Short Communication

The Influence of Statin Use on Breast Density

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Abstract

Objective: **To evaluate if 3-hydroxy-3-methylglutaryl CoA reductase reductase inhibitor use (statins) alters mammography measured breast density.**
Methods: **Cohort study of women ages 50 to 80 years with two mammography screenings. Changes in BI-RADS breast density between screenings was compared for nonusers, initiators, discontinuers, continuers, and any users of statins.**
Results: **Statin use was not associated with increases or decreases in breast density compared with nonusers after adjusting for age, body mass index, change in body mass index, hormone therapy use, and time between screenings. Cumulative days of statin use during the year before screening was not associated with changes in breast density in any of the groups of statin users. When hormone therapy users were excluded, any statin use was associated with an increase in breast density compared with nonusers (odds ratio, 1.2; 95% confidence interval, 1.0-1.5).**
Conclusions: **We found no association between statin use and change in breast density in general, but statin use may be associated with increases in breast density among nonusers of hormone therapy.** (Cancer Epidemiol Biomarkers Prev 2006;15(5):1026–9)

Introduction

3-Hydroxy-3-methylglutaryl CoA reductase inhibitors (statins) are a class of drugs that lower plasma cholesterol levels by inhibiting a rate-limiting enzyme in cholesterol synthesis (1). Early studies raised concern that statins may increase cancer risk, but a growing body of evidence suggests that statins are associated with reduced cancer risk (2), including breast carcinoma (3-8).

We explored whether statin use alters mammographic measured breast density, a risk factor for breast cancer (9, 10). Cholesterol is a precursor to endogenous sex hormones, which have been linked to mammographic measured breast density (11). Our hypothesis was that statin use decreases breast density.

Materials and Methods

Study Setting. The study was approved by Group Health Cooperative's (GHC) Institutional Review Board. Subjects were women enrolled in GHC, an integrated health plan that provides comprehensive health care to ~550,000 enrollees throughout western Washington State. Information on enrollment, diagnoses, procedures, and health care use are recorded and maintained in automated databases.

Most mammogram screening at GHC is delivered through GHC's Breast Cancer Screening Program that women are invited to join when they turn 40 years old or when they join GHC if older than 40 at enrollment (12). Screening includes a two-view mammogram. Women who participate in the Breast Cancer Screening Program complete a breast cancer risk factor questionnaire at program enrollment and update this information at each screening (12). GHC recommends screening intervals based on age and risk factors, but physicians may order screening mammograms as part of well care.

Study Sample. We selected perimenopausal/postmenopausal women between 50 and 80 years if they had two or more bilateral screening mammograms with density recorded on at least one breast at both screenings occurring between January 1, 1998 and July 30, 2002. We used the highest density category when there were differences in the density ratings of each breast; differences occurred in only one subject. The second screen had to occur within 11 to 26 months after the first screen. We chose the most recent screening mammogram pair for woman with two or more screenings. We required women to be continuously enrolled (defined as <2 months lapse in enrollment) in GHC's integrated group practice delivery system for 12 months before and after each screening. We used self-reported perimenopausal/postmenopausal status collected at screening, which included women with hormone therapy use, bilateral oophorectomy, natural menopause, and those ages ≥55 years. We excluded women with a previous diagnosis of breast cancer, mastectomy, or breast augmentation.

Measures. We used automated pharmacy records, which capture all prescriptions dispensed at GHC pharmacies, to estimate statin use during the year before each screening. We estimated the date when the prescription ran out (run-out date) based on the pill quantity dispensed, text instructions for use, and an adjustment factor of 80% compliance. A new run-out date was set with each successive dispensing rather than using cumulative number of pills from all dispensings. We considered women statin users at the time of screening if they were dispensed at least two statins during the year before the screening and if at least one dispensing was estimated to run out <6 weeks before the screening mammogram. Among statin users, we calculated cumulative days of exposure during the year before each screening. We classified women as nonusers if they were dispensed zero to one statins during the year before screening or who were dispensed a prescription for statins that was estimated to run out >24 weeks before the screening.

We categorized women as nonusers, continuers, discontinuers, and initiators at the time of the second screening. We

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defined nonusers as women who were not using statins at either screen, discontinuers as users of statins at the first screening but nonusers at the second screen, initiators as nonusers of statins at the first screening but users of statins at the second screen, and continuers as users of statins at both screens (13). Any statin use was defined as two or more statin dispensings during the year before screening.

At each mammogram, radiologists categorize breast density based on the four ratings of density recommended by the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS): almost entirely fat, scattered fibroglandular tissue, heterogeneously dense, and extremely dense (14). To evaluate change in breast density from the first to second screening, we categorized breast density change as increase in density by one or more BI-RADS categories, decrease in density by one or more BI-RADS categories, or no change. Inter-rater reliability of BI-RADS is high in some research settings, (15, 16), but one study found only moderate agreement between readers (17), and another found poor agreement (18).

We used self-reported data to evaluate potential confounders. We calculated body mass index (BMI) from weight in kilograms (kg) divided by height in meters square (m^2). Change in BMI from the first to second screening was grouped into categories of <1 kg/m^2 change, ≥1 kg/m^2 decrease, and ≥1 kg/m^2 increase (13).

Statistical Analysis. We evaluated differences in subject characteristics across statin groups and across density changes using the χ^2 test statistic for categorical variables and ANOVA for continuous variables. *P*s ≤ 0.05 were considered a statistically significant difference.

We used polytomous logistic regression to explore the association between statin use and change in breast density. Statin use was compared between women experiencing a decrease in breast density of ≥1 BI-RADS categories and women with no change in breast density between screenings. Similarly, statin use was compared between women experiencing an increase in breast density and women with no change in breast density. We evaluated age, race, age at menopause, parity, hormone therapy use, BMI, change in BMI between screenings, and family history of breast cancer as potential confounders. We tested for differential effects of statin use by including interactions between statin use and age, BMI, and hormone therapy use in our models. We excluded women without statin use patterns that corresponded to one of the four groups and women without complete information on confounders. The association between cumulative days of exposure to statins before screening and change in breast density was evaluated for discontinuers (<120, 120-240, and ≥240 days), initiators (<120, 120-240, and ≥240 days), and continuers (<365, 365-549, and ≥550 days) compared with nonusers. In separate sensitivity analysis, we excluded women with only one statin dispensing, BMI ≥40 kg/m^2, and hormone therapy use.

Results

Of the 20,223 women who met the eligibility criteria, 177 were excluded because they did not fall into one of the four statin groups, and 1,899 were excluded because of missing data on BMI. The final sample size was 18,147.

Table 1. Subject characteristics by statin use

Characteristics	Statin use*			
	Nonuser (*n* = 16,611)	Discontinuer (*n* = 84)	Initiator (*n* = 452)	Continuer (*n* = 1,000)
Age at 1st screen, mean (SD), y	62.5 (8.5)	65.8 (7.6)	65.1 (8.2)	66.6 (7.7)
BMI at 1st screen, mean (SD), kg/m^2	27.7 (6.5)	30.2 (5.2)	29.5 (6.5)	29.4 (6.1)
Race (%)				
White	91.8	86.9	93.1	91.1
Black	2.5	3.6	2.2	3.0
Asian/Pacific Islander	4.9	7.1	4.0	5.4
Other/unknown	0.8	2.4	0.7	0.5
Unit change (kg/m^2) in BMI (%)				
No change	57.3	51.2	54.9	53.2
Decrease of ≥1 units	19.2	23.8	24.3	22.9
Increase of ≥1 units	23.5	25.0	20.8	23.9
Family history of breast cancer	39.4	46.4	37.4	36.8
Parous	85.3	84.5	86.3	88.1
Age at menopause, y (%)				
<30	6.0	4.8	6.0	4.7
30-39	11.3	15.5	12.4	13.7
40-49	37.7	45.2	35.2	40.1
50-59	44.2	34.5	44.4	40.6
≥60	0.8	0.0	2.0	0.9
Hormone use (%)				
Never user	41.5	40.4	50.2	42.9
Discontinuer	7.9	16.7	7.5	8.3
Initiator	4.0	1.2	5.1	2.2
Continuer	46.6	41.7	37.2	46.6
BI-RADS breast density category at 1st screen (%)				
Almost entirely fat	7.7	10.7	13.1	12.5
Scattered fibroglandular tissue	42.5	53.5	49.3	49.0
Heterogeneously dense	42.6	33.3	35.2	35.0
Extremely dense	7.3	2.4	2.4	3.5
Change in BI-RADS breast density category (%)				
No change	66.4	60.7	66.8	64.3
Decrease of ≥1 categories	17.4	17.9	16.4	17.2
Increase of ≥1 categories	16.2	21.4	16.8	18.5

*We defined nonusers as women who were not using statins at either screen, discontinuers as users of statins at the 1st screen but nonusers at the 2nd screen, initiators as nonusers of statins at the 1st screen but users of statins at the 2nd screen, and continuers as users of statins at both screens.

Table 2. Subject characteristics by change in mammographic BI-RADS breast density from 1st to 2nd mammographic screening

Characteristics	Change in BI-RADS breast density category		
	No change (n = 12,020)	Decrease of ≥1 category (n = 3,153)	Increase of ≥1 category (n = 2,974)
Age at 1st screen, mean (SD), y	62.6 (8.5)	62.7 (8.6)	63.6 (8.5)
BMI at 1st screen, mean (SD), kg/m^2	27.8 (6.3)	27.5 (6.0)	28.4 (7.5)
Race			
White	91.8	91.2	92.0
Black	2.5	2.7	2.5
Asian/Pacific Islander	4.8	5.3	4.9
Other/unknown	0.8	0.8	0.7
Unit change in body mass index, (kg/m^2)			
No change	57.1	59.1	54.6
Decrease of ≥1 units	19.4	17.1	22.6
Increase of ≥1 units	23.5	23.8	22.9
Family history of breast cancer	39.2	40.4	38.1
Parous	85.4	85.4	85.7
Age at menopause, y			
<30	6.2	6.0	4.6
30-39	11.3	12.3	11.7
40-49	37.9	36.6	38.7
50-59	43.8	44.0	44.3
≥60	0.8	1.1	0.8
Hormone use			
Never user	41.5	42.3	43.0
Discontinuer	7.8	9.8	6.6
Initiator	4.0	3.1	4.3
Continuer	46.7	44.8	46.1
BI-RADS breast density category at 1st screen			
Almost entirely fat	5.7	0.0	26.4
Scattered fibroglandular tissue	44.8	22.1	58.4
Heterogeneously dense	44.9	55.8	15.2
Extremely dense	4.6	22.1	0.0
Statin use at 2nd screen*			
Nonuser	91.7	91.7	90.6
Discontinuer	0.4	0.5	0.6
Initiator	2.5	2.3	2.6
Continuer	5.4	5.5	6.2

*We defined nonusers as women who were not using statins at either screen, discontinuers as users of statins at the 1st screen but nonusers at the 2nd screen, initiators as nonusers of statins at the 1st screen but users of statins at the 2nd screen, and continuers as users of statins at both screens.

At the second screening, 91.5% of women were nonusers, 0.5% were discontinuers, and 8.0% were current users of statins, including 2.5% initiators and 5.5% continuers (Table 1). The majority of statin users at the first screening (78%) and second screening (81%) were using statins for at least 240 days during the year before screening. Simvastatin accounted for the majority (89%) of statins dispensed. Compared with nonusers, current statin users at second screening were older, had less dense breasts at the first screening, and had higher BMIs. Current statin users were less likely to be hormone therapy users and more likely parous than nonusers of statins.

A decrease in breast density of ≥1 BI-RADS category from first to second screening was experienced by 17.4% of women, an increase by 16.4% of women, and no change by 66.2% of women (Table 2). The average time between screenings was 22 months. Among women with no measurable change in breast density between screenings, 50% had low (almost fat or scattered fibroglandular tissue), and 50% had high breast density (heterogeneously dense or extremely dense). Compared with women with no change in breast density between screenings, women experiencing a decrease in breast density had denser breasts at the first screening and were more likely to be discontinuers of hormone therapy. Women with an increase in breast density were older and had higher BMIs and less dense breasts at the first screening.

The association between statin use and change in breast density are displayed in Table 3. We included age (continuous), BMI (continuous), change in BMI (no change, ≥1 kg/m^2

Table 3. The odds of ≥1 increase and decrease in BI-RADS mammographic breast density category relative to no change in breast density category by statin use

Statin use*	Decrease in breast density		Increase in breast density	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
Nonuser	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Discontinuer	1.1 (0.6-2.0)	1.1 (0.6-2.0)	1.4 (0.8-2.5)	1.3 (0.8-2.3)
Initiator	0.9 (0.7-1.2)	1.0 (0.7-1.2)	1.0 (0.8-1.3)	1.0 (0.7-1.2)
Continuer	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.2 (1.0-1.4)	1.1 (0.9-1.3)
Any use	1.0 (0.9-1.1)	1.0 (0.9-1.2)	1.1 (1.0-1.3)	1.0 (0.9-1.2)

*We defined nonusers as women who were not using statins at either screen, discontinuers as users of statins at the 1st screen but nonusers at the 2nd screen, initiators as nonusers of statins at the 1st screen but users of statins at the 2nd screen, continuers as users of statins at both screens; and any use as women who were dispensed ≥2 statins during year before 2nd screen.

†Odds ratios compared with no change group and adjusted for age (continuous), BMI (continuous), change in BMI (≥1 kg/m^2 increase or decrease and no change), hormone therapy use (nonuser, current, discontinuer), and time between screens (continuous).

increase, and ≥1 kg/m^2 decrease), hormone therapy use at second screening (nonuser, current user, discontinuer), and time between screenings (continuous) in the multivariate models. Relative to nonusers, there was no association between any of the groups of statin users and decrease in breast density. Similarly, statin use was not associated with an increase in breast density. Cumulative number of days exposed to statins during the year before screening was not associated with changes in breast density among any of the groups of statin users compared with nonusers. There were no significant interactions between statin use and age, hormone therapy use, or BMI.

When hormone therapy users (n = 10,553) were excluded from the analyses, any statin use during the year before second screening was associated with an increase in breast density (odds ratio, 1.2; 95% confidence interval, 1.0-1.5) compared with nonusers of statins. The association was similar for continuers of statins (odds ratio, 1.3; 95% confidence interval, 1.0-1.7) and suggestive for discontinuers of statins (odds ratio, 1.8; 95% confidence interval, 0.8-2.3). Excluding women with only one statin dispensed during the year before either screening (n = 127) or women with BMI ≥ 40 kg/m^2 (n = 870) produced trivial changes in results.

Discussion

This population-based study of women undergoing two successive mammography screenings does not support an association between statin use and change in breast density. However, it remains plausible that statin use alters breast density. Studies have found high-density lipoprotein cholesterol (19, 20), low-density lipoprotein cholesterol (19), and dietary cholesterol intake (21) to be associated with breast density, independent of age and BMI.

It is possible that any change in breast density associated with statin use becomes masked when combined with characteristics of statin users, such as high BMI, old age, or concomitant use of hormone therapy. Age and breast density are highly correlated, with breast density decreasing as women age (22). Overweight women tend to have less dense breasts (23). In our study, current statin use at the time of screening and any statin use during the study period was associated with having less dense breasts compared with nonusers even after adjusting for age, BMI, and hormone therapy use. In addition, mammographic breast density was categorized into four broad categories that may be too crude to detect small but clinically meaningful changes in breast density. Hormone therapy has been associated with an increase in breast density (13), and excluding hormone therapy users altered our study findings to indicate a possible increase in breast density with statin use, which is in the opposite direction of our hypothesized relation.

Our study has some notable limitations. Subjects were predominantly Caucasian and from a single health plan. Although sample sizes were adequate to show main effects of statin use on changes in breast density, we may have lacked adequate power to detect differences among smaller groups and to detect effect modifiers. GHC pharmacy records are considered an accurate source of medication exposure, (24), but misclassification cannot be ruled out. Low prevalence of statin use is a limitation, and there may be selection bias in who was using statins at the time of our study. Residual confounding is also possible. A woman's choice to use statins may be related to unmeasured factors that affect study outcomes. For example, women prescribed statins may be more likely to have diseases or use other medications that influence breast density than nonusers. Bias in self-reported height and weight estimates, especially in heavy and older women (25), may have resulted in inadequate adjustment for BMI among statin users. This would have weakened the observed association between statin use and breast density among nonusers of hormone therapy in particular. The results of this study should be considered within their nonrandomized nature.

To our knowledge, this is the first study to evaluate the relationship between statins and breast density. Although effects of statin use on breast cancer risk or breast density is complex, we found no association between statin use and breast density changes. Strengths of this study include its large population with equal access to comprehensive health care, complete and unbiased data on medication use and mammography screening, and information on factors that influence breast density.

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