



Risk of Stomach Cancer in Patients with Peptic Ulcer Disease

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Abstract. The relation between peptic ulcer and stomach cancer has long been disputed, but there is accumulating evidence that gastric ulcer disease is positively associated and duodenal ulcerations negatively associated with the risk of developing stomach cancer. As *Helicobacter pylori* infection is associated with both types of ulceration and stomach cancer, the varying outcomes of the infection indicate that factors other than the infection must be of importance. At present, there is no convincing evidence that pharmacologic inhibition of acid secretion for treatment of peptic ulcer increases the risk of stomach cancer. However, some recent studies indicate that prolonged treatment with proton pump inhibitors may accelerate the development of atrophic gastritis, a risk factor for stomach cancer, in individuals infected with *H. pylori*. It has repeatedly been shown that there is an at least twofold increased risk of stomach cancer 15 years after gastric resection for peptic ulcer disease, and that the risk increases with the passage of time. Whether vagotomy has the same risk-increasing effect is still unclear.

The purpose of this review is first to explore the relation between peptic ulceration and stomach cancer. Because some treatment modalities for peptic ulceration, both surgical and medical, have been linked to stomach cancer, the second aim of this review is to briefly examine the evidence for this association. Unfortunately, the term peptic ulcer is confusing in that it does not sharply delineate the pathologic differences between gastric and duodenal ulcers, most clearly demonstrated in their differing relations to stomach cancer. However, as the term has long been accepted for these two types of ulceration, it is used in this review.

The relation between peptic ulcer and stomach cancer has been disputed ever since Cruveilhier in 1839 first distinguished clearly between chronic ulcer and cancer both clinically and pathologically [1]. Later, during the 1940s and 1950s, there was a debate about the differences between gastric and duodenal ulcer disease [2, 3]. These diseases tended to be mutually exclusive, but no explanations were offered for the differences observed. The discovery of *Helicobacter pylori* by Warren [4] and Marshall [5] in 1982 changed forever the perception of gastroduodenal disease, and it is now generally accepted that this bacterium causes 95% of duodenal ulcers and at least 60% to 70% of gastric ulcers [6].

The risk for peptic ulcer rose in generations (i.e., birth cohorts) born before the end of the nineteenth century but has declined in all subsequent generations [7]. The birth cohorts with the highest risk of developing stomach ulcer were born 10 to 20 years before those with the highest risk for duodenal ulcer. The decreasing incidence of peptic ulcer disease shows a clear birth cohort pat-

tern, indicating that the relevant risk factors occur during early life. Since the first half of the twentieth century the incidence of stomach cancer has been declining in most industrialized countries, and a birth cohort pattern has been revealed [8]. Stomach cancer is still estimated to be the second most common cancer worldwide, with more than 1 million new cases diagnosed 1996 [9]. The decreased susceptibility for developing peptic ulcer and stomach cancer that has taken place during the twentieth century most likely reflects similar temporal trends in the infection rate with *H. pylori*. The high prevalence rates of *H. pylori* infection found in the elderly represent the historic scars of high infection rates experienced 50 to 70 years ago during childhood. Several studies have suggested that *H. pylori* seroprevalence has decreased over time, and that consecutive birth cohorts in developed countries were exposed to decreasing incidence rates of *H. pylori* infection [10, 11]. This conjecture provides additional support for the contention that the birth cohort phenomenon of peptic ulcer and possibly also of stomach cancer stems from an underlying birth cohort phenomenon of the *H. pylori* infection. Individuals who became infected with *H. pylori* at a young age are likely to develop chronic or atrophic gastritis with a subsequent reduction of their acid secretion that protects them against duodenal ulcer but increases the risk of developing stomach ulcer and cancer. Duodenal ulcer seems to develop primarily in individuals who contract *H. pylori* infection at the end of childhood or later [12]. Neither *H. pylori* infection nor peptic ulcer disease has been associated with cancer of the gastric cardia [13–15].

Peptic Ulceration and Risk of Stomach Cancer

Gastric Ulcer

A coexisting stomach cancer has been reported in 2% of patients with a diagnosis of gastric ulcer [16], but the malignant degeneration of gastric ulcers appears to be rare [16–19]. Tumors that are chemically induced in rodents tend to develop in or near ulcers, but the presence of ulcers in rats does not increase the overall incidence of tumors [20]. Thus although gastric ulcers are probably not a cause of gastric cancer, the positive association between the two diseases suggests they have certain risk factors in common.

A number of follow-up studies have failed to demonstrate any increased long-term risk of stomach cancer in patients with gastric

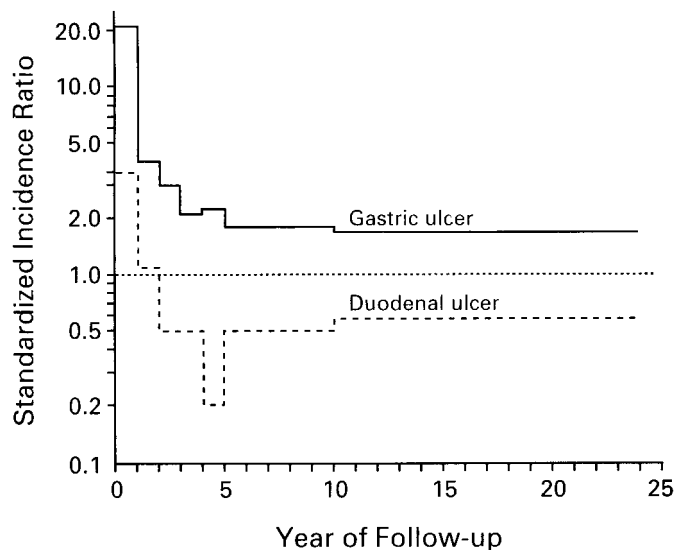


Fig. 1. Standardized incidence ratio for stomach cancer in patients with gastric or duodenal ulcers, according to the year of follow-up. The scale for the standardized incidence ratio is logarithmic. (From Hansson et al. [15], with permission. Copyright © 1996 Massachusetts Medical Society. All rights reserved.)

ulcers [17, 21–25], but these studies have suffered from some limitations: (1) Stomach cancer has become a comparatively rare disease, and the number of patients followed has not been enough to give statistically reliable results. (2) It is difficult to follow patients with peptic ulcer, and in most studies the length of observation has been too short. (3) Because of the short observation period in several studies it has been difficult to distinguish true gastric ulcers from ulcerated cancers whose benignity was misdiagnosed initially. (4) Reliance has been on radiologic diagnosis [21, 22, 24], which is a less precise technique than endoscopy [26, 27].

A Swedish cohort study [15] overcame the shortcomings of previous studies. Among 29,287 patients with gastric ulcer followed for an average of 8.3 years, the standardized incidence ratio for gastric cancer after the third year was 1.8 [95% confidence interval (CI) 1.6–2.0] (Fig. 1). In this cohort the relative risk was higher among women than among men ($p = 0.02$). The standardized incidence ratios were higher in patients who were younger at the start of follow-up. Prepyloric ulcers were not associated with an increased risk of subsequent gastric cancer, and there was no association between peptic ulcer disease and cancer of the gastric cardia.

Duodenal Ulcer

By contrast, duodenal ulcer disease has often been inversely associated with stomach cancer; but the evidence comes largely from small studies or case series [17, 28–30]. In the previously mentioned Swedish cohort study [15] of 24,456 patients hospitalized for duodenal ulcer disease followed for an average of 10.1 years, the incidence of gastric cancer was significantly lower than expected. After the second year of follow-up, the standardized incidence ratio was only 0.6 (95% CI 0.4–0.7) (Fig. 1).

The issue of relatedness between peptic ulcer and stomach

cancer remains important, particularly after the discovery of *H. pylori*, which seems to play an essential role in the development of duodenal ulcer, gastric ulcer, and stomach cancer [6]. Close to 100% of patients with duodenal ulcers are infected with *H. pylori*, recently designated a carcinogen in humans by the International Agency for Research on Cancer [31]. *H. pylori* infection may affect the early stages of gastric carcinogenesis by inducing chronic gastritis, with which there is (1) formation of free radicals by inflammatory cells [32]; (2) production of nitric oxide, nitrates, and nitrosamines by macrophages [33, 34]; and (3) increased cell turnover [35]. It seems likely that some factors at work in patients with duodenal ulcers modify the risk of stomach cancer associated with *H. pylori*. A clue to one such protective factor comes from the observation that whereas multifocal atrophic gastritis predisposes patients to both gastric ulcer disease and stomach cancer [36–38] the relation between this type of gastritis and duodenal ulcers is less clear [39]. *H. pylori* infection is related to atrophic gastritis in groups of unselected patients [40, 41], but the positive association appears more pronounced in patients with gastric ulcers than in those with duodenal ulcers [42]. Atrophic gastritis, in which there is a loss of gastric acidity, contributes to a gastric bacterial flora that promotes the endogenous formation of *N*-nitroso carcinogens [43]. Furthermore, infiltration of leukocytes into the gastric mucosa, combined with an alkaline pH in gastric juice, results in low levels of ascorbic acid [44] and thus diminished ability to block the *N*-nitrosation process [45]. Patients with duodenal ulcers, however, are reported to have high levels of ascorbic acid in the gastric juice [46].

Medical Therapy for Peptic Ulcer and Its Relation to Stomach Cancer

Histamine (H_2)-receptor antagonists and proton pump inhibitors (PPIs) are now widely used for disorders of the esophagus, stomach, and duodenum. During the 1980s the use of these drugs increased substantially without a corresponding increase in peptic ulcer disease [47], indicating that these drugs are used increasingly to treat nonulcer dyspepsia and other unspecific gastrointestinal (GI) discomfort for which these antisecretory agents are of little value [48]. Since the introduction of cimetidine during the late 1970s, caution has repeatedly been urged against inadvertently treating cancer of the stomach by an empiric course of H_2 -receptor antagonists or PPIs [49, 50]; some workers have reported initial healing and relief of symptoms of “gastric ulcers” that later were shown to be malignant [51]. Because symptoms of stomach cancer can mimic those of peptic ulcer, it is not surprising that occasional patients with cancer have undergone treatment with these drugs.

The fact that patients with pernicious anemia, invariably associated with gastric atrophy and hypochlorhydria, have an increased risk of developing stomach cancer [52, 53] has raised the question of whether therapeutic hypochlorhydria is carcinogenic to the stomach. Pharmacologically induced hypochlorhydria has been shown to be associated with increased gastric bacterial growth, reduction of nitrate to nitrite, and increased concentration of carcinogenic *N*-nitroso compounds in the gastric juice [54, 55]. Some studies have indicated that long-term treatment with PPIs may accelerate the development of atrophic changes of the gastric mucosa in individuals infected with *H. pylori* [56–58].

Chronic *H. pylori* gastritis also predisposes to the development of gastric atrophy [59, 60], which has been reported to be associated with an increased incidence of stomach cancer [61]. A Danish population-based cohort study of 16,739 patients prescribed cimetidine showed a statistically increased relative risk (RR; approximately 2.0) of gastric cancer as long as 5 years or more after diagnosis [62]. It is likely that many of these patients were treated for duodenal ulcers and thus initially had a lower than average risk of stomach cancer [15]. Consequently, a slight increase in risk reported after pharmacologically induced hypochlorhydria (compared with the general population) may represent an important excess. Taking into account the long induction time (16–24 years) [63] of stomach cancer, the H₂-receptor antagonists and PPIs have not been in use for a sufficient time to evaluate their effects on the long-term incidence of stomach cancer. Consequently, it is important to address this question in future studies.

Stomach Cancer following Peptic Ulcer Surgery

Distal Partial Gastrectomy

Gastric stump cancer is defined as an adenocarcinoma of the stomach occurring 5 years or more after gastric resectional surgery for benign conditions. During the first half of the twentieth century distal partial gastrectomy became the predominant surgical treatment of peptic ulcer disease [64]. This procedure involves resection of the distal 50% to 75% of the stomach, followed by reconstruction with a gastroduodenostomy (Billroth I) or a gastrojejunostomy (Billroth II). One might expect the risk of stomach cancer after partial gastrectomy for peptic ulcer to be lower than in the general population because of resection of the distal portion of the stomach, which has been the most common location of stomach cancer.

During the past decade a number of well designed, large, retrospective, cohort studies were conducted with almost complete follow-up extending 30 years or more after gastric surgery [65–73]. In summary, these studies have revealed the following: (1) Patients treated with partial distal gastrectomy for duodenal ulcer have a low RR (approximately 0.6) of gastric cancer during the first 20 years after surgery [65, 66, 69, 71, 72]. After about 20 years the RR increases to about 2.0. (2) If the indication for surgery was gastric ulcer, the patients experienced the same RR as the general population during the first 20 years after the operation [69, 71, 72] or had a higher risk. After 20 years the RR was clearly elevated (approximately 3.0) [66]. The reason for this higher risk compared to patients with duodenal ulcer disease is probably the higher prevalence of gastric mucosal atrophy in gastric ulcer patients at the time of the initial operation [74, 75]. (3) Stomach cancer risk increases with time after partial distal gastrectomy, such that the relative risk is about 3.0 to 5.0 after 25 to 30 years [67–69, 71, 72].

With respect to gender, the risk assessment has varied. Depending on the study, a higher risk has been found for men [67, 76, 77] and women [66, 69]; and in some studies no difference was found [70, 78]. An inverse association of age at operation with risk of stomach cancer, which remained even after adjustment for differences in follow-up time, was reported in one study [69]. Gastric ulcer at operation has generally been found to increase the risk of subsequent stump cancer compared to patients with a duodenal ulcer [66, 69, 70]. Stomach cancer rates are consistently higher

following treatment with a Billroth II procedure than after Billroth I [66, 69, 70]. A meta-analysis revealed an RR of stomach cancer of 1.60 (95% CI 1.15–2.18) after distal partial gastrectomy with Billroth II gastrojejunostomy and 1.20 (95% CI 1.01–1.42) with Billroth I gastroduodenostomy [79].

The mechanism thought to underlie the increased risk of stomach cancer is production of *N*-nitroso carcinogens in the gastric remnant due to bacterial overgrowth secondary to postoperative hypochlorhydria. In addition, experimental studies indicate that operations that promote duodenogastric bile reflux increase the susceptibility of the stomach to neoplastic change [80]. Bacterial deconjugation of refluxed bile acids at high intragastric pH may generate co-carcinogens; unconjugated lithocholic and deoxycholic acids can enhance experimental colorectal carcinogenesis [81]. Alternatively, bile reflux may play a promotional part by increasing permeability to initiating carcinogens. Experimentally, bile acids, lysolecithin, and trypsin all digest gastric mucus, thereby increasing the exposure of gastric mucosal cells to hydrogen ions, resulting in atrophic gastritis [82, 83]. This enterogastric reflux has been reported to be more pronounced after a gastrojejunostomy than after a gastroduodenostomy [84], which may explain the higher stomach cancer risk after a Billroth II operation than after Billroth I.

Vagotomy

Highly selective vagotomy (below included in the term “vagotomy”) rapidly replaced gastric resection as the preferred surgical procedure during the early 1970s. Stomach cancer risk after vagotomy with or without drainage may be greater than that after partial distal gastrectomy because the entire gastric mucosa is at risk after this procedure. Duodenal ulcer patients up to 8 years after vagotomy were found to have a significantly increased frequency of gastritis and atrophy compared to nonoperated patients with active ulcer who had virtually no body gastritis [85]. The proportion of patients with the most severe grades of *H. pylori* infection was higher in the vagotomy group than in the nonoperated group. The concentration of nitrosamines in the stomach of patients after vagotomy has been found to be greatly increased [86]. Vagotomized juxtapyloric ulcer patients followed longitudinally showed a statistically significant increase in the prevalence and degree of chronic body gastritis [87]; dysplasia may be a common finding after vagotomy [88, 89]. However, experimental studies have failed to show any increased tumor yield in rats exposed to unconjugated bile acids after truncal vagotomy [90].

A population-based Swedish study of 7198 vagotomized patients followed for 9 to 18 years showed a standardized incidence ratio of 1.33 (95% CI 0.92–1.86) [91]. This is in contrast with previous reported smaller studies, which showed an up to 3.3-fold death risk from gastric cancer [66, 73, 92–94]. However, most of these patients were probably operated for duodenal ulcer disease associated with a decreased risk of stomach cancer. Consequently, even a slight increase in risk compared to the general population reported after surgically induced hypochlorhydria may represent an important excess for patients with duodenal ulcer.

Conclusions

There is accumulating evidence that gastric ulcer disease is positively associated and duodenal ulcerations negatively associated

with the risk of developing stomach cancer. As *H. pylori* infection is associated with both types of ulceration and stomach cancer, the varying outcomes of the infection indicate that factors in addition to the infection must foster one disease while working against the other. At present, there is no convincing evidence that pharmacologic inhibition of acid secretion increases the risk of stomach cancer. However, some studies indicate that prolonged treatment with PPIs may accelerate the development of atrophic gastritis, a risk factor of stomach cancer, in individuals infected with *H. pylori*. Thus long-term use of acid-inhibiting therapy should be viewed with caution. A link between previous gastric resection and stomach cancer has been found in a number of studies and appears to be real. The risk increases with the passage of time, and a twofold risk can be expected more than 15 years after the initial operation. In the future this problem of stomach cancer developing after peptic ulcer surgery should steadily decline as a public health issue, as the number of surgical procedures for peptic ulcer has been decreasing since the 1960s [95]. The reason for this decline is that the incidence of peptic ulcer disease has been declining. Moreover, the medical management of peptic ulcer was revolutionized during the late 1970s with the introduction of H₂-receptor antagonists.

Résumé

Le rapport entre la maladie ulcéreuse et le cancer gastrique a été soulevé depuis fort longtemps; il existe de plus en plus d'évidence que cette transformation ne concerne pratiquement que l'estomac mais pas la maladie ulcéreuse duodénale. Comme l'infection par *H. pylori* est associée avec les deux types d'ulcères ainsi qu'avec le cancer gastrique, il doit y avoir d'autres facteurs pathogéniques en dehors de l'infection. Jusqu'à présent, il n'existe aucune évidence que l'inhibition pharmacologique de la sécrétion acide augmente le risque de cancer gastrique. Cependant, quelques études récentes indiquent que le traitement prolongé par les inhibiteurs de la pompe à protons pourrait accélérer le développement de l'atrophie gastrique chez le patient infecté par l'*H. pylori*, celui-ci étant un facteur de risque pour le cancer gastrique. On a démontré de façon répétée que le risque de cancer de l'estomac est augmenté d'au moins deux fois, 15 ans après la résection gastrique pour maladie ulcéreuse, et que ce risque augmente avec le temps. Le rôle de la vagotomie dans cet enchaînement n'est pas clair.

Resumen

Desde hace tiempo se discute la posible relación entre la úlcera péptica y el cáncer gástrico. En la actualidad, existe información suficiente para afirmar que la úlcera gástrica constituye un importante factor de riesgo en el desarrollo del cáncer gástrico, mientras que por el contrario, la úlcera duodenal no se asocia al mismo. Como la infección por el "*H. pylori*" aparece en ambos tipos de úlcera así como en el cáncer de estómago, estos resultados indican que además de la infección ha de haber otros factores de gran importancia en la génesis del cáncer gástrico. En la actualidad no hay evidencia convincente de que la inhibición farmacológica de la secreción ácida, durante el tratamiento de la úlcera péptica, incremente el riesgo de cáncer gástrico; algunos estudios recientes señalan que un prolongado tratamiento con inhibidores de la bomba de protones acelera el desarrollo de una

gastritis atrófica, que sí constituye un factor de riesgo, sobre todo en individuos infectados por el "*H. pylori*". Se ha demostrado que el riesgo de cáncer gástrico se multiplica al menos por dos, en pacientes que sufrieron gastrectomía por úlcus péptico hace 15 años y que este riesgo se incrementa con el paso del tiempo. Se desconoce si la vagotomía representa un factor de riesgo semejante.

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