The Role of Overdiagnosis and Reclassification in the Marked Increase of Esophageal Adenocarcinoma Incidence

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Background: **The incidence of esophageal adenocarcinoma is rising dramatically. This increase may reflect increased disease burden, reclassification of related cancers, or overdiagnosis resulting from increased diagnostic intensity, particularly upper endoscopy for patients with gastroesophageal reflux disease or Barrett esophagus.** ***Methods:*** **We used the National Cancer Institute's Surveillance, Epidemiology, and End Results database to extract information on incidence, stage distribution, and disease-specific mortality for esophageal adenocarcinoma as well as information on related cancers.** ***Results:*** **From 1975 to 2001, the incidence of esophageal adenocarcinoma rose approximately sixfold in the United States (from 4 to 23 cases per million), a relative increase greater than that for melanoma, breast, or prostate cancer. Reclassification of squamous cell carcinoma is an unlikely explanation for the rise in incidence, because the anatomic distribution of esophageal cancer in general has changed. The only location with increased incidence is the lower third of the esophagus—the site where adenocarcinoma typically arises. Reclassification of adjacent gastric cancer is also unlikely because its incidence has also increased. Because there has been little change in the proportion of patients found with in situ or localized disease at diagnosis since 1975 (from 25% to 31%) and because esophageal adenocarcinoma mortality has increased more than sevenfold (from 2 to 15 deaths per million), overdiagnosis can be excluded as an explanation for the rise in incidence.** ***Conclusion:*** **The rising incidence of esophageal adenocarcinoma represents a real increase in disease burden. [J Natl Cancer Inst 2005;97:142–6]**

In 2004, esophageal cancer will be diagnosed in an estimated 14 250 people in the United States, roughly half of whom will have adenocarcinoma *(1).* Although esophageal adenocarcinoma is uncommon, its incidence has increased dramatically over the past 25 years *(2–5).* The increase in disease incidence may represent a true rise in disease burden; however, it may also be the result of overdiagnosis or reclassification. Overdiagnosis—the detection of disease that would not have produced signs or symptoms before death—should be suspected if a rapid rise in incidence reflects a large increase in the detection of early-stage disease while mortality remains unchanged *(6).* The best known example for overdiagnosis due to increased screening is prostate cancer *(7).* Reclassification—a change in how diagnostic terminology is applied—may also explain changes in incidence.

Could overdiagnosis or reclassification explain the observed increase in the incidence of esophageal adenocarcinoma? It is possible that increased diagnostic intensity, particularly with the rapid rise in the use of upper endoscopy for patients with dyspepsia, gastroesophageal reflux disease, or Barrett esophagus *(8,9),* has resulted in overdiagnosis. Further, an incidence increase of in situ and localized disease *(10)* and a decrease in distant disease at the time of diagnosis have recently been reported *(10,11),* suggesting a shift in stage distribution toward earlier stages, raising the possibility of overdiagnosis. Reclassification, for instance, of gastric adenocarcinoma of the cardia, has also been considered *(4,12–14).*

In this study, we examine the incidence, stage distribution, and disease-specific mortality of esophageal adenocarcinoma, and the incidence of adjacent cancers to determine whether the observed increase in incidence of esophageal adenocarcinoma over the past 25 years represents overdiagnosis or reclassification. For this analysis, we used data from the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER[1]) database.

Subjects and Methods

Data Source

We performed a population-based study using data from the SEER 9 program. This group of nationwide cancer registries collects information on all malignancies newly diagnosed within the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the cities of Atlanta, Detroit, San Francisco, and Seattle and represents approximately 10% of the U.S. population. Our analysis included data from all available years (1973–2001). Although we focused on patients with histologically confirmed esophageal adenocarcinoma, we also selected patients with other malignancies to provide context and to assess the problem of reclassification.

Analysis

We first examined the change in the age-adjusted incidence of esophageal adenocarcinoma, defined anatomically as being in the esophagus (International Classification of Diseases for Oncology, third edition [ICD-O-3] codes 150–159) and histologically as adenocarcinoma (ICD-O-3 codes 8140–8573). In addition, we retrieved information on the incidence of esophageal squamous cell carcinoma using the same anatomic codes and histologic ICD-O-3 codes 8050–8082 and on the incidence of adenocarcinoma of the gastric cardia (ICD-O-3 codes—ana-

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DOI: 10.1093/jnci/dji024

tomic code 160 and histologic codes 8140–8573). To provide a perspective on incidence trends, we also examined other common malignancies as reported annually and defined by SEER.

The possibility of histologic reclassification was evaluated by examining the incidence trends after categorizing all esophageal cancers into one of three different anatomic locations: upper third of the esophagus (ICD-O-3 anatomic code 150 "cervical" and 153 "upper third"), middle third (154 "middle third"), and lower third (152 "abdominal" and 155 "lower third"). Cancer cases coded as "thoracic esophagus" (151) may include upper, middle, and lower thirds of the esophagus. Therefore, cancer cases that were coded as "thoracic esophagus" (151) were combined with cases that were coded as "overlapping" (158) and "not otherwise specified" (159) into a single category, "not clearly categorized."

To examine whether overdiagnosis may be responsible for the observed increase of esophageal adenocarcinoma, we retrieved information on the change in incidence of each stage at diagnosis using the SEER historic stage A (in situ, localized, regional, and distant). Although newer staging systems are available for several cancers, e.g., tumor–node–metastasis (TNM) staging, stage I–IV, SEER does not provide more detailed stage information for esophageal cancer.

We also examined the issue of overdiagnosis by determining the annual mortality from esophageal adenocarcinoma using the recently constructed incidence-based mortality database maintained by SEER. This database makes it possible to isolate mortality by histologic type, which is not possible with U.S. mortality data from the National Death Index.

Statistical Analysis

We reported an incidence increase using a relative rate—the ratio of incidence in each year to the incidence at baseline. Because the incidence of esophageal adenocarcinoma was low in the 1970s and therefore unstable, we used the average incidence from 1973 to 1975 as the baseline. The same approach (i.e., the use of rates relative to a 1975–1973 baseline) was used to describe changes in mortality.

Results

The rate of increase in esophageal adenocarcinoma in the last 25 years is greater than that of any other major malignancy in the United States (Fig. 1). The absolute incidence increased approximately sixfold, from 3.8 per million in 1973–1975 to 23.3 per million in 2001.

Is the Rising Incidence the Result of Reclassification?

During the same period (1975–2001), the incidence of the other major esophageal cancer, squamous cell carcinoma, fell from 31 to 19 per million (Fig. 2). Thus, it is possible that some of the rise in the observed incidence of esophageal adenocarcinoma could be explained by histologic reclassification—in other words, if what was once called squamous cell carcinoma is now called adenocarcinoma. However, this is unlikely. For histologic reclassification to be a plausible explanation, one would expect to find a relatively stable anatomic distribution of all esophageal cancers. Instead, the anatomic distribution has changed over time (Fig. 3). The only site with increased incidence has been the lower third of the esophagus, near the gastroesophageal junction, the site where adenocarcinomas most commonly arise (Fig. 3).

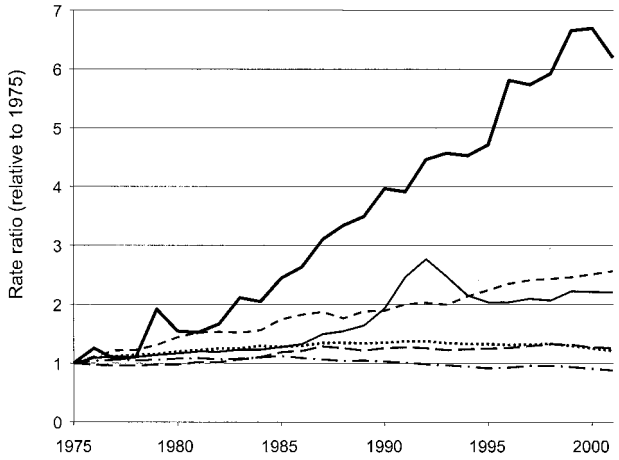

Fig. 1. Relative change in incidence of esophageal adenocarcinoma and other malignancies (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age-adjustment using the 2000 U.S. standard population. Baseline was the average incidence between 1973 and 1975. **Solid black line** = esophageal adenocarcinoma; **short dashed line** = melanoma; **line** = prostate cancer; **dashed line** = breast cancer; **dotted line** = lung cancer; **dashes and dotted line** = colorectal cancer.

Because the increased incidence has occurred near the stomach, another possible explanation for the rise in incidence is anatomic reclassification—in other words, if what was once called adenocarcinoma of the gastric cardia is now called adenocarcinoma of the esophagus. If that explanation were correct, the incidence of adenocarcinoma of the gastric cardia would be expected to have decreased during the same period. The incidence of this cancer, however, almost doubled, from 12 per million in 1975 to 22 per million in 1988 and has now stabilized (Fig. 4).

Is the Rising Incidence the Result of Overdiagnosis?

Increased diagnostic intensity could lead to the detection of formerly undiagnosed cancers and a shift to earlier stages at

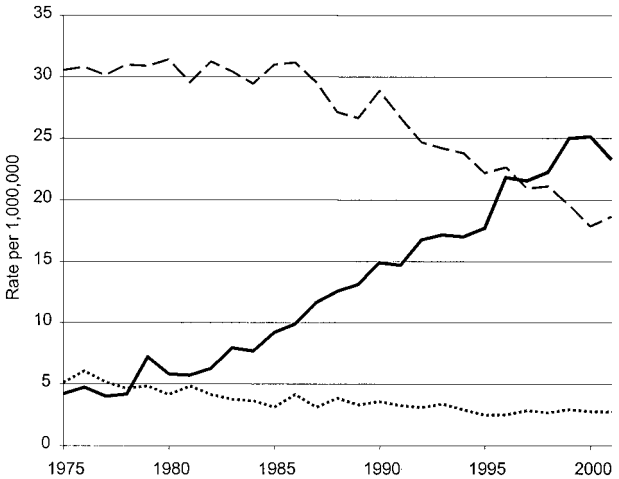

Fig. 2. Histology and esophageal cancer incidence (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age-adjustment using the 2000 U.S. standard population. **Solid black line** = adenocarcinoma; **dashed line** = squamous cell carcinoma; **dotted line** = not otherwise specified.

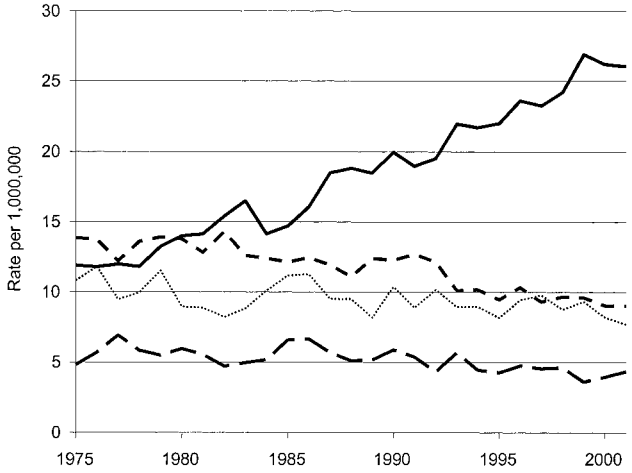

Fig. 3. Anatomic location and esophageal cancer incidence (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age-adjustment using the 2000 U.S. standard population. **Solid black line** = lower third of the esophagus; **short dashed line** = middle third of the esophagus; **long dashed line =** upper third of the esophagus; **dotted line** = not clearly categorized.

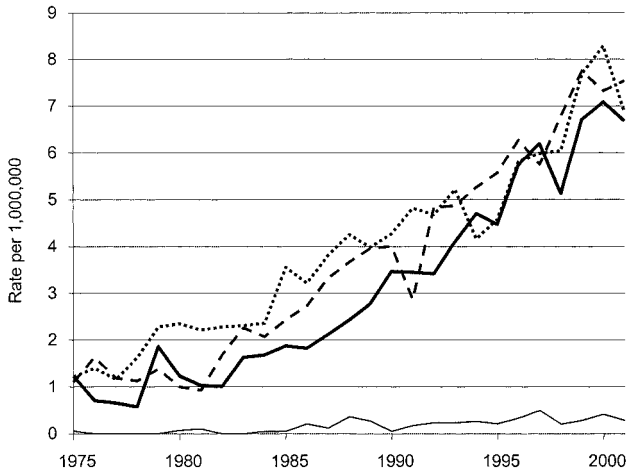

Fig. 5. Trends in stages of esophageal adenocarcinoma at diagnosis (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age-adjustment using the 2000 U.S. standard population. **Dotted line** = distant; **dashed line** = regional; **solid black line** = localized; **line** = in situ.

diagnosis. However, we found only a small increase over time in the proportion of early-stage disease at diagnosis (in situ and localized cancers rose from 25% of all esophageal adenocarcinomas diagnosed in 1975 to 31% in 2001). Furthermore, the incidence of regional and distant disease has risen just as rapidly as that of local disease (Fig. 5).

A different way to examine the possibility of overdiagnosis is to determine disease-specific mortality. If increased diagnostic intensity were responsible for the rise in esophageal adenocarcinoma, the rate of death from this cancer would not change over time. However, mortality increased markedly, from 2 per million in 1975 to 15 per million in 2001 (Fig. 6). The ratio of mortality to incidence has been fairly stable over this period (with the exception of 1980, which reflects a preceding incidence peak).

Discussion

Dramatic increases in disease incidence need to be explained. For example, the sharp increase in the incidence of prostate cancer in the late 1980s is generally attributed to early detection and overdiagnosis after the introduction of screening for PSA *(7).* Our results suggest that the increase in the incidence of esophageal adenocarcinoma, in contrast, represents a real increase in disease burden.

The argument that the incidence increase is real is based on the lack of evidence to support alternative explanations. Specifically, we did not find evidence for either histologic reclassification of esophageal squamous cell carcinoma or anatomic reclassification of adenocarcinoma of the gastric cardia. We also did not find evidence for overdiagnosis; the incidence of all stages increased simultaneously, and mortality increased in parallel with incidence.

It may be questioned how evaluating incidence in specific anatomic locations can clarify whether increased incidence can be explained by histologic reclassification. We believe it can, because squamous cell carcinoma originates from squamous cell

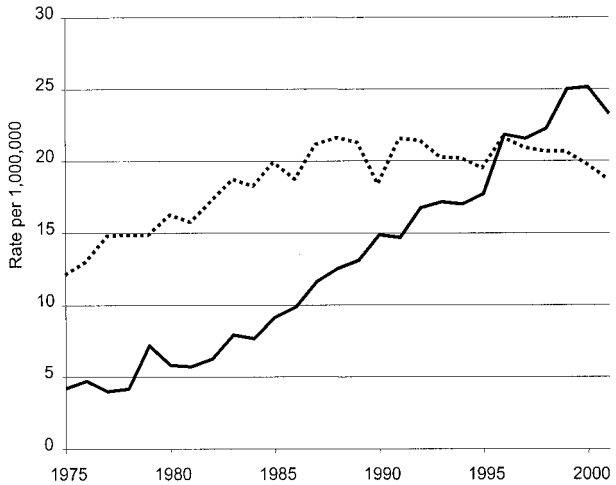

Fig. 4. Trends in incidence of adenocarcinoma of the cardia and the esophagus (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age-adjustment using the 2000 U.S. standard population. **Solid black line** = adenocarcinoma of the esophagus; **dotted line** = adenocarcinoma of the gastric cardia.

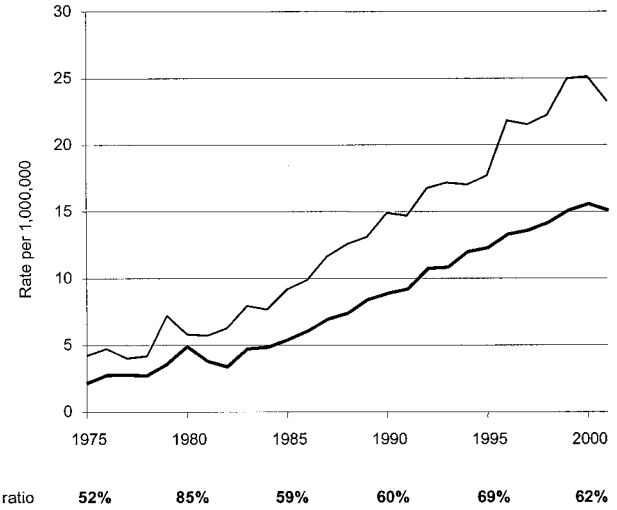

Fig. 6. Disease-specific mortality and incidence of esophageal adenocarcinoma (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age-adjustment using the 2000 U.S. standard population. Baseline was the average incidence (or mortality) between 1973 and 1975. **Line** = incidence; **solid black line** = mortality.

epithelium and may develop anywhere in the esophagus. Adenocarcinoma, in contrast, always arises from columnar epithelium. Most esophageal adenocarcinomas develop from Barrett esophagus—intestinal metaplasia that originates at the gastroesophageal junction and extends to the lower third and, less commonly, the middle and upper thirds of the esophagus. Therefore, the majority of adenocarcinomas are located in the lower third of the esophagus. We indeed found an increase in the incidence of esophageal cancers only in the lower third of the organ—the site where most adenocarcinomas arise. Thus, histologic reclassification of squamous cell carcinoma represents a very unlikely explanation for the increased incidence of esophageal adenocarcinoma.

Similarly, our analysis of incidence of adenocarcinoma of the gastric cardia argues against anatomic reclassification of this cancer as a possible explanation for the increased incidence of esophageal adenocarcinoma. We found, as have others *(3,5,15),* that incidence of adenocarcinoma of the gastric cardia rose substantially in the 1970s and 1980s and has since stabilized. Because incidence of adenocarcinoma of the gastric cardia did not fall as that of esophageal adenocarcinoma rose, reclassification is, again, unlikely.

We believe that the pattern of the change in incidence also makes reclassification an unlikely explanation. Changes in diagnostic practice or in pathologic classification that lead to reclassification would be expected to be adopted and implemented in a relatively limited period (i.e., less then 10 years). What we observed was not a discrete change in incidence but a steady rise over the past three decades.

Another possible limitation to our study is missing or incomplete data. Of all patients with esophageal cancers, we selected only those who had a histologic diagnosis for esophageal adenocarcinoma or squamous cell carcinoma. However, these diagnoses made up 82% of all esophageal cancers in 1975 and 89% in 2001. Thus, the proportion of esophageal cancers that received other histologic diagnosis was small (18% in 1975 to 11% in 2001) and cannot explain the rising incidence in esophageal adenocarcinoma.

This study also shares the limitations of all investigations using the SEER data. The SEER 9 regions represent only approximately 10% of the U.S. population. On the other hand, these data include a broad cross-section of the population and are, without a doubt, the most representative cancer incidence data in the United States. This study also shares the limitations of any investigation using secondary data. Our inferences are wholly dependent on the quality of the underlying data—a reality that leads SEER to provide extensive training for cancer registrars and to conduct regular audits to evaluate both the quality and completeness of the data being reported *(16).*

Our results strongly indicate that the increase in esophageal adenocarcinoma represents a true increase in disease burden. In fact, this cancer constitutes the fastest rising malignancy in the United States. Changes in the prevalence of commonly reported risk factors [i.e., gastroesophageal reflux disease *(17),* increased body mass index *(18,19),* and low fruit and vegetable intake *(18,20)*] or of *Helicobacter pylori* infection *(21,22)* have been discussed as possible explanations for the increase in incidence. To explain a rise of this magnitude, however, the prevalence of a strong risk factor must also rise dramatically—as was the case for smoking and lung cancer. Such a risk factor has not yet been identified and defining it should be a priority.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

We acknowledge the contribution of our colleagues in the VA Outcomes Group. Their feedback enhanced both our thinking and the presentation of our results. H. Pohl was supported by a Veterans Affairs Special Fellowship Program in Outcomes Research. This study was also supported by a Research Enhancement Award from the Department of Veterans Affairs to investigate the harms from excessive medical care. The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs.

Manuscript received July 16, 2004; revised November 17, 2004; accepted November 26, 2004.