Original Article

Statin Type and Cancer Outcomes in Patients with Diabetes Type 2 and Solid Tumors

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ABSTRACT

Objective: Type 2 diabetes mellitus (T2DM) affects 10% of Americans and is associated with an increased incidence of cancer. Statins are first-line cholesterol-lowering medications in the treatment of hyperlipidemia. Several studies have demonstrated a relationship between statin use and reduced cancer incidence. We examined the cancer benefits of statin subtypes, with specific attention to disease-free survival (DFS) and overall survival (OS). **Methods:** This retrospective review included adults with T2DM diagnosed with solid tumors at Roswell Park Cancer Institute in Buffalo, NY, USA (2003–2010). Individuals with gestational diabetes, incomplete records, or diagnosed with rare solid tumors were excluded. Follow-up began at the date of diagnosis and ended with the first confirmed recurrence, death, or loss of contact. Demographics were assessed by Chi-square, Kaplan–Meier survival analyses, and Cox proportional hazards regression. **Findings:** Overall, 1102 patients met inclusion criteria, 52.1% of the study participants were female, and 578 participants (52.5%) died during the follow-up period which ranged from 0 to 156 months. Hydrophilic statin use was associated with improved DFS at 5-year follow-up (41.0% vs. 36.9%, $P = 0.0077$) compared to lipophilic statin use. Multivariate regression revealed that hydrophilic statins were associated with improved DFS (hazard ratio [HR]: 0.706, 95% confidence interval [CI]: 0.526–0.947) and OS (HR: 0.685, 95% CI: 0.503–0.934). Pravastatin was associated with improved OS (HR: 0.674, 95% CI: 0.471–0.964). **Conclusion:** In patients with T2DM and cancer, hydrophilic statins, and pravastatin in particular, are associated with improved DFS as well as OS. Further research examining the cancer-specific effects of hydrophilic and lipophilic statins is needed to better understand their beneficial effects.

KEYWORDS: Cancer mortality, cancer recurrence, diabetes mellitus, hydrophilic statins, lipophilic statins, pravastatin

INTRODUCTION

According to the most recent data from the American Cancer Society, over 1.8 million newly diagnosed cancer cases and over 600,000 deaths from cancer-related causes are estimated to have occurred in 2020.[1] Type 2 diabetes mellitus (T2DM), another ubiquitous medical condition, is estimated to affect almost 10% of Americans and has previously been associated with an increased cancer incidence.[2] Reviews and meta-analyses of the available data have corroborated that diabetes appears to impart a modest increase in the risk of developing several different types of solid organ cancers, while it may actually reduce the risk of the development of prostate cancer.[3,4] Although the exact mechanism underlying this association between cancer and diabetes is not fully understood, it appears that it may be related to the hyperglycemia and proinflammatory state associated with diabetes.[5,6]

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Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_21_3

How to cite this article: Ceacareanu AC, Jolly SD, Nimako GK, Wintrob ZA. Statin type and cancer outcomes in patients with diabetes type 2 and solid tumors. J Res Pharm Pract 2021;10:50-6.

Statins are primarily considered cholesterol-lowering medications, exerting their primary effects through the inhibition of hydroxymethylglutaryl-coenzyme A reductase (HMGCR), the rate-limiting step in cholesterol synthesis. These medications are routinely prescribed to individuals with diabetes, because of evidence supporting tight cholesterol control to aid in the prevention of cardiovascular (CV) disease in diabetic individuals. In addition to these primary cholesterol-lowering effects, statins have been found to exert other pleiotropic beneficial effects throughout the body. Statins have been shown to act in both antioxidant and anti-inflammatory capacities, as well as demonstrating antiproliferative activities against a number of cancers.[7,8]

Given their putative anticancer effects in addition to the beneficial lowering of cholesterol in patients with DM, several studies have investigated the potential association between statin use and reduced cancer incidence in patients with and without T2DM.[9-11] The results of these studies have been mixed, with several concluding that statins may be associated with a lower overall incidence of cancer; however, this effect may be potentiated by the type of statin used (hydrophilic vs. lipophilic).[12] In addition, although several studies have examined the relationship between statin use and cancer incidence, few have investigated the association between statin use and progression or disease-free survival (DFS) in patients with T2DM. Herein, we report the results of our study of the relationship between statin use in patients with T2DM and the development of cancer as well as the duration of overall survival (OS) and DFS, with special attention to the specific type of statin used.

METHODS

This retrospective hospital cohort study has been approved by the institutional review boards of Roswell Park Cancer Institute and the University at Buffalo. All patients with a new diagnosis of cancer of the breast, ovary, prostate, gastrointestinal tract, lung, or kidney at our institution were reviewed under the approved protocol. Including criteria consisted of patients diagnosed with solid malignancies between January 1, 2003, and December 31, 2010, who were 18 years or older, and who had preexisting T2DM. The presence of solid malignancy and diabetes was determined by our tumor registry, based on the cancer center coding of the International Classification of Diseases, Ninth Revision (ICD-9). A total of 1102 newly diagnosed patients having T2DM at the time of the cancer diagnosis were identified. Exclusion criteria consisted of diagnosis of gestational diabetes or incomplete medical records. Moreover, if there were

fewer than 50 cases of a specific cancer type, they were excluded from the analysis. The remaining 1102 patients were included in the analysis.

The baseline clinical and demographic information and self-reported treatment histories along with cancer outcomes were documented by reviewing individual charts [Table 1]. The cumulative comorbidity was calculated as the total of cancer center-documented ICD-9 comorbid disease diagnosis codes for each case. Specific treatment groups were defined based on the mechanism of action of the respective hyperlipidemia treatment, as follows: (a) "nonstatin users" group, and (b) "statin users" group with the specific subgroups "hydrophilic statin users," for pravastatin and rosuvastatin users and "lipophilic statin users," for the users of all other statins except rosuvastatin and pravastatin. Outcomes of interest were DFS, OS, and death. If alive, individuals were followed through their last day of contact or vital status update, whichever was more recent. Follow-up began at the date of diagnosis and ended with the first confirmed recurrence and/or death depending on the analysis. OS was defined as time to death with patients alive at last follow-up treated as censored. DFS was defined as time to cancer recurrence or death with patients alive with no recurrence treated as censored. Cases lost to follow-up were censored at the date of last contact. Event documentation was limited to data collected through September 30, 2015.

A primary assessment of survival outcomes (OS and DFS) was performed using the univariate Kaplan–Meier survival probability estimated with log-rank and Wilcoxon statistics. Multivariate survival analyses were done using Cox proportional hazards models including age (continuous); gender; race; body mass index (BMI) (continuous); alcohol history; tumor location (breast, head and neck, lower gastrointestinal tract, lung, melanoma, ovaries, prostate, kidney, and upper gastrointestinal tract); baseline American Joint Committee on Cancer (AJCC) stage category 0, I, II, III, IV, or unknown; and cumulative CV comorbidity (CV index including five categories, 0 or 1, 2, 3, 4, and 5 or more CV comorbidities). Potential continuous covariates for Cox models were assessed for normality using the Anderson–Darling test.

HR 95% confidence bounds were computed, and 95% confidence intervals (CI) representing the association between a defined event and the use of a specific cholesterol therapy were computed using Cox models. A nominal significance threshold of 0.05 was used in all testing, and all analyses and plots were done using SAS statistical software (version 9.4; SAS Institute Inc., Cary, North Carolina, USA).

Table 1: Study demographics by cholesterol drug category					
Cholesterol treatment category	None, *n* (%)	Nonstatin, *n* (%)	Statin, *n* (%)	Statin + nonstatin, *n* (%)	*P*
Sex					0.685
Female	234 (52.1)	34 (48,6)	229 (52.9)	85 (56.7)	
Male	215 (47.9)	36 (51.4)	204 (47.1)	65 (43.3)	
Age (years)					0.001
Under 50	48 (10.7)	9 (12.9)	21 (4.8)	5 (3.3)	
50-59	105 (23.4)	16 (22.9)	88 (20.8)	28 (18.7)	
60-69	146 (32.5)	22 (31.4)	144 (33.3)	66 (44.0)	
70-79	111 (24.7)	18 (25.7)	133 (30.7)	45 (30.0)	
80 and over	39 (8.7)	5 (7.1)	47 (10.9)	6 (4.0)	
BMI (kg/m^2)					<0.001
Underweight (<18.5)	4 (0.9)	0	21 (4.8)	5 (3.3)	
Healthy (18.5-24.9)	32 (7.1)	7 (10.0)	39 (9.0)	7 (4.7)	
Overweight (25.0-29.9)	102 (22.7)	10 (14.3)	101 (23.3)	30 (20.0)	
Obese (30.0-39.9)	166 (37.0)	33 (47.1)	175 (40.0)	72 (48.0)	
Morbidly obese (≥40.0)	59 (13.1)	17 (24.3)	38 (8.8)	26 (17.3)	
Unknown	86 (19.2)	3 (4.3)	77 (17.8)	14 (9.3)	
Race					0.068
African-American	58 (12.9)	4 (5.7)	53 (12.2)	11 (7.3)	
Caucasian	370 (82.4)	65 (92.9)	356 (82.2)	136 (90.7)	
Others	21 (4.7)	1 (1.4)	24 (5.5)	3 (2.0)	
Cardiovascular index					<0.001
0 or 1	280 (62.4)	45 (64.3)	167 (38.6)	57 (38.0)	
2	104 (23.2)	18 (25.7)	156 (36.0)	51 (34.0)	
3	36 (8.0)	4 (5.7)	69 (15.9)	19 (12.7)	
4	18 (4.0)	3 (4.3)	28 (6.5)	13 (8.7)	
5 and >	11 (2.4)	0	13 (3.0)	10 (6.7)	

BMI=Body mass index

RESULTS

Overall, 1102 patients met the study's inclusion and exclusion criteria and were included in the analysis [Table 1]. Approximately 52.1% of the participants included in the study were female, and 82.4% were white and 12.9% were black. Roughly half, 50.1%, of the patients included in the study had a BMI over 30 kg/m^2. Within the cohort, 578 participants (52.4%) died during the follow-up period which ranged from 0 to 156 months. Of the 1102 patients included in the study, 449 received no anticholesterol pharmacologic intervention, 433 received statin monotherapy, 70 received nonstatin monotherapy, and 150 received combination therapy. In both the no-treatment and statin monotherapy groups, the most common cancers diagnosed were breast (17.8% vs. 21.5%) and lung (16.7% vs. 18.0%). In the no-treatment group, the distribution of AJCC stage at diagnosis was I (23.4%), IV (22.1%), III (18.7%), II (18.0%), 0 (3.3%), and unknown in 14.5%. Within the statin monotherapy group, the distribution was Stage I (29.7%), Stage III (19.4%), Stage II (19.2%), Stage IV (18.7%), Stage 0 (5.5%), and 7.4% for unknown stage at diagnosis.

Figure 1 illustrates the Kaplan–Meier analysis for DFS and OS with respect to overall statin use and specific categories of statin use as well as anticholesterol medication use. Any cholesterol therapy was associated with improved OS (43.6% vs. 35.2%, overall *P* = 0.0048) and DFS (39.2% vs. 30.3%, overall *P* = 0.0059) at 5-year follow-up. The OS and DFS were not significantly different when comparing the control group to any statin usage [Table 2]. When analyzing the association between lipophilic or hydrophilic status and survival, hydrophilic statin use was associated with improved DFS at 5-year follow-up (41.3% vs. 36.9% vs. 33.1%, overall *P* = 0.0054) compared to lipophilic statin use and no statin use [Figure 2].

Based on the results of multivariate regression utilizing the Cox proportional hazards model, the use of any cholesterol therapy seemed to prolong DFS (HR: 0.859, 95% CI: 0.714–1.034) and was associated with prolonged OS (HR: 0.821, 95% CI: 0.674–0.999) [Table 2]. While no association was found between overall statin use and DFS or OS, subgroup analysis revealed that hydrophilic statins in general and pravastatin in particular may improve DFS and OS.
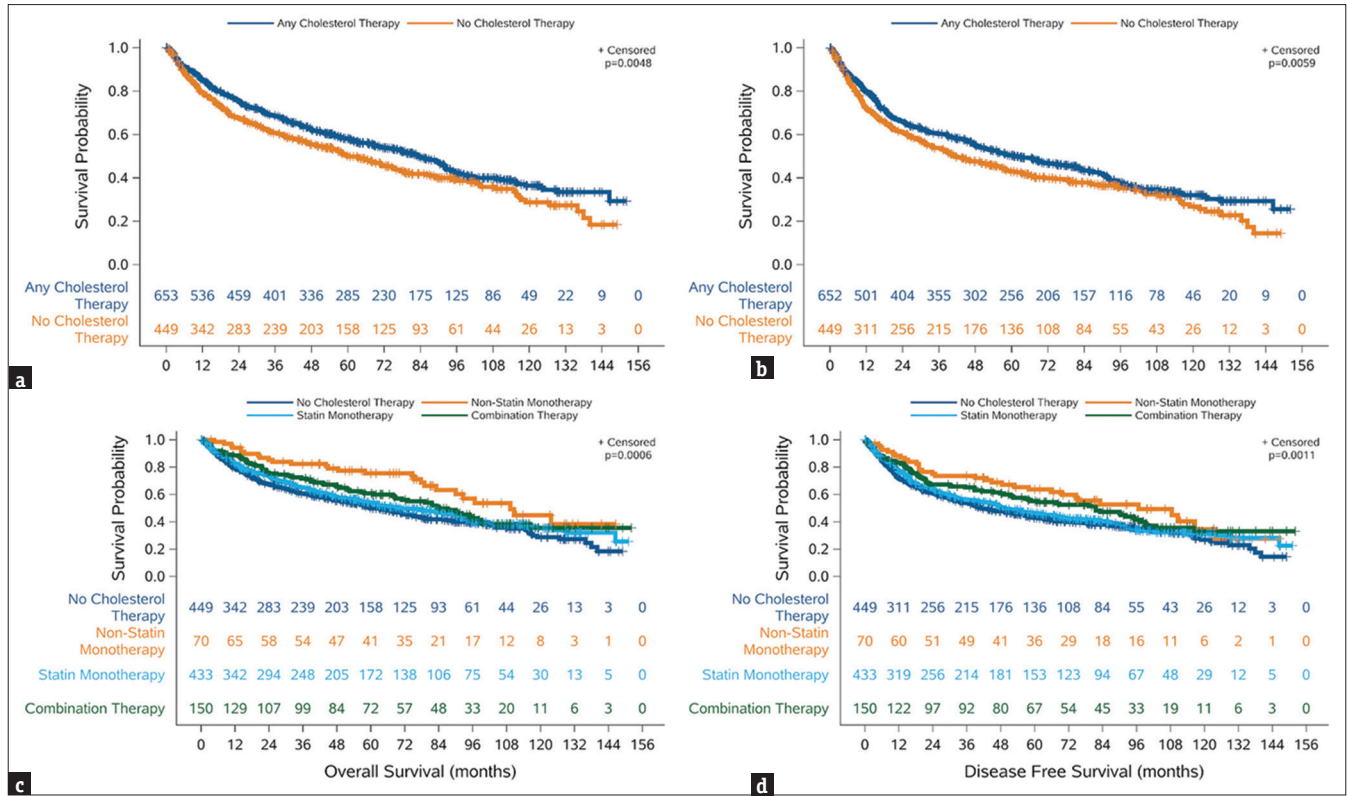
Figure 1: Overall survival (panels a and c) and disease-free survival (panels b and d) by type of cholesterol treatment use in individuals with preexisting type 2 diabetes mellitus diagnosed with solid tumors
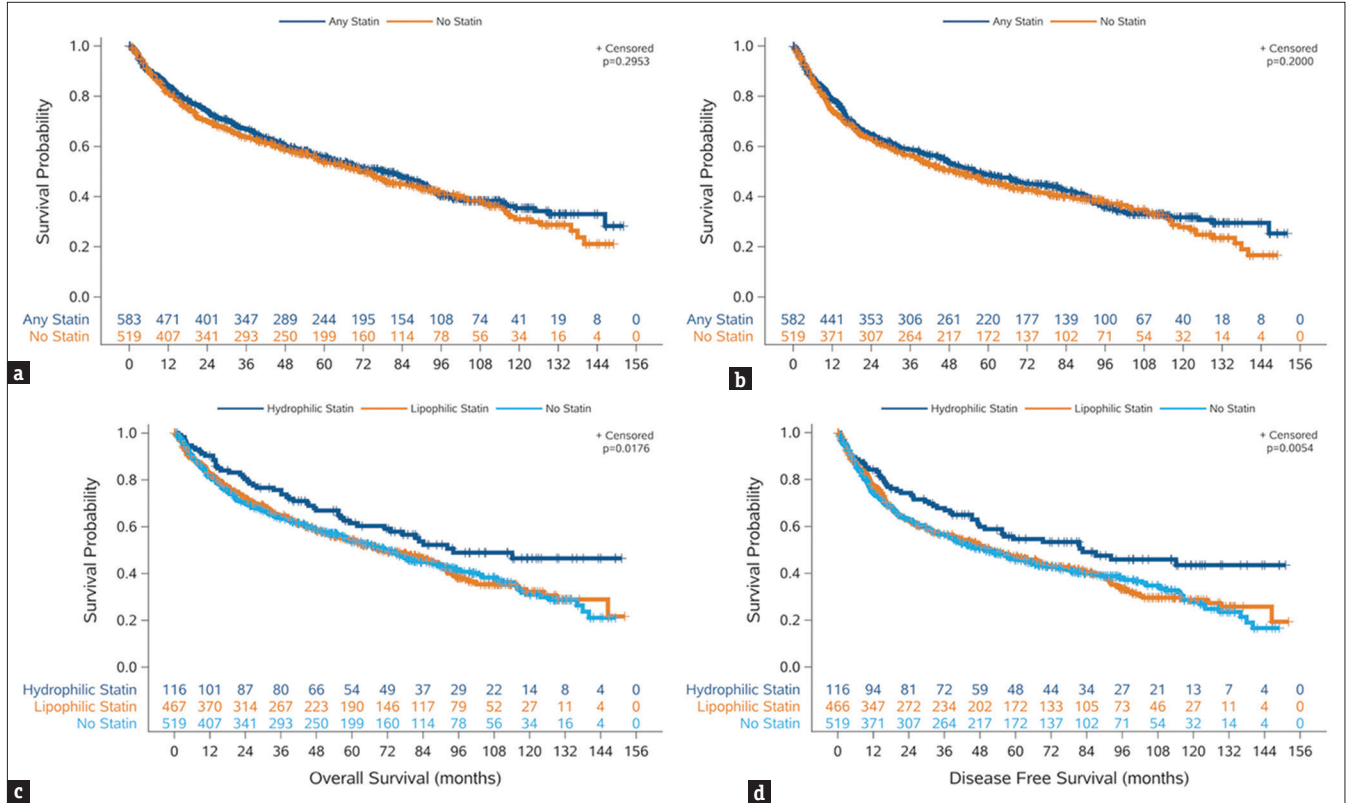

Figure 2: Disease-free survival (panels a and c) and overall survival (panels b and d) by statin treatment use in individuals with preexisting type 2 diabetes mellitus diagnosed with solid tumors

Table 2: Disease-free survival and overall survival hazard ratios for specific statins and cholesterol drug categories

Cholesterol treatment category	n	DFS				OS			
		Events	HR (95% CI)	P	χ^2	Events	HR (95% CI)	P	χ^2
None	449	274	Reference	-	-	250	Reference	-	-
Any	653	369	0.859 (0.714-1.034)	0.1083	2.5787	328	0.821 (0.674-0.999)	0.0484	3.8967
No statin	519	308	Reference	-	-	277	Reference		
Any statin	583	335	0.880 (0.732-1.058)	0.1725	1.8612	301	0.866 (0.712-1.053)	0.1496	2.0763
No statin	519	308	Reference	-	-	277	Reference		
Hydrophilic statin	116	56	0.706 (0.526-0.947)	0.0201	5.4021	51	0.685 (0.503-0.934)	0.0166	5.7354
Lipophilic statin	467	279	0.905 (0.762-1.074)	0.2535	1.3039	250	0.891 (0.743-1.069)	0.2144	1.5417
No statin	519	308	Reference	-	-	277	Reference	-	-
Atorvastatin	259	150	0.857 (0.700-1.050)	0.1369	2.2127	138	0.871 (0.705-1.077)	0.2035	1.6168
Fluvastatin	8	4	0.790 (0.287-2.174)	0.6488	0.2074	4	0.768 (0.277-2.126)	0.6108	0.2590
Lovastatin	44	27	0.839 (0.559-1.259)	0.3954	0.7223	23	0.774 (0.500-1.198)	0.2499	1.3240
Simvastatin	156	98	1.025 (0.807-1.302)	0.8371	0.0423	85	0.984 (0.761-1.273)	0.9040	0.0145
Pravastatin	78	41	0.742 (0.532-1.037)	0.0804	3.0564	36	0.674 (0.471-0.964)	0.0308	4.6656
Rosuvastatin	38	15	0.630 (0.372-1.068)	0.0861	2.9465	15	0.726 (0.428-1.232)	0.2358	1.4056

χ^2=Chi-square associated with the analysis of maximum likelihood estimates. This model was adjusted for age, gender, cancer type, AJCC stage, BMI, alcohol use history, and cardiovascular comorbidity. CI=Confidence interval, HR=Hazard ratio, DFS=Disease-free survival, OS=Overall survival, BMI=Body mass index, AJCC=American Joint Committee on Cancer

Hydrophilic statins were associated with significantly improved DFS (HR: 0.706, 95% CI: 0.526–0.947) and OS (HR: 0.685, 95% CI: 0.503–0.934). Pravastatin was associated with improved OS (HR: 0.674, 95% CI: 0.471–0.964) but showed a nonsignificant trend toward improvement in DFS (HR: 0.742, 95% CI: 0.532–1.037) [Table 2].

DISCUSSION

In our study of 1102 patients, we found that hydrophilic statin use was associated with a 24.8% improvement in DFS at 5-year follow-up and a 3.3-fold improvement in DFS at 12-year follow-up compared to no statin use. In contrast, there was no significant difference in the DFS between patients taking lipophilic statins and those taking no statins. Multivariate regression of the survival data further demonstrated that of all the statins prescribed, only pravastatin, a hydrophilic statin, was associated with a significant improvement in OS (HR: 0.674, 95% CI: 0.471–0.964) [Table 2]. The results of this study, exploring longitudinal DFS as well as OS, build on previous reports that described a potential decrease in cancer incidence in patients with T2DM who took statin medications. Furthermore, these results add to the body of literature which suggests that hydrophilic and lipophilic statins may have disparate antineoplastic properties.

With the increasing burden of obesity throughout the world, the overall incidence of diabetes continues to increase. In the United States, the prevalence of T2DM is estimated to exceed 10% of the general population.[2] While the effects of T2DM on the CV system, the eyes,

the peripheral nervous system, and the kidneys are well documented, recent evidence has raised the concern that T2DM may increase the overall risk of cancer development. A study based on observational data from the Emerging Risk Factors Collaboration found that in a cohort of 820,900 people, T2DM was associated with an overall increase in the risk of death from cancer (HR: 2.32, 95% CI: 2.11–2.56).[13] An additional large meta-analysis of 33 studies including over 1 million patients found that the increased cancer incidence may vary by ethnicity.[14] The study concluded that the presence of T2DM increased cancer incidence by 23% in Asians and 15% in non-Asians. Furthermore, the risk of cancer-related mortality associated was 32% higher in Asians with T2DM and 16% higher in non-Asians with T2DM. While the exact mechanism of the increased incidence of cancer in people with T2DM is not completely understood, the current research suggests that it may be related to the hyperglycemia or increased inflammation typically associated with T2DM.[5,6]

Because of the routine co-occurrence of dyslipidemia with T2DM and the potential for vascular complications in the setting of combined dyslipidemia and hyperglycemia, statin medications are regularly prescribed to patients with T2DM. The primary mechanism of action of statin medications relies on the inhibition of HMGCR, the rate-limiting step in cholesterol synthesis. The inhibition of cholesterol synthesis ultimately leads to a relative decrease in cholesterol availability for new membrane synthesis, which may have an antiproliferative effect, slowing cancer progression. In addition to their direct action on HMGCR, preclinical studies have elucidated several pleiotropic mechanisms by which statins may

exert their antineoplastic effects. These studies have found that statins can be potent inducers of apoptosis, and can lower protein prenylation, which is an important posttranscriptional process involved in the pathogenesis of several cancers.[7,15]

The results of our study confirm the previously reported finding that not all statins have similar antineoplastic effects. When evaluating DFS in relationship to statin type, hydrophilic statin use was associated with a 24.8% improvement at 5-year follow-up as compared to lipophilic statins. In contrast, there was no statistically significant difference in DFS among participants who were taking lipophilic statins and those not taking any statin medication. In addition, multivariate regression by statin type found that only pravastatin was significantly associated with improved OS. The disparate anticancer effects of statins have been reported in several previous studies. Interestingly, the difference does not appear to be an "all-or-none" phenomenon where one class is simply more efficacious. Several clinical and preclinical studies have found that lipophilic statins appear to possess superior anticancer properties against breast, esophageal, and pancreatic cancers.[16-18] In contrast, hydrophilic statins appear to be superior to lipophilic statins in the case of prostate cancer.[19] Our data, which were inclusive of several different types of cancer, found that hydrophilic statins may have superior anticancer effects.

While the potential mechanism for different anticancer effects for lipophilic and hydrophilic statins is still being investigated, preclinical evidence does suggest that the two classes of statins may have different effects on the phospholipid bilayer, cancer cell growth, and cell signaling.[20,21] Based on the conflicting results across several papers, we postulate that the overall anticancer effects of statins may be dependent on the specific cancer type.[16-18,20,21] In addition, the superiority of hydrophilic statins in prostate cancer also raises the possibility that in addition to cancer specificity, gender may play a role in potentiating the anticancer effects of statins. Another study investigating the anticancer effects of statins in prostate cancer found that significant benefit was only realized if the men taking statins were also on androgen deprivation therapy for their prostate cancer.[22] This concept is further corroborated by the results of a recent retrospective cohort study which found that the largest anticancer effects of statins were experienced by women who were taking lipophilic statin medication.[23]

One of the most significant limitations of this study is the relative lack of statistical power to do subgroup analyses based on cancer subtypes and statin use. Based on previous papers in the literature, as well as our results,

the antineoplastic properties of statins may be cancer specific or modulated by gender, two hypotheses which should be further explored in future studies. In addition, because this study is a retrospective cohort study, we could not quantify the degree of disease progression or the rate and type of metastases, two variables which may be meaningfully impacted by the anticancer effects associated with statins.

Our study builds on previous studies that have demonstrated a relationship between statin use in patients with diabetes and a reduced cancer incidence by examining the OS and DFS. Our results indicate that hydrophilic statins, and pravastatin in particular, may confer a superior survival benefit in patients with diabetes who are diagnosed with cancer. Further research is needed to better understand if this survival benefit is specific to the subtype of cancer or is modulated by gender.

Authors' Contribution

Alice C. Ceacareanu designed the study, supervised data collection and analysis, and gave scientific approval for publication; Shanria D. Jolly conducted literature review, prepared tables and figures for publication, and drafted the manuscript; George K. Nimako supervised pharmacy interns and conducted data collection; Zachary A. P. Wintrob contributed to study design and analyzed the data.

Conflicts of interest

Zachary A. P. Wintrob is affiliated with ROAKETIN Inc. and Alice C. Ceacareanu owns stock in ROAKETIN Inc. None of the authors report any relevant personal or financial conflicts of interest to disclose.

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