

How Long Will It Take to Reduce Gastric Cancer Incidence by Eradicating *Helicobacter Pylori* Infection?

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Abstract

Helicobacter pylori (*H. pylori*) is the most important risk factor for the development of gastric cancer. The objective of this article is to estimate how the number of clinically diagnosed cases caused by *H. pylori* would reduce in the years after the eradication of the infection from a population. It is assumed that the eradication of *H. pylori* will prevent the start of some new gastric tumors, but those that have passed the "point of no return" will continue to develop until diagnosed clinically. The observed reduction in the number of clinically diagnosed cases of gastric cancer will depend on the form and parameters of the distribution of the time *t* taken for tumor to develop into a clinical case after passing the "point of no return." This analysis assumes that the time *t* follows normal and log-normal distributions with means 5, 10, and 15 years. If the mean value of time *t* were 5 years, *H. pylori* caused cases should be almost eliminated after 10 years, whereas if the mean were 10 years, the number of cases should be halved. If the mean were 15 years, the reduction would only be about 15% after 10 years. The eradication of *H. pylori* from a population will reduce the incidence of gastric cancer, but the follow-up time needed to show and evaluate the reduction may be longer than that that has been used in studies published so far. *Cancer Prev Res*; 6(7); 695–700. ©2013 AACR.

Introduction

Gastric cancer is the fourth highest incident cancer in the world and it is the second highest cause of cancer death. There were an estimated 989,000 new cases and 737,000 deaths worldwide in 2008 (1).

Knowledge of the etiology and epidemiology of gastric cancer has changed dramatically since infection with *Helicobacter pylori* (*H. pylori*) was identified as its main risk factor and cause (2, 3). Although the role of *H. pylori* had been hypothesized 20 years before, it was only in 2005 that the Nobel Prize in Physiology or Medicine was awarded jointly to B.J. Marshall and J.R. Warren for their discovery of "the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease" (4). By the time they received their prize, much more was known about the harmful consequences of *H. pylori* infection and research after the early 1980s led the International Agency for Research on Cancer (IARC) to classify *H. pylori* as carcinogenic for humans in 1994 (5). Other important risk factors for gastric cancer include smoking, diet, occupation, and radiation. That the main risk factor is an infectious agent, is not novel; human

papillomavirus is a cause of cervical cancer and there are campaigns for the vaccination of pubertal girls to prevent it. There are no similar campaigns for the treatment of *H. pylori* infection to prevent gastric cancer yet. Indeed, the evidence to show that the eradication of *H. pylori* can prevent gastric cancer obtained from single clinical trials is not particularly convincing. There have been few randomized controlled trials, and those that have been published relate to areas with very high prevalence of *H. pylori* infection. A meta-analysis (6) of 7 trials included 4 trials from China, 2 from Japan, and only 1 outside Asia, from Colombia. This meta-analysis evaluated a total of 6,695 participants and produced an overall relative risk of 0.65 (95% CI, 0.43–0.98). The result is statistically significant, but the confidence interval is wide. This is because, even though the total number of participants is large, there were only 37 cases in the treated groups and 56 among the controls. The median follow-up time was only 6 years with a range from 3 to 10 years. This study has been criticized because one study was included twice (7), but the authors of the original meta-analysis re-analyzed the data excluding the duplicated data obtaining very similar results, OR = 0.65 (95% CI, 0.42–1.01). Furthermore, an analysis of one of the included studies was re-evaluated extending the follow-up to 14.7 years and concluded that *H. pylori* eradication reduced gastric cancer incidence (OR = 0.61; 95% CI, 0.38–0.96; ref. 8). However, given the low incidence of gastric cancer and thus the long period of follow-up necessary to accrue a sufficient number of cases, and the ethical issues involved with recruiting infected individuals who may be randomized to receive a placebo, it may be that the randomized clinical trial is not necessarily the most

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appropriate method of evaluating the effect of the elimination of *H. pylori* on gastric cancer incidence. Although the randomized controlled trial is regarded as the gold standard for producing evidence of the effect of an intervention, in this case it is not easy to conduct. An alternative is to study the incidence of gastric cancer in a well-defined population before and after the eradication of *H. pylori*. This strategy was adopted for the population of the small island of Matsu, which is midway between Taiwan and mainland China. This study (9) compared the prevalence of gastric lesions between 1995 and 2003 before a program of mass eradication of *H. pylori* and in 2004 to 2008 after the intervention. The main findings were that population-based eradication of *H. pylori* infection substantially reduced the prevalence of the infection and the incidence of gastric atrophy and peptic ulcer within the short period of the study. The intervention did not reduce the incidence of intestinal metaplasia or decrease its severity. Critical is the "point of no return" (10–12) when mucosal alterations are no longer reversible. Although "before and after" intervention studies may be easier, there are clearly more opportunities for biases to influence the results than would be the case of a randomized controlled trial. At least an external control of time trends in gastric cancer incidence should be incorporated.

Assuming that the "gastric precancerous cascade" (13) hypothesis holds, if the follow-up period is sufficiently long, the reduction in gastric atrophy should lead to a reduction in the observed incidence of, and mortality from gastric cancer.

Eradication of *H. pylori* infection would, in the long term, seem to be the best population-based strategy for the prevention of gastric cancer.

A population-based project to reduce the incidence of gastric cancer by eradicating *H. pylori* is due to begin in the city of Bologna in 2013. Briefly, the whole adult population, about 330,000 persons, will be invited to have a stool test to determine the presence of the antigen for *H. pylori* (14). The participants found to be positive, about one third, will have a confirmatory Urea Breath test (^{13}C UBT; ref. 15). After sequential antibiotic therapy, they will repeat it to confirm that the infection is eliminated (16). An annual clinical check-up will continue for 10 years, by which time it is hoped that the effects of the eradication of *H. pylori* on the incidence of gastric cancer will be evident.

As in all the other studies that have tried to show the beneficial effect of eradicating *H. pylori* on gastric cancer incidence, the period of follow-up has been chosen somewhat arbitrarily.

The objective of this analysis is to try to gain some insight into how long the follow-up should be after *H. pylori* eradication, to be "sufficiently long" to observe an important reduction in the number of incident cases of gastric cancer. It is not specific to the Bologna study; it assumes a constant number, 100 incident cases of gastric cancer caused by *H. pylori* per year before eradication and that everything else remains constant, in particular there is no change in incidence, timing, or techniques of diagnosis, the tumor is neither more nor less aggressive after the eradication of *H. pylori*, age at reaching the "point of no return" and mortality from other causes do not change.

Materials and Methods

The evolution of gastric cancer starts with infection with *H. pylori*, usually at a very young age, which if not treated remains until death. For many infected people there will be no symptoms, but for some the bacterium will cause gastritis and peptic ulcer. For relatively few (1–2%), gastric cancer will develop. The "point of no return" hypothesis presumes that the elimination of the infection before a critical point in the evolution will prevent the further development of gastric cancer. After this point, elimination of *H. pylori* will do nothing to impede or accelerate the development of the tumor. Consider a person who becomes infected with *H. pylori* at age A_0 and reaches the "point of no return" at age A_1 . It is supposed that between ages A_0 and A_1 eradication of the infection will prevent the development of the tumor. After age A_1 , the tumor will continue to develop until a clinical diagnosis is made at age A_2 , whether or not the infection is eradicated (Fig. 1).

The number of years between age A_0 and A_1 and between A_1 and A_2 will not be the same for every patient but will vary for many reasons, including patient characteristics such as age and gender, infection characteristics such as location in the stomach and infection load, and tumor characteristic such as tumor location and "aggressiveness" that may in turn be affected by the infection characteristics.

Suppose $t = A_2 - A_1$ years, is the time during which the tumor is unaffected by eradication of *H. pylori*. Thus, t is the time in years during which the development of the tumor cannot be halted. Because t will not be the same for all patients, the form and parameters of the distribution of t will determine how rapidly the number of newly diagnosed cases of gastric cancer reduces after the elimination of *H. pylori* from a population.

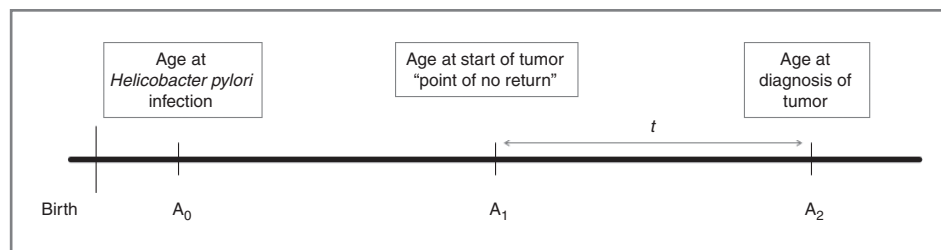


Figure 1. Schematic process of the development of a gastric tumor after *H. Pylori* infection.

For example, 10 years after the eradication program, the number of newly diagnosed cases should be relatively low if the mean value of t were say 5 years, but might be still high if the mean were 20 years. Similarly, if the standard deviation of t were small, the decline, once started, would be rapid, whereas if t were more variable, the decline would be slower. Furthermore, the decline in the number of incident cases would be affected by the shape of the distribution of t ; if the distribution were skew to the left, the decline immediately after eradication would be slow for several years, followed by a more rapid decline. Conversely, if the distribution were skew to the right (a more plausible assumption), the decline would be more rapid in the first years after eradication, but there would be a smaller residual number of cases observed many years later. If the distribution were symmetrical, for example the Gaussian or normal distribution, the decline will be symmetrical about the mean value of t years after eradication. Although very little is known about the form of the distribution, we consider 2 possibilities, normal and log-normal, and hypothesize mean and standard deviations that may be considered to imply a rapid evolution of the tumor, a medium progression time, and a slow progression.

The normal range of a variable is defined to be the interval that contains the central 95% of the values of the variable observed in a population. If the distribution is normal, this interval is the mean \pm twice the SD (more precisely, mean \pm 1.960 SDs).

A variable say x is said to be log-normally distributed, if the variable $y = \log x$ is normally distributed.

The normal range of a normal distribution has its limits equally distant from the arithmetic mean. In contrast, if the distribution of t is log-normal, the limits of the normal range are proportionately equally distant from the geometric mean.

To investigate the effect of the assumptions about the form and parameters of the distribution of t on the decline in the number of diagnosed cases of gastric cancer, we have made the following assumptions:

1. Eradication of *H. pylori* in a population is achieved at an "instant," say in the year 2013.
2. The number of incident cases of *H. pylori* caused gastric cancer diagnosed each year is 100 before eradication of *H. pylori* and in the absence of eradication this number would remain constant.
3. Eradication of *H. pylori* has no effect on the evolution of gastric cancer after the "point of no return."
4. Six hypotheses for the form and parameters of the distribution of t have been considered, corresponding to what we have called rapid, medium, and long evolution time:
 - i. Normal distribution, arithmetic mean 5 years, normal range 1 to 9 years. RAPID
 - ii. Normal distribution, arithmetic mean 10 years, normal range 5 to 15 years. MEDIUM.
 - iii. Normal distribution, arithmetic mean 15 years, normal range 5 to 25 years. SLOW.
 - iv. Log-normal distribution, geometric mean 5 years, normal range 2 to 12.5 years. RAPID.
 - v. Log-normal distribution, geometric mean 10 years, normal range 5 to 20 years. MEDIUM.
 - vi. Log-normal distribution, geometric mean 15 years, normal range 7.5 to 30 years. SLOW.

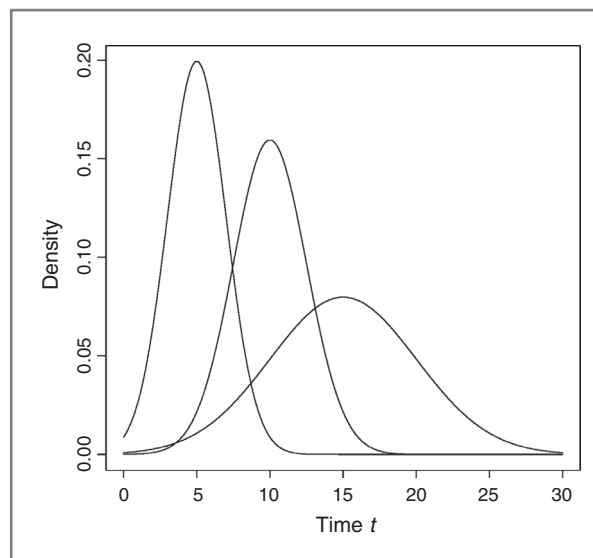


Figure 2. Normal distributions of time t with means 5, 10, and 15 years and with normal ranges 1 to 9, 5 to 15, and 5 to 25 years.

- iv. Log-normal distribution, geometric mean 5 years, normal range 2 to 12.5 years. RAPID.
- v. Log-normal distribution, geometric mean 10 years, normal range 5 to 20 years. MEDIUM.
- vi. Log-normal distribution, geometric mean 15 years, normal range 7.5 to 30 years. SLOW.

Results

Figures 2 and 3 show the distributions of t , the time between the "point of no return," and the clinical diagnosis of gastric cancer, for the 3 normal distributions hypothesized and the 3 log-normal distributions. If the evolution of

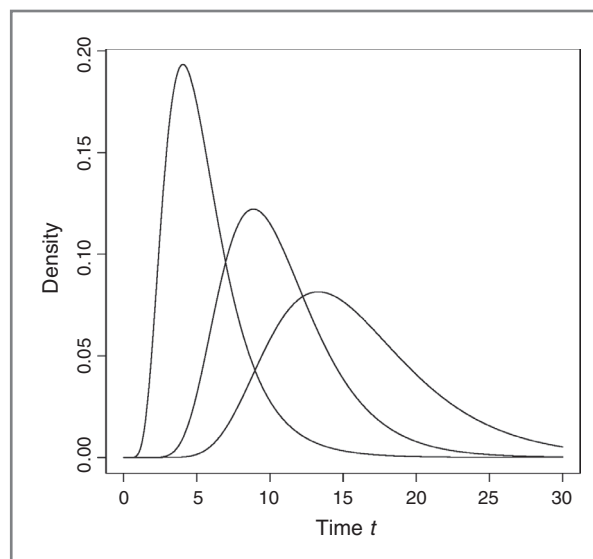


Figure 3. Log-normal distributions of time t with geometric means 5, 10, and 15 years and with normal ranges 2 to 12.5, 5 to 20, and 7.5 to 30 years.

the tumor is "rapid," *H. pylori* caused gastric cancer will be effectively eliminated by 2023, 10 years after the eradication program. In contrast, if the evolution of the tumor is a slow process, by 2023 there will still be an important number of cases diagnosed each year.

For the patients who reach the "point of no return" before 2013, the presupposed date of the eradication of *H. pylori*, their tumors will continue to develop until they are clinically diagnosed. In 2014, the number of diagnosed cases

will be very close to 100 (the assumed constant annual number of diagnosed cases before the eradication of *H. pylori*), but in successive years this number should decrease according to the assumed form of the distribution of *t*. Table 1 shows the number of cases expected from 2014 onward according to the assumptions made about the form of the distribution of *t*. It is evident that the number of years of follow-up required to reduce the incidence from 100 new cases per year to 50 cases per year is equal to the chosen

Table 1. Number of cases expected to be diagnosed in the years from 2014 onward according to the assumptions made about the form, mean^a, and normal range of the distribution of *t*

Distribution	Normal	Normal	Normal	Log-normal	Log-normal	Log-normal
Mean ^a	5 years	10 years	15 years	5 years	10 years	15 years
Normal range	1-9 years	5-15 years	5-25 years	2-12.5 years	5-20 years	7.5-30 years
2014	98	100	100	100	100	100
2015	93	100	100	98	100	100
2016	84	100	100	87	100	100
2017	69	99	100	69	100	100
2018	50	98	98	50	98	100
2019	31	95	96	34	93	100
2020	16	88	94	23	85	99
2021	7	79	92	15	74	97
2022	2	66	88	10	62	93
2023	1	50	84	6	50	88
2024		34	79	4	39	81
2025		21	73	3	30	74
2026		12	65	2	22	66
2027		5	58	1	17	58
2028		2	50	1	12	50
2029		1	42		9	43
2030			34		6	36
2031			27		5	30
2032			21		3	25
2033			16		2	20
2034			12		2	17
2035			8		1	13
2036			6		1	11
2037			4		1	9
2038			2			7
2039			1			6
2040						5
2041						4
2042						3
2043						2
2044						2
2045						1
2046						1
2047						1
2048						1
2049						
2050						

^aFor the normal distributions, the mean is the arithmetic mean; whereas for the log-normal distributions, the mean is the geometric mean.

Table 2. Percentages of cancers prevented 5, 10, 15, and 20 years after the eradication program, according to the different assumptions made about the form, mean^a, and normal range of the distribution of *t*

Distribution	Normal	Normal	Normal	Log-normal	Log-normal	Log-normal
Mean ^a	5 years	10 years	15 years	5 years	10 years	15 years
Normal range	1–9 years	5–15 years	5–25 years	2–12.5 years	5–20 years	7.5–30 years
5 years	50	2	2	50	2	0
10 years	99	50	16	94	50	12
15 years	100	98	50	99	88	50
20 years	100	100	84	100	98	80

^aFor the normal distributions, the mean is the arithmetic mean; whereas for the log-normal distributions, the mean is the geometric mean.

values of the arithmetic mean for the normal distributions and the geometric mean for the log-normal distributions. (For the normal distribution, the arithmetic mean and the median are equal; for the log-normal distribution, the geometric mean is equal to the median). The follow-up time suggested for the proposed Bologna study is 10 years, which is the same as the longest follow-up time of any published trial or intervention study of the effect of *H. pylori* eradication on the incidence of gastric cancer. From Table 1, it can be seen that after 10 years, if the distribution of *t* were normal with mean 5 years and normal range 1 to 9 years, the expected incidence of *H. pylori* caused gastric cancer would be reduced from 100 cases to 0, whereas if the distribution were log-normal with geometric mean 5 years and normal range 2 to 12.5, the incidence would be 6 cases after 10 years. In contrast, if the arithmetic mean and geometric mean of the 2 distributions were 10 years, considered medium evolution time, there would still be 50 cases expected after a follow-up of 10 years. In the third scenario, of a slow evolution of the tumor with mean 15 years, the expected number of cases would be 84 assuming the normal distribution and 88 if the distribution were log-normal. Clearly, in this case, 10 years of follow-up after *H. pylori* eradication is insufficient to convincingly show the benefit of the intervention. These percentages of gastric cancers prevented by the eradication of *H. pylori* are shown in Table 2.

Discussion

This article provides a quantitative theoretical perspective on one of the problems facing those seeking to show the effectiveness of *H. pylori* eradication in preventing gastric cancer. This analysis does not pretend to predict the results of the eradication of *H. pylori* on the incidence of gastric cancer. It is known that *H. pylori* is a cause of gastric cancer, but it is certainly not the only cause. It is neither sufficient nor necessary for the development of the tumor. If eradication of the infection can prevent some cases of gastric cancer, then the intervention should reduce the incidence, but the size of the reduction obviously will depend on the fraction of all gastric tumors that are caused by *H. pylori*. This has been estimated to be about 60% for noncardia gastric

cancer cases and about one third of all gastric cancers (17). We have considered only those cases of gastric cancer that are caused by *H. pylori*.

Furthermore, the analysis is not based on hard evidence of the time scale of the "gastric precancerous cascade" but rather on what we consider reasonable but critical assumptions. First, we have assumed that "the point of no return" hypothesis holds. That is, elimination of *H. pylori* infection before a critical point will prevent the development of the tumor, but after this point, the elimination will have no effect on the subsequent evolution of the tumor. This is central to the calculation of the reduction in the number of cases after elimination of *H. pylori* and even if it were true for gastric cancer, it might not hold for other diseases. Furthermore, we have made assumptions about the likely mean and distribution of the time *t* between the "point of no return" and the clinical diagnosis of gastric cancer. The distribution of *t* is not estimable from data because the "point of no return" is not directly observable. This is crucial. Indeed, there have been no studies published, to our knowledge, which describe the characteristics of the distribution of *t*, and thus it is important to treat the results that we present as no more than speculations based on what we consider to be reasonable assumptions. We have considered 3 categories of the time for the evolution of the tumor, which we have called rapid, medium, and slow, which correspond to mean values of 5, 10, and 15 years. Only time and further research will reveal how reasonable these assumptions really are.

It is also true that our analysis is oversimplified in the sense that we have calculated the expected number of gastric cancer cases assuming that no other factors affect the incidence. This is clearly not the case; in Italy (18, 19) and all developed countries of the world, the incidence of gastric cancer is slowly but surely declining even in the absence of programs to eradicate *H. pylori* infection. In fact, the incidence of the infection is becoming less presumably because of improved living standards, hygiene, general antibiotic use, etc.; and thus, the number of incident cases of gastric cancer will tend to decline even without an active intervention eradication program. The evaluation of the eradication program will need to take the effect of these other factors

seriously into account. For example, age is the most important factor in determining the risk of gastric cancer. The age incidence curve rises steeply at ages over about 60 years. Because infection with *H. pylori* usually occurs at a very young age, the more youthful the population, the greater should be the effect of *H. pylori* eradication on the percentage of cancers prevented, even though the actual number will be relatively small. An older population would be expected to have a higher incidence of gastric cancer, but the percentage of new cases prevented would require more time to become evident. Furthermore, the demonstration and evaluation of the effect of *H. pylori* eradication will require statistical significance tests and confidence intervals. The power of the tests and the width of the confidence intervals will be determined by the number of incident cases before and in the years after the intervention. For convenience, we have assumed 100 cases per year before the intervention. In our analysis, with mean time 5 years, after 5 years of follow-up, the expected number of cases from an initial level of 100 is 50 (Table 2). The number of observed cases has an approximate Poisson distribution and thus the observed number may reasonably be between about 36 and 64. (The SD of a Poisson variable is the square root of the expected number. Thus, the SD is $\sqrt{50}$, which is approximately 7; the normal range is $50 \pm 2 \times 7$.) Unless the program involves a relatively large population with a correspondingly high number of incident gastric cancer cases, the statistical significance test may be underpowered. It is

concluded that the eradication of *H. pylori* from a population will reduce the incidence of gastric cancer, but the follow-up time needed to show and evaluate the reduction may be longer than that has been used in studies published so far.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: J.F. Osborn, M.S. Cattaruzza, D. Vaira
Development of methodology: J.F. Osborn, M.S. Cattaruzza
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.M. Ferri, F. De Angelis, D. Renzi, A. Marani
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.F. Osborn, M.S. Cattaruzza
Writing, review, and/or revision of the manuscript: J.F. Osborn, M.S. Cattaruzza, A.M. Ferri, F. De Angelis, D. Renzi, A. Marani, D. Vaira
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.M. Ferri, F. De Angelis, D. Renzi, A. Marani
Study supervision: J.F. Osborn, M.S. Cattaruzza

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