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Medication use and mammographic breast density

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Abstract

Purpose—A dense breast on mammogram is a strong risk factor for breast cancer. Identifying factors that reduce mammographic breast density could thus provide insight into breast cancer prevention. Due to the limited number of studies and conflicting findings, we investigated the associations of medication use (specifically statins, aspirin, and ibuprofen) with mammographic breast density.

Methods—We evaluated these associations in 775 women who were recruited during an annual screening mammogram at Washington University School of Medicine, St. Louis. We measured mammographic breast density using Volpara. We used multivariable-adjusted linear regressions to determine the associations of medication use (statins, aspirin, and ibuprofen) with mammographic breast density. Least squared means were generated and back-transformed for easier interpretation.

Results—The mean age of study participants was 52.9 years. Statin use in the prior 12 months was not associated with volumetric percent density or dense volume, but was positively associated with non-dense volume. The mean volumetric percent density was 8.6% among statin non-users,

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Author Contributions

ATT designed the study, contributed to the conception and data collection, and provided critical revision of the manuscript. YH and CTL performed the literature search and drafted the manuscript. YH, CTL, XM, CRP, and ATT contributed to the data review. XM and SX performed data analyses, and produced the tables. YH, CTL, XM, SX, CRP, and ATT contributed to data interpretation. All authors contributed to manuscript revision and approved the final submitted version.

Code Availability

Please contact the authors for any questions related to code.

Ethics Statement

The studies involving human participants were reviewed and approved by the institutional review boards of the Washington University School of Medicine. Written informed consent to participate in this study was provided by all the participants.

Conflict of Interest

The authors declare no conflicts of interest.

7.2% among women who used statins 1–3 days/week, and 7.3% among women who used statins ≥4 days/week (p-trend=0.07). The non-dense volume was 1297.1cm^3 among statin non-users, 1368.7cm^3 among women who used statins 1–3 days/week, and 1408.4cm^3 among those who used statins ≥4 days/week (p-trend=0.02). We did not observe statistically significant differences in mammographic breast density by aspirin or ibuprofen use.

Conclusion—Statin, aspirin, and ibuprofen use was not associated with volumetric percent density and dense volume, but statin use was positively associated with non-dense volume. Any potential associations of these medications with breast cancer risk are unlikely to be mediated through an effect on volumetric percent density.

Keywords

mammographic breast density; breast cancer; statin; NSAID; Aspirin; Ibuprofen

Introduction

Mammographic breast density reflects the proportion of radiographically dense fibrous and glandular tissue in relation to fat tissue of the breast [1, 2]. A dense breast on mammogram is a strong risk factor for breast cancer [3, 4] and is also an intermediate phenotype for breast cancer [5]. Women with dense breasts have a 4 to 6-fold increased risk of breast cancer compared to women with little or no dense breast tissue [2, 3, 5, 6]. It is estimated that the population attributable risk proportion of breast cancer due to having highly dense breasts is 39% in premenopausal women and 26% in postmenopausal women [7]. Therefore, identifying how to reduce mammographic breast density could provide insight into breast cancer prevention.

This question has led to studies investigating the associations of commonly used medications such as cholesterol-lowering medications (e.g. statins) or nonsteroidal anti-inflammatory drugs (NSAIDs) with mammographic breast density, but the evidence is limited and inconclusive [8–17]. Studies suggest that statins [22] and NSAIDs [23, 24] are potential chemoprevention agents for breast cancer. Statins inhibit 3-hydroxy-3-methylglutaryl-Coenzyme A reductase (HMG-CoA reductase), a rate-limiting enzyme in cholesterol synthesis [18, 19]. Reduced activity of HMG-CoA reductase decreases mevalonate levels, and mevalonate plays an important role in regulating downstream signaling pathways involved in critical cellular functions and breast cancer development [20]. To the best of our knowledge, no studies have investigated the associations between HMG-CoA reductase level and breast density or changes in breast tissues. NSAIDs inhibit cyclooxygenase-2 (COX-2), which mediates prostaglandin E_2 (PGE_2) synthesis [21]. PGE_2 plays a role in carcinogenesis by influencing estrogen biosynthesis, cell proliferation, angiogenesis, and apoptosis [21].

Five studies have investigated the associations of statin use with mammographic breast density; one study reported a reduction in mammographic breast density with statin use [12] while others did not [8–11]. Likewise, while one study reported an inverse association between NSAID use (aspirin) and mammographic breast density [17], others did not [13–15]. We therefore investigated the associations between statin and NSAID use and

mammographic breast density using Volpara. Volpara provides automated, reproducible, and quantitative volumetric measures of mammographic breast density and has been used and validated in several studies [25–29].

Materials and Methods

Study populations

Between December 2015 and September 2018, we recruited 775 cancer-free women who were undergoing annual screening mammograms at the Joanne Knight Breast Health Center, which is part of the Siteman Cancer Centre at Washington University School of Medicine, St. Louis, MO. Eligible participants in this study have been described in detail previously [30, 31]. Briefly, participants met the following inclusion criteria: (i) between 35–64 years of age, (ii) able to comply with all required study procedures and schedules, including the provision of blood samples at the time of enrollment; (iii) no serious medical condition that would prevent the participant from returning for their annual mammogram in 12 months, (iv) not pregnant. Exclusion criteria included (i) history of any cancer, including breast cancer; (ii) history of breast augmentation, reduction, or implants; (iii) history of selective estrogen receptor modulators (SERM) during the previous 6 months. Participants completed detailed questionnaires that ascertained potential breast cancer risk factors and medication use on the day of their mammogram. The study was approved by the institutional review boards of the Washington University School of Medicine. All study participants provided informed consent.

Medication Use

Medication use information was obtained by self-report using questionnaires. Participants were asked about the use of statins, aspirin, and ibuprofen during the past 12 months (yes or never) and frequency of medication use (never, 1 day per week, 2–3 days per week, 4–5 days per week, and 6+ days per week). Of the 775 women enrolled in the study, there were 113 women with missing information on statin use, 52 women with missing information on aspirin use, and 62 women with missing information on ibuprofen use. We excluded women who had missing information on medication use from the analysis, along with 32 women whose raw mammogram images produced error messages when converted to volumetric measures using Volpara. Therefore, our study included 635 women who had used statins, 694 women who had used aspirin, and 684 women who had used ibuprofen in the final analysis.

Volumetric mammographic breast density measures

We used Volpara (version 1.5) to obtain volumetric mammographic breast density measurements. Volpara uses a computerized algorithm that calculates the X-ray attenuation at each pixel of the image and converts the attenuation to an estimate of the tissue composition to create a density map [32]. The cranial-caudal and mediolateral oblique views of the left and right breasts are then averaged. Volpara measures volumetric percent density (VPD, %), dense volume (DV, cm^3), and non-dense volume (NDV, cm^3). Compared with the Breast Imaging Reporting and Data System (BI-RADs) 5th edition, Volpara volumetric percent density translates to (i) < 3.5% (almost entirely fatty breasts); (ii) ≥ 3.5 and < 7.5%

(scattered areas of fibroglandular density); (iii) ≥ 7.5 and < 15.5% (heterogeneously dense breasts); and (iv) ≥ 15.5% (extremely dense breasts) [33].

Statistical analysis

We evaluated differences in participants' characteristics and medication use using chi-square tests for categorical variables and Student's t-test or Wilcoxon rank-sum tests for continuous variables as appropriate. We performed $\log_{10}$ transformations on volumetric percent density, dense volume and non-dense volume for conformation to normality. We used multivariable-adjusted linear regression models to evaluate the associations between medication use and mammographic breast density. We adjusted for age (continuous), body mass index (continuous), family history of breast cancer in a first-degree relative (no, yes, missing), race (non-Hispanic White, African American, others), age at menarche (continuous), current alcohol intake (no, yes), parity and age at first birth (nulliparous; 1–2 children and < 25 years at first birth; 1–2 children and 25–29 years at first birth;1–2 children and ≥ 30 years at first birth; ≥ 3 children and < 25 years at first birth; ≥ 3 children and ≥ 25 years at first birth). In analyses evaluating the frequency of medication, we re-categorized responses into three groups (never, 1–3 days per week, 4+ days per week) because of the small sample size. We report $\log_{10}$-transformed and back-transformed least square means and corresponding 95% confidence intervals (CIs) for mammographic breast density measures. We tested linear trends across the frequency of medication use using Wald tests by ordinal modeling of group medians. In addition, we examined race (non-Hispanic White vs. African American) and family history of breast cancer (no vs. yes) as effect modifiers. We repeated the main analysis associating medication use with mammographic breast density by race and family history of breast cancer in stratified analyses. We examined the interactions of medication use and race/ family history of breast cancer by introducing an interaction term within our model and assessed the corresponding p-values for these associations. All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant. All analyses were performed using Statistical Analyses Systems (SAS) version 9.4 (SAS Institute Inc, Cary, NC).

Results

Medication users and non-users were similar in many characteristics (Table 1). The mean age at the time of mammogram was 52.9 years (range: 32–64 years). The majority (63.2%) of participants were non-Hispanic White, while 33.0% were African American. The mean body mass index (BMI) was 31.1 kg/m^2. The mean volumetric percent density was 7.9%, the mean dense volume was 100.8 cm^3, and the mean non-dense volume was 1601.7 cm^3. Among the 662 women with complete information on statin use, 8.2% had used a statin in the past 12 months. Among the 723 women with complete information on aspirin use, 23.8% had used aspirin in the past 12 months. Among the 713 women with complete information on ibuprofen use, 54.1% had used ibuprofen in the past 12 months.

Statins

In the multivariable-adjusted models, we did not observe statistically significant association between statin use and volumetric percent density (Table 2). However, the mean volumetric

percent density was lower for statin users (7.3%) than non-users (8.6%) (p-value=0.09, Table 2). When evaluating the frequency of use, the mean volumetric percent density was 8.6% among statin non-users, 7.2% among women who used statins 1–3 days/week, and 7.3% among those who used statins ≥ 4 days/week (p-trend=0.07, Table 2). We also did not find statistically significant associations between statin use and dense volume (Table 2). The mean dense volume among statin users was 84.9 cm^3 compared to 88.8cm^3 among non-users (p-value=0.48). However, statin use was associated with higher non-dense volume: 1394.3 cm^3 among users compared to 1297.1cm^3 among non-users (p-value=0.03, Table 2). Further, there was evidence of a linear increase in non-dense volume with increasing statin use. The non-dense volume was 1297.1cm^3 among non-users, 1368.7cm^3 among women who used statins 1–3 days/week, and 1408.4cm^3 among those who used statins ≥ 4 days/week (p-trend=0.02).

NSAIDs

In the multivariable-adjusted models, we did not observe statistically significant associations between NSAID use and mammographic breast density (Table 2). The mean volumetric percent density was 7.9% for aspirin users and 8.5% for non-users (p-value=0.15, Table 2). When evaluating the frequency of use, the mean volumetric percent density was 7.3% among women who used aspirin 1–3 days/week and 8.6% among women who used aspirin ≥ 4 days/week (p-trend =0.38, Table 2). Similarly, aspirin use was not significantly associated with either dense volume or non-dense volume (Table 2). Likewise, the associations were not statistically significant between ibuprofen use and any mammographic breast density measures.

Stratified analysis

We further performed analyses stratified by race (non-Hispanic White vs. African American) and family history of breast cancer (no vs. yes). We did not observe any evidence of effect modification by race or family history of breast cancer (data not shown).

Discussion

In this study among women undergoing screening mammogram, we did not observe statistically significant associations between statin, aspirin, or ibuprofen use and volumetric percent density or dense volume. Statin use was however, positively associated with non-dense volume.

Our findings are similar to those reported in a large Swedish study [12]. The authors reported a weak inverse association between statin use and volumetric percent density, as well as a positive association between statin use and non-dense volume. Non-dense volume is a measure of the fatty component of the breast. One possible explanation for the positive association between statin use and non-dense volume is that women with fatty breast tissue on their mammogram are likely to have higher body adiposity and may be more likely to be prescribed statins for obesity-associated cardiovascular disease [34]. Our findings, however, differ from those of other studies [8–11]. In one study, statin use had a weak positive association only when women who used hormone therapy were excluded from the analyses

[8]. A few small clinical trials (sample sizes ranging from N=30 to 50) did not observe an association between statin use and mammographic breast density [9–11]. The null findings may be due to the short duration of simvastatin use, as some authors have suggested that a longer duration of use (1–2 years) may be necessary to observe an effect [35, 36]. In addition, several studies have investigated the association between statin use and breast cancer risk, and while some studies have shown that statin use is associated with reduced breast cancer risk [35, 37–39], others have not [40, 41]. Further studies should explore the potential pathways that the statins affect breast cancer risk than breast density.

Our findings on NSAID use are consistent with those of four previous studies [13–16], two of which were performed with postmenopausal women [14, 16]. One of the largest studies (N=3286) also found no associations between NSAID use and percent dense area or dense area, and examined the dose and duration of aspirin use [13]. In contrast, Wood et al. reported that aspirin users were 27% less likely to have extremely dense breasts (BI-RADS 4), and 18% less likely to have dense breasts (BI-RADS 3–4) among 26,000 women, after controlling for age, BMI, and race [17]. However, their study participants were older, with an age range extending to 89 years (mean age: 57.3 years), compared to women enrolled in our study (mean age: 52.9 years; maximum: 64 years). In addition, the mean BMI of their population was lower compared to women enrolled in our study (28.9 kg/m^2 vs. 31.1 kg/m^2). Further, they did not evaluate mammographic breast density using quantitative measures.

Our study had some limitations. First, we did not collect information on the type of statin taken by participants (e.g. lipophilic or hydrophilic statins), so we were not able to determine if associations differ by the type of statin used, similar to other studies that have suggested that simvastatin (a lipophilic statin) may be more relevant for cancer prevention [42]. Another limitation is that the frequency of statin use in our study population was low, which did not allow us to evaluate how greater levels of use may be associated with mammographic breast density.

Our study has several strengths. First, we recruited healthy women undergoing annual screening mammograms. Our study population mirrors women who attend screening mammogram at the Breast Health Centre at Siteman Cancer Centre in terms of characteristics. Hence, our study can be generalized to this population. Second, our study population is diverse (33% are African Americans), which enabled us to evaluate, for the first time, the associations of statin use with mammographic breast density in African American women.

In conclusion, medication use (statin, aspirin, and ibuprofen) was not associated with volumetric percent density or dense volume, but statin use was positively associated with non-dense volume. Any possible associations of these medications with breast cancer risk are unlikely to be mediated through their effect on volumetric percent density.

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Data Availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

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Table 1.

Characteristics of women recruited during annual screening mammogram at the Joanne Knight Breast Health Center, Washington University School of Medicine, St. Louis, MO, stratified by medication use

Characteristics	Total[a] (N=775)	Statin (N=662)		Aspirin (N=723)		Ibuprofen (N=713)	
		Non-User N=608 (91.8%)	User N=54 (8.2%)	Non-User N=551 (76.2%)	User N=172 (23.8%)	Non-User N=327 (45.9%)	User N=386 (54.1%)
	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]
Age (years)	52.9 (6.8)	52.3 (6.9)	52.3 (6.0)	52.0 (6.8)	55.3 (6.5)	54.0 (6.7)	51.5 (6.7)
Age at menarche (years)	12.8 (1.9)	12.8 (2.0)	12.6 (1.8)	12.8 (2.0)	12.8 (1.9)	12.9 (2.2)	12.7 (1.7)
Race							
Non-Hispanic White	490 (63.2%)	395 (65.0%)	34 (63.0%)	357 (64.8%)	102 (59.3%)	180 (55.1%)	278 (72.0%)
African American	256 (33.0%)	189 (31.1%)	20 (37.0%)	169 (30.7%)	68 (39.5%)	133 (40.7%)	98 (25.4%)
Others	29 (3.7%)	24 (4.0%)	0 (0.0%)	25 (4.5%)	2 (1.2%)	14 (4.3%)	10 (2.6%)
Menopausal status							
Premenopausal	375 (48.4%)	317 (52.1%)	33 (61.1%)	316 (57.4%)	49 (28.5%)	145 (44.3%)	217 (56.2%)
Postmenopausal	400 (51.6%)	291 (47.9%)	21 (38.9%)	235 (42.7%)	123 (71.5%)	182 (55.7%)	169 (43.8%)
Body Mass Index (kg/m ^{2})	31.1 (7.9)	30.5 (7.8)	31.9 (7.2)	30.3 (7.7)	32.8 (8.4)	30.9 (8.1)	31.1 (7.8)
Parity and age at first birth							
Nulliparous	137 (17.7%)	104 (17.1%)	8 (14.8%)	97 (17.6%)	30 (17.4%)	59 (18.0%)	70 (18.1%)
1–2 children, <25 years	157 (20.3%)	122 (20.1%)	9 (16.7%)	105 (19.1%)	45 (26.2%)	71 (21.7%)	75 (19.4%)
1–2 children, 25–29 years	127 (16.4%)	99 (16.3%)	11 (20.4%)	96 (7.4%)	23 (13.4%)	54 (16.5%)	62 (16.1%)
1–2 children, ≥30 years	140 (18.1%)	115 (18.9%)	10 (18.5%)	108 (19.6%)	21 (12.2%)	54 (16.5%)	78 (20.2%)
≥3 children, <25 years	134 (17.3%)	99 (16.3%)	13 (24.1%)	86 (15.6%)	36 (20.9%)	60 (18.4%)	57 (14.8%)
≥3 children, ≥25 years	73 (9.4%)	63 (10.4%)	2 (3.7%)	54 (9.8%)	15 (8.7%)	24 (7.3%)	42 (10.9%)
Missing	7 (0.9%)	6 (1.0%)	1 (1.9%)	5 (0.9%)	2 (1.2%)	5 (1.5%)	2 (0.5%)
Family history of breast cancer							
No	565 (72.9%)	436 (71.7%)	41 (75.9%)	390 (70.8%)	134 (77.9%)	240 (73.4%)	276 (71.5%)
Yes	189 (24.4%)	154 (25.3%)	12 (22.2%)	142 (25.8%)	36 (20.9%)	72 (23.9%)	98 (25.4%)
Missing	21 (2.7%)	18 (3.0%)	1 (1.9%)	19 (3.5%)	2 (1.2%)	9 (2.8%)	12 (3.1%)
Current alcohol intake							
No	291 (37.6%)	221 (36.4%)	20 (37.0%)	198 (35.9%)	71 (41.3%)	142 (43.4%)	126 (32.6%)

Characteristics	Total[a] (N=775)	Statin (N=662)		Aspirin (N=723)		Ibuprofen (N=713)	
		Non-User N=608 (91.8%)	User N=54 (8.2%)	Non-User N=551 (76.2%)	User N=172 (23.8%)	Non-User N=327 (45.9%)	User N=386 (54.1%)
	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]	N (%) or mean (SD)[b]
Yes	481 (62.1%)	384 (63.2%)	34 (63.0%)	351 (63.7%)	100 (58.1%)	183 (56.0%)	260 (67.4%)
Missing	3 (0.4%)	3 (0.5%)	0 (0.0%)	2 (0.4%)	1 (0.6%)	2 (0.6%)	0 (0.0%)
Mammographic breast density							
Volumetric percent density (%)	7.9 (5.7)	8.4 (6.0)	6.4 (3.8)	8.4 (6.0)	6.3 (4.4)	7.3 (4.9)	8.3 (6.2)
<3.5%	86 (11.1%)	59 (9.7%)	9 (16.7%)	53 (9.6%)	26 (15.1%)	37 (11.3%)	40 (10.4%)
3.5%–7.5%	392 (50.6%)	292 (48.0%)	29 (53.7%)	273 (49.6%)	94 (54.7%)	176 (53.8%)	187 (48.5%)
≥7.5%–15.5%	189 (24.4%)	163 (26.8%)	10 (18.5%)	140 (25.4%)	33 (19.2%)	71 (21.7%)	101 (26.2%)
>15.5%	76 (9.8%)	71 (11.7%)	2 (3.7%)	67 (12.2%)	8 (4.7%)	28 (8.6%)	40 (10.4%)
Missing	32 (4.1%)	23 (3.8%)	4 (7.4%)	18 (3.3%)	11 (6.4%)	15 (4.6%)	14 (3.6%)
Dense volume (cm^3)	100.8 (95.2)	98.0 (93.1)	94.9 (57.3)	98.0 (86.8)	109.8 (119.8)	105.1 (104.2)	97.9 (88.9)
Non-dense volume (cm^3)	1601.7 (1631.5)	1465.6 (1504.2)	1641.9 (1142.8)	1498.2 (1527.3)	1959.0 (1977.6)	1728.0 (1848.5)	1504.5 (1440.0)
Log_{10}-transformed mammographic breast density							
Volumetric percent density (%)	0.8 (0.3)	0.8 (0.3)	0.8 (0.2)	0.8 (0.3)	0.7 (0.2)	0.8 (0.2)	0.8 (0.3)
Dense volume (cm^3)	1.9 (0.3)	1.9 (0.3)	1.9 (0.2)	1.9 (0.3)	1.9 (0.3)	1.9 (0.3)	1.9 (0.3)
Non-dense volume (cm^3)	3.0 (0.4)	3.0 (0.4)	3.1 (0.3)	3.0 (0.4)	3.1 (0.4)	3.1 (0.4)	3.0 (0.4)

Abbreviations: N, Number; SD, Standard deviation

[a] 113 women had missing information for statin use, 52 women had missing information for aspirin use; 62 women had missing information for ibuprofen use

[b] Presented as number and column percentage or mean and standard deviation.

Table 2.

Multivariable-adjusted associations of medication use with mammographic breast density

Medication	N	Back-transformed Least Square Mean (95% CI)	P-value	P-trend
Volumetric Percent Density				
Statin use				
Non-user	585	8.6 (7.8, 9.4)	Reference	
User	50	7.3 (5.7, 8.8)	0.09	
Frequency [a]				0.07
Non-user	585	8.6 (7.8, 9.4)	Reference	
1–3 days/week	18	7.2 (4.8, 9.6)	0.54	
4+ days/week	32	7.3 (5.4, 9.2)	0.09	
Aspirin use				
Non-user	533	8.5 (7.7, 9.2)	Reference	
User	161	7.9 (6.9, 9.0)	0.15	
Frequency [a]				0.38
Non-user	533	8.5 (7.7, 9.2)	Reference	
1–3 days/week	75	7.3 (6.0, 8.5)	0.06	
4+ days/week	86	8.6 (7.4, 9.9)	0.79	
Ibuprofen use				
Non-user	312	7.8 (7.0, 8.7)	Reference	
User	372	8.5 (7.6, 9.3)	0.22	
Frequency [a]				0.41
Non-user	312	7.8 (7.0, 8.7)	Reference	
1–3 days/week	284	8.5 (7.6, 9.4)	0.18	
4+ days/week	88	8.2 (7.0, 9.5)	0.70	
Dense volume				
Statin Use				
Non-user	585	88.8 (74.3, 103.4)	Reference	
User	50	84.9 (55.9, 113.9)	0.48	
Frequency [a]				0.47
Non-user	585	88.8 (74.3, 103.1)	Reference	
1–3 days/week	18	88.2 (43.4, 133.1)	0.78	
4+ days/week	32	83.1 (48.6, 117.7)	0.50	
Aspirin Use				
Non-user	533	93.9 (79.4, 108.4)	Reference	
User	161	96.0 (75.8, 116.2)	0.62	
Frequency [a]				0.90
Non-user	533	94.0 (79.4, 108.5)	Reference	
1–3 days/week	75	94.1 (69.1, 119.1)	0.33	
4+ days/week	86	98.0 (72.7, 123.3)	0.82	
Ibuprofen Use				

Medication	N	Back-transformed Least Square Mean (95% CI)	P-value	P-trend
Volumetric Percent Density				
Non-user	312	97.3 (80.3, 114.3)	Reference	
User	372	91.5 (74.7, 108.2)	0.86	
Frequency [a]				0.40
Non-user	312	97.1 (80.1, 114.1)	Reference	
1–3 days/week	284	93.2 (75.8, 110.6)	0.74	
4+ days/week	88	84.9 (60.2, 109.6)	0.22	
Non-dense Volume				
Statin Use				
Non-user	585	1297.1 (1083.7, 1510.5)	Reference	
User	50	**1394.3 (968.3, 1820.4)**	**0.03**	
Frequency [a]				**0.02**
Non-user	585	1297.1 (1083.7, 1510.5)	Reference	
1–3 days/week	18	1368.7 (709.7, 2027.6)	0.37	
4+ days/week	32	**1408.4 (901.0, 1915.8)**	**0.04**	
Aspirin Use				
Non-user	533	1458.1 (1231.8, 1684.3)	Reference	
User	161	1544.8 (1229.9, 1859.6)	0.46	
Frequency [a]				0.51
Non-user	533	1458.8 (1232.3, 1685.2)	Reference	
1–3 days/week	75	1515.0 (1124.7, 1905.2)	0.52	
4+ days/week	86	1575.4 (1181.2, 1969.6)	0.62	
Ibuprofen Use				
Non-user	312	1545.5 (1283.8, 1807.1)	Reference	
User	372	1416.7 (1159.0, 1674.4)	0.56	
Frequency [a]				0.31
Non-user	312	1542.4 (1280.5, 1804.2)	Reference	
1–3 days/week	284	1443.3 (1175.1, 1711.4)	0.85	
4+ days/week	88	1316.0 (935.7, 1696.3)	0.23	

Abbreviations: CI, Confidence interval; N, Number.

Bold indicates statistical significance ($p<0.05$).

All models were adjusted for age (continuous), body mass index (continuous), family history of breast cancer in a first-degree relative (no, yes, unknown), race (non-Hispanic White, African American, others), age at menarche (continuous), current alcohol intake (no, yes), parity and age at first birth (nulliparous; 1–2 children and <25 years at first birth; 1–2 children and 25–29 years at first birth;1–2 children and ≥30 years at first birth; ≥3 children and <25 years at first birth; ≥3 children and ≥25 years at first birth).