Cigarette Smoking and Esophageal and Gastric Cardia Adenocarcinoma

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Adenocarcinomas of the esophagus and gastric cardia have increased in incidence over the past few decades in the United States, while the incidence of squamous esophageal carcinoma has changed little and that of distal gastric adenocarcinoma has decreased (1,2). Similar trends have been seen in Denmark, the U.K., Switzerland, and Sweden. Unexplained increases in adenocarcinomas of the lung and cervix have also occurred (in contrast to squamous carcinomas at these sites) both in the United States and elsewhere and are believed to be real. The causes of the increased incidence of adenocarcinomas of the esophagus and gastric cardia are still unknown.

In 1993, the National Cancer Institute launched a 3-year multicenter population-based, case–control study to identify the potential causes of the increase in the incidence of this disease. The results of this large, carefully designed and executed study have been eagerly awaited. In this issue of the Journal, Gammon et al. (3) present the first findings. They observe a strong association between tobacco smoking and increased risk of adenocarcinomas of the esophagus and gastric cardia. Risk of adenocarcinomas of the esophagus and gastric cardia appears to be more than doubled, with a dose–response pattern, among smokers. Little reduction in risk was observed until smoking cessation for more than 30 years.

This study, which employed a well-developed and standardized questionnaire, was conducted in centers in New Jersey, Connecticut, and Washington State. Five separate groups were sampled: case patients with esophageal adenocarcinoma, case patients with adenocarcinoma of the gastric cardia, case patients with other gastric adenocarcinoma, case patients with squamous cell carcinoma of the esophagus, and control subjects. This is the largest population-based, case–control study of these adenocarcinomas conducted to date. The data resulting from this study will afford examination of a rich set of etiologic hypotheses.

The response rates are reported by the authors as approximately 80% among case patients with adenocarcinomas of the esophagus and gastric cardia, 74% among those with the other cancers (comparison subjects), and 70% among control subjects. Unfortunately, the rapid course of these diseases means that substantial proportions of all case patients were not available for interview by the time the investigators identified them. Thus, for approximately one third of the targeted case patients and comparison subjects, a proxy respondent provided exposure data. The authors express some comfort with the data extracted from these proxy respondents, and they indicate that the exclusion of subjects with proxy data made little difference in the results. It is important that in one of the studies (4) cited by the investigators on the quality of smoking data extracted from proxy respondents, 35% of proxy respondents were not able to estimate the age at which the subject began smoking. Among those who were able to make an estimate, there was clear evidence of underestimation of the years of smoking (4). Thus, Gammon et al.’s estimates of the effects of smoking on risk may be conservative.

Gammon et al.’s estimates of the effects of education, income, smoking, and alcohol consumption on risk are adjusted for body mass. Considering that smoking may affect body weight and that esophageal cancer itself may induce weight loss prior to the diagnosis of the disease, controlling for body mass may induce bias. Whether body mass was assessed prior to or at diagnosis or whether it was assessed at interview would seem to be an important consideration. It is difficult to predict the direction of the bias that might result from confounding by body mass.

Estimates of the association between smoking and adenocarcinomas of the esophagus and gastric cardia have varied in several earlier case–control studies (5–15). This larger scale case–control study adds definitive evidence on the effect of smoking on risk. The finding is consistent with six other case–control studies (5–10). In four case–control studies (5–8) of a combination of adenocarcinomas of the esophagus and gastric cardia, all identified a statistically significant association between cigarette smoking and disease. Among five studies (9–13) looking at only adenocarcinomas of the gastric cardia, two (9,10) demonstrated an association. In two studies (14,15) with only adenocarcinomas of the esophagus and relatively small sample sizes, no association with smoking was found. This variable outcome may simply be explained by the sample sizes or the power of the studies, since among six studies (5–10) finding a positive association with tobacco, five (5–8,10) had relatively larger sample sizes. These findings may also indicate that the influence of tobacco on adenocarcinoma of the esophagus might be different from that on adenocarcinoma of the gastric cardia. Although the incidence rate of adenocarcinoma of the esophagus was still rising from 1988 through 1990, no further increase in the incidence of gastric cardia adenocarcinoma was observed (2).

Whether adenocarcinomas of the esophagus and gastric cardia are a single neoplastic entity or two different diseases still needs more study. In view of the large sample size, the moderate effect of smoking, and the demonstrated dose–response relationship,
the relationship between smoking and disease observed in the current study (3) was probably not a simple artifact of chance. However, smoking cessation was not significantly associated with a reduced risk of disease, unlike the situation with other smoking-related cancers, such as cancer of the lung, squamous cell carcinoma of the esophagus, cancer of the head and neck, and cancer of the bladder. The authors argue that the observed slight reduction of risk after 30 years of smoking cessation indicates that smoking may affect an early stage in carcinogenesis. Age at which smoking started, though not presented, might be a superior descriptor of exposure to tobacco for early stage carcinogenesis.

Recent molecular studies have found that the prevalence of mutations in the p53 gene (also known as TP53) is approximately 80% for both squamous cell carcinomas and Barrett’s adenocarcinomas of the esophagus. However, distinctive mutational patterns in the p53 gene were observed. In adenocarcinoma of the esophagus, a very high frequency of G to T transitions at CpG dinucleotides was observed, suggesting an endogenous mechanism. But in squamous cell carcinoma of the esophagus, mutations at A:T base pairs were comparatively high, indicating the effect of an exogenous carcinogen, such as tobacco smoke (16,17). The different patterns of p53 mutations observed may represent the distinctive molecular fingerprints of critical risk involved in the development of these two cancers (18). According to the different patterns of molecular fingerprints between squamous cell carcinoma and adenocarcinoma of the esophagus, and considering recent reductions in the prevalence of cigarette smoking (19) and decreases in the incidence of smoking-related tumors (20), cigarette smoking may not sufficiently explain the rising incidence of adenocarcinomas of the esophagus and gastric cardia (5).

Gammon et al. (3) found neither beer nor liquor drinking to be associated with risk of adenocarcinomas of the esophagus and gastric cardia, but wine drinking was related to a significantly reduced risk of the disease. The difference in the alcohol associations observed for the adenocarcinomas and that observed for squamous cell carcinoma is striking. These data clearly confirm that liquor and beer intakes are relevant to the risk of squamous cell carcinoma of the esophagus but that they are not related to the risk of esophageal and gastric cardia adenocarcinomas. Wine consumption apparently does not increase the risk of even squamous cell carcinoma of the esophagus in these populations; it apparently does in other populations (21,22). The divergence of this latter result for squamous cell esophageal cancer from the results of several earlier studies (21,22) is of some concern. For adenocarcinomas of the esophagus and gastric cardia in earlier case–control studies, three (5–7) of the four (5–8) studies that combined esophageal and gastric cardia adenocarcinomas found a significantly elevated risk associated with alcohol use. Three (9,11,13) of five (9–13) studies of gastric cardia adenocarcinoma revealed a positive association with alcohol consumption. None of two (14,15) studies of adenocarcinoma of the esophagus reported a positive association. Like cigarette smoking, alcohol use may not be fully responsible for the rising incidence of adenocarcinomas of the esophagus and gastric cardia. In addition, socioeconomic factors, such as income and education, were associated with all four types of tumor but were not specific to adenocarcinomas of the esophagus and gastric cardia.

Future studies should focus on evaluation of the effects of pharmaceutical agents that relax the lower esophageal sphincter [resulting in gastroesophageal reflux (23)], dietary and nutritional factors [such as dietary fiber and fat (24)], and etiologic factors for Barrett’s esophagus, a precursor lesion for adenocarcinoma of the esophagus (25). To explore further the molecular mechanisms for tobacco exposure in the development of adenocarcinomas of the esophagus and gastric cardia, additional studies are warranted to measure the biologically effective dose (defined as the amount of carcinogen[s] bound to DNA [i.e., DNA adducts]) in the target tissue or surrogate measurements that represent exposure levels in the target tissue [e.g., hemoglobin adducts]; to assay genetic susceptibility markers, such as polymorphism of N-acetyl transferase (NAT), which is involved in both metabolic activation and deactivation of carcinogenic arylamines, or glutathione S-transferase (GST) M1, one of the phase II detoxification enzymes; to link the specific exposures measured in the target tissue to the mutational spectrum of specific genes; and to assess potential gene-environment interactions (26).

The results reported by Gammon et al. (3) are important for several reasons. In spite of their limitations—and Gammon et al. are well aware of them—they represent the product of an extensive effort to identify the epidemiology of adenocarcinomas of the esophagus and gastric cardia. These findings provide strong additional evidence regarding the cancer burden imposed by tobacco smoking. They indicate that the lag between smoking and esophageal and gastric cardia adenocarcinomas is extraordinarily long; it may exceed 30 years! The findings also indicate that alcohol consumption is probably not a risk factor for adenocarcinomas of the esophagus and gastric cardia. Publication of the findings regarding other risk factors for adenocarcinomas of the esophagus and gastric cardia will be critical to our efforts to prevent them.

References


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