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Use of statins and risk of glioma: a nationwide case–control study in Denmark

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Background: Laboratory studies and a single case–control study have suggested a protective effect of statins on the risk of glioma. We wished to investigate the influence of statin use on the risk of glioma in a population-based setting.

Methods: We conducted a nationwide case–control study in Denmark based on population-based medical registries. We identified all patients aged 20 to 85 years with a first diagnosis of histologically verified glioma during 2000–2009. These cases were matched on birth year and sex with population controls. Prior use of statins since 1995 was classified into short-term use (<5 years) and long-term use (5+ years). We used conditional logistic regression to compute odds ratios (ORs), with 95% confidence intervals (CIs), for glioma associated with statin use, adjusted for potential confounders.

Results: A total of 2656 cases and 18 480 controls were included in the study. The risk of glioma was reduced among long-term statin users (OR = 0.76; 95% CI: 0.59–0.98) compared with never users of statins, and was inversely related to the intensity of statin treatment among users (OR = 0.71; 95% CI: 0.44–1.15 for highest intensity). The inverse association between long-term statin treatment and glioma risk was more pronounced among men aged ⩽60 years (OR = 0.40; 95% CI: 0.17–0.91) compared with men aged 60+ years (OR = 0.71; 95% CI: 0.49–1.03). An inverse association was also observed among women aged ⩽60 years (OR = 0.28; 95% CI: 0.06–1.25), but not among women over age 60 years (OR = 1.23; 95% CI: 0.82–1.85).

Conclusion: Long-term statin use may reduce the risk of glioma.

Given the widespread and rapidly increasing use of statins, any association with cancer development or progression would have a substantial impact on public health. At present, statins cannot be recommended for primary cancer prevention or therapy because of conflicting evidence (Boudreau *et al*, 2010).

However, preclinical findings of antineoplastic activity of statins warrant their further evaluation as potential chemopreventive agents (Chan *et al*, 2003; Sassano and Platania, 2008; Tapia-Pérez *et al*, 2010). One line of investigation deserving particular attention is the effect of statins on gliomas, a group of central nervous system tumours of largely unknown aetiology. The most common histological subtype, glioblastoma multiforme, accounts for more than 50% of gliomas, and has an incidence rate of 3.5 per 1 00 000 person-years in Nordic countries and male predominance (Lönn *et al*, 2004).

Laboratory studies of human glioma cell lines indicate that statins may exert antitumour activity through such mechanisms as inhibition of cellular proliferation, growth, migration, and by induction of apoptosis (Jones *et al*, 1994; Soma *et al*, 1994; Bouterfa *et al*, 2000; Obara *et al*, 2002; Gliemroth *et al*, 2003; Jiang *et al*, 2004; Chan *et al*, 2008; Wu *et al*, 2009; Yanae *et al*, 2011). In a phase I/II study of 18 patients with malignant gliomas, lovastatin with and without radiotherapy was well tolerated, but had minimal effect on tumour progression (Larner *et al*, 1998). To date, only one

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case–control study has addressed the risk of glioma among statin users (Ferris *et al*, 2012). This study reported that ⩾6 months of simvastatin use was inversely associated with glioma risk (odds ratio (OR) = 0.72; 95% confidence interval (CI): 0.52–1.00). Recall bias was a potential shortcoming of this interview-based study, with information collected from proxies in ~19% of cases.

We therefore conducted a nationwide population-based case–control study utilising registry data to further investigate the association between statin use and glioma risk.

MATERIALS AND METHODS

We conducted a nested case–control study based on information from population-based Danish registries: the Danish Cancer Registry (DCR) (Storm *et al*, 1997; Gjerstorff, 2011), the Danish Civil Registration System (Pedersen, 2011), the Danish National Prescription Registry (Kildemoes *et al*, 2011), the Danish National Patient Register (DNPR) (Lynge *et al*, 2011), and Statistics Denmark. Unambiguous linkage between the registries was possible using the civil registration number assigned to all Danish residents since 1968, at birth or upon immigration to the country (Pedersen, 2011). Danish citizens, who are mainly Caucasians, have equal tax-supported access to health care provided by the Danish National Health Service.

Case ascertainment. The DCR has recorded incident cases of cancer on a nationwide basis since 1943 and has been shown to have an almost complete ascertainment of cancer cases (Storm *et al*, 1997; Gjerstorff, 2011). Reporting of gliomas to the DCR is mandatory for all levels of malignancy. Cancer diagnoses in the DCR are recorded according to the International Classification of Diseases, version 10 (ICD-10), and the ICD for Oncology (ICD-O-3) for topography and morphology codes.

Eligible cases were individuals with a first diagnosis of cranial or spinal glioma irrespective of level of malignancy, and no prior cancer diagnoses (except nonmelanoma skin cancer) in the DCR during the period from 1 January 2000 to 31 December 2009. A diagnosis of glioma was determined on the basis of ICD-10 diagnoses (see Appendix Table A1 for codes) that were histologically confirmed, that is, with morphology codes (ICD-O-3; see Appendix Table A1). We further classified cases by glioma subtype, that is, glioblastoma multiforme (see Appendix Table A1), astrocytoma grades II and III, oligodendroglioma grades II and III, and 'other'. The date of diagnosis recorded in the DCR was defined as the index date. We restricted the cases to individuals aged 20 to 85 years at diagnosis.

Selection of population controls. For each case, eight controls matched on birth year and sex were selected from the total Danish population through the Civil Registration System (Pedersen, 2011) using risk-set sampling (Rothman *et al*, 2008); that is, the controls had to be alive and at risk for a first diagnosis of cancer (except nonmelanoma skin cancer) at the time the corresponding case was diagnosed (index date). The Civil Registration System is continuously updated and includes information on vital status and migration. We used this information to restrict cases and controls to individuals who had resided in Denmark for at least 10 consecutive years before the index date. As the latter restriction was imposed after sampling of controls, the final ratio of cases to controls deviated slightly from 1 : 8.

Statin exposure. Information on use of statins and other drugs was obtained from the National Prescription Registry, which contains information on all prescriptions dispensed at community pharmacies in Denmark since 1995 (Kildemoes *et al*, 2011). For each prescription, the Prescription Registry records date and a full description of the dispensed product, including the anatomical therapeutic code (ATC) (WHO, 2010) and the total number of defined daily doses (DDDs). A DDD, established by a group of experts, represents the typical daily dose required by an adult when the drug is used for its main indication (WHO, 2010). Drugs used for the same indication are in principle equipotent when measured in DDD.

We retrieved all information available from the Prescription Registry from 1995 to the index date for both cases and controls. Based on the number of statin prescriptions dispensed during the period from 1995 up to 1 year before the index date, study subjects were classified as statin ever users (⩾2 prescriptions recorded under ATC codes C10AA) and statin never users (no prescriptions for statins). Subjects with a single statin prescription were not included in the main analyses. The risk of a 'reverse causation' bias (Csizmadl *et al*, 2007, pp 791–810) is inherent to the study, as the first symptoms of glioma in some cases might be interpreted as a manifestation of cerebrovascular disease and result in the patient being prescribed a statin. At a later stage, it becomes evident that the patient has a tumour. Such a scenario would create a spurious excess of cancer diagnoses after statin initiation or would mask a possible genuine preventive effect. To minimise this potential bias, we disregarded statin prescriptions dispensed within 1 year before the index date.

Duration of statin use was defined as the time period between the first and last redeemed statin prescription and classified as short duration (1–5 years before index date) or long duration (5+ years before index date). We defined intensity of statin use as the cumulative number of DDDs of statins prescribed to a study subject divided by the number of days between the first and last eligible statin prescription plus 60 days. Using tertiles of intensity of statin use among controls as cutoff values, we classified intensity of use as low (lower tertile), medium (middle tertile), and high (upper tertile). In subanalyses, we classified statins as lipophilic (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin) and hydrophilic (pravastatin and rosuvastatin).

Potential confounders. As a marker of socioeconomic status, we used the highest educational level achieved by subjects according to annually updated information from Statistics Denmark (Jensen and Rasmussen, 2011). We divided study subjects into three categories according to the number of years of schooling (7–10, 11–12, and 13+ years).

Patients suffering from a stroke are frequently prescribed statins and undergo neuroimaging. The latter might in some instances coincidentally reveal gliomas. We therefore regarded a history of stroke as a potential confounder. We defined subjects as having a history of stroke if they were recorded with ICD codes compatible with this diagnosis (see Appendix Table A1 for codes) in the DNPR, which contains data on all admissions to nonpsychiatric hospitals in Denmark since 1977 and on all outpatient contacts since 1995, including patients' civil registration number, date of admission/contact, and diagnosis codes.

Because diabetes is under intense scrutiny for its possible association with cancer (Carstensen *et al*, 2012) and is associated with statin use, we classified study subjects as diabetics if they had a history of diabetes mellitus according to the DNRP (Lynge *et al*, 2011) or had redeemed prescriptions for antidiabetic drugs before the index date (see Appendix Table A1 for codes). We also considered use of certain drugs previously reported to modify the risk of some cancers. Study subjects were classified as ever users of the following individual compounds if they had redeemed two or more prescriptions one or more years before the index date: hormone replacement therapy (HRT), low-dose aspirin, selective Cox-2 inhibitors, and other non-aspirin (NA)-NSAIDs (see Appendix Table A1 for codes).

We used parity as a proxy measure for exposure to endogenous sex hormones in women, as these may influence their glioma risk (Fisher *et al*, 2007). We calculated parity as of the index date for female cases and controls based on information available in the

nationwide Fertility Database maintained by Statistics Denmark (Blenstrup and Knudsen, 2011). The women were classified into the following categories according to the number of live births: 0 (nullipara), 1, 2, 3+, or 'missing information'.

Statistical analysis. We used conditional logistic regression to compute adjusted ORs (and 95% CI) for glioma associated with statin use, adjusting for age (birth year), sex, and time period (year of index date) and for potential confounders (years of schooling, diabetes, stroke, and use of aspirin, selective Cox2 inhibitors, and NA-NSAIDs). We tested the effect of intensity of statin treatment for trend. To explore potential effect measure modification, we performed analyses stratified by age (dichotomised according to median age of controls, i.e., <60 *vs* $\geqslant 60$ years) and gender. Information on HRT use and parity was included only in models restricted to female study subjects used in sensitivity analyses. All analyses were performed using Stata SE 12.1 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency and the Danish Medicinal Agency.

Table 1. Characteristics of study subjects in a nationwide case–control study of glioma in Denmark, 2000–2009

Characteristic	Cases (*N* = 2656)	Controls (*N* = 18 480)
Gender		
Female	1070 (40.3)	7050 (38.2)
Male	1586 (59.7)	11 430 (61.9)
Age, years		
20–29	119 (4.5)	789 (4.3)
30–39	215 (8.1)	1485 (8.0)
40–49	421 (15.9)	3019 (16.3)
50–59	681 (25.6)	4905 (26.5)
60–69	731 (27.5)	5094 (27. 6)
70–79	426 (16.0)	2805 (15.2)
80–85	63 (2.4)	383 (2.1)
Parity, number of children[a,b]		
0	97 (9.1)	652 (9.3)
1	165 (15.4)	1100 (15. 6)
2	418 (39.1)	2686 (38.1)
3+	235 (22.0)	1624 (23.0)
Missing	155 (14.5)	988 (14.0)
Schooling, number of years		
7–10	940 (35.4)	6395 (34.6)
11–12	1086 (40.9)	7608 (41.2)
13+	587 (22.1)	4117 (22.3)
Missing	43 (1.6)	360 (2.0)
Diabetes	105 (4.0)	838 (4.5)
Stroke	313 (11.8)	463 (2.5)
Drug use		
Statins	214 (8.1)	1601 (8.7)
Aspirin, low dose	251 (9.5)	1900 (10.3)
Selective Cox2 inhibitors	82 (3.1)	489 (2.7)
NA-NSAIDs[c]	1047 (39.4)	7263 (39.3)
Hormone replacement therapy[a]	290 (27.1)	2070 (29.4)

Abbreviations: Cox-2 = cyclooxygenase 2; NA-NSAIDs = non-aspirin-nonsteroidal anti-inflammatory drugs.
[a]Women only.
[b]Data incomplete for women born before 1945. No data available on births in 2009.
[c]NA-NSAIDs other than Cox2 inhibitors.
Shown are numbers (percentages).

RESULTS

Our study population comprised 2656 cases and 18 480 controls. Of these, 1586 cases (59.7%) and 11 430 controls (61.9%) were male. Cases and controls were also similar with regard to the distribution of age, parity, years of schooling, prevalence of diabetes, and use of aspirin, selective Cox2 inhibitors, NA-NSAIDs, and HRT, but not stroke (Table 1). Among subjects treated with statins ($\geqslant 2$ prescriptions), the median (interquartile range (IQR)) dose was 724 DDD (IQR: 387–1262 DDD) in cases and 720 DDD (IQR, 372–1391 DDD) in controls, and the median duration of treatment was 2.4 years (IQR, 1.1–4.7 years) in cases and 2.8 years (IQR, 1.2–5.2 years) in controls (excluding prescriptions dispensed during the year before the index date).

Long-term statin use was associated with a reduced risk of glioma (OR = 0.76; 95% CI: 0.59–0.98; Table 2) and was inversely related to treatment intensity (high-intensity treatment: OR = 0.71; 95% CI: 0.44–1.15; *P*-value for trend: 0.041; Table 3). The effect of long-term high-intensity use was restricted to lipophilic statins (OR = 0.69; 95% CI: 0.38–1.25). The corresponding risk estimate for hydrophilic statins exceeded unity (OR = 1.45; 95% CI: 0.31–6.69), although based on small numbers. Reduction in glioma risk varied across age and gender strata (Table 4). Risk of glioma among long-term statin users was OR = 0.37 (95% CI: 0.18–0.75) among subjects under age 60 years as compared with OR = 0.91 (95% CI: 0.69–1.19) among subjects aged 60+ years. Long-term statin use was inversely related with the risk of glioma among men (OR = 0.61; 95% CI: 0.44–0.86), but not among women (OR = 1.01; 95% CI: 0.69–1.49; Table 4). However, among female long-term statin users under age 60 years, the risk of glioma was OR = 0.28 (95% CI: 0.06–1.25). Among men, the risk reduction was also more pronounced among those under age 60 years (OR = 0.40; 95% CI: 0.17–0.91), but was also substantial among men aged 60+ years (OR = 0.71; 95% CI: 0.49–1.03). Ever use of statins reduced the risk of glioblastoma multiforme (OR = 0.90; 95% CI: 0.73–1.12), the most frequent type of glioma (57.9% of cases; Supplementary eTable 1). The risk reduction for glioblastoma multiforme was more pronounced among long-term statin users (OR = 0.79; 95% CI: 0.59–1.06), in particular among subjects with high intensity statin use (OR = 0.67; 95% CI: 0.37–1.20).

We performed a number of sensitivity analyses. We first repeated all analyses including those with one prescription only in the non-use reference group, then with long-term use defined as 7+ years of statin use, and lastly excluding NSAIDs as a covariate. Analyses with women in separate strata were repeated with HRT and parity included as confounder variables. The results of the sensitivity analyses were very similar to those of the main analyses (data not presented).

Table 2. Ever use of statins and risk of glioma

Use of statin	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Never	2442	16 879	1 (ref.)	1 (ref.)
Ever	214	1601	0.89 (0.76–1.05)	0.88 (0.73–1.05)
<5 years	118	770	1.02 (0.83–1.26)	0.96 (0.76–1.20)
5+ years	96	831	0.77 (0.61–0.96)	0.76 (0.59–0.98)

Abbreviations: CI = confidence interval; OR = odds ratio; ref. = reference.
[a]Adjusted for years of schooling, diabetes, stroke, and use of aspirin, selective cyclooxygenase 2 (Cox2) inhibitors, and non-aspirin-nonsteroidal anti-inflammatory drugs (NA-NSAIDs).

Table 3. Duration and intensity of statin use and glioma risk

Statin use	Cases	Controls	Crude odds ratio (95% confidence interval (CI))	Adjusted odds ratio[a] (95% CI)
Never use	2442	16 879	1 (reference)	1 (reference)
Short-term use[b,c]				
Low intensity	24	179	0.87 (0.57–1.34)	0.94 (0.60–1.47)
Medium intensity	41	250	1.11 (0.79–1.57)	1.10 (0.77–1.56)
High intensity	53	341	1.04 (0.77–1.41)	1.01 (0.73–1.39)
Long-term use[b,c]				
Low intensity	42	352	0.81 (0.58–1.12)	0.81 (0.57–1.14)
Medium intensity	33	273	0.78 (0.54–1.14)	0.86 (0.58–1.26)
High intensity	21	206	0.67 (0.42–1.06)	0.71 (0.44–1.15)

[a]Adjusted for years of schooling, diabetes, stroke, and use of aspirin, selective cyclooxygenase 2 (Cox2) inhibitors, and non-aspirin-nonsteroidal anti-inflammatory drugs (NA-NSAIDs).
[b]Short term: <5 years of use; long term: 5+ years of use.
[c]Cutoff values for low-, medium-, and high-intensity statin use defined by tertiles of intensity of use among controls.

DISCUSSION

We found that long-term use of statins was associated with a reduced risk of glioma. Although based on limited statistical precision, the potential chemopreventive effect was limited to users of lipophilic statins. This may be explained by the physiological properties of lipophilic statins, that is, their better ability to cross the blood–brain barrier compared with hydrophilic statins (Botti *et al*, 1991; Vuletic *et al*, 2006). Furthermore, the effect of long-term statin use may be more pronounced among men and, for both genders, among those <60 years of age. We found it particularly intriguing that the point estimates for our main findings remained unchanged when we limited to cases with histologically verified glioblastoma multiforme, the most aggressive form of glioma, with only 3.3% of patients surviving for 5 years (Bondy *et al*, 2008).

In the only other epidemiological study that has addressed the relation between statin use and glioma risk, a case–control study conducted in the United States, statin use among 458 cases was compared with that among 353 controls (Ferris *et al*, 2012). Statin use for ⩾6 months was associated with a reduced risk of glioma (OR = 0.72; 95% CI: 0.52–1.00) and the risk was further reduced in subjects with a long treatment duration (>120 months of use, OR = 0.44; 95% CI: 0.15–0.97). The OR of glioma associated with statin use was 0.59 (95% CI: 0.38–0.92) among men and 0.85 (95% CI: 0.51–1.43) among women. Our findings are compatible with this study, including the gender difference in the risk estimates for glioma, although direct comparisons between the two studies are hampered by differences in design and setting.

Our study has a number of strengths. Our study was performed in a setting with free access to health services independent of income. We used nationwide registries with complete coverage and continuously collected data on all Danish residents. Our approach thus eliminated recall bias and minimised selection bias. The DCR enabled us to identify incident cases of glioma and cancer-free controls with minimal misclassification. We also restricted our sample to histologically verified cases, which enhanced case validity and allowed us to perform analyses on subtypes of glioma. Our study also has some potential weaknesses that should be considered. Because the National Prescription Registry has collected nationwide data only since 1995, the medication histories of our subjects spanned 5 to 15 years, depending on their index dates. This left-truncation of Prescription Registry data may give rise to two potential problems. First, subjects who stopped using statins before 1995 were misclassified as never users in our study. Second, the duration of current use may be underestimated in subjects with statin use before 1995. However, such misclassifications most likely would produce a conservative misclassification bias, that is, reduce the association between statin use and glioma risk. Furthermore, as statins were only used sparsely in Denmark before the publication of the Scandinavian Simvastatin Survival Study (4S) (Scandinavian Simvastatin Survival Study Group, 1994) in 1994 (Riahi *et al*, 2001), we believe that such misclassification is minor. Our study was also limited by our inability to evaluate compliance with statin prescriptions; however, a drug utilisation study of statin use in the Danish population indicates that degree of statin persistence is high (Larsen *et al*, 2002).

It is conceivable that before their detection, brain tumours could exert influences on adherence to medication use, for example, by influencing cognitive skills. By ignoring the use of statins in the year before the index date, we believe that we have severely reduced the impact of such effects, particularly in our analyses restricted to cases of glioblastoma multiforme, a glioma subtype with well-established rapid development.

Exposure to ionising radiation is the only established environmental cause of glioma (Fisher *et al*, 2007; Bondy *et al*, 2008). Although we were not able to adjust for this covariate, the attributable risk proportion of radiation is small and unlikely to be associated with statin use. More importantly, we only included study subjects with an initial primary cancer, so that individuals with previous cancers who may have been exposed to ionising radiation were excluded by design. As well, lifestyle factors indirectly could influence our study findings if such factors were both related to the likelihood of being prescribed statins and risk of glioma. According to a recent Danish study linking prescription data on statin use to data from a survey of 13 996 subjects (including 1641 current statin users), there was no indication of a particularly healthy lifestyle associated with statin use (Thomsen *et al*, 2011). However, another Danish study based primarily on statin use in the initial years following the launch of these drugs showed a clear socioeconomic gradient in statin use among men but not women (Thomsen *et al*, 2005). Another concern is that we only accounted for highest achieved level of schooling, which may have resulted in residual confounding of socioeconomic indicators. Importantly, however, a Danish study based on DCR data found no association between incidence of central nervous system tumours and socioeconomic status (Schmidt *et al*, 2008).

Table 4. Effect of duration of statin use on glioma risk by gender and age strata

	Cases (exposed/ unexposed)	Controls (exposed/ unexposed)	Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Age				
<60 years				
Short term	28/1398	205/9834	0.97 (0.65–1.46)	0.78 (0.48–1.27)
Long term	10/1398	159/9834	0.46 (0.24–0.89)	0.37 (0.18–0.75)
60+ years				
Short term	90/1044	565/7045	1.04 (0.82–1.32)	1.02 (0.79–1.32)
Long term	86/1044	672/7045	0.84 (0.66–1.07)	0.91 (0.69–1.19)
Gender				
Female				
Short term	48/980	260/6520	1.20 (0.87–1.67)	1.12 (0.79–1.61)
Long term	42/980	270/6520	1.00 (0.71–1.42)	1.01 (0.69–1.49)
Male				
Short term	70/1462	510/10 359	0.93 (0.71–1.21)	0.86 (0.64–1.16)
Long term	54/1462	561/10 359	0.65 (0.48–0.87)	0.61 (0.44–0.86)
Gender and age				
Female, <60 years				
Short term	7/550	59/3654	0.79 (0.35–1.75)	0.73 (0.30–1.77)
Long term	2/550	37/3654	0.37 (0.09–1.54)	0.28 (0.06–1.25)
Female, 60+ years				
Short term	41/430	201/2866	1.33 (0.93–1.92)	1.26 (0.85–1.87)
Long term	40/430	233/2866	1.11 (0.77–1.59)	1.23 (0.82–1.85)
Male, <60 years				
Short term	21/848	146/6180	1.06 (0.66–1.69)	0.80 (0.44–1.44)
Long term	8/848	122/6180	0.49 (0.24–1.03)	0.40 (0.17–0.91)
Male, 60+ years				
Short term	49/614	364/4179	0.88 (0.64–1.21)	0.87 (0.61–1.23)
Long term	46/614	439/4179	0.69 (0.50–0.96)	0.71 (0.49–1.03)

Abbreviation: CI = Confidnce interval. Short term: <5 years of use; long term: 5+ years of use.
[a]Adjusted for years of schooling, diabetes, stroke, and use of aspirin, selective cyclooxygenase 2 (Cox2) inhibitors, and non-aspirin-nonsteroidal anti-inflammatory drugs (NA-NSAIDs).

Therefore, lifestyle factors and socioeconomic status are not likely to have substantially affected our findings.

Because of the observational design of our study, we cannot exclude the possibility that inadequately measured confounders influenced our results, although at present only a limited number of risk factors have been established for glioma (Fisher *et al*, 2007; Bondy *et al*, 2008).

Therefore, our finding of a reduced risk of glioma associated with long-term statin use may be causal. The possibility of gender- and age-specific effects, indicated by our study, if replicated in other settings, could potentially provide guidance to targeted therapeutic intervention trials.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)

APPENDIX

Table A1. List of codes used in the analysis

Cancer codes

Glioma
- ICD-10
  - C71.0-C71.9, C72.0, D33.0-D33.4, D43.0–D43.4
- ICD-0-3
  - 94403 – glioblastoma multiforme
  - 94003, 94013, 94103, 94113 – astrocytoma grade II and III
  - 94503, 94513, 94603 – oligodendroglioma grade II and III
  - 93801, 93803, 93813, 93823, 93831, 93900–94001, 94121–94401, 94413–94501 – 'other'

Anatomical therapeutic classification codes

Statins
- C10AA01 – Simvastatin
- C10AA02 – Lovastatin
- C10AA03 – Pravastatin*
- C10AA04 – Fluvastatin
- C10AA05 – Atorvastatin
- C10AA06 – Cerivastatin
- C10AA07 – Rosuvastatin*

Table A1. *(Continued)*

Other drugs (covariates)
- Antidiabetics
- A10A – insulin
- A10B – oral antidiabetics
- Hormone replacement therapy
- G03C, G03D, G03F, G03HB01
- Aspirin, low dose (tablet size 75, 100, or 150 mg)
- B01AC06
- Selective Cox-2 inhibitors
- M01AH
- Non-aspirin NSAIDs
  - M01A, except M01AH and M01AX

Hospital discharge codes

Diabetes
- ICD-8: 249, 250
- ICD-10: E10–E14

Stroke
- ICD-8: 431, 433, 434
- ICD-10: I60, I61, I63

Abbreviations: ICD = International Classification of Diseases; Cox-2 = cyclooxygenase 2; NSAIDs = nonsteroidal anti-inflammatory drugs.
*Classified as hydrophilic; other statins classified as lipophilic.