High Prevalence of Barrett's Esophagus and Esophageal Squamous Cell Carcinoma After Repair of Esophageal Atresia

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BACKGROUND & AIMS: **Esophageal atresia is rare, but improved surgical and intensive care techniques have increased rates of survival in children, so there are now many adults with this disorder. Many patients with esophageal atresia develop gastroesophageal reflux (GER), raising concerns about increased risk of Barrett's esophagus (BE; prevalence of 1.3%–1.6% in general population) and esophageal carcinoma. We assessed the prevalence of BE and esophageal carcinoma in this population.**

METHODS: **We performed a prospective study of 289 patients with esophageal atresia at the Department of Gastroenterology and Hepatology at Erasmus MC University Medical Center in The Netherlands, from May 2012 through March 2017. A total of 151 (median age, 25.4 y; age range, 16.8–68.6 y) underwent upper endoscopies as part of a surveillance program for (pre)malignant esophageal lesions. Biopsies were collected and analyzed by histology. We collected data on patients' use of medications, tobacco, and alcohol; gastrointestinal symptoms; ability to swallow; complaints of GER; and type of atresia and surgeries. Prevalence of esophageal squamous cell carcinoma (ESCC) was determined using data from The Netherlands Cancer Registry. The number of persons alive on January 1, 2016, in the esophageal atresia cohort and in the general Dutch population were used to calculate the 10-year prevalence of ESCC per 100,000 persons in both populations.**

RESULTS: **Forty-seven percent of patients with esophageal atresia had a history of GER and 20.5% had undergone fundoplication surgery. Endoscopy revealed normal esophagus in 68.2% of patients, esophagitis in 7.3%, and columnar-lined esophagus in 24.5%. Histology revealed normal mucosa in 50.3% of patients, esophagitis in 23.2%, gastric metaplasia in 17.2%, and BE in 6.6% (at a median age of 31.6 years). A history of fundoplication surgery was associated with BE ($P = .03$). Three ESCCs developed, in 2 men, at ages 42, 44, and 60 years. This corresponded to a prevalence of 0.7% in patients with esophageal atresia—a value 108-fold higher than in the same age group in the general population.**

CONCLUSIONS: **The prevalence of BE is 4-fold higher in young adults with esophageal atresia, and the prevalence of ESCC is 108-fold higher than in the general population. This finding could have important implications for transition of young adults from pediatric care to adult gastroenterology departments to receive life-long endoscopic follow-up evaluation to facilitate early diagnosis of relevant lesions.**

Keywords: Tumor; Esophageal Neoplasm; Inflammation; Screening.

Esophageal atresia (EA) is a rare anatomic anomaly (worldwide prevalence, 2.43/10,000 births).[1] Surgical correction is needed soon after birth. In the past 40 years, improved surgical and intensive care techniques have increased survival rates up to 93% in expert centers, and therefore more of these children have reached adulthood.[2]

Many EA patients suffer from gastroesophageal reflux (GER), with a reported prevalence of 32.8% to 54.2% in infancy/childhood and 5.9% to 66.7% in adolescence/adulthood.[3] Chronic GER may lead to esophageal mucosal injury, resulting in esophagitis, gastric metaplasia (GM), or intestinal metaplasia (IM), also called

Abbreviations used in this paper: ACG, American College of Gastroenterology; BE, Barrett's esophagus; EA, esophageal atresia; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction/gastric folds; GER, gastroesophageal reflux; GM, gastric metaplasia; IM, intestinal metaplasia.

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Barrett's esophagus (BE).[4] In the general adult population, the prevalence of BE is 1.3% to 1.6% and is diagnosed predominantly in middle-aged white men.[5–7] BE is a premalignant lesion and predisposes to esophageal adenocarcinoma (EAC), with an estimated incidence rate of 0.5% per year of follow-up evaluation.[8]

The high prevalence of GER in EA patients raises concerns about an increased risk of developing BE and EAC in this population.[3] Carcinoma of the upper gastrointestinal tract at a relatively young age has been described in EA patients: 8 esophageal carcinomas (3 EAC and 5 esophageal squamous cell carcinoma [ESCC])[9–13] and 2 squamous cell carcinomas not related to the native esophagus.[14,15]

Given these findings and the dismal prognosis of patients with symptomatic esophageal cancer, endoscopic surveillance in EA patients was recommended recently in an European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) - North American Society for Pediatric Gastroenterology, Hepatology and Nutritio (NASPGHAN) guideline.[16] We assessed the prevalence of BE and esophageal cancer in a prospective screening and surveillance program in adult EA patients.

Methods

Patients

Since 1999, all EA patients have joined a longitudinal follow-up program at the Pediatric Surgery Department of our tertiary referral center.[17] Since April 2013, all adult EA patients (≥17 y) routinely have been referred to the Gastroenterology Department for clinical assessment and endoscopic screening and surveillance of (pre)malignant esophageal lesions. We searched our patient registry system and written surgical records for patients born in 1948 to 1999 to identify all EA patients treated at our center and invited these patients to our endoscopic screening and surveillance program.

Ethics

The study protocol was reviewed by the Institutional Review Board of the Erasmus Medical Center (Medical Research and Ethics Committee Erasmus MC, protocol ID MEC-2015-093). Formal approval was waived because all handling to the subjects was part of standard clinical care.

Data Collection

All data were collected prospectively. Data on medication, tobacco, and alcohol use, and the occurrence of gastrointestinal symptoms were collected at the outpatient clinic before the endoscopy. The ability to swallow was assessed from dysphagia scores (Supplementary Table 1). Complaints of GER were defined as chest pain, pyrosis, or regurgitation. Data retrieved from patient records included type of EA (Gross[18] classification), type of primary surgery, and additional relevant medical history.

GER was considered clinically significant if patients needed fundoplication surgery, if pH monitoring showed pathologic reflux, or if, according to the American College of Gastroenterology (ACG) guidelines for GER, upper endoscopy showed typical reflux-induced mucosal lesions.[19]

All endoscopic procedures were performed by an experienced gastroenterologist according to a standardized protocol. The mucosa of the esophagus was examined using white light. In case of suspicion of BE it was switched to narrow-band imaging. From the age of 25 years the esophagus also was stained with Lugol to detect early squamous lesions.[20] Endoscopic landmarks, such as the squamocolumnar junction (Z-line), the proximal margin of gastric folds (gastroesophageal junction [GEJ]), and the diaphragm, were identified and described. All remarkable findings were noted. Esophagitis and Barrett's epithelium were scored according to the Los Angeles Classification[21] and Prague criteria.[22] Four random biopsy specimens were taken from above the GEJ (if end-to-end anastomosis or gastric pull-up had been performed) or above the proximal anastomosis (if a colon, jejunal, or ileocecal interposition had been performed). In case of BE, 4-quadrant biopsy specimens were taken every 2 cm, according to the Seattle protocol.[23] The proposed surveillance intervals for BE are in accordance with the ACG guidelines.[4] In addition, in the absence of BE surveillance intervals of 5 years (age, <30 y) or 3 years (age, ≥30 y) were advised (Supplementary Figure 1). Endoscopic findings were classified according to the most severe abnormality found at upper endoscopy.

All deceased and nonresponding patients were linked to The Netherlands Cancer Registry, managed by The Netherlands Comprehensive Cancer Organisation.[24] Since 1989, The Netherlands Cancer Registry registers all participants diagnosed with cancer in The Netherlands and provides a unique and fully covered database. The 10-year prevalence of ESCC was determined on January 1, 2016 (all patients alive on this date, who were diagnosed with ESCC in the 10 preceding years). The number of persons alive on January 1, 2016, in the EA cohort and in the general Dutch population were used to calculate the 10-year prevalence of ESCC per 100,000 persons in both populations.

Histology and Immunohistochemistry

Biopsy specimens were processed at the Pathology Department according to standard procedures: formalin-fixed, paraffin-embedded, serially sectioned, and stained with H&E. Biopsy specimens were evaluated by an expert gastrointestinal pathologist for the presence of esophagitis, metaplasia, and dysplastic changes