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Diet, Obesity and Reflux in the Etiology of Adenocarcinomas of the Esophagus and Gastric Cardia in Humans[1,2]

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ABSTRACT Incidence rates for esophageal adenocarcinoma have increased >350% since the mid-1970s. Rates for gastric cardia adenocarcinoma have also increased, although less steeply. This led to the initiation of large population-based case-control studies, particularly in the United States and Sweden, aimed at identifying risk factors for these cancers. Results have been emerging from these studies, with the consistent finding that obesity and gastroesophageal reflux disease are important risk factors for these cancers. Analyses of dietary factors are also available and indicate that diets high in total fat, saturated fat and cholesterol are associated with an increased risk of these cancers, whereas several nutrients, particularly those found in plant foods (fiber, vitamin C, β-carotene, folate), are associated with a reduced risk. Considering the incidence trends of these cancers and the trends in the prevalence of risk factors, the increasing prevalence of obesity in the United States likely accounts for some of the increased incidence. However, other contributors to the increasing trends have been suggested and will be discussed. Because diet, obesity and gastroesophageal reflux disease may not act independently in contributing to these cancers, current research is attempting to identify associations between the three risk factors and potential mechanisms of action to better understand the etiology of these cancers. J. Nutr. 132: 3467S–3470S, 2002.

KEY WORDS: • *obesity* • *reflux* • *diet* • *esophageal neoplasms* • *gastric neoplasms*

Adenocarcinomas of the esophagus and gastric cardia have been of considerable interest recently as a consequence of the rapid increases in incidence noted for these cancers (1). Devesa et al. (2) evaluated incidence trends in the United States and noted a 350% increase in the incidence of esophageal adenocarcinoma between 1976 and 1994. Others have estimated an average annual increase in incidence of 20.6% for the United States, with even higher incidence rates currently noted for Great Britain, Australia and the Netherlands (3). Although the incidence of noncardia gastric adenocarcinomas has remained stable and declined among black and white males, respectively, the incidence of adenocarcinomas of the gastric cardia has also increased from 2.1 to 3.3 per 100,000 among white males, from 1.0 to 1.9 among black males and from 0.3 to 0.6 among white females (2). An analysis of data from the Surveillance, Epidemiology and End Results (SEER)[4] program found that age-adjusted incidence rates of esophageal adenocarcinoma were 6–8 times higher in men than in women and 3–4 times higher in whites than in blacks and that white men represented ~82% of all cases (4). Similarly, there were 3–5 times more men with adenocarcinoma of the gastric cardia than women and 1.5–2 times as many whites as blacks (4). These race differences are opposite that seen for squamous cell carcinoma of the esophagus, where black men are affected 5 times more often than white men in the United States (1,5).

Given the rapid increase in incidence of adenocarcinomas of the esophagus and gastric cardia, there emerged a critical need to initiate large research studies to identify risk factors in general as well as risk factors that might account for the rapid increases in incidence. Adenocarcinomas of the esophagus and gastric cardia are located in anatomic proximity, are sometimes difficult to distinguish and may share similar etiologies. Given this, large population-based case-control studies to evaluate risk factors for both adenocarcinoma of the esophagus and gastric cardia were launched in the United States and in Sweden in the mid 1990s. Major findings from these large studies are now available and, as will be described in detail later, indicate that a variety of lifestyle factors are implicated

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[4] Abbreviations used: BMI, body mass index; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; SEER, Surveillance, Epidemiology and End Results.

in the etiology of these cancers. The following section briefly reviews the epidemiology of these cancers, with a particular emphasis on obesity, reflux and dietary factors.

Obesity

One risk factor that has emerged as being strongly associated with the risk of adenocarcinoma of the esophagus is obesity. Beginning with the multicenter population-based case-control study in the United States, Chow et al. reported in 1998 (6) that being in the highest quartile of body mass index (BMI, a commonly used measure of adiposity, expressed in kg/m^2) compared with being in the lowest quartile was associated with a fourfold increase in the risk of esophageal adenocarcinoma and an approximate doubling of risk of gastric cardia adenocarcinoma (men and women combined). Similar results emerged from a large study of Swedish residents, wherein Lagergren et al. (7) found that individuals in the highest compared with the lowest BMI quartile had an almost eightfold increased risk of esophageal adenocarcinoma. When a BMI cutoff associated with being obese was used (BMI > 30), this risk increased to 16-fold compared with persons with a BMI < 22. As was seen in the U.S. study, the findings for gastric cardia adenocarcinoma were weaker than those for esophageal adenocarcinoma; the odds ratios (ORs) were 2.3 [95% confidence interval (CI), 1.5–3.6] for the highest compared with the lowest quartile and 4.3 (95% CI, 2.1–8.7) for BMI >30 versus BMI <22 (7). Likewise, Vaughan et al. (8) reported a 2.5-fold increased risk of esophageal adenocarcinoma among subjects in the top decile for BMI compared with those in the 10–49th percentile in another U.S. study. Brown et al. (9) observed a significant threefold increase in the risk of esophageal adenocarcinoma for subjects in the heaviest quartile of BMI. Thus obesity has emerged as a strong and consistent risk factor associated with risk of both adenocarcinoma of the esophagus and gastric cardia, albeit more strongly associated with the former.

Reflux

Chronic reflux, also known as gastroesophageal reflux disease (GERD), is emerging along with obesity as one of the strongest risk factors for adenocarcinoma of the esophagus. Lagergren et al. (10) evaluated the association between weekly reflux frequency and risk of adenocarcinoma of the esophagus in the Swedish case-control study and reported a dose-dependent increase in risk as weekly self-reported frequency of reflux symptoms increased. Having reflux symptoms more than three times per week was associated with an OR of 16.7 (95% CI, 8.7–28.3) compared with not having any reflux symptoms. Reflux was only weakly associated with risk of adenocarcinoma of the gastric cardia (OR, 2.3; 95% CI, 1.2–4.3; >3 times/wk versus none). The large U.S. study also found reflux to be related to risk, although the risk estimates were somewhat less than those in the Swedish study. More specifically, Farrow et al. (11) reported a fivefold increased risk of esophageal adenocarcinoma among subjects reporting daily GERD symptoms, although no association was found with adenocarcinomas of the gastric cardia. Chow et al. (12) conducted a medical record–based case-control study and, after adjusting for potential confounders, found a twofold to fourfold increased risk of adenocarcinomas of the esophagus and gastric cardia combined and history of reflux, hiatal hernia, esophagitis/esophageal ulcer and difficulty swallowing.

GERD is a known risk factor for Barrett's esophagus, a metaplastic precursor to esophageal adenocarcinoma (13). It is estimated that 8–14% of patients with chronic GERD may develop Barrett's esophagus (14). Given this, along with the magnitude of risks associated with frequent GERD, GERD should be considered a primary etiologic factor in adenocarcinoma of the esophagus.

Dietary factors

Dietary factors were a primary exposure of interest in the large U.S. population-based case-control study of adenocarcinomas of the esophagus and gastric cardia (15). Case-control studies are susceptible to recall bias, wherein case subjects may recall exposures differently from control subjects because of the presence of their illness; dietary factors could be especially susceptible to recall bias for case subjects with digestive tract cancers because of the presence of symptoms. To take these considerations into account, the U.S. study also interviewed case subjects with squamous cell carcinomas of the esophagus and noncardia gastric adenocarcinoma. In this study, dietary fat intake was significantly associated only with risk of adenocarcinoma of the esophagus. Other nutrients were associated with risk of both types of esophageal cancer and both types of gastric cancer. More specifically, increased intake of fiber, β-carotene, folate and vitamins C and B_6 from foods was associated with a reduction in risk, whereas increased intake of dietary cholesterol, animal protein and dietary vitamin B_{12} was associated with an increase in risk. This study also investigated associations between self-reported use of nutrient supplements and risk of the four cancer sites. Supplemental vitamin C was associated with a significantly lower risk of noncardia gastric cancer. Self-reported use of supplemental calcium/Tums® was associated with a significant increase in the risk of adenocarcinomas of the esophagus and gastric cardia. The greater intake of calcium by these subjects was as expected because of the excess risk of these cancers associated with GERD. The excess risk in these two case groups but not in the other two case groups (squamous cell carcinoma of the esophagus, noncardia gastric cancer) suggests that the supplemental intakes were reported reliably.

The nutrients associated with a lower risk in this study are predominantly derived from plant-based foods, whereas those associated with an increase in risk are predominantly derived from foods of animal origin. Correlations among nutrients could thus account for some of the observed associations. To further investigate this possibility, multivariate analyses were undertaken using likelihood ratio statistics to determine which of the nutrients had the greatest effect on the fit of models predicting risk of adenocarcinoma of the esophagus and gastric cardia (15). These analyses revealed that dietary fiber had the greatest effect on the fit of prediction models after adjustments were made for other nutrients and covariates of interest.

The finding in the U.S. study that dietary fiber was particularly strongly associated with risk is consistent with findings from the Swedish case-control study (16). In that study, total fiber and especially cereal fiber were inversely associated with risk of esophageal adenocarcinoma and gastric cardia adenocarcinoma, with the effect more striking for gastric cardia cancers (OR for total fiber, 0.4; 95% CI, 0.3–0.8 for the highest versus lowest quartile). Inverse associations between dietary fiber and risk of adenocarcinoma of the esophagus were also noted in earlier, smaller case-control studies of these cancers (9,17–19).

The Swedish case-control study, like the U.S. study, also observed that high intake of antioxidant nutrients (vitamin C, β-carotene, vitamin E) was associated with a lower risk of adenocarcinomas of the esophagus, but in contrast to the U.S.

study, this association was not seen for gastric cardia adenocarcinoma (20). As was found in the U.S. study, these nutrients were also inversely associated with risk of esophageal squamous cell carcinomas.

We are in the process of evaluating food groups and the risk of these cancers in the U.S. population-based case-control study, but given the nutrient associations, we expect that some measures of plant food consumption will be particularly inversely associated. This would be consistent with limited evidence from smaller studies of food groups, where various indices of fruits and vegetables are inversely associated with risk (9,17,21).

Helicobacter pylori infection

Infection with *H. pylori*, particularly *cag*A+ strains, is considered an important risk factor for noncardia gastric cancers. The U.S. population-based case-control study obtained blood samples from a subsample of cases and controls, and serum levels of immunoglobulin G antibodies to *H. pylori* were assessed to evaluate associations with adenocarcinomas of the esophagus and gastric cardia (22). As expected, infection with *cag*A+ strains was positively (OR, 1.4), although not significantly, associated with risk of noncardia gastric cancers. In contrast, infection with *H. pylori* and particularly *cag*A+ strains was inversely associated with the risk of adenocarcinoma of the esophagus and gastric cardia (OR, 0.4; 95% CI, 0.2–0.8). This result is biologically plausible in that *H. pylori* infection can lead to chronic atrophic gastritis, which is accompanied by the lowering of gastric acidity (22). These provocative results could have important implications for discussions regarding the risks and benefits of *H. pylori* eradication and thus require replication in other large studies.

Tobacco and alcohol

Cigarette smoking and alcohol consumption have been found to be significant risk factors for esophageal squamous cell carcinoma and, to a lesser degree, adenocarcinomas of the esophagus and gastric cardia. For example, Vaughan et al. (8), in a case-control study of adenocarcinomas compared with squamous cell carcinomas, found a 5-, 8- and 17-fold increased risk of squamous cell carcinoma, respectively, for subjects currently smoking 1–39, 40–79 and 80+ cigarettes/d as compared with nonsmokers. The risks associated with current smoking for adenocarcinomas were significantly lower than those for squamous cell carcinoma, although they remained statistically significant (8). For subjects reporting an alcohol intake of 21+ drinks/wk, the OR was 9.5 (95% CI, 4.0–22.3) for squamous cell carcinoma and 1.8 (95% CI, 1.1–3.1) for adenocarcinoma (8). Gammon et al. (23) likewise found statistically significant increased risks associated with smoking for esophageal and gastric cardia adenocarcinomas. In this study, alcohol intake was strongly associated with squamous cell carcinomas of the esophagus, but neither beer nor liquor drinking was significantly associated with risk of adenocarcinomas of the esophagus and gastric cardia and wine drinking was associated with a significant decrease in risk.

Interrelationships between risk factors

Most cancers are multifactorial, often involving combinations of both host and genetic factors in determining risk. We have described several risk factors for these cancers, some of which may be linked. For example, the striking risk associated with both obesity and chronic reflux raises the question of whether obesity contributes to reflux and thus to these cancers indirectly. The association between obesity and reflux was evaluated in the 820 control subjects from the Swedish population-based study. If reflux is defined as having symptoms at least once per week, then 16% of the control subjects met the definition for reflux. Obesity was not significantly associated with reflux in these subjects (24). This suggests that obesity may be increasing the risk of these cancers through other mechanisms, such as hormonal effects. We are embarking on a similar analysis of dietary factors as they relate to reflux in the control subjects from the U.S. population-based case-control study.

Explanations for time trends

A primary goal of the epidemiologic studies of adenocarcinoma of the esophagus and gastric cardia was to identify factors that might explain the rapid increase in incidence, to guide interventions to reduce the incidence of these cancers. Obesity is known to be increasing in the United States and in many other countries throughout the world, both developed and developing (25). The rapid increase in obesity is likely to contribute at least in part to the increase in incidence. With regard to reflux, data on the population prevalence of reflux are somewhat limited and data on trends in reflux are even more limited. Thus the contribution of increasing reflux to the increased incidence remains unknown. Chow et al. (22) suggested that declines in the prevalence of infection with *H. pylori,* including *cag*A+ strains, may have contributed to the upward incidence trends, although this possibility is based on limited evidence. The decline in squamous cell carcinomas of the esophagus in the United States is likely related to the decrease in smoking, particularly among men, because smoking is more strongly related to this cancer than to the other tumor sites.

Implications for prevention

Adenocarcinomas of the esophagus and gastric cardia are increasing rapidly in many countries throughout the world. These malignancies have relatively poor survival outcomes, so prevention remains the most promising approach for intervention in these malignancies. As is the case with many cancers, a working model of risk progression can be envisioned, starting with chronic reflux that develops into Barrett's esophagus in some proportion of individuals with reflux and then progresses to the development of invasive malignancy in a subgroup of those with Barrett's. It is currently believed that many patients with Barrett's esophagus go undiagnosed (14), so interventions cannot be targeted solely to patients with clinically diagnosed Barrett's esophagus. Most studies have evaluated risk factors for invasive cancer in comparison with healthy control subjects; we do not yet understand where in the disease process each of these risk factors exerts its effect. This suggests the need for studies aimed at identifying determinants of disease progression in populations at risk (e.g., cohort studies of patients with reflux and with Barrett's esophagus). In the meantime, research has identified several prudent measures for consideration to begin to combat the increasing incidence of adenocarcinoma of the esophagus and gastric cardia.

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