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Journal

Cancer Causes & Control, 27(3)

ISSN

0957-5243

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Publication Date

2016-03-01

DOI

10.1007/s10552-016-0717-6

Peer reviewed

HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2019 November 12.

Published in final edited form as:

Cancer Causes Control. 2016 March ; 27(3): 415–423. doi:10.1007/s10552-016-0717-6.

Prospective analysis of association between statins and pancreatic cancer risk in the Women's Health Initiative

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Abstract

Purpose—To determine whether HMG-CoA reductase inhibitors (statins) are associated with a lower risk of pancreatic cancer.

Methods—The population included 160,578 postmenopausal women enrolled in the Women's Health Initiative (WHI) in which 385 incident cases of pancreatic cancer were identified over an average of 8.69 (SD ±4.59) years. All diagnoses were confirmed by medical record and pathology review. Information on statin use and other risk factors was collected at baseline and during follow-up. Multivariable-adjusted hazards ratios (HRs) and 95 % confidence intervals (CIs) evaluating the relationship between prior statin use (at baseline only as well as in a time-dependent manner) and risk of pancreatic cancer were computed from Cox proportional hazards regression analyses after adjusting for appropriate confounders. We also evaluated the effect of statin type, potency, lipophilic status, and duration of use. All statistical tests were two-sided.

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This work was presented as a poster at the 2013 annual WHI investigators meeting in Seattle, WA.

Results—Statins were used at baseline by 12,243 (7.5 %) women. The annualized rate of pancreatic cancer in statin users and nonusers, respectively, was 0.0298 versus 0.0271 %. The multivariable-adjusted HR for statin users versus nonusers at baseline was 0.92 and 95 % CI 0.57–1.48. In a time-dependent model, the HR for low-potency statins was 0.46, 95 % CI 0.20–1.04. There was no significant effect seen by statin lipophilicity or duration of use.

Conclusions—There was no significant relationship between statins and pancreatic cancer risk in the WHI; however, there was a marginal inverse association noted for low-potency statins. Analyses of larger numbers of cases are needed to further explore this relationship.

Keywords

Pancreatic cancer; Cancer risk; Statins

Introduction

In 2014, it is estimated that there were 46,420 new cases of pancreatic cancer in the USA with 39,590 deaths as a result of the disease [1]. The estimated 5-year survival rate from 2004 to 2010 was 6.7 % [1]. Given the overall poor survival and the lack of effective treatment options [2], it is important to explore and consider new agents that can be utilized for chemoprevention and/or treatment of pancreatic cancer [3].

Statins have known efficacy for cholesterol reduction and prevention of cardiovascular disease [4], and preclinical studies suggest a potential anticancer effect through inhibition of HMG-CoA reductase leading to down-regulation of downstream products in the mevalonate pathway which are involved in multiple molecular pathways known to be deregulated in cancer including Ras, MEK, PI3K/Akt [5, 6], Rho kinases [7, 8], and BC12 [9]. Since pancreatic cancers frequently contain mutations in the Ras and PI3K/Akt genes [10–12], this tumor type may be a potential target for preventative strategies using statins, a hypothesis that is supported by both in vitro [13] and mouse model studies [14, 15]. Despite promising preclinical data, epidemiologic studies of statins and pancreatic cancer have yielded mixed results with the majority showing no association, as reviewed in a recent meta-analysis [16]. However, a reduction in risk was reported in two recent case-control studies [17, 18] and an increase in risk in a cohort analysis [19].

In this report, we examine the relationship between statins and risk of pancreatic cancer in the WHI. Our hypothesis was that prior statin use would be associated with a reduced risk of pancreatic cancer. The WHI is the largest multicenter longitudinal study of postmenopausal women in the USA with follow-up on cancer diagnoses through September 2012 [20].

Methods

Study population

The population included 161,808 postmenopausal women age 50–79 enrolled in the WHI clinical trial (CT) and observational study (OS) from 1 October 1993 through 31 December 1998. Study implementation details have been published previously [20–22]. Follow-up continued from study initiation until planned termination on March 2005 and thereafter for

participants providing re-consent with data collection updated through September 2012. We excluded from the analysis 1,228 women with a prior history of pancreatitis as well as two women for whom there was no information on statin use.

Statin exposure

Statin exposure and duration were determined at baseline in the CT and OS participants. The participants were asked to bring all prescription medications to the clinic visit (or first interview at baseline), and each medication name was directly entered from the medication containers into the WHI database, which assigned drug codes using Medispan software (First DataBank, Inc., San Bruno, CA). Statin duration was measured by in-person questionnaire at baseline, and information provided was based on participant self-report. For the current analysis, information on statin duration was only based on baseline data. In order to carry out a time-dependent analysis (see “Statistical analysis” section), we utilized reported statin use that was updated in year 3 in the OS and years 1, 3, 6, and 9 in the CT.

Statin intake was defined as use of any 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. Statins were classified as lipophilic (lovastatin, simvastatin, fluvastatin, atorvastatin) or hydrophilic (pravastatin) [23, 24] and by potency: low potency (fluvastatin and lovastatin), medium potency (pravastatin), and high potency (simvastatin and atorvastatin) [24, 25].

Outcomes

The outcome of interest was pathologically confirmed invasive pancreatic cancer. Reported cancer cases were initially confirmed by medical record review by trained physician adjudicators at the clinical centers. Final adjudication was done at the Clinical Coordinating Center.

Covariates

Information regarding potential confounding and modifying variables was collected by baseline questionnaire which ascertained socio-demographic characteristics, known risk factors for pancreatic cancer (age, race/ethnicity, smoking status, and history of diabetes mellitus), other variables potentially associated with cancer risk, variables associated with statin use, and other variables associated with healthcare utilization which might impact both statin utilization and cancer detection. Information on baseline food habits was determined by the WHI Food Frequency Questionnaire [26]. The covariates considered are listed in Tables 1 and 2. The medical history variable includes a personal history of diabetes, high cholesterol, myocardial infarction, angina, and/or pancreatic disease. BMI was adjusted for as a continuous variable.

Statistical analysis

The characteristics of statin users versus nonusers at baseline as well as pancreatic cases versus non-cases were compared by Chi-square tests. Annualized rates of pancreatic cancer were calculated according to the use of statins at baseline. Planned selected subgroup analyses were conducted by statin use duration as determined at baseline (<1, 1 to <3, and ≥3 years), statin type, potency, and lipophilic status. Women reporting use of two or more

statins were included in analyses that compared statin use to none, but were excluded from analyses that examine details of statin use by type, potency, or lipophilic status. Hazard ratios (HRs) and 95 % confidence intervals (CIs) for risk of pancreatic cancer among statin users versus nonusers were computed from Cox proportional hazards models. Tests for the proportional hazards assumptions were conducted by fitting a Cox model that included statin use and the interaction of statin use with follow-up time, and testing for a zero coefficient on the interaction term. An a priori selection of covariates with a backward elimination using a 10 % level of statistical significance in Cox modeling was utilized to create a final multivariable-adjusted model. The base models were adjusted by age and stratified by WHI trial (hormone therapy, dietary modification, or OS), extension study participation, and age group.

The multivariable model was adjusted for age and BMI as continuous variables and ethnicity, smoking status, education, alcohol use, physical activity, >30 % energy intake from fat, waist circumference, current medical care provider, aspirin and NSAID use, self-reported health status, and medical history as categorical variables. Subgroup analyses were conducted to look at the impact of history of diabetes, BMI, and smoking on the relationship between statins and pancreatic cancer risk.

To evaluate the effect of change in statin use over time, final models were rerun by entering statin use as a time-dependent exposure and using updated information on statins gathered at year three in the OS and years one, three, six, and nine in the CT. We censored cancer outcomes in OS participants 3 years after the last medication update in order to closely parallel measurement of statin exposure in the CT.

All statistical tests were two-sided, and nominal P values of 0.05 or less were regarded as statistically significant. Analyses were performed using Statistical Analysis Software (SAS) version 9.4.

Results

Table 1 describes the baseline demographic and clinical characteristics of WHI participants stratified by statin use. Many of the differences noted were statistically significant given the large sample size. There were 12,243 (7.6 %) women who reported statin use at baseline. Of note, statin users were more likely to be older than nonusers (median age 65.6 vs. 63.0 years), report a history of smoking, have a higher BMI and waist circumference, report consuming more than 30 % of energy from fat, and report a history of diabetes requiring treatment. Table 2 describes the characteristics of pancreatic cases compared with non-cases. There were 381 women diagnosed with pancreatic cancer during the follow-up period. Women with pancreatic cancer were more likely to be older, have a larger waist circumference, consume a higher % of energy from fat, use NSIADS, and report a history of diabetes. Table 3 shows the distribution of statin use at baseline by type, duration, potency, and lipophilicity. Table 4 shows the annualized incidence and HRs of pancreatic cancer by statin use, type, lipophilicity, potency, and duration. The annualized incidence rates of pancreatic cancer among statin users and nonusers were 0.0298 % (median follow-up 8.0 years) and 0.0271 % (median follow-up 8.8 years), respectively. There was no association

between statin use at baseline and pancreatic cancer risk (HR 0.92, 95 % CI 0.57–1.48), and there was no significant relationship by statin type, lipophilicity, potency, or duration of use.

Table 5 shows the relationship between statin use and pancreatic cancer using a time-dependent model. In this model, lovastatin was associated with a nonsignificant lower risk of pancreatic cancer (HR 0.269, 95 % CI 0.067–1.09). A similar relationship was seen in the subgroup analysis of low-potency statins (lovastatin and fluvastatin), which also revealed a nonsignificant lower risk of pancreatic cancer (HR 0.46, 95 % CI 0.20–1.04). There was no other significant relationship by individual statin type or lipophilicity in the time-dependent analysis. In addition, there was no relationship between statins and pancreatic cancer by current smoking status (yes vs. no), BMI at baseline (<25, 25 to <30, ≥30), or history of diabetes mellitus (data not shown). In an analysis excluding 28 cases of pancreatic cancer which occurred within 1 year of study enrollment, there were no differences in our findings (data not shown).

Discussion

Overall, in the present study statins were not associated with a reduced risk of pancreatic cancer in the WHI cohort. However, in a time-dependent analysis there was a marginal, nonsignificant reduction in risk of pancreatic cancer associated with lovastatin and the combined grouping of lovastatin and fluvastatin (low-potency statins). There was, however, no significant relationship by lipophilicity or duration of use, and no interaction with BMI, history of diabetes, or smoking history. Ras and PI3K/Akt are mutated in approximately 95 % of pancreatic cancers [10, 12, 27], and we hypothesized that statins may impact cancer risk through alteration in these pathways [5–9, 14, 28].

Despite the evidence for biologic plausibility, the majority of clinical evidence does not demonstrate a relationship between statins and pancreatic cancer risk. In a meta-analysis of 16 studies involving 1,692,863 participants and 7,807 pancreatic cancer cases, pooled results revealed a nonsignificant lower risk of pancreatic cancer among users of any statins (RR 0.89, 95 % CI 0.74–1.07). Similar results were obtained in the subgroup analyses for long-term use (>4 years), and a null association was seen for lipophilic statins (RR 1.03, 95 % CI 0.92–1.16) [16]. No specific results were provided in the meta-analysis for users of specific types of statins or by potency. There was, however, a marked heterogeneity of results with one case-control study of male veterans contributing the most showing a significantly lower risk of pancreatic cancer (HR 0.37, 95 % CI 0.3–0.46) [18] and an analysis from the Cancer Prevention Study II Nutrition Cohort showing an increased risk of pancreatic cancer (HR 1.33, 95 % CI 1.03–1.72) [19]. There is also a recently published hospital-based case-control study showing a lower risk of pancreatic cancer among male smokers; however, these results were based on small numbers with only one out of 25 male cases reporting prior use of statins (OR 0.11, 95 % CI 0.01–0.96) [17].

Our results show no significant interaction by smoking history and are consistent with the literature showing no overall effect of statins on risk of pancreatic cancer risk. The suggestion of a lower risk of pancreatic cancer associated with low-potency statins is mostly driven by the effect of lovastatin which is also a lipophilic statin and which is of interest

given other studies that suggest that lipophilic statins have a greater anticancer potential than hydrophilic statins [23, 24].

Prior analyses of statins and cancer in the WHI showed no relationship between statins and breast cancer [29] [31] or melanoma [32]; however, a similar marginal lower risk of colorectal cancer was seen among prior users of lovastatin [30].

The strengths of our study include the prospective design and the large and diverse population which included a large sample size (381 cases) and longer period of follow-up than any of the other studies reported in the meta-analysis [16]. In addition, we were able to evaluate the effect of statins by individual type of statin and statin potency. Other strengths include the well-characterized risk factors for pancreatic cancer and cardiovascular risk, outcome verification by central review, and serial update of statin use. Limitations include the low prevalence of statin use at baseline, although the time-dependent analysis enabled us to capture changes in statin use over time. Other limitations include lack of information on medication compliance, the fact that statin use was self-reported, collection of medication use at only selected intervals of time, and recall bias. It is also possible that the estimated association between low-potency statins and pancreatic cancer risk is confounded by unknown or unmeasured factors associated with both exposure and outcome.

In conclusion, we found no overall association between statin use and pancreatic cancer risk. However, the marginal lower risk associated with lovastatin implies a potential protective effect of low-potency or lipophilic statins. Further studies in larger populations are needed to clarify these findings.

Acknowledgments

We acknowledge the dedicated efforts of investigators and staff at the Women's Health Initiative (WHI) clinical centers, the WHI Clinical Coordinating Center, and the National Heart, Lung, and Blood program office (listing available at http://www.whi.org). We also recognize the WHI participants for their extraordinary commitment to the WHI program. For a list of all the investigators who have contributed to WHI science, please visit: http://www.whiscience.org/publications/WHI_investigators_longlist.pdf.

Funding The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through Contracts N01WH22110, 24152, 32100–2, 32105–6, 32108–9, 32111–13, 32115, 32118–32119, 32122, 42107–26, 42129–32, and 44221, and the Cancer Center Support Grant NIH:NCI P30CA022453.

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Table 1

Baseline characteristics by statin use

	Nonuser		User		*p* value
	n	%	*n*	%	
Age group at screening					
50–59	51,368	34.35	2,189	17.88	<.0001
60–69	66,219	44.27	6,370	52.03	
70–79	31,976	21.38	3,684	30.09	
Race/ethnicity					
White	123,494	82.57	10,046	82.06	<.0001
Black	13,499	9.03	1,118	9.13	
Hispanic	6,100	4.08	384	3.14	
American Indian	665	0.44	48	0.39	
Asian/Pacific Islander	3,720	2.49	470	3.84	
Unknown	2,085	1.39	177	1.45	
Education					
<HS diploma/GED	7,850	5.29	794	6.53	<.0001
HS diploma/GED	25,061	16.88	2,563	21.07	
>HS diploma/GED	115,517	77.83	8,805	72.40	
Smoking status					
Never	75,545	51.18	5,884	48.78	<.0001
Past	61,667	41.77	5,442	45.12	
Current	10,406	7.05	736	6.10	
Alcohol					
Nondrinker	43,579	29.36	4,221	34.70	<.0001
≤1 drink/day	48,774	32.86	4,088	33.60	
>1 drink/day	56,064	37.77	3,856	31.70	
Body mass index (kg/m^2)					
<25	53,313	35.96	3,021	24.88	<.0001
25 to <30	50,858	34.31	4,822	39.72	
≥30	44,068	29.73	4,297	35.40	

	Nonuser		User		*p* value
	n	%	*n*	%	
Physical activity (met/week)					
Inactive 0 METs	22,703	15.94	1,759	14.73	<.0001
[0,3.75) METs	20,789	14.60	1,831	15.33	
[3.75, 8.75) METs	29,140	20.46	2,626	21.99	
[8.75, 17.5) METs	32,101	22.54	2,784	23.31	
≥17.5 METs	37,660	26.45	2,942	24.64	
Waist circumference >88 cm					
No	91,023	61.08	6,153	50.43	<.0001
Yes	58,000	38.92	6,049	49.57	
≥30 % energy from fat					
No	52,486	35.16	5,370	43.92	<.0001
Yes	96,800	64.84	6,856	56.08	
Aspirin use ≥80 mg for at least 30 days					
No	121,169	81.02	7,952	64.95	<.0001
Yes	28,394	18.98	4,291	35.05	
NSAIDS use					
No	99,988	66.85	6,453	52.71	<.0001
Yes	49,575	33.15	5,790	47.29	
Self-reported health status					
Excellent	26,475	17.82	912	7.50	<.0001
Very good	61,512	41.40	4,124	33.91	
Good	47,746	32.13	5,296	43.55	
Fair	11,775	7.92	1,686	13.86	
Poor	1,089	0.73	143	1.18	
Diabetes requiring treatment					
No	143,463	96.00	11,028	90.19	<.0001
Yes	5,970	4.00	1,199	9.81	
History of angina					
No	141,638	95.34	10,126	83.44	<.0001
Yes	6,920	4.66	2,009	16.56	

	Nonuser		User		*p* value
	n	%	*n*	%	
History of hyperlipidemia requiring medical treatment					
No	130,466	92.84	430	3.61	<.0001
Yes	10,066	7.16	11,469	96.39	
History of MI					
No	146,877	98.25	11,137	91.06	<.0001
Yes	2,610	1.75	1,094	8.94	
Antihyperlipidemic group					
No	147,619	98.70			<.0001
Yes	1,944	1.30	12,243	100.00	
Current healthcare provider					
No	9,800	6.62	195	1.61	<.0001
Yes	138,286	93.38	11,950	98.39	

Table 2

Baseline characteristics by pancreatic cancer case status

	Pancreatic cancer				
	No		Yes		*p* value
	n	%	*n*	%	
Age group at screening					
50–59	53,489	33.14	70	18.18	<.0001
60–69	72,408	44.86	181	47.01	
70–79	35,526	22.01	134	34.81	
Race/ethnicity					
White	133,213	82.52	328	85.19	0.1259
Black	14,586	9.04	32	8.31	
Hispanic	6,478	4.01	6	1.56	
American Indian	712	0.44	1	0.26	
Asian/Pacific Islander	4,176	2.59	14	3.64	
Unknown	2,258	1.40	4	1.04	
Education					
<HS diploma/GED	8,619	5.38	25	6.54	0.5505
HS diploma/GED	27,556	17.20	68	17.80	
>HS diploma/GED	124,035	77.42	289	75.65	
Smoking status					
Never	81,242	51.00	188	49.21	0.3216
Past	66,950	42.03	160	41.88	
Current	11,108	6.97	34	8.90	
Alcohol					
Nondrinker	47,693	29.77	107	28.01	0.2608
≤1 drink/day	52,746	32.92	117	30.63	
>1 drink/day	59,763	37.30	158	41.36	
Body mass index (kg/m^2)					
<25	56,216	35.14	119	31.15	0.2210
25 to <30	55,544	34.72	136	35.60	
≥30	48,239	30.15	127	33.25	
Physical activity (met/week)					
Inactive 0 METs	24,413	15.85	49	13.80	0.6162
[0,3.75) METs	22,568	14.66	52	14.65	
[3.75, 8.75) METs	31,683	20.58	84	23.66	
[8.75, 17.5) METs	34,806	22.60	79	22.25	
≥17.5 METs	40,512	26.31	91	25.63	
Waist circumference >88 cm					
No	96,976	60.29	201	52.34	0.0015
Yes	63,867	39.71	183	47.66	
≥30 % energy from fat					

	Pancreatic cancer				
	No		Yes		*p* value
	n	%	*n*	%	
No	57,767	35.85	90	23.44	<.0001
Yes	103,363	64.15	294	76.56	
Gail risk score ≥1.67					
No	95,822	59.36	208	54.03	0.0333
Yes	65,601	40.64	177	45.97	
Aspirin use ≥80 mg for at least 30 days					
No	128,821	79.80	300	77.92	0.3582
Yes	32,600	20.20	85	22.08	
NSAIDS use					
No	106,214	65.80	227	58.96	0.0047
Yes	55,207	34.20	158	41.04	
Self-reported health status					
Excellent	27,332	17.04	56	14.58	0.5162
Very good	65,485	40.83	151	39.32	
Good	52,905	32.99	137	35.68	
Fair	13,426	8.37	36	9.38	
Poor	1,228	0.77	4	1.04	
Diabetes requiring treatment					
No	154,142	95.58	351	91.17	<.0001
Yes	7,135	4.42	34	8.83	
History of angina					
No	151,412	94.45	354	91.95	0.0324
Yes	8,898	5.55	31	8.05	
History of hyperlipidemia requiring medical treatment					
No	130,590	85.87	308	87.75	0.3122
Yes	21,492	14.13	43	12.25	
History of MI					
No	157,642	97.71	374	97.14	0.4567
Yes	3,693	2.29	11	2.86	
Antihyperlipidemic group					
No	147,269	91.23	350	90.91	0.8225
Yes	14,152	8.77	35	9.09	
Current healthcare provider					
No	9,972	6.24	23	6.04	0.8709
Yes	149,880	93.76	358	93.96	

Table 3

Distribution of statin use at baseline by type, duration, and other statin characteristics

	No		Yes	
	n	**%**	***n***	**%**
Statin type				
No statin use	149,563	100.00		
Atorvastatin calcium			961	7.85
Fluvastatin sodium			1,484	12.12
Lovastatin			3,204	26.17
Pravastatin sodium			2,686	21.94
Simvastatin			3,589	29.31
2 or more statins			319	2.61
Statin potency				
No statin use	149,563	100.00		
Low (lovastatin, fluvastatin)			4,688	39.32
Medium (pravastatin)			2,686	22.53
High (simvastatin, atorvastatin)			4,550	38.16
Lipophilicity				
No statin use	149,563	100.00		
Hydrophobic statin			9,238	77.47
Other statin			2,686	22.53
Statin use in year 0 (years)				
No statin use	149,563	100.00		
<1			4,054	33.11
1 to <3			4,151	33.91
≥3			4,038	32.98

Table 4

Pancreatic cancer incidence (annualized %) and hours by statin use

	n	Case	Annualized %	Mean follow-up (years)	Age adjusted[a]				Multivariable adjusted[b]			
					Hazard ratio	Lower CL	Upper CL	*p* value	Hazard ratio	Lower CL	Upper CL	*p* value
Statin												
No	148,451	352	0.03	8.75	1.00				1.00			
Yes	12,127	29	0.03	8.03	0.95	0.65	1.38	0.78	0.92	0.57	1.48	0.73
Statin type												
Atorvastatin calcium	951	1	0.01	7.10	0.48	0.07	3.43	0.82	0.54	0.07	3.87	0.81
Fluvastatin sodium	1,469	2	0.02	7.96	0.53	0.13	2.12		0.57	0.14	2.34	
Lovastatin	3,180	7	0.03	8.39	0.81	0.38	1.71		0.68	0.27	1.71	
No statin use	148,451	352	0.03	8.75	1.00				1.00			
Pravastatin sodium	2,663	9	0.04	8.07	1.28	0.66	2.48		1.30	0.62	2.74	
Simvastatin	3,549	8	0.03	7.92	0.95	0.47	1.93		0.92	0.42	2.02	
Lipophilic												
No statin use	148,451	352	0.03	8.75	1.00				1.00			
Lipophilic statin	9,149	18	0.02	8.00	0.79	0.49	1.26	0.46	0.74	0.42	1.31	0.40
Other statin	2,663	9	0.04	8.07	1.28	0.66	2.48		1.30	0.62	2.74	
Statin potency												
No statin use	148,451	352	0.03	8.75	1.00				1.00			
High (simvastatin, atorvastatin)	4,500	9	0.03	7.75	0.86	0.44	1.67		0.84	0.40	1.78	
Low (lovastatin, fluvastatin)	4,649	9	0.02	8.25	0.72	0.37	1.41	0.64	0.65	0.29	1.42	0.56
Medium (pravastatin)	2,663	9	0.04	8.07	1.28	0.66	2.48		1.30	0.62	2.74	
Statin duration												
0	148,451	352	0.03	8.75	1.00				1.00			
1 to <3 years	3,993	9	0.03	7.98	0.91	0.47	1.76		0.93	0.44	1.95	
<1 year	3,946	9	0.03	8.17	0.88	0.45	1.70	0.96	0.89	0.42	1.87	0.94
≥3 years	3,873	9	0.03	7.91	0.92	0.48	1.79		0.79	0.36	1.75	

[a]Stratified by trial, Women's Health Initiative extension study, and age group. Base model was adjusted by age

[b] Multivariable model adjusted for age, body mass index, ethnicity, smoking status, education, alcohol use, physical activity, >30 % energy from fat, waist circumference, current medical care provider, aspirin (80 mg) use, NSAID use, general health, medical history

Table 5

Pancreatic cancer incidence (annualized %) and HRs by time-dependent statin use

	Age adjusted[a]			Multivariable adjusted[b]		
	Hazard ratio	**Lower CL**	**Upper CL**	**Hazard ratio**	**Lower CL**	**Upper CL**
Statin						
No	1.00			1.00		
Yes	0.922	0.716	1.189	0.920	0.681	1.242
Statin type						
No statin use	1.00			1.00		
Atorvastatin calcium	0.952	0.654	1.384	0.951	0.630	1.434
Fluvastatin sodium	0.785	0.324	1.900	0.710	0.261	1.928
Lovastatin	0.241	0.060	0.969	0.269	0.066	1.090
Pravastatin sodium	1.317	0.796	2.180	1.222	0.687	2.173
Simvastatin	0.879	0.552	1.399	0.904	0.543	1.508
Lipophilic						
No statin use	1.00			1.00		
Hydrophobic statin	0.810	0.605	1.084	0.830	0.595	1.156
Other statin	1.293	0.813	2.057	1.180	0.685	2.033
Statin potency						
No statin use	1.00			1.00		
Low (lovastatin, fluvastatin)	0.473	0.223	1.001	0.455	0.200	1.038
Medium (pravastatin)	1.300	0.785	2.151	1.205	0.677	2.143
High (simvastatin, atorvastatin)	0.927	0.687	1.249	0.940	0.670	1.317

[a]Stratified by trial, Women's Health Initiative extension study, and age group. Base model was adjusted by age

[b]Multivariable model adjusted for age, body mass index, ethnicity, smoking status, education, alcohol use, physical activity,>30 % energy from fat, waist circumference, current medical care provider, aspirin (80 mg) use, NSAID use, general health, medical history