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ORIGINAL RESEARCH

Cost-effectiveness Analysis of *Helicobacter pylori* Eradication Therapy in First-Degree Relatives of Patients with Gastric Cancer

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Background: *Helicobacter pylori (H. pylori)* eradication therapy has been shown to reduce the risk of gastric cancer in patients who have a family history of gastric cancer in first-degree relatives. The aim of this study was to assess the cost-effectiveness of *H. pylori* eradication therapy in a select population in the People's Republic of China.

Methods: A Markov model was applied to evaluate the cost-effectiveness of *H. pylori* eradication therapy. The long-term costs of *H. pylori* eradication therapy were calculated from the Chinese perspective. Health outcomes were measured by quality-adjusted life years (QALYs). Epidemiological information and health utilities used in the model were collected from published literatures or statistical bureaus. A sensitivity analysis was conducted to explore the influence of parameters on the uncertainty of the model.

Results: Compared with the no eradication therapy group, *H. pylori* eradication therapy prolonged an average of 4.52 QALYs (32.64 QALYs vs 28.12 QALYs) and saved $3227.07 ($2472.83 vs $5699.90). The cost-effectiveness analysis demonstrated that no *H. pylori* eradication therapy cost more and produced less QALYs. It was dominated by *H. pylori* eradication therapy. The one-way sensitive analyses proved that the results were robust to the fluctuations of the input parameters.

Conclusion: *H. pylori* eradication therapy not only reduced the risk of gastric cancer in first-degree relatives of patients with gastric cancer but also was an economical strategy with lower costs and greater efficacy.

Keywords: *Helicobacter pylori*, eradication therapy, gastric cancer, cost-effectiveness analysis

Introduction

Currently, cancer remains an important focus of public health, and gastric cancer is the third cause of cancer-related death.[1] *Helicobacter pylori (H. pylori)* is a Gram-negative bacterium, which could colonize in the stomach leading to gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma.[2] As the most common infectious agent, *H. pylori* contributes to approximately 89% non-cardia gastric cancer in the world.[3] The People's Republic of China is the most populous country in the world, with an approximately 56% prevalence of *H. pylori* infection, accounting for more than 40% of global gastric cancer-related deaths.[4–6]

Considering that *H. pylori* plays an important role in gastric cancer, eradication therapy for *H. pylori* infected patients is an effective measure to decrease the incidence of gastric cancer. The Kyoto global consensus report agreed that

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eradication therapy of *H. pylori* infection was a primary strategy for preventing gastric cancer, which could reduce the risk of gastric cancer.[7] However, it is challenging to actively screen and treat all *H. pylori*-positive patients on a national scale in countries where *H. pylori* infection is highly prevalent in reality. In fact, the indication of *H. pylori* screening and eradication is influenced by clinical judgment and the patient's condition. *H. pylori*-infected patients who can reap more benefits from *H. pylori* eradication therapy are recommended for treatment. Peptic ulcer (regardless of activity or complications), chronic gastritis with dyspepsia and family history of gastric cancer had been listed as *H. pylori* eradication indications in the Fifth Chinese National Consensus Report.[8] Although the fact that individuals with a family history of gastric cancer had strong correlation to gastric cancer, not all consensus or guidelines recommended the relatives of gastric cancer patients to receive routine screening for *H. pylori* infection and eradication therapy due to insufficient evidence.[9–11] Recently, a research in Korea demonstrated that *H. pylori* eradication therapy in *H. pylori*-infected patients who had a family history of gastric cancer in first-degree relatives reduced the risk of gastric cancer.[12] In this research, 1,676 individuals were randomly assigned to two groups. Therein, 1.2% in the *H. pylori* eradication therapy group and 2.7% in the placebo group developed gastric cancer (hazard ratio, 0.45; 95% confidence interval, 0.21 to 0.94. P=0.03 by Log rank test).

Nevertheless, whether *H. pylori* eradication therapy is cost-effective is unknown in these populations. The following concern has been raised about its application. Adverse events including diarrhea and vomiting induced by *H. pylori* eradication therapy may have an impact on the quality of life. Costs of drugs, costs of screening for *H. pylori* also cause economic burden for these people. Another concern is that the heavy antibiotic consumption would worsen antibiotic resistance. On account of these factors, conducting a cost-effectiveness analysis to estimate *H. pylori* eradication is of great importance, especially in countries with high *H. pylori* prevalence. The aim of our research was to evaluate the cost-effectiveness of eradication therapy for *H. pylori*-infected patients who had a family history of gastric cancer in first-degree relatives from a healthcare payer perspective in the People's Republic of China.

Methods

Clinical Information

Clinical information was derived from a randomized trial performed in Korea.[12] The eligibility criterion was *H. pylori*-positive persons older than 40 years who had at least a first-degree relative with gastric cancer. A total of 1,676 people were randomly divided into two groups: one received eradication therapy and the other received placebo therapy. Patients in both groups received endoscopic monitoring every 2 years. These two groups had no significant differences in age, sex or other basic characteristics at baseline. The status of *H. pylori* infection was evaluated based on a rapid urease test and Wright-Giemsa staining of biopsy specimens. After follow-up, *H. pylori* was eradicated in 551 of 786 patients in the treatment group. Participants who still had *H. pylor*i infection received bismuth-based quadruple therapy (a proton-pump inhibitor, bismuth, metronidazole, and tetracycline) for 10 days after the trial ended. Gastric cancer was confirmed by the use of biopsy in 5 of 608 *H. pylori*-negative participants, and 28 of 979 *H. pylori*-positive participants.

Decision Model

We used the TreeAge Pro (TreeAge Software, Williamstown, MA, USA) to construct a Markov model, which compared two treatment strategies: 1) subjects received eradication therapy (30 mg lansoprazole, 1000 mg amoxicillin, and 500 mg clarithromycin, each taken twice daily for 7 days); and 2) subjects received no therapy. The treatment group comprised four exclusive health states (*H. pylori* infection, *H. pylori* eradication, gastric cancer, dead) and the control group comprised three exclusive health states (*H. pylori* infection, gastric cancer, dead). These health states in the Markov model were applied to simulate the disease process of *H. pylori*-infected patients (Figure 1).

Model Parameters

Transition probabilities were calculated by the formula: Probability=1-exp(-rt), where r is the incidence of event over time period t.[13] The parameters in the model such as the eradication rate of *H. pylori* and the incidence of gastric cancer in first-degree relatives of patients with gastric cancer were derived from the clinical trial in South Korea.[12] We ignored the recurrence rate after *H. pylori* eradication, because it was rare with an annual incidence of 1.75‰.[14]

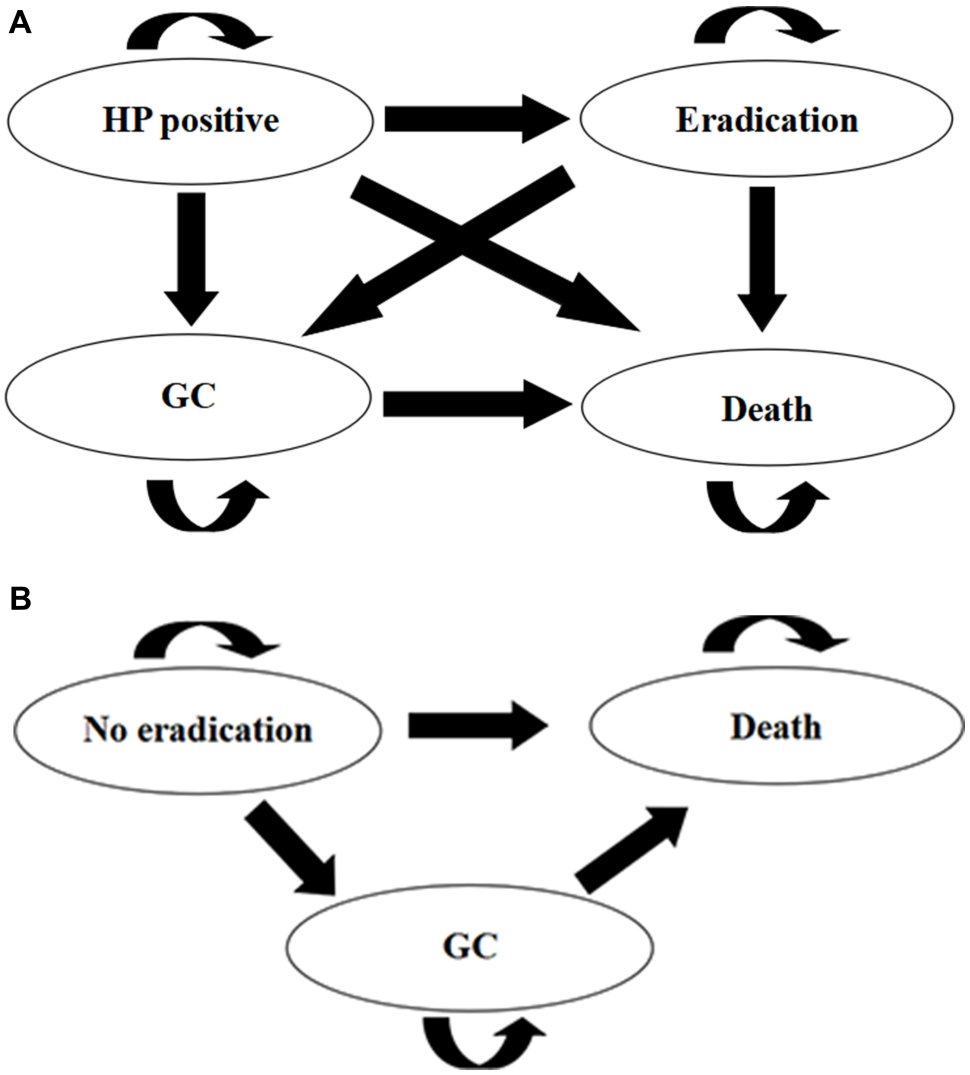

Figure 1 The Markov model was used to compare two strategies comprising health states. (**A**) Eradication therapy group. (**B**) No eradication therapy group.
Abbreviations: HP, *Helicobacter pylori*; GC, gastric cancer.

The population mortality was obtained from the China Statistics Bureau and the mortality of gastric cancer was 22.5 per 100,000 people.[5] Therefore, the mortality rate for non-gastric cancer was approximately 6.92‰. The 5-year survival rate of gastric cancer patients in the People's Republic of China was 35.9%.[15] By using the following formula: $P=Pt^{(1/t)}$, the mortality rate of gastric cancer patients was about 19% per year. Details are shown in Table 1. The model cycle was 1 year. Based on the average life expectancy of 76.34 years in the People's Republic of China, the operation time of this model was set at 40 years.

Costs and Utilities

Only direct costs included were calculated. The costs of *H. pylori* eradication therapy, costs of endoscopy screening, costs of *H. pylori* testing, and costs of adverse events management were estimated based on the prices in Sichuan province, the People's Republic of China. Costs of gastric cancer treatment were derived from a multicenter cross-sectional survey.[16] All costs were converted into US dollars and quality-adjusted life years (QALYs) were used to measure health outcomes. The discount of costs and QALYs was 3% each year. We assumed that the health utility of participants who successfully eradicated *H. pylori* was 1. The health utilities of patients with *H. pylori* infection and gastric cancer came from the published literature, and were 0.89 and 0.38, respectively.[17]

Sensitivity Analysis

A sensitivity analysis was performed to explore the impact of parameters fluctuation on the robustness of the results.

Table 1 Base Parameters in the Markov Model

Parameters	Value	Source
Clinical variables		
H. pylori prevalence rate	56%	[2]
Incidence of gastric cancer in *H. pylori*-positive population (%)	2.9%	[13]
Incidence of gastric cancer in *H. pylori* eradication population (%)	0.8%	[13]
Success *H. pylori* eradication rate (%)	70.10%	[13]
Population mortality (‰)	7.14‰	National Bureau of Statistics of China
Nongastric cancer mortality rate (‰)	6.92‰	
Five-year survival rate for gastric cancer (%)	35.9%	[16]
Costs variables ($)		
H. pylori eradication therapy	77.83	
Gastric cancer screening	29.96	
H. pylori testing	81.85	
AEs of eradication therapy	1.99	
Average annual gastric cancer treatment	9891	[17]
Health utility		
After *H. pylori* eradication	1	
H. pylori infection	0.89	[18]
Gastric cancer	0.38	[18]

Note: *H. pylori*, *Helicobacter pylori*.
Abbreviation: AE, adverse events.

Probabilistic sensitivity analysis was conducted using the Monte Carlo simulation to iterate 1,000 times. The analysis results are shown by incremental cost-effect scatter plots.

Results

Base Case Analysis

The baseline results of our analysis are presented in Table 2. Within a 40-year time horizon, *H. pylori* eradication therapy in first-degree relatives of patients with gastric cancer yielded more benefits than no eradication therapy (32.64 QALYs vs 28.12 QALYs), leading to an extended 4.52 QALYs. It also yielded much lower costs than no eradication therapy ($2472.83 vs $5699.90). Therefore, incremental cost-effectiveness ratio (ICER) of *H. pylori* eradication therapy was $-713.95 per QALY compared to no eradication therapy, indicating that *H. pylori* eradication therapy was in the ascendant for having fewer costs and more benefits.

Table 2 Results of Cost-Effectiveness Analysis

Results	Cost ($)	Effectiveness (QALYs)	ICER ($/QALY)
Eradication group	2472.83	32.64	Dominant
Control group	5699.90	28.12	

Note: Dominant: more effective and less costly than others.
Abbreviations: QALYs, quality adjusted life-years; ICER, incremental cost-effectiveness ratio.

Sensitivity Analysis

With 1,000 Monte Carlo simulations, the incremental cost-effectiveness scatterplots of eradication therapy and no eradication therapy are shown in Figure 2. The *H. pylori* eradication strategy cost less and generated more QALYs than no *H. pylori* eradication. As a result, no *H. pylori* eradication therapy was dominated by *H. pylori* eradication therapy. One-way sensitivity analyses of selected parameters are displayed in Table 3. The utility of *H. pylori*-infected people, the incidence of gastric cancer in the *H. pylori*-positive population, and the costs of gastric cancer treatment were the factors most affecting the results of the model. Although these parameters changed within the range of ± 20%, *H. pylori* eradication therapy produced more QALYs with lower costs, proving that *H. pylori* eradication therapy remains the dominant strategy. Additionally, we constructed a three-way sensitivity analysis on three parameters that had the greatest impact on the results. When the parameters were the most unfavorable for the implementation of the strategy, *H. pylori* eradication therapy still rendered net monetary benefit (Figure 3). The results were robust to the ranges of the variables.

Discussion

Gastric cancer is one of the common malignant tumors, with a fatality rate of up to 75% in most regions of the world and it is a serious threat to public health.[18] Of note, the highest fatality rates of gastric cancer are seen in Eastern Asia, especially in the People's Republic of China, Japan and Singapore.[19] Risk factors of gastric cancer included *H. pylori*-infection, smoking, obesity, food habits and the environment.[20] As the greatest risk factor for gastric cancer, the World Health Organization has classified *H. pylori* as a group I carcinogen.[21,22] Another common risk factor of gastric cancer is a family history of gastric cancer. Several studies have found that

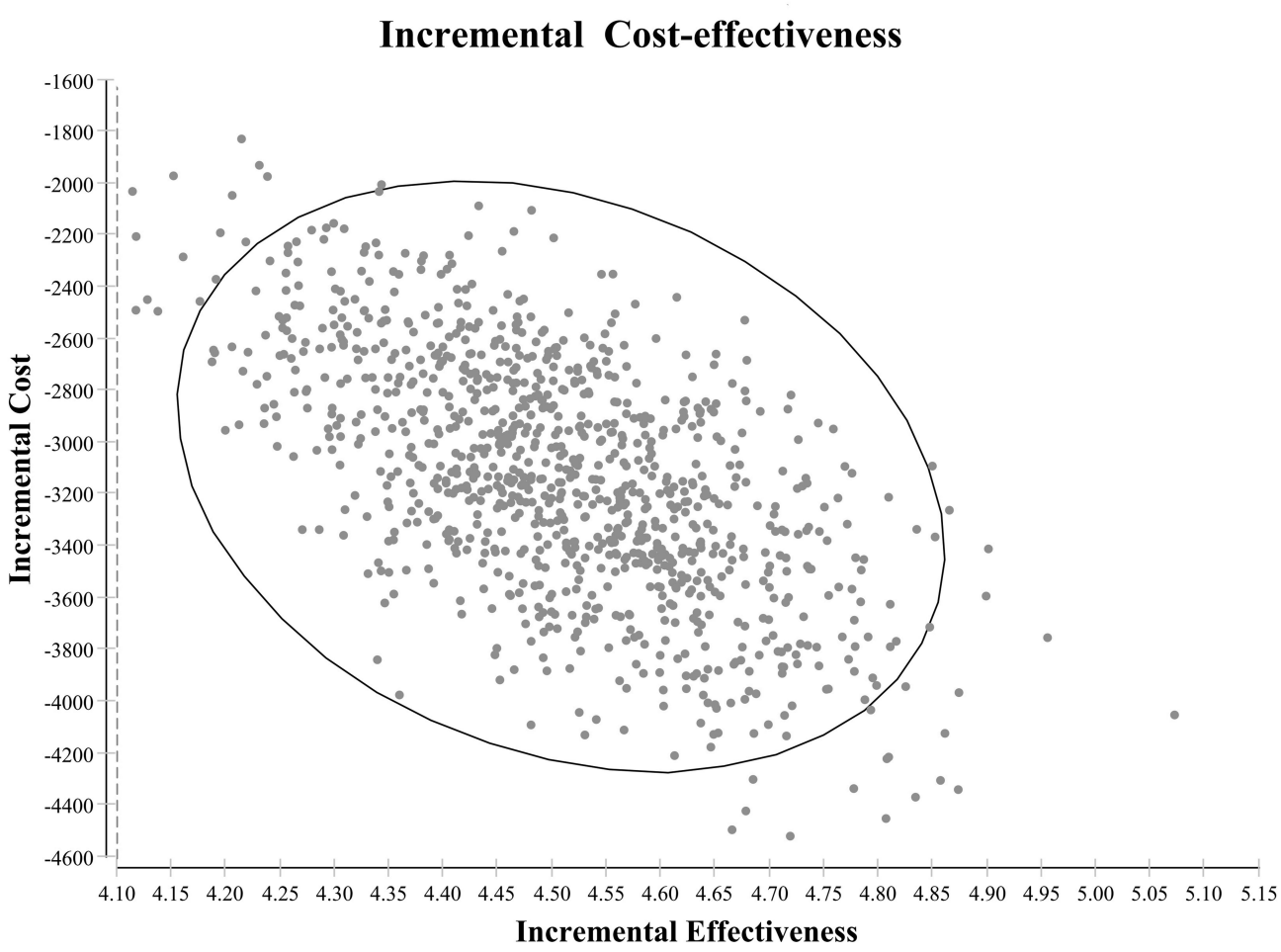

Figure 2 An incremental cost-effectiveness scatterplot comparing eradication therapy with no eradication therapy.

a family history of gastric cancer patients significantly increased the incidence of gastric cancer, especially in first-degree relatives of patients.[23] The familial clustering of gastric cancer attributed to the shared exposure to carcinogens, eating habits, and genetic susceptibility.[24] Moreover, *H. pylori* infection and family history of gastric cancer had a synergistic effect on the development of gastric cancer.[11] The incidence of gastric cancer can be reduced by the management high-risk gastric cancer population. A phase III clinical trial has proved that eradication of *H. pylori* reduced the risk of gastric cancer in first-degree relatives of patients with gastric cancer. Hence, the implementation of screening and eradication for *H. pylori* is a critical intervention to combat gastric cancer.

To the best of our knowledge, this is the first study to assess the economic influence of *H. pylori* eradication in first-degree relatives of patients with gastric cancer. In this study, we found that *H. pylori* eradication therapy for people who had at least one first-degree relative with gastric cancer resulted in an average of 4.52 longer QALYs (32.64 QALYs vs 28.12 QALYs) and the costs were reduced by $3,213.05 ($2,472.41 vs $5685.46). It was proved that *H. pylori* eradication therapy cost less and was more effective compared with no *H. pylori* eradication therapy in the People's Republic of China.

There have been several economic studies focused on *H. pylori* screening and eradication therapy in Asia. A cost-effectiveness analysis of Chinese in Singapore showed that among the Chinese population with a high incidence of gastric cancer, serology screening and eradication therapy were the dominant strategy compared to no screening.[25] It was similar to our conclusion that we recommended *H. pylori* screening and eradication therapy for people who had first-degree family history of gastric cancer. Han et al[17] performed a study to evaluate the cost-effectiveness of *H. pylori* screening and eradication therapy in the People's Republic of China, proving that *H. pylori* screening followed by eradication therapy was

Table 3 One-Way Sensitivity Analyses of Parameters

	Eradication Therapy		No Eradication Therapy		
	Cost ($)	**Effectiveness (QALYs)**	**Cost ($)**	**Effectiveness (QALYs)**	
Costs of gastric cancer treatment ($)					
7912.80 11,869.20	2174.85 2770.81	32.64 32.64	4760.89 6638.90	28.12 28.12	Dominated Dominated
Costs of eradication therapy ($)					
62.26 93.40	2472.47 2473.18	32.64 32.64	5699.90 5699.90	28.12 28.12	Dominated Dominated
Costs of *H. pylori* testing ($)					
65.48 98.23	2472.46 2473.18	32.64 32.64	5687.02 5699.90	28.12 28.12	Dominated Dominated
Costs of gastric cancer screening ($)					
23.97 35.95	2277.07 2668.58	32.64 32.64	5511.85 5887.94	28.12 28.12	Dominated Dominated
Costs of adverse events related to eradication therapy ($)					
1.59 2.39	2472.79 2472.86	32.64 32.64	5699.90 5699.90	28.12 28.12	Dominated Dominated
Success *H. pylori* eradication rate					
56.08% 84.12%	2513.66 2445.42	32.58 32.68	5699.90 5699.90	28.12 28.12	Dominated Dominated
Probability of developing gastric cancer in *H. pylori*-positive population					
0.26% 0.38%	2428.77 2516.80	32.67 32.61	4812.13 6569.05	28.42 27.83	Dominated Dominated
Probability of developing gastric cancer in *H. pylori* eradication population					
0.69‰ 1.04‰	2226.78 2717.51	32.73 32.55	5699.90 5699.90	28.12 28.12	Dominated Dominated
Utility of *H. pylori* infection					
0.71 1	2472.83 2472.83	32.48 32.74	5699.90 5699.90	22.53 31.57	Dominated Dominated
Utility of gastric cancer					
0.30 0.46	2472.83 2472.83	32.63 32.65	5699.90 5699.90	28.08 28.16	Dominated Dominated

a cost-saving strategy. By this measure, it could save $168.45 per QALY per person. Kowada[26] conducted decision trees to assess the cost-effectiveness of *H. pylori* screening followed by eradication therapy for employees aged 20, 30, 40, 50 and 60 years. Given that it gained more benefits with less costs than no screening, it could be popularized in Japan. Following this study, Kowada[27] also found that people aged 50 years or older yielded more benefits in *H. pylori* screening than upper gastrointestinal series and endoscopy in high prevalence countries.

A recent consensus in the People's Republic of China announced that *H. pylori* eradication therapy was a cost-

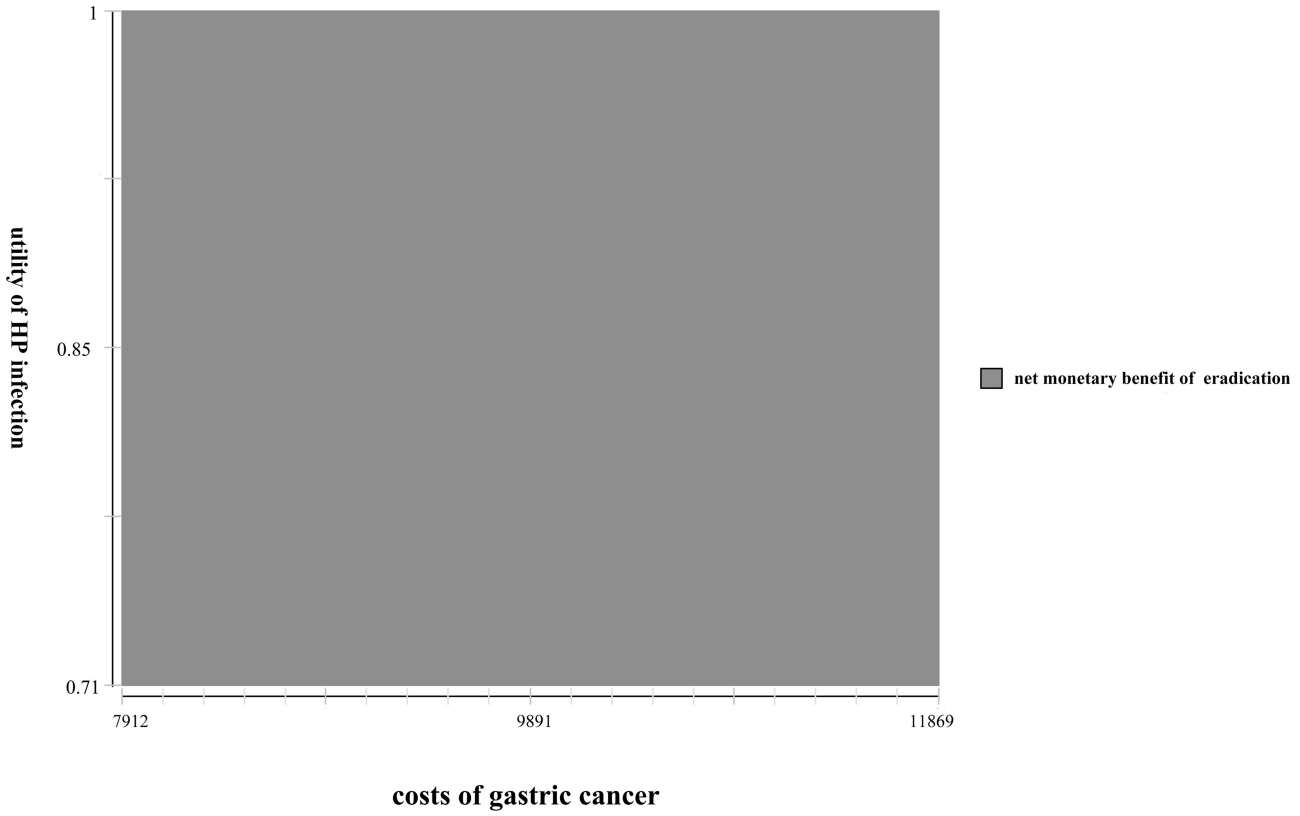

Figure 3 Sensitivity analysis on utility of HP-infected people and the costs of gastric cancer treatment when the probability of developing gastric cancer in the *H. pylori*-positive population was 0.26%.
Abbreviation: HP, *Helicobacter pylori*.

effective strategy in high-risk areas.[28] The main reason for economic gains of *H. pylori* eradication therapy was that it reduced the incidence of gastric cancer, thereby reducing the total costs of gastric cancer. Nevertheless, in addition to the treatment costs, multiple factors including drug availability, and antibiotic resistance needs to be taken into consideration when carrying out a screen-and-treat program for *H. pylori* in the whole country, especially in countries with large populations and limited medical resources. Indeed, *H. pylori* has an increasing high primary resistance rate of clarithromycin, metronidazole, and levofloxacin in the People's Republic of China.[29] The universal eradication treatment of *H. pylori* might increase serious antibiotic resistance and affect the application of antibacterial drugs in the future. In addition, the implementation of population-based screening would cause some intangible costs, such as human resources, publicity expenses of health authority. These obstacles have made *H. pylori* screening and treatment a complicated issue. Our results were similar to the situation described in the previous section and refined the detected population. At the same time, it was relatively easier to implement this program in first-degree relatives of patients with gastric cancer. Screening and eradication therapy of *H. pylori* infection in a high-risk gastric cancer population is relatively achievable from the perspective of health authorities.

Subjected to the insufficient data, several limitations existed in our analysis that deserve attention. Firstly, the eradication rate of *H. pylori* and the incidence of gastric cancer in first-degree relatives of patients with gastric cancer used in our study were derived from a single-center trial in Korea. Nevertheless, family history of gastric cancer was a global risk factor, so our results may be generally applicable.[30] Secondly, the utility values of early gastric cancer and advanced gastric cancer may be different. Due to the lack of tumor staging for patients in this trial, we used an average utility of gastric cancer. Thirdly, regarding costs information, we only considered direct costs, neglecting the costs of lost working time and transportation fees. Additionally, the costs of rescue therapy for patients who failed first-line *H. pylori* therapy, secondary infection after antibiotic treatment and the daily expenses incurred by life extension were not calculated. As a result, the costs may be underestimated. However, they had little effect on the

results according to the sensitivity analysis. Finally, the characteristics of the population in clinical trials may differ from the patients in clinical practice. Real world studies could be carried out in the future.

In summary, *H. pylori* eradication therapy significantly reduced the incidence of gastric cancer in first-degree relatives of patients with gastric cancer with economic benefits in the People's Republic of China. Based on our analysis, *H. pylori* eradication therapy is a dominant strategy. At present, in the People's Republic of China, where disease burden is heavy and economic resources are limited, eradication therapy is a cost-effective prevention strategy to prevent gastric cancer. The persistent *H. pylori* infection not only increased the risk of spreading among people, but also the risk of gastric cancer. It is worthy of being applied and promoted in clinical practice, especially in countries with high *H. pylori* prevalence.

Ethics Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Disclosure

The authors report no conflicts of interest in this work.

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