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DIVERGING TRENDS IN THE INCIDENCE OF REFLUX-RELATED AND *HELICOBACTER PYLORI*-RELATED GASTRIC CARDIA CANCER

Julian A. Abrams, MD, MS^{1,2}, Lou Gonsalves, PhD³, and Alfred I. Neugut, MD, PhD^{1,2,4}

¹Department of Medicine, Columbia University Medical Center, New York, NY, USA

²Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA

³Connecticut Tumor Registry, Connecticut Department of Public Health, Hartford, CT, USA

⁴Department of Epidemiology, Mailman School of Public Health, New York, NY, USA

Abstract

Goals—To describe historical incidence trends of two subtypes of gastric cardia cancer.

Background—The incidence of gastric cardia cancer has increased in western countries. Prior studies have treated cardia cancer as a single entity, but recent data suggest that there are two distinct subtypes: reflux-related and *Helicobacter pylori*-related.

Study—We conducted a population-based study using Connecticut Tumor Registry data from 1955–2007. Age-adjusted incidence rates (per 100,000 person-years) were calculated for gastric cancer, as a whole and by anatomic subsite, and for esophageal adenocarcinoma. Cardia and non-cardia cancer incidence rates were further adjusted to account for cases with unspecified subsite. Mathematical formulas were derived to calculate incidence rates for reflux-related and *H. pylori*-related cardia cancer.

Results—The adjusted incidence of cardia cancer was 4.0 per 100,000 in 1955–59, decreased to 2.4 per 100,000 in 1965–69 before increasing to 3.4 per 100,000 by 2003–07. The incidence of *H. pylori*-related cardia cancer decreased from 3.7 to 1.0 per 100,000 over the study period, whereas reflux-related cardia cancer increased progressively from 0.3 to 2.4 per 100,000. The curves for reflux-related cardia cancer and esophageal adenocarcinoma closely mirrored each other, and their combined incidence rose from 0.5 per 100,000 in 1955–59 to 5.6 per 100,000 in 2003–07.

Conclusions—The incidence of reflux-related cardia cancer has steadily increased, while *H. pylori*-related cardia cancer has declined progressively since the mid-20th century. Trends in reflux-related cardia cancer and esophageal adenocarcinoma incidence are very similar, suggesting that these two cancers share a similar etiology and pathophysiologic process.

Keywords

stomach neoplasms; epidemiology; *Helicobacter pylori*; gastro-esophageal reflux

Corresponding Author: Julian A. Abrams, MD, MS, Division of Digestive & Liver Diseases, 622 W 168th Street, PH 20-303, New York, NY 10032, United States, (212) 342-0476, Fax: (212) 342-5759, ja660@columbia.edu.

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INTRODUCTION

The age-adjusted incidence of gastric cardia cancer in the United States has risen substantially over the past several decades.¹ Additionally, cardia cancer now represents 27% of gastric tumors, up from 10% in 1975.² The reasons underlying this major shift are unclear. Anatomically, the cardia effectively represents the border region between the esophagus and the remainder of the stomach, and is uniquely exposed both to *Helicobacter pylori* and to gastro-esophageal reflux.

Epidemiologic studies have traditionally treated cardia cancer as a single entity. Studies of gastro-esophageal reflux, *H. pylori*, and their associations with cardia cancer have had mixed findings, with both increased and decreased risks associated with each of these exposures.^{3–11} Interestingly, a recent meta-analysis found that, in studies from countries at “high risk” for gastric cancer, *H. pylori* was associated with an increased risk of cardia cancer, but an inverse association existed in countries at “low risk” for gastric cancer (i.e., Western countries).¹²

Recently, Derakhshan et al. performed a case-control study of cardia cancer, with stratified analyses by the presence of atrophic gastritis, a morphologic change induced by *H. pylori*.¹³ Reflux was associated with a significantly increased risk of cardia cancer but only in patients without atrophic gastritis, raising the possibility that *H. pylori* may mediate or even inhibit the effects of reflux in the cardia. The implication of this and other recent data is that there are actually two distinct subtypes of cardia cancer: reflux-related and *H. pylori*-related.^{13, 14}

H. pylori, a well-established risk factor for non-cardia gastric cancer, is traditionally viewed as an infection of the gastric antrum; however, the cardia is also infected in >90% of cases and with similar degrees of inflammation.^{15, 16} *H. pylori* is inversely associated with esophageal adenocarcinoma (EAC)¹⁷ and presumably has a similar association with reflux-related cardia cancer. As such, any estimates of *H. pylori*, reflux, and cardia cancer risk will be strongly influenced by the relative proportions of reflux-related and *H. pylori*-related cardia cancer in the study population.

Interpretation of trends in the incidence of gastric cardia cancer is further complicated by the fact that the prevalence of gastro-esophageal reflux disease has increased significantly over the past several decades,¹⁸ while the prevalence of *H. pylori* has declined in the U.S. since the mid-20th century.^{19, 20} In order to understand better the epidemiology of gastric cardia cancer, we used data from the Connecticut Tumor Registry to construct estimated curves for the incidence of both *H. pylori*-related and reflux-related gastric cardia cancer.

MATERIALS AND METHODS

The Connecticut Tumor Registry is the oldest population-based tumor registry in the United States, with data collection dating back to 1935. Description of the Tumor Registry data has been published previously.²¹ The case registry was >75% complete in 1940–44 and considered nearly complete (>97%) by 1968–72.²² Starting in 1973, the Connecticut Tumor Registry also submitted case data to the Surveillance, Epidemiology, and End Results (SEER) program. Prior work has demonstrated that the Connecticut data closely resembles that seen on a national level with SEER data.¹ Five-year summary data were available from 1935–39 through 1975–79 and from 1973–77 through 2003–07. In order to minimize overlap, we excluded the 1975–79 data from analyses.

Data were obtained with regard to the number of cases of gastric cancer and esophageal cancer. Gastric cancer cases were further classified as cardia, non-cardia, or subsite not

specified. Age-adjusted incidence rates were calculated based on the 2000 U.S. standard population. Population data were provided by the Connecticut Tumor Registry and downloaded from the SEER website.²³

This study was approved by the Columbia University Institutional Review Board.

Cardia cancer incidence

Subsite was not recorded for a significant proportion of gastric cancer cases, particularly in the earlier years of the analyses (1950s – 1970s) (Table 1). We used a formula previously derived by Corley et al.²⁴ to calculate adjusted incidence for both cardia and non-cardia gastric cancer. In brief, this formula assumes that the proportions of cases with subsite not specified will be distributed in the same proportions between cardia and non-cardia as those cases that do have subsite labeled. Therefore, we calculated adjusted incidence of gastric cardia cancer as follows:

$$\text{Adjusted cardia incidence} = \text{cardia incidence} + [(\text{unspec. subsite incidence}) \times (\text{cardia incidence}) / (\text{cardia incidence} + \text{non-cardia incidence})]$$

We calculated adjusted cardia incidence for each 5-year time period using corresponding unadjusted incidence data for each time period. We chose 1955–59 as the first period to analyze. Prior to this point, <5% of the cases had subsite specified, and we felt that there existed too much uncertainty with any estimates using data from these time periods. In 1955–59, the figure rose to 20.3% (Table 1). In the study by Corley et al.,²⁴ a single time period (1986–88) was used as the reference to “correct” for all of the time periods studied. This is reasonable so long as the cardia:non-cardia ratio remains relatively constant over time. However, we hypothesize that there are two sub-types of cardia cancer: *H. pylori*-related and reflux-related. Due to the changing epidemiology of these two exposures, we expected that the trends in incidence of these two sub-types would be very different, and therefore the cardia:non-cardia ratio would not be constant. As such, we chose to use the relative proportions of cardia and non-cardia cancers from *each* time period to calculate adjusted incidence of gastric cardia cancer. The adjusted incidence of non-cardia gastric cancer was calculated in the same manner as for cardia cancer, except substituting non-cardia incidence for cardia incidence in the above formula.

Estimation of *H. pylori*-related and reflux-related incidence

Historical population-based data do not allow for direct assessment of whether specific gastric cardia cancer cases were *H. pylori*-related or reflux-related. We therefore first derived an estimate of the proportions of each of the two subtypes from the earliest time period. In light of the comparable incidence of esophageal adenocarcinoma (the prototypical “reflux-related” cancer) and cardia cancer today, we made the assumption that the incidence of reflux-related cardia cancer was the same as for EAC (0.27 per 100,000) during the period 1955–59. Using the adjusted total cardia cancer incidence from the same time period as the denominator, we were able to calculate the proportion of cardia cancers that were reflux-related (6.9%) and *H. pylori*-related (93.1%) from 1955–59. As this figure is based on hypothetical speculation, we performed a broad sensitivity analyses by multiplying and dividing by a factor of 3 the proportion of cardia cancers that were reflux-related (2.3–20.7%) for the period 1955–59.

We subsequently made the assumption that the decrease in non-cardia gastric cancer incidence over time reflected a decrease in *H. pylori*-related gastric cancer as a whole. For each time period subsequent to 1955–59, we calculated the proportional decrease in non-cardia gastric cancer compared to the incidence from 1955–59 (Table 2). We assumed that

the incidence of *H. pylori*-related cardia cancer decreased by the same proportion for each respective time period as did non-cardia gastric cancer. We therefore used the following formula to calculate the incidence of *H. pylori*-related cardia cancer for a particular time period (“period-x”):

$$\text{Incidence of Hp-CC}_{\text{period-x}} = (\text{Incidence of cardia cancer}_{\text{period-x}}) \times (\text{Proportion of cardia cancer}_{1955-59} \text{ that was Hp-CC}) \times [(\text{Incidence of non-cardia cancer}_{\text{period-x}}) / (\text{Incidence of non-cardia cancer}_{1955-59})]$$

The incidence of reflux-related cardia cancer was then calculated as follows:

$$\text{Incidence of Reflux-CC}_{\text{period-x}} = (\text{Incidence of cardia cancer}_{\text{period-x}}) - (\text{Incidence of Hp-CC}_{\text{period-x}})$$

Esophageal adenocarcinoma incidence

The proportion of esophageal cancer cases with histologic confirmation was available for every year of the study period, and ranged from 45% (1940–44) to 97% (2003–07). In order to account for variable rates of histologic confirmation, we calculated corrected age-adjusted incidence rates for EAC. We obtained the corrected rate by dividing the calculated age-adjusted incidence by the proportion of cases with histologic confirmation for the associated five-year time period. We employed this method previously in a study of historical trends of EAC incidence using the Connecticut Tumor Registry data.¹

Reflux-related upper gastrointestinal cancer

We defined the term “reflux-related upper GI cancer” to consist of esophageal adenocarcinoma and reflux-related cardia cancers. We calculated the incidence of reflux-related upper gastrointestinal cancers for each time period by adding the corrected EAC incidence to the estimated incidence of reflux-related gastric cardia cancer.

RESULTS

The age-adjusted incidence rates of gastric cancer, cardia cancer, non-cardia cancer, and gastric cancer without specified subsite are shown in Table 1. From the period 1955–59 to 2003–07, there was a progressive decline in the overall incidence of gastric cancer from 23.5 to 9.4 per 100,000 person-years. The proportion of cases without specified subsite also decreased substantially from 80% to 21%. The incidence of cardia cancer appeared to increase steadily over the examined time period. However, after adjustment for unspecified subsite cancers, our calculations suggested that the incidence of cardia cancer over time actually resembled a U-shaped curve (Figure 1). Based on our estimates, there was a decrease until the late 1960s, followed by a plateau and then a steady increase since the 1970s.

H. pylori-related vs. reflux-related cardia cancer

As shown in Table 2, the adjusted incidence of non-cardia gastric cancer steadily decreased from the late 1950s onward. We made the assumption that non-cardia cancer and *H. pylori*-related cardia cancer decreased at the same proportional rates over the study period. We calculated the incidence of *H. pylori*-related cardia cancer, which decreased from 3.7 per 100,000 in 1955–59 to 1.0 per 100,000 in 2003–07 (Table 2). Conversely, we estimated that the incidence of reflux-related cardia cancer rose steadily starting in the 1960s (Figure 2). The incidence of reflux-related cardia cancer surpassed that of *H. pylori*-related cardia cancer by the 1978–82 period. In the most recent 5-year period (2003–07), we calculated that 71.5% of cardia cancers were reflux-related.

Reflux-related upper GI cancers

We plotted the incidence of EAC over the same time period, and found that the EAC and reflux-related cardia cancer curves were very similar (Figure 3). The incidence of reflux-related upper GI cancers, calculated as the sum of EAC and reflux-related cardia cancer, rose roughly 10-fold from 0.5 per 100,000 in 1955–59 to 5.6 per 100,000 in 2003–07.

Sensitivity Analyses

We made a baseline assumption that 6.9% of cardia cancers were reflux-related in the period 1955–59. We performed sensitivity analyses by halving and doubling the proportion of reflux-related cardia cancers (3.5–13.8%) for this period, and then re-calculated the incidence of reflux- and *H. pylori*-related cardia cancer for the subsequent time periods. As shown in Figure 2, there was little qualitative change in the trends over time.

DISCUSSION

Our analyses of data from the Connecticut Tumor Registry demonstrate that, since the late 1950s, there has been a persistent decline in the incidence of *H. pylori*-related cardia cancer, accompanied by a steady rise in the incidence of reflux-related cardia cancer. Furthermore, the trend in incidence of reflux-related cardia cancer very closely mirrors that observed for esophageal adenocarcinoma, with a resulting 10-fold increase in the incidence of reflux-related upper GI cancers in the past five decades.

Prior studies of cardia cancer incidence in western countries have suggested a rise over time with a possible recent plateau.^{1, 25, 26} These studies, however, did not account for the significant proportions of gastric cancer cases without an assigned subsite. Corley et al. first addressed this problem and devised a formula to calculate the incidence of gastric cardia cancer, adjusted for cases not assigned a subsite.²⁴ We made minor modifications to this formula and plotted the incidence of cardia cancer dating back to the 1950s. Interestingly, we found that cardia cancer incidence has a U-shaped curve over time, a trend only observable with the use of pre-SEER data. This phenomenon can be accounted for by the changes in incidence of reflux-related and *H. pylori*-related cardia cancer, which parallel the epidemiology of their respective associated major risk factors. Gastro-esophageal reflux has steadily increased in prevalence over the past several decades,¹⁸ while the prevalence of *H. pylori* infection has decreased substantially in the United States and other western countries.^{19, 20, 27}

It is important not to interpret the terms “reflux-related” and “*H. pylori*-related” to denote that gastro-esophageal reflux and *H. pylori* are the only two associated exposures. There are several other risk factors for cardia cancer, including smoking and obesity.^{7, 28} Rather, the terms serve to divide cardia cancer into phenotypes that more closely represent either esophageal adenocarcinoma (“reflux-related”) or non-cardia gastric cancer (“*H. pylori*-related”). For unclear reasons, *H. pylori* in particular seems to exert opposite effects on these two cancer types. The infection can cause non-cardia gastric cancer, yet is associated with a decreased risk of esophageal adenocarcinoma.^{17, 29}

H. pylori is traditionally viewed as an infection of the gastric antrum, and leads to atrophic gastritis and cancer.²⁹ Interestingly, in the setting of *H. pylori* infection of the antrum, the cardia is also infected in >90% of cases and with similar degrees of inflammation.^{15, 16} In a nested case control study from Norway, *H. pylori* seropositivity was inversely associated with cardia cancer (OR 0.27).¹⁴ However, *H. pylori* positive cardia cancer cases were associated with atrophic gastritis as measured by a decreased serum pepsinogen I:II ratio, and histologically more closely resembled non-cardia cancer cases. Derakhshan et al. performed a case-control and found that both atrophic gastritis and gastro-esophageal reflux

were significantly associated with cardia cancer.¹³ In stratified analyses the positive association with reflux was only observed in patients without atrophic gastritis, which suggests that *H. pylori* may mediate or even inhibit the effects of reflux in the cardia. In a recent meta-analysis, *H. pylori* was associated with an increased risk of cardia cancer in studies from countries at “high risk” for gastric cancer, but an inverse association existed in countries at “low risk” for gastric cancer (i.e., Western countries).¹² Two conclusions can thus potentially be drawn: 1) there are two distinct subtypes of cardia cancer (reflux-related and *H. pylori*-related); and 2) estimates of reflux or *H. pylori* and cardia cancer risk will be strongly influenced by the relative proportions of the two cardia cancer subtypes in the study population.

We made several assumptions in the construction of these historical incidence curves. Firstly, we calculated cardia cancer incidence adjusted for gastric cancer cases not assigned a specific subsite. A major proportion of cases are not assigned a subsite, and this proportion has changed over time. We made the assumption that unspecified subsite gastric cancers would be distributed between cardia and non-cardia in the same proportion as tumors with an assigned subsite, as was done previously in the study by Corley et al.²⁴ We then derived estimates of the proportion of cases from the earliest time period that were either reflux- or *H. pylori*-related. There is obviously little historical data on which to base these figures. As reflux-related cardia cancer and EAC presumably share very similar risk factors and epidemiology, we assumed that the incidence of reflux-related cardia cancer in 1955–59 would be similar to that of EAC. We then performed sensitivity analyses by halving and doubling this figure and found little qualitative difference in the overall results. Interestingly, over time the curve for reflux-related cardia cancer very closely mirrored that of EAC, suggestive that these two may represent a spectrum of the same disease.

Our study has several particular strengths. The Connecticut Tumor Registry is the oldest tumor registry in the United States and represents a unique resource to study historical patterns in cancer incidence. Only with the use of pre-SEER data did we observe the original decline in cardia cancer until the 1960s, followed by a plateau and a subsequent increase. Further estimations of the incidence of reflux- and *H. pylori*-related cardia cancer allowed us to make sense of this interesting pattern. Our findings are likely applicable to the United States as a whole. Connecticut is one of the regions that contributes data to Surveillance, Epidemiology, and End Results; our previous analyses of esophageal adenocarcinoma showed that incidence data from Connecticut closely resemble that observed on a national level with SEER.¹

There are certain limitations to our analyses. By necessity, the calculations are based on several assumptions regarding gastric cancer cases with unspecified subsite, distribution of cardia cancer cases that are reflux- or *H. pylori*-related, and correlation between decrease in the incidence of non-cardia gastric cancer and *H. pylori*-related cardia cancer. However, we made use of statistical methods that have been published previously,^{1, 24} and we performed sensitivity analyses to assess the effects of variation in some of our assumptions. We recognize that there are other risk factors for cardia cancer, and that these risk factors may vary among subtypes as well. The terms “reflux-related” and “*H. pylori*-related” are overly simplistic and merely serve to distinguish between the two subtypes. We did not account for familial gastric cancers that occur in the cardia; however, we believe that these would not have had a major impact on our analyses, as it is estimated that only 1–3% of all gastric cancers are familial.³⁰

In conclusion, the results of our analyses using the Connecticut Tumor Registry data demonstrate that the incidence of gastric cardia cancer since the 1950s has a U-shaped curve, and that this phenomenon can be explained by the diverging trends of the two

subtypes of cardia cancer: reflux-related and *H. pylori*-related. The incidence of *H. pylori*-related cardia cancer has declined progressively since the mid-20th century, in line with the patterns of non-cardia cancer and *H. pylori* infection. Reflux-related cardia cancer has steadily increased in incidence over the past several decades, and surpassed *H. pylori*-related cardia cancer by the late 1970s. Furthermore, the curves for reflux-related cardia cancer and esophageal adenocarcinoma closely mirror each other, supporting the notion that these two cancers may actually represent a spectrum of the same disease. Further research in cardia cancer should focus on the identification of distinct risk factors and biology of these two subtypes of gastric cardia cancer.

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Figure 1. Age-adjusted incidence of cardia cancer, both without (“crude”) and with adjustment for gastric cancer cases with unspecified subsite, Connecticut, 1955–2007.

Figure 2.

Incidence of *H. pylori*-related and reflux-related cardia cancer over time. Also shown as dotted lines are the incidence curves for each subtype, varying the baseline proportion of gastric cardia cancers that were *H. pylori*- or reflux-related.

Figure 3.
The incidence of reflux-related cardia cancer, esophageal adenocarcinoma, and reflux-related upper gastrointestinal cancers, Connecticut, 1955–2007.

Age-adjusted incidence (per 100,000 person-years) of gastric cancer, overall and by subsite, in Connecticut from 1955–2007.

Table 1

	Gastric cancer	Cardia	Non-cardia	Cardia: Non-cardia	Subsite NOS	% NOS
1955–1959	23.5	0.8	4.0	0.2	18.8	80%
1960–1964	21.2	1.0	5.5	0.2	14.7	70%
1965–1969	16.6	0.9	5.1	0.2	10.6	64%
1970–1974	14.8	1.4	7.4	0.2	5.9	40%
1973–1977	13.3	1.6	7.5	0.2	4.2	32%
1978–1982	12.7	1.9	6.8	0.3	3.9	31%
1983–1987	11.6	2.0	5.7	0.4	4.0	34%
1988–1992	11.5	2.7	5.7	0.5	3.1	27%
1993–1997	10.3	2.5	5.6	0.4	2.3	22%
1998–2002	9.9	2.6	5.0	0.5	2.3	23%
2003–2007	9.4	2.7	4.7	0.6	2.0	21%

NOS, subsite not specified

Table 2

Adjusted incidence (per 100,000 person-years) of non-cardia gastric cancer, cardia cancer, *H. pylori*-related cardia cancer, and reflux-related cardia cancer, Connecticut, 1955–2007.

	Adjusted non-cardia cancer incidence	Proportional decline	Adjusted cardia cancer incidence	<i>H. pylori</i> -related cardia cancer incidence	Reflux-related cardia cancer incidence
1955–1959	19.6	-	4.0	3.7	0.3
1960–1964	17.9	0.91	3.3	2.8	0.5
1965–1969	14.1	0.72	2.4	1.6	0.8
1970–1974	12.4	0.63	2.4	1.4	1.0
1973–1977	10.9	0.56	2.4	1.2	1.1
1978–1982	9.9	0.50	2.8	1.3	1.5
1983–1987	8.7	0.44	3.0	1.2	1.8
1988–1992	7.8	0.40	3.7	1.4	2.3
1993–1997	7.2	0.37	3.2	1.1	2.1
1998–2002	6.6	0.33	3.3	1.0	2.3
2003–2007	6.0	0.31	3.4	1.0	2.4