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Lipid-lowering drugs, dyslipidemia, and breast cancer risk in a Medicare population

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Abstract

Purpose: We sought to disentangle the effects of statins and other lipid-lowering drugs and the underlying dyslipidemia for which they are prescribed on breast cancer risk.

Methods: We conducted a case-control study within the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data. Cases were women with invasive breast cancer aged 66+ years (N=30,004) identified by SEER registries (years 2007–2011). Controls were women (N=198,969) identified from a 5% random sample of Medicare recipients alive and breast cancer free in year of selection. Participants had a minimum of 13 months of Part A, Part B non-health maintenance organization Medicare and Part D Medicare coverage at least 13 months preceding cancer diagnosis/selection. Exposures were assessed until 12 months before diagnosis/control selection. Odds ratios (OR) and 99.9% confidence intervals (CI) were estimated using adjusted unconditional and multinomial logistic regression.

Results: ORs of invasive breast cancer associated with dyslipidemia, statins, and non-statin lipid-lowering drugs were 0.86 (99.9% CI 0.81–0.90), 1.07 (99.9% CI 1.03–1.13) and 1.03 (99.9% CI 0.95–1.11), respectively. Risk reductions with dyslipidemia were slightly greater when untreated than treated and did not vary much by time between dyslipidemia and breast cancer diagnosis. Whether treated or untreated, dyslipidemia was associated with greater reductions in risk for later stage than earlier stage breast cancer (p-heterogeneity <.0001).

Conclusions: Lipid lowering drugs did not account for the lower breast cancer risk associated with dyslipidemia. Our data do not support using statins or other lipid-lowering drugs to prevent breast cancer.

Keywords

breast cancer; dyslipidemia; statins; lipid-lowering drugs

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Ethical Standards

Study complies with the current laws of the United States, the country within which it was performed.

Data availability

Conflict of interest

The authors declare that they have no conflict of interest.

Introduction

Although some laboratory evidence and early observational studies suggest that statin use may reduce breast cancer risk, at least two meta-analyses of observational studies and clinical trials have reported no such association [1–2]. More recent studies have been inconsistent, reporting no association [3], decreased risk [4–5], and increased risk with long-term use [6]. It is possible that observed associations are related to the underlying dyslipidemia for which statins are prescribed. Our previous report of SEER-Medicare data for years 1992–2011 found that dyslipidemia was associated with a reduced risk of breast cancer other than localized disease [7]. Because prescription drug data were not available for the entire study period, we did not assess whether this association reflected treatment with statins or other lipid-lowering drugs. Recent suggestions that statins may be attractive chemoprevention agents based on preclinical data and some observational studies [8–9] compel a careful examination of the role of statins and other lipid lowering drugs versus dyslipidemia on breast cancer risk.

Dyslipidemia is characterized by increased levels of triglycerides and small, dense LDL-cholesterol, and decreased HDL-cholesterol levels [10]. Higher levels of triglycerides [11] and HDL-cholesterol [11–12], but not LDL-cholesterol [11–12], have been associated with reduced breast cancer risk in meta-analyses. The potential influence of cancer, including preclinical disease, on levels of these substances (known as reverse causation) has been described [12]. Statins and other lipid lowering drugs are also known to influence levels of these substances; they reduce LDL-cholesterol [13–14] and triglycerides [15], may increase HDL-C [13–14], but also have other effects that may increase or decrease breast cancer risk [15–16].

Few studies have attempted to untangle the effects of dyslipidemia and lipid-lowering drugs on breast cancer risk [4,17–19]; case numbers included in these analyses ranged from 224 [18] to 5,228 [19]. In this analysis of 30,004 invasive breast cancer cases, we use a subset of our previous study population for which prescription drug data are available to examine whether lower breast cancer risk associated with dyslipidemia [7] reflects treatment with statins or other lipid-lowering drugs or reverse causation. Further, following upon our earlier results [7], we assess associations according to stage of disease at breast cancer diagnosis.

Materials and Methods

We developed a case-control study within the SEER-Medicare linked database, with cases identified by SEER registries and information on medical exposures and medications obtained from SEER-Medicare linked claims and pharmacy data.

The dataset was limited to females, aged 66 years of age or older (persons of age 65 were excluded to ensure that subjects had sufficient time to accrue exposure information) with a minimum of 13 months of Medicare coverage (Part A, Part B, not including health maintenance organization participation) preceding cancer diagnosis, as assessed using Medicare claims data. Participants were also limited to those with Part D Medicare coverage during the period more than 13 months prior to diagnosis/selection. Part D coverage is

available only for the years 2007 on. First breast cancers were diagnosed between January 1, 2007, and December 31, 2011, from 18 SEER registries. Table 1 shows how we arrived at 30,004 cases available for analysis.

We initially analyzed associations for inflammatory breast cancer (IBC), non-IBC locally advanced breast cancer, and by stage (localized, regional, distant, unstaged) for other breast cancers, as we had done in our previous analysis [7]. We then grouped cases with similar findings into two groups: 1) earlier stage disease (N = 26,601) consisting of localized (N = 20,114) and regional other breast cancer (N = 6,487), and; 2) later stage disease (N = 3,403) consisting of locally advanced breast cancer (N = 1,422) and distant (N = 1,260) and unstaged other breast cancer (N = 721). Locally advanced breast cancers consisted of 334 IBC cases all diagnosed at distant stage and 1,088 other non-IBC locally advanced breast cancers, 65.6% of which were diagnosed at regional stage and 34.3% at distant stage. Seventy-nine percent of total breast cancers were estrogen-receptor (ER)-positive (+), 14.2% ER-negative (–), and the rest with unknown or borderline ER-status.

A total of 198,969 female controls were selected from a file created from two subsets of a 5% random sample of Medicare recipients: the SUMDENOM file, which is made of 5% random sample of Medicare recipients who never developed cancer and the PEDSF5% file, which is a 5% random sample of all people with cancer. Recipients who were alive and breast cancer free as of July 1 in the calendar year of selection and had Part D coverage more than 13 months prior to selection were chosen in strata by calendar year and age (in 5-year categories) and were frequency-matched to the distribution among breast cancer cases overall. Note that both cases and controls may have had a prior cancer other than breast cancer.

To qualify as a user of one of the drugs, there must have been at least two prescriptions for the drug on different dates, both of which occurred more than 13 months before the diagnosis/selection date for the cases/controls. We also counted the number of prescriptions filled on different dates up until 13 months prior to diagnosis/selection, including the first two dates that defined subjects as a user.

We defined medical conditions as shown in Table 2. We included these conditions if the first claim qualifying them for inclusion in the study was at least 13 months prior to cancer diagnosis or selection date and there was at least one inpatient or two outpatient/physician claims with relevant ICD-9-CM diagnosis codes in any position on the claim with a minimum of 30 days between claims. Because body mass index (BMI) is generally not recorded in Medicare claims, we used ICD-9-CM codes 278 (overweight, obesity, and other hyperalimentation), 783.1 (abnormal weight gain), and V77.8 (screening for obesity) to create a surrogate “obesity” variable that we used for adjustment in supplemental analyses. Categories of drugs used to treat dyslipidemia are shown in Table 3. Combination drugs including a statin and non-statin were included as statins in the analyses.

We calculated the number of months of Medicare coverage (Part A, Part B, not including health maintenance organization coverage) between entry date and date of diagnosis for cases (median and range were 80.1, 15–95) and between entry date and July 1 in the year of

selection for controls (median and range were 78.0, 15–90). We restricted the entry date to the time period where we had available Medicare records for both cases and controls. We similarly determined the months of Part D coverage separately for cases (median and range were 21.0, 1–46) and controls (median and range were 17.0, 1–41). We also accounted for number of physician visits between study entry and date of diagnosis/selection, yielding medians of 68 and 57 for cases and controls, respectively. We based the number of physician visits on carrier claims with the following HCPCS codes: 99201–99255, 99261–99263, 99271–99275, 99301–99340, 99341–99353, 99354–99357, 99381–99429. Records with a HCFASPEC value of radiology (30, 31), anesthesiology (5, 43) or pathology (21, 22) were excluded. In addition, only one record per day was counted.

We calculated odds ratios (OR) and 99.9% confidence intervals (CI) (to account for multiple comparisons) using unconditional logistic regression analyses. We performed statistical analyses using SAS version 9.3 (SAS Institute). Unless otherwise noted, all analyses were adjusted for the matching factors of age (categorized into 5-year age groups) and year of diagnosis/selection in single years, and additionally for race/ethnicity (white, black, mixed, Asian, Hispanic, North American Indian, other, unknown), grouped SEER region based on the location of the SEER registry, categorized as western (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, greater California), northeastern (Connecticut, New Jersey), north-central (Detroit, Iowa), and southern (Atlanta, rural Georgia, Kentucky, Louisiana, greater Georgia), duration between study entry and date of diagnosis/selection in months, number of physician visits between entry date and date of diagnosis/selection, total number of months of Part D enrollment excluding the 13 months before diagnosis/selection, history of mammography (any mammography claim recorded from 12 months to a maximum of 48 months before case-control selection) and diabetes. Additional adjustment for the surrogate “obesity” variable did not change estimates.

To assess the possible effect of pre-clinical breast cancer on a dyslipidemia diagnosis, we calculated the median time between the first dyslipidemia claim and breast cancer diagnosis/control selection (62.2 months) and did analyses according to whether the first claim was within or before this median time. We used multinomial logistic regression with nominal outcomes for analyses by stage of disease and ER-status compared to controls and used the Wald test for assessing whether the effects of a risk factor for different disease types were statistically significantly different.

For selected sensitivity analyses, we considered those who had been prescribed a statin or non-statin lipid-lowering drug but without a claim for dyslipidemia as having dyslipidemia to account for the possibility that these individuals may have had a claim indicating dyslipidemia before the study period.

Results

The mean age at diagnosis for cases was 76.7 years and at selection of controls was 76.8 years. Seventy-six percent of the controls were diagnosed with dyslipidemia at least 13 months prior to selection and 43 percent had at least two prescriptions for a statin, more often a lipophilic statin (Table 3). Other characteristics of lipid-lowering drug use are

presented in Table 3. Dyslipidemia and prescriptions for statins were associated with more frequent health-care (doctor's visits and mammograms), diabetes, and the surrogate variable for "obesity" among controls (Table 4).

Unadjusted ORs for invasive breast cancer associated with dyslipidemia, statins, and non-statin lipid lowering drugs were 0.95 (99.9% CI 0.91–1.0), 1.04 (99.9% CI 1.00–1.09), and 1.06 (99.9% CI 0.98–1.14), respectively. Adjustment for variables noted in the methods section as well as mutual adjustment for dyslipidemia, statins, and non-statins yielded corresponding ORs of 0.86 (99.9% CI 0.81–0.90), 1.07 (99.9% CI 1.03–1.13) and 1.03 (99.9% CI 0.95–1.11). Results did not differ substantially for lipophilic or hydrophilic statins, number of statin prescriptions (categorized as ≤ 5 , 6–10, 11–18, 18+), or type of non-statin lipid-lowering drug.

Associations with dyslipidemia varied by stage of disease, with reductions in risk greater for later stage (OR = 0.70; 99.9% CI 0.60–0.81) than earlier stage disease (OR = 0.88; 99.9% CI 0.83–0.93) (p-heterogeneity < .0001). There was no such variation for statins (p-heterogeneity .23) or other non-statin lipid-lowering drugs (p-heterogeneity .22). There was also no variation for either dyslipidemia or drug use by tumor ER-status (p-heterogeneity > .29 for all variables).

In comparison to a reference group of those who neither had dyslipidemia nor took statins or other lipid-lowering drugs, the ORs of invasive breast cancer associated with untreated dyslipidemia were 0.91 (99.9% CI 0.85–0.97) and 0.83 (99.9% CI 0.77–0.90), depending on time of dyslipidemia diagnosis (Table 5). ORs were closer to the null for treated dyslipidemia. Statins use without a diagnosis of dyslipidemia was associated with a statistically significant increased risk (OR = 1.30; 99.9% CI 1.15–1.47).

Reductions in risk with dyslipidemia, whether treated or untreated, were greater for later stage than earlier stage breast cancer (p-heterogeneity < .0001) (Table 5). For example, the OR for later stage disease associated with untreated dyslipidemia with a first claim more than 62.2 months before breast cancer diagnosis/control selection was 0.64 (99.9% CI 0.52–0.78), while the corresponding OR for earlier stage disease was 0.87 (99.9% CI 0.80–0.94). It is notable that for later stage breast cancer, where pre-clinical disease might more likely affect lipid and triglyceride levels, results were similar for dyslipidemia first recorded within or before 62.1 months of diagnosis/selection.

When we classified those prescribed statins without a claim for dyslipidemia as having dyslipidemia (without regard to timing of dyslipidemia claim), the ORs associated with statin treatment in those with dyslipidemia compared to those who neither had dyslipidemia nor took statins or other lipid-lowering drugs were 1.00 (99.9% CI 0.94–1.06) for earlier stage disease and 0.72 (99.9% CI 0.62–0.84) for later stage disease.

Discussion

In this population of female Medicare beneficiaries, dyslipidemia was associated with lower breast cancer risk, but statins and other lipid-lowering drugs were not. In fact, statin use without a diagnosis of dyslipidemia was associated with increased risk. Reductions in risk

for untreated dyslipidemia were slightly greater than for treated dyslipidemia, suggesting that reductions in risk were not due to lipid-lowering drugs. Reductions in risk with dyslipidemia, whether treated or untreated, were greater for later stage disease and were not attributable to reverse causation.

In our previous analysis within the Medicare population which included cases diagnosed between 1992–2011, we found no association between all invasive breast cancer and dyslipidemia, largely because there was no association with localized disease [7]. We did, however, find reductions in risk with regional and more advanced disease. It is possible that the more restricted case series in the current analysis and a different series of controls contributed to these differences.

Our results are generally consistent with meta-analyses of breast cancer showing an inverse association with triglyceride levels [11], no association with statins [1–2], and no association with fibrates [15], a non-statin lipid lowering drug. The finding by Desai et al. that lipophilic statins are associated with a reduced risk of late stage breast cancer [5] may reflect the effect of dyslipidemia rather than the effect of statins themselves.

Results from the largest study that attempted to untangle the effects of dyslipidemia and statins were consistent with ours [19]; inverse associations with measured total serum cholesterol were evident in analyses conducted both before statins were used as well as for the entire observation period, including the time-frame when statins were used. In contrast, three smaller studies, with number of cases ranging from 224 [18] to 3,177 [17], found no association [4,17] or increased risk [18] with elevated cholesterol levels and breast cancer risk in those not using lipid-lowering drugs. A statistically significant reduction in risk was found for those using lipid-lowering drugs in one [4] and no increased risk with statins in the others [17–18]. Two relied on self-reported cholesterol levels and lipid-lowering drug use [4,17], with the percentage of unreported cholesterol levels fairly high in one [4]. The smallest study used the General Practice Research Database in England [18].

It is not clear how dyslipidemia might influence breast cancer risk. Biological mechanisms underlying an inverse association between triglycerides and breast cancer risk have not been well investigated [11]. The anti-oxidative and anti-inflammatory properties of HDL-C have been offered as an explanation [11], but low, not high, HDL-C may be associated with dyslipidemia and an indication for lipid therapy [20]. We may have found no overall-association with statins, which are thought to primarily lower LDL-C [13], because LDL-C levels have not been associated with breast cancer risk [11–12]. It is possible that the increased risk with statins we observed in those without dyslipidemia reflects their carcinogenic effects through disruption of immune system function or the enhancement of the genotoxicity of other substances [16] or it could be a chance finding.

Strengths of this study include the very large number of cases, information on tumor type and stage at diagnosis, the population-based nature of the study dataset, and claim-based data on both drug use and indication for use, as well as frequency of medical visits and mammographic screening to address the intensity of medical surveillance. The study design ensured that there was no bias in recall of dyslipidemia diagnosis or drug use. We were also

able to assess when dyslipidemia was recorded in relationship to cancer diagnosis/control selection (within and before approximately 5 years), enabling us to largely rule out the possibility of reverse-causation bias in our results.

Our study also has several limitations. We had a relatively short period of ascertainment of dyslipidemia and prescriptions for lipid-lowering drugs, on average approximately 6 years for dyslipidemia and somewhat less than 2 years for prescription coverage. This limited ascertainment window may have led to misclassification of our exposure variables. Those in our analysis without a claim indicating dyslipidemia but with a prescription for lipid-lowering drugs may include those with dyslipidemia diagnosed before the study period or those with minimally elevated LDL-levels but high cardiovascular risk due to other risk factors [21]. In sensitivity analyses, we found no increased risk with statins when this group was combined with those who had a claim for dyslipidemia. Those with a claim indicating dyslipidemia without a prescription for lipid-lowering drugs may include those undergoing therapeutic lifestyle changes [21], former users of lipid-lowering drugs, or current users with a coverage period that was too short to capture such use. Notably, the percentage of statin users among the controls in our study (43 percent) is slightly higher than the 36–39 percent reported in women 65 years of age and older in 2005–2008 by the National Center for Health Statistics [22], suggesting that we most likely did not seriously underestimate statin use. The limited prescription coverage also hampered our ability to assess risk with long-term statin use, although this did not impact our evaluation of risk associated with untreated dyslipidemia.

Missing information on some breast cancer risk factors is another limitation. Other studies have reported that statin users were older [3,5], had a higher mean BMI [3,5], had a higher prevalence of diabetes [3], were more likely to undergo mammographic screening [3, 17], and had a higher prevalence of menopausal hormone use [17]. Slight differences between statin and non-statin users were also reported for other variables, but were not emphasized [5]. In one analysis, only adjusting for menopausal hormone use changed risk estimates for statins by more than 10 percent [6]. We adjusted for age, diabetes, and mammographic screening, and as best we could for obesity requiring medical attention, but not for menopausal hormone use. Estimated prevalence of oral estrogen-progestin use is very low in the age group included in this analysis [23], minimizing concerns about not having this information. Had we been able to adjust more fully for BMI, our associations with dyslipidemia would most likely have been further from the null [24].

We also had no information on actual intake of prescribed medications. To address this, we defined medication users as those who had at least two prescriptions on different days, under the assumption that the second prescription would not have been received unless the medications from the first had been used. As in other studies [4,17], we had no information on measured cholesterol levels in those untreated and treated with statins and other lipid lowering drugs. According to a report from the National Health and Nutrition Examination Survey [25], only about 38% of those over 65 years of age treated for hyperlipidemia met treatment goal levels for all three of LDL, HDL-cholesterol and triglycerides. Thus, a subset of those who were prescribed statins or other lipid-lowering drugs in our study may have had residual dyslipidemia due to either non-compliance or ineffectiveness of the drugs. Our

study also included an older population and results may not be generalizable to younger women.

In conclusion, these data do not support a role for statins or other lipid-lowering drugs in preventing breast cancer in elderly women. Rather the evidence suggests that dyslipidemia, for which lipid-lowering drugs are prescribed, is associated with lower risk, particularly of later stage breast cancers. Our findings need to be confirmed in a dataset with more coverage of medication use, confounding factors and prevalent disease. If confirmed, it would be of great interest to pursue the reasons for reduced breast cancer risk, particularly of more advanced tumors, in elderly women with dyslipidemia.

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The data that support the findings of this study are available from the National Cancer Institute, but restrictions apply to the availability of these data, which are under license for the study, and so are not publicly available.

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Table 1.

Reasons for breast cancer exclusion

All Release #5 Female Malignant Breast Cancer Cases of all ages in SEER	N = 646,026
Reason for retention	# remaining
Age >= 66 years	359,408
Diagnosis between Jan. 1, 2007 and Dec. 31, 2011	100,569
Diagnosis assessed before death (source not death certificate/autopsy)	99,654
Known month of diagnosis	99,197
Has 1+ Medicare claims	80,254
Has 13 months of Medicare Part A/Part B non-HMO	70,531
Date of diagnosis before date of death (dates are reasonable)	70,527
13 months of Part D enrollment	31,434
Part D enrollment before 13 months before diagnosis	30,004

Table 2.

Codes used to define breast cancer groups and medical conditions

Outcomes	Codes
Invasive breast cancer	ICD-O-3 site codes C50.0-C50.9 where behavior = 3
Inflammatory breast cancer (IBC)	ICD-O-3 site codes C50.0-C50.9 where behavior = 3 (malignant) and Site and Morphology Histologic Type ICD-0-3 = 8530 or Extent of Disease-Historic EOD 10 – extent (1998–2003) = 70 or Extent of Disease – CS.CS extension (2004+) = 71,73, 600, 710, 715, 720, 725, 730, 750, 780 or AJCC TNM = T4d
Locally Advanced Non-Inflammatory Breast Cancer (LABC)	ICD-O-3 site codes C50.0-C50.9 where behavior = 3 (malignant) and Site and Morphology Histologic Type ICD-0-3 = 8530 and (Extent of Disease-Historic EOD 10 – extent (1998–2003) = 40, 50, 60 or Extent of Disease – CS.CS extension (2004+) = 400, 410, 510, 512, 514, 516, 518–520, 575, 580, 585, 605, 610, 612–613, 615, 620, 680 or Stage – AJCC.Derived AJCC Stage Group, 7 th ed (2010+) = IVA, IVA1, IVA2, IVB, IVC or Stage – AJCC.AJCC stage 3 rd edition (1988–2003) = 40, 41, 42
Other invasive breast cancers	ICD-O-3 site codes C50.0-C50.9 where behavior = 3 (malignant) and not included in IBC and LABC groups
Exposures	
Dyslipidemia	ICD-9 = 272
Adjustment variable	
Diabetes	ICD-9-CM diagnosis codes 250; 357.2x for polyneuropathy in diabetes; 362.0x for diabetic retinopathy; 366.41 for diabetic cataract; 249.xx for secondary diabetes.
Surrogate for “obesity”	ICD-9 278, 783.1, V77.8

Table 3.

Medication use until 13 months prior to date of selection (SEER-Medicare 2007–2011 with Part D) among 198,969 controls

	N (%)
Prescribed any statin	86,077 (43.3)
Prescribed lipophilic statins	75,096 (37.7)
Simvastatin	40,028 (20.1)
Atorvastatin	32,228 (16.2)
Lovastatin	9,907 (5.0)
Fluvastatin	1,079 (0.5)
Pitavastatin	0 (0.0)
Prescribed hydrophilic statins	15,676 (7.9)
Rosuvastatin	8,060 (4.1)
Pravastatin	7,954 (4.0)
Prescribed both lipophilic and hydrophilic statins	4,961 (2.5)
Prescribed any non-statin lipid lowering drug	15,821 (8.0)
Ezetimibe	7,801 (3.9)
Fibrate	6,764 (3.4)
Niacin	1,471 (0.7)
Bile acid sequestrant	1,264 (0.6)
Prescribed both a statin and non-statin lipid lowering drug	10,257 (5.2)

Table 4.

Characteristics of Controls According to Dyslipidemia and Statin Exposure

Characteristic	Dyslipidemia (N = 150,952) No. (%)	No dyslipidemia (N = 48,017) No. (%)
Median age (years)	76	74
Median # doctor visits	65	34
Caucasian race	115,985 (76.8)	38,222 (79.6)
Mammogram	83,984 (55.6)	17,221 (35.9)
Diabetes	58,193 (38.6)	6,041 (12.6)
“Obesity” surrogate	16,179 (10.7)	2,342 (4.9)
	Statin users (N = 86077) No. (%)	Non-statin users (N = 112,892) No. (%)
Median age (years)	76	76
Median # doctor visits	64	52
Caucasian race	64,849 (75.3)	89,358 (79.2)
Mammogram	48,195 (56.0)	53,010 (50.0)
Diabetes	37,580 (43.7)	26,654 (23.6)
“Obesity” surrogate	10,163 (11.8)	8,358 (7.4)

Table 5.

ORs associated with dyslipidemia in those without and with lipid-lowering drugs (statins and non-statins) for breast cancer overall and by tumor characteristics

All invasive breast cancer (N = 30,004)			
	No dyslipidemia claim between study entry and 12 months before cancer dx/control selection OR ^a (99.9% CI) (cases, controls)	First dyslipidemia claim from 13 to 62.1 months before breast cancer dx/control selection OR ^a (99.9% CI) (cases, controls)	First dyslipidemia claim more than 62.2 months before breast cancer dx/control selection OR ^a (99.9% CI) (cases, controls)
No statin or non-statin lipid lowering drugs	1.0 (7,315, 48,017)	0.91 (0.85–0.97) (5,127, 35,500)	0.83 (0.77–0.90) (3,389, 23,811)
Statin prescriptions	1.30 (1.15–1.47) (1,018, 5,359)	0.96 (0.90–1.03) (5,313, 35,037)	0.89 (0.83–0.95) (6,943, 45,681)
Only non-statin lipid-lowering drugs	1.24 (0.82–1.87) (80, 429)	0.94 (0.77–1.15) (331, 2,202)	0.94 (0.80–1.12) (488, 2,933)
Earlier stage disease-(Localized and regional non-locally advanced breast cancer) (N = 26,601)			
No statin or non-statin lipid lowering drugs	1.0 (6,202, 48,017)	0.94 (0.88–1.01) (4,631, 35,500)	0.87 (0.80–0.94) (3,005, 23,811)
Statin prescriptions	1.38 (1.21–1.56) (918, 5,359)	0.99 (0.92–1.06) (4,784, 35,037)	0.94 (0.87–1.00) (6,238, 45,681)
Only non-statin lipid-lowering drugs	1.32 (0.87–2.02) (73, 429)	0.99 (0.80–1.22) (307, 2,202)	0.99 (0.83–1.19) (443, 2,933)
Later stage disease-(Locally advanced breast cancer and distant and unstaged non-locally advanced breast cancer) (N = 3,403)			
No statin or non-statin lipid lowering drugs	1.0 (1,113, 48,017)	0.69 (0.57–0.83) (496, 35,500)	0.64 (0.52–0.78) (384, 23,811)
Statin prescriptions	0.87 (0.61–1.24) (100, 5,359)	0.80 (0.66–0.96) (529, 35,037)	0.64 (0.54–0.77) (705, 45,681)
Only non-statin lipid-lowering drugs	0.76 (0.21–2.73) (7, 429)	0.63 (0.31–1.25) (24, 2,202)	0.69 (0.41–1.15) (45, 2,933)

^a Adjusted for age (in 5-year categories), year of diagnosis/selection, race/ethnicity (white, black, mixed, Asian, Hispanic, North American Indian, other, unknown), SEER region (western, northeastern, north-central, southern), duration of study participation, number of physician visits, total number of months of Part D enrollment excluding the 13 months before diagnosis/selection, mammography, diabetes.