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Statin use and survival following glioblastoma multiforme

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ABSTRACT

Aim: While some studies indicate a potential chemopreventive effect of statin use on the risk of glioma, the effect of statins on the prognosis of brain tumours has not yet been examined. We thus conducted a cohort study evaluating the influence of statin use on survival in patients with glioblastoma multiforme (GBM).

Methods: We identified 1562 patients diagnosed with GBM during 2000–2009 from the Danish Cancer Registry and linked this cohort to Danish nationwide demographic and health registries. Within the GBM cohort, each patient recorded as using statins prior to diagnosis (defined as ≥2 redeemed prescriptions) was matched to two statin non-users (<2 redeemed prescriptions) by propensity scores based on age, gender, year of diagnosis, comorbidity, and use of selected drugs. Cox proportional hazard models were used to compute hazard ratios (HRs) and 95% confidence intervals (CI) for all-cause death associated with prediagnostic statin use.

Results: A total of 339 GBM patients were included in the analyses. Of these, 325 died during median follow-up of 6.9 months (interquartile range: 3.8–13.4 months). Prediagnostic statin use was associated with a reduced HR of death (0.79; 95% CI: 0.63–1.00). The HRs decreased with increasing duration or intensity of prediagnostic statin use [long-term (≥5 years) statin use: HR 0.75 (95% CI: 0.47–1.20); high-intensity statin use: HR 0.66 (95% CI: 0.44–0.98)]. Additional adjustment for oncotherapeutic modalities yielded similar results (overall HR 0.80, 95% CI: 0.63–1.01).

Conclusion: Long-term prediagnostic statin use may improve survival following GBM.

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1. Introduction

Glioblastoma multiforme (GBM) is the most common malignant brain tumour, comprising 18.5% of all brain tumours and 54% of all gliomas in adults in the United States population [1]. GBM holds a poor prognosis, with 5-year survival of only 3.3% [2]. In Denmark, surgical resection of GBM is recommended, if feasible, followed by concomitant radiation therapy/chemotherapy and adjuvant chemotherapy with temozolomide [3,4]. Other factors influencing survival include age and functional status (Karnofsky Performance Status score), extent of initial tumour resection, and genetic alterations, *e.g.*, MGMT promoter methylation and IDH1/2 mutation [5–7].

Numerous studies have examined the potential chemopreventive effects of statins on cancer incidence [8]. Recent Danish studies found that statin use reduced cancer-related mortality and recurrence of breast cancer [9,10]. While long-term statin use has been associated with reduced risk of glioma [11,12], the effect of statin use on progression of gliomas, including GBM, has not yet been examined. We therefore undertook the present study to investigate whether prediagnostic statin use influences survival in patients with GBM.

2. Methods

We conducted an inception cohort study based on information from the following population-based Danish registries: the Danish

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Cancer Registry (DCR) [13], the Danish Civil Registration System [14], the Danish National Prescription Registry [15], the Danish National Registry of Patients (DNRP) [16], and demographic registries within Statistics Denmark. The registry codes used to identify patients with GBM and their characteristics, including drug use, medical history, and treatment, are provided in Appendix A.

Unambiguous linkage between the registries is made possible by the civil registration number assigned since 1968 to all Danish residents at birth or upon immigration to the country [14]. Danish citizens have uniform access to tax-supported health care provided by the Danish National Health Service.

2.1. Eligibility criteria, follow up, and outcome

Eligible subjects were all Danish residents with a first-time diagnosis of GBM during the period 1 January 2000–31 December 2009. Diagnoses of GBM were ascertained from ICD-10 and ICD-O-3 morphology codes in the DCR (see Appendix A) [13]. The diagnosis date registered in the DCR was defined as the *index date*.

To be included in the study, potential subjects could not have a cancer history (including any central nervous system tumours but excluding non-melanoma skin cancers) prior to the index date. We required furthermore that subjects be aged between 20 and 85 years on the index date, with continuous residence in Denmark for 10 years prior to the index date.

Subjects were followed up from the index date until death, emigration, or end of study (31 December 2011), whichever came first. All-cause death was the study outcome. Data on follow up and outcome were retrieved from the Civil Registration System, which keeps continuous records of addresses, migration, and vital status of all Danish citizens.

2.2. Assessment of statin exposure

Since 1995, data on all prescriptions redeemed at community pharmacies in Denmark have been recorded in the Danish National Prescription Registry [15]. Records in the Prescription Registry include civil registration number, ATC codes [17], date of dispensing, and type and quantity of drug dispensed [including defined daily dose (DDD)]. Indication and prescribed dose are not recorded in the Prescription Registry.

We retrieved all information available for cohort members in the Prescription Registry between 1995 and the index date. First-time statin use within 1 year prior to the index date was disregarded to avoid inclusion of drug use initiated in relation to occurrence of brain tumour symptoms. Further, as prescription data derive from community pharmacies only, we disregarded all exposure for statins, and other drugs included as covariates, within 3 months prior to the index date to avoid differential exposure misclassification during glioma-related hospitalisations [18]. Thus, the exposure period spanned between 1995 and up to 3 months before the index date.

Statin exposure among patients was classified as non-use (0 or 1 prescription during the exposure period) or ever use ($\geq$2 prescriptions during the exposure period). Ever use was further categorized into recent use (prescriptions within 3–12 months prior to the index date) and past use (last prescription redeemed $>$1 year prior to the index date). We defined duration of statin use based on prescription dates and the number of days covered by individual prescriptions. The coverage period of each prescription was calculated as the sum of dispensed tablets, as most statin regimens are based on one tablet per day [19,20]. Cumulative duration of statin use, estimated as the total number of statin tablets prescribed to each patient, was categorized into four mutually exclusive strata: $<$1 year, 1 to $<$3 years, 3 to $<$5 years, and $\geq$5 years.

In addition, we defined intensity of statin use as the cumulative number of DDDs of statins prescribed to each study patient, divided by the number of days between the first and last eligible statin prescription plus 60 days. Using tertiles of intensity of statin use in the general population as cut-off values [12], we classified intensity of use as low (lower tertile), medium (middle tertile), and high (upper tertile). Finally, we classified statins as lipophilic (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin) or hydrophilic (pravastatin and rosuvastatin).

2.3. Potential confounders

Using information on oncological treatment extracted from the DNRP, we classified treatment into dichotomous variables for surgery, chemotherapy, and radiation therapy. We also identified the first recorded date for each treatment type. This allowed us to adjust for the effect of oncological treatment on prognosis (see Section 2.4).

Experimental studies have demonstrated a cytotoxic effect of thiazolidinediones (a specific class of oral anti-diabetic drugs) on malignant glioma cells [21]. Epidemiological studies have indicated a reduced risk of glioma among diabetes patients [22,23], although results are inconsistent [24]. We therefore included a history of diabetes as a potential confounder in our analyses. Patients were classified as diabetics if they fulfilled either of the following criteria: (i) $\geq$2 prescriptions for one or more anti-diabetic drugs (*i.e.*, insulin or oral anti-diabetic drug) during the exposure period or (ii) history of diabetes mellitus based on hospital discharge diagnoses or outpatient contacts recorded up to 3 months prior to the index date.

A recent meta-analysis of 12 observational studies examining the association between allergies and glioma risk reported a pooled odds ratio of 0.60 (95% CI: 0.52–0.69) [25]. Inverse associations with glioma risk were observed for asthma (0.70), eczema (0.69), and hay fever (0.78). McCarthy et al. [26] reported an inverse association between antihistamine use and glioma incidence that could be attributed entirely to antihistamine use among patients with allergies. In contrast, long-term use of antihistamines has been associated with increased risk of anaplastic glioma, a specific type of glioma [27]. We thus included history of allergies and use of antihistamines as potential confounders. Patients were classified as suffering from allergy or asthma based on hospital discharge diagnoses or outpatient contacts up to 1 year prior to the index date. We also characterized patients according to ever use ($\geq$2 prescriptions) of antihistamines or anti-asthma medication based on information from the Prescription Registry.

As an overall measure of comorbidity, we calculated the Charlson Comorbidity Index (CCI) score for all study patients [28]. In addition, we classified patients according to previous use of drugs suggested to be associated with glioma risk, *i.e.*, postmenopausal hormone replacement therapy (HRT), low-dose aspirin, and non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs). Exposure to these drugs was defined as $\geq$2 prescriptions during the exposure period.

Socioeconomic status (*SES*) was associated with survival in patients with central nervous system (CNS) tumours in a recent Danish study [29]. To adjust for potential confounding by SES, we used the highest education achieved by study patients, based on information from demographic registries in Statistics Denmark [30].

2.4. Statistical analyses

To avoid overfitting, as we expected the number of surviving patients to be low, we chose to analyze the data using propensity

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