Familial Barrett Esophagus and Adenocarcinoma of the Gastroesophageal Junction

Charis Eng,1 Stuart Jon Spechler, Robert Ruben, and Frederick P. Li2

CRC Human Cancer Genetics Research Group, University of Cambridge, United Kingdom [C. E.]; Department of Medicine, Dana-Farber Cancer Institute [C. E., F. P. L.], Division of Gastroenterology, Beth Israel Hospital [S. J. S.], Harvard Medical School [C. E., S. J. S., F. P. L.] and Harvard School of Public Health [F. P. L.], Boston, Massachusetts 02115 and Division of Gastroenterology, Wentworth-Douglass Hospital, Dover, New Hampshire [R. R.]

Abstract

Barrett esophagus was found in seven members of a single family. Two of these patients also had adenocarcinoma of the gastroesophageal junction. Among family members who did not have Barrett epithelium, one had esophageal ulcerations with dysplasia in squamous epithelium and another had an esophageal stricture. The pattern of involvement suggests autosomal dominant inheritance of Barrett esophagus and/or gastroesophageal reflux disease in this family, with a strong predisposition for adenocarcinoma of the esophagus.

Introduction

In Barrett esophagus, the squamous epithelium that normally lines the distal esophagus is replaced by metaplastic columnar mucosa that is predisposed to develop cancer (1-3). Although Barrett esophagus clearly is associated with gastroesophageal reflux disease, the pathogenesis of the metaplastic mucosa remains poorly understood (3). There appears to be a familial form of Barrett esophagus that may be inherited as an autosomal dominant trait (4, 5). A recent report has suggested that the risk of esophageal cancer may be especially high for members of these families (5). In support of this suggestion, we describe a family with 7 members who had Barrett esophagus, 2 of whom developed esophageal adenocarcinoma.

Materials and Methods

The proband and her family came to attention when the proband presented to the Dana-Farber Cancer Institute for treatment of esophageal adenocarcinoma.

Results

Proband. The proband (Fig. 1, II-3), a 66-year-old woman, had a 20-year history of symptoms of gastroesophageal reflux. She did not smoke or drink alcohol. In July 1990, she noted dysphagia, and EGD revealed a hiatal hernia, severe reflux, and a mass at the gastroesophageal junction (Table 1). Surgical resection showed Barrett esophagus, severe dysplasia, and a poorly differentiated adenocarcinoma. Despite chemotherapy, she died 8 months later.

Family. Six family members of the proband, 3 living and 3 deceased, had Barrett esophagus (Table 1). The proband’s eldest sister (II-1) was found at age 70 (all ages referred to are in years) to have anemia and a 10-pound weight loss. She did not smoke but drank 2–4 highballs a night. Upper gastrointestinal series showed a constricting lesion in the distal esophagus just above a hiatal hernia. Biopsies revealed Barrett esophagus, dysplasia, and adenocarcinoma. She had regional lymphadenopathy and hepatic metastases, which were treated with chemotherapy and radiotherapy. She died and no autopsy was performed. A brother (II-2) of the proband was a heavy user of alcohol and tobacco and had longstanding symptoms of gastroesophageal reflux. He died of myocardial infarction at age 64. Postmortem examination revealed Barrett esophagus and severe esphagitis. A third sibling of the proband (II-4) was found by EGD to
have Barrett esophagus, a hiatal hernia, and gastroesophageal reflux at the age of 57. She neither drank nor smoked, but complained of heartburn and dysphagia. A fourth sibling, II-6, had a longstanding history of heartburn and moderate alcohol use. When he was 57, an EGD showed Barrett esophagus, severe reflux, and a hiatal hernia. An asymptomatic 40-year-old niece of the proband, III-2, had a screening EGD because of her family history. Biopsy demonstrated Barrett esophagus. Her constitutional karyotype was 46, XX. A 26-year-old niece of the proband, III-11, had severe heartburn for approximately 1 year. EGD demonstrated a 2-cm circumferential area of Barrett epithelium in the distal esophagus. She smoked 5 pack-years and drank 1 beer a week. In addition to the 7 family members with Barrett esophagus, another sibling of the proband (II-5) developed symptoms of gastroesophageal reflux at age 56. An EGD demonstrated linear ulcerations and moderate dysplasia in the distal esophagus but no Barrett’s epithelium. The proband’s father, I-1, had dysphagia due to an esophageal stricture of unknown etiology; Barrett’s epithelium was never demonstrated. He died of a myocardial infarction at age 84, and no autopsy was performed.

Barrett esophagus was not found on EGD in 2 symptomatic individuals (III-7, age 34; III-13, age 27) and one asymptomatic relative (III-8, age 33).

The family is of Irish and Italian ancestry. There was no history of consanguinity or progressive systemic sclerosis. In addition to esophageal adenocarcinoma in patients II-1 and II-3, cancers of other sites developed in several family members: head and neck cancer at an unknown age in I-1 and his brother, both of whom were smokers; and basal cell carcinoma of the skin at age 56 in II-4.

**Discussion**

Published studies reveal the frequency of Barrett’s epithelium varies with the indication for EGD. Reported rates are 1–4% for patients evaluated for primarily extraesophageal symptoms including abdominal pain or melena, 8–20% for those assessed for esophagitis, and 44% for those with chronic peptic esophageal strictures (1, 3). Barrett esophagus predominates in males, whites, and those aged over 40. The reported incidence of adenocarcinoma in Barrett esophagus ranged 30–125-fold above that of the general population (1-3, 6). Although each study was small, the age and sex distribution of patients who developed esophageal adenocarcinoma was similar to that in the population-at-large.

Inherited factors appear to play a role in the development of Barrett esophagus. A few families with Barrett esophagus have been reported previously. Barrett esophagus has been described in 4 of 16 close relatives in a family, 2 of whom subsequently developed adenocarcinoma of the esophagus (4). A second family had 6 members with Barrett esophagus, 3 of whom had esophageal adenocarcinoma (5). Both families also had a high prevalence of gastroesophageal reflux. Additional reports described Barrett esophagus in father and 2 sons (7), a pair of female twins (8), and 2 sisters (9). In a retrospective review of 241 patients with Barrett esophagus, 6 were noted to have a family history of esophageal adenocarcinoma but no mention was made of Barrett’s changes in these family members (10). The reports of multiple affected generations, together with our family, suggest that susceptibility to Barrett esophagus and/or gastroesophageal reflux can be inherited in an autosomal dominant pattern. Despite the absence of Barrett esophagus, I-1 and II-5 are likely to be gene carriers by virtue of having offspring with Barrett esophagus, under the presumption of autosomal dominant inheritance.

Members of reported Barrett esophagus families appear to be at an exceptionally high risk of developing esophageal adenocarcinoma. However, it is unclear whether publication bias may be playing a role in this observation. Perhaps only families with Barrett esophagus with a high prevalence of esophagus cancer appear in print. Identification and molecular genetic analysis of large families with Barrett esophagus might be useful in isolating the predisposing gene(s), which also appear(s) to be involved in the pathogenesis of esophageal adenocarcinoma. Furthermore, members of Barrett esophagus families, particularly those with symptoms of gastroesophageal reflux, should be counseled to seek early medical attention. Benefits of periodic screening for esophagus adenocarcinoma in affected families remain to be established.

**Note Added in Proof**

Family member III-6 recently developed reflux esophagitis.
Acknowledgments
We thank Dr. S. Jhanwar for performing the karyotype on patient III-2.

References
Familial Barrett esophagus and adenocarcinoma of the gastroesophageal junction.

C Eng, S J Spechler, R Ruben, et al.

Cancer Epidemiol Biomarkers Prev 1993;2:397-399.