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The Risk of Cancer in Users of Statins

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ABSTRACT

Purpose
Several preclinical studies suggested a role for 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) in the treatment of cancer. The objective of this study was to compare the risk of incident cancer between users of statins and users of other cardiovascular medication.

Methods
Data were used from the PHARMO database, containing drug dispensing records from community pharmacies and linked hospital discharge records for residents of eight Dutch cities. The study base included all patients with one or more prescriptions for cardiovascular drugs in the period between January 1, 1985 and December 31, 1998. Cases were identified as patients in the study base with a diagnosis of incident cancer and matched with four to six controls on sex, year of birth, geographic region, duration of follow-up, and index date. The analysis was adjusted for diabetes mellitus; prior hospitalizations; comorbidity; and use of diuretics, angiotensin-converting enzyme inhibitors, calcium-channel blockers, nonsteroidal anti-inflammatory drugs, sex hormones, and other lipid-lowering drug therapies.

Results
In the study base, 3,129 patients were identified and matched to 16,976 controls. Statin use was associated with a risk reduction of cancer of 20% (adjusted odds ratio [OR], 0.80; 95% CI, 0.66 to 0.96). Our data suggest that statins are protective when used longer than 4 years (adjusted OR, 0.64; 95% CI, 0.44 to 0.93) or when more than 1,350 defined daily doses are taken (adjusted OR, 0.60; 95% CI, 0.40 to 0.91).

Conclusion
This observational study suggests that statins may have a protective effect against cancer.

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INTRODUCTION

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are efficient and widely used drugs in the treatment of lipid disorders, especially hypercholesterolemia. In large follow-up studies their efficacy on cardiovascular events has been proven irrefutably for both reduction of morbidity and mortality.[1-5] Accordingly, the use of statins in the Netherlands increased four-fold in the period from 1995 to 1999.[6] The mechanism of action of this class of drugs is considered to be the inhibition of cholesterol biosynthesis through inhibition of the enzyme HMG-CoA reductase. This results in depletion of mevalonate, which is a precursor of cholesterol. Mevalonate also is a precursor of farnesyl and geranylgeranyl moieties, which are essential for the activation of a variety of intracellular proteins through so-called farnesylation or geranylgeranylation (prenylation).[7] Several proteins involved in signaling are dependent on prenylation for their activity, such as Ras, Rho, nuclear lamins, transducin γ, Rap1, and Cdc42. The Ras protein is important in the regulation of cell differentiation and proliferation. Given that approximately 30% of the human tumors have a mutation of *k-Ras* oncogene, expression of this oncogene is thought to be related to aberrant cellular growth.[8]

Given that statins are able to inhibit farnesylation and hence activation of Ras, they might have the capacity to inhibit the

expression of the malignant phenotype of a tumor cell and to restore normal cellular growth. Several in vitro studies have suggested that statins do have antitumor potential.[9-15] In addition, in vivo experiments in laboratory animals indicated that pancreatic tumors and tumors of the colon and the breast are sensitive to statins.[11,16,17] Furthermore, in a phase I clinical study with lovastatin, one minor response was observed in a patient with recurrent high-grade glioma.[18] Recently, a small, nonblinded, randomized, controlled clinical trial was performed in patients with advanced hepatocellular carcinoma. Both a reduction in maximum tumor diameter and a prolonged survival were observed in the pravastatin group compared with the control group.[19]

In contrast, Newman and Hulley[20] reviewed animal studies with lipid-lowering therapy and concluded that statins and fibrates might cause cancer in rodents. However, no carcinogenicity of statins has been observed in individual clinical trials and meta-analyses.[1-5,21] Blais et al[22] investigated the association between the use of statins and the incidence of cancer in a cohort of patients using lipid-lowering therapy. Lower risk of cancer was found in patients using statins, as compared with patients using bile acid–binding resins (relative risk, 0.72; 95% CI, 0.57 to 0.92). However, the median follow-up time (2.7 years) was relatively short.[23] In addition, statin users were defined on the basis of one prescription of statins, irrespective of the duration of therapy.

The aim of this study was to investigate the association between statin therapy and the risk of cancer. Therefore, we conducted a population-based, nested, case-control study exploring prospectively gathered automated pharmacy data and linked hospital morbidity data.

METHODS

Setting

Data were used from the PHARMO record linkage system, a database that contains drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of approximately 300,000 residents of eight medium-sized cities in the Netherlands from 1985 onward. Because almost all individuals designate a single pharmacy to fill their prescriptions from general practitioners or medical specialists, dispensing histories are virtually complete.[24] In the PHARMO system, the drug dispensing history of each individual is linked to hospital discharge records using a validated and reliable probabilistic algorithm.[25] The computerized drug dispensing histories contain data regarding all dispensed prescriptions and include type and quantity of the dispensed drug, dosage form, strength, type of prescriber, dispensing date, and prescribed daily dose. Hospital discharge records include detailed information regarding primary and secondary diagnoses, performed medical procedures, and dates of admission and discharge. All diagnoses are coded according to the International Classification of Disease (9th revision, clinical modification; ICD9-CM). The potential study period consisted of the 14-year period between January 1, 1985 and December 31, 1998. Participants of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are observed until the last prescription.

Study Population

The study base included all patients with one or more prescriptions for cardiovascular drugs (lipid-lowering agents, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, calcium-channel blockers, diuretics, nitrates, and digoxin) in the period between January 1, 1985 and December 31, 1998. Within this study base of patients likely to suffer from cardiovascular disease, we performed a nested case-control study. Cases were defined as patients who were registered with an incident primary discharge diagnosis of cancer (on the basis of ICD9-CM codes 140 to 208) between January 1, 1991 and December 31, 1998. All patients with a history of cancer, chemotherapy, or radiotherapy before the date of diagnosis were excluded.

Controls were sampled from patients in the study base that had not been discharged with a primary or secondary code for cancer, who had not filled prescriptions for anticancer medication (defined by Anatomical Therapeutic Chemical Classification codes L01, L02, L03), and who never underwent chemotherapy or radiotherapy. A potential latent period between the inhibition of malignant cell growth and the diagnosis of cancer of 6 months was assumed. Therefore, the index date was calculated by subtracting 6 months from the date of diagnosis. For every case, four to six controls were matched on sex, year of birth (± 2.5 years), geographic region, duration of follow-up (± 20%), and index date. Duration of follow-up was defined as the difference between the date of entry in PHARMO and the index date.

Drug Exposure

Exposure was defined as use of HMG-CoA reductase inhibitors (all commercially available and approved statins in the Netherlands: pravastatin, simvastatin, cerivastatin, atorvastatin, and fluvastatin) before the index date. According to the hypothesized underlying biologic mechanism, a minimal exposure period was assumed to be required for statins to have any effect on the development of cancer. Therefore, statin use was defined with a threshold of at least 6 months. Cumulative exposure until the index date (in years) was assessed, as well as cumulative dosage, calculated as the sum of dispensed defined daily doses before the index date.

End Points

The primary end point of the study was diagnosis of any malignancy. Subsequently, the effect of statins on individual cancer sites was investigated as a secondary end point.

Potential Confounders

The potential confounding effect of diabetes mellitus, number of hospitalizations before the date of diagnosis, comorbidity, and chronic use of diuretics, ACE inhibitors, calcium-channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), sex hormones, and other lipid-lowering therapies (bile acid–binding resins, fibrates, and nicotinic acid and its derivatives) was evaluated. Patients were classified as diabetic when they had a diagnosis of diabetes (identified by ICD9-CM codes 250.1 to 250.9, 357.2, 362.0, 366.41, and 775.1) or when they received antidiabetic therapy (identified by Anatomical Therapeutic Chemical Classification code A10) up to 1 year after the index date. Chronic drug use was defined as a minimum use of 6 months before the index date. The degree of comorbidity was estimated by using the chronic disease score, which is based on the type of drug prescriptions in the year preceding the date of diagnosis.[26]

Data Analysis

For comparisons of proportions, χ^2 statistics were used (or the Fisher's exact test whenever the expected cell counts were < 5). Conditional logistic regression was used to estimate the relative magnitude of the association between statin use and the risk of cancer, expressed as odds ratios (ORs) and 95% CIs. The analysis was adjusted for diabetes mellitus; number of hospitalizations; comorbidity; and use of diuretics, ACE inhibitors, calcium-channel blockers, NSAIDs, sex hormones, and other lipid-lowering therapies. Because the time since last exposure might be important, the effect of lag time was assessed; this was defined as the time between last statin use and the index date. All statistical tests were performed two-sided with a rejection of the null hypothesis at a P value of less than .05. All statistical analyses were performed using SPSS 10.0 (SPSS Inc, Chicago, IL).

RESULTS

In the study population, 3,789 patients with a primary diagnosis of cancer were identified. Of these patients, 630 had a history of cancer, chemotherapy, or radiotherapy before the date of diagnosis and were excluded because of an increased baseline risk due to reoccurrence of cancer. For 30 patients, no controls could be found. On the basis of the matching criteria, 3,129 patients could be matched to 16,976 controls.

The baseline characteristics for patients and controls are listed in Table 1. Patients were present in PHARMO for a mean of 7.2 years. The chronic disease score was not statistically different for patients and controls. The median number of hospital admissions before the date of diagnosis of cancer in the patient was lower for controls than for patients. In contrast, patients used less comedication, such as diuretics, ACE inhibitors, calcium-channel blockers, and NSAIDs, compared with controls. The use of hormones was comparable in groups of patients and controls.

Approximately 6% of controls received statin therapy before the index date for at least 6 months, as compared with 5% of patients ($P < .01$). Participants that received prescriptions of statins for at least 6 months were prescribed

Table 1. Baseline Characteristics of Study Participants

Characteristic	Patients (n = 3,129)		Controls (n = 16,976)	
	No.	%	No.	%
Age at index date, years				
≤ 64	939	30	5,323	31
65-74	1,080	35	5,790	34
75-84	880	28	4,638	27
≥ 85	230	7	1,225	7
Sex				
Male	1,524	49	8,261	49
Female	1,605	51	8,715	51
Follow-up time, years				
Mean	7.2		7.3	
Standard deviation	3.0		2.9	
Comorbidity				
Diabetes mellitus	559	18	2,866	17
Chronic disease score				
Median	4.0		4.0	
25th-75th ct	1.0-6.0		1.0-6.0	
Number of hospitalizations				
Median	1.0		0.0	
25th-75th ct*	0.0-2.0		0.0-2.0†	
Comedication				
Diuretics	969	31	5,909	35†
ACE inhibitors	439	14	2,839	17†
Calcium channel blockers	519	17	3,151	19†
Hormones	259	8	1,468	9
NSAIDs	907	29	5,449	32†
Other lipid-lowering therapy‡	50	2	337	2
Duration of statin use within study period, years				
0	2,936	94	15,725	93†
< 0.5	49	2	265	2
≥ 0.5	144	5	986	6†

Abbreviations: ct, centile; ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.
*Tested with Mann-Whitney independent sample test.
†Statistical significant difference ($P < .05$).
‡Other lipid-lowering therapy: bile acid–binding resins, fibrates, nicotinic acid and derivatives.

mainly simvastatin (79.6%). Other prescribed statins were pravastatin (6.6%), fluvastatin (2.5%), atorvastatin (0.4%), or a combination (10.9%). Cerivastatin was not prescribed during the study period. In general, the prescribed dose was approximately 0.6 defined daily doses or approximately 1.3 defined daily doses. The use of other lipid-lowering therapy did not differ between patients and controls.

Table 2 lists the effect of statin therapy on incident cancer. Statin use (at least 6 months) was associated with a risk reduction of incident cancer of 20% compared with no use of statins (adjusted OR, 0.80; 95% CI, 0.66 to 0.96). No significant difference between men and women or between different age groups was detected (data not shown). When users of statins were compared with users of other lipid-lowering therapies, an adjusted risk estimate of 0.89 (95% CI, 0.56 to 1.41) was found.

Furthermore, the effect of duration of statin use and cumulative dose is presented in Table 2. The risk decreased with duration of statin use, although the *P* value for trend was not statistically significant ($P = .08$). For cumulative dose, a significant risk reduction was found only for statin users that received more than 1,350 defined daily doses. However, an effect of the prescribed daily dose was not found (data not shown). In addition, the effect of latent period (lag time) is listed in Table 2. Patients who were past statin users and had their therapy stopped for at least 6 months had the same risk of incident cancer as nonusers of statins. In contrast, current statin users and past users that stopped for less than 6 months before the index date had a significant risk reduction of 22% to be diagnosed with cancer (OR, 0.78; 95% CI, 0.63 to 0.95).

Table 3 lists the effect of statins on individual cancer sites. In the adjusted model, risk reduction was statistically significant only for renal cancer. Nonsignificant risk reductions were found for other cancer sites, except for lung, bladder, and breast cancer. Although an increased risk of lung, bladder, and breast cancer was found, numbers were small and statistical significance was not reached. To enlarge the number of patients that were diagnosed to have a cancer in the investigated sites, patients with a second diagnosis of cancer within 1 year after the primary diagnosis were included. However, this did not affect the risk estimates significantly (data not shown).

DISCUSSION

Our study suggests that the risk of incident cancer is decreased by the use of statins (OR, 0.80; 95% CI, 0.66 to

Table 2. Effect of Statin Therapy on the Incidence of Cancer

Variable	No. of Patients	No. of Controls	Crude Risk Estimate	95% CI	Adjusted Risk Estimate	95% CI*
Overall						
Nonexposed	2,936	15,725	1.00	Referent	1.00	Referent
Statin use ≥ 0.5 years	144	986	0.80	0.66 to 0.96	0.80	0.66 to 0.96
Duration of statin use, years†						
0	2,936	15,725	1.00	Referent	1.00	Referent
0.5-1.0	27	201	0.73	0.49 to 1.10	0.72	0.48 to 1.08
1.0-2.0	42	240	0.96	0.69 to 1.34	0.98	0.70 to 1.37
2.0-4.0	42	269	0.86	0.62 to 1.20	0.85	0.61 to 1.19
> 4.0	33	276	0.64	0.44 to 0.93	0.64	0.44 to 0.93
Cumulative dose‡						
0	2,936	15,725	1.00	Referent	1.00	Referent
1-350§	30	240	0.68	0.46 to 1.00	0.68	0.46 to 1.00
351-700	47	247	1.04	0.76 to 1.43	1.05	0.76 to 1.45
701-1,350	40	255	0.86	0.61 to 1.21	0.84	0.60 to 1.19
≥ 1,351	27	244	0.60	0.40 to 0.90	0.60	0.40 to 0.91
Lag time, years‖						
Nonexposed	2,936	15,725	1.00	Referent	1.00	Referent
< 0.5¶	131	910	0.78	0.65 to 0.95	0.78	0.64 to 0.95
≥ 0.5#	13	76	0.94	0.52 to 1.71	1.00	0.55 to 1.83

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.
* Adjusted for diabetes mellitus, prior hospitalizations, chronic disease score, chronic use of diuretics, ACE inhibitors, calcium channel blockers, hormones, NSAIDs, and other lipid-lowering therapy.
† Categories of duration based on number of controls.
‡ Number of dispensed defined daily doses from entry in PHARMO to the index date.
§ Patients who received between 1 and 350 defined daily doses and used statins for at least 6 months.
‖ Index date minus date of last statin use.
¶ Patients who used statins for at least 6 months and had their last statin use less than 6 months before the index date or were still using statins at the index date.
#Patients who used statins for at least 6 months in the past and had their last statin use more than 6 months before the index date.

Table 3. Effect of Statins on Different Cancer Sites

Cancer Site	No. of Patients	Crude Risk Estimate	95% CI	Adjusted Risk Estimate	95% CI*
Skin	91	0.90	0.35 to 2.30	0.63	0.22 to 1.84
Colon	292	0.78	0.44 to 1.37	0.87	0.48 to 1.57
Rectum	148	0.46	0.16 to 1.30	0.48	0.16 to 1.48
Stomach	104	0.94	0.41 to 2.14	0.88	0.36 to 2.15
Lung	449	1.05	0.67 to 1.65	0.89	0.56 to 1.42
Breast	467	0.98	0.61 to 1.56	1.07	0.65 to 1.74
Prostate	186	0.32	0.10 to 1.04	0.37	0.11 to 1.25
Kidney	101	0.37	0.11 to 1.23	0.27	0.08 to 0.95
Bladder	249	1.19	0.65 to 2.17	1.24	0.66 to 2.34
Pancreas	78	0.71	0.21 to 2.43	0.89	0.24 to 3.34
Lymphoma	93	0.31	0.07 to 1.31	0.28	0.06 to 1.30

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs; nonsteroidal anti-inflammatory drugs.
* Adjusted for diabetes mellitus, prior hospitalizations, chronic disease score, chronic use of diuretics; ACE inhibitors, calcium channel blockers, hormones, NSAIDs, and other lipid-lowering therapy.

0.96). Although the observed relative risk reduction is only 20%, given the high prevalence of statin use[6] and the high incidence of cancer,[27] even a modest risk reduction means a considerable effect on public health. Our data suggest that statin use for a longer period and in high dosages decreases the risk of incident cancer. The protective effect was only present in current users and past users that had their therapy stopped for less than 6 months before the index date.

Although statins are approved only for the treatment of lipid disorders, there is mounting evidence that they might be useful in the treatment of other diseases, such as Alzheimer's[28-30] and osteoporosis.[31] In addition, in vivo studies with laboratory animals[11,16,17] and in vitro studies[9-15] suggest a possible role for statins in the treatment of malignancies. Although the underlying biologic mechanism was originally assumed to be inhibition of Ras farnesylation, recent studies indicate that inhibition of prenylation of other proteins might be involved.[32] These observations prompted us to perform a case-control study to investigate the risk of cancer among users of statins, as compared with cardiovascular patients that never used statins.

One of the strengths of our study is the use of a computerized database, allowing the inclusion of 3,129 patients with 22,470 person years of follow-up. The availability of pharmacy data that were prospectively gathered before disease onset allowed us to calculate various levels of exposure of prescribed drugs. Therefore, recall bias was avoided. Using pharmacy records representing dispensing data rather than usage data might have introduced an overestimation of statin use. However, we excluded nonchronic statin users and therefore reduced the likelihood of overestimation. Prevalent cancer or the onset of cancer is not considered to exhibit symptoms that lead to a prescription of statins. In addition, we introduced a latent period of 6 months, thereby reducing protopathic bias. Furthermore, risk factors for cancer do not play a role in the prescription of statins. Therefore, it is not likely that our findings can be explained by confounding by indication.

As with observational studies in general, we cannot rule out unknown biases or confounders as possible explanations for our findings. However, patients and controls were matched on sex, age, geographic region, follow-up time, and calendar time. In addition, the analysis was adjusted for diabetes mellitus and chronic use of diuretics, ACE inhibitors, calcium antagonists, NSAIDs, hormones, and other lipid-lowering therapies. Furthermore, we investigated potential confounding effects of polyposis coli and familiar hypercholesterolemia. Because of the chronic character of these diseases, we searched medical discharge records until 1 year after the index date for diagnoses of these diseases. However, neither polyposis coli nor familiar hypercholesterolemia seemed to affect the analysis significantly (data not shown). The confounding effect of medical attention could be corrected for by introducing a general score of comorbidity and the number of hospitalizations into the conditional logistic regression model.

The PHARMO database does not provide information on lifestyle variables, such as body-mass index and smoking status. Nevertheless, we made an attempt to minimize the effect of these variables by confining the base population to cardiovascular patients. This group of patients is likely to receive strong recommendations regarding lifestyle from their physician. Not all of these patients will follow their doctor's orders strictly, but given that the chronic disease score was found comparable between patients and controls, there is no reason to assume that controls were more likely to improve their lifestyle habits than were patients. Moreover, coincidental differences between groups might become diluted because of the magnitude of both the patient and control group.

A limitation of our study is caused by the relatively high frequency of simvastatin prescriptions: 79.6% of the statin-exposed patients were prescribed simvastatin. Because the inhibitory potency of different statins is not equal,[33] the results of this study cannot be generalized to the use of other statins. Furthermore, diagnoses recorded in the PHARMO database came from hospital discharge records, but were not verified with original medical charts. This might have introduced misclassification. However, there is no reason to assume that this would be different for patients and controls.

The results of our study are consistent with the assumed biologic mechanism of statins. The enzyme HMG-CoA reductase is inhibited by statins. As a consequence, statins reduce protein farnesylation and geranylgeranylation, resulting in decreased activation of proteins. Possibly, activation of oncoproteins such as k-Ras is prevented by this mechanism. However, transcription of oncogenes is not affected. Therefore, statins might prevent the expression of the oncogenic phenotype without affecting the malignant genotype. We propose that statins are able to decrease the development of existing cancer, rather than the initiation of cancer. On the basis of this hypothesis, it is expected that after patients stop statin therapy, the cancer risk returns to baseline values because of normalization of oncoprotein activation.

The mean duration of observation was 7.2 years for patients and 7.3 years for controls. This period might be too short to study the influence of statins on the initiation of cancer. However, the aim of our study is to investigate the effect of statins on the development of cancer. There is no reason to assume that statins can only influence the development of the malignant phenotype when statins are used during the entire period between the initiation of cancer and the diagnosis of cancer. Therefore, the duration of follow-up is sufficient to investigate the end point of the study.

Our data are consistent with the study performed by Blais et al,[22] who found a risk reduction of 28% for statin users compared with users of bile acid–binding resins (risk estimate, 0.72; 95% CI, 0.57 to 0.92). Other epidemiologic studies did not find a significant effect of statins on the incident cancer risk. However, in contrast to the current study and the study performed by Blais et al,[22] these epidemiologic studies were not designed to investigate the effect of statins on the occurrence of cancer. Given that these studies were aimed at investigating cardiovascular end points, patients with pre-existing cancer were not excluded.[1-5] Blais et al[22] compared users of statins with users of bile acid–binding resins. Their results indicate that the protective effect of statins cannot be explained by their lipid-lowering effect. We found a risk reduction when users of statins were compared with users of other lipid-lowering therapies, although the protective effect was not statistically significant.

Inhibition of HMG-CoA reductase by statins has been associated with upregulation of this enzyme.[34] This feedback system would theoretically indicate that cells might acquire resistance against statins by extended treatment. As a consequence, the risk of incident cancer would be expected to return to baseline values after extended statin treatment. However, this phenomenon did not appear in our study; we found a decreased risk in patients who used statins for more than 4 years, indicating that protection by statins is not temporary.

In conclusion, our observational study suggests a protective effect of statins against cancer. In addition to experimental studies on the underlying mechanisms of the anticancer activity of statins, prospective randomized studies are necessary to validate the value of statins in cancer prevention.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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