REVIEW

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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

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Introduction

Gastric cancer is one of the leading causes of cancer incidence and mortality in Japan (Hori et al., 2015). Early detection is important toward 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 evaluating several 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

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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.,

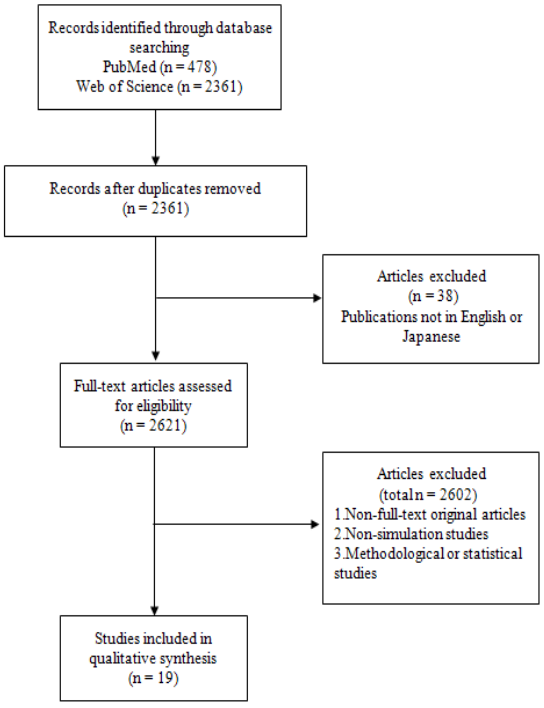

Figure 1. Flow Chart of Article-Selection Process

Table 1. Summary of Characteristics in Selected Articles

ID	Study	Year	Country	Population			Model type	Sensitivity analysis	Validation	Intervention and comparison	"Sensitivity of screening % (95%CI #)"	"Specificity of screening % (95%CI #)"
				Target population	n	Age (years)	"A: Markov model B: Computer simulation (unspecified)"					
1	Parsonnet J	1996	United States	General population	11,646,000	50–54	A	Yes	NR	"(1) Neither screening nor treating (2) Screening for H. pylori and treating individuals who test positive "	90% (80-100)	90% (80-100)
2	Harris RA	1999	United States	General population	11,646,000	50–54	A	Yes	NR	"(1) Neither screening nor treating (2) Screening and treating all H. pylori–infected individuals (3) Screening and treatingonly those infected with CagA-positive H. pylori"	90% (80-100)	90% (80-100)
3	Fendrick AM	1999	United States	General population	NR	NR	A	Yes	NR	"(1) No screening (2) H. pylori serological testing, treating those positive for H. pylori, no follow-up testing (3) H. pylori serological testing, treating those positive for H, pylori, followed by a test to confirm H. pylori eradication, retreating those who test positive"	"(2) 90% (85-95) (3) 95% (90-100)"	"(2) 90% (85-95) (3) 95% (90-100)"
4	Davies R	2002	United Kingdom	General population	4,900,000	≥50	"B (patient-orientated simulation technique: POST)"	Yes	NR	"(1) No screening (2) Screening for H. pylori infection"	"Serology test: 90% urea breath test: 100%"	"Serology test: 95% urea breath test: 100%"
5	Mason J	2002	United Kingdom	General population	1,000,000	40-49	A	Yes	NR	"(1) No screening (2) Screening for H. pylori infection (Attendance rate for screening was assumed to be 60%, which is higher than the response rate achieved in the trial.)"	90% (60-98)	90% (60-98)
6	Roderick P	2003	United Kingdom	General population	25,000,000	20-50	"B (patient-orientated simulation technique: POST)"	Yes	NR	"(1) No screening (2) Screening for H. pylori infection"	"Serology test: 95% (85-98) urea breath test: 98%"	"Serology test: 90% (78-90) urea breath test: 96%"
7	Leivo T	2004	Finland	General population	5,228	" 15–40(1996) 15 and 45 (1997, 1998)"	B	Yes	NR	"(1) No screening for H. pylori, and test and treat H. pylori only if related clinical symptoms appear (2) Screening for H. pylori infection and treat those individuals who test positive"	93%	97%
8	Dan YY	2006	Singapore	General population	600,839	50-70	A	Yes	NR	"(1) No screening endoscopy, investigation only for alarm symptoms (2) 2-yearly endoscopic mass screening"	70%-95%	95%-100%
9	Lee YC	2007	Taiwan	General population	~3,700	≥30	A	Yes	Yes	"(1) No screening (2) Chemoprevention with C-urea breath testing followed by H. pylori eradication (primary prevention) (3) High-risk surveillance based on serum pepsinogen measurement and confirmed by endoscopy (secondary prevention)"	"(2) 97.8% (3) endoscopy: 93%, serum pepsinogen: 70.5% (50-90)"	"(2) 96.8% (3) endoscopy: 100% serum pepsinogen: 97%"
10	Xie F	2008	Singapore	General population	237,900	35-44	A	Yes	NR	"(1) No screening and no eradication therapy (strategy 1) (2) H. pylori serology screening with eradication therapy (strategy 2) (3) C-urea breath test with eradication therapy (strategy 3)"	"(2) 93% (82-95) (3) 97.9% (90-100)"	"(2) 95.8% (90-100) (3) 79% (70-92)"

Table 1. Continued

ID	Study	Year	Country	Population			Model type	Sensitivity analysis	Validation	Intervention and comparison	"Sensitivity of screening % (95%CI #)"	"Specificity of screening % (95%CI #)"
				Target population	n	Age (years)	A: Markov model B: Computer simulation (unspecified					
11	Xie F	2008	Singapore	General population	478,500	40	A	Yes	NR	"(1) No screening (2) H. pylori serology screening (3) 13C-urea breath test for gastric cancer (UBT)"	"(2) 93% (82-95) (3) 97.9% (90-100)"	"(2) 95.8% (90-100) (3) 79% (70-92)"
12	Shin DW	2009	South Korea	General population	NR	NR	A	Yes	NR	"(1) Eradicate H. pylori after complete resection of EGC by endoscopy (2) Do not eradicate"	NR	NR
13	Xie F	2009	Canada	General population	"10000 (men)"	35	A	Yes	NR	"(1) No screening (2) Serology test by enzyme-linkedimmunosorbentassay (ELISA) (3) Stool antigen test (SAT) (4) 13C-urea-urea breath test (UBT)"	"(2) 85% (84-87) (3) 94% (93-95) (4) 99% (95-100)"	"(2) 79% (78-81) (3) 97% (96-98) (4) 99% (97-100)"
14	Yeh JM	2009	China	General population	NR	20-60	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 antibotics"	"Serology test: 90% (85-95) urea breath test: 95% (92-98)"	"Serology test: 90% (79-98) urea breath test: 95% (94-99)"
15	Chang HS	2012	South Korea	General population	NR	≥30	A	Yes	NR	"(1) No screening (2) Screening using endoscopy (3) Screening using upper gastrointestinal X-ray (UGI)"	NR	NR
16	Zhou HJ	2013	Singapore	General population	NR	50-69	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"	93% (44-99)	100% (95-100)
17	Yeh JM	2016	United States	General population	"NR (men)"	50	"B (Intestinal-type noncardia gastric adenocarcinoma (NCGA) microsimulation model)"	Yes	NR	"(1) Serum pepsinogen screening (2) Endoscopic-based screening (3) H. pylori screening."	"(1) 71% (2) 81% (3) 85% "	"(1) 98% (2) 100% (3) 79% "
18	Yeh JM	2010	United States	"Patients (dysplasia/ intestinal metaplasia/ atrophy)"	"NR (men)"	50	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)"	81% (78-95)	100% (98-100)
19	Hassan C	2010	United States	"Patients (intestinal metaplasia)"	10,000	60	"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"	NR	NR

NR, Not reported; # 95%CI: 95% Confidence interval

Table 2. Study Outcome Measures and Findings

ID	First author	Year	Country	"Target population"	Intervention			Outcomes measures					Main findings
					H. pylori test		Endoscopy	Cost		Except cost			
					Screening	Eradication	Screening		(95%CI #)			(95%CI #)	
1	Parsonnet J	1996	United States	Population	●	"● (omeprazole, clarithromycin, and metronidazole)"		"Cost-effectiveness of screening and treatment (per year of life saved)"	"50 years; US population 51 years; women 52 years; men 53 years; African-Americans 54 years; Japanese-Americans 55 years; whites"	"$25,000 (4800-152,100) $35,700 (6600-220.400) $19,900 (3600-119,900) $13,700 (2500-81,600) $4500 (1400-26,600) $34,900 (6500-21,400)"			The 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	●	"● (triple antibiotic therapy)"		"Incremental cost (per life-year saved)"	"Screening and treating all H. pylori Screening and treating only CagA-positive H. pylori"	"$25,100 $23,900 "	Life-years	"Screen and treat all H. pylori Screen and treat only CagA-positive H. pylori No screening"	"18.039 18.038 18.035"	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	●	●		"Discounted cost (per life-year saved); assuming eradiation eliminates excess gastric cancer risk"	"H. pylori serology H. pylori serology and confirmatory test"	"$6,264 $11,313"	"Discounted life-years saved (per 1000 patients screened); assuming eradiation eliminates excess gastric cancer risk"	"H. pylori serology H. pylori serology and confirmatory test"	"12.1 14.4"	"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. pyloli 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	"Target population"	Intervention			Outcomes measures					Main findings
					H. pylori test		Endoscopy	Cost		Except cost			
					Screening	Eradication	Screening		(95%CI #)			(95%CI #)	
4	Davies R	2002	United Kingdom	Population	●	●		"Costs incurred in 1st year Present value of costs incurred in screen-ing and treatment at 6% Present value; costs and benefits at 6%"	"Mean; (18,600,000 (Lower limit; 11,600,000 Up-per limit; 23,600,000) Mean; (37,800,000 (Lower limit; 33,100,000 Up-per limit; 48,800,000) Mean;) (6,500,000 (Lower limit; 23,500,000 Up-per limit; 39,800,000)"	"Total deaths prevented Life-years saved"		"Mean; 34,456 (33,178-35,734) Mean; 368,045 (352,686-383,404)"	"The initial cost of the screening program is likely to be around £18.7 million, but if the costs of pathology tests and drugs fall, there are likely to be considerable cost savings from reduced morbidity as a result of a screening program (present value, costs and benefits at 6%: £26.5 million). Further work is ongoing to relate the costs to the lives and life-years saved (mean: 368,045). The incidence of gastric cancer in the population and the prevalence of H. pylori both have a significant effect on deaths prevented (mean: 34,456) with a screening program. Screening programs for the general population may be beneficial. The modeling could be extended to examine the effects of screening of groups of the population that are at higher risk, such as males and those who live in areas of higher prevalence."
5	Mason J	2002	United Kingdom	Population	●	"● (randomized to receive omepra-zole, clarithromy-cin and tinidazole or placebos)"		Total health care cost; eradiation-placebo	"All patients Men Women"	"(-11.42 (-30.04-7.19) (-27.17 (-50.01--4.32) (6.68 (-37.4-50.78)"	"Life-years saved (per 1,000,000 screened)"	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.
6	Roder-ick P	2003	United Kingdom	Population	●	"● (proton pump inhibitor, clarithromycin, and metranida-zole)"		"Cost (per life-years saved)"		(5,866 (1,858-9,023)	Deaths prevented	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."

Table 2. Continued

ID	First author	Year	Country	"Target population"	Intervention			Outcomes measures					Main findings
					H. pylori test		Endoscopy	Cost	Except cost				
					Screening	Eradication	Screening		(95%CI #)			(95%CI #)	
7	Leivo T	2004	Finland	Population	●	"● (amoxycillin, metronidazole, lanzoprazole) "		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 treated H. pylori infection due to screening was $412. 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"	"$45,982 $63,298 $38,435 $26,836"	" Deaths prevented Life-years saved"	"Total population Women Men Chinese men Total population Women Men Chinese men"	"1,144 369 775 743 18,273 4,139 8,336 8,234"	Screening of the high-risk group of Chinese men aged 50–70 years is highly cost-effective, with cost benefits of $26,836 per QALY and $22,346 per year of life saved. Screening this cohort of 199,000 subjects prevents 743 stomach cancer deaths and saves 8,234 absolute life-years. Cost of averting one cancer death is $247,600. Cost-effectiveness was most sensitive to the incidence of stomach cancer and cost of screening endoscopy.
9	Lee YC	2007	Taiwan	Population	●	●	●	ICER	"Primary prevention (C-urea breath test + H. pylori eradiation) Secondary prevention (serum pepsinogen testing + endoscopy)"	" $17,044 $29,741"	" Relative risk of mortality from gastric cancer Life expectancy"	"Primary prevention Secondary prevention Primary prevention Secondary prevention"	"0.86 0.87 71.382 71.379"	"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."

Table 2. Continued

ID	First author	Year	Country	"Target population"	Intervention			Outcomes measures						Main findings
					H. pylori test		Endoscopy	Cost		Except cost				
					Screening	Eradication	Screening			(95%CI #)			(95%CI #)	
10	Xie F	2008	Singapore	Population	•	•		"ICER (per life-years saved) ICER (per QALY)"	"Serology C-urea breath test Serology C-urea breath test "	"$16,166 $38,792 $13,571 $32,525 "				"Strategy 2, which implemented serology screening on all cohort members with treatment for those with positive tests, cost $9.8 million, which saved 523 life-years or gained 623 QALYs by preventing 272 gastric cancer cases. Strategy 3, which implemented the UBT on this cohort with treatment for those with positive tests, cost $23.0 million, which saved 550 life-years or gained 656 QALYs by preventing 281 gastric cancer cases. In all, 875 and 847 people were screened for each case of gastric cancer prevented in strategy 2 and 3, respectively. The serology screening avoided $1.4 million of discounted expenditure on treatment of gastric cancer; the UBT avoided $1.5 million. The ICER were $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."
11	Xie F	2008	Singapore	Population	•	•		"ICER (per QALY)"	"Serology screening; by comparing serology screening with no screening UBT; by comparing UBT with serology screening"	"$25,881 $471,746"	"Life-years saved QALYs"	" Serology screening UBT Serology screening UBT "	"9,492,138 9,492,190 8,886,545 8,886,596"	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.
12	Shin DW	2009	South Korea	Population	•	•		ICER	Eradication	Dominant	Life expectancy	Eradication	13.6	"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."

Table 2. Continued

ID	First author	Year	Country	"Target population"	Intervention			Outcomes measures						Main findings
					H. pylori test		Endoscopy	Cost		Except cost				
					Screening	Eradication	Screening		(95%CI #)				(95%CI #)	
13	Xie F	2009	Canada	Population	•	•		"ICER (per QALY)"	"Serology test by enzyme-linked immunosorbent assay (ELISA) Stool antigen test (SAT); by comparing the SAT with no screening UBT; by comparing the UBT with the SAT"	"$33,115 $29,850 $533,000"	QALYs	"ELISA SAT UBT"	"19.8887 19.8889 19.8890"	"The no-screening strategy detected and treated 61 gastric cancer cases, cost a total of $157,300, and led to 19.8873 QALYs (for the treatment of gastric cancer). The corresponding values were 56 cases, $627,200, and 19.8887 QALYs for the serology test by ELISA, 55 cases, $625,700, and 19.8887 QALYs for SAT, and 55 cases, $982,000, and 19.88890 QALYs for the UBT. Compared with the no-screening strategy, the ICER was $33,000 per QALY for the ELISA, $29,800 per QALY for SAT, and $50,400 per QALY for the UBT. The incremental cost per gastric cancer case prevented was $115,000 for the ELISA, $103,000 for the SAT, and $208,000 for the UBT. Although UBT had the highest sensitivity and specificity, either no screening or SAT could be the most cost-effective strategy depending on the willingness to pay (WTP) threshold values from an economic perspective."
14	Yeh JM	2009	China	Population	•	•		"ICER (per life-years saved) ICER (per QALY)"	"Screen: men Screen + rescreen once: men Universal treatment (eradiation): men Screen + rescreen twice: men Screen: women Screen + rescreen once: women Universal treatment (eradiation): women Screen + rescreen twice: women Screen: men Screen + rescreen once: men Universal treatment (eradiation): men Screen + rescreen twice: men Screen: women Screen + rescreen once: women Universal treatment (eradiation): women Screen + rescreen twice: women "	"$1,340 dominated $2,720 dominated $1,230 dominated $2,510 dominated $1,560 dominated $3,250 dominated $1,500 dominated $3,060 dominated "	Gastric cancer incidence reduction	"Screen: men Screen + rescreen once: men Universal treatment (eradication): men Screen + rescreen twice: men Screen: women Screen + rescreen once: women Universal treatment (eradication): women Screen + rescreen twice: women"	"14.5% (6.5-30.2) 15.6% (7.0-32.5) 16.1% (7.2-33.6) 15.7% (7.0-32.7) 26.6% (12.9-40.0) 28.8% (13.9-43.3) 29.5% (14.3-44.5) 28.9% (14.0-43.6)"	"Screening and treatment for H. pylori at age 20 reduced the mean lifetime cancer risk by 14.5% (men) to 26.6% (women) and cost less than $1,500 per year of life saved (YLS) compared with no screening. Universal H. pylori treatment at age 20 reduced lifetime risk by 16.1%. In the absence of H. pylori screening or treatment, the discounted per person average lifetime cost was $19 and the discounted average life expectancy was 25.8015 years. Screening once at age 20 provided a mean reduction of 14.5% in the lifetime risk of gastric cancer, providing an average increase in life expectancy of 3.2 days and an increase in lifetime costs of $12. ICER was $1,340/YLS compared with no screening. Universal treatment dominated strategies that included rescreening in that they were less costly and less cost-effective, or more costly and less effective. Results in which life expectancy was quality-adjusted were similar, with an ICER of $1,560 per QALY for screening once and $3,250 per QALY for universal treatment. Rescreening individuals with negative results and targeting older ages was less cost-effective. Universal treatment prevented an additional 1.5%–2.3% of risk reduction, but incremental cost-effectiveness ratios exceeded $2,500 per YLS."
17	Chang HS	2012	South Korea	Population			•	"ICER (per QALY)"	"Males 50-80 age, 2 years endoscopy Males 50-80 age, 2 years upper gastrointestinal X-ray (UGI) Females 50-80 age, 2 years endoscopy Females 50-80 age, 2 years upper gastrointestinal X-ray (UGI)"	"$5,116 dominated $11,378 dominated"				"Based on commonly accepted thresholds of society's willingness to pay per QALY of $19,162, the endoscopic gastric cancer screening at the starting age of 50 years may be highly cost-effective in the Korean population. Comparing the net health benefit among these strategies, annual endoscopic screening for Korean men aged 50–80 was the most cost-effective strategy for the defined willingness-to-pay threshold. The 2-year-interval endoscopic screening of Korean women from the age of 50 to 80 was the most cost-effective screening strategy for the defined willingness-to-pay threshold. Endoscopic gastric cancer screening starting at the age of 50 years was highly cost-effective in the Korean population."

Table 2. Continued

ID	First author	Year	Country	"Target population"	Intervention			Outcomes measures						Main findings
					H. pylori test		Endoscopy	Cost			Except cost			
					Screening	Eradication	Screening			(95%CI #)			(95%CI #)	
18	Zhou HJ	2013	Singapore	Population			●	"ICER (per QALY)"	"2-year surveillance Annual surveillance 2-yearly screening 2-yearly screening + annual surveillance"	"$25,949 $44,098 $79,673 $59,565"	QALYs	"No esophagogastroduodenoscopy (OGD) intervention 2-year surveillance Annual surveillance 2-yearly screening 2-yearly screening + annual surveillance"	"18.22 18.27 18.29 18.33 18.36"	"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	●		●	Incremental cost-effectiveness	"H. pylori screening Serum pepsinogen screening Endoscopic screening"	"Eliminated by extended dominance (less effective and less cost-effective than a more expensive strategy) $105,400.00 Eliminated by strong dominance (less effective and more costly than another strategy) "	" Conditional life-expectancy (years) QALYs"	" No screening H. pylori screening Serum pepsinogen screening Endoscopic screening No screening H. pylori screening Serum pepsinogen screening Endoscopic screening "	" 56.8009 56.8009 56.8084 56.8074 23.7820 23.7820 23.7833 23.7827 "	"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)."

Table 2. Continued

ID	First author	Year	Country	"Target population"	Intervention			Outcomes measures						Main findings
					H. pylori test		Endoscopy	Cost		Except cost				
					Screening	Eradiation	Screening		(95%CI #)				(95%CI #)	
15	Yeh JM	2010	United States	Patients			●	Incremental cost-effectiveness	"Dysplasia EMR with surveillance every 10 years EMR with surveillance every 5 years EMR with surveillance every 1 year EMR with surveillance every 1 year and post-treatment surveillance every 10 years Intestinal metaplasia EMR with surveillance every 10 years EMR with surveillance every 10 years and post-treatment surveillance every 10 years"	" $18,600 $20,900 $39,800 $1,048,000 $544,500 $25,930,000"	Undiscounted life expectancy	"Dysplasia No treatment or surveillance EMR with surveillance every 10 years EMR with surveillance every 5 years EMR with surveillance every 1 year EMR with surveillance every 1 year and post-treatment surveillance every 10 years Intestinal metaplasia No treatment or surveillance EMR with surveillance every 10 years EMR with surveillance every 10 years and post-treatment surveillance every 10 years "	" 28.0839 28.4888 28.5093 28.5238 28.5314 28.711 28.7303 28.7305 "	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)"	Intestinal metaplasia (IM) compared with nonsurveillance	0.041	"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."

#, 95% Confidence interval; ●, Screening using H. pylori test and eradiation if necessary, or endoscopy carried out; QALYs, quality-adjusted life-years; ICER: incremental cost-effectiveness ratio

Table 3. Summary of Population Screening Assessment in 17 Studies

Intervention	Outcomes	Effective	Not effective	Total[*4]
H. pylori	Cost	14[*1*2]	3[*1*2*3]	14
	Except for cost	11	0	11
Endoscopy	Cost	5[*2]	1[*2]	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; Shin et al., 2009; Xie 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., 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; Xie et al., 2009; Yeh 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

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 the *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.

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