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

Pohl and Welch consider whether the reported dramatic increase in esophageal adenocarcinoma represents a real increase in disease burden or whether it can be explained by artifacts introduced by classification problems and/or increased diagnostic intensity (1). Based on an analysis of the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) database, they conclude that the observed increase not only represents a true increase in disease but also that the rate of increase makes this cancer “the fastest rising malignancy in the United States.” They show an approximate sixfold increase in incidence between 1973–1975 and 1999–2001, a rate substantially higher than that for other cancers known to be increasing in incidence (e.g., two- to threefold increases for melanoma and prostate cancer).

The authors dismiss reclassification of gastric cardia adenocarcinoma as an artifactual explanation for the increase in esophageal adenocarcinoma because incidence of the former is also increasing over time and, they argue, if the reclassification were to explain the increase in esophageal adenocarcinoma, cardia adenocarcinoma incidence should decrease. This is true if the entirety of the increase were to occur through reclassification, but changes over time in the approach to cardia adenocarcinoma classification could profoundly affect the magnitude of the increase in cancers in this region of the body. The esophagus and cardia are anatomically juxtaposed, and their respective tumors cannot be distinguished by microscopic pathology. It can be difficult, and sometimes impossible, to assign many tumors unambiguously to the stomach or the esophagus. After the growth in interest in esophageal adenocarcinoma, it is also likely that a potential bias is operating, such that, given uncertainty, surgeons and gastroenterologists may have become increasingly more prone to assign tumors at the gastroesophageal junction to the esophagus.

When making comparisons over time using routinely acquired data, it is prudent to combine results for adenocarcinoma at both the gastric cardia and the esophagus. By combining, the sixfold increase reported by Pohl and Welch between 1975 and 2001 reduces to less than threefold.

Pohl and Welch also fail to take into account overall trends in gastric cancer incidence, especially those for which subsite information is unavailable. Fig. 1 shows, using the same SEER data (2) and the same time period considered by Pohl and Welch, trends in gastric adenocarcinoma incidence separately for the cardia, other specified subsites, and unspecified for subsite. The most substantial change over time has been in unspecified gastric cancer, which has fallen from 3 to 1 case(s) per million people between 1975 and 2001. In 1975–1977, 42% of gastric cancers were unspecified for subsite compared with 27% in 1999–2001. This decline confirms a clinical view that in the 1970s and 1980s there was little interest in subsite classification and that gastric cancer was largely thought of as a single entity. Again, a growing interest in gastric cardia adenocarcinoma in the 1990s is likely to have led to an increase in subsite classification.

It is unclear what proportion of subsite unspecified gastric cancer may have been localized to the cardia region, but, if the proportion were the same as that for subsite-specified cancers, then the rate of cardia adenocarcinoma would increase only marginally between 1975 and 2001 (from 18 to 19 cases per million
people). An estimate of the combined rate for both esophageal and cardia adenocarcinoma, corrected for unspecified cancer, would then be approximately 22 cases per million in 1975 and 42 per million in 2001, a less than twofold increase. This increase is important but not nearly as dramatic as the results presented by Pohl and Welch.

**Response**

We thank Dr. Forman for his interest in our study and appreciate his comments. Dr. Forman suggests that there are two reasons why changes in the classification of stomach cancers near the gastroesophageal junction may have led us to overstate the observed increase in esophageal adenocarcinoma.

First, he argues that because adenocarcinoma of the cardia and the esophagus cannot be reliably distinguished microscopically, the two sites should be combined when making comparisons over time. Although the distinction between adenocarcinoma of the cardia and the esophagus can be difficult, the presence of Barrett’s epithelium may help to make this distinction, as will the macroscopic description by the gastroenterologist or the surgeon. Furthermore, if misclassification were common, then the distinctions between the two cancers in epidemiologic and etiologic studies would not be made. The incidence ratios of men to women and whites to blacks (1) are different for esophageal adenocarcinoma and adenocarcinoma of the cardia. Gastroesophageal reflux disease (2) and obesity (3) are strong risk factors for esophageal adenocarcinoma but are weak risk factors for cardia adenocarcinoma. Although the absence of *Helicobacter pylori* infection appears to be associated with an increased risk for esophageal adenocarcinoma, it is not associated with cardia adenocarcinoma (4). Thus, we find it hard to accept the idea that the two cancers cannot be reasonably well distinguished and must, therefore, be combined.

Second, Dr. Forman suggests that the falling incidence of unspecified gastric cancers may have contributed to a spurious rise in cancers of the gastroesophageal junction. However, the decrease in unspecified gastric cancer may also relate to the falling incidence of gastric cancer in general. This decrease in gastric cancer incidence began more than 50 years ago and preceded the rise in adenocarcinoma of the cardia and of the esophagus by many years, arguing less for a problem of reporting and classification, but perhaps for the presence of a common etiologic factor. This factor may be associated with an increased risk of gastric cancer and a decreased risk of esophageal adenocarcinoma, but its presence may have declined over the past decades. *H. pylori* infection may present such a factor.

Of course, some portion of the rise in esophageal adenocarcinoma incidence may be due to changes in classification. However, based on our work, we think that this portion is small.

**Heiko Pohl**

**H. Gilbert Welch**

**References**

(1) El-Serag HB, Mason AC, Petersen N, Key CR. Epidemiological differences between adenocarcinoma of the esophagus and adenocarcinoma of the cardia in the USA. Gut 2002;50:368–72.


**Notes**

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