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CLINICAL—ALIMENTARY TRACT

Association Between Statin Use After Diagnosis of Esophageal Cancer and Survival: A Population-Based Cohort Study

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This article has an accompanying continuing medical education activity on page e16. Learning Objective: Upon completion of this exam, successful learners will be able to define the association between statin use and survival in patients with esophageal carcinoma and identify relevant sources of bias in such pharmaco-epidemiological studies.

BACKGROUND & AIMS: Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), commonly prescribed in the primary and secondary prevention of cardiovascular disease, promote apoptosis and limit proliferation of esophageal cancer cell lines. We investigated whether statin use after a diagnosis of esophageal cancer is associated with reduced esophageal cancer–specific and all-cause mortality. **METHODS:** We identified a cohort of 4445 men and women in the United Kingdom diagnosed with esophageal cancer from January 2000 through November 2009 using the General Practice Research Database. The National Cancer Registry and Office of National Statistics datasets established the histologic subtype and cancer-specific mortality, respectively. Cox proportional hazard regression analysis with time-dependent exposures estimated the association between statin use after diagnosis and esophageal cancer–specific and all-cause mortality. **RESULTS:** The median survival time of the entire cohort was 9.2 months (interquartile range [IQR], 3.7–23.2 mo). Among subjects who used statins after a diagnosis of esophageal cancer, the median survival time was 14.9 months (IQR, 7.1–52.3 mo) compared with 8.1 months for nonusers (IQR, 3.3–20 mo). In the entire cohort, statin use after diagnosis was associated with a decreased risk of esophageal cancer–specific mortality (adjusted hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.44–0.86) and all-cause mortality (HR, 0.67; 95% CI, 0.58–0.77). In patients with esophageal adenocarcinoma, statin use after diagnosis was associated with a decreased risk of esophageal cancer–specific mortality (HR, 0.61; 95% CI 0.38–0.96) and all-cause mortality (HR, 0.63; 95% 0.43–0.92). This effect was not observed in patients with esophageal squamous cell carcinoma. There was no evidence for effect modification of these associations with statin use before the cancer diagnosis. **CONCLUSIONS:** In a large population-based cohort, statin use after a diagnosis of esophageal adenocarcinoma, but not esophageal squamous cell carcinoma, was associated with reduced esophageal cancer–specific and all-cause mortality.

Keywords: HMG-CoA; Pleiotropy; Esophagus; CPRD.

Esophageal cancer (EC) is the fifth and eighth most common cause of cancer-related death in men and women, respectively, worldwide.[1] Of the 2 main histologic subtypes, esophageal squamous cell carcinoma (ESCC) is globally predominant, whereas esophageal adenocarcinoma (EAC), the incidence of which has increased rapidly since the 1970s, is the most common form in the West.[1,2] Most patients with EC present with advanced disease and often are amenable only to palliative management. Consequently, the overall 5-year survival rate is approximately only 15%.[3]

Novel clinical interventions to improve the prognosis in patients with EC are required. There has been considerable research focus on the potential anticancer effects of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), which commonly are prescribed for the primary and secondary prevention of cardiovascular disease.[4] A body of basic research has shown that statins promote apoptosis and limit proliferation in EAC and ESCC cell lines.[5–8] Epidemiologic investigations have shown that use of statins after diagnosis is associated with a reduced risk of cancer-specific mortality in a number of malignancies, including prostate, breast, and colorectal carcinomas.[9–11] Furthermore, at a population level, their use is associated inversely with the development of the histologic subtypes of EC.[12] A population-based cohort study in Denmark showed that statin use before a diagnosis of EC was associated with a 19% decrease in cancer-specific mortality.[13] Whether statin use after a diagnosis of EC, a more relevant time period for clinical intervention, improves survival is unknown. Furthermore, whether or not statins exert differential effects on survival for the 2 main histologic subtypes, EAC and ESCC, is unknown. Therefore, the primary aim of this epidemiologic study was to determine whether statin use after a diagnosis

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; DDD, defined-daily dose; EAC, esophageal adenocarcinoma; EC, esophageal cancer; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GP, general practitioner; GPRD, General Practice Research Database; HR, hazard ratio; IQR, interquartile range; NCR, National Cancer Registry; ONS, Office of National Statistics.**

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of EC, including the histologic subtypes, is associated with reduced EC-specific and all-cause mortality. Secondary aims were as follows: to determine whether prediagnostic statin use is an effect modifier on the association between postdiagnostic statin use and survival, to determine whether a dose-response relationship exists, and to determine whether differential effects exist according to statin type.

Methods

Data Sources

This study was conducted using 3 databases: the United Kingdom General Practice Research Database (GPRD), the UK National Cancer Registry (NCR), and the Office of National Statistics (ONS) database. The GPRD is the world's largest electronic database of prospective demographic, lifestyle, and medical data in a primary care setting.[14] At the time of data extraction, 4 million patients were registered at 488 general practices, covering 6% of the UK population. The age and sex distributions of participants in the GPRD are comparable with the National Population Census, and the distribution of participating practices is representative of the UK population.[15] General practitioners (GPs) prospectively record incident diagnoses and medical procedures using a modified Read/Oxford Medical Information System classification system. Filled drug prescriptions issued by GPs are recorded automatically and coded using the UK Prescription Pricing Authority Dictionary. Data recorded on diagnostic codes to identify diseases, including EC, and drug prescriptions in the GPRD have been shown to be valid in independent studies.[16–18] Linkage between databases used a deterministic algorithm based on the patient National Health Service number, postcode, sex, and date of birth. The NCR contains information on tumor site (coded using the International Classification of Diseases, 10th revision), histology, cancer stage, and treatment modalities. Approximately half of GPRD practices were linked to the NCR at the time of data extraction. For patients with data linked to the NCR, ONS data were available to determine the cause of death. The GPRD group has obtained blanket approval from a multicenter ethics committee for observational research conducted within the database.

Study Cohort

Participants with incident esophageal or esophagogastric junction cancers, diagnosed between January 1, 2000, and November 30, 2009, and followed up until November 1, 2011, were identified from the GPRD. Patients were included with no prior history of cancer. All patients were required to be diagnosed at least 1 year after the contributing practice had received its "up-to-standard" date: the time from which the practice was considered to generate continuous high-quality data fit for research. The histologic subtype for a subset of patients was determined through linkage to the NCR. International Classification of Diseases codes were used to confirm esophageal (C15) and esophagogastric junctional (C16) cancers, and specific morphology codes were used to obtain the histologic subtypes: EAC, esophagogastric junctional adenocarcinoma (EGJA), and ESCC. The follow-up period was from the date of diagnosis until death, or until the patient was transferred out of the GPRD or the date of last data entry, whichever came first.

Statin Use

Exposure to the following statins currently in clinical use in the United Kingdom were extracted: simvastatin, atorvastatin, pravastatin, rosuvastatin, and fluvastatin. Postdiagnostic statin use was defined as a prescription for any of these statins recorded in the GPRD at any time after the date of diagnosis. Postdiagnostic statin use was included as a time-dependent covariate in the models to avoid immortal-time bias: whereby a span of cohort follow-up evaluation during which death could not occur (ie, between the diagnosis and the first statin prescription) was introduced inappropriately owing to the definition of the exposure of interest.[19] Patients were considered unexposed until the first postdiagnosis prescription, from which point they were considered continuously exposed until the end of follow-up evaluation. Deeming patients continuously exposed sought to minimize reverse-causation bias, whereby, ultimately, discontinuation could reflect a poor prognosis and therefore death may have been more likely to be classified inappropriately during an "unexposed" period.[20] Exposure to the individual statins listed earlier also was considered in survival analyses. To investigate the possibility of healthy survivor bias in the statin users after diagnosis, the intervals between diagnosis and statin initiation for all statin users after diagnosis were presented using a Kaplan–Meier plot (Supplementary Figure 1).

Prediagnosis statin use was also an exposure of interest. It was defined as a prescription of any of the statins recorded earlier in the GPRD for a minimum of 2 months between 6 and 18 months before diagnosis. This definition sought to minimize reverse-causation bias, whereby symptomatic EC (and, hence, likely more advanced disease) could influence prescribing practice or medication use. Prediagnosis statin use was determined for the following 3 reasons: it was entered as a covariate in models of postdiagnostic statin use to determine whether it modified the effect of postdiagnosis statin use on survival; in sensitivity analyses the association between prediagnosis statin use on survival was determined to consider an exposure to statin use, alternative to postdiagnosis statin use, in which the potential effect of reverse-causation bias would be expected to be minimal; and, finally, it was used to determine categories for dose-response analyses. Statin users were categorized as low (equivalent to $\leq$20 mg simvastatin) or high (equivalent to $>$20 mg simvastatin) dose users based on the mean daily dose for statin prescriptions collected between 6 and 18 months before diagnosis. Cumulative statin dose was determined using categories of cumulative defined-daily dose (DDD). The DDD, a standardized measure of drug exposure as defined by the World Health Organization, is the assumed average maintenance dose per day for a drug used for its main indication in adults.[21] For example, 1 DDD is equivalent to a single dose of 30 mg simvastatin or 20 mg atorvastatin. The median cumulative DDD collected between 6 and 18 months before diagnosis in the whole cohort was the threshold for cumulative dose categories. Postdiagnostic mean or cumulative dose-response analyses were not examined a priori because the dose categories would be expected to be a function of survival time. In a