The Problems with Surveillance of Barrett’s Esophagus

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In patients with Barrett’s esophagus, the native squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium that is subject to dysplasia and mutation into esophageal adenocarcinoma. The incidence of esophageal adenocarcinoma, a particularly lethal form of cancer, increased by a factor of 6 in the United States between 1975 and 2001. Identified risk factors for esophageal adenocarcinoma are Barrett’s esophagus, frequent heartburn, white race, older age, male sex, and obesity. Among these, the most important risk and the one offering the greatest opportunity for a cancer-prevention strategy is Barrett’s esophagus. Consequently, substantial resources are expended on endoscopically identifying and monitoring Barrett’s esophagus to control the “epidemic” of esophageal adenocarcinoma. However, the usefulness of this strategy is determined by a set of risk and effectiveness estimates, and crucial among these is the estimate of the risk that esophageal adenocarcinoma will develop in patients with nondysplastic Barrett’s esophagus. In their report of an epidemiologic study from Denmark in this issue of the Journal, Hvid-Jensen et al. suggest that the risk is much lower than previously estimated, profoundly questioning the usefulness of the screening and surveillance strategy.

The link between Barrett’s esophagus and esophageal adenocarcinoma was well established by the 1970s. Early estimates suggested that the risk of esophageal adenocarcinoma among patients with Barrett’s esophagus was 0.8% per year, or about one case per 125 patient-years — an increase by a factor of 30 or 40 relative to the risk in the general population. Since then, this risk estimate has been progressively lowered. It was first reduced to about one case per 200 patient-years with the recognition that publication bias (overemphasis of studies with small numbers of patients) had resulted in a systematic overestimation of the risk. The risk estimate was further downgraded to about one case per every 300 patient-years in a recent meta-analysis in which a number of oversights in earlier meta-analyses were corrected, such as inclusion of prevalent cancers, inclusion of patients with dysplasia, and duplicate counting. Now we have two very large, population-based studies that further reduce the risk estimate. A report capturing the entire population of Northern Ireland (1.7 million persons) with a mean follow-up of 7 years estimated the risk of esophageal adenocarcinoma to be 0.13%, or one case per 769 patient-years. Hvid-Jensen et al. accessed a high-quality database encompassing the entire population of Denmark (5.4 million persons) to derive a risk estimate of 0.12%, or one case per 860 patient-years. With the use of that estimate, the relative risk of esophageal adenocarcinoma for a patient with Barrett’s esophagus as compared with the general population was 11.3, a substantial drop from the increase by a factor of 30 or 40 estimated in early reports.

So the problems with the screening and surveillance strategy for patients with Barrett’s esophagus lie not in the logic but in the numbers. An abundance of evidence points to frequent heartburn and Barrett’s esophagus as risk factors for esophageal adenocarcinoma. However, the magnitude of the risk is small. Even after the precipitous increase in cases of esophageal adenocarcinoma in recent years, this cancer occurs infrequently in the United States, with only an estimated 8000 cases in 2004. Furthermore, an estimated 40% of patients with esophageal adenocarcinoma report no history of frequent heartburn.
burn. Hence, the target of a protocol for screening and surveillance of patients with Barrett’s esophagus in the United States would be about 5000 cases of esophageal adenocarcinoma per year. On the other hand, the population at risk for esophageal adenocarcinoma because of frequent heartburn is very large. The 2010 U.S. census counted about 121 million Americans older than 45 years of age. Among these, an estimated 6% (7.3 million persons) have frequent heartburn, 5 to 15% of whom are likely to have Barrett’s esophagus. Consequently, the probability that esophageal adenocarcinoma will be detected with the use of endoscopy is only about 1 of every 1460 screening endoscopic examinations, but 146 patients with Barrett’s esophagus will be detected in the process.

Endoscopy is unquestionably effective in detecting Barrett’s esophagus. The problem is that as our knowledge of the biologic characteristics of Barrett’s esophagus has matured, the significance of the lesion has dwindled. In fact, patients with Barrett’s esophagus have the same life expectancy as does the general population, and esophageal cancer proves to be an uncommon cause of death in patients with Barrett’s esophagus, regardless of surveillance. Furthermore, currently available evidence has not shown that the current strategy of screening and surveillance of patients with Barrett’s esophagus is cost-effective or reduces mortality from esophageal adenocarcinoma. As reinforced by the elegant epidemiologic data reported by Hvid-Jensen et al., the problems with surveillance of Barrett’s esophagus lie in the numbers.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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