Smoking Found to Increase the Rate of Progression of Barrett Esophagus to Adenocarcinoma

A recent study has reported that smoking doubles the risk of progression of Barrett esophagus (BE) to adenocarcinoma (Gastroenterology. 2012;142:233-240).

“This study shows that smoking is a major reason for the progression of BE to high-grade dysplasia or cancer and is the first study to show a temporal association between the 2,” says lead author Helen Coleman, PhD, a postdoctoral research fellow at the Center for Public Health at Queen’s University in Belfast, Northern Ireland.

The incidence of esophageal adenocarcinoma has been increasing and BE is a premalignant lesion that may become dysplastic and progress to cancer. Most people with BE, however, do not develop dysplasia or esophageal cancer, making it important to identify risk factors that may affect the rate of progression to facilitate optimal management (Am J Gastroenterol. 2010;105:1490-1502). “We need to find out what the differences are between the <0.5% of BE patients who progress each year to cancer and those who do not progress,” Dr. Coleman says. The goal of the current study was to identify a modifiable lifestyle risk factor for progression of BE to esophageal adenocarcinoma.

All Smoking Levels at Increased Risk

Dr. Coleman and her colleagues identified patients with specialized intestinal metaplasia through the Northern Ireland Barrett’s Esophagus Registry. The registry includes all adults diagnosed with columnar epithelium-lined esophagus between 1993 and 2005 in Northern Ireland. The patients identified from the BE registry were linked to the Northern Ireland Cancer Registry to identify patients whose disease progressed to malignancy. Medical records were reviewed by trained data abstractors. Of the 3167 patients in whom BE was identified, 117 progressed to high-grade dysplasia or adenocarcinoma. The mean time from a diagnosis of BE to progression was 4.5 years.

Smoking status was reported in over 90% of the records reviewed and, after adjustment for confounders, an elevated risk was identified for former smokers (hazards ratio [HR], 1.53) and current smokers (HR, 1.83). Confounders included were age, sex, presence of low-grade dysplasia, socioeconomic status, reflux symptoms, and length of the Barrett segment of the esophagus. The amount smoked was recorded in about one-half of the medical records and no difference was seen in the rate of progression between participants who smoked more or less than one pack a day. Pipe smoking was also found to be a risk factor for progression after adjustment for confounders (HR, 2.18). Cigar smoking did not appear to affect progression, but it was reported in <1% of the study population.

Smoking tobacco in any form, after adjustment, approximately doubled the risk of progression of BE to carcinoma or high-grade dysplasia (HR, 2.07). “Our findings showed BE patients smoking less than one pack of cigarettes per day were still at a 2-fold increased risk of progression; therefore, clinicians should emphasize the importance of stopping cigarette smoking altogether, rather than just reducing the number of cigarettes smoked,” Dr. Coleman says.

Mean age at BE diagnosis, socioeconomic status, and the recording of reflux symptoms did not differ between those patients whose disease progressed and those whose disease did not progress. Patients who developed cancer were more likely to be male, have indefinite or low-grade dysplasia at the time of diagnosis of BE, and have long-segment BE. Approximately one-half of all patients, however, did not have their segment length recorded. Few patients had both their height and weight recorded, but an exploratory analysis showed no relationship between height or weight and neoplastic progression. Similarly, for those patients for whom a BMI could be calculated, no association was found.
Data regarding alcohol consumption was recorded in about 70% of patients and no difference was found in the rate of progression between participants who abstained from alcohol and those with any level of alcohol intake.

**Future Directions**

According to the authors, this is the largest study to date analyzing lifestyle factors as related to the risk of progression of BE, which could explain the differences noted compared with smaller studies. “More studies are needed to confirm our findings. However, within our study, the increased risk was consistent across different analyses and tobacco types, indicating our findings are robust,” Dr. Coleman says.

The main limitations of the study are that the data were collected retrospectively from medical records and that a fair number of patients did not have body measurements or alcohol intake reported. A further limitation noted by Dr. Coleman is that the population was relatively homogenous in that it was based in Northern Ireland and included mostly white patients.

According to the authors, there are conflicting results from recent, smaller prospective studies. One study that included 19 patients who progressed to carcinoma from a cohort of patients with BE demonstrated an association between progression and former, but not current, smoking (Am J Gastroenterol. 2011;106:1447-1455). Another prospective study of 713 patients with BE identified 26 patients who developed high-grade dysplasia or esophageal adenocarcinoma and found no association between smoking and disease progression (Am J Gastroenterol. 2011;106:1231-1238).

“Prevention of Barrett’s esophagus-related neoplasia is now focused on good acid control and ablation of the metaplastic mucosa using a wide variety of endoscopic methods including radiofrequency ablation, cryotherapy, and photodynamic therapy,” says Kenneth Wang, MD, director of the Advanced Endoscopy Group and Esophageal Neoplasia Clinic at the Mayo Clinic in Rochester, Minnesota. Dr. Wang, who coauthored guidelines for the management of BE (Am J Gastroenterol. 2008;103:788-797), added that while smoking does increase the rate of progression of BE, it should be discouraged for its overall deleterious health effects and because of the low rate of progression to esophageal carcinoma, it does not change the overall management recommendations.

Molecular analysis is an important area of research that may help to tailor the surveillance and treatment of BE to the progression risk of an individual patient more specifically than lifestyle factors. A biomarker that is sensitive and specific for the progression of BE has not been identified, but research is advancing. “Phase 3 biomarker studies with reasonably large cohorts have shown that evidence of genetic or chromosomal instability increases cancer risk,” Dr. Wang says. He went on to say researchers are now examining ways to detect chromosomal instability in a clinically adaptable way using fluorescence in situ hybridization (FISH) and single-nucleotide polymorphism arrays, with FISH likely being the most clinically available method. ■

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