

Dating the Rise of Esophageal Adenocarcinoma: Analysis of Connecticut Tumor Registry Data, 1940–2007

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Abstract

Background: The timing of onset of the rise in incidence of esophageal adenocarcinoma (EAC) has not been clearly defined, and doing so may provide clues with regard to exposures associated with the changed epidemiology of this malignancy. We therefore aimed to investigate historical trends in the incidence of EAC and other upper gastrointestinal malignancies.

Methods: We did a population-based study using Connecticut Tumor Registry (1940–2007) and Surveillance, Epidemiology, and End Results (SEER; 1973–2007) data. Age-adjusted incidence rates (per 100,000 person-years) were calculated for EAC and other upper gastrointestinal malignancies.

Results: The incidence of EAC remained relatively constant until 1965–69, and then rose from 0.41 (95%CI, 0.26–0.56) to 1.31 (95%CI 1.07–1.54) in 1978–82 and 5.31 (95%CI 4.89–5.73) in 2003–07. The incidence of gastric cardia cancer began to rise in the 1950s and plateaued in the 1990s. The incidence of esophageal squamous cell carcinoma began to decrease around 1980. The trends from Connecticut Tumor Registry data closely mirrored those from SEER data.

Conclusions: The incidence of EAC began to rise in the late 1960s, predating the rise in obesity by a decade. Reduced infection rates of *Helicobacter pylori*, changes in microbiome, or other exposures may have contributed to the changed epidemiology of this malignancy.

Impact: Analysis of historical data of trends in EAC incidence implicate a change in environmental factors from the mid-20th century as primarily responsible for the initial rise in EAC incidence, predating the rise in obesity prevalence in the United States by over a decade. *Cancer Epidemiol Biomarkers Prev*; 20(1); 183–6. ©2011 AACR.

Introduction

There has been a widely recognized dramatic rise in the incidence of esophageal adenocarcinoma (EAC) over the past 3 decades. In particular, this increase has been shown using data from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, which found a roughly 5-fold increase in incidence of EAC in the United States from 1975 to 2005 (1). This increase was paralleled by a similar rise in the incidence of gastric cardia adenocarcinoma, but the rise in gastric cardia cancer plateaued around 1990 (2). How-

ever, there is scant published data on EAC incidence in the United States from the pre-SEER era (3).

Factors precipitating this dramatic rise are incompletely understood; although, a corresponding rise in the prevalence of obesity is frequently cited. Obesity increases the risk of EAC via increased gastroesophageal reflux disease (GERD) and potentially through other mechanisms as well (4). Other risk factors for EAC have been identified, including a protective effect of *Helicobacter pylori* (5, 6). The prevalence of *H. pylori* infection in the United States has decreased substantially over the past several decades and is presumably responsible in part for the marked decline in the incidence of noncardia gastric cancer. It is unknown whether other historical exposures have played a role in the changed epidemiology of EAC. We therefore decided to investigate trends in the incidence of EAC before and after SEER reporting began to determine the timing of the initial rise in incidence of EAC.

Methods

The Connecticut Tumor Registry is the oldest population-based tumor registry in the United States, with data

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collection dating back to 1935. Description of the Tumor Registry data have been published previously (7). The case registry was more than 75% complete in 1940–44 and considered nearly complete (>97%) by 1968–72 (8). Data were obtained with regard to number of cases of EAC, esophageal squamous cell cancer (ESCC), gastric cardia, and gastric noncardia cancers. Starting in the 1970s, the Connecticut Tumor Registry submitted case data to SEER. Five-year summary data were available from 1935–39 through 1975–79 and from 1973–77 through 2003–07. To minimize overlap, we excluded the 1975–79 data from analyses. Presumably, the first 5 years of the registry (1935–39) had the least complete reporting, and this period was also excluded from analyses.

Age-adjusted incidence rates were calculated using corresponding 5-year summary statistics for the population ages 25 years and more, broken down by sex and age group. Population data were provided by the Connecticut Tumor Registry and downloaded from the SEER website (9). 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). To account for variable rates of histologic confirmation, "corrected" age-adjusted incidence rates for EAC and ESCC were calculated. The "corrected" rate was obtained by dividing the calculated age-adjusted incidence by the proportion of cases with histologic confirmation for the associated 5-year time period.

Age-adjusted incidence rates for EAC for the population ages 25 years and more were also calculated using SEER data from 1973 to 2007 (10). These data encompassed 9 state and regional registries, representing approximately 10% of the U.S. population. EAC cases were identified using International Classification of Diseases for Oncology (ICD-O-3) topography codes C15.0–C15.9 for esophageal cancer, and histology codes 8140–8573 for adenocarcinoma. Age-adjusted rates were calculated on the basis of the 2000 U.S. standard. Analyses were done using SEER*Stat 6.6.2.

Results

The incidence of EAC remained relatively constant from 1940–44 through 1965–69 (Fig. 1). The corrected age-adjusted incidence then steadily increased from 0.41 cases per 100,000 person-years (95%CI, 0.26–0.56) in 1965–69 to 1.31 per 100,000 person-years (95%CI 1.07–1.54) in 1978–82. The incidence continued to rise, with 5.31 cases per 100,000 person-years (95%CI 4.89–5.73) in 2003–07. The patterns of incidence for men and women were similar, with both rates beginning to rise in the late 1960s. The male/female ratio for age-adjusted incidence ranged from 3:1 to 5:1, and did not change appreciably over time. The uncorrected incidence rates for EAC, ESCC, and esophageal cancer without histologic confirmation are shown in Table 1.

The pattern of incidence of EAC based on SEER data closely mirrored the results from the Connecticut Tumor

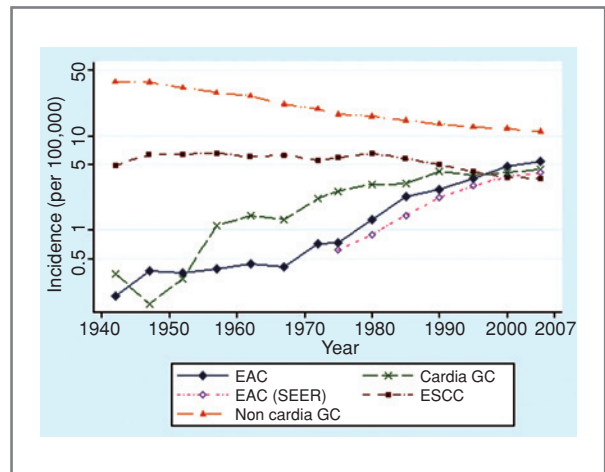


Figure 1. Age-adjusted incidence of esophageal adenocarcinoma (EAC), esophageal squamous cell cancer (ESCC), gastric cardia cancer (Cardia GC), and gastric noncardia cancer (Noncardia GC), Connecticut 1940–2007. Age-adjusted incidence of EAC from SEER data also shown [EAC (SEER)]. Note: y-axis scale is logarithmic.

Registry (Fig. 1). The incidence of gastric cardia cancer began to rise approximately a decade earlier than EAC, and has plateaued since the mid-1990s. The incidence of ESCC was relatively constant until the mid-1980s, and has been declining since this time. As expected, the incidence of noncardia gastric cancer has steadily decreased since the early 1950s. The age-adjusted incidence curves using SEER data from 1973 to 2007 for ESCC, cardia cancer, and noncardia gastric cancer all closely paralleled the corresponding curves generated from Connecticut Tumor Registry data from the same time period.

Discussion

These data from the Connecticut Tumor Registry suggest that the rise in incidence in EAC began in the late 1960s. This trend is consistent with 2 prior reports from Sweden and the United Kingdom (11, 12). The data from this study suggest that environmental exposures prior to the late 1960s may have contributed to a subsequent rise in EAC incidence (Fig. 2). According to results from the National Health and Nutrition Examination Survey (NHANES), a marked increase in the prevalence of obesity [defined as body mass index (BMI) ≥ 30] in the United States was not observed until the period between NHANES II (1976–80) and NHANES III (1988–94; 13). Interestingly, there was no marked change in the prevalence of overweight individuals ($25.0 \leq \text{BMI} < 29.9$) from 1960 through 1994 (14). Therefore, obesity does not seem to play a major role in the initial 3- to 4-fold rise in incidence of EAC.

Barrett's esophagus (BE) is the primary precursor lesion for the development of EAC, and a rise in BE incidence would likely have preceded a rise in EAC

Table 1. Percentage of esophageal cancer cases with histologic confirmation and uncorrected age-adjusted incidence (per 100,000) of EAC, ESCC, and esophageal cancer without histologic confirmation, Connecticut Tumor Registry, 1940–2007

Time period	Histologic confirmation for EC (%)	Incidence of EC without histologic confirmation	Uncorrected EAC incidence	Uncorrected ESCC incidence
1940–1944	45	3.34	0.09	2.19
1945–1949	54	3.33	0.20	3.44
1950–1954	66	2.64	0.23	4.22
1955–1959	76	1.88	0.29	5.00
1960–1964	82	1.31	0.35	4.90
1965–1969	88	0.95	0.36	5.49
1970–1974	90	0.70	0.64	4.99
1973–1977	92	0.59	0.67	5.55
1978–1982	94	0.46	1.23	6.07
1983–1987	95	0.40	2.15	5.45
1988–1992	97	0.31	2.59	4.78
1993–1997	97	0.27	3.39	4.04
1998–2002	97	0.17	4.64	3.51
2003–2007	97	0.20	5.15	3.42

incidence. Although difficult to estimate precisely, the average time for progression to EAC (among those BE patients who ultimately progress) is approximately 5 years (15). One would expect an additional lag time between a new or altered exposure and a rise in the incidence of BE, which may have begun in the 1950s.

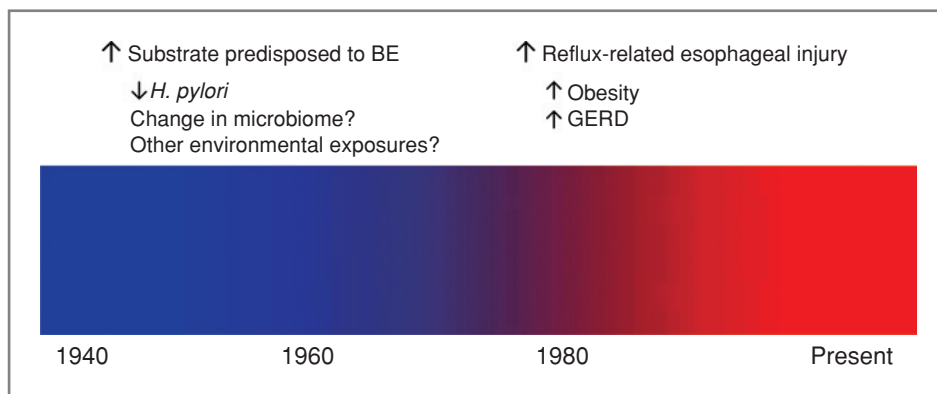
Infection with *H. pylori* is associated with a moderately decreased risk of EAC (5, 6), and infection rates with *H. pylori* have been decreasing since the middle part of the 20th century (16, 17). *H. pylori* infection seems to be associated with reduced odds of BE (18). Data are inconsistent with regard to a potential inverse association between *H. pylori* and other complications of GERD such as erosive esophagitis (18–20). A recent meta-analysis showed that there is no association between eradication of *H. pylori* and subsequent risk of GERD symptoms or erosive esophagitis (21), suggestive that *H. pylori* may impact risk of EAC at the level of development of BE. It is unclear whether *H. pylori*

itself protects against the development of EAC, or whether the absence of *H. pylori* reflects an overall change in the microbiome of the upper gastrointestinal tract (22), which in turn increases the risk of EAC.

Cigarette smoking is an established risk factor for EAC (23), and the prevalence of smoking rose markedly during the first half of the 20th century (24). However, it is unlikely that smoking was a major contributor to the initial rise in incidence of EAC. Cigarette smoking is an established risk factor for numerous gastrointestinal cancers, yet similar historical patterns in incidence are not observed for other malignancies such as noncardia gastric cancer and ESCC.

Gastric cardia cancer and EAC share many risk factors. The rise in incidence of gastric cardia cancer preceded the rise in EAC by a decade; the incidence of gastric cardia cancer plateaued roughly 2 decades ago, and perhaps a similar plateau will be observed for EAC incidence in the

Figure 2. Schematic of potential historical factors responsible for the observed rise in incidence of esophageal adenocarcinoma.



near future. However, comparisons with gastric cardia cancer are not straightforward, as adjustment for improved subsite classification over time suggests a much earlier plateau (25).

Although the data from this study are from a single state, the incidence curves for EAC, ESCC, and cardia and noncardia gastric cancer mirror the overall SEER incidence data. Underdiagnosis of esophageal cancer in the pre-endoscopy era could result in an exaggerated increase in EAC incidence, although this effect should also have been observed for ESCC. Historically, esophageal cancer is one of the most accurately classified tumors, based on studies comparing antemortem diagnoses to autopsy findings (7).

The incidence of EAC began to rise in the late 1960s, and has continued to increase through the present. It is likely that a change in local or systemic exposures predated this rise by several years. Changing trends in obesity do not seem to be responsible for the initial rise in EAC incidence, whereas declining rates of infection with *H. pylori* are temporally associated. Future investi-

gations into new or altered exposures from the mid-20th century may reveal important information with regard to the pathogenesis of EAC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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