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Statin Use Is Associated With Reduced Risk of Histologic Subtypes of Esophageal Cancer: A Nested Case-Control Analysis

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BACKGROUND & AIMS: Most patients with esophageal adenocarcinoma (EAC) or squamous cell cancer (ESCC) present with advanced, incurable disease. Statins have reported anti-carcinogenic effects and may be chemoprotective. We investigated the association between regular use of statins and the main histologic subtypes of esophageal malignancy (EAC, esophagogastric junctional adenocarcinoma, and ESCC) in the UK general population. **METHODS:** We identified all individuals in the UK General Practice Research Database diagnosed with esophageal cancer from 2000 through 2009. Patients were linked to the National Cancer Registry to confirm histologic subtypes. Each patient was matched with up to 4 controls for age, sex, and practice. We performed a nested case-control analysis using conditional logistic regression to estimate the risk of each subtype with regular statin use, adjusted for body mass index, smoking, alcohol intake, and concomitant use of medications. **RESULTS:** In total, 581 participants with EAC, 213 with esophagogastric junctional adenocarcinoma, and 332 with ESCC were matched to 2167, 783, and 1242 controls, respectively. Regular statin use was inversely associated with development of EAC (odds ratio = 0.58; 95% confidence interval: 0.39−0.87) (with significant dose and duration responses) and esophagogastric junctional adenocarcinoma (odds ratio = 0.29; 95% confidence interval: 0.09−0.92) (with high-dose use only). Statin use for 1−4 years was inversely associated with ESCC (odds ratio = 0.51; 95% confidence interval: 0.27−0.98). **CONCLUSIONS:** In a nested case-control analysis of a UK population-based cohort, statin use was inversely associated with histologic subtypes of esophageal cancer. Randomized controlled trials are warranted to determine whether statins have chemopreventive effects in high-risk groups.

Keywords: Esophagus; Tumor; Squamous Cell Carcinoma; HMG-CoA.

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With 482,000 incident cases and 400,000 annual deaths worldwide, esophageal cancer (EC) is an aggressive malignancy associated with a poor prognosis.[1] Of the 2 main histologic subtypes, the incidence of esophageal adenocarcinoma (EAC) has risen dramatically in the last 4 decades in Western countries, and that of esophageal squamous cell cancer (ESCC) has remained stable or declined.[2,3] Most patients with EC present with advanced disease and are often only amenable to palliative therapies. Of the minority suitable for curative treatment, 5-year survival rates are 47% at best.[4] Accordingly, potential preventive public health measures need to be considered.

There is emerging evidence that statins, currently used in the primary and secondary prevention of cardiovascular disease, can have preventive effects against development of EC. Statins are potentially attractive chemoprotective agents, given their established and modest side-effect profile and low cost.[5] Experimental studies have demonstrated statins promote apoptosis and inhibit proliferation in EAC and ESCC cell lines.[6–9] In addition, observational investigations have examined the risk of EC with prior statin use,[10–20] and several demonstrated significant inverse associations.[13,14,18–20] However, studies based in general population cohorts considered EC as a single disease and did not differentiate risk estimates for the 2 main histologic types. It is important to do so, as these cancers are separate disease entities, associated with differing natural histories and risk factor profiles.[21] The main risk factors for EAC include Caucasian race, male sex, increased body mass index (BMI), gastroesophageal reflux disease (GERD), and smoking; and nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin are both inversely associated.[22–25] In contrast, the strongest risk factors for ESCC include smoking and alcohol, and the disease is associated with reduced BMI.[24,26] Therefore, the aim of this study was to investigate for the first time if there are inverse associations between prior statin use and the

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GERD, gastroesophageal reflux disease; GPRD, General Practice Research Database; IQR, interquartile range; NCR, National Cancer Registry; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor.**

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development of EAC, esophagogastric junctional adenocarcinoma (EGJA), and ESCC at a population level.

Materials and Methods

Study Population and Data Source

This study was conducted using the General Practice Research Database (GPRD), the world's largest source of longitudinal medical data in primary care.[27] At the time of data extraction, 4 million patients were registered with 488 general practices throughout the United Kingdom. For each participant, information was prospectively recorded by their general practitioner on prescription medications (including the drug name, formulation, and dose), symptoms, and incident diagnoses. Data recorded on diagnostic codes used to identify diseases, including EC, and drug prescriptions in the GPRD have been shown to be accurate in independent studies.[28,29] All information received by the investigators was anonymous. Ethical approval to obtain histology in patients diagnosed with EC was granted by the Research Ethics Committee, East of England (reference 10/H0305/65).

Case-Control Definitions

After initial registration in the GPRD, the men and women who developed incident esophageal or esophagogastric junctional cancers, diagnosed between January 1, 2000 and December 31, 2009, were identified using Read codes. The date of diagnosis of EC first recorded in the GPRD for each patient was the index date. Each patient was matched with up to 4 controls without a history of any cancer (malignant, benign, or of an uncertain nature), according to sex, year of birth ($\pm$3 years), and general practice (a proxy for socioeconomic status). The same index date for each patient was assigned to each of the matched controls, who had to be alive at this time, to ensure similar follow-up times between patients and controls. Included participants were required to be registered with the GPRD for at least 1 year before the index date. Patients identified were linked to the National Cancer Registry (NCR) to determine histology and confirm the site using ICD-10 codes, to identify those with EAC, EGJA, or ESCC. EGJA tumors could not be further classified according to the Siewert classification, as these data were unavailable in either the GPRD or NCR. At the time of data extraction (November 2011), approximately half of GPRD practices were linked to the NCR.

Statin Prescription and Categorization

A "regular statin" prescription was defined as a prescription of any statin for a minimum of 10 months in the year preceding the index date. Cases and controls prescribed a statin for any shorter duration were excluded. This definition served to minimize reverse causation bias, whereby failing to collect a statin prescription could be associated with new symptom onset, such as dysphagia. The statin name, dosage (mg/day), and total duration of statin prescriptions preceding the index date were extracted.

Covariates

Relevant covariates implicated in the etiology of EAC, EGJA, or ESCC were extracted for time periods preceding the index date, including smoking status (ever or never smoked); alcohol intake ($\geq$0 to $<$7, $\geq$7 to $<$14, $\geq$14 to $<$21, and $\geq$21 units/week); earliest recorded BMI ($<$25 [normal], $\geq$25 to $<$30 [overweight], $\geq$30 [obese]) and any prescription of medications (aspirin, nonaspirin NSAIDs, and proton pump inhibitors [PPIs]) in the year before the index date. GERD was not included as a covariate in the primary analyses of EAC and EGJA, as it was under-reported in the GPRD.[30]

Statistical Analysis

To account for missing data (including BMI, smoking status, and dose of statin prescriptions) multiple imputation was conducted separately for statin users, the histologic subtypes and their matched controls. Ten imputed datasets were created using iterative chain equations with all covariates and outcomes included in the model. The results presented are those averaged over the imputed datasets. Baseline characteristics, excluding matching demographics (age and sex), were compared between patients (EAC, EGJA, and ESCC) and their matched controls. Nested case-control analyses were performed, using conditional logistic regression, to investigate the association between regular statin use and risk of each of the subtypes. Participants not prescribed statins in the year preceding the index date were used as the reference group to calculate odds ratios (ORs) with 95% confidence intervals (95% CI). Age, sex, and follow-up were controlled for using the matching procedure. In multivariate analyses, adjustment for covariates differed for each histologic subtype, to reflect the individual risk factor profiles. Analyses of EAC and EGJA were adjusted for smoking, BMI, aspirin, NSAIDs, and PPIs. Analyses of ESCC were adjusted for smoking, alcohol, BMI, aspirin, and NSAIDs only. The effect of statin lipophilicity (hydrophilic and lipophilic groups) on risk of the subtypes was examined. Dose and duration responses were examined between statin use and risk of EAC, EGJA, and ESCC for users who met the "regular statin" exposure definition. Participants were assigned to either "high-" (at least equivalent to simvastatin 40 mg daily) or "low"-dose categories according to the mean monthly dosage of statin prescription in the year preceding the index date. The duration of statin prescriptions was classified as no use, $\geq$1 to $<$4 years, $\geq$4 to $<$6 years, or $\geq$6 years. For each year of statin use included in duration response calculations, participants were required to have filled a prescription for at least 10 months of that year. Participants who changed statins during follow-up (classified as "mixed" use) were included in these analyses. A test for trend was applied across dosage and duration categories. The effect of statin prescriptions with concomitant medication use (either aspirin, NSAIDs, or PPIs) on risk of the histologic subtypes was estimated using linear contrasts from the final adjusted model. A test for an interaction between regular statin and concomitant medication use was carried out in the final adjusted model. We conducted a sensitivity analysis to ensure our findings were robust by restricting all analyses to participants with at least 5 years' follow-up and excluding "former statin users": those users who did not use statins in the year before diagnosis, but who received at least 1 prescription before this. All analyses were performed with STATA software, version 11 (StataCorp LP, College Station, TX).