Rates and predictors of progression to esophageal carcinoma in a large population-based Barrett's esophagus cohort CME

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Background and Aims: Rates of progression to esophageal adenocarcinoma in subjects with Barrett's esophagus (BE) are lower than previously estimated. Identification of predictors of progression will enable risk stratification of BE subjects, potentially making current surveillance programs more efficient. We aimed to assess the potential of demographic and lifestyle factors, obesity, and medications in predicting progression in BE.

Methods: BE subjects were identified from the General Practice Research Database using validated diagnostic codes. BE subjects developing esophageal cancer (EC) 12 months after their index BE diagnosis were defined as progressors. Time-to-event analysis was used to assess the overall risk of progression to EC. Cox proportional hazards models and time-varying marginal structural models were used to assess predictors of progression.

Results: Included in the analysis were 9660 BE patients. The mean age (SD) of the study subjects was 63 (13.5) years; 62.6% were men. One hundred three subjects (1.1%) progressed to EC. The mean (SD) follow-up since initial diagnosis was 4.8 (3.3) years. The incidence of EC was 2.23 per 1000 person-years of follow-up. Increasing age, male gender, and being overweight (body mass index, 25-29.9) were found to be independent predictors of progression. When time-varying models were used, proton pump inhibitor (PPI) and statin use were protective against progression.

Conclusions: In this large population-based cohort of patients with BE, increasing age, male gender, and being overweight predicted progression to EC, whereas PPI and statin use were protective against EC development. These factors may aid in developing a risk score to predict the risk of progression and chemopreventive strategies in patients with BE. (Gastrointest Endosc 2016;84:40-6.)

Barrett's esophagus (BE) is a premalignant condition in which the normal squamous epithelium lining the lower esophagus is replaced by metaplastic columnar epithelium.[1,2] BE is a strong risk factor for esophageal adenocarcinoma (EAC), a malignancy associated with a dismal 5-year survival rate of less than 20%.[3] The incidence of EAC in the Western world has increased by 6-fold over the past 4 decades.[4]

EAC is diagnosed at an earlier stage in BE patients enrolled in a surveillance program and has a better prognosis than EAC diagnosed outside surveillance.[5-7] Despite the evidence from retrospective studies that support endoscopic surveillance,[5,8] current practice patterns may not be effective in reducing EAC-related mortality.[9] Although patients with BE have a 30- to 40-times higher risk of EAC compared with the general population, the absolute risk of progression to

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; DM2, diabetes mellitus type 2; EAC, esophageal adenocarcinoma; EC, esophageal cancer; GPRD, General Practice Research Database; HR, hazard ratio; IM, intestinal metaplasia; NSAID, nonsteroidal anti-inflammatory drug; PDC, proportion of days covered; PPI, proton pump inhibitor.

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adenocarcinoma is low and is estimated to be .5% or less annually.[10] This could explain the lack of consensus on cost-effectiveness of current surveillance programs.[11,12]

Predictors of progression to EAC in patients with BE are currently not well understood. This has led to uniform recommendations on surveillance intervals for all patients with BE, with dysplasia grade being the primary risk stratification tool.[13] Identification of additional risk factors would enable the stratification of patients with BE into high-risk and low-risk groups, potentially enabling surveillance and/or therapy to be focused on high-risk groups, rendering this approach more effective and efficient.

Studies have suggested male sex,[11,14] increasing age,[11] central obesity,[15] hiatal hernia size,[16] BE segment length,[17] duration of BE,[18] presence of specialized intestinal metaplasia (IM),[14] and BE-associated dysplasia grade[14,17] as potential predictors of malignant transformation in BE. Additionally, medications such as aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs),[19-21] statins,[22-26] and proton pump inhibitors (PPIs)[27-31] have been reported to protect against progression.

Several of these studies were done on small single-center cohorts with contradictory results. Moreover, adjustment for confounding variables was not performed because of small sample sizes. Several studies assessing the impact of medications on BE progression also used only baseline data on drug exposure to assess the impact on progression, rendering the results biased given the lack of availability of data on consumption during the study interval. We therefore aimed to identify factors predictive of progression, particularly obesity, and protective against progression to esophageal carcinoma (EC) in a large population-based cohort of patients with BE from the General Practice Research Database (GPRD). GPRD is a claims-based database which provides additional data on drug exposure during patient follow-up.

METHODS

The study was approved by the University Hospitals Case Medical Center Institutional Review Board and the Independent Scientific Advisory Committee at the GPRD. GPRD is a large primary care database from the United Kingdom. It was established in 1987 and currently has data on over 8 million people. GPRD is representative of the United Kingdom population and is now part of the Clinical Practice Research Datalink. Previous studies on GPRD have shown excellent agreement between the diagnoses recorded in the database and that on paper-based records.[32] GPRD data have been used to perform successful epidemiologic studies investigating associations between risk factors and malignancies.[33] We have previously validated the diagnosis of BE from the GPRD database using specific diagnostic codes in a study assessing the association between BE and diabetes mellitus type 2 (DM2).[34]

All patients with a diagnosis of BE in the GPRD database between May 1991 and April 2010 were identified using GPRD specific diagnostic codes (see Supplementary Appendix 1, available online at www.giejournal.org). The first date of BE diagnosis in the GPRD database was defined as the index date. The collected data were analyzed to identify patients with BE who progressed to EC. EC was identified using GPRD-specific diagnostic codes (Supplementary Appendix 1, available online at www.giejournal.org). Because pathology reports were not available for review in the GPRD database, all esophageal cancers identified in patients with BE were assumed to be histologically adenocarcinoma given that the occurrence of squamous cell EC in patients with BE is rare. Additional sensitivity analyses were conducted varying the estimates of this proportion to 93% given previous studies.[35]

"Progressors" were defined as patients with BE who developed EC 12 months after the index date. Patients who developed EC within 12 months of the index date were excluded from the study because these could potentially be prevalent cancers. "Nonprogressors" were defined as BE subjects who did not have a diagnosis of EC in the entire GPRD follow-up.

Predictors of interest investigated in the current study were age, gender, smoking status, hiatal hernia (presence or absence), obesity, DM2, and medications (which were previously reported to be associated with BE progression). Other potential predictors of progression such as length of BE segment and BE-associated dysplasia grade were not included in the study because those variables were not available for review in the GPRD database.

Age was modeled as a continuous variable. History of smoking was abstracted as to whether the patient "ever smoked" (consisting of current and ex-smokers) or "never smoked." Information on presence of hiatal hernia was abstracted using specific diagnostic codes (Supplementary Appendix 1, available online at www.giejournal.org).

Obesity was defined using body mass index (BMI). Study subjects were classified into 3 categories: overweight (BMI 25-29.9), obese I (BMI 30-34.9), and obese II (>34.9). We analyzed the variation in weight of study subjects throughout the entire follow-up period in GPRD. A mean change of only .0122 kg/m^2 with a standard deviation of 2.54 was observed during a median follow-up duration of 4.04 years (interquartile range, 2.05-6.92 years). To enable maximal sample size and power, we used the weight over the entire follow-up period available in the GPRD. The most recent weight and height values were used to construct the BMI variable. When multiple weight values were available, the average of weights was used.

DM2 was defined as a diagnosis of DM2 at baseline (by standard diagnosis codes for DM2 in GPRD) and a medication code indicating either an oral hypoglycemic or insulin prescription being filled at least once before the index date. This definition was designed to increase