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Original research article

Statin use after esophageal cancer diagnosis and survival: A population based cohort study

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ABSTRACT

Background: A recent epidemiological study of esophageal cancer patients concluded statin use post-diagnosis was associated with large (38%) and significant reductions in cancer-specific mortality. We investigated statin use and cancer-specific mortality in a large population-based cohort of esophageal cancer patients.

Methods: Newly diagnosed [2009–2012] esophageal cancer patients were identified from the Scottish Cancer Registry and linked with the Prescribing Information System and Scotland Death Records (to January 2015). Time-dependent Cox regression models were used to calculate hazard ratios (HR) for cancer-specific mortality and 95% confidence intervals (CIs) by post-diagnostic statin use (using a 6 month lag to reduce reverse causation) and to adjust these HRs for potential confounders.

Results: 1921 esophageal cancer patients were included in the main analysis, of whom 651 (34%) used statins after diagnosis. There was little evidence of a reduction in esophageal cancer-specific mortality in statin users compared with non-users after diagnosis (adjusted HR = 0.93, 95% CI, 0.81, 1.07) and no dose response associations were seen. However, statin users compared with non-users in the year before diagnosis had a weak reduction in esophageal cancer-specific mortality (adjusted HR = 0.88, 95% CI, 0.79, 0.99).

Conclusions: In this large population-based esophageal cancer cohort, there was little evidence of a reduction in esophageal cancer-specific mortality with statin use after diagnosis.

1. Introduction

In the UK each year over 8000 people are diagnosed with esophageal cancer [1]. The prognosis is poor (5 year survival rates are 8%) [2], and so research into new treatment strategies are warranted. Although mainly used to treat hypercholesterolaemia [3], there is increasing evidence from both cell lines and animal models that statins have antitumor properties [4]. Preclinical studies have shown, by inhibiting a rate-limiting enzyme (3-hydroxy-3-methylglutaryl Coenzyme A reductase) in the mevalonate pathway, statins induce apoptosis and inhibit angiogenesis [5,6]. Of specific relevance to esophageal cancer, Ogunwobi et al. showed that statins inhibit proliferation and induce apoptosis in esophageal adenocarcinoma cell lines [7]. In humans, recent epidemiological studies have shown reductions in esophageal cancer risk in statin users [8].

Despite these promising findings, there has been little research into the effect of statin use after diagnosis on survival from esophageal cancer. The only previous epidemiological study to investigate statin use after diagnosis in esophageal cancer patients concluded that statins were associated with large and significant reductions in cancer-specific and all-cause mortality [9].

The association between statin use and esophageal cancer-specific mortality is of importance because it will inform the decision to conduct clinical trials of statins as adjuvant cancer therapy in esophageal cancer patients. Therefore, to clarify this association we investigated whether statin use after cancer diagnosis was associated with reduced esophageal cancer-specific and all-cause mortality in a population-based cohort of esophageal cancer patients.

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2. Materials and methods

2.1. Data source

The study utilised linkages between national datasets from Scotland including the Scottish Cancer Registry (SMR06), the Prescribing Information System, the General/Acute Inpatient and Day Case dataset (SMR01), the Outpatient Attendance dataset (SMR00) and the National Records of Scotland Death Records. The Scottish Cancer Registry captures information on all cancers occurring in Scotland including date and site of primary cancer diagnosis, stage, grade and treatment data. The Prescribing Information System (available from January 2009 to January 2015) holds all medicines dispensed in the community in Scotland. The General/Acute Inpatient and Day Case dataset (available from January 1999 to January 2015) contains information on hospital diagnoses and operations and the Outpatient Attendance dataset (available from January 1999 to January 2015) contains diagnosis and procedures from new and follow up appointments at outpatient clinics. The National Records of Scotland Death Records contain date and cause of death up to January 2015. Linkages between data sources were conducted using the Community Health Index number (a unique number to individuals in Scotland).

2.2. Study population

A cohort of newly diagnosed esophageal cancer patients was identified on the basis of a Scottish Cancer Registry recorded primary diagnosis of esophageal cancer (ICD code C15) between Jan 2009 and Dec 2012. Cohort members with previous Scottish Cancer Registry cancer diagnosis (after January 1999), apart from in situ neoplasms and non-melanoma skin cancers, were excluded.

Deaths were identified from National Records of Scotland with coverage up to 1st January 2015 (or from Scottish Cancer Registry death records) with esophageal cancer-specific deaths defined as those with underlying cause of death esophageal cancer (C15), gastric cancer (C16), or malignant neoplasm of other and ill-defined digestive organs (C26). Patients who died in the first 6 months after their esophageal cancer diagnosis were excluded because it seemed unlikely that post diagnostic medication use could influence such deaths, therefore the follow-up date started 6 months after diagnosis. The patients were followed from 6 months after date of esophageal cancer diagnosis to death, the date they left Scotland or 1st January 2015.

2.3. Study design

2.3.1. Exposure data

Statins dispensed in the community (identified from the Prescribing Information System) consisted of all medications in the Statins section of the British National Formulary (Section 2.12) [10]. A quantity of 28 tablets was assumed for the less than 0.1% of prescriptions where quantity was assumed incorrect. Daily defined doses (DDD) were calculated on the basis of quantity and strength (as defined by the World Health Organisation [11]). Statin use was investigated as a time varying covariate [12]. Patients were initially

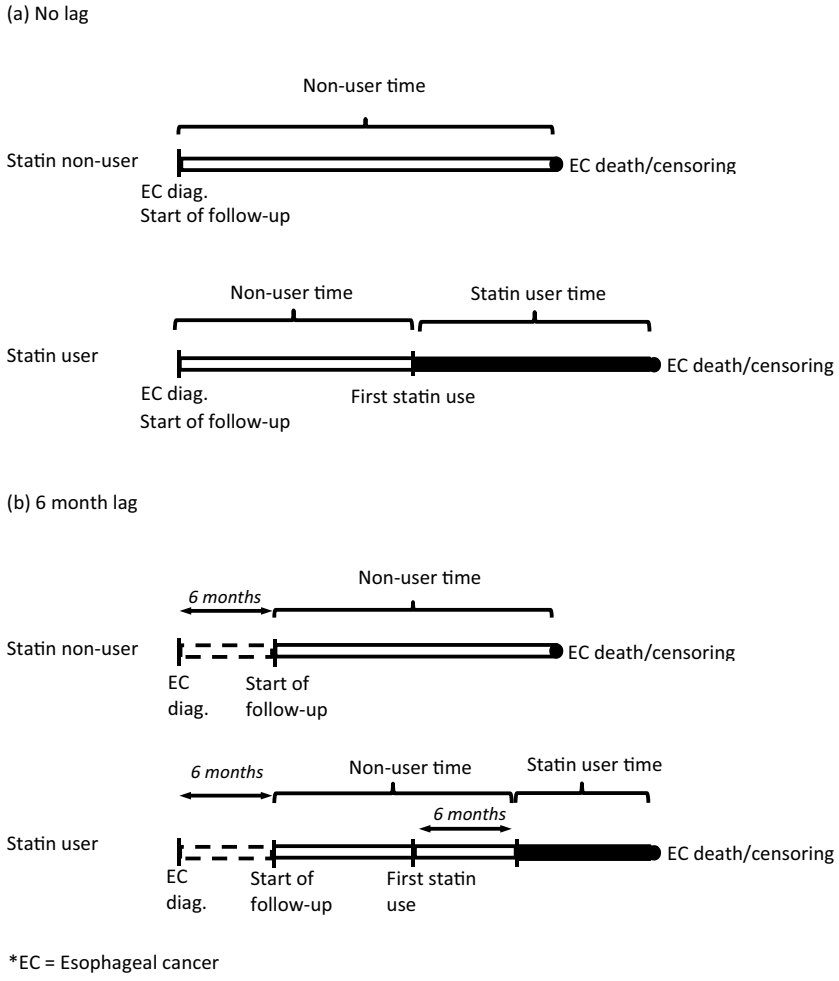

Fig. 1. Diagram showing time accumulated in analysis without a lag (a) and in with a 6 month lag (main analysis) (b).