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Statin use and survival in elderly patients with endometrial cancer

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HIGHLIGHTS

- Statins demonstrate anti-carcinogenic properties in experimental studies.
- We analyzed data 2987 elderly patients with primary endometrial cancer in the U.S.
- Statin use was not associated with survival after accounting for biases.

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ABSTRACT

Background. Endometrial cancer is the most common gynecologic cancer in the United States. Statins have demonstrated anti-cancer effects in other tumor types, such as the breast and lung cancers.

Aim. The objective of our study was to determine the association between statin use and endometrial cancer survival in a nationally-representative elderly population with endometrial cancer in the U.S.

Methods. We employed the linked Surveillance, Epidemiology and End Results registries and Medicare claims files to collect data from 2987 patients who were diagnosed with endometrial cancer between 2007 and 2009 and who received a hysterectomy. The association between statin use and overall survival was examined using Cox regression models adjusting for follow-up time, age, race, neighborhood income, cancer stage, tumor grade, hysterectomy type, chemotherapy, radiation, impaired glucose tolerance, obesity, dyslipidemia and diabetes.

Results. The mortality rate was lower in statin users compared to non-users for both type I (4.6 *vs.* 5.7 deaths/100 person-years, p = 0.08) and type II (11.2 *vs.* 16.5 deaths/100 person-years, p = 0.01) cancer types. However, after adjustment for the time from surgery to statin use and confounding, statin use after a hysterectomy was not significantly associated with a reduction in hazard of death for both type I (hazard ratio [HR] 0.92, 95%CI 0.70,1.2) and type II (HR = 0.92, 95%CI 0.65, 1.29, p = 0.62) endometrial cancer patients.

Conclusion. Accounting for all confounders and biases considered, statin use on or after a hysterectomy was not associated with survival in those with type I or type II disease.

Introduction

Statins (3-hydroxy-3-methylglutaryl-CoA, HMG-CoA, reductase inhibitors) are widely prescribed to treat hypercholesterolemia and to prevent cardiovascular disease [1]. HMG-CoA reductase is an enzyme that controls biosynthesis in the mevalonate pathway, a metabolic pathway that produces endogenous cholesterols in addition to prenyl carbon chains that are key post-translational modifiers of membrane-associating proteins. Statins are thought to mitigate cancer cell growth through inhibition of the mevalonate pathway, by preventing the prenylation of *Ras* and *Rho*, essential proteins involved in cancer cell proliferation and migration [2].

In vitro and animal model studies have demonstrated that statin has anti-carcinogenic effects in several cancer cell lines, including renal, breast, macroglobulinemia, and lymphoma cells [3–7]. Most recently, Schointuch et al. demonstrated that simvastatin inhibits cell growth, adhesion, and invasion, and induces apoptosis in endometrial cancer cell lines [8].

To date only one study has examined the association between statin use and endometrial cancer survival. The Cancer in The Ovary and Uterus Study (CITOUS) showed evidence of improved survival rates in endometrial cancer patients who used statins after the cancer diagnosis (age-adjusted HR = 0.45, 0.23–0.87) [9], suggesting a potential therapeutic effect of statins. This effect has not been demonstrated in a

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population-based study with attention to statin type and histologic subtypes.

The objective of our study was to determine the association between statin use and endometrial cancer survival in a nationally-represented elderly population in the U.S. We employed the linked Surveillance, Epidemiology and End Results registries and Medicare claims files to investigate our aim. A particular advantage of these data is the provision of detailed information on histology, comorbidities, as well as the timing and dosage of specific types of statin prescriptions filled by the patients.

Methods

Study population

We conducted a retrospective cohort study of endometrial cancer patients represented in the SEER-Medicare database. Since 1973, the SEER program has routinely collected population-based data from participating tumor registries in the United States. Currently, the program includes 18 registries and covers approximately 28% of the U.S. population. Data collected by the registries include patient demographics and pathologic characteristics of the tumor [10]. Collaboration between the National Cancer Institute, SEER registries, and the Centers of Medicare and Medicaid Services (CMS) began in 1991 to link SEER to Medicare claims data on 97% of U.S. elderly aged 65 year or older who are enrolled in this federal health insurance program. This combination of population-based cancer registries data and claims-based data has facilitated epidemiologic and health services research related to cancer screening, treatment, and outcomes [11].

As of 2014, SEER program data were available for cancers diagnosed through 2009 and Medicare claims were available through 2010 [12]. Medicare Part D was included in the SEER-Medicare linkage beginning in 2007. Therefore, we analyzed data from patients with primary endometrial cancer diagnosed from 2007 to 2009 in whom we assessed exposure to statin until the end of 2010. Patients were required to have at least 12 months of continuous enrollment in Medicare Parts A and B prior to cancer diagnosis until end of follow-up and 3 months of continuous enrollment in Part D prior to cancer diagnosis until death or end of follow-up. This allowed for identification of comorbid conditions present in Medicare files and of statin use at the time of the hysterectomy. The analysis was limited to patients who received a hysterectomy, the standard treatment for the majority of endometrial cancer cases, in the 6 months following cancer diagnosis. Furthermore, we excluded patients who died within 90 days of hysterectomy to reduce bias resulting from post-surgical complications. Lastly, patients without histological-confirmation, who were diagnosed at autopsy or had an unknown date of diagnosis, and patients without known histologic type were excluded from the analyses. A total of 2987 patients made up the final analytic population for study (Fig. 1).

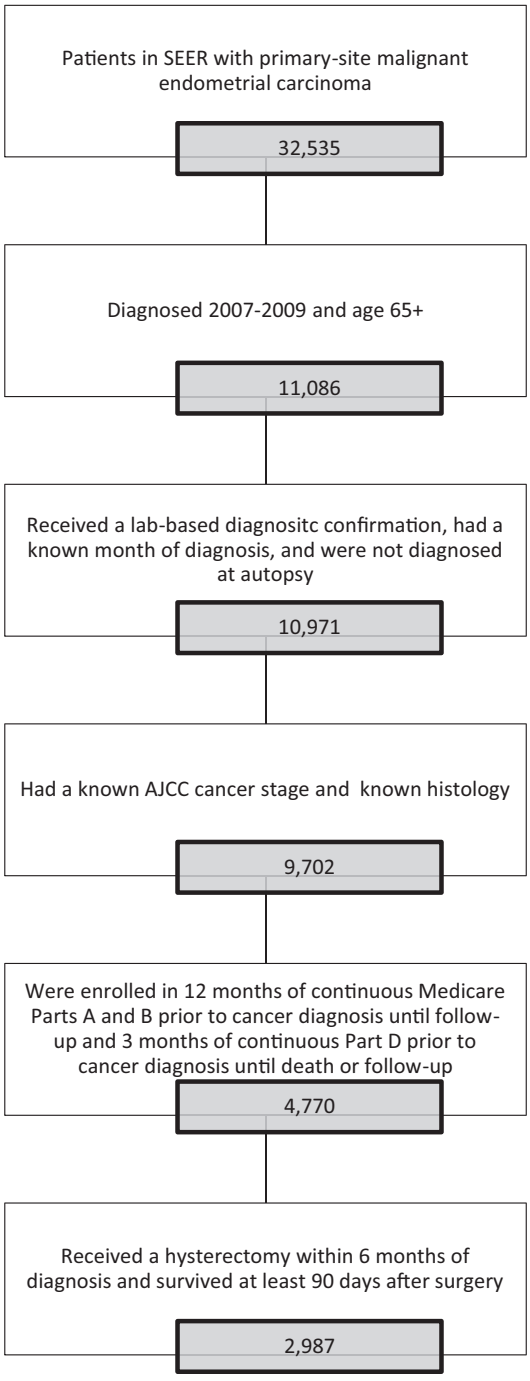

Fig. 1. Flowchart of patients who met inclusion criteria for the study population.

Statin exposure

Data on statin prescription fills were extracted from the Medicare Part D prescription event data. Detailed prescription information allowed us to determine the date of filling, dose, number of days of supply, and type of statin. Ever exposure to statins after cancer diagnosis was defined as any use on or after the hysterectomy until death or end of follow-up. Statin prescription strength was categorized into low, moderate, and high dose based on the classification set by the American Heart Association and the American College of Cardiologists [13]. We also explored potential heterogeneity in effect on endometrial cancer survival by lipid affinity (lipophilic statins: atorvastatin, simvastatin, lovastatin and fluvastatin *versus* hydrophilic statins: pravastatin and rosuvastatin) and potency (high potency statins: atorvastatin, rosuvastatin and simvastatin *versus* moderate potency statins: lovastatin, fluvastatin, and pravastatin).

Outcome

The primary outcome of this study was overall survival, measured in months from hysterectomy date until death or December 31st, 2010, which was the last date of available Medicare claims data.

Demographic factors, including age, race, neighborhood income, and clinical factors, including tumor grade and stage were obtained from SEER files. Histologic type (type 1 endometrioid cancers, type II high grade endometrial and serous, clear-cell cancer types) was determined using ICD-O-3 codes present in the SEER data (Appendix A). Type of hysterectomy (vaginal, abdominal, or laparoscopic) was determined using ICD9 procedure codes from Medicare inpatient files (Appendix A). We identified comorbid conditions including diabetes, impaired glucose tolerance (IGT), obesity, dyslipidemia, and