

Peptic Ulcer Disease and the Risk of Bladder Cancer in a Prospective Study of Male Health Professionals

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Abstract

Helicobacter pylori is a risk factor for gastric and duodenal ulcers, but gastric ulcers generally occur in individuals who have low acid production and diffuse gastritis, whereas duodenal ulcers are more likely to occur with high acid output and antrum-predominant gastritis. Low acid production, gastritis, and ulcer healing each contribute to poor antioxidant absorption, oxidative stress, and elevated nitrite levels in the stomach. *N*-Nitrosamines are known carcinogens, and nitrate ingestion has been related to bladder cancer risk. Consequently, we hypothesized that the gastric conditions associated with gastric ulcers may contribute to elevated bladder cancer risk. We thus examined the association between self-reported history of peptic ulcer disease and the risk of bladder cancer (414 cases) over 14 years of follow-up in the Health Professional Follow-Up Study. Cox proportional hazards models were performed to adjust for known risk factors of bladder cancer. Men who reported a gastric ulcer before 1986 had a significantly higher risk of bladder cancer compared with those with no history of gastric ulcer (relative risk = 1.55, 95% confidence interval = 1.03–2.33, controlling for smoking and other potential confounders). No association was observed for duodenal ulcers (multivariate relative risk = 0.97, 95% confidence interval = 0.68–1.38). The ulcers in this study were based solely on self-report and not medical records; consequently, misclassification of ulcers may have occurred. Although intriguing, these findings need to be replicated.

Introduction

Helicobacter pylori infection increases the risk for duodenal and gastric ulcers, but these two types of peptic ulcers have

different pathophysiologies (1). Whereas some hosts will not be affected by *H. pylori* infection, others will develop low acid production, gastritis, and in severe cases, gastric ulcers. Environmental and genetic factors are likely to interact with *H. pylori* to mediate the level of gastric damage to the mucosa. Gastric ulcers are observed in individuals with low acid production and diffuse gastritis (1). In contrast, duodenal ulcers are found in individuals with high acid output and antrum-predominant gastritis (1).

Nitrosamines are known bladder carcinogens in animal models (2) and are likely to be important in the development of human bladder cancer. One well-established cause of bladder cancer, tobacco smoke (3), contains high levels of tobacco-specific nitrosamines (4), some of which may be involved in bladder carcinogenesis (5). Nitrate ingestion contributes to stomach nitrite levels, which can react with amines (nitrosation) to form endogenous nitrosamines (6). In a recent epidemiological study, drinking water nitrate levels were associated with a significant elevation in bladder cancer risk (7).

In the achlorhydric stomach (absent acid secretion), the neutral pH allows for bacterial colonization, and in this environment, bacterial nitrosation becomes an important source of nitrosamines (8). In addition, products of nitric oxide, generated by macrophages during inflammation, can react with water at neutral pH to form nitrite and nitrate and with amines to form nitrosamines (6). High levels of gastric juice nitrites and elevated urine levels of nitrosamines have been reported in patients with chronic atrophic gastritis or high intragastric pH levels (9–12). In one study, patients with endoscopically and histologically confirmed chronic atrophic gastritis had higher than normal mutagenic activity in their urine, even among nonsmokers (11). In another study, urinary nitrosamines were significantly higher ($P = 0.001$) in patients on long-term gastric acid suppression therapy with omeprazole than in healthy subjects (these patients had significantly higher intragastric pH levels; Ref. 12).

Inflammation from chronic gastritis and gastric ulcer healing generate substantial free radicals/oxidative stress in the stomach and may deplete antioxidant levels. In a recent study of nonsmokers, serum and mucosal levels of seven common antioxidants (including vitamins E and C) were markedly decreased in patients with gastric ulcers compared with patients with gastritis or patients with normal mucosa (13). In another study, low serum levels of vitamins C and E were found in patients with chronic atrophic gastritis compared with patients with normal mucosa (10). Low levels of vitamin C can contribute to elevated nitrosamines because vitamin C is a known inhibitor of this reaction (4, 14). In addition, low vitamin E levels may play a role in bladder carcinogenesis through other antioxidant mechanisms. In two recent studies, inverse associations were observed between vitamin E supplement use and the bladder cancer incidence (15) and mortality (16).

The conditions that give rise to gastric ulcers create an

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ideal environment for the generation of nitrosamines and additionally contribute to low serum antioxidant levels. Because nitrosamines generated in the stomach are excreted in the urine, these conditions may be sufficient to affect the risk of bladder cancer. Fig. 1 summarizes the proposed mechanism for the relation between gastric ulcers and bladder cancer risk. We hypothesize that gastric ulcers provide a marker for severe gastritis and inflammation in the stomach. To investigate this possibility, we examined the association between self-reported history of gastric and duodenal ulcers and bladder cancer risk in a prospective cohort of men.

Materials and Methods

Study Population. The Health Professionals Follow-Up Study was initiated in 1986 when 51,529 predominantly white men ages 40–75 years answered a detailed mailed questionnaire on medical history, diet, and other characteristics. Dentists (57.6%), veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%), osteopathic physicians (4.3%), and podiatrists (3.1%) living in 50 United States states completed the questionnaire. Every 2 years, follow-up questionnaires were mailed to surviving cohort members to update data on medical conditions and other time-dependent covariates.

To form the cohort for analysis, we excluded men with cancers diagnosed before 1986 (excluding nonmelanoma skin

cancer; $n = 2076$), with incomplete dietary data ($n = 1596$), with date of death before baseline questionnaire return date ($n = 34$), and with missing age of birth ($n = 49$). The remaining 47,848 men were eligible for follow-up. The National Death Index was used to determine vital status for nonrespondents, and the remaining nonrespondents were assumed to be alive and at risk for bladder cancer incidence.

Assessment of Smoking, Medication Use, Diet, and Other Factors. At baseline, and biennially thereafter, men provided information on their current smoking status, medication use, weight, height, and geographic location. The baseline questionnaire provided detailed information on past smoking habits, time since quitting, average number of cigarettes smoked/day before age 15 and at ages 15–19, 20–29, 30–39, 40–49, 50–59, and 60 and older. To control for smoking, total pack-years of smoking was derived to incorporate all past smoking experience. One cigarette pack-year is equivalent to having smoked one pack or 20 cigarettes/day over an entire year. Questions on current medication use in 1986 included commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) and two H_2 -receptor antagonists (cimetidine and ranitidine; as one question).

A 131-item semiquantitative food frequency questionnaire (17) was completed at baseline. This questionnaire assesses average frequency of dietary intake over the previous year. Total fluid intake was calculated using the 22 beverage items, including water, on the food frequency questionnaire. The information on frequency and serving size was combined to give each member a score in milliliters (ml). Vitamin E intake was calculated from the food frequency questionnaire using both dietary and supplement data. Frequency of cruciferous vegetable intake was summed across its individual constituents (broccoli, cauliflower, cabbage, Brussels sprouts, kale, sauerkraut, and coleslaw).

Identification of Peptic Ulcers. At baseline, participants were asked whether they ever had gastric or duodenal ulcers (assessed separately) and to record the time of occurrence for each type (categories included: before 1955; 1955–64; 1965–74; and 1975–86). In a follow-up questionnaire (1988), participants were asked again for any history of ulcer with an approximate time of occurrence (with a category for diagnoses before 1986). Our analyses are based on self-reported ulcers that were diagnosed before 1986 (using both 1986 and 1988 responses; the 1988 responses provided a secondary source of information for those who may have missed the question on the 1986 questionnaire). We did not have medical records for ulcers before 1986, and consequently, ulcers may have been misclassified in this study. No incident ulcers were included in our analyses.

Bladder Cancer Ascertainment. Every other year, participants provided information on a number of medical conditions, including any new diagnosis of cancer or heart disease. We confirmed the self-reported diagnosis of bladder cancer by review of medical records. When permission to obtain medical records was denied, we attempted to confirm the initial cancer report and date of diagnosis with an additional letter or phone call. If the primary cause of death, reported by the National Death Index, was a previously unreported bladder cancer, we contacted family members to obtain permission to retrieve medical records or, in the least, to confirm the diagnosis of bladder cancer. On the basis of pathology reports, >90% of bladder cancer cases were transitional cell carcinomas. Carcinoma *in situ* tumors were included as these superficial lesions have a high risk of progression (18). Between 1986 and January 31, 2000, 414 incident bladder cancer cases were reported in this cohort.

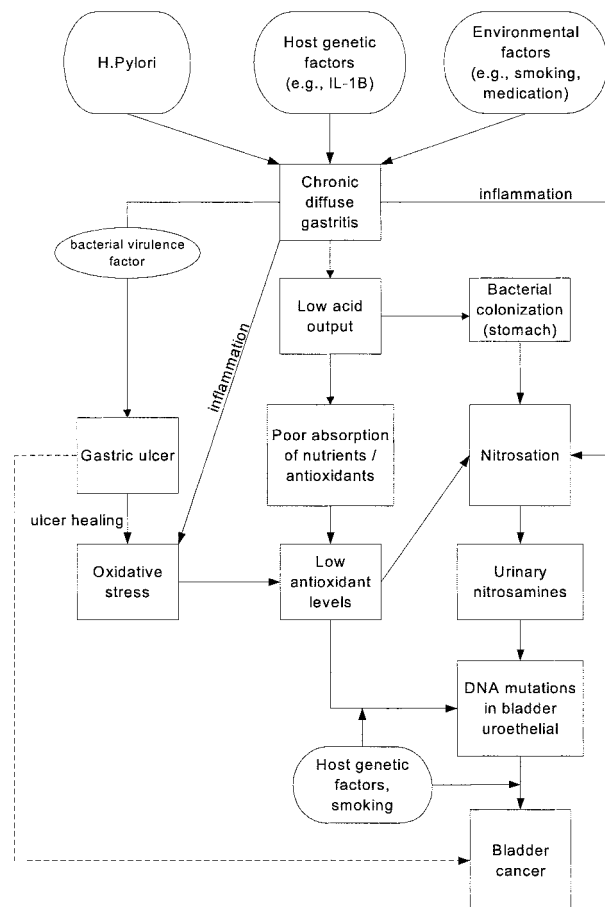


Fig. 1. Proposed mechanism for association between gastric ulcer and bladder cancer.

Statistical Analysis. We computed person-time of follow-up for each participant from the return date of the 1986 questionnaire to the date of bladder cancer diagnosis or death from any cause or January 31, 2000, whichever came first. We categorized participants according to ulcer diagnosis (ever *versus* never and date of diagnosis by decade). We used Cox proportional hazards models to adjust for potential confounding variables, including age (5-year categories), pack-years of smoking, current smoking status, geographic region, and total fluid, cruciferous vegetable, and vitamin E intakes.

Results

At baseline, 5.5% of the men in this cohort reported a duodenal ulcer and 3.0% reported a gastric ulcer before 1986. Men with a history of duodenal or gastric ulcer were slightly older and more likely to be current smokers and NSAID users than men who did not report a history of ulcer (Table 1). Other characteristics, including dietary intakes, did not differ much by history of peptic ulcer.

Men with a reported history of gastric ulcer had a 74% increase in the risk of bladder cancer compared with those with

Table 1 Characteristics of the Health Professionals Follow-up Study members in 1986 by history of gastric and duodenum ulcer, age-standardized to the entire cohort

	Gastric ulcer	Duodenum ulcer	None
Cohort numbers	1,376	2,488	43,984
Age in years (mean)	57.8	57.9	54.2
Race			
Asian American (%)	2	2	2
African American (%)	1	1	1
Scandinavian (%)	10	12	11
South European (%)	22	24	24
Other Caucasian (%)	63	59	61
Other/unknown (%)	3	2	2
Religion ^a			
Catholic (%)	21	21	21
Protestant/other Christian (%)	56	52	53
Ashkenazi Jewish (%)	12	16	16
Other religions (%)	3	4	3
Missing (%)	8	7	7
Region			
West (%)	23	23	21
Midwest (%)	29	26	27
South (%)	32	28	27
Northeast (%)	16	22	23
Smoking history			
Pack-years (mean) ^b	30	29	25
Current smoker (%)	15	14	9
Medical history			
Aspirin use (%)	31	28	30
Nonsteroidal anti-inflammatory drug use (%)	46	39	36
Routine physical (%) ^c	49	52	52
Vasectomy (%)	23	21	21
Diet (intake/day)			
Calories (kcal)	2,070	2,000	1,982
Total fat (%)	33.0	32.2	31.9
Vitamin E (mg)	98.0	94.4	97.0
Total fluid (ml)	2019	1997	1936

^a Religion was asked on the 1998 questionnaire; 27% of cohort did not respond to this question (missed question or questionnaire).

^b Among ever-smokers only.

^c Question asked in 1988, refers to previous 2-year period (*i.e.*, between 1986 and 1988).

no history of gastric ulcer (Table 2). In contrast, men with a reported history of duodenal ulcer did not have an elevated risk of bladder cancer (Table 2). Controlling for potential confounding variables, including smoking, slightly attenuated the association [multivariate relative risk MV RR = 1.55, 95% confidence interval (CI) = 1.03–2.33]. When examining time since occurrence of the reported gastric ulcer, we observed a 2-fold elevation in bladder cancer risk among those men who reported ulcer occurrence between 1965 and 1974; more recent occurrence of gastric ulcer was not associated with an elevation in risk, but the CI was wide (Table 2). Removing from the analysis men who reported a recent ulcer (between 75 and 86) resulted in a stronger association between gastric ulcer and bladder cancer (MV RR = 1.76, 95% CI = 1.11–2.80).

Although we did not know which gastric ulcers were NSAID induced, we were able to stratify our data by NSAID use in 1986. In the subanalysis, the association between gastric ulcer and bladder cancer risk was similar in both strata (MV RR = 1.81, 95% CI = 1.04–3.14, for no use of NSAID in 1986, and MV RR = 1.56, 95% CI = 0.82–2.93, for NSAID use). Additional adjustment for NSAIDs did not alter the association between gastric ulcer and bladder cancer risk (data not shown).

The association between gastric ulcers and bladder cancer risk was more pronounced among younger men (MV RR = 2.13, 95% CI = 1.16–3.90; age < 62 years) than among older men (MV RR = 1.25, 95% CI = 0.72–2.17; age ≥ 62 years). The association was weaker among never smokers (MV RR = 1.26, 95% CI = 0.39–4.08).

Tagamet (cimetidine) and Zantac (ranitidine) have been commonly used for the treatment of peptic ulcers, as well as for other gastric conditions, since their introduction on the market in the late 1970s. We observed an increase in bladder cancer risk among men who reported taking either of these medications in 1986 (MV RR = 1.58; 95% CI = 0.93–2.69). Only 20% of men with a history of gastric or duodenal ulcer reported currently taking these medications in 1986. In a combined MV analysis, the RRs of bladder cancer remained elevated for both Tagamet/Zantac use and history of gastric ulcer [MV RR = 1.46, 95% CI = 0.85–2.50 for Tagamet/Zantac; MV RR = 1.48 (0.98–2.24 for gastric ulcer)].

Discussion

In this prospective study of health professionals, a reported history of gastric ulcer was associated with a significantly greater risk of bladder cancer. In contrast, no risk increase was observed in relation to a history of duodenal ulcer. Potential risk factors of bladder cancer could not explain these findings. Recent use of ulcer treatment medication (Tagamet and Zantac) was also related to the risk of bladder cancer, and this association was independent of the elevated risk observed with gastric ulcers.

Bladder carcinogens, which were first detected as a result of occupational exposures (*e.g.*, benzidine and 2-naphthalamine), have been associated with latency periods of 10–30 years (19). The effects of tobacco smoking on bladder cancer are also greatest after a latency of ≥30 years (20). With gastric ulcers, the association was strongest for ulcers that occurred 12–45 years before bladder cancer diagnosis, which is consistent with a long latency period between initiation and diagnosis for other known bladder carcinogens.

We considered an alternative mechanism to explain our findings. Chronic NSAID use could explain our findings because chronic NSAID use is a cause of ulcer (21) and may also

Table 2 Relation between gastric and duodenum ulcers and bladder cancer incidence in the Health Professionals Follow-up Study, 1986–2000

	Gastric ulcer			Duodenum ulcer		
	Case no.	Relative risk ^a (95% confidence interval)	Multivariate relative risk ^b (95% confidence interval)	Case no.	Relative risk ^a (95% confidence interval)	Multivariate relative risk ^b (95% confidence interval)
None	388	1.0	1.0	378	1.0	1.0
Ever	26	1.74 (1.16–2.62)	1.55 (1.03–2.33)	36	1.09 (0.77–1.55)	0.97 (0.68–1.38)
Before 1955	3	1.38 (0.44–4.34)	1.19 (0.38–3.77)	9	0.90 (0.46–1.76)	0.79 (0.40–1.55)
1955–64	6	1.90 (0.82–4.39)	1.58 (0.68–3.66)	10	1.20 (0.64–2.26)	1.11 (0.59–2.10)
1965–74	7	2.55 (1.19–5.50)	2.31 (1.06–4.99)	8	1.58 (0.78–3.21)	1.43 (0.70–2.92)
1975–86	5	1.13 (0.46–2.75)	1.07 (0.44–2.61)	8	1.25 (0.59–2.66)	1.08 (0.51–2.31)
Unknown date	5	2.10 (0.85–5.18)	1.84 (0.74–4.58)	1	0.32 (0.04–2.26)	0.27 (0.04–1.92)

^a Age-adjusted relative risks.

^b Multivariate relative risks from proportional hazard models adjusting for age, pack-years of smoking, current smoking status, region, and total fluid intake.

be a cause of bladder cancer. Three case-control studies have observed elevated incidences of bladder cancer with heavy acetaminophen use (22–24), although two were not statistically significant (23, 24). Another two studies did not report any associations with acetaminophen use (25, 26). In contrast, aspirin use has been inversely related to bladder cancer risk (22, 26). NSAID use may also be a marker of previous phenacetin use. Phenacetin-based analgesics have been related to the risk of bladder cancer in epidemiological studies (23, 27–32). Because phenacetin is no longer available in most markets, acetaminophen has been substituted for phenacetin. To rule out the possibility that NSAID use explained our findings, we controlled and stratified by NSAID use in 1986; similar findings were observed in the two strata and adjusting for NSAID did not alter the association between gastric ulcers and bladder cancer risk. In addition, because NSAID at the time of ulcer diagnosis may have been different then in 1986, we examined the association between a group of individuals who are known chronic NSAID users (because of arthritis) and bladder cancer risk; we did not observe any elevated risk in this group (data not shown). These subanalyses suggest that NSAID use is unlikely to explain our findings.

Antacids were the major treatment for ulcers before the late 1970s when the H₂ receptor antagonists became available. More than 75% of the ulcers reported in this study were diagnosed before 1975. Because antacids are used indiscriminately for gastric and duodenal ulcers, they are unlikely to be responsible for the elevated risk observed exclusively with gastric ulcers.

One of the major limitations of this study is that it was based on self-reported ulcer diagnoses. In some cases, the location of the peptic ulcer may have been misclassified (gastric versus duodenal), although men in this cohort, being health professionals, are well informed and less likely to misreport health conditions. Although there may be some misclassification, the proportion of duodenal to gastric ulcers is as expected (33). Alternatively, some reported gastric ulcers could have been confused with other gastric conditions, including gastritis, duodenitis, duodenal erosions, or dyspepsia. However, given that our proposed mechanism for the association between gastric ulcer and bladder cancer includes gastritis as a major component, the actual diagnosis of an ulcer is less important than the presence of gastritis. It is less likely that an ulcer was reported when there was absolutely no gastric condition present, given that reporting was reasonably accurate among men who reported ulcers in follow-up questionnaires (26% of the self-reported ulcers were rejected because the hospital records did not confirm self-reporting). Furthermore, ulcer misclassifi-

cation would have led to the attenuation of the RRs and, therefore, cannot explain our positive finding with gastric ulcer.

Other explanations for our findings were considered. Of these, detection bias, which would result if ulcer patients received more medical attention, is unlikely to have occurred because the risk of bladder cancer was not elevated among those with duodenal cancer or recent ulcer diagnosis. In addition, percentage of men reporting a recent routine physical exam was not higher among men with gastric ulcers (Table 1). Although we tightly controlled for smoking history, current smoking status, and for potential risk factors of bladder cancer, we cannot completely rule out the possibility that the association observed was a result of shared risk factors or host susceptibility. Finally, although the association observed was statistically significant, we cannot exclude the possibility that this is a chance finding. Given that no study has previously reported this type of association, these findings should be interpreted with caution.

In this study, we observed an elevated risk of bladder cancer among men with a history of gastric ulcer but not for duodenal ulcers. The association was strongest among those who reported a gastric ulcer 14–35 years before the cancer diagnosis, which is consistent with a long latency period often seen with bladder carcinogens. Our finding needs to be replicated in other populations to confirm that it was not due to chance.

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