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Early adulthood body mass index, cumulative smoking, and esophageal adenocarcinoma survival

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ABSTRACT

Background: Smoking and obesity are esophageal adenocarcinoma (EAC) risk factors. However, the same risk factors may also affect biological aggressiveness and cancer outcomes. Our study evaluated the combined effects of early-adulthood obesity and cumulative smoking on the EAC survival.

Patients and methods: In two EAC cohorts, Toronto (TO; $N = 235$) and Boston (BO; $N = 329$), associations between early adulthood body mass index (EA-BMI), BMI at 1 year prior to diagnosis (BMI-1), and smoking with overall survival (OS) were assessed using Cox proportional hazard models, adjusted for relevant covariates.

Results: Both cohorts were predominantly Caucasian (89%), male (88%), ever-smokers (73%) with locally advanced/metastatic EAC (78%), and good ECOG performance status (90%); median packyears was 34; median EA-BMI, 24; median BMI-1, 25. No relationships with survival were found with BMI-1. For smoking and EA-BMI, TO, BO, and combined TO-BO analyses showed similar associations: smoking conferred worse OS in the combined TO-BO cohort, with adjusted hazard ratios (aHR) of 1.22 (95%CI: 1.15–1.43; $p < 0.0001$) for each 20 pack-year increase. Likewise, EA-BMI $\geq$25 was associated with worse OS (EA-BMI of 25– < 30, aHR = 1.84,95%CI: 1.37–2.48; and EA-BMI > 30, aHR = 2.78, 95%CI: 1.94–3.99). Risk of death was also increased in remotely underweight patients with EA-BMI < 18.5 (aHR = 2.03,95%CI: 1.27–3.24), when compared to normal-EA-BMI ($18 \leq$ EA-BMI < 25).

Conclusions: Two key modifiable behaviors, elevated BMI in early adulthood and heavy cumulative smoking history are independently associated with increased mortality risk in two North American cohorts of EAC patients.

1. Introduction

Esophageal cancer in the sixth most frequently diagnosed cancer of males with 326,600 estimated new cases worldwide [1]. The two main pathological types of esophageal cancer are squamous cell carcinoma (SCC), more common in the Asian countries, related to poor nutritional status, low intake of fruits and vegetables, drinking beverages at high temperatures, and increased tobacco and alcohol use [2], and esophageal adenocarcinoma (EAC), the predominant type in the Western world where smoking, obesity, chronic gastroesophageal reflux disease (GERD), and Barrett's esophagus are the major risk factors [3]. Overall, an increasingly overweight and obese population corresponds with increased incidence rates of EAC in Western countries [4], partially ascribed to increased GERD from increased intra-abdominal pressure in obese individuals [5]. However, studies have demonstrated higher EAC risk in obese individuals independent of GERD symptoms [6]. If carcinogenic pathways associated with some forms of EAC development are linked with obesity, then the clinical course of the resultant cancer may also be affected by these same pathways.

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Risk factors for EAC have been studied, in limited form, for their potential prognostic implications. In the case of EAC, relationships between GERD, GERD and genetics, and survival after a diagnosis of EAC were also recently evaluated [7]. Body Mass Index measured around the time of diagnosis (BMI) has also been linked with overall survival [8]. Focusing on obesity at a more distant past, such as several decades prior to diagnosis, may be more relevant where carcinogenic mechanisms are concerned. Previous studies of other cancer types have described associations between a remote history of obesity and survival [9].

In addition to obesity, smoking is a poor prognostic factor across many cancer sites [10,11]. For instance, never smokers who have lung cancer with distinct molecular features have improved survival [12,13]. Smoking is also associated with obesity, and can jointly increase all-cause mortality [14]. If smoking enhances the carcinogenic effects of obesity-related pathways, such effects may translate not only in increase cancer risk, but also into poorer outcomes after cancer diagnosis. Pack-years, which combines intensity with duration of cigarette smoking, is a summary measure of cumulative smoking exposure.

The focus of the present study was to evaluate the role of a remote history of obesity and cumulative smoking, two other important risk factors during the latent period of carcinogenesis, and their individual and combined impact on cancer survival. We hypothesize that obesity in early adulthood (EA), measured through patient-reported BMI, is associated with worse prognosis, independent of more recent BMI values and other clinical prognostic factors. We further hypothesize that cumulative smoking is associated with worse outcomes, and that the combined effects of obesity and heavy smoking adversely influence EAC survival.

2. Methods

2.1. Study design and patient population

Two independent EAC cohorts from Boston (BO) and Toronto (TO) were evaluated for the role of early adulthood (EA)-BMI and smoking on survival. Lifestyle and epidemiological factors were collected retrospectively, while survival and clinical prognostic factors were collected prospectively.

The study populations were serial, incident (<6 months since diagnosis) EAC patients recruited in prospective epidemiological studies at Massachusetts General Hospital/Dana Farber Cancer Institute (Boston, USA. 1999–2004; $N = 329$; participation, 82%) and at Princess Margaret Cancer Centre in (Toronto, Canada. 2006–2011; $N = 235$; participation rate, 77%). The institutional review boards of all hospitals approved the study.

2.2. Data collection, abstraction, and categorization

A self-administered questionnaire at study entry collected data retrospectively on cumulative cigarette smoking, adulthood height, and weight at different times: at age 18–25 years (Early adulthood, or EA), one year prior to diagnosis, and at diagnosis. Smoking questions included age of onset and quitting, number of and duration of successful quit attempts, average intensity of daily cigarette smoking (number of cigarettes/day), and duration of smoking (subtracting periods of quitting greater than 6 months). Questionnaire data also collected medical information/comorbidities, family history, and performance status at diagnosis.

We systematically collected clinical information and outcomes [15]. Abstracted data included date of histological diagnosis, histological subtype, treatments, follow-up and survival. Disease staging utilized the 6th edition of UICC/AJCC classification (Boston) and 7th edition (Toronto) as reference. Dates of disease progression were based on clinico-radiological evidence, and confirmed with treating physicians. The primary outcome variable was overall survival (OS); progression-free survival (PFS), where death or disease progression were considered events, served as a secondary endpoint.

Patients with gastric tumors, or who were Siewert 3 gastro-esophageal cancers were excluded from all analyses. Staging used the 7th edition of the UICC TNM staging manual [16]; because clinical staging was performed across time periods where endoscopic ultrasound and biopsy of suspicious lymph nodes were not always systematically performed, confirmation of clinical staging with treating oncologists was performed; staging is reported into three groups: early stage (Stage I-IIA; node-negative disease); locally advanced stage (Stage IIB-IVA; node-positive non-metastatic disease); and metastatic disease (Stage IVB).

2.3. Statistical methods

Descriptive analyses comparing TO and BO cohorts on major demographic and clinical variables utilized Fisher's exact tests, Pearson's Chi-squared tests, and Kruskal Wallis tests. Univariable and multivariable analyses compared the role of BMI, smoking, and potential confounding variables on overall (OS) and progression-free survival (PFS) using the method of Kaplan Meier, log-rank tests, and Cox proportional Hazard models. Hazard Ratios (HR's) and 95% confidence intervals were generated. To determine if BMI or cumulative smoking should be treated as linear variables, adjusted restricted cubic spline analyses were performed for both smoking and BMI to test the assumptions of linearity. For multivariable analysis using backwards regression, age (continuous variable), clinical stage, treatment with a cisplatin regimen (yes-no), family history (yes-no), and performance status (Eastern Cooperative Oncology Group 0–1 vs 2 vs 3) were considered. Because BMI at diagnosis and BMI one-year prior to diagnosis were highly correlated ($P < 0.0001$), only BMI one-year prior to diagnosis was included in the base model. The final base multivariate model included all variables significant at $P < 0.10$. To these base models, the effect of additional variables: (i) early adulthood BMI (EA-BMI), calculated from patient-reported adulthood height and average weight from 18 to 25 years old; (ii) cumulative smoking, calculated as pack-years (intensity, the average number of regular-sized packs (20 cigarettes) smoked per day, multiplied by duration, measured in years); and (iii) both variables together on survival were examined. Early adulthood and 1-year prior diagnosis BMI were firstly considered as continuous variables and clinically-defined categories, and finally using adjusted cubic splines if the variable failed assumptions of linearity. For cumulative smoking, smokers were divided into quartiles with each of 4 categories compared to never-smokers (<100 cigarettes lifetime) as the reference group. Analyses combining the two datasets are considered exploratory.

3. Results

3.1. Patient characteristics

In both cohorts (Table 1), patients were mainly Caucasian (89%) males (88%), with a median age of 64 years (range 21–91), ECOG PS 0–1 (90%), and locally advanced or metastatic EAC (78%). All patients previously underwent one or more treatment modalities including surgery, chemotherapy or chemoradiotherapy. Demographic information was similar between cohorts. In Table 2 (BMI data), the median EA-BMI was 24, while median BMI 1-year prior to diagnosis was 25. In both cohorts the majority (53%) presented a normal (between 18.5 and 25) EA-BMI, while over 40% had an EA-BMI ≥ 25. In comparison, the majority of patients were overweight or obese at 1 year prior to diagnosis.