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Review

Eradication of gastric cancer is now both possible and practical

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ABSTRACT

In 1994, *Helicobacter pylori* was declared a human carcinogen. Evidence has now accumulated to show that at least 95% of gastric cancers are etiologically related to *H. pylori*. An extensive literature regarding atrophic gastritis and its effects on acid secretion, gastric microflora, and its tight association with gastric cancer has been rediscovered, confirmed, and expanded. Methods to stratify cancer risk based on endoscopic and histologic findings or serologic testing of pepsinogen levels and *H. pylori* testing have been developed producing practical primary and secondary gastric cancer prevention strategies. *H. pylori* eradication halts progressive mucosal damage. Cure of the infection in those with non-atrophic gastritis will essentially prevent subsequent development of gastric cancer. For all, the age-related progression in cancer risk is halted and likely reduced as eradication reduces or eliminates mucosal inflammation and reverses or reduces *H. pylori*-associated molecular events such aberrant activation-induced cytidine deaminase expression, double strand DNA breaks, impaired DNA mismatch repair and aberrant DNA methylation. Those who have developed atrophic gastritis/gastric atrophy however retain some residual risk for gastric cancer which is proportional to the extent and severity of atrophic gastritis. Primary and secondary cancer prevention starts with *H. pylori* eradication and cancer risk stratification to identify those at higher risk who should also be considered for secondary cancer prevention programs. Japan has embarked on population-wide *H. pylori* eradication coupled with surveillance targeted to those with significant remaining risk. We anticipate that countries with high gastric cancer burdens will follow their lead. We provide specific recommendations on instituting practical primary and secondary gastric cancer prevention programs as well identifying research needed to make elimination of gastric cancer both efficient and cost effective.

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1. Introduction

Gastric cancer is the fourth most common cancer and second leading cause of cancer deaths worldwide with more than 700,000 deaths annually [1]. Currently the highest incidence rates are in Japan, Korea, China, Eastern Europe and parts of Central and South America [2]. This is a marked change from the early 20th century when gastric cancer was the most common cancer in many Western countries including the United States [3]. It is now recognized that the vast majority of gastric cancers are etiologically related to infection with the bacterium *Helicobacter pylori* (*H. pylori*) [4]. The different clinical outcomes of *H. pylori* infections (e.g., duodenal ulcer, gastric ulcer, gastric cancer) relate to the different pattern of gastritis that occur (e.g., antral predominant gastritis is associated with duodenal ulcer disease whereas atrophic pangastritis is associated with gastric ulcer and gastric cancer). The predominant pattern of gastritis depends on interactions between the predominant *H. pylori* strain (and its virulence), host factors (especially those related to genes that enhance or reduce the inflammatory response to the infection), and environmental factors (of which diet appears to be the most important).

The prevalence of *H. pylori* and pattern of gastritis can change rapidly within a population [5,6]. The incidence of gastric cancer can also change rapidly. For example, between 1965 and 1995 the incidence of gastric cancer in Japan fell approximately 60% in the age groups between 40 and 69 (Fig. 1) [7]. During this short period there was no change in host genes, the prevalence of *H. pylori* within these age groups, or the predominant *H. pylori* strain, emphasizing the key role of environmental factors such as methods of food

Abbreviations: AID, activation-induced cytidine deaminase; *H. pylori*, *Helicobacter pylori*; IARC, International Agency for Research on Cancer; GI, gastrointestinal; CI, confidence interval; KLF5, Krüppel-like factor 5; VCP, valosin-containing protein; OLGA, Operative Link on Gastritis Assessment; *hMLH1*, human mutL homolog 1; *BRCA1*, breast cancer susceptibility gene 1; *MGMT*, methylated-DNA–protein-cysteine methyltransferase; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *CDH1*, cadherin-1; *MLH1*, mutL homolog 1; *RUNX3*, runt-related transcription factor 3; CpG, cytosine-phosphate-guanine are regions of DNA.

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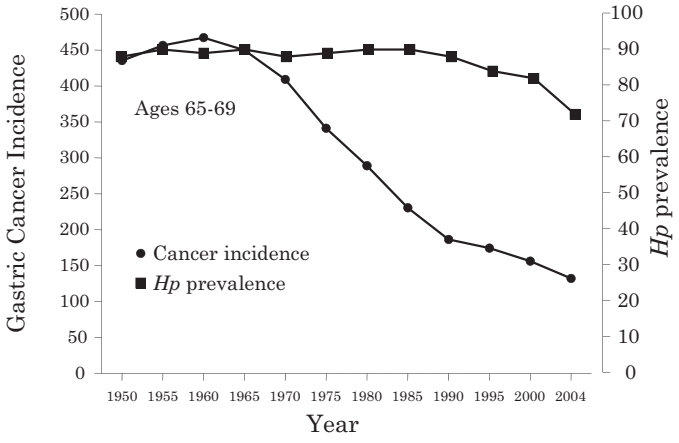

Fig. 1. Changes in the incidence of gastric cancer and *Helicobacter pylori* infection among Japanese men age 65–69 during the latter half of the 20th century (Constance Wang and David Y. Graham, unpublished observations).
From reference [7], with permission.

preservation and diet in defining the risk of different outcomes [7].

A causal role for *H. pylori* in gastric cancer was first accepted by the International Agency for Research on Cancer (IARC) in 1994 when they labeled *H. pylori* a class I carcinogen [8]. However, this did not immediately result in the worldwide *H. pylori* eradication programs or even eradication programs in regions where gastric cancer was especially common. One problem with moving forward might have been that the actual risk of gastric cancer attributable to *H. pylori* was greatly underestimated. This occurred, in part, because those studying *H. pylori* seemed unaware of (or chose to ignore) the tremendous body of prior research linking atrophic gastritis with gastric cancer [9]. Early *H. pylori* investigators used serology to assess its prevalence of *H. pylori* which systematically underestimated its prevalence, and thus the role of *H. pylori* in gastric cancer. The problem with serology was that the results were frequently falsely negative which occurred because the majority with cancer also had severe atrophic gastritis/gastric atrophy with extensive intestinal metaplasia which produced a gastric environment unsuitable for persistence of *H. pylori*. Thus, despite the fact that *H. pylori* had caused the precancerous changes and the serology had once been positive, it had become negative [10]. This bias coupled with a failure to correlate gastric histology to serologic results or to reconcile these new findings with the extensive older literature showing a tight association between atrophic gastritis and gastric cancer likely set back *H. pylori* eradication programs by many decades, a time during which many millions died of their gastric cancers. This bias was only corrected recently by the addition of CagA serology which generally remains positive despite loss of the active infection as well as a renewed attention to previously extensively studied atrophic gastritis-cancer link [9,11,12].

2. Pre-*H. pylori* studies of gastritis and gastric cancer (late 1800s to 1950 the atrophy–achlorhydria period)

In 1879, [i.e., before endoscopy, gastrointestinal (GI) surgery, or radiology were available], von den Velden reported that gastric cancer was linked to achlorhydria which for the first time provided a diagnostic test for the presence of gastric cancer [9,13]. The era around the beginning of the 20th century saw a virtual explosion in GI research and was recognized that prior conclusions based on histological examination of post mortem stomachs often provided misleading information because the findings described largely were due to autolysis [14]. The period between 1880 and 1920 saw marked advances in histology, chemistry, GI physiology, as well as the development of safe gastric surgery and contrast radiology. This was a time when many of the heroic figures in gastroenterology were active including Faber, Pavlov, Einhorn, Ewald, Cannon, Moynihan, Sippy, and Mayo. It was also a time when the pattern of gastritis had changed sufficiently such that atrophic gastritis was becoming less common and antral predominant gastritis with duodenal ulcer was becoming a common clinical problem.

At mid-20th century, Comfort summarized the research relating acid secretion, gastritis, and gastric cancer from first half of the 20th century [13]. The data showed that (1) gastric cancer was associated with loss of secretory activity, (2) the reduction in gastric secretion was progressive, (3) that gastric secretory activity was subnormal before cancer developed, (4) that acid secretion was subnormal in each decade of life among patients destined to develop gastric cancer, and (5) these observations were true no matter how many years gastric secretion was tested before the cancer developed [13]. Comfort concluded that atrophy of the acid secreting cells was the most likely cause of abnormal gastric acidity in the precancerous stomach and that it (atrophic gastritis) was the soil in which a majority of gastric cancers appeared [13]. These critical insights seem to have been largely unknown to most investigators embarking on the study of *H. pylori*-related gastritis and its sequalae.

3. Research in the second half of the 20th century

Two Finnish pathologists, Jarvi and Lauren, classified gastric cancer as intestinal type, diffuse type, and mixed type and proposed that gastric cancer might originate from islands of intestinal epithelium within the gastric mucosa [15,16]. They also suggested that islands of intestinal metaplasia arose in a background of chronic gastritis and noted that intestinal-type cancer was surrounded by metaplastic mucosa more frequently than diffuse carcinomas. Finally, they recommended that "prophylaxis should obviously be directed against gastritis".

Correa in 1975 described a series of sequential steps that culminated in intestinal-type of adenocarcinoma consisting of chronic active nonatrophic gastritis, atrophic gastritis, intestinal metaplasia and finally intraepithelial neoplasia (then called dysplasia) [2,17–20]. Correa also hypothesized that the initial stages of inflammation and atrophy might create a microenvironment favoring engraftment of cancer stem cells [2]. However, the origin of the cancer stem cell remains unsettled with data supporting stem cells being locally derived and other data suggesting they are bone marrow-derived [21,22]. It is now thought unlikely that cancer evolves directly from intestinal metaplasia and most agree that the presence, extent, and possibly the type of intestinal metaplasia should best be considered an easily recognized biomarker associated with increasing degrees of risk for gastric cancer [23–28].

By the late 1930s it was recognized that if one could find the cause of gastritis one should be able to prevent peptic ulcer and gastric cancer and in the period between 1960 through period of the discovery of *H. pylori* there were many experimental and epidemiologic studies. Many different associations with gastritis were reported from different areas of the world [29] and overall they failed to find a common denominator. The discovery of *H. pylori*, the proof it caused gastritis, and that *H. pylori* eradication led to healing of gastritis in the 1980s provided the key to breaking the chain of events leading to gastric cancer.

4. The natural history of gastritis within the stomach – the advancing atrophic front

H. pylori gastritis is characterized by infiltration of the gastric mucosa with both chronic inflammatory cells (lymphocytes,

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