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EPIDEMIOLOGY

Impact of long-term lipid-lowering therapy on clinical outcomes in breast cancer

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Abstract

Introduction The use of statins has been associated with improved survival in patients with breast cancer in several studies but results have been mixed. This study evaluates the impact of duration of statin use on breast cancer patient outcomes.

Methods This is a single-institution, retrospective cohort, examining the impact of statin use on the outcomes of 1523 women diagnosed with operable breast cancer between1995 and 2015. Clinical variables were compared using Student's *t* test, Fisher's exact and Chi square tests. Overall (OS) and disease-free (DFS) survival were performed using Kaplan–Meier and Cox-Proportional Hazard (Cox-PH) analysis in the statistical software *R*.

Results Patients were grouped by duration of statin use: never-statin user [N] ($n=1092$), short (< 3 years) [S] ($n=115$), moderate [M] (3–5 years) ($n=109$) and long [L] (> 5 years) ($n=207$) term. Over a median follow-up of 70.2 months, 138 women died (84 died of breast cancer) and 125 had disease recurrence. On multivariable Cox-PH analysis adjusting for clinical variables including metabolic comorbidities using the Charlson comorbidity index, OS in the [S] and [M] subgroups did not differ [N], while OS was improved in [L] (adjusted hazard ratio (AHR) 0.38, confidence interval (CI) 0.17–0.85, $p<0.018$). DFS was also significantly improved in the [L] subgroup (adjusted HR 0.15, CI 0.05–0.48, $p<0.001$). Subanalysis stratified by receptor status showed a trend towards improved DFS in all tumor subtypes including triple-negative breast cancer.

Conclusions Our retrospective analyses suggest that long-term statin use (> 5 years) was associated with improved OS and DFS in women with breast cancer regardless of receptor subtype, even after adjusting for metabolic comorbidities.

Keywords Statins · Breast Cancer · Cancer recurrence risk · Lipid-lowering agents · Metabolic syndrome · Cancer outcomes

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide [1] and is second only to lung cancer as the leading cause of cancer death in women in the United States. In addition to genetic risk factors, a woman's lifetime risk of breast cancer is modified by lifestyle and environmental risk factors that are strongly tied to hormonal status, such as obesity and the metabolic syndrome. In parallel, as the prevalence of obesity and its associated comorbidities including dyslipidemia and the metabolic syndrome have continued to rise, statins and lipid-lowering agents are now among the most common medications used by older adults. Intriguingly, a number of retrospective studies suggest that statins, specifically lipophilic statins, may also have anti-cancer properties. Even though a clear mechanism has not been established, multiple preclinical studies have shown

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that statins may inhibit the proliferation of cancer cells by halting the cell cycle [2]. In addition, statins have been shown to induce apoptosis in multiple cancer cell lines, including colon cancer cells [3], prostate cancer cells [4, 5], and breast cancer cells [6–8]. Importantly, statins are well-tolerated and have a limited set of known drug interactions.

Statins first became commercially available in the 1980s [9] and have since revolutionized the field of cardiovascular medicine with improved clinical outcomes associated with reductions in low-density lipoproteins (LDL) [10]. As a class, statins are generally well-tolerated. Thus far, there is no evidence that there is a lower bound for serum LDL with regards to cardiovascular protection: patients with the lowest LDL showed fewer cardiovascular events than those who had LDL levels closer to guideline levels, supporting the idea that achieving lower LDL levels is better [11]. Patients treated with statins who achieved the lowest LDL levels (< 40 mg/dL) showed similar risks of adverse outcomes such as rhabdomyolysis, abnormal liver enzyme levels, or strokes when compared to those who achieved levels closer to guideline recommendations (< 100 mg/dL).

A number of studies have shown an association between statin use and improved outcomes for breast cancer [12–19]. In a key study, the Breast International Group (BIG) conducted a randomized, phase III trial with 8010 postmenopausal women with early stage hormone receptor-positive invasive breast cancer [19]. Patients were randomized to different endocrine therapy treatments. Use of cholesterol-lowering medications was documented at the start of endocrine therapy and at follow-up visits. The study found that patients exposed to cholesterol-lowering medications prior to start of endocrine therapy had improved disease-free survival (DFS) (HR 0.82, 95% C.I. 0.68–0.99). Furthermore, initiation of cholesterol-lowering medications during any endocrine therapy was associated with improved DFS, reduced breast cancer recurrence, and reduced distant recurrence compared to never-users (HR 0.79, 95% C.I. 0.66–0.95, $p = 0.01$; HR 0.74, 95% C.I. 0.56–0.97, $p = 0.02$; and HR 0.74, 95% C.I. 0.56–0.97, $p = 0.03$, respectively).

Another landmark prospective study by the Danish Breast Cancer Cooperative Group utilized the Danish Registry to evaluate the impact of statin on breast cancer outcome. Of the 18,769 study participants who were diagnosed with breast cancer, 3282 were prescribed a statin during the period of follow-up after breast cancer diagnosis [18]. Of the 3282 patients who were on statin, 2524 were prescribed lipophilic statins while only 206 were prescribed hydrophilic statins. Compared to statin non-users, patients taking exclusively lipophilic statins were found to have a lower breast cancer recurrence risk with a 10-year adjusted HR of 0.73 (95% C.I. 0.60–0.89). The 10-year adjusted HR for breast cancer recurrence was similar in those on hydrophilic statins and non-users.

In contrast, other studies have failed to show a significant association between statin use and breast cancer outcomes [20–23]. One of the largest retrospective study included the Scottish Cancer Registry which examined statin use and breast cancer mortality among 15,140 breast cancer patients [22]. The study found that statin use after diagnosis was not associated with lowered breast cancer mortality compared to non-user (adjusted HR 0.95, 95% C.I. 0.79–1.15). Statin use did not affect breast cancer outcomes after adjusting for confounding variables including age, socioeconomic status, hormone receptor status, tumor grade, tumor stage, treatment type, comorbidities, and use of aspirin or metformin. Limitations of the study included a study population that was not ethnically diverse and data on disease recurrence were not provided. Interestingly, the study did report a significant association between the use of statin before breast cancer diagnosis and improved survival with an adjusted HR of 0.85 (95% CI 0.74, 0.98).

Given these conflicting reports, several meta-analyses have attempted to resolve this question [24–26]. However, meta-analyses would still have limitations of the included studies which may lack information on potential confounding variables such as body mass index (BMI), data on tumor receptor status, usage of other medications, and data on comorbidities, e.g. cardiovascular disease.

Using a large retrospective database of women with breast cancer who were treated at our institution, we collected data to include detailed tumor prognostic information, BMI, and comorbidities that were typically difficult to obtain in large population studies to evaluate the association of statin use and breast cancer outcomes. We hypothesize that statin use would improve both disease-free survival and overall survival in patients with breast cancer.

Methods

Study population

After obtaining IRB approval, we identified all patients with primary operable breast cancer, including DCIS, who had undergone breast cancer surgery to treat their operable primary breast cancer between 1995 and 2015 at our institution using our electronic medical records (EMR). Patients with an ICD-9 diagnosis code of invasive breast cancer on at least two separate in-person visits who underwent breast cancer surgery with follow-up data at our institution were included.

To be included for analysis, age at diagnosis, clinical documentation including history of statin prescriptions, and postoperative follow-up of greater than 30 days must be available. Clinical variables including self-reported race, BMI at the time of breast cancer diagnosis, breast cancer prognostic variables such as tumor size, nodal status, tumor

grade, estrogen (ER), progesterone (PR), and Her-2/neu (Her2) receptor status, and existing medical comorbidities necessary for the calculation of the Charlson comorbidity index were recorded. Tumors were stratified into four subtypes according to receptor status: ER/PR+ Her2−, ER/PR− Her2+, ER/PR+ Her2+ and ER/PR− Her2−. Patients were grouped by duration of statin use into 4 subgroups: never-user [N] ($n=1092$) vs short (< 3 years) [S] ($n=115$], moderate [M] (3–5 years) ($n=109$] and long [L] (> 5 years) ($n=207$) term user. The Charlson comorbidity index was calculated as described previously [27, 28] and considered the following diagnoses: Score of 1 [Heart attack (myocardial infarction), Peripheral arterial disease, Other diagnosed heart problems, Stroke, Asthma, Ulcer disease, Insulin-dependent diabetes, Arthritis], Score of 2 [Renal disease/kidney stones, Other diagnosed cancer], and Score of 3 [Cirrhosis]. All data were collected between 2016 and 2017.

Statistical analyses

Association between statin use, clinical and pathologic variables, and disease status was performed using Student's *t* test, Fisher's exact, or Chi square test, where appropriate. Cochran–Mantel–Haenszel Chi square test was used to evaluate for conditional independence. *p*-values less than or equal to 0.05 were accepted as statistically significant.

Univariable and multivariable survival analyses for OS and DFS were performed using Kaplan–Meier and Cox-Proportional Hazard models. Forward–backward stepwise regression was used to determine independent covariates contributing to the final survival models on multivariable analysis. All analyses were performed in 2017.

Results

A total of 1523 women were followed over a median of 70.2 months (Table 1). A total of 431 patients (28.3%) used statins, 48% of whom used statins for over 5 years. Black women were significantly more likely to receive statins than non-black women (39.6% vs. 23.8%, $p<0.001$). As expected, being overweight/obese, of older age, and having multiple comorbidities as assessed by the Charlson comorbidity index are associated with statin use, $p<0.001$. In addition, the distribution of tumor receptor subtypes differed significantly as subgroup [L] was more likely to present with ER/PR+, Her2− tumors (50%) as compared to [N] (40%), [S] (36%), and [M] (41%) ($p=0.002$).

On univariable analysis, older age at diagnosis, black race, larger tumor size, higher tumor grade, the presence of tumor lymphovascular invasion, higher nodal stage, the presence of extracapsular extension in involved axillary nodes, and receipt of mastectomy were all associated with worse OS and DFS (Sup Table 1). The presence of metabolic comorbidities such as diabetes and coronary artery disease as well as the cumulative Charlson comorbidity index were associated with worse OS but not DFS. Patients in the [S] subgroup (statin use < 3 years) had worse OS as compared to [N] subgroup (no statin use) (HR 2.34, 95% C.I. 1.19–4.62, $p<0.014$) (Supplementary Table 1 and Fig. 1a). However, there was no significant difference between these two groups in DFS (Fig. 1b). Interestingly, patients in the [L] subgroup (> 5 years) had better DFS than the [N] subgroup (HR 0.37, 95% C.I. 0.19–0.70, $p<2.4\times10^{-3}$), but there was no difference in OS between these two subgroups ($p>0.1$) (Fig. 1a).

On multivariable analysis using a Cox-Proportional Hazard model, we found that patients with larger tumor size, higher nodal stage, the presence of extracapsular extension, triple-negative tumor subtype, and the Charlson comorbidity index were independently associated with worse DFS and OS (Table 2). Higher tumor grade and age were associated with DFS, but not OS, while black race was associated with worse OS, but not DFS. Overall, patients in the [L] subgroup have improved DFS and OS when compared with the [N] subgroup (HR: 0.15, 95% C.I. 0.05–0.48, $p<1.0\times10^{-3}$ and HR: 0.38, 95% C.I. 0.17–0.85, $p<0.018$, respectively). The same protective effect was not observed in patients in [S] or [M] subgroups who had shorter duration of statin use ($p>0.2$). While there was no statistical difference in the rates of local recurrence across statin groups ($p>0.4$), the rates of metastasis in the [L] subgroup (6%) were significantly lower than for patients in [N] subgroup (9%), [S] subgroup(16%), and [M] subgroup (15%) ($p<0.012$) (Table 1).

As prior studies have suggested that the beneficial effects of statins may be limited to hormone receptor-positive tumors, we evaluated the impact of statin use duration on DFS in our patients as stratified by four common tumor subtypes according to receptor status. Results were illustrated in the respective Kaplan–Meier plots (Fig. 2a–d). As previously reported, the protective effect of long-term statin use ([L] subgroup) only reached statistical significance in patients with ER/PR+ Her2− tumors though there was a trend towards a reduced HR in the [L] subgroups in both ER/PR+ HER2+ tumors as well as the ER/PR− Her2− (also known as triple-negative) tumors (Supplementary Table 2). This likely reflects a limited statistical power. Interestingly, statin use of any duration appeared to have a trend towards favorable impact on patients with triple-negative breast cancer (Supplementary Table 2). We performed subanalyses to compare the DFS between those who had never used statin and those who had statin use of any duration, stratified by receptor subtypes. We observed an improved DFS in the combined [S], [M], and [L] subgroups with statin use of any duration compared to the [N] subgroup ($p<0.043$, log-rank test). Results were illustrated in the Kaplan–Meier plot in Fig. 1d.

Table 1 Demographic, comorbidity, and breast cancer characteristics

	Overall	Never statin	Statins < 3 years	Statins 3–5 years	Statins > 5 years	*p* value
n	1523	1092	115	109	207	
Mean age at diagnosis [years (SD)]	64.9 (13.95)	62.7 (13.29)	71.97 (11.7)	72.51 (12.1)	73.05 (10.21)	
Race						
Black	470 (0.31)	286 (0.26)	50 (0.43)	48 (0.44)	86 (0.42)	< 0.001
White	919 (0.6)	701 (0.64)	57 (0.50)	52 (0.48)	109 (0.53)	
Other	117 (0.08)	92 (0.08)	6 (0.05)	7 (0.06)	12 (0.06)	
NA	17 (0.01)	13 (0.01)	2 (0.02)	2 (0.02)	0 (0)	
BMI						
Normal (< 24.9)	377 (0.25)	314 (0.29)	20 (0.17)	14 (0.13)	29 (0.14)	< 0.001
Overweight (25–29.9)	315 (0.21)	212 (0.19)	26 (0.23)	26 (0.24)	51 (0.25)	
Obese (> 30)	408 (0.27)	257 (0.24)	39 (0.34)	30 (0.28)	82 (0.4)	
NA	423 (0.28)	309 (0.28)	30 (0.26)	39 (0.36)	45 (0.22)	
Tumor grade						
1	241 (0.16)	170 (0.16)	15 (0.13)	17 (0.16)	39 (0.19)	0.502
2	442 (0.29)	325 (0.30)	29 (0.25)	34 (0.31)	54 (0.26)	
3	314 (0.21)	231 (0.21)	27 (0.23)	23 (0.21)	33 (0.16)	
NA	526 (0.35)	366 (0.34)	44 (0.38)	35 (0.32)	81 (0.39)	
Lymphovascular invasion						
Absent	827 (0.54)	594 (0.54)	54 (0.47)	60 (0.55)	119 (0.57)	0.03
Present	177 (0.12)	145 (0.13)	10 (0.09)	9 (0.08)	13 (0.06)	
NA	519 (0.34)	353 (0.32)	51 (0.44)	40 (0.37)	75 (0.36)	
Tumor Stage (tumor size)						
1 (< 2 cm)	770 (0.51)	541 (0.50)	62 (0.54)	54 (0.5)	113 (0.55)	0.899
2 (2–5 cm)	406 (0.27)	295 (0.27)	31 (0.27)	31 (0.28)	49 (0.24)	
3 (> 5 cm)	57 (0.04)	39 (0.04)	5 (0.04)	4 (0.04)	9 (0.04)	
NA	290 (0.19)	217 (0.20)	17 (0.15)	20 (0.18)	36 (0.17)	
Nodal stage (number of positive axillary nodes)						
0	923 (0.61)	664 (0.61)	65 (0.57)	64 (0.59)	130 (0.63)	0.384
1 (1–3)	354 (0.23)	260 (0.24)	29 (0.25)	29 (0.27)	36 (0.17)	
2 (4–9)	82 (0.05)	65 (0.06)	5 (0.04)	2 (0.02)	10 (0.05)	
3 (> 9)	32 (0.02)	21 (0.02)	2 (0.02)	2 (0.02)	7 (0.03)	
NA	132 (0.09)	82 (0.08)	14 (0.12)	12 (0.11)	24 (0.12)	
Extracapsular extension						
Absent	1070 (0.7)	767 (0.70)	83 (0.72)	72 (0.66)	148 (0.71)	0.467
Present	123 (0.08)	94 (0.09)	7 (0.06)	10 (0.09)	12 (0.06)	
NA	330 (0.22)	231 (0.21)	25 (0.22)	27 (0.25)	47 (0.23)	
Tumor subtype						
ER+ or PR+ and Her2−	624 (0.41)	434 (0.40)	41 (0.36)	45 (0.41)	104 (0.5)	0.002
ER−/PR− and Her2+	76 (0.05)	57 (0.05)	9 (0.08)	6 (0.06)	4 (0.02)	
ER+, PR+ and Her2+	317 (0.21)	242 (0.22)	22 (0.19)	23 (0.21)	30 (0.14)	
ER−, PR− and Her2−	156 (0.1)	112 (0.10)	10 (0.09)	12 (0.11)	22 (0.11)	
NA	350 (0.23)	247 (0.23)	33 (0.29)	23 (0.21)	47 (0.23)	
Initial surgery type						
Lumpectomy	846 (0.56)	574 (0.53)	76 (0.66)	59 (0.54)	137 (0.66)	<0.001
Mastectomy	677 (0.44)	518 (0.47)	39 (0.34)	50 (0.46)	70 (0.34)	
Comorbidities						
None	1181 (0.78)	952 (0.87)	68 (0.59)	64 (0.59)	97 (0.47)	<0.001
Diabetes	318 (0.21)	128 (0.12)	43 (0.37)	44 (0.40)	103 (0.50)	<0.001
Coronary artery disease	32 (0.02)	4 (0.00)	6 (0.05)	2 (0.02)	20 (0.1)	<0.001

Table 1 (continued)

	Overall	Never statin	Statins < 3 years	Statins 3–5 years	Statins > 5 years	*p* value
Cerebral vascular accident	29 (0.02)	13 (0.01)	2 (0.02)	1 (0.01)	13 (0.06)	0.002
Chronic obstructive pulm disease	6 (0)	5 (0.00)	0 (0.00)	0 (0)	1 (0)	0.005
Charlson comorbidity index (1)	302 (0.20)	130 (0.12)	43 (0.37)	43 (0.39)	86 (0.42)	<0.001
Charlson comorbidity index (2)	40 (0.03)	10 (0.01)	4 (0.03)	2 (0.02)	24 (0.12)	
Follow-up (months)						
Mean	66.78	64.46	64.32	67.47	80.04	<0.001
Range	33.36-100.2	33.08-95.84	23.27-105.37	34.53-100.41	43.6-116.48	
Local recurrence	107 (0.07)	72 (0.07)	7 (0.06)	8 (0.07)	20 (0.10)	0.438
Metastasis	145 (0.10)	98 (0.09)	18 (0.16)	16 (0.15)	13 (0.06)	0.012
Disease status						
No evidence of disease	1304 (0.86)	944 (0.86)	88 (0.77)	89 (0.82)	183 (0.88)	<0.001
Alive with disease	81 (0.05)	62 (0.06)	9 (0.08)	6 (0.06)	4 (0.02)	
Died of disease	84 (0.06)	61 (0.06)	9 (0.08)	8 (0.07)	6 (0.03)	
Died of other causes	35 (0.02)	15 (0.01)	6 (0.05)	3 (0.03)	11 (0.05)	
Died of unknown causes	19 (0.01)	10 (0.01)	3 (0.03)	3 (0.03)	3 (0.01)	

Patients were stratified by length of statin use into 4 groups: never a statin user, short-term (< 3 years), intermediate (3–5 years), and long-term user (> 5 years). Chi square and one-way ANOVA analyses were performed to detect differences between length of statin use

SD standard deviation; *NA* not applicable

Given the strong impact of age on both BMI and statin use and the correlation between high BMI and statin use, we evaluated the interaction of these three terms on the OS and DFS in our cohort. On univariable analysis, the only interaction term that showed marginal association with OS outcome was age–statin use; however, this was not significant on multivariable analysis.

Discussion

Our study evaluated the impact of the duration of statin use on the clinical outcomes of 1523 women with operable breast cancer. We found that patients who have a history of receiving statins for more than 5 years have significantly improved DFS and OS as compared to non-statin users in a multivariable Cox-Proportional Hazard model accounting for clinical covariates including age, race, comorbidities, and pathologic features. Our results suggested that the benefits of statins may be proportional to length of exposure.

In the design of this study, we pursued a clinical data abstraction strategy to incorporate data, which were typically difficult to obtain in large population study, to include demographic covariates as well as pathologic and surgical covariates including tumor subtype, tumor grade, pathologic staging, type of definitive surgery, and other clinical variables such as BMI and diagnosis of other comorbidities. Breast cancer receptor status was available in over 75% of our patients. One of the strengths of our study was that our study population was ethnically diverse. As the majority of our patients had surgery and subsequent treatment at a single institution, heterogeneity in treatment patterns was less likely to confound the clinical outcomes of our study cohort.

Our study had several limitations, which included a limited sample size, being retrospective in nature, missingness in data, potential sampling bias, and limited ability to assess medication compliance. Our study did not attempt to take into account the potential differences in lipophilic versus hydrophilic statin classes partly because of the heterogeneity of statin use in our cohort and that some patients may have switched to different statins over time. Along the same lines, we were unable to take into account of dosing effects. Finally, given the limited sample size, we cannot exclude entirely the possibility of confounding and/or the impact of interaction between related factors such as BMI, age, and statin use, although in our analysis we did not identify a significant interaction term between these factors that impacted OS or DFS.

Studies have been and are being performed to evaluate the benefit of statins in early stage breast cancer patients both in the adjuvant and neoadjuvant setting. For example, a phase II window of opportunity clinical trial investigated the effect of oral fluvastatin at both low and high doses for 3–6 weeks prior to definitive surgery on tumor proliferation and apoptosis in DCIS or stage I breast cancer patients [29]. This study found decreased proliferation markers and increased apoptotic markers in patients who received pre-operative fluvastatin. Despite promising results from these clinical studies, data from large-scale prospective, randomized trials are needed to confirm the clinical efficacy of statins for

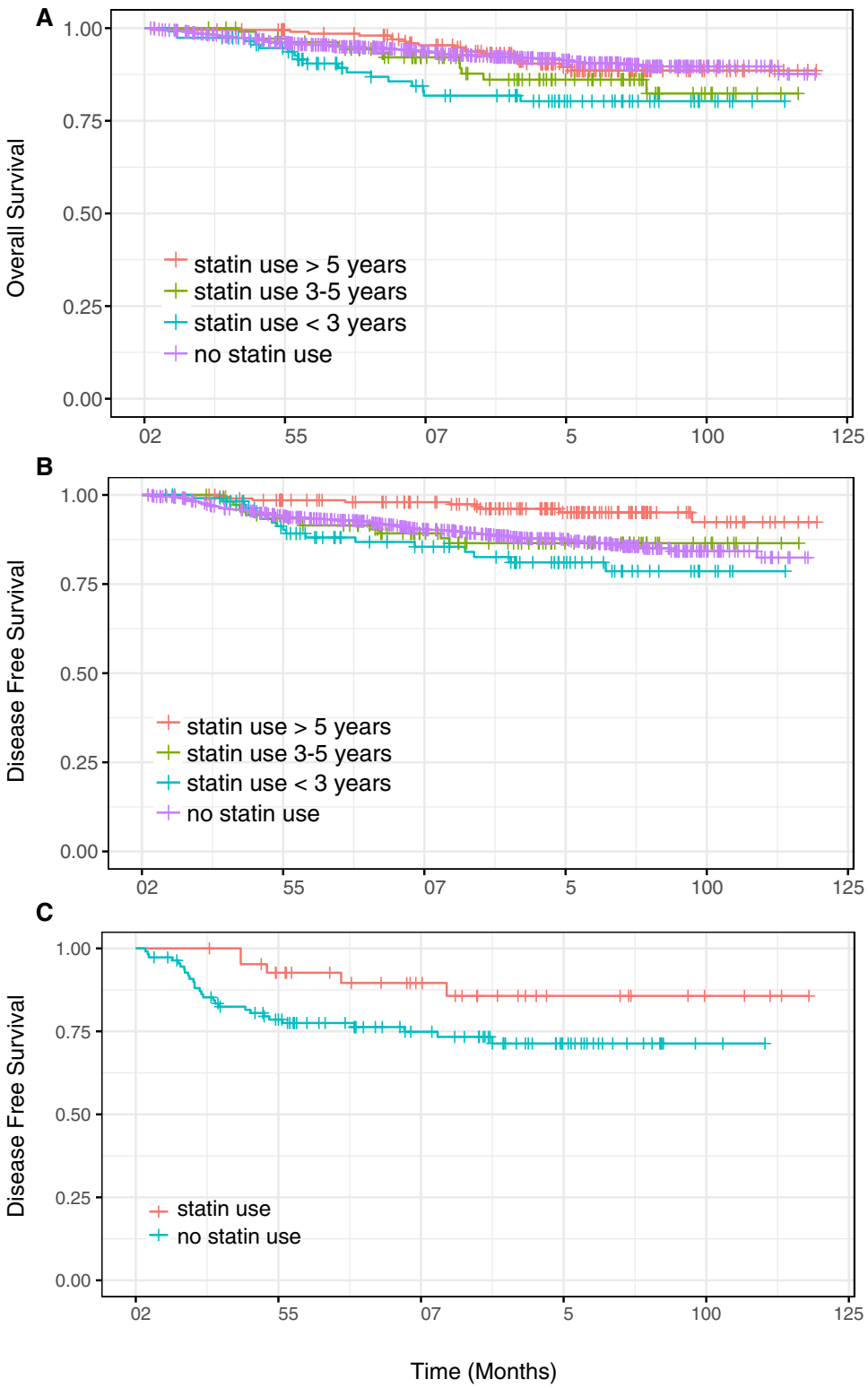

Fig. 1 **a** Impact of duration of statin use on overall survival. Kaplan–Meier analysis examining the impact of duration of statin exposure on overall survival. Comparisons were made between patients with different length of statin exposure; see text for details. **b** Impact of duration of statin use on disease-free survival. Kaplan–Meier analysis examining the impact of duration of statin exposure on disease-free survival. Comparisons were made between patients with different length of statin exposure; see text for details. **c** Subanalysis of patients with triple-negative breast cancer. Patients with any statin use were combined into a single group and compared to statin-never users. Plot shows disease-free survival by Kaplan–Meier analysis

the primary treatment of breast cancer. An ongoing phase III clinical trial (NCT02201381) is currently investigating the outcomes of patients receiving metabolic combination regiments, consisting of atorvastatin, metformin, doxycycline, and mebendazole in cancer patients. This study is expected to be completed in 2023.

Table 2 Multivariable overall and disease-free survival analysis

	Overall survival				Disease-free survival			
	Hazard ratio	95% C.I.	p	Total events	Hazard ratio	95% C.I.	*p*	Total events
Age at diagnosis (years)	[a]							
Continuous				94	0.98	0.96–1.00	0.016	99
Race					[b]			
White (reference)				39				
Other	0.98	0.41–2.34	0.957	6				
Black	1.84	1.16–2.90	0.009	49				
Statin Use								
Never (reference)				60				80
Statins < 3 years	1.50	0.79–2.86	0.219	13	0.84	0.35–2.04	0.707	6
Statins 3–5 years	1.07	0.52–2.15	0.858	10	1.04	0.48–2.26	0.912	9
Statins > 5 years	0.38	0.17–0.85	0.018	11	0.15	0.05–0.48	0.001	4
Tumor size [T stage (cm)] (ordered categorical)								
T1 (≤ 2) (reference)				40				34
T2 (2–5)				42				53
T3 (> 5)	1.70	1.19–2.42	0.003	12	1.92	1.35–2.74	<0.001	12
Tumor grade	[a]							
1 (reference)								7
2								51
3					1.50	1.06–2.13	0.022	60
Nodal Stage (ordered categorical)								
0 (reference)				29				29
1 (1–3)				44				44
2 (4–9)				18				18
3 (> 9)	1.52	1.15–2.01	0.004	8	1.50	1.06–2.13	0.002	8
Extracapsular extension								
Absent (reference)				67				69
Present	1.80	0.99–3.28	0.056	27	1.65	0.95–2.87	0.075	30
Tumor subtype								
ER+ or PR+ and Her2− (reference)								37
ER−/PR− and Her2+	1.72	0.81–3.67	0.161	36	1.37	0.58–3.25	0.471	7
ER−, PR− and Her2−	2.61	1.54–4.45	<0.001	25	1.86	1.04–3.32	0.036	25
ER+, PR+ and Her2+	1.38	0.81–2.36	0.228	24	1.35	0.81–2.23	0.251	30
Charlson comorbidity index								
0 (reference)				58				76
1	1.93	1.15–3.24	0.012	29	2.10	1.18–3.75	0.012	20
2	3.71	1.39–9.94	0.009	7	7.00	1.80–27.2	0.005	1

Forward–backward stepwise regression was used to determine independent covariates contributing to the overall and disease-free survival models

HR hormone receptor

[a]Age and tumor grade were not included in the final analysis model for OS

[b]Race was not included in the final model for DFS based on forward–backward stepwise analysis

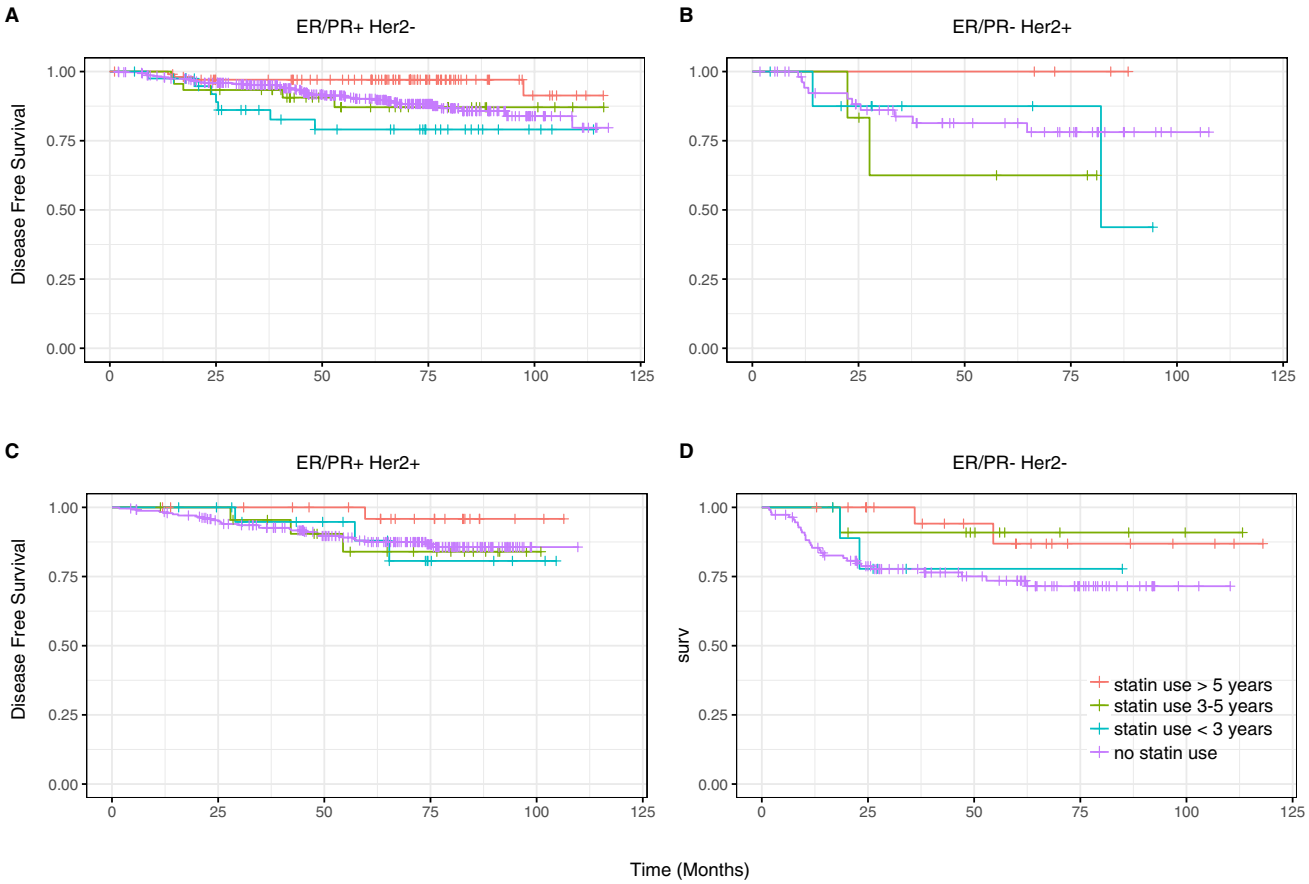

Fig. 2 Subanalysis of disease-free survival in patients stratified by receptor status. Patients were divided into four groups including triple-positive (ER/PR+ and Her2+), ER/PR+ and Her2−, ER/PR− and Her2+ and triple-negative (ER/PR−, Her2−) groups. Kaplan–Meier analysis examining the impact of duration of statin exposure on disease-free survival was then

In summary, our results supported the findings previously reported by other longitudinal registry and retrospective cohort analyses, highlighting a potential clinical benefit of statin use. In addition, consistent with findings recently reported by the Breast International Group 1-98 investigators, we observed a benefit of statin use particularly in hormone receptor-positive women. One future direction is to evaluate if the beneficial effects of statins on breast cancer outcomes are proportional to the magnitude of serum LDL reduction. Although there is currently insufficient evidence to justify prescribing statins to breast cancer patients who otherwise have no cardiovascular risk factors, results from phase III clinical trials will provide guidance in the use of statins in the preventative/adjuvant setting for breast cancer patients.

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Author contributions LS, EC, JN, AW, AS, and VR performed data collection. YRL and AW performed data analysis. YRL, VR, and JT wrote the manuscript. All authors have approved the final article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patient healthcare record data used for this setting was retrospective in nature and approved by the University of Pennsylvania Institutional Review Board for Human Subjects Research. All patient health records were maintained in strict confidentiality in compliance with HIPPA requirements, and research conducted was considered to be minimal risk.

Informed consent No prospective ascertainment of informed consent was required.

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