increase in lifetime costs of $12. ICER was $1,340/YLS compared with no screening. Universal H. pylori treatment at age 20 reduced the lifetime risk of gastric cancer, providing an average increase in lifetime cancer risk by 14.5% (men) to 26.6% (women) and the discounted average life expectancy was 25.8015 years.

The no-screening strategy detected and treated 61 gastric cancer cases, cost a total of $157,300, and led to 19.8873 QALYs (for men) and 19.8875 QALYs (for women). Universal treatment prevented an increase in lifetime costs of $12. ICER was $1,340/YLS compared with no screening. Universal H. pylori treatment at age 20 reduced the lifetime risk of gastric cancer, providing an average increase in lifetime cancer risk by 14.5% (men) to 26.6% (women) and the discounted average life expectancy was 25.8015 years.

Table 2. Continued
| ID | First author | Year | Country | Target population | Intervention | Outcomes measures | Main findings |
|----|--------------|------|---------|-------------------|--------------|-------------------|---------------|
| 18 | Zhou HJ      | 2013 | Singapore | Population      | H. pylori test Endoscopy | Screening Eradication Screening (95%CI) | The 2-yearly esophagogastroduodenoscopy (OGD) surveillance was the most cost-effective strategy with the lowest ICER of $25,949/QALY. The annual OGD surveillance was projected to create 0.05 more QALYs and prevent 2,140 more GC deaths than the 2-yearly surveillance strategy. Endoscopic surveillance is potentially cost-effective in the prevention of GC for populations at low to intermediate risk. |
| 19 | Yeh JM       | 2016 | United States | Population | H. pylori screening Serum pepsinogen screening Endoscopic screening | Eliminated by extended dominance | Screening the general population at age 50 years reduced the lifetime intestinal-type noncardia gastric adenocarcinoma (NCGA) risk (0.24%). The relative reduction in intestinal-type NCGA lifetime risk was 26.4% with serum pepsinogen screening, 21.2% with endoscopic-based screening, and 0.2% with H. pylori screening at age 50 years. The gain in life expectancy was greatest for serum pepsinogen screening (2.7 days) compared with endoscopy with EMR (2.4 days) and H. pylori screening and treatment (0.01 days). For the overall cohort, compared with no screening, serum pepsinogen screening had an ICER of $105,400 per QALY gained. Serum pepsinogen screening dominated the other screening strategies as it was either less costly and more effective (endoscopic screening) or more effective and more cost-effective (H. pylori screening). |
| ID | First Author | Year | Country | “Target population” | Intervention | Outcomes measures | Cost (95%CI #) | Except cost (95%CI #) | Main findings |
|----|--------------|------|---------|---------------------|--------------|-------------------|----------------|---------------------|---------------|
| 15 | Yeh JM       | 2010 | United States | Patients | Incremental cost-effectiveness | Dysplasia EMR with surveillance every 10 years | $18,600 $20,900 $39,800 | undiscounted life expectancy | $28,488 $28,503 $544,500 $25,930,000 | Lifetime gastric cancer risk was 5.9%. EMR with annual surveillance reduced lifetime cancer risk by 90% and cost $39,800 per QALY. Strategies with EMR and surveillance every 10, 5, or 1 years had ICER less than $50,000/QALY. For EMR and annual surveillance, the addition of post-treatment surveillance every 10 years increased quality-adjusted life expectancy by 0.5 days (5%) at a cost of $1,048,000/QALY. All other strategies were either more costly and less effective or less costly and less cost-effective. |
| 16 | Hassan C     | 2010 | United States | Patients | “ICER (per QALY)” | Endoscopic surveillance | $72,519 (54,843-98,853) | Discounted years of saving (per person) | $28,7305 | The strategy of endoscopic surveillance for patients with IM compared with nonsurveillance was associated with the discounted saving of 0.041 year per person and with a discounted increase in cost of $2,969 per person. The incremental cost-effectiveness of endoscopic surveillance was $72,519, so this strategy appeared to be a cost-effective option compared with no surveillance, being the ICER less than the adopted threshold of $100,000. The relatively high risk of cancer in patients with IM and the substantial efficacy of endoscopic surveillance in reducing cancer-related mortality would support the cost-effectiveness of an endoscopic surveillance program in patients with IM. |
Table 3. Summary of Population Screening Assessment in 17 Studies

| Intervention | Outcomes | Effective | Not effective | Total* |
|-------------|----------|-----------|---------------|--------|
| H. pylori   | Cost     | 14⟨1⟩    | 3⟨2⟩          | 14     |
|             | Except for cost | 11       | 0              | 11     |
| Endoscopy   | Cost     | 5⟨3⟩     | 1⟨4⟩          | 5      |
|             | Except for cost | 4       | 0              | 4      |

*1, One study (Mason et al., 2002) showed a sex difference (effective in men, not beneficial in women); *2, One study (Yeh et al., 2016) showed efficacy only in pepsinogen screening; *3, One study (Yeh et al., 2009) showed less cost-effectiveness for the strategy considering eradication, although the strategy that did not consider eradication was cost-effective; *4, Number of studies that evaluated each item.

2009; Xie et al., 2009; Yeh et al., 2009; Chang et al., 2012; Zhou et al., 2013; Yeh et al., 2016) were conducted among healthy populations; two (Yeh et al., 2010; Hassan et al., 2010) were carried out on patients with dysplasia, intestinal metaplasia, or atrophy. Most of the studies adopted a Markov model and performed a sensitivity analysis. With regard to the effect of interventions, the sensitivity and specificity of the H. pylori test was set as 81%–99% and 79%–100%, respectively; the sensitivity and specificity of endoscopy was set at 70%–95% and 95%–100%, respectively.

Assessment of results of main outcomes

Details of the selected 19 studies appear in Table 2. A summary of the population screening assessment appears in Table 3.

Of all the 19 studies, 14 (Parsonnet et al., 1996; Harris et al., 1999; Fendrick et al., 1999; Davies et al., 2002; Mason et al., 2002; Roderick et al., 2003; Leivo et al., 2004; Lee et al., 2007; Xie et al., 2008; Xie et al., 2008; Xie et al., 2009; Shin et al., 2009; Yeh et al., 2009; Yeh et al., 2016) dealt with H. pylori screening. Seven studies (Dan et al., 2006; Lee et al., 2007; Chang et al., 2012; Zhou et al., 2013; Yeh et al., 2016; Yeh et al., 2010; Hassan et al., 2010) covered endoscopy. Two studies (Lee et al., 2007; Yeh et al., 2016) examined both H. pylori and endoscopy screening. All the studies evaluated cost-effectiveness, and 15 studies evaluated the outcomes except cost.

Both H. pylori screening and endoscopy screening were found to be cost-effective in all the studies evaluated. However, one study (Mason et al., 2002) reported a sex difference, whereby H. pylori screening was found to be beneficial for men but not for women. One study (Yeh et al., 2016) determined that serum pepsinogen screening was more cost-effective than H. pylori screening, but it was less costly than endoscopic screening. Another study (Yeh et al., 2009) showed that serum pepsinogen screening was less cost-effective in a strategy that considered eradication, although such screening was cost-effective in a strategy that did not consider eradication.

For an evaluation of the effect except cost, among the 11 studies on H. pylori screening and four studies on endoscopy screening, all 11 studies on H. pylori (Harris et al., 1999; Fendrick et al., 1999; Davies et al., 2002; Mason et al., 2002; Roderick et al., 2003; Lee et al., 2007; Xie et al., 2008; Shin et al., 2009; Xie et al., 2009; Yeh et al., 2009; Yeh et al., 2010; Yeh et al., 2016) and all the studies on endoscopy determined that screening had an effect on the number of deaths prevented, incidence reduction, life-years saved, greater life expectancy, or higher QALYs.

Discussion

We systematically reviewed published studies on gastric cancer screening that adopted simulation models. In all the selected studies, gastric cancer screening with endoscopy and the H. pylori test were cost-effective according to analyses using simulation models. This result is in line with previously reported cost-effectiveness analyses (Areia et al., 2013; Earnshaw et al., 2013). Omidvari et al., (2016) suggested that more research is needed about the efficacy of surveillance to inform more evidence-based cost-effective studies that aim to optimize surveillance programs for gastrointestinal cancers.

Studies on cancer screening using simulation models can provide important information, and the results of the present review are noteworthy. However, it is necessary to evaluate our findings with some caution: the results of simulation studies depend on the quality of the inputted data. That observation is particularly true of studies that do not adopt a good design, such as that of a randomized control study. Assessments based on simulation models are greatly influenced by the inputted data used in those models. For example, among the 14 studies dealing with H. pylori screening, 13 (Parsonnet et al., 1996; Harris et al., 1999; Fendrick et al., 1999; Davies et al., 2002; Mason et al., 2002; Roderick et al., 2003; Leivo et al., 2004; Lee et al., 2007; Xie et al., 2008; Xie et al., 2008; Shin et al., 2009; Yeh et al., 2009; Xie et al., 2016) considered H. pylori eradication as a treatment for individuals with H. pylori infection; the magnitude of eradication varied according to the study. Nine studies (Harris et al., 1999; Davies et al., 2002; Mason et al., 2002; Roderick et al., 2003; Leivo et al., 2004; Xie et al., 2008; Xie et al., 2008; Shin et al., 2009; Xie et al., 2009) determined that eradication of H. pylori reduced 30%–55% of the incidence of gastric cancer; those values are similar to ones identified in a meta-analysis (Ford et al., 2014). Several studies found that no gastric cancer occurred among subjects who underwent successful eradication treatment (Parsonnet et al., 1996) or the risk of gastric cancer became the same as among subjects who had never been infected by H. pylori (Fendrick et al., 1999; Lee et al., 2007; Yeh et al., 2009; Yeh et al., 2016).

Thus, simulation analysis for cancer screening strategy should basically not be conducted unless the effect has been demonstrated by means of strong evidence. The US Preventive Services Task Force is developing evidenced-based recommendations about preventive care using models for a preventive service that depend on the service under consideration, state of existing empirical evidence, suitability of models for specific purposes, and available resources (Owens et al., 2016). Therefore the use of modeling studies to develop recommendations should be regarded as supplemental measures. In the Japanese
Simulations and guidelines for gastric cancer screening, simulation studies were not considered because the recommendation of a new screening method should be based on strong scientific evidence obtained through highly reliable means, such as randomized control trials and large-scale cohort studies.

In the present study, using simulation model studies we showed that H. pylori screening test was cost-effective. However, that screening test should not ordinarily be recommended because there is a lack of sufficient evidence for gastric cancer screening with H. pylori testing being able to reduce gastric cancer mortality, and, therefore, no guidelines in the world recommend its use. Model-based evaluations have been used in health policy discussions and recommendations in such places as the United States and Canada. Simulation models can be used to identify appropriate age-ranges and intervals between screening tests; they cannot be employed to evaluate the effect on main outcomes, such as mortality reduction (Van et al., 1995).

In conclusion, when assessing cancer screening through the appropriate use of simulation models, the results should be beneficial to research and policy decisions. Chang et al., (2012) used Japanese and Korea data in a simulation model. In Japan, it is necessary to employ simulation modeling when planning for cancer control while sufficiently addressing the appropriate future use of simulation models.

Acknowledgments

This work was supported by Health and Labor Sciences Research Grants and by the Ministry of Education, Culture, Sports, Science and Technology in Japan Grant-in-Aid for Scientific Research Grant B.

We thank the Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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