ORIGINAL INVESTIGATION

# Clinical and Economic Effects of Population-Based *Helicobacter pylori* Screening to Prevent Gastric Cancer

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**Background:** *Helicobacter pylori* infection has been identified as a risk factor for certain types of gastric cancer. However, the extent to which *H pylori* eradication decreases the risk of gastric cancer is unknown, raising the question of whether population-based *H pylori* screening should be undertaken.

**Objective:** To compare clinical and economic effects of *H pylori* screening, with and without confirmatory testing, with no screening to prevent gastric cancer.

**Design:** Decision analysis incorporating a Markov simulation.

**Patients:** Simulated cohorts of men and women with varying risk of gastric cancer.

**Intervention:** Three strategies were evaluated: (1) no screening; (2) *H pylori* serologic testing, treat those positive for *H pylori*, no follow-up testing; and (3) *H pylori* serologic testing, treat those positive for *H pylori*, followed by a test to confirm *H pylori* eradication, retreat those who test positive. In the principal analysis, the risk of gastric cancer after *H pylori* eradication was assumed to be similar to that for those without *H pylori* infection. Scenarios with less optimistic assumptions regarding risk reduction of cancer were evaluated.

**Main Outcome Measures:** Gastric cancer rates, discounted cost per life-year saved.

**Results:** If *H pylori* eradication reduced the risk of cancer to that of people never infected, both *H pylori* intervention strategies reduced gastric cancer rates so that each yielded at least 12 additional life-years per 1000 40-year-old white men screened when compared with no screening. *Helicobacter pylori* serologic testing without posttreatment confirmatory testing resulted in the lowest cost per additional life-year saved ($6264). The cost-effectiveness of the *H pylori* screening strategies varied substantially as the level of risk reduction of cancer was varied, but remained cost-effective even at moderate rates (<30%) of excess risk reduction of cancer in all cohorts evaluated.

**Conclusions:** Population-based *H pylori* screening has the potential to produce important health benefits at a reasonable cost at moderate rates of excess risk reduction of cancer. Controlled studies are necessary to confirm and quantify the impact of *H pylori* eradication on the risk of gastric cancer.

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EPIDEMIOLOGICAL investigations have demonstrated individuals infected with *Helicobacter pylori* to be at an increased risk for cancer of the gastric body and antrum.[1,2] In response to these findings, the International Agency for Research on Cancer classified *H pylori* as a group 1 carcinogen in humans, raising the question whether population-based screening should be undertaken.[3] To date, no controlled trials have demonstrated that *H pylori* eradication alters the risk of gastric cancer. Moreover, results from prospective studies that directly quantify the impact of *H pylori* eradication on the risk of cancer on low-risk individuals are decades away.

In the absence of definitive clinical evidence of the effect of *H pylori* eradication on the risk of cancer, decision analytic modeling can be used to estimate the potential health and economic consequences of *H pylori* screening over a range of cancer risk reduction. Using this methodology, Parsonnet and colleagues[4] reported in 1996 that a screening program incorporating a single *H pylori* serologic test was potentially cost-effective, particularly in populations at high-risk of gastric cancer. The development of accurate, inexpensive diagnostic tests to detect *H pylori* infection that produce immediate results necessitate that screening of low-risk individuals be considered as a public health interven-

## PATIENTS AND METHODS

### DECISION ANALYTIC MODEL

Using the best available published data, we used decision analysis to estimate the clinical and economic consequences of 3 strategies: strategy 1, no screening for *H pylori*; strategy 2, single *H pylori* serologic testing—individuals who tested positive for *H pylori* received eradication therapy. Treated patients did not receive a posttreatment test to confirm *H pylori* eradication; and strategy 3, serologic testing followed by *H pylori* confirmatory testing—individuals who tested positive for *H pylori* received eradication therapy, followed 6 weeks later by a test to confirm eradication after treatment. Those testing positive for *H pylori* on confirmatory testing received a second course of eradication therapy.

**Table 1** contains a list of the epidemiological parameters, clinical probabilities, and costs used in the model. Inputs and ranges for use in sensitivity analysis were derived from a critical review of the published literature.

### SCREENING

The screening interventions included no testing or treatment (strategy 1) to up to 2 *H pylori* diagnostic tests and 2 courses of eradication therapy (strategy 3). Asymptomatic populations with varying risk of gastric cancer would enter the model with a probability of *H pylori* infection derived from published population-based serology surveys.[5,6] The sensitivity and specificity of the *H pylori* screening test(s) determined the likelihood of treatment. An individual could undergo initial screening only once. Individuals testing negative for *Helicobacter pylori* falsely identified as infected (false positives) incurred the cost and potential morbidity of therapy, but received no clinical benefit. Individuals infected with *H pylori* but identified as not infected (false negatives) incurred the test cost, but did not receive eradication therapy, and therefore had a life expectancy identical to the untreated infected population.

### TREATMENT

Eradication therapy was prescribed for each individual who tested positive for *H pylori*. Since active peptic ulcer disease was not anticipated in the asymptomatic population, a course of eradication therapy did not exceed 2 weeks. Treatment-associated adverse events were included. Efficacy, compliance, and adverse event rates were included in estimating the effectiveness and cost of eradication therapy.

For those patients who had evidence of active infection following confirmatory testing in strategy 3, a different *H pylori* eradication regimen was selected to maximize effectiveness and minimize the impact of antibiotic resistance. No more than 2 courses of eradication therapy per patient were assessed in the model. While *H pylori* reinfection after cure was possible in the model (1% annually in the principal analysis), spontaneous eradication in the absence of therapy was not. Patients who remained infected despite attempts at eradication had life expectancies similar to infected individuals who did not undergo treatment.

### CONFIRMATORY TESTING

A test that assessed the presence of active *H pylori* infection (eg, urea breath test or fecal antigen test) was performed after therapy was completed in strategy 3. It was assumed in the principal analysis that all treated patients would undergo confirmatory testing if made available to them. The sensitivity and specificity of the confirmatory test determined that individuals received a second eradication regimen.

### GASTRIC CANCER

After the screening and treatment period, the risk of gastric cancer and overall life expectancy were modeled

Continued on next page

tion. Moreover, improvements in, and patient demand for, diagnostic testing to establish the presence or absence of active *H pylori* infection after therapy requires a strategy that includes a test to confirm cure be evaluated.

## RESULTS

### GASTRIC CANCERS AVERTED

Under the best-case scenario, where eradication completely eliminated *H pylori*–associated excess risk of cancer, each of the *H pylori* screening programs decreased the rate of gastric cancer in white men when compared with a strategy of no screening (**Table 2**). To prevent 1 case of gastric cancer, 434 individuals were screened in the serology-only strategy (strategy 2), and 370 in the serology and confirmatory testing strategy (strategy 3) (Table 2). When gastric cancers prevented were translated into life expectancy, both of the screening strategies yielded more than 12 discounted life-years saved per 1000 screened when compared with no screening (Table 2). Confirmatory testing and re-treatment of those testing positive for *H pylori* after therapy led to 2.3 additional life-years saved compared with the serology-only strategy.

### SCREENING PROGRAM COSTS AND COST-EFFECTIVENESS

The cost per patient screened for each of the intervention strategies is shown in **Table 3**. While the estimated cost for either of the *H pylori* screening strategies was less than $200 per patient, the *H pylori* serology-only strategy was less expensive per patient ($76) than the screening strategy incorporated confirmatory testing ($163). When the 2 *H pylori* screening programs were compared with no screening, the resultant cost per life-year saved (serology-only strategy, $6264; serology and confirmatory testing, $11 313 per life-year saved) was considerably lower than $50 000 per life-year saved threshold (Table 3).

using a Markov process (**Figure 1**).[7] Baseline risk of gastric cancer was determined from available age, race, and sex-specific epidemiological data.[8-11] For the principal analysis, a cohort of 1000 40-year-old white men was entered into the model. The cost-effectiveness of screening in white women (half the risk of white men), African American and Hispanic men (twice the risk of white men), and Japanese American men (4 times the risk of white men) was also examined. Patient-specific gastric cancer incidence rates were based on history of *H pylori* infection, current *H pylori* infection status, relative risk of gastric cancer of infected compared with uninfected individuals, and the level of risk reduction of gastric cancer attributable to eradication. It was assumed that only cancers of the gastric body and antrum (60% of all gastric cancers) were attributable to *H pylori* and therefore preventable by eradication.

In the principal analysis, the risk of gastric cancer for individuals who were cured of *H pylori* infection was assumed to be identical to the risk of individuals who were never infected. This optimistic assumption that *H pylori* eradication completely eliminated any increased risk of gastric cancer attributable to *H pylori* represents a best-case scenario for the intervention programs. Since the impact of *H pylori* eradication and the risk reduction of gastric cancer is unknown, a cost-effectiveness ratio was calculated for each of the intervention strategies over a full range of risk reduction, from no benefit to complete elimination of excess risk. A primary goal of the sensitivity analyses was to identify the necessary level of risk reduction of cancer that would yield a cost-effectiveness ratio of $50 000 per discounted life-year saved, a value suggested as a threshold for acceptable health care interventions.[12] Additional sensitivity analyses assessed how changes in specific clinical and economic inputs altered the level of risk reduction of cancer necessary to yield this threshold.

Individuals remained in the simulation until they died of gastric cancer or of other causes. Age, race, and sex-specific life-expectancy data were drawn from life tables.[13] In the principal analysis, patients with gastric cancer were assumed to have died in the year in which the cancer was diagnosed. Neither treatment costs for gastric cancer nor medical care costs attributable to prolonged survival were included in the principal analysis. However, the impact of gastric cancer survival (0%-20%), cost of cancer treatment ($50 000), direct medical costs of prolonged life expectancy ($3500 per year), and costs of a nongastric cancer death were evaluated in the sensitivity analysis.

### COSTS

Health care costs used in the different strategies are shown in Table 1. Values for direct medical costs of health care services used in the model for diagnostic testing, drugs, and professional services were derived from published reports and obtained from actual payments made by third-party payers. Adverse events from eradication therapy that warranted medical intervention were included. Costs of lost productivity (eg, indirect costs) and nonmedical direct costs (eg, travel to medical visits) were not included. All costs were reported in 1996 US dollars. Costs were discounted at 3% per year[14]; discount rates between 0% and 7% were tested in the sensitivity analysis.

### COST-EFFECTIVENESS RATIOS

Cost-effectiveness ratios compared clinical outcomes (measured as discounted life-years saved) and associated costs (discounted dollars) among the alternative screening programs. Incremental cost-effectiveness ratios were calculated for the 2 screening strategies (strategies 2-3) compared with no screening (strategy 1). In addition, incremental cost-effectiveness ratios between the intervention strategies were calculated when one intervention strategy yielded additional life-years saved at an additional cost.

## SENSITIVITY ANALYSIS

### Risk Reduction of Gastric Cancer Attributable to *H pylori* Eradication

When the level of risk reduction of gastric cancer was evaluated over the complete range of effectiveness from complete risk reduction (as used in the principal analysis) to no effect, the cost-effectiveness of each screening strategy varied (**Figure 2**). Using $50 000 per life-year saved as a threshold, this sensitivity analysis revealed that the serology-only strategy was cost-effective in white men if *H pylori* eradication reduced excess risk of gastric cancer by 15% or more. The risk reduction threshold necessary for the confirmatory testing strategy was higher; excess risk of gastric cancer had to be reduced by nearly 30% to meet the $50 000 per life-year saved threshold (Figure 2).

### Populations With Varying Risk of Gastric Cancer

The potential effects of *H pylori* screening in middle-aged, white women (half the risk of white men), African American and Hispanic men (twice the risk of white men), and Japanese American men (4 times the risk of white men) were evaluated. **Figure 3** demonstrates the level of risk reduction of cancer necessary for a serology-only strategy to achieve the $50 000 life-year saved threshold. For African American and Hispanic men, *H pylori* screening appears cost-effective at very low reductions (≤10%) in the risk of cancer. For Japanese men, the model estimated that if *H pylori* eradication had practically any impact on reducing the risk of cancer, universal screening in this high-risk group would be cost-effective.

When inputs such as *H pylori* screening test characteristics or the efficacy and cost of *H pylori* eradication therapy were varied, there was minimal change in the risk reduction threshold of cancer for cost-effectiveness in each of the intervention strategies. For example, when the cost of eradication therapy was examined over a range of $40 to $250, the risk reduction threshold for cost-effectiveness for the single serologic testing strategy varied from 13% to 22%. The probability of survival from gastric cancer had a small

**Table 1. Clinical Inputs and Cost Estimates***

| Variable | Input | Range | Reference |
|---|---|---|---|
| Clinical Inputs, % | | | |
| *Helicobacter pylori* prevalence | 40 | 15-60 | 5, 6 |
| *H pylori* serology sensitivity | 90 | 85-95 | 25, 26 |
| *H pylori* serology specificity | 90 | 85-95 | 25, 26 |
| *H pylori* confirmatory test sensitivity | 95 | 90-100 | 27, 28 |
| *H pylori* confirmatory test specificity | 95 | 90-100 | 27, 28 |
| Effectiveness of *H pylori* eradication therapy | 80 | 65-95 | 29 |
| *H pylori* eradication therapy adverse events necessitating medical attention | 2.5 | 2-5 | 30, 31 |
| Relative risk of gastric cancer if infected (compared with not infected with *H pylori*) | 3.6 | 2-8 | 1, 2, 32 |
| Relative risk of cancer if not infected or eradicated (principal analysis) | 1.0 | 0.0-1.0 | . . . |
| *H pylori* reinfection rate, per year | 1.0 | 0-5 | 33 |
| Cost estimates, $ | | | |
| *H pylori* serology | 20 | 8-60 | . . . |
| *H pylori* eradication therapy | 80 | 40-200 | . . . |
| Test to confirm *H pylori* eradication | 150 | 50-350 | . . . |
| Primary care physician visit | 39 | 25-75 | . . . |
| Cost of eradication therapy-related adverse event | 50 | 5-100 | . . . |

*Ellipses indicate not applicable.

impact on the risk reduction threshold, ranging from 15% (principal analysis, 0% survival) to 18% (20% survival) in the serology-only strategy. Increases in the discount rate raised the level of risk reduction of cancer to achieve the $50 000 per life-year saved threshold. In the extreme case, a 7% annual rate necessitated a 35% risk reduction in the serology-only strategy, compared with the 15% necessary in the principal analysis (3%).

When variations in the costs of gastric cancer care (direct medical costs of prolonged life expectancy) and direct costs (a nongastric cancer cause of death) were included into the simulation, the risk reduction threshold for cost-effectiveness for each strategy was not significantly affected.

### Incremental Cost-effectiveness Among Screening Strategies

Analyses were performed to quantify the incremental cost-effectiveness of recommending a test to confirm *H pylori* eradication after treatment (strategy 3). Compared with a single serology strategy (strategy 2), the serology and confirmatory testing strategy (strategy 3) prevented an additional case of gastric cancer for every 1050 patients screened, resulting in a cost per additional life-year of $37 870 under a scenario of perfect excess risk reduction of cancer. Sensitivity analysis revealed that the incremental cost-effectiveness of performing a confirmatory test after treatment remained below the $50 000 per life-year saved threshold only at an excess risk reduction of cancer of 80% or more. As the cost of the confirmatory test was reduced from $150 to $50, the risk reduction of cancer necessary to achieve cost-effectiveness remained more than 50%.

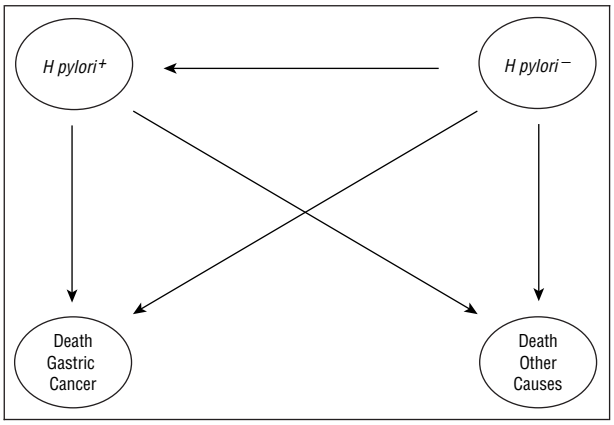


**Figure 1.** *Transition diagram of Markov Model.* H *indicates* Helicobacter.

## COMMENT

The rapid improvement and ease in our ability to diagnose and treat *H pylori* infection requires a careful examination of the indications for which a diagnostic test is performed and eradication therapy is prescribed. The evidence for prompt eradication for individuals with *H pylori*–associated peptic ulcer disease and mucosa-associated lymphoid tissue lymphoma is overwhelming.[15,16] However, controlled investigations supporting eradication to prevent the most morbid complication of *H pylori* infection, adenocarcinoma of the stomach, are anticipated.

Since gastric cancer conceptually evolves from *H pylori*–associated chronic atrophic gastritis to intestinal metaplasia and finally dysplasia, an intervention that arrests this progression may prevent gastric cancer. While primary prevention trials are ongoing, investigations using high-risk patients and intermediate precancerous end points may provide useful information regarding the role of *H pylori* eradication in reducing the risk of gastric cancer. While we admit that the use of these surrogate outcomes is no substitute for carefully controlled trials, if eradication prevents the cascade of events that lead to gastric cancer, the argument for screening is strengthened. Ongoing investigations in Mexico, China, and Columbia[17-19] have focused on whether diminishing *H pylori*–associated inflammation prevents the progression of normal mucosa to atrophic gastritis or from worrisome intermediate stages (eg, metaplasia) to cancer. Further support for *H pylori* screening can be derived from a nonrandomized secondary prevention trial from Japan. Uemura and colleagues[20] demonstrated that *H pylori* eradication eliminated the incidence of recurrent gastric cancer at 2 years after endoscopic tumor resection in 65 patients with gastric cancer. This was compared with a 9% (6/67) cancer recurrence rate in persistently infected patients.[20]

Epidemiological studies[1,2] have concluded that *H pylori* is associated with an excess risk of gastric cancer. The World Health Organization[3] has placed this prevalent organism into a class of carcinogens that includes plutonium. The decision is complicated whether to adopt a population-based screening program for which data are suggestive, but not conclusive of a benefit. This

**Table 2. Clinical Results: 40-Year-Old White Men**

| Variable | No Screening | *Helicobacter pylori* Serology | *Helicobacter pylori* Serology and Confirmatory Test |
|---|---|---|---|
| Gastric cancer rate per 1000 patients screened* | 12.9 | 10.6 | 10.2 |
| Patients screened to prevent a case of gastric cancer*† | Not applicable | 434 | 370 |
| Discounted life-years saved per 1000 patients screened*† | Not applicable | 12.1 | 14.4 |

**Assuming eradication eliminates excess gastric cancer risk.*
*†Compared with a strategy of no screening.*

**Table 3. Screening Program Costs and Cost-Effectiveness**

| Variable | *Helicobacter pylori* Serology | *Helicobacter pylori* Serology and Confirmatory Test |
|---|---|---|
| Discounted cost per patient screened, $* | 75.80 | 162.90 |
| Discounted cost per life-year saved, $*† | 6264 | 11 313 |

**Compared with a strategy of no screening.*
*†Assuming eradication eliminates excess gastric cancer risk.*

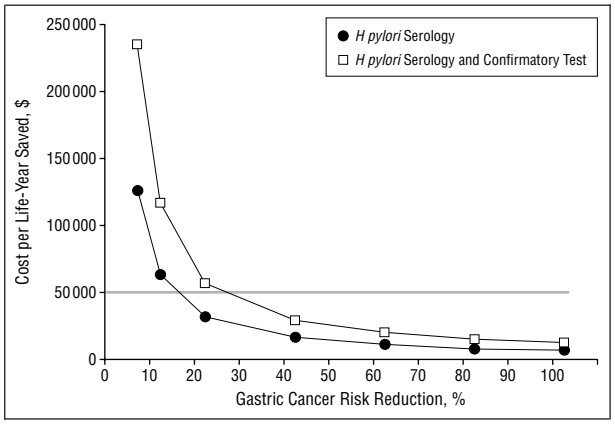


**Figure 2.** *Sensitivity analysis: risk reduction of cancer attributable to eradication by screening strategy.* H *indicates* Helicobacter.

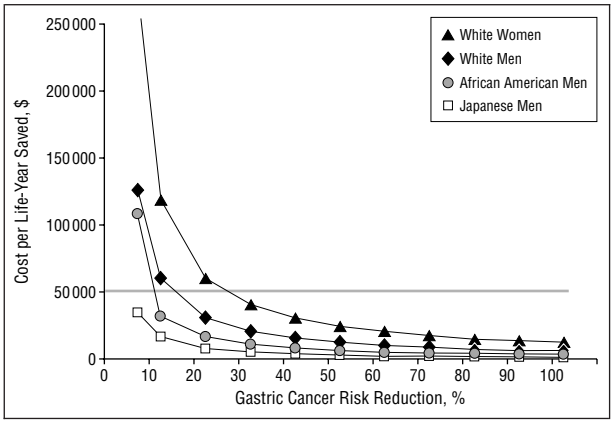


**Figure 3.** *Sensitivity analysis: risk reduction of cancer attributable to eradication in a serology-only strategy by population.*

complexity is not unique to *H pylori* and prevention of gastric cancer. A similar controversy surrounds prostate-specific antigen screening to detect prostate cancer. Current practice patterns suggest that many men are willing to undergo prostate cancer screening at regular intervals—a multistage process associated with measurable morbidity—to reduce the potential risk of cancer-related mortality, even in the absence of definitive evidence of mortality reduction.[21] When data from well-controlled trials critical to the decision to undertake screening are unavailable or under debate, decision analysis allows a standardized approach to estimate the impact of uncertainty. Outcomes generated by a model can be reproducibly examined under an infinite number of possible scenarios, which can be used to test hypotheses and examine which clinical and cost parameters influence the final results.

Theoretically, the potential effects of *H pylori* eradication on the risk of gastric cancer range from complete and immediate elimination of excess risk of cancer to no benefit at all, which would argue that infection was merely a marker associated with, but not the only cause of, excess risk. In the principal analysis, we chose to model a best-case scenario (perfect risk reduction) for the screening interventions to establish that there was potential for a *H pylori*–based gastric cancer prevention program to be cost-effective. While the assumption of complete risk reduction strongly biased the model results in favor of *H pylori* screening, the sensitivity analysis examining how changes in this crucial variable influenced the cost-effectiveness of screening (Figure 2) should be viewed as our primary finding.

Our results, like those of Parsonnet et al,[4] found that a *H pylori* serologic testing strategy (strategy 2) that did not include a test to confirm eradication was potentially cost-effective. The fact that this screening strategy was cost-effective for 40-year-old white women (low risk of gastric cancer) when *H pylori* eradication eliminated only 30% of the excess risk of cancer makes it difficult not to consider population-based *H pylori* screening while waiting for conclusive data. Since the available pathophysiological data suggest that the likelihood of reversing the cascade of events leading to malignancy would be greater the earlier therapy is initiated, we evaluated a screening strategy at age 40 years, a stage of life when other health maintenance interventions (eg, cholesterol level) are recommended.

The model estimated that a serology and confirmatory test strategy (strategy 3) was cost-effective compared with serologic testing alone (strategy 2) only when an excess risk of cancer was reduced by more than 80%. This high rate of risk reduction necessary to achieve cost-effectiveness decreased as the price of confirmatory testing was reduced or if the intangible ben-

efits certain patients may receive from the knowledge that a potentially carcinogenic infection had been cured were included. Survey data obtained from *H pylori*–infected patients with peptic ulcer disease suggest a strong desire to confirm a cure.[22] Patient expectations and the availability of a reasonably priced, noninvasive test to document eradication may impede the adoption of a screening program that does not include confirmatory testing. The desire of individuals and clinicians to confirm cure of *H pylori* after treatment will likely lead to a significant number of people undergoing a second diagnostic test and potentially, an additional course of therapy. It remains to be seen whether these intangible benefits and resultant patient demand for evidence of cure will lead physicians to prescribe and payers to reimburse a confirmatory test.

Since *H pylori* is predominantly an infection of childhood and *H pylori* reinfection after eradication is unlikely, screening need only be performed once during adult life.[6] It may be more important from an operational standpoint that noninvasive diagnostic testing and eradication treatment can be executed during a single visit to a primary care provider. Moreover, unlike carcinoma of the prostate, mortality after the diagnosis of gastric cancer is high. Therefore, until an effective treatment becomes available, each case of gastric cancer prevented translates into real life-expectancy benefits.

Without definitive evidence of the risk reduction of cancer, there remains legitimate anxiety over the indiscriminate use of antibiotic therapy leading to bacterial resistance. In response to this concern, a screening strategy focused on those *H pylori*–infected individuals deemed to be at highest risk for cancer should be considered. In addition to estimating the cost-effectiveness of screening in demographic groups associated with varying risk of gastric cancer (Figure 3), we investigated an alternative approach to identify high-risk individuals through the use of a test for a virulent *H pylori* strain associated with an increased risk of cancer. Using recent data and the most optimistic assumptions regarding the risk reduction of cancer, this strategy was not cost-effective ($243 000 per life-year saved) when compared with *H pylori* serologic testing only.[23] As more specific *H pylori* markers denoting the relative risk of cancer are identified, the decision analytical framework allows continued assessment of the cost-effectiveness of a screening strategy incorporating their use.

The media coverage surrounding the World Health Organization designation of *H pylori* as a carcinogen will encourage the screening of asymptomatic individuals.[24] In addition, the potential availability of home-based *H pylori* test kits will allow self-diagnosis of their infection, requiring clinicians to confront the scenario when a patient presents for advice regarding the benefits of treatment after *H pylori* infection has been diagnosed. As we await definitive studies quantifying the impact of *H pylori* eradication on the risk of gastric cancer, decision analysis can define the risk reduction parameters necessary for various screening strategies to be cost-effective in specific demographic groups.

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