ORIGINAL ARTICLE

Statin Use and Reduced Cancer-Related Mortality

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ABSTRACT

BACKGROUND

A reduction in the availability of cholesterol may limit the cellular proliferation required for cancer growth and metastasis. We tested the hypothesis that statin use begun before a cancer diagnosis is associated with reduced cancer-related mortality.

METHODS

We assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007, with follow-up until December 31, 2009. Among patients 40 years of age or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins.

RESULTS

Multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, were 0.85 (95% confidence interval [CI], 0.83 to 0.87) for death from any cause and 0.85 (95% CI, 0.82 to 0.87) for death from cancer. Adjusted hazard ratios for death from any cause according to the defined daily statin dose (the assumed average maintenance dose per day) were 0.82 (95% CI, 0.81 to 0.85) for a dose of 0.01 to 0.75 defined daily dose per day, 0.87 (95% CI, 0.83 to 0.89) for 0.76 to 1.50 defined daily dose per day, and 0.87 (95% CI, 0.81 to 0.91) for higher than 1.50 defined daily dose per day; the corresponding hazard ratios for death from cancer were 0.83 (95% CI, 0.81 to 0.86), 0.87 (95% CI, 0.83 to 0.91), and 0.87 (95% CI, 0.81 to 0.92). The reduced cancer-related mortality among statin users as compared with those who had never used statins was observed for each of 13 cancer types.

CONCLUSIONS

Statin use in patients with cancer is associated with reduced cancer-related mortality. This suggests a need for trials of statins in patients with cancer.

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Cholesterol is a fundamental structural component of mammalian cell membranes and is essential for cellular proliferation.[1,2] Statins inhibit the production of endogenous cholesterol[3] and block protein prenylation, and statin use may therefore influence cell proliferation and migration.[4,5]

Cancer-cell proliferation is seen clinically as cancer growth and metastasis, and it ultimately results in the death of the patient. A reduction in the availability of cholesterol could lead to decreased proliferation and migration of cancer cells.[6,7] Also, a reduction in the downstream products in the mevalonate pathway due to statin use has been associated with several potential anticancer properties[8-12] and a reduced risk of cancer recurrence.[13,14] At the cellular level, statins have been linked to the halting of cell-cycle progression and to increased radiosensitization in cancer cells.[10,15,16] Thus, regular statin use before and after a diagnosis of cancer could theoretically reduce cancer-related mortality. In large-scale trials of statins to reduce the risk of cardiovascular disease among persons without cancer, statin use did not influence the incidence of cancer or related mortality.[17,18]

We hypothesized that statin use begun before a cancer diagnosis would be associated with reduced cancer-related mortality. To test this hypothesis, we analyzed data on patients with cancer in the entire Danish population for the period from 1995 through 2009, comparing mortality among patients who had used statins before the diagnosis with mortality among those who had never used statins.

Methods

Study Population and Data Collection

The Danish Civil Registration System records all births, immigrations, emigrations, and deaths in Denmark by means of civil registration numbers, which uniquely identify all inhabitants of Denmark and include information regarding age and sex. The Danish Civil Registration System is 100% complete, so for practical purposes, no persons are lost to follow-up.[19]

Persons with cancer diagnosed between January 1, 1995, and December 31, 2007, were identified with the use of the Danish Cancer Registry, which tracks data on 98% of all incident cancers in Denmark[20,21] and is blinded to the recording of statin use. By including only patients who received a diagnosis of cancer through 2007, we allowed at least 2 years of follow-up for all patients. All diagnoses in the registry are assigned on the basis of histologic examination by a fully trained pathologist. Cancer diagnoses were classified according to the *International Classification of Diseases, 10th Revision* (ICD-10) codes C00.0–C43.0, C45.0–C96.0, D00.0–D03.0, and D05.0–D09.0.[22,23]

The tumor–node–metastasis (TNM) staging system[24] was adopted by the Danish Cancer Registry on January 1, 2004, so information regarding the size of the primary tumor, spread to the lymphatic system, and distant metastasis at the time of diagnosis was available during the period from 2004 through 2007. Tumor size was classified as small (T0, T1, or T2) or large (T3 or T4), cancer spread to the lymphatic system as none (N0) or any (N1, N2, or N3), and distant metastasis as none (M0) or any (M1).

From 1995 through 2003, the Danish Cancer Registry recorded treatment information dichotomously (none vs. any) for both radiotherapy and chemotherapy started within 4 months after a cancer diagnosis. However, no details were available regarding the specific type of treatment administered.

Statin Use

The Danish Registry of Medicinal Products Statistics has recorded information on all prescribed drugs dispensed at Danish pharmacies since 1995 and is blinded to the recording of cancer diagnoses. Statins were classified as Anatomical Therapeutic Chemical code C10AA; the codes for other cholesterol-lowering medications were C10AB, C10AC, C10AD, C10AX, and C10BA (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). For each filled prescription for each study participant, we recorded the drug name, the date of dispensing, and the total amount of the recommended defined daily dose (i.e., the assumed average maintenance dose per day). Table S1 in the Supplementary Appendix lists the distributions of the different types of statin medication and other cholesterol-lowering medications prescribed.

The daily dose for statin users was estimated as dose_2 divided by $|t_1 - t_2|$, where dose_2 is the penultimate prescription of a statin before the cancer diagnosis, measured in total defined daily doses (i.e., the total milligrams dispensed,

divided by the defined daily dose for the specific statin) (Table S1 in the Supplementary Appendix). The value of $|t_1 - t_2|$ is the interval between the dates of the last statin prescription (t_1) and the penultimate statin prescription (t_2) before the cancer diagnosis (Fig. S4 in the Supplementary Appendix). Statin doses were analyzed in the following categories of defined daily dose per day: 0.00 (reference), 0.01 to 0.75, 0.76 to 1.50, and more than 1.50.

To exclude reverse causation, statin use was only measured before the date of cancer diagnosis and was used to indicate statin use before and after the cancer diagnosis. We also considered whether patients had ever used statins, in an analysis in which all patients with cancer who had ever received a statin before the cancer diagnosis were compared with those who had never used statins.

Patients who had statin prescriptions filled within 6 months before the date of the cancer diagnosis and within 2 years before the date of diagnosis were classified as regular statin users (see Fig. S1 and S4 in the Supplementary Appendix). Figure S2 in the Supplementary Appendix shows that the pattern of filled prescriptions for statins was roughly symmetric before and after the cancer diagnosis. All patients who had used statins before the cancer diagnosis but whose use was outside the specified time frames were classified as irregular statin users.

Because the use of statins has been increasing and the information on TNM classification and treatment for each patient with cancer changed during the observation period, we also conducted a nested 1:3 matched study (i.e., a study that matched each statin user with three patients who had never used statins), with matching for

Table 1. Baseline Characteristics of the Patients, According to Statin Use, in the Nationwide and Matched Studies.*

Characteristic	Nationwide Study			Nested 1:3 Matched Study		
	Statin Use (N=18,721)	No Statin Use (N=277,204)	P Value	Statin Use (N=15,247)	No Statin Use (N=45,741)	P Value
Age — yr			<0.001			1.00
Median	70	69		69	69	
Interquartile range	63–76	59–77		63–76	63–76	
Sex — no. (%)			<0.001			1.00
Female	8,077 (43)	148,881 (54)		6,726 (44)	20,178 (44)	
Male	10,644 (57)	128,323 (46)		8,521 (56)	25,563 (56)	
Tumor size — no. (%)†			<0.001			0.02
Small	6,032 (32)	36,509 (13)		4,842 (32)	13,629 (30)	
Large	6,416 (34)	38,052 (14)		4,935 (32)	15,677 (34)	
Missing data	6,273 (34)	202,643 (73)		5,470 (36)	16,435 (36)	
Cancer spread to lymphatic system — no. (%)†			<0.001			0.14
None	4,503 (24)	27,899 (10)		3,604 (24)	10,277 (22)	
Any	7,945 (42)	46,662 (17)		6,173 (40)	19,029 (42)	
Missing data	6,273 (34)	202,643 (73)		5,470 (36)	16,435 (36)	
Distant metastasis — no. (%)†			<0.001			0.26
None	6,798 (36)	42,575 (15)		5,471 (36)	16,002 (35)	
Any	5,620 (30)	31,986 (12)		4,306 (28)	13,304 (29)	
Missing data	6,303 (34)	202,643 (73)		5,470 (36)	16,435 (36)	
Chemotherapy — no. (%)‡			<0.001			1.00
None	4,557 (24)	170,665 (62)		4,224 (28)	12,511 (27)	
Any	669 (4)	25,034 (9)		623 (4)	2,062 (5)	
Missing data	13,495 (72)	81,505 (29)		10,400 (68)	31,168 (68)	

Table 1. (Continued.)

Characteristic	Nationwide Study			Nested 1:3 Matched Study		
	Statin Use (N=18,721)	No Statin Use (N=277,204)	P Value	Statin Use (N=15,247)	No Statin Use (N=45,741)	P Value
Radiotherapy — no. (%)‡			<0.001			1.00
None	4,486 (24)	169,023 (61)		4,164 (27)	12,587 (28)	
Any	740 (4)	26,676 (10)		683 (4)	1,986 (4)	
Missing data	13,495 (72)	81,505 (29)		10,400 (68)	31,168 (68)	
Cardiovascular disease before cancer — no. (%)			<0.001			<0.001
No	5,677 (30)	219,388 (79)		4,724 (31)	33,232 (73)	
Yes	13,044 (70)	57,816 (21)		10,523 (69)	12,509 (27)	
Diabetes mellitus before cancer — no. (%)			<0.001			<0.001
No	15,314 (82)	268,202 (97)		12,529 (82)	43,854 (96)	
Yes	3,407 (18)	9,002 (3)		2,718 (18)	1,887 (4)	
Size of residential area — no. (%)§			<0.001			0.11
<12,000 residents	7,508 (40)	108,684 (39)		6,118 (40)	18,724 (41)	
12,000–100,000 residents	5,027 (27)	72,361 (26)		4,070 (27)	12,105 (26)	
>100,000 residents	6,186 (33)	96,159 (35)		5,059 (33)	14,895 (33)	
Highest level of education — no. (%)			<0.001			0.003
Primary and high school	8,990 (48)	110,591 (40)		7,332 (48)	21,376 (47)	
Vocational training	6,249 (33)	73,956 (27)		5,077 (33)	14,762 (32)	
College degree	2,589 (14)	39,262 (14)		2,117 (14)	7,290 (16)	
Missing data	893 (5)	53,395 (19)		721 (5)	2,313 (5)	

* Data were recorded at the time of the cancer diagnosis, except chemotherapy and radiotherapy, which included therapy started within 4 months after the cancer diagnosis. The nested 1:3 matched study was matched on the characteristics of sex, age at diagnosis, year of diagnosis, and cancer type; only statin users who had been matched with exactly three patients who had never used statins were included.
† Data on tumor size, spread to the lymphatic system, and distant metastasis were available only for the period from 2004 through 2007. On the basis of the tumor–node–metastasis (TNM) staging system,[24] tumors were classified as small (T0, T1, or T2) or large (T3 or T4), spread to the lymphatic system as either none (N0) or any (N1, N2, or N3), and distant metastasis as either none (M0) or any (M1).
‡ Data on cancer treatment (chemotherapy and radiotherapy) were available only for the period from 1995 through 2003.
§ Residential area was defined as the location where the patient resided for the longest period.

sex, age at cancer diagnosis, year of diagnosis, and cancer type (Fig. S3, S11, and S14 in the Supplementary Appendix).[23] To address unknown patterns and other potential biases between statin users and patients who had never used statins, a propensity-score analysis and adjustment for the area code where the provider was located were performed (see the Supplementary Appendix).

CARDIOVASCULAR DISEASE AND DIABETES MELLITUS

Diagnoses of cardiovascular disease and diabetes mellitus before the cancer diagnosis were identified with the use of the National Registry of Patients,[20] which records all hospital admissions in Denmark. Diagnoses for cardiovascular disease and diabetes mellitus were classified according to the ICD-10 codes I00–I99 and E10–E14, respectively.

CAUSES OF DEATH

The Danish Civil Registration System records the date of death for all persons in Denmark. For all deaths in Denmark, the Danish Register of Causes of Death[25] records up to three ranked causes of death, as reported by the attending physician in general practice or at a hospital or by a physician in a forensic or pathology department. Diagnoses listed as causes of death are classified with the use of the ICD-10. For this study, the cause of death was defined as the first of the three ranked

causes of death, as assessed by any of the physicians listed above to be the primary cause of death. In sensitivity analyses, other categorizations of cause-specific death were also examined.

OTHER COVARIATES

Since 1980, Statistics Denmark has gathered information concerning all persons living in Denmark. For this study, we obtained data on race and ethnic descent, highest level of education, and size of residential area.

STATISTICAL ANALYSIS

We excluded from the analyses patients with cancer who were less than 40 years of age, because such patients are unlikely to receive statins. The missing-indicator method was used to account for missing information.[26]

Cumulative incidence curves were estimated by means of the method of Fine and Gray[27] and were compared with the use of log-rank tests. Cox regression models with the time (in years) after a cancer diagnosis as the time scale were used to calculate hazard ratios with 95% confidence intervals. Multivariable Cox models were adjusted for age at diagnosis; cancer stage (tumor size, presence or absence of spread to the lymphatic system, and presence or absence of distant metastasis); status with regard to chemotherapy, radiotherapy, diagnosis of cardiovascular disease before cancer, and diagnosis of diabetes mellitus before cancer; year of birth; sex; race and ethnic descent (97% of the patients were white persons of Danish descent); highest level of education; and size of residential area.

All 295,925 patients were followed from the date of cancer diagnosis; data were censored at the date of death (195,594 patients) or emigration (635) or on December 31, 2009 (99,696), whichever came first. Thus, the competing risk of death was accounted for in the analysis by means of censoring at the date of death (information that is 100% complete in the Danish registries). The effect of competing events was also modeled by calculating subhazard ratios, as a measure of relative risk taking death into consideration, with the use of the method of Fine and Gray.[27] For Cox proportional-hazards regression analyses, we detected no major violations of the proportional-hazards assumption graphically after plotting the log of the cumulative hazard for different statin-dose categories as a function of the log of the length of follow-up after the cancer diagnosis.

Subgroups were prespecified and encompassed 27 cancer types (Fig. S14 in the Supplementary Appendix) and nine characteristics of the patients. We performed all calculations with the use of Stata software, version 12.0MP (StataCorp).

RESULTS

STUDY PATIENTS

We included patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007 and followed them until December 31, 2009 (median, 2.6 years; range, 0 to 15). Among patients 40 years of age or older, 18,721 used statins regularly up until the cancer diagnosis, whereas 277,204 had never used statins or any other cholesterol-lowering medication before the cancer diagnosis (Fig. S1 in the Supplementary Appendix). The baseline characteristics of the patients are shown in Table 1. During 1,072,503 person-years of follow-up, 195,594 patients died: 162,067 from cancer, 14,489 from cardiovascular causes, and 19,038 from other causes.

STATIN USE AND MORTALITY

The cumulative incidence of death from any cause as a function of follow-up time from the date of the cancer diagnosis was lower among statin users than among patients who had never used statins ($P<0.001$ by the log-rank test) (Fig. 1A). The two cumulative incidence curves converge after 5 years of follow-up, probably because of the increased cardiovascular mortality among statin users, as compared with patients who had never used statins (Fig. S5 in the Supplementary Appendix). The multivariable-adjusted hazard ratio for death from any cause among statin users, as compared with patients who had never used statins, was 0.85 (95% confidence interval [CI], 0.83 to 0.87). The results of the nested 1:3 matched study were similar (Fig. 1B).

The cumulative incidence of death from cancer as a function of follow-up time from the date of the cancer diagnosis was also lower among statin users than among patients who had never used statins ($P<0.001$ by the log-rank test) (Fig. 1A). The multivariable-adjusted hazard ratio for death from cancer among statin users, as compared with patients who had never used statins,

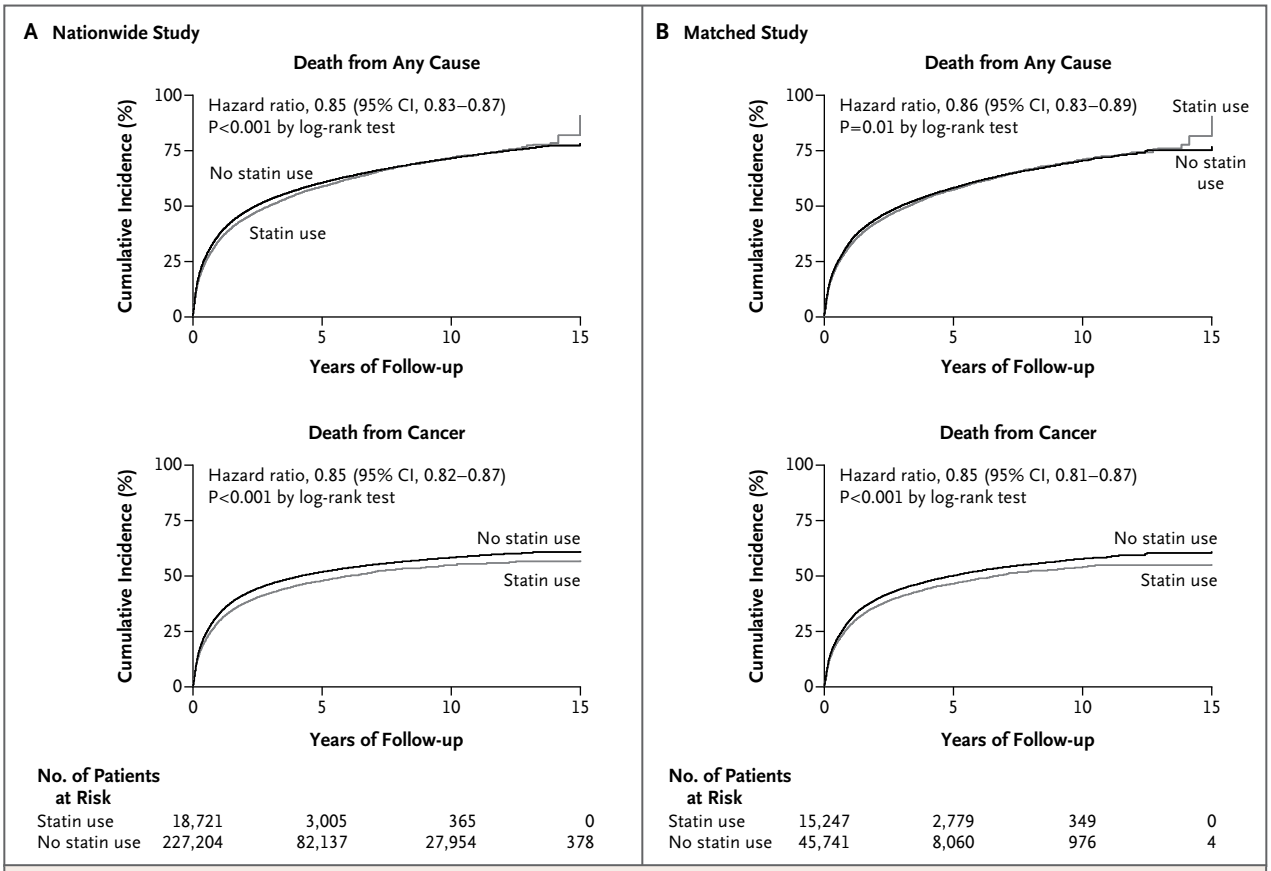


Figure 1. Regular Statin Use and Cumulative Incidence of Death from Any Cause and Death from Cancer, According to Time after the Cancer Diagnosis.

We included patients from the entire Danish population who received a diagnosis of cancer during the period from 1995 through 2007 and followed them until the end of 2009. Among patients 40 years of age or older who were followed for up to 15 years, 195,594 patients died and 162,067 of those deaths were registered as due to cancer. Hazard ratios were multivariable-adjusted for age at diagnosis; cancer stage (according to tumor size [small: T0, T1, or T2; or large: T3 or T4], spread to the lymphatic system [none: N0; or any: N1, N2, or N3], and distant metastasis [none: M0; or any: M1]); status with regard to chemotherapy, radiotherapy, diagnosis of cardiovascular disease before cancer, and diagnosis of diabetes mellitus before cancer; year of birth; sex; race and ethnic descent (97% of patients were white persons of Danish descent, as determined by the Danish Civil Registration System); highest level of education; and size of residential area. For the nested 1:3 matched study, matching was performed on the characteristics of sex, age at diagnosis, year of diagnosis, and cancer type[23]; hazard ratios were adjusted as in the nationwide study except for the matching variables. P values were obtained with the use of the log-rank test. CI denotes confidence interval.

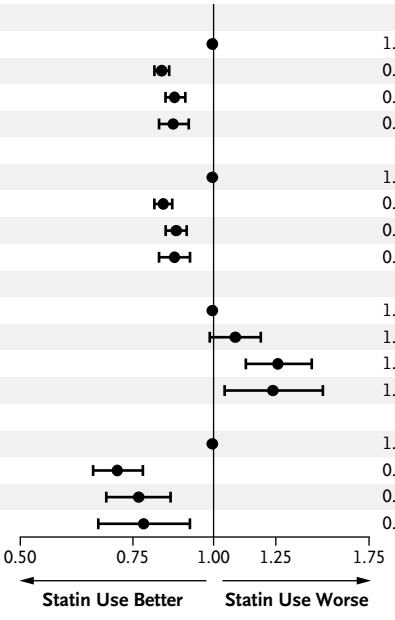
was 0.85 (95% CI, 0.82 to 0.87), with similar results in the nested 1:3 matched study (Fig. 1B).

STATIN DOSE AND MORTALITY

The multivariable-adjusted hazard ratios for death from any cause according to the defined daily statin dose, as compared with no statin use, were 0.82 (95% CI, 0.81 to 0.85) for a dose of 0.01 to 0.75 defined daily dose, 0.87 (95% CI, 0.83 to 0.89) for 0.76 to 1.50 defined daily dose, and 0.87 (95% CI, 0.81 to 0.91) for higher than 1.50 defined daily dose (Fig. 2A). The corresponding hazard ratios for death from cancer were 0.83 (95% CI, 0.81 to 0.86), 0.87 (95% CI, 0.83 to 0.91), and 0.87 (95% CI, 0.81 to 0.92). The corresponding hazard ratios for death from cardiovascular causes were 1.08 (95% CI, 0.99 to 1.19), 1.25 (95% CI, 1.12 to 1.41), and 1.24 (95% CI, 1.03 to 1.48). Finally, the corresponding hazard ratios for death from other causes were 0.70 (95% CI, 0.64 to 0.77), 0.76 (95% CI, 0.68 to 0.86), and 0.77 (95% CI, 0.66 to 0.92). The nested 1:3 matched study had similar results (Fig. 2B).

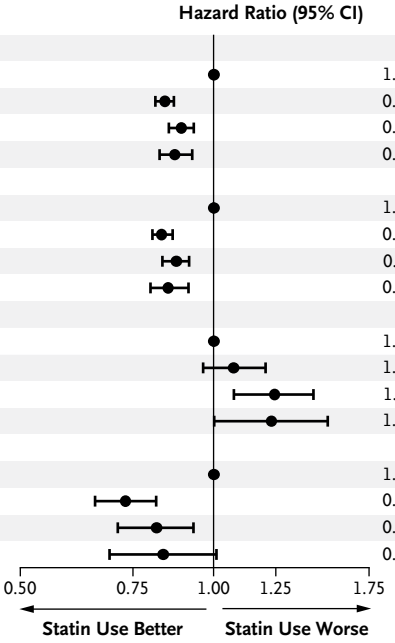
A Nationwide Study

Cause of Death and Statin Dose	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Any cause				
0.00	277,204	184,895	1.00	
0.01–0.75	9,780	5,730	0.82 (0.81–0.85)	<0.001
0.76–1.50	6,181	3,438	0.87 (0.83–0.89)	<0.001
>1.50	2,760	1,531	0.87 (0.81–0.91)	<0.001
Cancer				
0.00	277,204	153,327	1.00	
0.01–0.75	9,780	4,680	0.83 (0.81–0.86)	<0.001
0.76–1.50	6,181	2,810	0.87 (0.83–0.91)	<0.001
>1.50	2,760	1,250	0.87 (0.81–0.92)	<0.001
Cardiovascular cause				
0.00	277,204	13,512	1.00	
0.01–0.75	9,780	529	1.08 (0.99–1.19)	0.08
0.76–1.50	6,181	314	1.25 (1.21–1.41)	<0.001
>1.50	2,760	134	1.24 (1.03–1.48)	0.01
Other cause				
0.00	277,204	18,056	1.00	
0.01–0.75	9,780	521	0.70 (0.64–0.77)	<0.001
0.76–1.50	6,181	314	0.76 (0.68–0.86)	<0.001
>1.50	2,760	147	0.77 (0.66–0.92)	0.003



B Matched Study

Cause of Death and Statin Dose	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Any cause				
0.00	45,741	26,271	1.00	
0.01–0.75	8,162	4,741	0.83 (0.81–0.87)	<0.001
0.76–1.50	4,927	2,721	0.88 (0.85–0.93)	<0.001
>1.50	2,158	1,176	0.87 (0.81–0.93)	<0.001
Cancer				
0.00	45,741	22,584	1.00	
0.01–0.75	8,162	3,844	0.82 (0.80–0.86)	<0.001
0.76–1.50	4,927	2,203	0.87 (0.82–0.91)	<0.001
>1.50	2,158	946	0.85 (0.80–0.91)	<0.001
Cardiovascular cause				
0.00	45,741	1,373	1.00	
0.01–0.75	8,162	468	1.08 (0.95–1.21)	0.19
0.76–1.50	4,927	258	1.24 (1.08–1.42)	0.002
>1.50	2,158	108	1.23 (1.00–1.50)	0.05
Other cause				
0.00	45,741	2,314	1.00	
0.01–0.75	8,162	429	0.73 (0.66–0.81)	<0.001
0.76–1.50	4,927	260	0.81 (0.70–0.93)	0.002
>1.50	2,158	122	0.82 (0.68–1.00)	0.06



SENSITIVITY ANALYSES

The results for cancer-related mortality remained similar when we accounted for the competing risk of death from other causes with the use of Fine and Gray subhazard regression (Fig. S6 in the Supplementary Appendix). An analysis that was limited to patients who had small cancers without metastases and an analysis that included

Figure 2 (facing page). Risk of Death from Various Causes, According to Defined Daily Dose of Statin.

Hazard ratios were calculated from multivariable analyses adjusted for age at diagnosis; cancer stage (size, presence or absence of spread to the lymphatic system, and presence or absence of distant metastasis); status with regard to previous chemotherapy, previous radiotherapy, diagnosis of cardiovascular disease before cancer, and diagnosis of diabetes mellitus before cancer; year of birth; sex; race and ethnic descent; highest level of education; and size of residential area. For the nested 1:3 matched study, matching was performed on the characteristics of sex, age at diagnosis, year of diagnosis, and cancer type; hazard ratios were adjusted as in the nationwide study except for the matching variables. The daily dose for statin users was estimated as $dose_2$ divided by $|t_1-t_2|$, where $dose_2$ is the penultimate prescription of a statin before the cancer diagnosis, measured in total defined daily doses (i.e., the total milligrams dispensed, divided by the defined daily dose for the specific statin) (Table S1 in the Supplementary Appendix). The value of $|t_1-t_2|$ is the interval between the dates of the last statin prescription (t_1) and the penultimate statin prescription (t_2) before the diagnosis (Fig. S4 in the Supplementary Appendix). Statin doses were analyzed in the following categories for the defined daily dose per day: 0.00 (reference), 0.01 to 0.75, 0.76 to 1.50, and more than 1.50. Horizontal bars indicate 95% confidence intervals.

patients who had ever used statins had similar results. In addition, the results were similar when we classified death according to all ranked causes of death from the Danish Register of Causes of Death, limited cancer-related mortality to the same cancer as the incident cancer, excluded adjustment for covariates with missing information for more than 0.1% of all patients, and adjusted for the provider's area code (Fig. S7 through S13 in the Supplementary Appendix).

The reduced cancer-related mortality among statin users as compared with patients who had never used statins was observed for 13 cancer types: the multivariable-adjusted hazard ratios for death from cancer among statin users ranged from 0.64 (95% CI, 0.46 to 0.88) for cervical cancer to 0.89 (95% CI, 0.81 to 0.98) for pancreatic cancer (Fig. S14 in the Supplementary Appendix). For the 14 remaining cancer types, the multivariable-adjusted hazard ratios were largely similar but with confidence intervals that overlapped 1.0. Results from the nested 1:3 matched study were also largely similar (Fig. S14, right panel, in the Supplementary Appendix).

In analyses stratified according to characteristics associated with an increased risk of death from any cause or from cancer (i.e., sex, age, treatment with chemotherapy, treatment with radiotherapy, larger tumor size, presence of metastasis at diagnosis, diagnosis of cardiovascular disease before cancer, and diagnosis of diabetes mellitus before cancer), cancer-related mortality was reduced among statin users, as compared with patients who had never used statins, in all strata except among patients with cancer who were receiving chemotherapy (Fig. 3). A history of diabetes or cardiovascular disease before or after the cancer diagnosis did not influence the results substantially (Fig. S15 and S16 and Table S2 in the Supplementary Appendix).

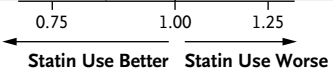
Attempting to adjust for differences in the medical history of patients with cancer in order to avoid a "healthy-user bias," we repeated the nested 1:3 matched study with propensity-score matching (Fig. S17 in the Supplementary Appendix). The results were similar to those shown in Figure 2, except that statin use was no longer associated with increased cardiovascular mortality.

DISCUSSION

In this nationwide study, we observed that statin use in patients with cancer was associated with reduced cancer-related mortality. Our findings are plausible because statins inhibit cholesterol synthesis within cells through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate and cholesterol-synthesis pathway.[28] Many of these downstream products are used in cell proliferation because they are required for critical cellular functions such as maintenance of membrane integrity, signaling, protein synthesis, and cell-cycle progression.[15,28] Disruptions of these processes in malignant cells result in the inhibition of cancer growth and metastasis.[15,29-31] In particular, the mevalonate pathway is up-regulated by mutated p53 (tumor suppressor protein),[32] which is common in cancer.[33] Accordingly, inhibition of this pathway with statins reverts the malignancy phenotype of p53-mutated cancer cells.[32] The decrease in downstream products of the mevalonate pathway has been linked to apoptosis and to reduced matrix-metalloproteinase production and angiogenesis, as well as a reduction in the invasiveness of in situ cancers.[8-12] Statins have been linked to the halting of cell-cycle progression in cancer cells with resulting antiproliferative effects, to the

A Cancer-Related Mortality in Nationwide Study

Subgroup	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Regular statin use	295,925	162,067	0.85 (0.82–0.87)	<0.001
Sex				
Female	156,958	77,649	0.92 (0.88–0.94)	<0.001
Male	138,967	84,418	0.82 (0.81–0.86)	<0.001
Age at diagnosis				
40–69 yr	150,559	70,479	0.87 (0.83–0.89)	<0.001
>69 yr	145,366	91,588	0.83 (0.81–0.86)	<0.001
Chemotherapy				
No	175,223	102,837	0.80 (0.76–0.82)	<0.001
Yes	25,703	17,522	1.04 (0.94–1.14)	0.34
Radiotherapy				
No	173,510	104,211	0.81 (0.79–0.86)	<0.001
Yes	27,416	16,148	0.85 (0.76–0.93)	<0.001
Tumor size				
Small	42,540	10,705	0.83 (0.79–0.88)	<0.001
Large	44,468	27,580	0.92 (0.87–0.94)	<0.001
Metastasis				
No	28,462	5,403	0.87 (0.80–0.93)	<0.001
Yes	58,546	32,862	0.88 (0.86–0.92)	<0.001
Cardiovascular disease before cancer				
No	225,064	122,137	0.83 (0.81–0.87)	<0.001
Yes	70,861	39,930	0.87 (0.85–0.89)	<0.001
Diabetes mellitus before cancer				
No	282,597	154,303	0.85 (0.82–0.87)	<0.001
Yes	13,328	7,764	0.86 (0.81–0.91)	<0.001
Calendar period				
1995–2002	156,179	74,293	0.76 (0.72–0.81)	<0.001
2003–2007	139,746	65,438	0.87 (0.86–0.91)	<0.001
Any statin use	300,492	164,247	0.87 (0.85–0.88)	<0.001



B Cancer-Related Mortality in Matched Study

Subgroup	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Regular statin use	60,988	29,577	0.85 (0.81–0.87)	<0.001
Sex				
Female	25,904	12,203	0.87 (0.83–0.92)	<0.001
Male	34,084	17,374	0.82 (0.80–0.86)	<0.001
Age at diagnosis				
40–69 yr	29,188	12,871	0.86 (0.81–0.89)	<0.001
>69 yr	31,800	16,706	0.83 (0.80–0.87)	<0.001
Chemotherapy				
No	16,735	9,280	0.79 (0.75–0.83)	<0.001
Yes	2,685	1,990	0.99 (0.87–1.12)	0.91
Radiotherapy				
No	16,751	9,633	0.81 (0.77–0.86)	<0.001
Yes	2,669	1,637	0.82 (0.73–0.93)	<0.001
Tumor size				
Small	18,471	4,825	0.81 (0.75–0.87)	<0.001
Large	20,612	12,447	0.87 (0.83–0.92)	<0.001
Metastasis				
No	12,118	2,383	0.86 (0.77–0.94)	0.003
Yes	26,965	14,889	0.86 (0.81–0.88)	<0.001
Cardiovascular disease before cancer				
No	37,956	17,977	0.81 (0.77–0.86)	<0.001
Yes	23,032	11,600	0.87 (0.83–0.89)	<0.001
Diabetes mellitus before cancer				
No	56,383	27,208	0.85 (0.81–0.87)	<0.001
Yes	4,605	2,369	0.81 (0.75–0.88)	<0.001
Calendar period				
1995–2002	9,956	3,932	0.80 (0.73–0.86)	<0.001
2003–2007	51,032	23,515	0.86 (0.82–0.88)	<0.001
Any statin use	75,988	36,966	0.86 (0.83–0.87)	<0.001

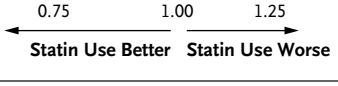


Figure 3 (facing page). Any Statin Use and Risk of Death from Cancer.

Data from patients with any history of statin use are shown (bottom of the figure) for comparison with data from patients with regular statin use (top). Hazard ratios were calculated from multivariable analyses adjusted for age at diagnosis; cancer stage (size, presence or absence of spread to the lymphatic system, and presence or absence of distant metastasis); status with regard to treatment with chemotherapy, treatment with radiotherapy, cardiovascular disease before cancer, and diabetes mellitus before cancer; year of birth; sex; race and ethnic descent; highest level of education; and size of residential area, except for the stratification variable. For the nested 1:3 matched study, matching was performed on the characteristics of sex, age at diagnosis, year of diagnosis, and cancer type; hazard ratios were adjusted as in the nationwide study except for the matching variables. Analyses stratified according to treatment with radiotherapy or chemotherapy were limited to the patients with cancer diagnosed during the period from 1995 through 2003. Analyses stratified according to tumor size and the presence of metastasis were limited to the patients with cancer diagnosed during the period of 2004 through 2007. The dashed line indicates the cancer-related mortality estimate for regular statin dose, and horizontal bars 95% confidence intervals.

inhibition of key cellular functions in cancer cells, and to increased radiosensitization.[10,15,16]

Because statins are selectively localized to the liver, less than 5% of a given dose reaches the circulatory system.[6,34] For cancer types other than liver and biliary cancer,[35] a plausible mechanism behind the observed reduced risk of death from cancer could be the reduction in plasma levels of cholesterol. Indeed, rapidly growing cancers require a high uptake of extracellular cholesterol, and patients with cancer have reduced plasma levels of cholesterol.[36,37] Therefore, a statin-induced reduction in locally synthesized or circulating cholesterol levels could inhibit cancer growth and metastasis and reduce mortality.

Our findings are also supported by the observation of reduced cancer-related mortality among patients with advanced prostate cancer who take statins[38] and a correspondingly reduced recurrence among patients with prostate[39] or breast[13,14] cancer. However, statin use in persons without cancer, with the aim of reducing the risk of cardiovascular disease, does not influence cancer incidence or cancer-related mortality.[17,18] Nevertheless, our observation that all-cause mortality among patients with cancer who were taking statins was reduced by 15% (95% CI, 13 to 17) is similar to the observed reduction in all-cause mortality of 10% (95% CI, 7 to 13) among patients at risk for death from cardiovascular causes.[40] The absence of a dose–response relationship for statins and cancer-related mortality suggests that any statin dose will suffice in reducing mortality among patients with cancer.

Theoretically possible limitations of this study include selection bias; however, this is not an issue because we followed all patients with cancer in the entire Danish population who were 40 years of age or older and eligible for statin use, without losses to follow-up. A related potential limitation concerns the availability and completeness of the diagnostic information; however, the Danish Cancer Registry captures data on 98% of all cancer diagnoses in Denmark, the Danish National Prescription Registry records 100% of all dispensed prescriptions of statins, and the Danish Civil Registration System and the Danish Register of Causes of Death capture data on 100% of all deaths. Data on characteristics of the cancers (size and presence or absence of metastasis at the time of diagnosis) were missing for many patients who had never used statins; however, this limitation does not appear to have distorted our findings, since the results of the nationwide study were similar to those of the nested 1:3 matched study, in which missing information was balanced between statin users and patients who had never used statins.

Another limitation is the possibility that statin use was a marker of increased health awareness, theoretically biasing our results. As we expected, statin users were more likely to be men and to have cardiovascular disease or diabetes, so the data could be prone to a healthy user bias, which could indicate the presence of bias by indication (i.e., patients in this study may have had more than one reason to be given the drug by the doctor). However, both the nested 1:3 matched study, which had equal numbers of men and women and excluded patients with cardiovascular disease or diabetes, and the propensity-score analysis, which matched for the probability that the patient received statins on the basis of patterns in the medical history, had results that were similar to those of the nationwide study. The similarity of the results among these three analyses argues against an influence of male sex, cardiovascular disease or diabetes mellitus, or increased health awareness among statin users.

Finally, because 97% of the patients were white persons of Danish descent, our results may not necessarily apply to other ethnic groups.

In conclusion, among patients with cancer, we observed an association between statin use at the time of diagnosis and a reduced risk of cancer-related mortality, with a reduction of up to 15%. Prospective evaluation of the hypothesis that statin use prolongs the survival of patients with cancer is needed.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Baserga R. Molecular biology of the cell cycle. Int J Radiat Biol 1986;49:219-26.
2. Lamond AI. Review of: *Molecular biology of the cell, 4th edition*. Nature 2002;417:383.
3. Lamb E. Top 200 drugs of 2008. Pharmacy Times. May 15, 2009.
4. Fenton RG, Kung HF, Longo DL, Smith M. Regulation of intracellular actin polymerization by prenylated cellular proteins. J Cell Biol 1992;117:347-56.
5. Herold G, Jungwirth R, Rogler G, Geerling I, Stange EF. Influence of cholesterol supply on cell growth and differentiation in cultured enterocytes (CaCo-2). Digestion 1995;56:57-66.
6. Boudreau DM, Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. Expert Opin Drug Saf 2010;9:603-21.
7. DeBerardinis RJ, Sayed N, Ditsworth D, Thompson CB. Brick by brick: metabolism and tumor cell growth. Curr Opin Genet Dev 2008;18:54-61.
8. Fritz G. HMG-CoA reductase inhibitors (statins) as anticancer drugs. Int J Oncol 2005;27:1401-9.
9. *Idem.* Targeting the mevalonate pathway for improved anticancer therapy. Curr Cancer Drug Targets 2009;9:626-38.
10. Jakobisiak M, Golab J. Potential antitumor effects of statins. Int J Oncol 2003; 23:1055-69.
11. Mannello F, Tonti GA. Statins and breast cancer: may matrix metalloproteinase be the missing link. Cancer Invest 2009;27:466-70.
12. Solomon KR, Freeman MR. Do the cholesterol-lowering properties of statins affect cancer risk? Trends Endocrinol Metab 2008;19:113-21.
13. Ahern TP, Pedersen L, Tarp M, et al. Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. J Natl Cancer Inst 2011;103:1461-8.
14. Kwan ML, Habel LA, Flick ED, Quesenberry CP, Caan B. Post-diagnosis statin use and breast cancer recurrence in a prospective cohort study of early stage breast cancer survivors. Breast Cancer Res Treat 2008;109:573-9.
15. Chan KKW, Oza AM, Siu LL. The statins as anticancer agents. Clin Cancer Res 2003;9:10-9.
16. Gauthaman K, Fong CY, Bongso A. Statins, stem cells, and cancer. J Cell Biochem 2009;106:975-83.
17. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012 May 16 (Epub ahead of print).
18. Emberson JR, Kearney PM, Blackwell L, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One 2012;7(1):e29849.
19. Pedersen CB, Gotzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System: a cohort of eight million persons. Dan Med Bull 2006;53:441-9.
20. Andersen TF, Madsen M, Jørgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register: a valuable source of data for modern health sciences. Dan Med Bull 1999;46:263-8.
21. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry — history, content, quality and use. Dan Med Bull 1997;44:535-9.
22. Nielsen SF, Bojesen SE, Birgens HS, Nordestgaard BG. Risk of thyroid cancer, brain cancer, and non-Hodgkin lymphoma after adult leukemia: a nationwide study. Blood 2011;118:4062-9.
23. Nielsen SF, Nordestgaard BG, Bojesen SE. Associations between first and second primary cancers: a population-based study. CMAJ 2012;184(1):E57-E69.
24. Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours. 7th ed. Hoboken, NJ: Wiley, 2009.
25. Helweg-Larsen K. The Danish register of causes of death. Scand J Public Health 2011;39:Suppl:26-9.
26. Donders AR, Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-91.
27. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94:496-509.
28. Wong WWL, Dimitroulakos J, Minden MD, Penn LZ. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis. Leukemia 2002;16:508-19.
29. Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. Nat Rev Cancer 2005;5:930-42.
30. Denoyelle C, Vasse M, Korner M, et al. Cerivastatin, an inhibitor of HMG-CoA reductase, inhibits the signaling pathways involved in the invasiveness and metastatic properties of highly invasive breast cancer cell lines: an in vitro study. Carcinogenesis 2001;22:1139-48.
31. Kusama T, Mukai M, Iwasaki T, et al. Inhibition of epidermal growth factor-induced RhoA translocation and invasion of human pancreatic cancer cells by 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. Cancer Res 2001;61: 4885-91.
32. Freed-Pastor WA, Mizuno H, Zhao X, et al. Mutant p53 disrupts mammary tissue architecture via the mevalonate pathway. Cell 2012;148:244-58.
33. Petitjean A, Mathe E, Kato S, et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. Hum Mutat 2007;28:622-9.
34. García MJ, Reinoso RF, Sánchez Navarro A, Prous JR. Clinical pharmacokinetics of statins. Methods Find Exp Clin Pharmacol 2003;25:457-81.
35. Kawata S, Yamasaki E, Nagase T, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma: a randomized controlled trial. Br J Cancer 2001;84:886-91.
36. Benn M, Tybjaerg-Hansen A, Stender S, Frikke-Schmidt R, Nordestgaard BG. Low-density lipoprotein cholesterol and the risk of cancer: a mendelian randomization study. J Natl Cancer Inst 2011;103:508-19.
37. Fiorenza AM, Branchi A, Sommariva D. Serum lipoprotein profile in patients with cancer: a comparison with non-cancer subjects. Int J Clin Lab Res 2000;30: 141-5.
38. Platz EA, Leitzmann MF, Visvanathan K, et al. Statin drugs and risk of advanced prostate cancer. J Natl Cancer Inst 2006; 98:1819-25.
39. Hamilton RJ, Banez LL, Aronson WJ, et al. Statin medication use and the risk of biochemical recurrence after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database. Cancer 2010;116:3389-98.
40. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.