**Abstract**

**Background:** Vitamin D, which influences cellular proliferation and breast tissue characteristics, has been inversely correlated with breast cancer risk. Dietary vitamin D intake has been associated with lower mammographic density (MD), a strong intermediate marker of breast cancer risk.

**Findings:** We examined the relationship between MD and serum 25-hydroxyvitamin D [25(OH)D], an integrated measure of vitamin D status from dietary sources and sunlight exposure, in a multi-ethnic cohort of women undergoing screening mammography. We recruited women age 40–60 years without a history of breast cancer at the time of their routine screening mammogram, and conducted in-person interviews and collected blood specimens. We enrolled 195 women from 2007–2008, 120 gave blood, and 114 were evaluable, including 25% white, 41% African American, 18% African Caribbean, and 16% Hispanic. We digitized mammograms and calculated percent density, dense area, and non-dense area on cranial-caudal images. We measured serum 25(OH)D in batched, archived specimens. Median serum 25(OH)D was 22 ng/ml (range, 8–66 ng/ml). In univariable analysis, higher serum 25(OH)D was associated with white race, higher educational level, ever breast feeding, and blood draw during the summer. After adjusting for body mass index and other confounders, we found no association between serum 25(OH)D and different measures of MD. However, when stratified by season, 25(OH)D was inversely associated with dense area during July-December (p = 0.034).

**Conclusions:** Overall, our findings suggest that circulating vitamin D, a potentially modifiable breast cancer risk factor, is not associated with MD; the seasonal effects we observed need to be replicated in larger cohorts.

**Keywords:** Vitamin D, 25-hydroxyvitamin D, Breast cancer, Mammographic density

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**Introduction**

Vitamin D has a number of anti-tumor properties, including inhibition of cell proliferation and induction of apoptosis and differentiation [1]. In observational studies of breast cancer and vitamin D status, women in the highest quantile of circulating vitamin D had a 45% reduced risk of breast cancer compared to those in the lowest quantile [2].

However, the effect of vitamin D on mammographic density (MD), one of the strongest predictors of breast cancer, remains unclear. MD refers to the relative proportions of radiolucent fat and radiodense fibroglandular tissue within the breast on mammography [3]. Serum 25-hydroxyvitamin D [25(OH)D] provides an integrated measure of vitamin D status from diet, supplements, and sunlight exposure and is considered the best indicator of vitamin D body stores [4]. We examined the association between MD and serum 25(OH)D in a cross-sectional study of racially/ethnically diverse women undergoing screening mammography.

**Methods**

We enrolled 195 women age 40–60 years without a personal history of breast cancer to the New York City Multiethnic Breast Cancer Project from January 2007 to April 2008. Participants were enrolled at their routine screening mammography visits at Long Island College Hospital (LICH) in Brooklyn, New York, as previously
described [5]. All participants completed in-person interviews providing information on demographics and breast cancer risk factors and consented to allow study investigators access to their mammograms; 120 (62%) participants provided a blood sample and 114 were evaluable for serum 25(OH)D measurements [5]. The study protocol was approved by the Institutional Review Boards of LICH, Long Island University and Columbia University Medical Center (CUMC).

We measured serum 25(OH)D in batched, archived specimens by Diasorin radioimmunoassay (Stillwater, MN). Interassay precision for quality controls were 14% and 18% at 15 ng/ml and 48 ng/ml, respectively. We evaluated digitized mammograms for dense area (cm²), non-dense

| Characteristic                                   | Total (N = 114) | Serum 25(OH)D | P-valueb |
|-------------------------------------------------|----------------|---------------|----------|
| Mean age at interview, years (SD)               | 50.0 (5.8)     | 49.4 (5.9)    | 50.7 (5.6) | 0.233 |
| Race/ethnicity, N (%):                          |                |               |          |
| White                                           | 28 (25)        | 8 (14)        | 20 (36)  | 0.008 |
| African American                                | 47 (41)        | 32 (54)       | 15 (27)  |          |
| African Caribbean                               | 21 (18)        | 9 (15)        | 12 (22)  |          |
| Hispanic/Other                                  | 18 (16)        | 10 (17)       | 8 (15)   |          |
| Menopausal status, N (%):                       |                |               |          |
| Pre/perimenopausal                              | 73 (64)        | 41 (69)       | 32 (58)  | 0.209 |
| Postmenopausal                                  | 41 (36)        | 18 (31)       | 23 (42)  |          |
| Highest level of education, N (%):              |                |               |          |
| ≤ High school                                   | 34 (30)        | 22 (37)       | 12 (22)  | 0.045 |
| Some college/associate degree                   | 35 (31)        | 20 (34)       | 15 (27)  |          |
| ≥ College degree                                | 45 (39)        | 17 (29)       | 28 (51)  |          |
| Mean body mass index, kg/m² (SD)                | 29.2 (6.3)     | 30.3 (6.1)    | 28.1 (6.3) | 0.055 |
| First-degree family history of breast cancer, N (%) |            |               |          |
| Yes                                             | 17 (15)        | 10 (17)       | 7 (13)   | 0.554 |
| No                                              | 96 (85)        | 49 (83)       | 47 (87)  |          |
| Mean age at menarche, years (SD)                | 12.5 (1.8)     | 12.3 (1.8)    | 12.6 (1.8) | 0.366 |
| Mean parity, N (SD)                             | 1.6 (1.4)      | 1.5 (1.5)     | 1.7 (1.3) | 0.534 |
| Mean age at first live birth, years (SD)        | 22.6 (6.8)     | 21.7 (6.9)    | 23.5 (6.7) | 0.248 |
| Ever breast fed, N (%)                          |                |               |          |
| Yes                                             | 46 (40)        | 17 (29)       | 29 (53)  | 0.009 |
| No                                              | 68 (60)        | 42 (71)       | 26 (47)  |          |
| Ever hormonal birth control use, N (%)          |                |               |          |
| Yes                                             | 78 (68)        | 43 (73)       | 35 (64)  | 0.289 |
| No                                              | 36 (32)        | 16 (27)       | 20 (36)  |          |
| Season of blood draw, N (%)                     |                |               |          |
| January-March                                   | 62 (54)        | 34 (58)       | 28 (51)  | 0.017 |
| April-June                                      | 29 (25)        | 19 (32)       | 10 (18)  |          |
| July-September                                  | 19 (17)        | 6 (10)        | 13 (24)  |          |
| October-December                                | 4 (4)          | 0 (0)         | 4 (7)    |          |
| Mean percent density, % (SD)                    | 12.9 (11.4)    | 13 (11.1)     | 12.7 (11.8) | 0.875 |
| Mean dense area, cm² (SD)                       | 17.4 (14.7)    | 19.7 (16.1)   | 14.9 (12.8) | 0.086 |
| Mean non-dense area, cm² (SD)                   | 148 (82.3)     | 158 (78.2)    | 137 (85.9) | 0.185 |

*Median 25(OH)D of 22 ng/ml.

bP-value based upon 2-sample t-tests for continuous variables and chi-square tests for categorical variables.
area (cm\(^2\)), and percent density (dense area divided by total breast area) on cranial-caudal images using Cumulus software, as previously described [5]. The Pearson correlation coefficients for repeated readings of a randomly selected 10% subset of mammograms were 0.99 and 0.9 for breast area and dense area, respectively.

We performed 2-sample t-tests and chi-square tests to determine whether the distribution of selected breast cancer risk factors differed by serum 25(OH)D. We used linear regression models to investigate the association of MD with serum 25(OH)D. We assessed for confounding by using the change in estimate criteria of 10% or more for estimates of the association between serum 25(OH)D and MD after adding each known potential confounding variable to the bivariant model. The multivariable models included age, race/ethnicity, education, body mass index (BMI, kg/m\(^2\)), ever breast-feeding, and season of blood draw (January-March, April-June, July-September, October-December). We also conducted stratified analyses based upon menopausal status, BMI (≤30 vs. >30 kg/m\(^2\)), and season (January-June vs. July-December). All statistical analyses were conducted using SAS version 9.2 (Cary, NC).

### Table 2 Multivariable Linear Regression Estimates of Percent Density (%), Dense Area (cm\(^2\)), and Non-Dense Area (cm\(^2\)), New York City Multiethnic Breast Cancer Project, 2007-2008

| Characteristic                  | β Coefficient | 95% CI    | P-value |
|--------------------------------|---------------|-----------|---------|
| **Percent Density (%)**        |               |           |         |
| Serum 25(OH)D (ng/ml)          | −0.013        | −0.188    | 0.161   | 0.880 |
| Age at mammogram (years)       | −0.576        | −0.921    | −0.230  | 0.001 |
| **Race/ethnicity**             |               |           |         |
| White                          | Reference     |           |         |
| African American                | 1.762         | −3.831    | 7.355   | 0.533 |
| African Caribbean               | 3.169         | −3.274    | 9.613   | 0.332 |
| Hispanic/Other                  | −2.094        | −8.860    | 4.672   | 0.541 |
| **Education**                  |               |           |         |
| ≤ High school                  | −2.017        | −7.157    | 3.123   | 0.438 |
| Some college/associate degree   | −3.646        | −8.600    | 1.308   | 0.147 |
| Bachelor, master, doctoral degree | Reference   |           |         |
| Body mass index (kg/m\(^2\))   | −0.503        | −0.873    | −0.133  | 0.008 |
| **Ever breast feeding**        |               |           |         |
| Yes                            | 1.038         | −3.015    | 5.091   | 0.612 |
| No                             | Reference     |           |         |
| **Season of blood draw**       |               |           |         |
| January-March                  | Reference     |           |         |
| April-June                     | 0.761         | −3.983    | 5.505   | 0.751 |
| July-September                 | −5.398        | −11.259   | 0.462   | 0.071 |
| October-December               | −5.464        | −16.201   | 5.274   | 0.315 |
| **Dense Area (cm\(^2\))**     |               |           |         |
| Serum 25(OH)D (ng/ml)          | −0.094        | −0.332    | 0.143   | 0.432 |
| Age at mammogram (years)       | −0.624        | −1.101    | −0.146  | 0.011 |
| **Race/ethnicity**             |               |           |         |
| White                          | Reference     |           |         |
| African American                | 5.421         | −2.299    | 13.142  | 0.167 |
| African Caribbean               | 5.838         | −2.899    | 14.576  | 0.188 |
| Hispanic/Other                  | −2.643        | −11.985   | 6.700   | 0.576 |
| **Education**                  |               |           |         |
| ≤ High school                  | −0.243        | −7.254    | 6.767   | 0.945 |
| Some college/associate degree   | −3.547        | −10.372   | 3.278   | 0.305 |
| Bachelor, master, doctoral degree | Reference   |           |         |
| Body mass index (kg/m\(^2\))   | −0.170        | −0.680    | 0.341   | 0.511 |
| **Season of blood draw**       |               |           |         |
| January-March                  | Reference     |           |         |
| April-June                     | 3.430         | −3.128    | 9.988   | 0.302 |
| July-September                 | −6.690        | −14.763   | 1.403   | 0.104 |
| October-December               | −6.718        | −21.564   | 8.128   | 0.371 |

### Table 2 Multivariable Linear Regression Estimates of Non-Dense Area (cm\(^2\)), New York City Multiethnic Breast Cancer Project, 2007-2008 (Continued)

| Characteristic                  | β Coefficient | 95% CI    | P-value |
|--------------------------------|---------------|-----------|---------|
| **Non-Dense Area (cm\(^2\))**  |               |           |         |
| Serum 25(OH)D (ng/ml)          | 0.209         | −0.823    | 1.242   | 0.688 |
| Age at mammogram (years)       | 3.346         | 1.302     | 5.390   | 0.002 |
| **Race/ethnicity**             |               |           |         |
| White                          | Reference     |           |         |
| African American                | 12.640        | −20.455   | 45.735  | 0.533 |
| African Caribbean               | 6.186         | −31.943   | 44.315  | 0.748 |
| Hispanic/Other                  | −2.090        | −42.125   | 37.946  | 0.918 |
| **Education**                  |               |           |         |
| ≤ High school                  | 22.854        | −7.560    | 53.269  | 0.139 |
| Some college/associate degree   | 21.506        | −7.809    | 50.821  | 0.149 |
| Bachelor, master, doctoral degree | Reference   |           |         |
| Body mass index (kg/m\(^2\))   | 7.142         | 4.952     | 9.331   | <0.001 |
| Ever breast feeding             | No            | Reference |         |
| Yes                            | −17.582       | −41.566   | 6.402   | 0.149 |
| **Season of blood draw**       |               |           |         |
| January-March                  | Reference     |           |         |
| April-June                     | −0.074        | −28.145   | 27.997  | 0.996 |
| July-September                 | 23.080        | −11.597   | 57.757  | 0.190 |
| October-December               | 8.404         | −55.132   | 71.940  | 0.794 |
Findings
The median serum 25(OH)D for the entire sample was 22 ng/ml (range 8–66 ng/ml). Forty-seven (41%) women had serum 25(OH)D levels in the deficient range (<20 ng/ml), 32 (28%) in the insufficient range (20–29 ng/ml), and 35 (31%) in the sufficient range (≥30 ng/ml). Baseline characteristics according to groups above and below the median serum 25(OH)D are shown in Table 1. In univariable analysis, having a serum 25(OH)D above the median was associated with white race, higher educational level, ever breast feeding, blood draw during the summer, and a trend toward lower dense area (p = 0.086).

After adjusting for age, race/ethnicity, education, BMI, ever breast feeding, and season of blood draw, we found no association between 25(OH)D and the different measures of MD (Table 2), even when stratified by menopausal status and BMI. We did, however, observe a trend toward lower percent density during the late summer (July-September), when the highest levels of serum 25(OH)D were observed. Stratified analysis by season (Table 3) revealed that serum 25(OH)D was inversely associated with dense area in multivariable analysis (p = 0.034) during the months of July-December.

Discussion
Overall, we observed a non-significant trend toward lower dense area in participants with higher serum 25(OH)D, which was no longer significant after adjustment for BMI and other confounders. However, during the months of July-December, we observed a significant inverse association between serum 25(OH)D and dense area, which may be a better a measure of MD in obese women.

A recent systematic review of fourteen studies examining the association between vitamin D and MD [6] included twelve cross-sectional studies [7-18] and two prospective studies [19,20]. Nine studies assessed vitamin D status by dietary and supplement intake [12-20] and five studies by circulating 25(OH)D levels [7-11]. Only four studies considered dense area as a measure of MD [7,10,11,15] and five studies included populations which were diverse by race and ethnicity [10,11,15-17].

Five out of nine studies which assessed dietary intake of vitamin D reported a significant inverse association between vitamin D and MD [8,13-15,18]. When stratified by menopausal status, much of the association was limited to premenopausal women [13-15]. In a sub-study of the Women's Health Initiative (WHI), no association was observed between vitamin D or calcium intake and MD among postmenopausal women, however, supplemental vitamin D use was associated with lower density in younger women [17]. Of note, we did not observe an association between 25(OH)D and MD when stratified by menopausal status, however, this subgroup analysis was limited by our relatively small sample size.

Table 3 Multivariable linear regression estimates of dense area (cm²) stratified by season of blood draw (January-June, July-December), New York City multiethnic breast cancer project, 2007-2008

| Characteristic                        | β coefficient | 95% CI       | P-value |
|---------------------------------------|---------------|--------------|---------|
| **January-June (N = 91)**             |               |              |         |
| Serum 25(OH)D (ng/ml)                 | −0.046        | −0.338, 0.246| 0.757   |
| Age at mammogram (years)              | −0.813        | −1.421, −0.205| 0.009   |
| Race/ethnicity                        |               |              |         |
| White                                 | Reference     |              |         |
| African American                      | 6.014         | −3.463, 15.491| 0.210   |
| African Caribbean                     | 8.406         | −2.912, 19.724| 0.143   |
| Hispanic/Other                        | −2.480        | −13.841, 8.882| 0.665   |
| Education                             |               |              |         |
| ≤High school                          | −1.405        | −9.837, 7.027| 0.741   |
| Some college/associate degree         | −4.541        | −13.109, 4.026| 0.295   |
| Bachelor, master, doctoral degree     | Reference     |              |         |
| Body mass index (kg/m²)               | 0.056         | −0.540, 0.653| 0.851   |
| **July-December (N = 23)**            |               |              |         |
| Serum 25(OH)D (ng/ml)                 | −0.254        | −0.487, −0.022| 0.034   |
| Age at mammogram (years)              | −0.272        | −0.711, 0.167| 0.204   |
| Race/ethnicity                        |               |              |         |
| White                                 | Reference     |              |         |
| African American                      | 5.525         | −1.281, 12.332| 0.103   |
| African Caribbean                     | 1.711         | −5.984, 9.406| 0.639   |
| Hispanic/Other                        | 3.002         | −8.678, 14.682| 0.588   |
| Education                             |               |              |         |
| ≤High school                          | 0.492         | −6.070, 7.053| 0.874   |
| Some college/associate degree         | −1.411        | −7.427, 4.604| 0.621   |
| Bachelor, master, doctoral degree     | Reference     |              |         |
| Body mass index (kg/m²)               | −0.089        | −1.323, −0.462| 0.001   |

More recent studies that assessed serum 25(OH)D levels in relation to MD have reported null findings [7-11]. One study found that women in the highest quartile of serum 25(OH)D had the lowest density measurements, although no significant relationship between serum 25(OH)D levels and MD was reported [7]. No association was found between circulating levels of 25(OH)D and MD among postmenopausal women in the Nurses’ Health Study. However, women in the highest tertile of MD and lowest tertile of plasma 25(OH)D had a 4-fold increased risk of breast cancer compared to women with the lowest MD and highest plasma 25(OH)D [9].

A limitation of all of these studies was that the blood collections for serum 25(OH)D and mammograms were...
not conducted at the same time point (with time intervals varying from 1–8 years), unlike our study in which the blood sample and mammograms were collected on the same day. Although most studies adjusted for time between blood draws and mammograms, this may not account for the seasonal variation in vitamin D status. Brisson et al. reported synchronized seasonal variations of MD and 25(OH)D blood levels, demonstrating that the lowest breast density was observed in early December, approximately 4 months after peak serum 25(OH)D [8]. During July-December when serum 25(OH)D are at their highest levels, we observed an inverse association between vitamin D status and dense area.

We measured serum 25(OH)D in batched archived blood samples using the well-validated Diasorin radioimmunoassay. Prior research has demonstrated that circulating 25(OH)D is very stable in serum with long-term storage [21]. There is increasing use of LS-MS technology, which allows for quantification of 25(OH)D$_2$ and 25(OH)D$_3$ separately. However, the clinical utility of separately measuring D2 and D3, as opposed to total 25(OH)D, is uncertain [21].

Percent density is a measurement of the dense breast tissue relative to non-dense, primarily fat tissue, and as such percent density partly accounts for differences in breast size. However, it may underestimate MD in obese women with large amounts of fat. We also assessed dense area and non-dense area, which were only evaluated in four other studies as measures of MD [7,10,11,15]. Given that the mean BMI of our study population was relatively high at 29.2 kg/m$^2$, dense area may be a more accurate way of assessing breast cancer risk in these women. Obesity has been positively associated with postmenopausal breast cancer risk [22] and is also inversely related to vitamin D status. People who are overweight and obese have a higher prevalence of vitamin D deficiency compared to lean individuals due to decreased bioavailability of fat-soluble vitamin D and sequestration in adipose tissue [23].

The main limitation of our study is the relatively small sample size. Strengths of our study include the large African American sample, comprehensive examination of risk factors, adjustment for season, use of an objective measure of vitamin D exposure, collection of blood and mammograms at the same time point, and assessment of three different measures of MD. In particular, dense area is less studied and may be more relevant in a study population with a high prevalence of obesity.

In conclusion, serum 25(OH)D status, a potentially modifiable breast cancer risk factor, was not associated with MD in this cross-sectional study. However, we did observe an inverse association with dense area based upon season, which needs to be replicated in larger studies. Since a one-time measurement of serum 25(OH)D may not reflect lifetime exposure to vitamin D, future prospective studies should examine changes in vitamin D exposure over time in relation to MD and breast cancer risk, since few longitudinal studies to date have documented changes in vitamin D status with changes in MD over time [24].

**Abbreviations**

BMI: Body mass index; CUMC: Columbia University Medical Center; IGF-1: Insulin-like growth factor-1; IGFBP-3: Insulin-like growth factor binding protein-3; LICH: Long Island College Hospital; MD: Mammographic density; NSABP: National surgical adjuvant breast and bowel project; WHI: Women’s health initiative; 25(OH)D: 25-hydroxyvitamin D.

**Competing interests**

The authors have no potential competing interests to disclose.

**Authors’ contributions**

DR participated in the design and coordination of the study and helped to draft the manuscript. JC participated in the design and coordination of the study and drafted the manuscript. JDF conducted the mammographic density measurements, participated in the design and coordination of the study and helped to draft the manuscript. KDC conceived of the study, participated in its design and coordination and drafted the manuscript. LF participated in the design and coordination of the study and helped to draft the manuscript. MBT conceived of the study, participated in its design and coordination, and drafted the manuscript. PT participated in the design and coordination of the study and helped to draft the manuscript. YL performed the statistical analysis, participated in the design and coordination of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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