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Use of statin medications and risk of esophageal adenocarcinoma in persons with Barrett's esophagus

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Abstract

Background—Persons with Barrett's esophagus experience increased incidence of esophageal adenocarcinoma (EA) and may benefit from use of preventives. Studies suggest that statin medications may have chemopreventive properties; we therefore assessed the association between statin use and progression to EA.

Methods—In a prospective cohort of 411 persons with Barrett's, Cox regression was used to calculate hazard ratios (HR) for NSAID and statin use accounting for variation in use during follow-up, and adjusting for age, sex, and smoking.

Results—The HRs for statin use among all participants were 0.59 (95% CI: 0.26–1.33) and 0.68 (95% CI: 0.30–1.54) before and after further adjustment for NSAID use, respectively. Among persons with high-grade dysplasia, the HRs for statin use were 0.31 (95% CI: 0.11–0.86) and 0.41 (95% CI: 0.13–1.26) before and after adding NSAIDs to the model, respectively.

Conclusions—While the reduced risk of EA observed among statin users may be explained by chance, the point estimates are similar in magnitude to those previously reported for NSAID use in this cohort, and are unlikely to be confounded by known risk factors.

Impact—Further study in larger cohorts and meta-analyses of the potential for statins to reduce risk of esophageal adenocarcinoma is warranted.

Keywords

Statins; chemoprevention; Barrett's esophagus; esophageal adenocarcinoma; esophageal cancer

Introduction

The incidence of esophageal adenocarcinoma (EA) has rapidly increased, with EA becoming the most common histological type of esophageal cancer in the United States (1).

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Barrett's esophagus (BE), a condition in which metaplastic columnar epithelium replaces the normal squamous epithelium of the esophagus, is associated with substantially increased risk of EA. Given the presence of an identifiable high-risk group and the poor prognosis associated with EA, a substantial cancer prevention opportunity exists if safe and effective preventive measures for EA can be identified.

While studies suggest a possible protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) on the progression of BE to EA (2), NSAIDs have not been formally recommended for cancer prevention. Consequently, there is interest in identifying other agents which could be used independently or in conjunction with NSAIDs so as to allow for a safe and effective preventive strategy.

One class of potential preventives is 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Used to reduce cholesterol, statins may inhibit neoplastic progression through posited anti-oxidant, anti-proliferative, pro-apoptotic, and anti-inflammatory effects (3–7). Consistent with these suggested effects, statins have been shown to induce apoptosis and inhibit proliferation in a Barrett's EA cell line (8). Observational studies between statin use and cancer risk are inconsistent (9–15), and only a few studies have reported on the association between statin use and risk of esophageal cancer (16–21). In this report, we examine the association between use of statins and risk of progressing from BE to EA using data from the Seattle Barrett's Esophagus Study.

Materials and Methods

This prospective cohort study was conducted using resources of the Seattle Barrett's Esophagus Study, a cohort of persons diagnosed with BE in the Seattle area. The study began in 1983 with endoscopic surveillance and expanded in 1995. After study expansion, participants provided an extensive baseline interview, after which they provided shorter follow-up interviews at subsequent endoscopies.

Endoscopic biopsy protocols used in the Seattle Barrett's Esophagus Study have been published previously (22). Briefly, for those without high-grade dysplasia (HGD), four-quadrant biopsies were taken every 2-cm throughout the Barrett's segment; persons without HGD were followed every 2–3 years by endoscopic surveillance. For those with a history of HGD, biopsies were taken from every 1-cm of the Barrett's segment. Persons with HGD at baseline endoscopy were further evaluated by an intensive protocol of four-quadrant biopsies every 1-cm throughout the Barrett's epithelium followed by two additional endoscopic biopsy surveillance procedures within the first four months to exclude co-existing EA. If no EA was detected, they were subsequently followed approximately every six months. All participants with a diagnosis of HGD have undergone a study counseling session on the risks and benefits of all management options for HGD.

All persons included in this study had BE, no history of esophageal cancer, baseline interview and at least one follow-up endoscopy between February 1, 1995 and September 30, 2009. Of the 411 persons fitting this criteria, 83 had HGD detected at baseline or at study endoscopies conducted prior to baseline interview.

Fourteen persons had less than five months of follow-up, 11 of whom were diagnosed with cancer during that interval. Given *a priori* concern that cancers found during this period may not have been detected at baseline, persons with less than five months of follow-up were excluded from analyses. We additionally excluded two people due to missing covariate information. Of the 395 eligible, 69 had HGD detected as of baseline interview.

Questions regarding history of NSAIDs made use of “show cards” to facilitate recall. NSAID use was classified as history of NSAID use as of baseline and as current use (reported at baseline and updated over follow-up). At each interview, participants were asked to list all medications used regularly during the past month, and this was the source of information on statin use. Current statin use at baseline and over follow-up was defined by whether study participants reported current use of statins at the time of each interview.

Person-time was calculated from date of baseline endoscopy (corresponding to the first interview) until date of EA diagnosis or date at last endoscopy prior to September 30, 2009. Cox regression was used to obtain estimates of the hazard ratios (HR) and 95% confidence intervals (95% CI). Analyses were adjusted for age at baseline (continuous linear), sex, pack-years of cigarettes smoked as of baseline (continuous linear), as well as current NSAID use or statin use (time-varying covariates). Adjustment for other potential confounding factors including waist-to-hip ratio, education, and history of NSAID use did not materially change the HRs and are therefore not presented. We have conducted two sets of analyses, the first of which includes all 395 persons with BE, and the second of which is specific to the 69 persons with HGD detected at or before baseline. Among those with HGD as of baseline, we have additionally conducted an analysis of joint statin and NSAID use in which use at each interview is modeled as a time-varying covariate and is categorized as follows: neither statin nor NSAID use, statin use only, NSAID use only, or use of both statins and NSAIDs. All statistical analyses were conducted using Stata11 software (StataCorp IC, College Station, TX). This study was approved by the Institutional Review Boards of the University of Washington and the Fred Hutchinson Cancer Research Center (Seattle, WA).

Results

The 411 persons in this study were followed for 2,804.7 person-years with a median of four follow-up visits. Age, sex, smoking history, education and NSAID use were associated with cumulative proportion of EA (Table 1). Participants reported current NSAID use at 41% of baseline interviews. Fifty-six of the 411 persons in this study (13.6%) reported statin use at baseline, while 35% reported use at baseline or over follow-up (Table 1). In univariate models, statin users were more likely to be male than non-users; at baseline interview, statin users were more likely than non-users to report history of smoking and current NSAID use (Table 2).

Table 3 presents the HRs of EA for users of statins and NSAIDs. One hundred and forty three persons reported ever use of statins over the course of the study, while 284 reported ever use of NSAIDs (Table 3). The HR for statin use was 0.68 (95% CI: 0.30–1.54) when modeling statin use as a time-varying covariate and adjusting for age, sex, pack-years smoked, and NSAID use. When analyses were limited to persons with HGD at baseline, a subgroup at particularly high risk of EA, the age, sex and smoking-adjusted HR for statin use was 0.31 (95% CI: 0.11–0.86); when NSAID use was added to the model, the HR attenuated (HR: 0.41, 95% CI: 0.13–1.26) and was no longer significant (Model 2 vs. Model 1).

Among the entire cohort, the association between EA and NSAID use was 0.62 (95% CI: 0.34–1.10) when adjusting for age, sex, pack-years smoked, and statin use. When limited to persons with HGD, the HR for NSAID use was 0.37 (95% CI: 0.17–0.83), though additional control for statin use attenuated the HR (0.46; 95% CI: 0.19–1.09). Among the HGD subset, the adjusted HR among joint statin and NSAID users as compared to those using neither was 0.19 (95% CI: 0.06–0.64). This HR is lower than that observed for use of statins only (HR: 0.40), and for NSAIDs only (HR: 0.45) (data not shown).

Discussion

We observed an inverse association between statin use and risk of progression to EA after controlling for age, sex and cigarette smoking. This significant association was attenuated and became non-significant when NSAID use was additionally included in the model, likely reflecting positively correlated use. Statin use was associated with a 32% reduced risk of EA among all persons in the cohort (HR: 0.68, 95% CI: 0.30–1.54) and a 59% reduced risk among those with HGD (HR: 0.41, 95% CI: 0.13–1.26). These point estimates are similar in magnitude to those observed for NSAID use, although with wider confidence intervals reflecting the lower prevalence of statin use. As previously reported, we observed an inverse association between NSAID use and EA risk when adjusting for age, sex, and pack-years smoked (2). Additional adjustment for statin use attenuated the association (Table 3, Models 1–2).

Persons with HGD are at substantially increased risk of EA, and may consequently alter behaviors regarding lifestyle and medication use. This high-risk group may be a likely target for preventive efforts, and we therefore stratified analyses by HGD status. The associations for both statin use and NSAID use were stronger when analyses were limited to persons with HGD. Furthermore, among those with HGD at baseline, we observed a substantial 81% (95% CI: 36%–94%) decreased risk among concurrent users of NSAIDs and statins compared to persons taking neither.

We were unable to estimate HRs with reasonable precision within the non-HGD group, as only 15 cases occurred in this group and all 15 cases occurred among men. Comparison across subgroups would therefore require that we further limit all analyses to men, which would act to reduce both generalizability and power.

Three recent studies reported significant inverse associations between statin use and risk of esophageal cancer. In a nested case-control study of persons with BE, Nguyen and colleagues observed a 44% (95% CI: 64%–13%) reduced risk of EA among persons with at least one statin prescription filled compared to persons with no statin prescriptions filled (17). In a large registry-based study, Hippisley-Cox et al reported a decreased risk of esophageal cancer associated with statin use: the HR for prescribed statin use was 0.68 (95% CI: 0.52–0.88) among women and 0.78 (95% CI: 0.66–0.91) among men (18). Kastelein and colleagues published on the association between statin use, NSAID use, and progression of BE to either HGD or EA (19). In this prospective study, an inverse association was observed between statin use and HGD/EA (HR: 0.46; 95% CI: 0.21–0.99). Study authors also observed the association between joint use and risk to be stronger than that observed for either drug alone: as compared to no use, they observed a HR of 0.22 for joint use (95% CI: 0.06–0.85), a HR of 0.46 for NSAID use, and a HR of 0.51 for statin use. The results of this study are very similar to those of our study and similarly ascertain exposure via interview. However, this study differs from our study in that it focuses on progression to HGD or EA, not specifically EA.

Other studies, however, have not observed a significant inverse association between statin use and esophageal cancer risk. In a prior study of persons with BE, Nguyen and colleagues reported an unadjusted HR of 0.73 for the association between statin use and EA/HGD risk (95% CI: 0.30–1.78) (16). Similarly, in a case-control study using data from a prescription database, Kaye et al observed a relative risk of 0.8 between statin use and esophageal cancer of any histologic type (95% CI: 0.3–1.8) (20). Lastly, in a large study in which statin use was ascertained by pharmacy record, statin use for more than five years was associated with a 70% increased risk of esophageal cancer in men (HR: 1.70; 95% CI: 1.05–2.75), though no

association was observed among women, nor was an association observed when exposure was defined by any duration of use (21).

Several of the aforementioned studies used records to define statin use. Data used in this study was obtained during personal interviews, allowing for detailed ascertainment of exposure information and adjustment for confounding effects of risk factors. We were also able to update information on use of statins and NSAIDs over the course of follow-up, and were therefore able to account for changes in use over time. Among previous studies on statin use and esophageal cancer, only the Nguyen and Kastelein studies have focused on persons with BE and to our knowledge, we are the first study to examine the association between statin use and EA risk among persons with HGD. This is important, as it is these high-risk populations who might benefit most from a preventive. Furthermore, our study focuses specifically on progression to adenocarcinoma, while the majority of the previous studies have either defined outcome as esophageal cancer of any histology or have grouped EA with HGD as a combined outcome. Since the risk factors for esophageal cancer are known to vary by histology, we believe that the association between statin use and esophageal cancer is best studied when limited to a specific histologic type.

The main limitation of this study is statistical power. When interviews began in 1995, statins were not as widely used as they are today. Returning to this study question at a later date in this cohort and other cohorts will likely yield more precise estimates. Although information on type of statin used was collected, we did not have power to stratify on lipophilic versus hydrophilic statin use. Also, timing between endoscopies (and thus follow-up interviews) was determined by severity of disease, and persons with HGD had more opportunity to update exposure information and have EA detected. This concern was reduced in analyses of persons with HGD, as all persons in this group had a similar frequency of follow-up. Furthermore, the method by which statin use was ascertained did not allow for duration-specific analyses, though we were able to use time-varying covariates to represent variations in use over the course of follow-up.

This study presents preliminary findings suggesting a possible protective effect of statins on risk of EA among persons with BE. While the results may have occurred by chance, they are unlikely to be confounded by known risk factors. We observed a strong inverse association among those with HGD taking both statins and NSAIDs. The potential for statins to serve as a chemopreventive, alone or in conjunction with NSAIDs, should be explored in future well-powered studies and meta-analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cumulative proportion of esophageal adenocarcinoma by demographic and health-related characteristics of all study participants

Characteristics	Number of people (n=411)[a]	Number of cases (n= 56)	Cumulative Proportion
Age (years)			
30–54	127 (30.9)	11 (19.6)	8.7%
55–69	176 (42.8)	23 (41.1)	13.1%
≥70	108 (26.3)	22 (39.3)	20.4%
Sex			
Men	334 (81.3)	49 (87.5)	14.7%
Women	77 (18.7)	7 (12.5)	9.1%
Smoking Status			
Never	148 (36.0)	14 (25.0)	9.5%
Ever	263 (64.0)	42 (75.0)	16.0%
Education			
No college education	135 (32.9)	25 (44.6)	18.5%
Any college education	275 (67.1)	31 (55.4)	11.3%
Waist-to-hip ratio[c]			
First quartile	104 (25.4)	11 (19.6)	10.6%
Second quartile	101 (24.7)	15 (26.8)	14.9%
Third quartile	100 (24.5)	14 (25.0)	14.0%
Fourth quartile	104 (25.4)	16 (28.6)	15.4%
NSAID use as of baseline			
Never	162 (39.5)	26 (46.4)	16.0%
Former	79 (19.3)	12 (21.4)	15.2%
Current	169 (41.2)	18 (32.1)	10.7%
High grade dysplasia at or before baseline			
No	328 (79.8)	15 (26.8)	4.6%
Yes	83 (20.2)	41 (73.2)	49.4%
Statin use at baseline			
No	355 (86.4)	50 (89.3)	14.1%
Yes	56 (13.6)	6 (10.7)	10.7%
Ever statin use over study			
No	265 (64.5)	42 (75.0)	15.8%
Yes	146 (35.5)	14 (25.0)	9.6%

[a] 1 value missing for education, baseline NSAIDs; 2 values missing waist-to-hip ratio

[c] Quartiles determined within-sex: Quartile 1 upper value= 0.9306 (men), 0.8086 (women); Quartile 2 upper value= 0.9616 (men), 0.8651 (women); Quartile 3 upper value=0.9970 (men), 0.9110 (women); Quartile 4 upper value=1.142 (men), 1.035(women)

Table 2

Demographic and health-related characteristics by statin use

Characteristics	No Statin Use[a] (n=265) N (%)	Ever Statin Use[a] (n=146) N (%)	p-value
Age (years)			
30–54	89 (33.6)	38 (26.0)	0.02[d]
55–69	100 (37.7)	76 (52.1)	
≥70	76 (28.7)	32 (21.9)	
Sex			
Men	205 (77.4)	129 (88.4)	<0.01[d]
Women	60 (22.6)	17 (11.6)	
Smoking Status			
Never	108 (40.8)	40 (27.4)	<0.01[d]
Ever	157 (59.3)	106 (72.6)	
Smoking (pack years)[b]			
Mean ± std dev	16.4 ± 23.9	22.5 ± 24.5	0.02[e]
Median (min - max)	3.0 (0–135)	17 (0–122.5)	
Education[b]			
No college education	89 (33.7)	46 (31.5)	0.65[d]
Any college education	175 (66.3)	100 (68.5)	
Waist-to-hip ratio[c]			
First quartile	63 (23.9)	41 (28.3)	0.27[d]
Second quartile	66 (25.0)	35 (24.1)	
Third quartile	72 (27.3)	28 (19.3)	
Fourth quartile	63 (23.9)	41 (28.3)	
NSAID use as of baseline[b]			
Never	123 (46.6)	39 (26.7)	<0.01[d]
Former	54 (20.5)	25 (17.1)	
Current	87 (33.0)	82 (56.2)	
High Grade Dysplasia at or before baseline			
No	210 (79.3)	118 (80.8)	0.70[d]
Yes	55 (20.8)	28 (19.2)	

[a] Ever use of statins defined by current use at baseline interview or over study-follow-up

[b] 1 missing value for smoking history, education, and use of NSAIDs among never--users

[c] 1 missing value for waist-to-hip ratio among never-users, as well as 1 missing value among ever-users

[d] X^2 test of overall distribution

[e] T-test assuming unequal variance

Table 3

Associations between time-varying statin and NSAID use and the risk of esophageal adenocarcinoma

Medication	Persons	Cases	Unadjusted HR (95% CI)	Age & Sex- Adjusted HR (95% CI)	Model 1[c] HR (95% CI)	Model 2 HR (95% CI)
All study population	**395**	**45**				
Statin	143[a]	11	0.71 (0.32, 1.61)	0.63 (0.28–1.42)	0.59 (0.26, 1.33)	0.68 (0.30, 1.54) [d]
NSAID	284[b]	23	0.68 (0.38, 1.23)	0.57 (0.32–1.01)	0.58 (0.32, 1.02)	0.62 (0.34, 1.10) [e]
High grade dysplasia at baseline	**69**	**30**				
Statin	25[a]	6	0.44 (0.16, 1.20)	0.35 (0.12- 1.07)	0.31 (0.11, 0.86)	0.41 (0.13, 1.26) [d]
NSAID	43[b]	12	0.44 (0.20, 0.96)	0.36 (0.16–0.80)	0.37 (0.17, 0.83)	0.46 (0.19, 1.09) [e]

[a] Ever used statins at baseline or over follow-up

[b] Ever used NSAIDs at baseline or over follow-up

[c] Adjusted sex, age (continuous linear), and pack-years smoked (continuous linear)

[d] Adjusted sex, age (continuous linear), pack-years smoked (continuous linear), and use of NSAIDs (yes/no) over follow-up

[e] Adjusted sex, age (continuous linear), pack-years smoked (continuous linear), and use of statins (yes/no) over-follow-up