Cost-effectiveness Analysis between Primary and Secondary Preventive Strategies for Gastric Cancer

Yi-Chia Lee,[1,2,3] Jaw-Town Lin,[3] Hui-Min Wu,[1] Tzeng-Ying Liu,[5] Ming-Fang Yen,[1] Han-Mo Chiu,[1,3] Hsiu-Po Wang,[4] Ming-Shiang Wu,[3] and Tony Hsiu-Hsi Chen[1,2]

[1]Institute of Preventive Medicine and [2]Division of Biostatistics, Graduate Institute of Epidemiology, College of Public Health; Departments of [3]Internal Medicine and [4]Emergency Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; and [5]Health Bureau of Lienchiang County, Matsu, Taiwan

Abstract

Objective: **The present study is done to assess the relative cost-effectiveness, optimal initial age, and interscreening interval between primary and secondary prevention strategies for gastric cancer.**

Methods: **Base-case estimates, including variables of natural history, efficacy of intervention, and relevant cost, were derived from two preventive programs targeting a high-risk population. Cost-effectiveness was compared between chemoprevention with ^{13}C urea breath testing followed by *Helicobacter pylori* (*H. pylori*) eradication and high-risk surveillance based on serum pepsinogen measurement and confirmed by endoscopy. The main outcome measure was cost per life-year gained with a 3% annual discount rate.**

Results: **The incremental cost-effectiveness ratio (ICER) for once-only chemoprevention at age 30 years versus no screening was U.S. $17,044 per life-year gained. Eradication of *H. pylori* at later age or with a periodic scheme yielded a less favorable result. Annual high-risk screening at age of 50 years versus no screening resulted in an ICER of U.S. $29,741 per life-year gained. The ICERs of surveillance did not substantially vary with different initial ages or interscreening intervals. Chemoprevention could be dominated by high-risk surveillance when the initial age was older than 44 years. Otherwise, chemoprevention was more cost-effective than high-risk surveillance, either at ceiling ratios of U.S. $15,762 or up to U.S. $50,000. The relative cost-effectiveness was most sensitive to the infection rate of *H. pylori* and proportion of early gastric cancer in all detectable cases.**

Conclusions: **Early *H. pylori* eradication once in lifetime seems more cost-effective than surveillance strategy. However, the choice is still subject to the risk of infection, detectability of early gastric cancer, and timing of intervention.** (Cancer Epidemiol Biomarkers Prev 2007;16(5):875–85)

Introduction

Despite the decreasing trend in gastric cancer in developed countries, the disease remains one of the most common cancers worldwide, especially in Central Europe, South America, and Asia (1). Gastric cancer detected at a symptomatic stage often results in poor survival and high recurrence in spite of various modalities for rescue treatment. These findings suggest that preventive strategies are of paramount importance.

The rationale of traditional cancer screening is to identify high-risk group at first stage and further refer them to receive confirmatory diagnosis and early treatment, namely secondary prevention (2). For instance, early detection of subjects with extensive atrophic gastritis who are at higher risk for gastric cancer can be achieved by measuring serum pepsinogen levels, or serologic biopsy, based on the mechanism related to the physiologic change of two enzyme secretions in stomach, with high circulating levels of both serum pepsinogen-I and pepsinogen-II initially in mild gastritis and accompanied by a decrease in pepsinogen-I levels but an increase or no change in pepsinogen-II levels due to gradual replacement of chief cells by pyloric glands when gastritis progresses (3, 4). Such a detection modality often finds early gastric cancer with tumor invasion restricted to the mucosa or to the mucosa and submucosa, leading to better long-term survival after early treatment (5-7). The pepsinogen method is proven efficacious as one of the major prevention strategies for high-risk populations (3, 4, 8-10).

Another newer approach with the eradication of *Helicobacter pylori* (*H. pylori*) infection has been suggested as primary prevention of gastric cancer. The theory is based on the strong association between *H. pylori* infection and risk of gastric cancer (11, 12). The rationale of primary prevention is to arrest the carcinogenesis cascade and prevent irreversible change (13). Several health economic models have suggested the cost-effectiveness of *H. pylori* eradication programs in decreasing the mortality of gastric cancer (14-18). However, these studies mainly focused on populations with low *H. pylori* prevalence and low gastric cancer incidence. For high-risk population, the acquisition/reinfection rate of *H. pylori* is higher and progression of carcinogenesis is accelerated. It remains uncertain whether *H. pylori* eradication can readily substitute high-risk surveillance as the first-line prevention strategy (19).

Therefore, although both primary and secondary prevention strategies are reasonable for population-based screening programs, the relative costs and benefits, particularly long-term outcome, still remain elusive. In Taiwan, two periods of gastric cancer prevention programs have been done targeting a high-risk population. At the inception of program conducted between 1995 and 1999, subjects with positive serum pepsinogen measurements were referred to receive the diagnostic endoscopy (20). A chemoprevention program with the eradication of *H. pylori* has been implemented between 2004 and 2005 (21). Both data offer an opportunity to compare the cost-effectiveness between these two strategies with a primary end-point of mortality reduction by using a computer simulation method, which is the major goal of this study.

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Requests for reprints: Tony Hsiu-Hsi Chen, Institute of Preventive Medicine and Division of Biostatistics, Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Room 521, No. 17, Hsu-Chow Road, 100 Taipei, Taiwan. Phone: 886-2-33228021; Fax: 886-2-23587707. E-mail: stony@episerv.cph.ntu.edu.tw

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Optimal initial age and interscreening interval were also assessed in subsidiary analysis.

Materials and Methods

Target Population. Our target population comprised ~3,700 native residents of Matsu Island ages 30 years or older who were registered on the island population list. Matsu is an offshore island located ~100 miles from the shores of Taiwan near the northern coast of Fujian Province on mainland China. Residents of Matsu have a high incidence of gastric cancer. According to a cancer registry report, annual incidence rate from 1985 through 1999 was ~103 per 100,000 population (22). Pregnant or lactating women, patients with major concomitant diseases, and those who had undergone gastric surgery were excluded from the study. Participants provided informed consent, and the Ethics Committee of National Taiwan University Hospital approved the study protocols in 1995 and 2004, respectively.

Primary and Secondary Interventions. We divided the gastric cancer prevention campaign into two periods: 1995 to 1999 and 2004 to 2005. In the first period, 2,184 residents participated in a secondary prevention program. Two-stage screening design was adopted to detect precancerous lesions or early gastric cancer. The first stage used a serologic test and a questionnaire. The second stage was the use of endoscopy to screen whose pepsinogen-I was lower than 30 ng/mL. Endoscopic biopsy was done at gastric antrum and corpus to obtain the histopathologic results. The details of screening and confirmatory diagnosis referred to the reports by Liu et al. (20). The program provided annual screening for 5 years and the whole population was linked to the Taiwan Cancer Registry to ascertain the development of noncardia gastric cancer.

In the second period, 1,654 participants were enrolled in a primary prevention program with a view to eradicating *H. pylori*. The first stage was testing for *H. pylori* via using the ^{13}C urea breath test. Participants with positive results for infection underwent *H. pylori* eradication. The process of enrollment, ^{13}C urea breath testing, and eradication referred to the report by Lee et al. (21).

Simulation Model DesignA Markov decision model was constructed with three different strategies using a commercially available software package (TreeAge Pro 2004; TreeAge Software, Inc.). These three strategies included (*a*) no intervention if the patient came to medical attention as a result of symptoms of gastric cancer; (*b*) chemoprevention with *H. pylori* eradication; and (*c*) annual screening for high-risk individuals using the serum pepsinogen method and subsequent endoscopic examinations. The length of the Markov cycle or time between state transitions was 1 year. Because the transmission of *H. pylori* began since birth, the model simulated the natural history of a hypothetical cohort with a time horizon from birth (with normal gastric mucosa) to 80 years of age.

Primary end points were based on life-year gained by converting the magnitude of mortality reduction as a result of each intervention. Economic measures included direct and indirect costs, which were imputed from the empirical data. Direct costs included those for screening, confirmatory diagnosis, treatment, and terminal care. Indirect costs were mainly related to loss of productivity. A 3% discount rate was applied to convert future cost and effectiveness to present values. An incremental cost-effectiveness ratio (ICER), the difference in costs divided by the difference gained in life-year between the program of interest and the comparator, was imputed to compare three prevention strategies. The ceiling ratio, the maximum amount of willingness to pay per life year gain, of ICER was set at the value of U.S. $15,762, very close to the average gross national product per person in 2004.

Estimates for Natural History. A six-state Markov model based on Correa's model (13) was applied to the data derived from the secondary prevention program (1995-1999) to estimate five step-by-step progression rates, including annual incidences of changes from normal to chronic active gastritis [λ_1, 0.0216 per year; 95% confidence interval (95% CI), 0.015-0.0281], from chronic active gastritis to atrophic gastritis (λ_2, 0.0647 per year; 95% CI, 0.0381-0.0914), from atrophic gastritis to intestinal metaplasia (λ_3, 0.0521 per year; 95% CI, 0.0227-0.0815), from intestinal metaplasia to gastric cancer (λ_4, 0.0031 per year; 95% CI, 0.0018-0.0044), and from gastric cancer to death (λ_5, 0.4776 per year; 95% CI,: 0.0096-0.9456). The conceptual framework is shown in Fig. 1. The details of estimation refer to the Liu et al. study (20). Annual transition probabilities converted by transition rates following Chen et al. method (23) are listed in Table 1.

As we were also interested in the effect of *H. pylori* infection on the carcinogenesis cascade, an exponential Markov regression model with *H. pylori* infection as a covariate was used to assess the effect of positive infection on each transition. The technique for variable estimation refers to the method by Shiu and Chen (24). Regarding the influence of *H. pylori* infection, the previous results showed that *H. pylori* infection was only statistically associated with the transition from normal to chronic active gastritis (relative risk, 1.6; 95% CI, 1.27-2.08), but not associated with two subsequent transitions, from chronic active gastritis to atrophic gastritis (relative risk, 1.12; 95% CI, 0.78-1.58) and from atrophic gastritis to intestinal metaplasia (relative risk, 0.63; 95% CI, 0.36-1.13; ref. 20). This suggests that *H. pylori* eradication was beneficial in arresting the carcinogenesis cascade only at the initial stage, which is consistent with the findings of a randomized controlled trial by Wong et al. (19). The corresponding transition probabilities given these variables are also listed in Table 1. The details of methodology have been described in full elsewhere (25).

The other model variables were also derived from estimates obtained from the two periods of gastric cancer prevention programs. When unavailable, the variables were cited from the literature. Base-case values and ranges used in sensitivity analyses are summarized in Table 1.

Intervention Strategies. *No Intervention.* The strategy without any intervention followed the natural history of gastric carcinogenesis cascade (Appendix Fig. 1). The patient seeks medical care when he or she has symptoms or signs of gastric cancer. The competing risk of death was taken into

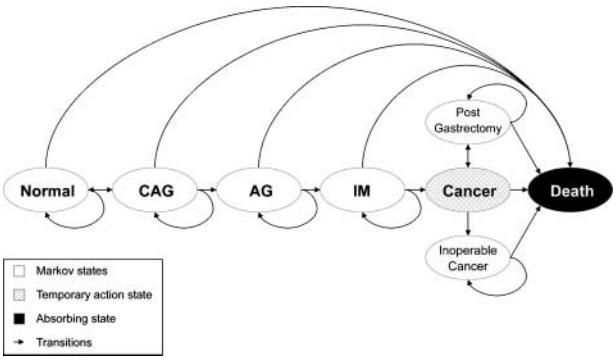


Figure 1. The conceptual framework on Markov state transition model. A simulated patient spends time in a Markov state every cycle until he dies. *Arrows,* transitions that are made with each cycle. A Markov state that points to itself represents continuing in that particular state. If the patient is found by endoscopy to have cancer, surgery is done if he is eligible for resection. *CAG,* chronic active gastritis; *AG,* atrophic gastritis; *IM,* intestinal metaplasia.

Table 1. Base-case estimates

Variable	Base-case analysis*	Distribution for probabilistic sensitivity analysis †	Source ‡
Natural history and prognosis per year, %			
Transition probabilities of gastric carcinogenesis			(20)
Normal to CAG with/without *H. pylori* infection	3.3; 2.1	β (41, 1175); β (42, 1941)	
CAG to AG	6.1	β (21, 327)	
AG to IM	5.1	β (11, 218)	
IM to gastric cancer	0.25	β (1, 398)	
Gastric cancer to death	38	β (2, 4)	
Postoperative mortality of early gastric cancer	3		(7)
Survival rate of early gastric cancer	97.9 (62-97.9)		(6)
Primary prevention characteristics, %			
Acquisition and reinfection of *H. pylori*, per year	1 (0.5-2.5)	Norm (1, 0.2)	(27, 28)
[^{13}C]UBT			
Attendance	64.2 (20-100)	Norm (60, 10)	(21)
Sensitivity	97.8		(29)
Specificity	96.8		(29)
H. pylori eradication with triple therapy	87		(21)
Secondary prevention characteristics, %			
Serum pepsinogen testing			
Attendance	61.7 (20-100)	Norm (60, 10)	(20)
Sensitivity for gastritis to AG	70.5 (50-90)	Norm (70, 10)	(8-10)
Specificity for gastritis to AG	97		(8-10)
Endoscopy			
Attendance	74 (30-74)	Norm (50, 10)	(20)
Sensitivity	93		(31)
Specificity	100		(31)
Early gastric cancers among detectable cases	30 (10-90)	Norm (50, 10)	(8, 9, 20, 21)
Complications	0.2		(32)
Mortality in patents with complications	0.05		(32)
Direct costs, U.S. $			
[^{13}C]UBT	36.3	Triang (10-36.3-140)	BNHI (33)
Triple therapy for *H. pylori* eradication	42.2	Triang (4.2-42.2-150)	BNHI (14)
Serum pepsinogen testing	19	Triang (10-19-40)	BNHI
Endoscopy with biopsy	68.8 (68.8-800)	Triang (10-68.8-800)	BNHI
Nonfatal complication of endoscopy	1,925	Triang (193-1,925-16,372)	NTUH (34)
Fatal complication of endoscopy	8,848	Triang (885-8,848-54,000)	NTUH (34)
Initial management of early gastric cancer	3,900	Triang (390-3900-27779)	NTUH (34)
Initial management of advanced gastric cancer	9,750	Triang (975-9,750-52,000)	NTUH (14)
Continuing treatment for advanced gastric cancer	294		NTUH
Incurable-cancer care	8,938	Triang (894-8,938-52,000)	NTUH (14)
Indirect costs			
Screening time, h	0.5		(20, 21)
Person accompanied for screening	0		(20, 21)
Confirmation time, h	1		(20, 21)
Person accompanied for confirmation	0.2		(20, 21)
Inpatient hospitalization, d	21		BNHI
Inpatient recovery at home, d	20		NTUH
Person accompanied for inpatient care	1.25		NTUH
Outpatient time per visit, h	4		NTUH
Outpatient visits per year	4.68		BNHI
Person accompanied for outpatient visit	0.2		NTUH
Average GNP per person, U.S. $	15,762	Triang (1,714-15,762-41,984)	DGBAS
Average monthly work, h	182		DGBAS
Production value per hour, U.S. $	7.2		DGBAS
Discount rate, %	3 (1-5)		CBC

Abbreviations: AG, atrophic gastritis; BNHI, Bureau of the National Health Insurance; CAG, chronic active gastritis; CBC, Central Bank of China; DGBAS, Directorate General of Budget, Accounting and Statistics; GNP, gross national product; IM, intestinal metaplasia; NTUH, National Taiwan University Hospital; UBT, urea breath test.

*Data in parentheses are the range used in sensitivity analysis.

† β (a,b) = β distribution with a transitions from b cases; Norm (a, b) = normal distribution with mean a, lower bound of 95% CI b. Triang (a,b,c) = triangular distribution with minimum a, mode b, maximum c. The base-case values were applied unless otherwise specified.

‡ Numbers are reference citations.

account by using the life table based on the database from annual statistics issued by Department of Health in Taiwan. Although the susceptibility of *H. pylori* infection remains debatable especially during childhood and adolescence, we used the local epidemiologic data and assumed an annual infection rate of 1% as the base-case value to estimate the acquisition and reinfection rates (26, 27). A wide range was repeated for sensitivity analysis to accommodate a series of infection rates across different regions (28).

Direct costs included those related to the initial management of gastric cancer, its continuing treatment, and care for incurable terminal cancer. Base-case values of the costs were derived from the statistics of the Bureau of National Health Insurance or our academic institute. Indirect costs were calculated based on the data from the Directorate General of Budget, Accounting and Statistics. All cost-effectiveness ratios were converted to U.S. dollars at the exchange rate used in the year of 2005 (NTD 32 were worth the same as U.S. $1).

Primary Prevention with H. pylori *Eradication.* Primary prevention was intended to arrest the progression of carcinogenesis cascade. However, patients came to medical attention

only if they developed symptoms of gastric cancer. Typical chemoprevention consisted of an initial ^{13}C urea breath test and individuals with positive results received standard triple therapy to eradicate *H. pylori* infection (19, 21). Endoscopy was not required (Appendix Fig. 2). With the use of an IR spectrometer, the ^{13}C urea breath test had a sensitivity of 97.8%, a specificity of 96.8%, and an accuracy of 97.5%, according to a validation study at our institution (29). By intention-to-treat analysis, including participants who had taken at least one tablet of the drug, we achieved an 87% eradication rate in our chemoprevention program between 2004 and 2005 (21). The efficacy of standard triple therapy with a 7-day regimen of esomeprazole 40 mg once daily, amoxicillin 1 g twice daily, and clarithromycin 500 mg twice daily had met the requirements of a consensus statement (30). The costs of screening, which included ^{13}C urea breath testing and standard triple therapy, were obtained from the Bureau of National Health Insurance.

Secondary Prevention with the Serum Pepsinogen Method. This strategy consisted of an initial serum pepsinogen measurement to identify subjects with extensive atrophic gastritis, whom were referred to the second stage to have endoscopic surveillance (Appendix Fig. 3). Typical secondary prevention provides screening at a regular interscreening interval. In the updated criterion for the serum pepsinogen method, atrophic is defined as a serum pepsinogen-I level ≤70 ng/mL and a ratio of pepsinogen-I to pepsinogen-II ≤3.0 (8, 9). The derived sensitivity and specificity were adopted as the base-case values. A recent biomarker incorporating the serum pepsinogen, gastrin-17, and *H. pylori* antibody may achieve 90% sensitivity for the diagnosis of atrophic gastritis, which was used as the upper bound for sensitivity analysis (10).

Two important factors may determine the efficacy of secondary prevention: the percentage of early-stage gastric cancers among all detectable cases and the survival rate of patients with early gastric cancer after treatment. For the first factor, we used data from our screening program as the base-case value and provided a wide range for sensitivity analysis according to the results of Miki et al. (8, 9). For the second factor, the 5-year survival rate of patients with early gastric cancer was ~90% (equivalent to a 97.7% annual probability of survival), which was consistent with the literature (6, 7). We selected a 62% probability of annual survival, which is identical to symptomatic gastric cancer as the lower limit for sensitivity analysis.

Published postoperative mortality rates for early gastric cancer are fraught with variation because they may include several modalities, such as gastrectomy with lymphadenectomy, en bloc local resection, and endoscopic mucosal resection. Base-case estimates used in the model referred to traditional surgery with extended resection (7). The detection and complication rates of endoscopy were based on the updated data (31, 32).

Direct and indirect costs for screening, endoscopy with biopsy, and surgery were obtained from the Bureau of the National Health Insurance. A wide range of values for the cost of endoscopy were tested and depended on the price mandated by local health insurance and on whether the conscious sedation was administered (33, 34).

Model Verification. To validate the credibility of the model given the assigned variables, we compared the predicted age-specific gastric cancer mortality rates with the data obtained from the 2000 year of Taiwan Mortality Registry.

Cost-Effectiveness Analysis

Deterministic Approach. A cohort expected-value analysis was done using the base-case estimates for all model variables. One-way sensitivity analyses were done to investigate the effects of changes in model variables across a wide range of assumptions. For the base-case screening regimens, the primary prevention strategy was modeled with once-only *H. pylori* eradication at 30 years of age and secondary prevention was done annually from 50 years onward (3, 4, 8, 19-21). Different initial ages and interscreening intervals were compared and shown on the cost-effectiveness planes.

Probabilistic Approach. To make allowance for the jointed effects of uncertainty across relevant variables, probabilistic sensitivity analyses specified different distributions over different variables and obtained repeated simulated values with Monte Carlo simulation (Table 1). The model was analyzed using a cohort of 100,000 individuals. The detailed theory and method referred to the work by Briggs et al. (35). Based on the best values of initial age, the probabilistic approach compared 13 strategies with selected screening intervals as follows: (*a*) no intervention; (*b*) chemoprevention with once-only, annual, biennial, triennial, four-yearly, and five-yearly schemes; and (*c*) high-risk surveillance with once-only, annual, biennial, triennial, four-yearly, and five-yearly schemes.

A series of acceptability curves based on repeated Monte Carlo–simulated points were also calculated to indicate the probability of being cost-effective for the main strategy of interest versus the comparator.

Results

Model Verification. To validate the model, we compared the observed gastric cancer mortality rates with those estimated from the six-state Markov model in the absence of intervention. Age-specific mortality rates of gastric cancer per 100,000 individuals for the underlying population in 2000 were as follows: 30 to 39 years, 3.4; 40 to 49 years, 10.3; 50 to 59 years, 22.7; 60 to 69 years, 53.4; and 70 to 79 years, 119.1. Estimated figures from the simulated model were as follows: 30 to 39 years, 6; 40 to 49 years, 8.1; 50 to 59 years, 19; 60 to 69 years, 54.8; and 70 to 79 years, 102.1. The lack of a significant difference ($\chi^2_4 = 1.74$, $P = 0.78$) indicated a good fit for this model.

Table 2. Results of base-case analysis

Outcome	No intervention	Primary prevention	Secondary prevention
Outcomes			
Cost per individual screened, U.S. $	249.6	346.6	352.8
Life expectancy, y	71.352	71.382	71.379
Relative risk of mortality from gastric cancer	1	0.86	0.87
Endoscopies per patient	0	0	0.83
Comparison using ICER values			
No intervention as reference	—	17,044	29,741
Secondary prevention as reference	—	Dominant*	—

*Dominant = more effective and less costly than reference strategy.

Table 3. Sensitivity analyses of selected variables with ICERs calculated to compare strategies

Variables	Strategy		
	Primary vs none	Secondary vs none	Primary vs secondary
Survival for early gastric cancer per year, %			
62	17.0K	*	Dominant †
70	17.0K	258.8K	Dominant
80	17.0K	120.2K	Dominant
90	17.0K	58.0K	Dominant
97.9, base	17.0K	29.7K	Dominant
Acquisition and reinfection of *H. pylori* per year, %			
0.5	10.3K	30.5K	Dominant
1, base	17.0K	29.7K	Dominant
1.5	22.5K	29.0K	12.6K
2.2, threshold ‡	29.6K	28.3K	28.3K
2.5	30.3K	28.0K	33.6K
Attendance rate for prevention program, %			
20	5.5K	31.5K	Dominant
40	10.9K	31.3K	Dominant
60, base	16.0K	31.4K	Dominant
80	20.9K	31.3K	Dominant
100	25.6K	31.3K	Dominant
Sensitivity of pepsinogen method for gastritis stages to AG, %			
50	17.0K	31.7K	Dominant
60	17.0K	29.9K	Dominant
70.5, base	17.0K	29.7K	Dominant
80	17.0K	28.3K	Dominant
90	17.0K	27.4K	Dominant
Attendance for endoscopy, %			
30	17.0K	49.6K	6.3K
40	17.0K	41.2K	5.1K
50	17.0K	36.3K	3.6K
60	17.0K	32.9K	1.6K
74, base	17.0K	29.7K	Dominant
Proportion of early gastric cancer detected on endoscopy, %			
10	17.0K	97.7K	Dominant
30, base	17.0K	29.7K	Dominant
50, threshold	17.0K	17.0K	20.3K
70	17.0K	11.7K	*
90	17.0K	8.7K	*
Costs of endoscopy with biopsy, U.S. $			
11, threshold	17.0K	16.9K	17.3K
68.8, base	17.0K	29.7K	Dominant
100	17.0K	41.9K	Dominant
400	17.0K	119.3K	Dominant
800	17.0K	139.8K	Dominant
Discount rate, %			
1	10.5K	25.8K	Dominant
2	13.5K	27.5K	Dominant
3, base	17.0K	29.7K	Dominant
4	20.9K	32.3K	8.7K
5	24.9K	35.5K	17.0K

NOTE: K = ×1,000.
*Reference strategy was dominant.
†Dominant = more effective and less costly than reference strategy.
‡Threshold = the value of variable giving a similar ICER among strategies.

Base-Case Analysis. In the base-case analysis (Table 2), both the primary and secondary prevention strategies led to more life years gained than no intervention but also increased cost, yielding U.S. $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 and lowering the cost by U.S. $6.2. Note that the mean number of endoscopy procedures was 0.83 per person for the secondary prevention strategy.

Sensitivity Analysis. Table 3 summarizes the results of the one-way sensitivity analyses for investigating the comparison between primary and secondary prevention strategies. The results showed extensive dominance of the primary prevention. However, the superiority of primary prevention was sensitive to two values of variables: an annual acquisition/reinfection rate of *H. pylori* <2.2% and the proportion of early gastric cancer among all detectable cases <50% during endoscopic surveillance. Secondary prevention became a dominant strategy once the proportion of early gastric cancer among all detectable cases was >70%. The following variables were not influential within reasonable ranges, including the survival rate of early gastric cancer, sensitivity of pepsinogen testing, attendance rate for endoscopy, attendance rate for prevention program, and the cost of endoscopy.

Compared with no intervention, a higher acquisition/reinfection rate of *H. pylori* led to an increase in the ICERs for the primary prevention but a decrease for result of secondary prevention. The ICERs of secondary prevention dwindled as a result of prognostic improvement of early gastric cancer, a higher sensitivity of pepsinogen testing, and a higher attendance rate for endoscopy.

Initial Age. The base-case analyses reported in Table 2 are based on once-only *H. pylori* eradication initiated at the age of 30 years and annual surveillance starting from age 50 years onward. Figure 2 shows the results of different initial ages in both strategies. Primary and secondary prevention strategies

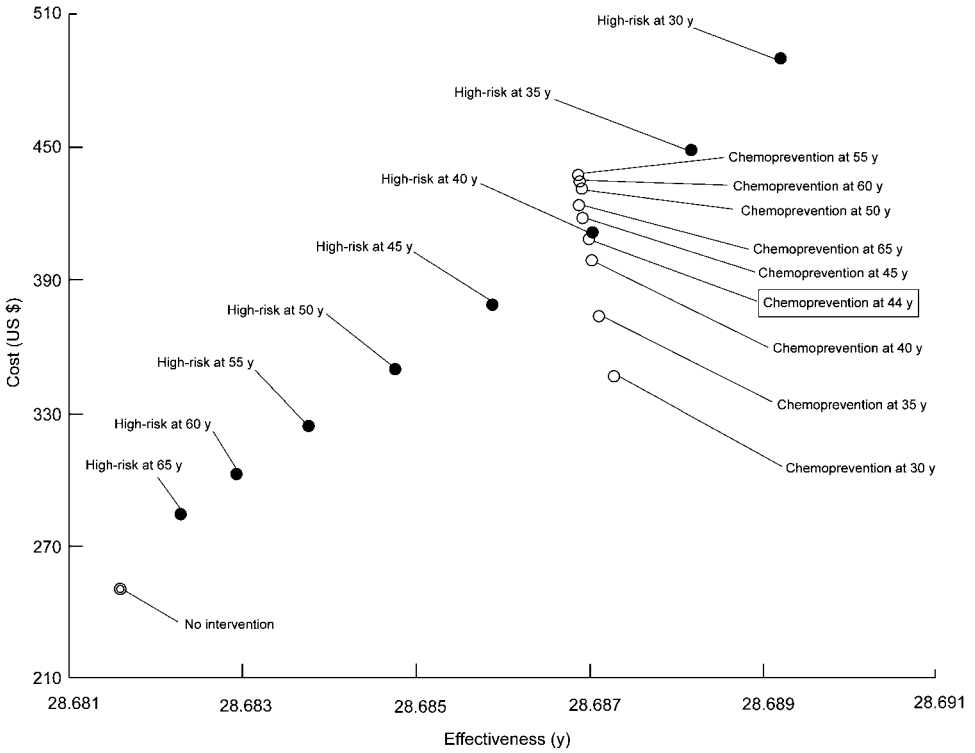


Figure 2. Results of different strategies with selected initial age presented on the cost-effectiveness plane. Strategies are leveled by the type and initial age of screening. ○, chemoprevention; ●, high-risk surveillance. *Highlight value,* threshold age when both prevention strategies have similar ICER values.

had different preferential regimens. The better benefit of primary prevention was achieved when an earlier intervention was administered. In contrast, secondary prevention at various initial ages showed a similar ICER in the cost-effectiveness plane. Chemoprevention programs initiated later than 44 years of age were internal to the linear combinations of high-risk surveillance, indicating they could be ruled out through the principle of extended dominance. The best initial ages of both prevention strategies would remain the same as the base-case values for further analyses.

Interscreening Intervals. Figure 3 shows the cost-effectiveness plane by comparing strategies with different interscreening intervals given the best-case of initial age. The linear combinations of annual chemoprevention, once-only chemoprevention, and no intervention consists the efficiency frontier. The slope of the efficiency frontier reflects the optimal ICER among all strategies considered. The once-only chemoprevention clearly dominated annual high-risk screening, having lower costs, and greater benefit. The biennial, triennial, four-yearly, and five-yearly schemes of both chemoprevention and high-risk screening, as well as once-only high-risk screening, were internal to the efficiency frontier, indicating they could be ruled out through the principle of extended dominance (i.e., strategies on the efficiency frontier could produce greater benefit at lower costs). The longer interscreening interval only exerted small changes internal to the frontier.

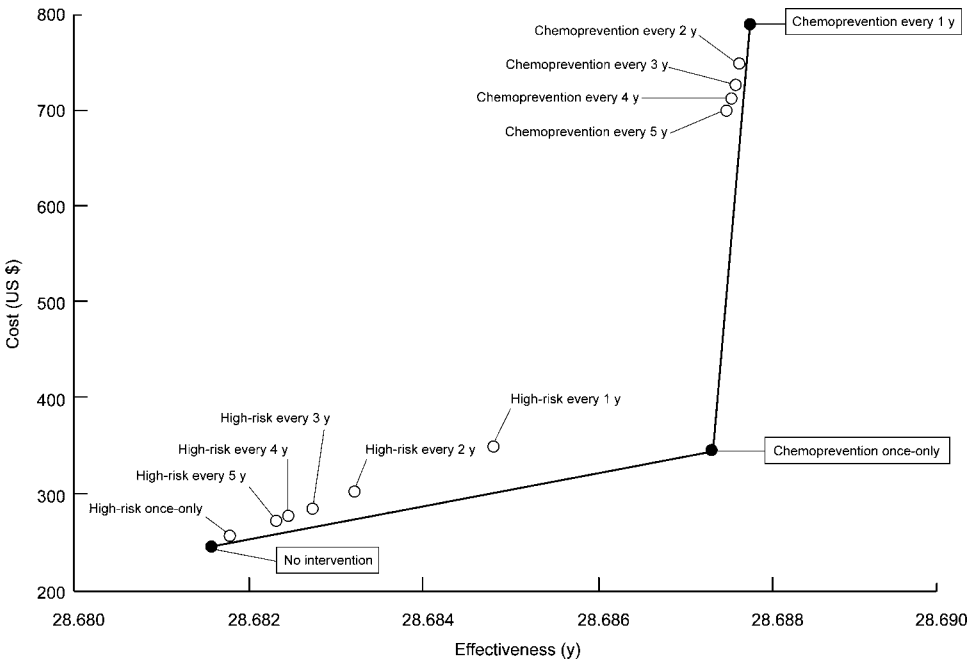


Figure 3. Results of different strategies with selected screening intervals presented on the cost-effectiveness plane. Strategies are leveled by the type and frequency of screening. ○, strategies that are less cost-effective or cost more and save fewer life-year than strategies on the efficiency frontier (●).

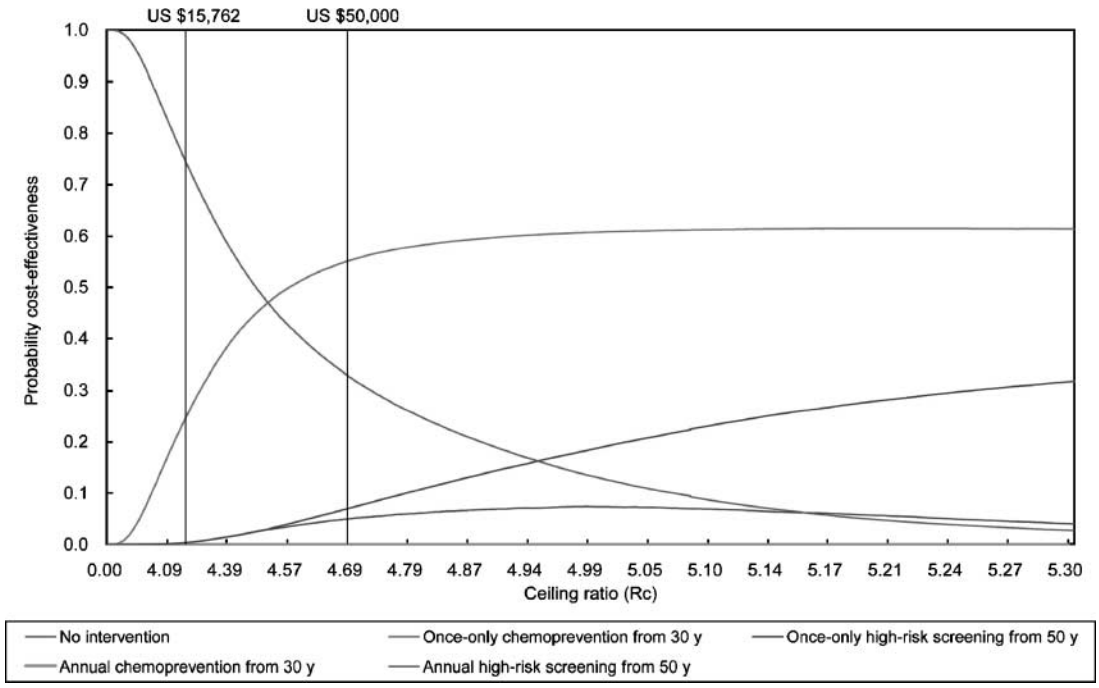


Figure 4. Acceptability curves for the choice of prevention strategy (a log scale is used on the ceiling ratio to better illustrate the low values).

Acceptability Curve. By specifying distributions for all the relevant variables, the results of the 100,000 replications from the Monte Carlo simulation are presented as acceptability curves (Fig. 4). Given the ceiling ratio (i.e., maximum willingness to pay), the acceptability curves provide the probability of each intervention being cost-effective given 100,000 replications. The absence of the biennial, triennial, four-yearly, and five-yearly schemes of both chemoprevention and high-risk screening shows a lower possibility of being cost-effective. Under a ceiling ratio of U.S. $15,762, only once-only chemoprevention was considered cost-effective with approximate 24% likelihood of being cost-effective. Once-only high-risk screening still had chance of being cost-effective but it was usually <10%. When the ceiling ratio increased to the level of U.S. $50,000 (14), once-only chemoprevention was still most favorable (55% likelihood of being cost-effective). When the ceiling ratio reached U.S. $1,500,000, the annual high-risk surveillance was as favorable as the once-only chemoprevention, with ~40% likelihood of being cost-effective. Annual chemoprevention strategy had the likelihood of being cost-effective as the ceiling ratio increased. However, it could become the strategy of choice if a cost higher than U.S. $3,000,000 was considered acceptable for a life-year gained. The choice of once-only chemoprevention at 30 years did not vary when we selected different initial ages for high-risk surveillance in the probabilistic analysis.

Discussion

Our cost-effectiveness analysis indicates that a once-only chemoprevention program should be initiated earlier in life. Although both chemoprevention and surveillance for high-risk groups can provide 13% to 14% mortality reduction under the best-case scenarios, the primary prevention appeared to dominate the secondary prevention strategy. This was sensitive to two variables, the acquisition/reinfection rate of *H. pylori* and the proportion of early detectable gastric cancer given a reasonable range of the ceiling ratio, the maximum willingness to pay.

Primary prevention is unsurpassed if an intervention can strongly block the carcinogenesis cascade (e.g., the relationship between the hepatitis B virus vaccination and the decline of liver cancer; ref. 36). However, the efficacy of *H. pylori* eradication in arresting the carcinogenesis cascade is mostly extrapolated from studies with surrogate outcomes of histologic regression, in which inconclusive results ensued (37-39). Based on an end-point of gastric cancer reduction, one randomized trial conducted in China has shown a 37% risk reduction after 7.5 years (19). Although the result was not statistically significant, our finding was consistent with the result of their subgroup analysis, which showed a substantial reduction in subsequent gastric cancer in those without premalignant changes (e.g., atrophic gastritis, intestinal metaplasia, and dysplasia). The biological plausibility is upheld by the concept of ''a point of no return,'' which may account for why the benefit of *H. pylori* eradication diminishes at the advanced stage when many irreversible molecular changes have developed. In keeping with this concept, our study first showed that only a reduction of transition rate at the initial stage can provide significant mortality reduction. In contrast to precancerous lesions, *H. pylori* eradication at this stage can effectively ameliorate the infiltration of acute inflammatory cells and protect the gastric mucosa from irreversible damage (40). Furthermore, our finding that a chemoprevention program should be administered early in life before advanced histologic changes develop contrasts with the suggestion from a previous simulation study in which the recommended initial age for such a program was 50 to 70 years (14).

Quantification of the carcinogenesis cascade has been barely addressed for gastric cancer. Based on a longitudinal study, the annual progression rates from atrophic gastritis to low-grade dysplasia, from intestinal metaplasia (type I-II-III) to low-grade dysplasia, and from low-grade dysplasia to high-grade dysplasia or carcinoma have been estimated at 5%; 4%, 11%, and 22%; and 7%, respectively (41). Furthermore, our model can be translated to a 5-year survival rate of 9% for patients with symptomatic gastric cancer (42). Both data support the credibility of our model. However, in terms of generalizability, we may have underestimated the benefit of chemoprevention. Some well-designed studies did show the reversibility of advanced gastric lesion (37, 39, 43). Moreover, our estimate in risk reduction after *H. pylori* eradication was less significant than those in previous health economic models (14-17). The result may reflect the environment where our target population resides (20). In high-risk

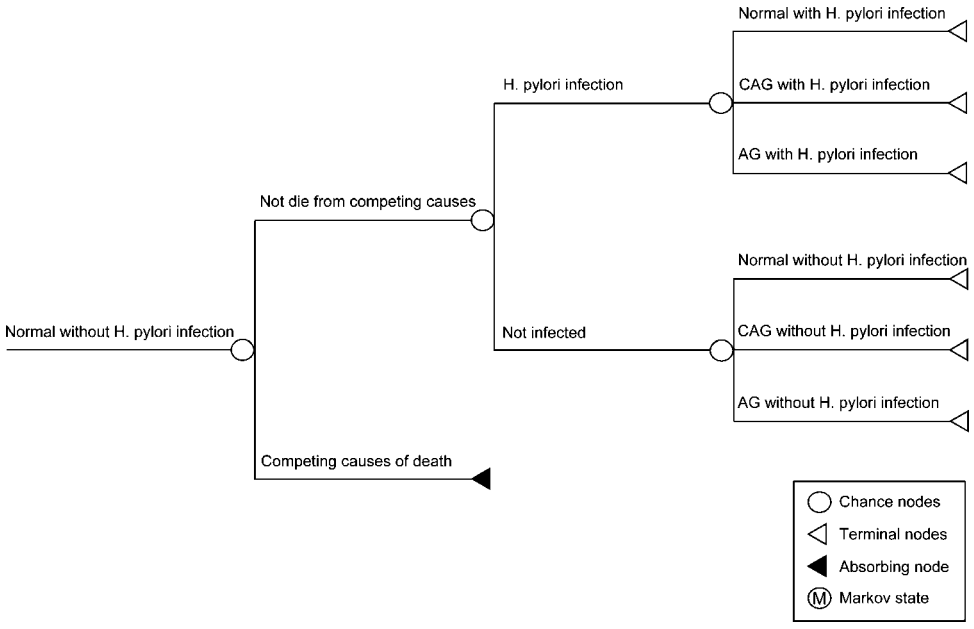
areas, some important factors are also associated with the histologic progression; examples are nutritional factors, *H. pylori* virulence (such as CagA variation), and the genetic susceptibility of hosts (44).

The sensitivity analyses show that the relative cost-effectiveness is highly sensitive to the acquisition/reinfection rate of *H. pylori*, which was not considered significant in previous health economic models (14-17). In fact, the published reinfection rate of *H. pylori* varies substantially from 0.4% in the United Kingdom to 13% in Bangladesh (45-47). Our model confirms that chemoprevention is the dominant strategy in developed countries, where the transmission of *H. pylori* is low but cost of endoscopy is usually high. However, in a developing country with higher risk of *H. pylori* infection, traditional cancer screening emphasizing the process of high-risk group identification and subsequent endoscopy cannot be abandoned. Two screening tools, including photofluorography and the serum pepsinogen method, have been adopted for gastric cancer screening in high-prevalence areas. Photofluorography has effectively prevented gastric cancer deaths in Japan, providing a mortality reduction of 50% to 60% (2). Avoiding the hazards of radiation exposure and the need for technical expertise, measurements of a biomarker such as serum pepsinogen can be a valuable alternative (48). By using the best-case value of 90% for early gastric cancer detection (8, 9), a similar effectiveness was obtained from our model.

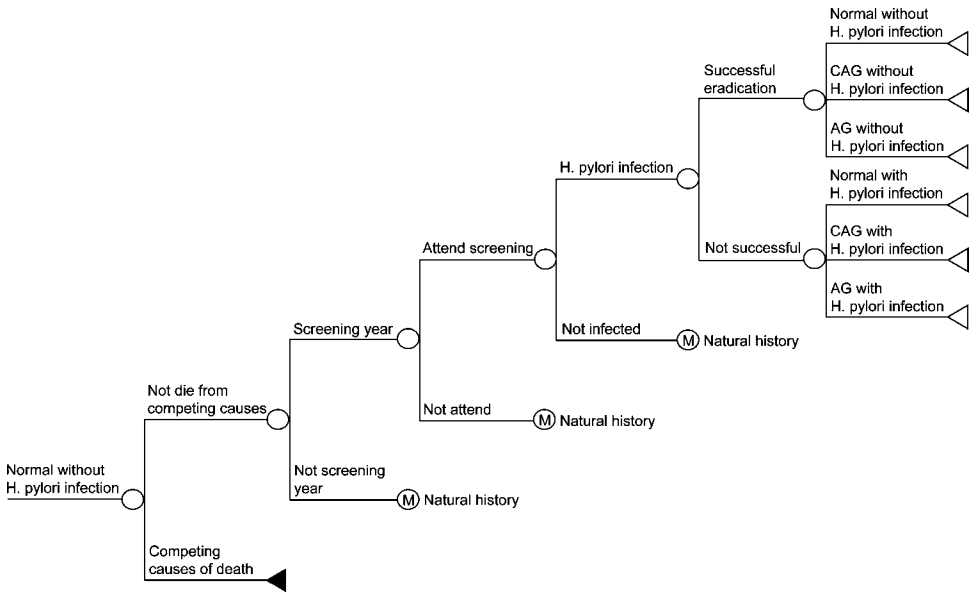
Our data have shown a critical role of early-stage gastric cancer detection in the secondary prevention. Dramatic differences in prognosis (5-year survival >90% versus <10%) and medical resource consumption between early and advanced gastric cancer explain why secondary prevention with an early detection rate above 70% can dominate chemoprevention. Currently, endoscopic detection of early gastric cancer can be improved by using magnification, chromoendoscopy, and optical device to identify or delineate the margin of small cancer foci (49). However, in cases with large population or limited clinical manpower, endoscopic surveillance may not be feasible. Another concern is that an intensive scheme including the administration of endoscopy may decrease the attendance rate. In contrast, a higher compliance rate may make the chemoprevention more worthwhile. The duration of *H. pylori* eradication is generally short and a chemoprevention program with the test-and-treat or even the test-treat-retest-retreat strategy has been confirmed safe, well-tolerated, and can achieve a high compliance rate (19, 21).

The credibility of our results can be assessed from the following points. First, the generation of variables was based on two empirical studies from the same population. This procedure has decreased the heterogeneity across studies and strengthened our ability to describe the natural history of gastric cancer. Second, the goodness of fit revealed by the internal validation suggests that the memoryless Markov property of natural history of gastric cancer may not be unreasonable. Third, taking time horizon into account, chemoprevention is still more cost-effective than high-risk group surveillance. This suggests the efficacy of chemoprevention in eradicating *H. pylori* is larger and cannot be outweighed by a disfavored discount rate as a result of different time horizons between early chemoprevention program and later benefit of averting advanced cancer.

H. pylori eradication as a primary prevention strategy may have concerns. First, cure of *H. pylori* does not guarantee protection from further infection. Our sensitivity analysis confirms that a high reinfection rate of *H. pylori* can significantly suppress the benefit of chemoprevention. Second, the eradication of *H. pylori* may increase the intragastric acidity and lead to an increasing risk for reflux-associated disease (50). Others found that the dyspepsia-related expenditure was reduced after eradication therapy (51-53). Whether the chemoprevention can change the expenditure in medical resources for functional gastrointestinal disorders deserves further observation. Third, a combination approach may be promising with a universal chemoprevention followed by endoscopic surveillance based on risk assessment

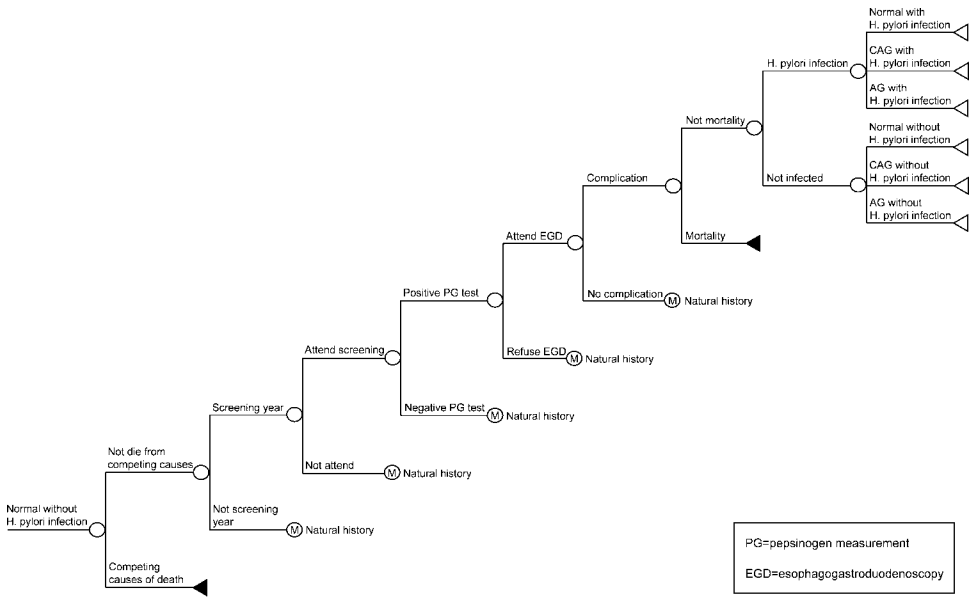


Appendix Figure 1. The tree diagram shows natural history of gastric carcinogenesis cascade without intervention by using a six-state Markov model. In this example, a simulated patient spends time in a Markov state and the transitions between states take place at discrete time intervals 1 y apart. In every cycle, the patient may die from competing causes of death (absorbing state), or the patient may be infected by *H. pylori* (temporary state). The intragastric mucosa may remain normal or it may progress to chronic active gastritis (*CAG*) or atrophic gastritis (*AG*), on the basis of transition probabilities with or without *H. pylori* infection. If the patient develops chronic active gastritis during this cycle, in the next cycle, he or she follows a similar pathway with an initial status of chronic active gastritis. In the new cycle, chronic active gastritis may persist, or it may progress to atrophic gastritis or to intestinal metaplasia.



Appendix Figure 2. The tree diagram shows the interruption of gastric carcinogenesis cascade by using the primary prevention strategy. In this example, the intervention can be modeled with different initial age and screening interval. Individuals who do not die from competing causes of death may acquire *H. pylori* infection. Those who attend the screening will undergo ^{13}C urea breath test and subsequent *H. pylori* eradication. Patients who are not infected or have undergone successful triple therapy will follow the natural history without *H. pylori* infection; otherwise, they will go through an accelerated path with *H. pylori* infection.

using pepsinogen measurement (54). The relative cost-effectiveness should be tested in the future study. Fourth, there are some types of intragastric malignancies, such as the diffuse-type gastric cancer, gastric lymphoma, and mucosa-associated lymphoid tissue lymphoma, that may not follow Correa's model (55). In addition, chemoprevention does have merit in preventing the medical burden from peptic ulcer disease (56). Our model may underestimate the benefit of *H. pylori* eradication because some are more closely linked to *H. pylori* infection. Finally, from the methodology viewpoint, a theoretical model concentrating on the essential elements in disease process may be still limited in representing reality. All included patients in our study were from different time periods and the time lag might result in some changes on the program effectiveness. Although clinical trials are mandatory, the problems of large sample size, long-term follow-up, and ethical issue may make such a randomized controlled trial impractical (54). Besides, we may have underestimated



Appendix Figure 3. The tree diagram demonstrates the interruption of gastric carcinogenesis cascade by using the secondary prevention strategy. In this example, the patient may die from competing causes of death or be infected by *H. pylori*. Subjects who attend the screening will undergo serum pepsinogen measurement and subsequent endoscopic confirmation, based on the sensitivity or specificity of the screening tests. In some cases, an individual may experience a complication event that the patient either dies of or survives during the period. At the end of this cycle, similarly, patients can move from one gastritis state to another or stay in the same gastritis state.

the augmented cost involved in other diseases not associated with gastric cancer when gastric cancer is prevented. However, as gastric cancer is a rare event and our primary interest is to test the relative cost-effectiveness between interventions, the neglect of augmented costs may not substantially affect the results. In addition, due to lack of empirical data on the quality for different stages of gastric cancer, we did not calculate quality-adjusted life-year gained. However, we believe that our result is more conservative because lower quality–adjusted life-year gained would be expected for the comparator (secondary prevention) if early eradication of *H. pylori* can be achieved in primary prevention group.

In conclusion, our study shows that early chemoprevention once in lifetime is more cost-effective than endoscopic surveillance for high-risk individuals. Their relative cost-effectiveness may vary from country to country and subject to risk of *H. pylori* infection, early detection of gastric cancer, and timing of intervention. It will be imperative to consider these assumptions when decisions about population-based prevention strategies need to be made.

Appendix Tree Diagrams

Appendix Fig. 1
Appendix Fig. 2
Appendix Fig. 3

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Cost-effectiveness Analysis between Primary and Secondary Preventive Strategies for Gastric Cancer

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