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Title: 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: 1,921 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 8,000 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.

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

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 considered non-users and then users thereafter for the remainder of follow-up, after a lag of 6 months (though this was varied in sensitivity analyses) which was applied to all individuals. The use of a lag is recommended(13) and in this study the lag, in effect, removed prescriptions in the 6 month period prior to death or end of follow-up, the former of which as these may reflect end of life treatment. The study design is described in Figure 1.

2.4 Covariates

Data available from the Scottish Cancer Registry included morphology (from ICD-O codes, allowing esophageal adenocarcinoma and squamous cell carcinoma to be identified), histological grade and surgery, chemotherapy and radiotherapy in the six months after diagnosis. Comorbidities that contribute to the Charlson index were determined prior to diagnosis based upon ICD10 diagnosis codes, as described previously(14) in Scottish hospital inpatient (SMR01) and outpatient data (SMR00). A deprivation measure was determined using the 2009 Scottish Index of Multiple Deprivation based upon postcode of residence.(14,15)

2.5 Statistical analysis

In the main analysis, time-dependent Cox regression models were used to calculate hazard ratios (HRs) for esophageal cancer-specific death and 95% confidence intervals (95% CIs) for statin users compared with non-users using a time varying covariate, as described previously. Adjusted analyses were conducted including the following potential confounders: sex, age, year of diagnosis, deprivation (in fifths), surgery (within 6 months), radiotherapy (within 6 months), chemotherapy (within 6 months), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin usage (as time varying covariate). A dose-response analysis was conducted with individuals considered non-users prior to 6 months after first use, a short term user between 6 months after first use and 6 months after the 12th prescription and a longer term user after this time. Analyses were repeated for all-cause mortality. Log-log plots were produced to check the proportional hazard assumptions. The main analysis was repeated

comparing simvastatin users to simvastatin non-users (and a separate analysis was conducted comparing simvastatin users to statin non-users but gave similar results, not shown).

Subgroup analyses were conducted by gender and histological subtype (esophageal adenocarcinoma and squamous cell carcinoma). A separate analysis was conducted stratified by statin use in the year prior to diagnosis. A sensitivity analysis was conducted additionally adjusting for statin use in the year prior to diagnosis and additionally adjusting for grade. A sensitivity analysis was conducted including gastric cancers of the cardia (C16.0) among the esophageal cancers. A sensitivity analysis was conducted varying the duration of the lag. Specifically, a time varying covariate analysis was conducted using no lag (following patients from esophageal cancer diagnosis and not excluding any deaths after cancer diagnosis), a 3 month lag (following patients from 3 months after esophageal cancer diagnosis and excluding deaths prior to 3 months after cancer diagnosis because such patients, by definition could not be medication users) and a 12 month lag. Figure 1 illustrates how statin user and non-user time was accumulated in the main analysis with a 6 month lag and in the unlagged analysis. A simplified analysis was conducted using Cox regression to compare statin users to statin non-users in the 6 months after esophageal cancer diagnosis in individuals living more than 6 months after diagnosis; this controls immortal time bias(16) without requiring time varying covariates.

Finally, an analysis was conducted comparing statin users to statin non-users in the year before diagnosis (excluding patients diagnosed in 2009 for whom a full year of prescription records prior to diagnosis may not be available), not excluding deaths after diagnosis. An adjusted analysis was first conducted omitting cancer treatment from adjustments for potential confounders to avoid over-adjustment(17,18) as these could be on the causal

pathway for esophageal cancer-specific mortality, but subsequently, a fully adjusted analysis was conducted including these variables.

3.0 Results

3.1 Patient cohort

There were 3,463 esophageal cancer patients diagnosed 2009 to 2012. Overall, 414 were excluded because of a previous cancer diagnosis, and 17 were removed because they died on the date of their cancer diagnosis, therefore 3,032 were eligible for analysis. The main analysis of post diagnosis statin use contained 1,921 esophageal cancer patients (because 1,128 esophageal cancer patients were excluded because they died within 6 months) in whom there was a mean of 2 years of follow-up (min=0.5 and maximum=6 years) and there were 1,502 deaths due to any cause, 1,373 of which were due to esophageal cancer.

Patient characteristics by statin use are shown in Table 1. Statin users were more likely to be male, older and diagnosed more recently. A greater proportion of statin users compared with non-users had esophageal adenocarcinoma (60% versus 55%, respectively) whilst a slightly smaller proportion had poorly differentiated tumours (44% versus 47%, respectively). Statin users were more likely to have radiotherapy and less likely to have surgery or chemotherapy compared with non-users. Statin users were more likely to have comorbidities (particularly for cerebrovascular disease, diabetes, stroke and myocardial infarction) and use low dose aspirin.

3.2 Association between statin use after diagnosis and survival

Table 2 shows the main findings. There was little evidence of a reduction in esophageal cancer-specific mortality in statin users after diagnosis (adjusted HR=0.93, 95% CI, 0.81, 1.07, respectively). There was also little evidence of a dose-response association when exposure was investigated by number of prescriptions. There was also no association when

simvastatin was investigated (adjusted HR=1.02, 95% CI 0.89, 1.17). Similar associations were observed for all-cause mortality.

3.3 Subgroup and sensitivity analyses

Table 3 shows subgroup and sensitivity analyses. The main findings were similar when including cancers of the cardia (C16.0) and additionally adjusting for grade. There was little evidence of an association after adjusting for statin use before diagnosis (HR=0.86 95% CI 0.68, 1.08) or when restricting to statin users in the year prior to diagnosis (HR=0.84 95% CI 0.64, 1.10) or statin non-users in the year prior to diagnosis (HR=0.69 95% CI 0.35, 1.37). Subgroup analyses did not reveal marked differences in the association between statin use and esophageal cancer-specific mortality by gender or histologic subtypes (in squamous cell carcinoma and esophageal adenocarcinoma the associations were adjusted HR=0.94, 95% CI 0.73, 1.21 and adjusted HR=0.90, 95% CI 0.75, 1.08, respectively). In a simplified analysis comparing statin users in the first 6 months versus non-users (restricted to individuals living 6 months), the association was similar (adjusted HR=0.90, 95% CI 0.79, 1.03). Associations between statins and esophageal cancer-specific mortality were apparent when no lag (adjusted HR=0.68 95% CI 0.61, 0.76) or a 3 month lag was used (adjusted HR=0.80 95% CI 0.70, 0.90) but when longer lags of 6 months (as in the main analysis) or 12 months were used the associations were attenuated.

3.4 Association between statin use before diagnosis and survival

Overall, statin users before diagnosis had a 12% reduction in the rate of esophageal cancer-specific mortality (fully adjusted HR=0.88, 95% CI 0.79, 0.99) compared with statin non-users following adjustment for confounders, Table 4. Comparable associations were observed for all-cause mortality.

4.0 Discussion

In this population-based cohort, there was little evidence of an association between statin use after diagnosis of esophageal cancer and esophageal cancer-specific mortality. There was however a weak association between statin use in the year prior to diagnosis and esophageal cancer-specific mortality.

The only previous study(9) to investigate statin use after diagnosis and esophageal cancer-specific mortality used Clinical Practice Research Datalink data from England (based upon GP prescribing data and linked cancer registry data and national mortality data). This study concluded that statins were associated with large and significant reductions in esophageal cancer specific mortality. This conclusion was based upon an unlagged analysis in which statin use was associated with marked reductions in esophageal cancer-specific mortality (adjusted HR=0.62 95% CI 0.44, 0.86) and this association was similar when the authors used a 3 month lag (adjusted HR=0.66, 95% CI 0.41, 1.07, respectively). We observed a similar association in unlagged analysis (adjusted HR=0.68 95% CI 0.61, 0.76), but in contrast to their study, this was markedly attenuated when using a 3 month lag (adjusted HR=0.80 95% CI 0.70, 0.90) and in our main analysis (using a 6 month lag) there was no association (adjusted HR=0.93 95% CI 0.81, 1.07). The use of a lag is recommended to reduce reverse causality(13) which could arise if esophageal cancer patients were less likely to start statins when they were obviously close to death. Observational studies in colorectal cancer patients have shown marked reductions in statin prescribing in the six months prior to death and stated that inclusion of an exposure lag is vital to account for reverse causation.(19) The use of a longer lag explains the difference in conclusion between our studies but the reason for the difference in the magnitude of the association when using a 3 month lag remains unclear.

Our findings of an approximate 10% reduction in cancer-specific and all-cause mortality in esophageal cancer patients who use statins before diagnosis is consistent with a nationwide Danish study which observed a reduction in cancer-specific mortality of around 20% with statin use before diagnosis (adjusted HR = 0.81, 95% CI 0.69, 0.95)(17,18) and the previously mentioned English study which observed around a 10% reduction in cancer-specific and all-cause mortality (adjusted HR=0.91, 95% CI 0.71, 1.16 and adjusted HR=0.86, 95% CI 0.55, 1.20, respectively). The cause of this reduction is unknown, and may not be causal, but could reflect the anticancer properties of statins on the developing esophageal cancer, seen in preclinical studies, which have shown that statins inhibit proliferation, and reduce apoptosis in esophageal adenocarcinoma cell lines.(7) The clinical utility of this finding is unclear as it is difficult to intervene prior to esophageal cancer diagnosis. Medication use prior to cancer diagnosis may be subject to a healthy user effect, whereby those with lesser disease experiencing less severe symptoms may be more likely to keep using the medications, compared with patients with more advanced disease discontinuing the drug.(20)

Our study has many strengths. It is the largest cohort to investigate statin use after diagnosis and esophageal cancer-specific mortality in esophageal cancer patients. Despite this, we cannot rule out a weak protective effect of statins after diagnosis that we could not detect as statistically significant due to lack of power. The study utilised high quality data sources from the Scottish Cancer Registry (allowing a population based cancer cohort to be identified), the Prescribing Information System (providing detailed information on the timing of medication use allowing temporal associations to be investigation) and the National Records of Scotland Death Records (allowing deaths to be captured comprehensively). Our

main analysis was conducted using a lag of 6 months, although a lag is recommended,(13) a weakness of this approach is that it will by necessity exclude patients who lived less than 6 months after esophageal cancer diagnosis, therefore restricting the generalizability of results. Misclassification of statin use by over the-counter use is likely to be limited as only low dose 10mg simvastatin is available in Scotland and this accounts for a very small proportion of statin use; a UK study recently estimated less than 1% of the population obtain statins the over the counter.(21) Similarly, there is the possibility of over-the-counter use of aspirin, which was included as a covariate, but previous studies suggest in this age group 70 to 95% of use will be captured by prescriptions.(22,23) However, misclassification of statin/aspirin use by non-compliance is possible. As with all observational studies there is the possibility of residual confounding, in this instance potential confounders include stage, smoking, alcohol and exercise.

In conclusion, in this population based cohort study of esophageal cancer patients, we found little evidence of an association between statin therapy after diagnosis and improved survival.

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Ethical approval: The study was approved by the Privacy Advisory Committee of the National Health Service (NHS) National Services Scotland (NSS).

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Table 1. Statin Use Before and After Esophageal Cancer Diagnosis, Scotland, 2009-2012.

	Statin use after diagnosis[a]				Statin use before diagnosis[b]			
	Statin		No Statin		Statin		No Statin	
	n	%	n	%	n	%	n	%
Year of diagnosis								
2009	163	25.3	312	24.5				
2010	150	23.3	329	25.8	298	32.7	493	35.5
2011	156	24.2	303	23.7	295	32.3	431	31
2012	176	27.3	332	26	319	35	466	33.5
Male	468	72.6	803	62.9	606	66.4	876	63
Age at diagnosis								
<60	68	10.5	326	25.5	69	7.6	307	22.1
60-69	205	31.8	396	31	237	26	383	27.6
70-79	248	38.4	350	27.4	345	37.8	384	27.6
80-89	114	17.7	170	13.3	238	26.1	243	17.5
≥ 90	10	1.6	34	2.7	23	2.5	73	5.3
Morphology								
Squamous cell	192	29.8	451	35.3	283	31	484	34.8
Adenocarcinoma	389	60.3	699	54.8	500	54.8	721	51.9
Missing	64	9.9	126	9.9	129	14.1	185	13.3
Grade								
1	8	1.2	29	2.3	16	1.8	22	1.6
2	219	34	412	32.3	289	31.7	405	29.1
3	281	43.6	602	47.2	400	43.9	686	49.4
Missing	137	21.2	233	18.3	207	22.7	277	19.9
Deprivation (fifth)								
1 (most deprived)	165	25.6	277	21.7	213	23.4	307	22.1
2	141	21.9	250	19.6	216	23.7	307	22.1
3	131	20.3	271	21.2	187	20.5	290	20.9
4	117	18.1	251	19.7	185	20.3	263	18.9
5 (least deprived)	91	14.1	227	17.8	111	12.2	223	16
Treatment (within 6 months)								
Surgery	110	17.1	246	19.3	89	9.8	192	13.8
Radiotherapy	229	35.5	383	30	245	26.9	318	22.9
Chemotherapy	352	54.6	787	61.7	326	35.7	620	44.6
Comorbidity prior to diagnosis								
Acute myocardial infarction	80	12.4	22	1.7	130	14.3	30	2.2
Congestive heart failure	49	7.6	36	2.8	84	9.2	42	3
Peripheral vascular disease	46	7.1	21	1.6	86	9.4	27	1.9
Cerebral vascular accident	70	10.9	29	2.3	118	12.9	48	3.5
Pulmonary disease	89	13.8	100	7.8	144	15.8	140	10.1
Peptic ulcer	23	3.6	56	4.4	32	3.5	67	4.8
Diabetes	97	15	36	2.8	148	16.2	36	2.6
Renal disease	33	5.1	19	1.5	53	5.8	28	2
Medication use[c]								
Aspirin	352	54.6	134	10.5	539	59.1	171	12.3

[a]Statin use in the 6 months after diagnosis restricted to esophageal cancer patients living 6 months after diagnosis.
[b]Statin use in the year prior to diagnosis.
[c]Refers to aspirin use in the 6 months after diagnosis in the first four columns and aspirin use in the year prior to diagnosis in the next four columns.

Table 2. Association Between Statin Use After Diagnosis and Cancer-specific and All-cause Mortality in Patients With Esophageal Cancer, Scotland, 2009-2012.

	Mortality	Patients	Person years	Unadjusted HR (95% CI)	P	Adjusted[a] HR (95%CI)	P
Cancer-specific mortality							
Statin non-user	948	1270	1677	1.00 (ref. cat.)		1.00 (ref. cat.)	
Statin user	425	651	874	0.97 (0.86,1.09)	0.62	0.93 (0.81,1.07)	0.29
1-12 prescriptions	387	496	677	0.97 (0.86,1.09)	0.94	0.92 (0.80,1.06)	0.27
≥ 12 prescriptions	38	155	198	1.01 (0.71,1.45)	0.58	0.97 (0.67,1.39)	0.86
Simvastatin non-user	1081	1479	1960	1.00 (ref. cat.)		1.00 (ref. cat.)	
Simvastatin user	292	442	592	1.03 (0.90,1.17)	0.70	1.02 (0.89,1.17)	0.78
All-cause mortality							
All-cause mortality							
Statin non-user	1017	1270	1677	1.00 (ref. cat.)		1.00 (ref. cat.)	
Statin user	485	651	874	1.02 (0.92,1.14)	0.70	0.94 (0.82,1.07)	0.36
1-12 prescriptions	426	496	677	1.00 (0.89,1.12)	0.13	0.92 (0.80,1.05)	0.22
≥ 12 prescriptions	59	155	198	1.25 (0.94,1.68)	0.98	1.15 (0.85,1.56)	0.35
Simvastatin non-user	1174	1479	1960	1.00 (ref. cat.)		1.00 (ref. cat.)	
Simvastatin user	328	442	592	1.05 (0.92,1.18)	0.48	1.01 (0.88,1.15)	0.91

[a]Time varying covariate analysis (with 6 month lag, removing deaths in the first 6 months) with adjusted estimates based upon model which contains sex, age, year of diagnosis, deprivation, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (as time varying covariate).

Table 3. Sensitivity Analysis of Association Between Statin Use and Cancer-specific and All-cause Mortality in Patients With Esophageal Cancer, Scotland, 2009-2012.

	Medication user			Medication non-user			Unadjusted HR (95% CI)	P	Adjusted HR (95%CI)	P
	Cancer-specific mortality	Patients	Person years	Cancer-specific mortality	Patients	Person years				
Subgroup analyses: Statin users versus non-users[a]										
Male	316	477	636	596	794	1046	0.97 (0.84,1.11)	0.66	0.94 (0.79,1.11)	0.466
Female	109	174	238	352	476	631	0.96 (0.77,1.19)	0.72	0.89 (0.69,1.14)	0.346
ESCC	126	192	246	340	451	571	0.99 (0.80,1.21)	0.89	0.94 (0.73,1.21)	0.629
EACC	255	395	538	513	693	954	0.97 (0.84,1.14)	0.74	0.90 (0.75,1.08)	0.267
In statin users in year prior[e]	306	456	540	105	122	128	0.84 (0.65,1.08)	0.179	0.84 (0.64,1.10)	0.214
In statin non-users in year prior[e]	9	35	50	596	833	1086	0.52 (0.27,1.02)	0.057	0.69 (0.35,1.37)	0.293
Statin user versus non-user[a]										
Adjusting for statin use in the year prior to diagnosis[f]	315	491	589	701	955	1214	1.01 (0.88,1.16)	0.884	0.86 (0.68,1.08)	0.184
Including cardia cancer[b]	531	824	1139	1194	1598	2157	0.94 (0.85,1.04)	0.24	0.89 (0.79,1.01)	0.072
Grade available (and adjusted for)	335	514	682	782	1037	1381	0.97 (0.85, 1.10)	0.60	0.90 (0.77, 1.06)	0.20
Statin user versus non-user										
Simplified analysis 6 months[c]	450	645	862	923	1276	1690	0.94 (0.84,1.05)	0.27	0.90 (0.79,1.03)	0.13
Statin user versus non-user[d]										
No lag	610	860	1255	1775	2172	2511	0.74 (0.67,0.81)	<0.001	0.68 (0.61,0.76)	<0.001
3 month lag	526	765	1049	1268	1618	2037	0.88 (0.79,0.97)	0.01	0.80 (0.70,0.90)	<0.001
12 months lag	216	418	614	481	785	1171	0.94 (0.80,1.10)	0.44	0.84 (0.69,1.02)	0.077

[a]Time varying covariate analysis (with 6 month lag, removing deaths in the first 6 months) in with adjusted estimates based upon model which contains sex, age, year of diagnosis, deprivation, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (as time varying covariate).

[b]Includes cancer of the cardia (C16.0) in esophageal cancer definition.

[c]Simplified analysis, comparing statin users to statin non-users in the 6 months after diagnosis in individuals living more than 6 months after cancer diagnosis, adjusted for all confounders in [a] but other medication use also restricted to first 6 months after diagnosis.

[d]Time varying covariate analysis (using model in [a]) varying the duration of lag from no lag (not removing any deaths after diagnosis), to a 3 month lag (removing deaths in the first 3 months after diagnosis), a 6 month lag (removing deaths in the first 6 months after diagnosis) or a 12 month lag (removing deaths within the first 12 months after diagnosis).

[e]Statin users versus non-users after diagnosis using model in a, stratified by statin use in the year prior to diagnosis, restricted to esophageal cancer cases diagnosed 2010 to 2012.

[f]Statin users versus non-users after diagnosis using model in a, adjusting for statin use in the year prior to diagnosis, restricted to esophageal cancer cases diagnosed 2010 to 2012.

Table 4. Association Between Statin Use Before Diagnosis and Cancer-specific and All-cause Mortality in Patients With Esophageal Cancer, Scotland, 2009-2012.

	Mortality	Patients	Person years	Unadjusted HR (95% CI)	P	Adjusted[1] HR (95%CI)	P	Fully adjusted[2]HR (95%CI)	P
				Cancer-specific mortality					
Statin non-user	1085	1390	1684	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Statin user	713	912	1036	1.03 (0.91, 1.13)	0.58	0.85 (0.76, 0.96)	0.01	0.88 (0.79, 0.99)	0.03
Simvastatin non-user	1283	1658	2016	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Simvastatin user	515	644	704	1.11 (1.00, 1.23)	0.05	0.98 (0.87, 1.09)	0.69	0.98 (0.88, 1.10)	0.72
				All-cause mortality					
Statin non-user	1169	1390	1684	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Statin user	789	912	1036	1.06 (0.97, 1.16)	0.23	0.86 (0.77, 0.96)	0.01	0.89 (0.80, 0.99)	0.04
Simvastatin non-user	1393	1658	2016	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Simvastatin user	565	644	704	1.12 (1.01,1.23)	0.02	0.97 (0.87,1.08)	0.55	0.97 (0.87,1.08)	0.59

[1]Model contains sex, age, year of diagnosis, deprivation, comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin and statin use (in year prior to diagnosis).
[2]Model contains all variables in [1] along with cancer treatment within 6 months (radiotherapy, chemotherapy, surgery).