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Atorvastatin correlates with decreased risk of esophageal cancer: a population-based case–control study from Taiwan

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Objectives: The aim of this study was to explore the association between the use of statins and esophageal cancer in Taiwan.

Methods: We designed a case–control study using database from the Taiwan National Health Insurance program. In all, 549 patients (cases) aged 20 years or older diagnosed recently with esophageal cancer, from 2000 to 2009, and 2,196 subjects (controls) without esophageal cancer participated in this study. The association between esophageal cancer and the use of statins and other co-morbidities was measured.

Results: After adjustment for covariates, multivariate logistic regression showed that patients with a cumulative duration of $\geq$12 months of using atorvastatin might have a reduced risk of esophageal cancer, compared with those who did not use statins (odds ratio [OR] 0.14, 95% confidence interval [CI] 0.04–0.56). The other statins could not show a significant association with esophageal cancer. Age (OR 1.01, 95% CI 1.00–1.01), alcoholism (OR 3.83, 95% CI 3.01–4.89), and esophageal diseases (OR 4.60, 95% CI 3.46–6.12) were independent factors significantly associated with esophageal cancer.

Conclusions: Use of atorvastatin $\geq$12 months may correlate with an 86% reduction of esophageal cancer risk.

Keywords: *atorvastatin*; *esophageal cancer*; *statin*

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Introduction

According to global estimates in 2008, esophageal cancer was the eighth commonly diagnosed cancer (482,300 new cases) and the sixth leading cause of cancer deaths (406,800 death cases) (1, 2). In 2010, esophageal cancer was the eighth leading cause of cancer deaths in Taiwan, with a mortality rate of 6.8 per 100,000 persons (1,563 fatalities, 3.8% of the total) (3).

The etiology of esophageal cancer remains inconclusive, but a number of risk factors have been reported to be associated with esophageal cancer in previous literature, including Barrett's esophagus, gastroesophageal reflux disease, obesity, cigarette smoking, excess alcohol consumption, use of spicy foods and hot drinks, and low intake of fresh fruit and vegetables (4–7). On the contrary, *Helicobacter pylori* infection and use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) correlate with decreased risk of esophageal cancer (4–6).

3-Hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, known as statins, are commonly used to reduce the cholesterol level and to further decrease the risk of cardiovascular disease.

Recently, two *in vitro* studies demonstrated that statins have the ability to inhibit proliferation and further increase apoptosis of esophageal adenocarcinoma cells (8, 9). A case–control study by Nguyen et al. in the

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United States showed that use of statins correlates with 45% reduction of esophageal cancer risk in patients with Barrett's esophagus (95% confidence interval [CI] 0.36–0.86) (10).

To date, there has been no study available on the association between the use of statins and esophageal cancer in Taiwan. With comprehensive understanding of esophageal cancer, new preventive strategies can be developed to help improve treatment outcomes and reduce related fatalities. Therefore, we conducted this case–control study using the National Health Insurance (NHI) program database in Taiwan to explore the following questions: (1) Is there an association between use of statins and esophageal cancer? (2) What are the effects of other co-morbidities and medications on the risk of esophageal cancer?

Materials and methods

Data sources

This case–control study used data from the NHI program in Taiwan, the details of which can be found in previous studies (11–14). To ensure patient privacy, all personal identification data on files related to this study were replaced with surrogate identification numbers. This study was exempt from full review by the Institutional Review Board.

Inclusion criteria

For subjects, we selected those who were diagnosed recently with esophageal cancer (*International Classification of Diseases Ninth Revision-Clinical Modification*, ICD-9 codes 150.X and A-code A090) during the period of 2000–2009 and aged 20 years or older at the time of diagnosis. The date of diagnosis of esophageal cancer was defined as the index date for each case. For each case of esophageal cancer, we randomly selected, from the same dataset, four subjects who were frequency matched for sex, age (per 5 years) and index date as controls. We excluded those subjects with esophageal cancer or any other cancer (ICD-9 codes 140–208 and A-code A08x-A14x) before the index date.

Potential co-morbidities and medications associated with esophageal cancer risk

To enumerate the effects of potential co-morbidities and medications on the risk of esophageal cancer, the following co-morbidities were included before the index date: obesity (ICD-9 codes 278.00, 278.01, and A-code A183), esophageal diseases (ICD-9 codes 530.x and 947.2), *H. pylori* infection (ICD-9 codes 041.86), alcoholism (ICD-9 codes 303, 305.00, 305.01, 305.02, 305.03, V11.3, and A-code A215), and tobacco use (ICD-9 codes 305.1). Medication history of six commercially available statins before the index date, including simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin, were included. The other medications included were as follows: non-statin lipid-lowering drugs, proton pump inhibitors, histamine-2 receptor antagonists, aspirin, other NSAIDs, and cyclooxygenase-2 inhibitors (COX-2 inhibitors).

Statistical analysis

We demonstrated the differences in demographic factors, co-morbidities, and medications between the esophageal cancer cases and the controls by the Chi-square test, *t*-test, and Fisher's exact test. The significant variables were further included in the multivariate logistic regression analysis to measure odds ratio (OR) and 95% CI for esophageal cancer. The statistical significance level was set at a probability value of <0.05 (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina).

Results

Baseline characteristics of the study population

In this study, 549 cases with esophageal cancer and 2,196 subjects as controls without esophageal cancer were presented. Table 1 compares the demographic characteristics, co-morbidities, and medications between esophageal cancer cases and controls. The cases had higher proportions of alcoholism, esophageal diseases, use of proton pump inhibitors, use of histamine-2 receptor antagonists, use of other NSAIDs, and use of COX-2 inhibitors.

Esophageal cancer associated with use of statins and covariates

After adjustment for covariates, multivariate logistic regression showed the adjusted OR of esophageal cancer as 0.66 (95% CI 0.45–0.95) for the group that uses statins, when compared with the group that does not use statins. Age (OR 1.01, 95% CI 1.00–1.01), alcoholism (OR 3.83, 95% CI 3.01–4.89), esophageal diseases (OR 4.60, 95% CI 3.46–6.12), and use of proton pump inhibitors (OR 3.83, 95% 3.01–4.89) were independent factors significantly associated with esophageal cancer (Table 2).

Sub-analysis of the association between the six types of statins and esophageal cancer

In sub-analysis, patients with a cumulative duration of using atorvastatin $\geq$12 months had a reduced risk of esophageal cancer, compared with those who does not use statins (OR 0.14, 95% CI 0.04–0.56). The other statins did not show a significant association with esophageal cancer (Table 3).

Discussion

A growing body of epidemiologic evidence has shown that use of statins correlates with risk reduction of some

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Table 1. Comparison by demographic factors and other medical conditions between esophageal cancer cases and controls

	Esophageal cancer		
	No ($N=2,196$) *n* (%)	Yes ($N=549$) *n* (%)	*P*
Sex			1.00
Women	156 (7.10)	39 (7.10)	
Men	2040 (92.9)	510 (92.9)	
Age (Mean and SD, years)*	60.3 (13.3)	60.9 (12.9)	0.33
Co-morbidities			
Alcoholism	31 (1.41)	78 (14.2)	<0.0001
Tobacco use disorder	37 (1.68)	9 (1.64)	0.94
Obesity†	4 (0.18)	3 (0.55)	0.15
Esophageal diseases	128 (5.83)	178 (32.4)	<0.0001
Helicobacter pylori infection	10 (0.46)	3 (0.55)	0.78
Medications			
Use of statins	238 (10.8)	49 (8.93)	0.19
Use of non-statin, lipid-lowering drugs	209 (9.52)	58 (10.6)	0.46
Use of proton pump inhibitors	284 (12.9)	262 (47.7)	<0.0001
Use of histamine-2 receptor antagonists	1139 (51.9)	391 (71.2)	<0.0001
Use of aspirin	715 (32.6)	187 (34.1)	0.50
Use of other NSAIDs	2021 (92.0)	526 (95.8)	0.002
Use of COX-2 inhibitors	534 (24.3)	157 (28.6)	0.04

Data are presented as the number of subjects in each group, with percentages given in parentheses. Chi-square test, **t*-test, and †Fisher's exact test comparing subjects with and without esophageal cancer.

digestive cancers, including those of stomach, colon–rectum, liver, and pancreas (15–18). To the best of our knowledge, the association between the use of statins and esophageal cancer is still under investigation. In this study, we found patients using statins had an overall 34% risk reduction of esophageal cancer, when compared with the group not using statins. In sub-analysis, atorvastatin could reduce 86% risk of esophageal cancer when used for ≥12 months. These results are consistent with a previous study by Nguyen et al. (10), which suggested that use of statins for more than 12 months can correlate with 48% risk reduction of esophageal cancer in patients with Barrett's esophagus (95% CI 0.30–0.91) (10). Although the mechanism behind the correlation of the use of statins

Table 2. Crude and adjusted odds ratios and 95% confidence intervals of esophageal cancer associated with use of statins and covariates

Variable	Crude OR (95%CI)	Adjusted OR (95%CI)
Sex		
Women	1.00	1.00
Men	1.00 (0.70–1.44)	0.88 (0.59–1.33)
Age (per year)	1.00 (1.00–1.01)	1.01 (1.00–1.01)
Co-morbidities (yes vs. no)		
Alcoholism	11.6 (7.54–17.7)	3.83 (3.01–4.89)
Esophageal diseases	7.75 (6.02–9.98)	4.60 (3.46–6.12)
Medications (use vs. non-use)		
Statins	0.81 (0.58–1.11)	0.66 (0.45–0.95)
Proton pump inhibitors	6.15 (4.99–7.57)	3.83 (3.01–4.89)
Histamine-2 receptor antagonists	2.30 (1.88–2.81)	1.21 (0.95–1.53)
Other NSAIDs	1.98 (1.27–3.09)	1.21 (0.75–1.97)
COX-2 inhibitors	1.25 (1.01–1.54)	0.80 (0.62–1.04)

Adjusted for sex, age, esophageal diseases, alcoholism, statins, proton pump inhibitors, histamine-2 receptor antagonists, other NSAIDs, and COX-2 inhibitors.

with decreased risk of esophageal cancer is not well elucidated, *in vitro* studies have demonstrated that statins have the effects of decreasing viability, decreasing proliferation, and increasing apoptosis of human esophageal adenocarcinoma cells (8, 9). More studies are needed to explore the links between esophageal cancer and the use of statins to gain a better understanding on the protective or harmful effects of statins on esophageal cancer risk.

Contrary to previous studies (19, 20), we found that proton pump inhibitors might be associated with increased risk of esophageal cancer (OR 3.83). In our opinion, this does not mean that proton pump inhibitors potentially cause esophageal cancer. Instead, patients treated with proton pump inhibitors might be those with early undiagnosed esophageal cancer who initially present with esophageal symptoms and use proton pump inhibitors. That is, proton pump inhibitors may mask the diagnosis of esophageal cancer. We also found that esophageal diseases correlate with increased risk of esophageal cancer (OR 4.60). Thus, these findings should alert clinicians to be more cautious of the potential risk of esophageal cancer when patients present with esophageal symptoms.

There are a number of limitations to this study. The first concern is that we cannot separately examine squamous cell cancer from adenocarcinoma of the esophagus because of inherent limitation of the dataset we used. This is a fundamental issue for analysis because these two cancers may be associated with different risk

Table 3. Odds ratios and 95% confidence intervals of esophageal cancer by duration of use of statins

	Case/*N*	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
Non-use of *statins* as a reference	500/2,458	1.00 (reference)	1.00 (reference)
Atorvastatin			
All	19/133	0.65 (0.40–1.07)	0.52 (0.30–0.92)
<6 months	10/68	0.68 (0.34–1.33)	0.57 (0.27–1.21)
6–11 months	6/20	1.68 (0.64–4.39)	1.86 (0.66–5.24)
≥12 months	3/45	0.28 (0.09–0.91)	0.14 (0.04–0.56)
Simvastatin			
All	20/103	0.94 (0.57–1.55)	0.79 (0.44–1.40)
<6 months	18/55	1.91 (1.08–3.38)	1.67 (0.86–3.25)
6–11 months	0/20	–	–
≥12 months	2/28	0.30 (0.07–1.27)	0.21 (0.04–1.01)
Lovastatin			
All	13/84	0.72 (0.39–1.31)	0.60 (0.30–1.18)
<6 months	8/57	0.64 (0.30–1.35)	0.50 (0.21–1.16)
6–11 months	3/14	1.07 (0.30–3.84)	1.29 (0.34–5.00)
≥12 months	2/13	0.71 (0.16–3.22)	0.48 (0.08–2.95)
Fluvastatin			
All	9/46	0.95 (0.46–1.99)	0.81 (0.35–1.86)
<6 months	5/30	0.78 (0.30–2.06)	0.65 (0.22–1.92)
6–11 months	1/7	0.65 (0.08–5.43)	0.58 (0.05–6.82)
≥12 months	3/9	1.96 (0.49–7.86)	1.68 (0.33–8.49)
Pravastatin			
All	4/29	0.63 (0.22–1.81)	0.50 (0.16–1.61)
<6 months	3/22	0.62 (0.18–2.10)	0.57 (0.15–2.19)
6–11 months	0/3	–	–
≥12 months	1/4	1.31 (0.14–12.6)	1.26 (0.12–13.8)
Rosuvastatin			
All	4/28	0.65 (0.23–1.89)	0.37 (0.11–1.21)
<6 months	2/17	0.52 (0.12–2.29)	0.25 (0.05–1.30)
6–11 months	1/3	1.96(0.18–21.6)	1.33 (0.11–16.3)
≥12 months	1/8	0.56(0.07–4.56)	0.35 (0.04–3.61)

†Adjusted for age, sex, esophageal diseases, alcoholism, statins, proton pump inhibitors, histamine-2 receptor antagonists, other NSAIDs, and COX-2 inhibitors.

factors (6, 7). This indicates a future direction for research into the effects of statins on squamous cell cancer and adenocarcinoma of the esophagus. Second, lack of control for potentially confounding factors, including use of spicy foods and hot drinks, low intake of fresh fruit and vegetables, is also because of inherent limitation of this dataset. Third, the number of subjects for each of the individual statins is relatively small. Particularly, only 19 cases suffered from esophageal cancer in the atorvastatin-use group and only 3 cases used it for ≥12 months. Albeit statistically significant, this result should be interpreted carefully because this figure is really too small to draw firm conclusions.

Conclusion

This study shows that use of atorvastatin ≥12 months may reduce 86% risk of esophageal cancer. Age, alcoholism, and esophageal diseases are independent factors significantly associated with esophageal cancer.

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Conflict of interest and funding

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