Synchronized Seasonal Variations of Mammographic Breast Density and Plasma 25-Hydroxyvitamin D

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Abstract

Background: **Dietary vitamin D has been associated with lower mammographic breast density, a strong biomarker for breast cancer risk. Blood 25-hydroxyvitamin D [25(OH)D] is an integrated measure of vitamin D status (from food, supplements, and sun exposure) and varies with season. Our objective was to assess seasonal variations of breast density and compare such variations, if any, with that of 25(OH)D.**
Methods: **This cross-sectional study includes 741 premenopausal women recruited at screening mammography. Plasma 25(OH)D at recruitment was measured by RIA. Breast density was evaluated using a computer-assisted method. Seasonal variations were modeled using multivariate linear regression and semi-parametric cubic smoothing splines.**
Results: **Season was strongly associated with 25(OH)D ($P < 0.0001$). The highest smoothed mean 25(OH)D levels were seen at the end of July (81.5 nmol/L) and the lowest in mid-April (52.4 nmol/L). Breast density showed modest seasonal variations ($P = 0.028$). The lowest smoothed mean breast density was observed in early December (38.5%) and the highest at the beginning of April (44.3%). When a 4-month lag time was presumed, seasonal variations of breast density appeared to be a mirror image of those of 25(OH)D, and the correlation of daily smoothed estimates of mean breast density and 25(OH)D was negative and strong ($r = -0.90$).**
Conclusion: **In premenopausal women, changes in blood vitamin D seem to be inversely related to changes in breast density with a lag time of about 4 months. This finding encourages further investigation of the possibility that vitamin D could reduce breast density and breast cancer risk.** (Cancer Epidemiol Biomarkers Prev 2007;16(5):929–33)

Introduction

Vitamin D may reduce incidence and mortality for several cancer sites, including breast cancer, but the evidence is still inconclusive (1-4). Mammographic breast density is one of the strongest breast cancer risk indicators (5) and is a promising intermediate biomarker for this disease (6, 7). In most (8-12), although not all (13, 14), studies, breast density was seen to be lower among women with high dietary vitamin D intakes, and this relation was often more apparent among premenopausal women (8-12).

Blood 25-hydroxyvitamin D [25(OH)D] is the principal circulating vitamin D metabolite and the best biomarker of total exposure to vitamin D (ingested from food or supplements, or produced by the skin after sun exposure; ref. 15). In a recent study by Knight et al. (16), breast density was not related to circulating 25(OH)D.

Circulating 25(OH)D is strongly season dependent (reviewed in refs. 2, 17), especially at higher latitudes. Thus, our objective was to examine whether breast density varied with season and whether the seasonal variations in breast density, if observed, were synchronized with those of 25(OH)D among premenopausal women. However, if variations in 25(OH)D levels are associated with variations in breast density, a delay (lag time) is likely between a change in 25(OH)D levels and the resulting change in breast density. Thus, seasonal variations of breast density (if present) may not be simultaneous to those of 25(OH)D but may be synchronized with the seasonal variations of 25(OH)D, with a delay between the two seasonal curves equal to the lag time.

Materials and Methods

Study Population and Recruitment Procedures. The study design and methods have been published elsewhere (10, 18). Study subjects were women recruited at screening mammogram in one private radiology clinic in Quebec City between February and December 2001. Eligible women had no personal history of cancer or breast surgery, no endocrine diseases, never took selective estrogen receptor modulators, and had not used oral contraceptives or hormone replacement therapy in the last 3 months before mammography. Among the 777 eligible premenopausal women (10), 741 provided written informed consent to use their blood samples for assays other than the ones planned at recruitment. This study was approved by a Research Ethics Committee.

Data Collection. Anthropometric measurements and blood samples (20 mL) were taken at recruitment. Known or suspected breast cancer risk factors were documented by telephone interview, including reproductive and menstrual history, family history of breast cancer, personal history of breast biopsies, past use of exogenous hormones, smoking status, alcohol intake, education, and physical activity. Finally, diet was assessed with a self-administered food frequency questionnaire.

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Table 1. Relation of vitamin D intake, leisure-time physical activity, and season to plasma 25(OH)D in premenopausal women

Vitamin D sources	β*	P
Vitamin D intake (IU/d)		
From food	0.028	<0.001
From supplements †	0.014	<0.001
Leisure-time physical activity (MET-hour/wk)	0.168	<0.001
Season †		
Spring	4.012	0.054
Summer	20.988	<0.001
Fall	4.736	0.026
Winter (reference)	—	

*β values are estimated from linear regression analysis [25(OH)D is treated as a continuous variable]. β values represent absolute mean difference in nmol/L of plasma 25(OH)D for increments of 1 IU vitamin D intake, 1 MET-hour/wk of physical activity, or for blood collected in spring, summer, or fall compared with winter (adjusted mean in winter, the season of reference, is 57.0 nmol/L). β values are estimated from a model that included age (y), body mass index (kg/m^2), and all variables in the table. $P_{season} < 0.0001$ (3 degrees of freedom).
†The number of women who took vitamin D supplements was 190. The number recruited in spring, summer, fall, and winter was 249, 184, 218, and 90, respectively.

Assessment of Mammographic Breast Density. Breast density was assessed by one reviewer (C.D.) using a computer-assisted method without information on women (18). Breast density is the proportion of the breast projection showing tissue density on one randomly selected craniocaudal view for each woman. The within-batch intraclass correlation coefficient was 0.98, and the between-batch coefficient of variation was 4%.

Assessment of Plasma 25(OH)D. At time of collection, blood constituents were rapidly aliquoted and stored at −80°C until analysis. Plasma 25(OH)D was measured between November 2005 and January 2006 by Dr. E. Delvin (Ste-Justine Hospital, Montreal, Canada), who participated in the international 25-Hydroxyvitamin D External Quality Assessment Scheme (DEQAS) and met the performance target set by the DEQAS Advisory Panel in 2004 to 2005. Plasma 25(OH)D levels were measured by RIA following acetonitrile extraction (DiaSorin Laboratories). The intra-batch and between-batch coefficients of variation were 7.3% and 8.8%, respectively (four blinded duplicates on average for each of the 24 batches).

Statistical Analysis. The association of plasma 25(OH)D with dietary vitamin D intake, leisure-time physical activity, and season of recruitment (proxy variables for sun exposure) was evaluated using multivariate linear regression, adjusting for age at recruitment and body mass index. The association of breast density with season was also examined using multivariate linear regression, adjusting for age and body mass index. The overall associations of season with 25(OH)D and breast density were assessed using an ANOVA type III test. Adjusted means in 25(OH)D levels and breast density by season were estimated by use of ANOVA.

Seasonal variations of plasma 25(OH)D and breast density were further examined separately using semi-parametric cubic smoothing splines fitted with SAS GAM Procedure (19). For plasma 25(OH)D or breast density as the response variables, semi-parametric cubic smoothing splines were used to model the effect of date of recruitment (20), adjusting for age at recruitment and body mass index. This approach allowed the estimation of smoothed mean plasma 25(OH)D and breast density from February to end of December 2001 (the recruitment period, 319 days). To extrapolate smoothed values for the beginning of 2001 (36 days), we assumed that the plasma 25(OH)D and breast density observed in December 2001 were representative of those in December 2000. To extrapolate smoothed values for the end of 2001 (10 days), we assumed that the plasma 25(OH)D and breast density observed in February 2001 were representative of those in February 2002. Seasonal variations of 25(OH)D and breast density were comparable when using moving averages or locally weighted smoothing regression models (21).

Seasonal variations of smoothed mean breast density were compared with those of smoothed mean plasma 25(OH)D visually and quantitatively with and without assuming lag time. Lag time was estimated by the delay between the day with the highest value of smoothed mean daily 25(OH)D and the subsequent day with the lowest smoothed mean breast density. To assess visually the synchronization of the seasonal curves, taking lag time into consideration, the seasonal curve for breast density was shifted backward in time by a number of days equal to the estimated lag time. This shift required the assumption that the seasonal variations of breast density estimated for the year of recruitment are representative of the seasonal variations of breast density of the subsequent year. To assess quantitatively the degree of synchronization of the seasonal curves, we calculated the correlation coefficient between the 365 smoothed mean daily values of breast density and the 365 smoothed mean daily values of 25(OH)D predicted by the spline models.

All statistical analyses were carried out using SAS version 9.1.3 (SAS Institute, Inc.) software system.

Results

The study population is described elsewhere (10). Briefly, the 741 premenopausal women were 46.8 (SD 4.6) years of age on average at recruitment. In the year before recruitment, mean ± SD daily vitamin D intake from food was 185 ± 117 IU; 25.6% of women reported vitamin D intake from supplements. Mean energy expenditure through leisure time physical activity was 27.2 ± 22.2 MET-hour/wk. At recruitment, mean plasma 25(OH)D was 65.0 ± 19.6 nmol/L.

Plasma 25(OH)D was related to vitamin D from food and supplements, leisure-time physical activity, and season (Table 1). These factors explained 24% of the variability in plasma 25(OH)D. Season was the strongest contributor to this variability (15.4%); mean ± SE plasma 25(OH)D was much higher among women recruited in summer (78.0 ± 1.2 nmol/L) compared with winter (57.0 ± 1.8 nmol/L). Vitamin D from food, supplements, and leisure-time physical activity explained 2.7%, 1.9%, and 4.2% of the variability in plasma 25(OH)D, respectively. Smoothing splines allow examination of seasonal variations in more detail (Fig. 1A). Smoothed mean plasma 25(OH)D tended to increase slightly until the end of February but then dipped until mid-April. Subsequently, mean plasma 25(OH)D increased progressively to reach its highest levels at the end of July and then decreased progressively until the end of November.

In multivariate regression, mean breast density also varied with season (P = 0.028; Table 2). Mean breast density was lowest in the fall (39.4%) and highest in spring (44.8%, β = 5.44%, P = 0.003). Smoothing spline analysis showed that smoothed mean breast density increased sharply through the beginning of April (Fig. 1B). From April to June, mean breast density was relatively stable. In June, mean breast density dipped slightly, increased in August, and then decreased progressively to its lowest levels at the beginning of December.

The highest levels of smoothed mean plasma 25(OH)D were experienced at the end of July, and the lowest smoothed mean breast density was seen at the beginning of December; thus, a lag time of about 4 months (135 days) seemed possible. Actually, there are four major inflections in the 25(OH)D curve (February 27, April 15, July 28, and November 26; Fig. 1A), and each of these matches an inflection of the breast density curve (Fig. 1B) in the opposite direction with delays between each of

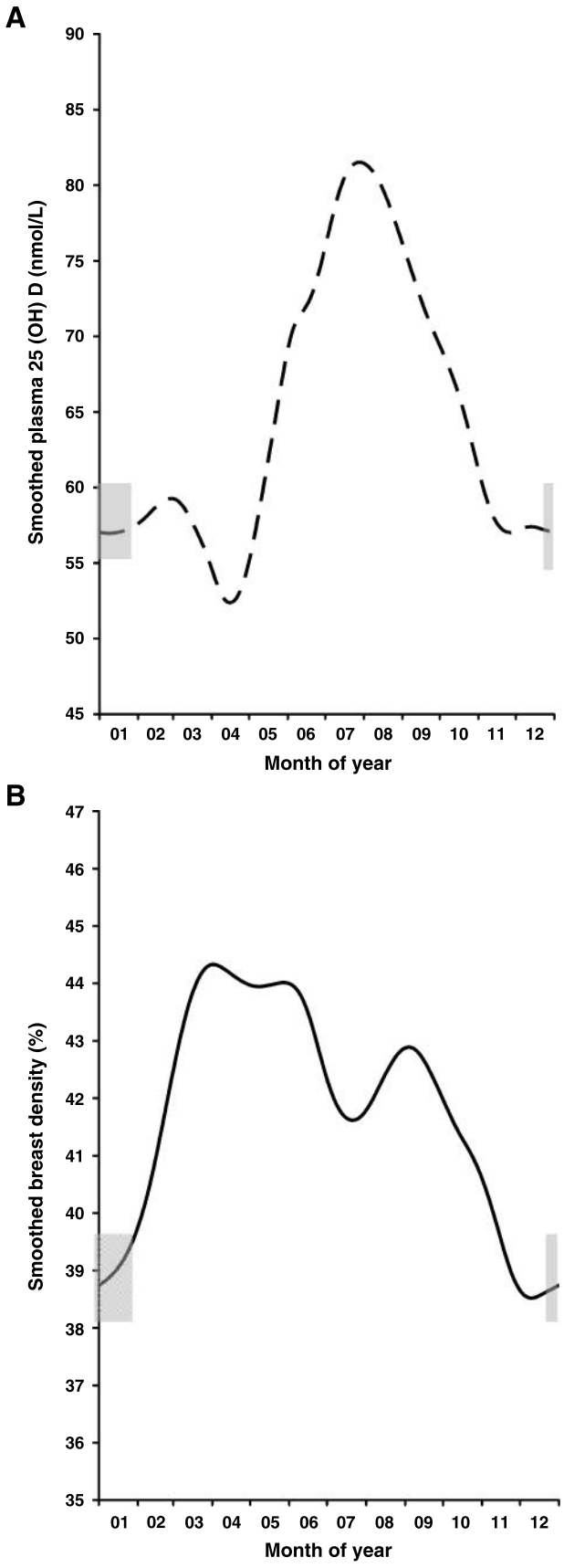

Figure 1. Seasonal variations of (*A*) smoothed plasma 25(OH)D and (*B*) smoothed breast density. The 25(OH)D curve (*dotted line*) and the breast density curve (*plain line*) refer to variations from January to December 2001. Extrapolated smoothed values for the 36 d at the beginning and 10 d at the end of 2001 are in the gray zones.

the inflections in the 25(OH)D curve and the corresponding inflections of the breast density curve of 144, 142, 135, and 127 days, respectively (average delay, 137 days).

Figure 2 simulates the superposition of the seasonal curves of 25(OH)D and breast density after shifting the breast density curve backward by 135 days (i.e., after presuming a 135-day lag time). The seasonal variations in the smoothed mean plasma 25(OH)D and the smoothed mean breast density seem remarkably synchronized. When no lag time is presumed, the two seasonal curves seem unrelated. Then, the correlation coefficient between smoothed mean breast density estimates for the 365 days of the year and the corresponding smoothed mean plasma 25(OH)D was positive rather than negative and relatively weak ($r = 0.21$, $R^2 = 0.04$). In contrast, after presuming a lag time of 135 days, the correlation between smoothed mean breast density and smoothed mean plasma 25(OH)D was negative and very strong ($r = -0.90$, $R^2 = 0.81$).

Confounding was explored. All results remained essentially unchanged when adjustments were made for a large set of potential confounders, including age at menarche, number of full-term pregnancies, age at first full-term pregnancy, duration of breast-feeding, duration of past use of oral contraceptives, duration of past use of hormonal replacement therapy, phase of the menstrual cycle, alcohol intake in the past year, mean daily caloric intake in the past year, family history of breast cancer in first degree relative, personal history of breast biopsies, smoking status, education, physical activity, dietary intakes of vitamin D and calcium in the past year and levels of insulin-like growth factor-I (IGF-I). For instance, with this full model, the difference in breast density comparing spring with fall remained essentially unchanged ($\beta = 5.25\%$, $P = 0.0056$). However, when level of IGFBP-3, the main binding protein for IGF-I, was added to the above list of variables in the model, the difference in breast density between fall and spring decreased slightly and remained statistically significant ($\beta = 4.54\%$, $P = 0.017$), but the overall effect of season was also slightly reduced and P increased to 0.11. Further adjustment for IGFBP-3 had little or no effect on other results.

Discussion

In this study of premenopausal women, breast density varied with season. Moreover, the seasonal variations of breast density were a mirror image of the seasonal variations of plasma 25(OH)D when a lag time of about 4 months was presumed.

Lag time could be a critical concept when assessing the relation of changes in circulating 25(OH)D to changes in breast density. Not taking lag time into consideration may explain why no relation was seen between circulating 25(OH)D and breast density in the study of Knight et al. (16). These authors (16) assessed circulating levels of 25(OH)D at variable and

Table 2. Relation of season to mammographic breast density in premenopausal women

Season*	β †	P
Spring	5.44	0.003
Summer	2.11	0.291
Fall (reference)	—	0.118
Winter	3.91	

*The number of women recruited in spring, summer, fall, and winter was 249, 184, 218, and 90, respectively.

†β values are estimated from linear regression analysis; breast density is treated as a continuous variable. β values represent absolute mean difference in breast density comparing winter, spring, or summer with fall (the adjusted mean in fall, the season of reference, is 39.4%). β values are adjusted for age (y) and body mass index (kg/m^2). $P_{season} = 0.028$ (3 degrees of freedom).

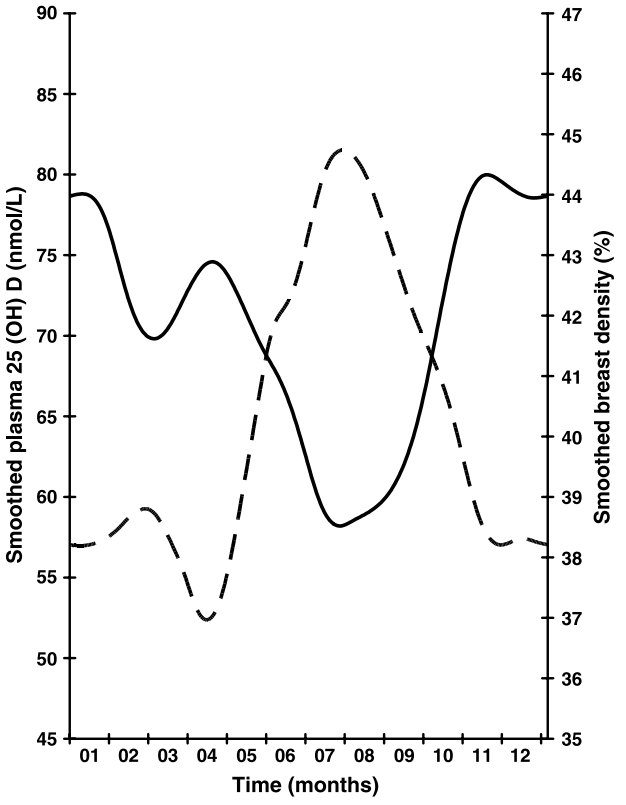

Figure 2. Superposition of seasonal variations of smoothed mean plasma 25(OH)D and smoothed mean breast density presuming a 135-d lag time. The 25(OH)D curve (*dotted line*) present variations from January to December of a given year, and the breast density curve (*plain line*) refers to variations from mid-May of a given year to mid-May of the subsequent year.

sometimes considerable times after the mammograms (within 1 year in 73% women and >1 year but within 4 years in 27% of women).

This study further supports the idea that vitamin D can affect breast density independently of calcium intake. In most previous reports, the relation of dietary vitamin D intake to breast density was studied (8-10, 12). In such studies, separation of effects of vitamin D from those of calcium was difficult because the main dietary sources of both of these nutrients (fortified dairy products) are the same. In this population, seasonal variations in breast density cannot be attributable to variations in calcium intake. Indeed, calcium intake did not vary with season and adding calcium intake in the model did not explain seasonal variations of breast density.

These data provide an idea of the possible strength of the relation of 25(OH)D to breast density among premenopausal women. In linear regression analysis, the difference in 25(OH)D between winter and summer is 21 nmol/L (corresponding roughly to an increase in daily intake of about 1,000 IU of vitamin D_3; ref. 22), whereas the seasonal difference of breast density comparing fall and spring is 5.4%. The clinical and public health significance of reductions in breast density remains to be determined. However, according to our previous data (10), the difference in breast density seen in women who have a child before age 20 compared with nulliparous women reaches 5.3%. Women who have had at least one child before age 20 have been reported to experience a 50% reduction in their breast cancer risk compared with nulliparous women (23). Thus, even modest changes in breast density may be significant.

Several aspects of this study may have facilitated the detection of the synchronized seasonal variations in plasma 25(OH)D and breast density. First, a relatively large number of women were recruited within a short period of time in a single mammography clinic. Thus, all women resided in a relatively limited geographic area and were exposed to similar climatic conditions during the study period. Second, Quebec City is located at northern latitudes (46°48′ N), and its residents experience substantial variations in sunlight exposure. Third, 95% of this population is composed of people of European descent who have low skin pigmentation and thus are more responsive to sunlight exposure (24). Fourth, all women were recruited in one radiology clinic performing high-quality mammography reducing variation in breast density related to technical factors. Finally, the high quality of our measurements of breast density and plasma 25(OH)D was also an advantage.

To our knowledge, this is the first report on seasonal variations of breast density and of its possible synchronization with seasonal variations of 25(OH)D. Thus, our findings need confirmation. In our view, the tight synchronization of the seasonal variations of breast density and 25(OH)D is unlikely to be due to selection and information biases because a continuous series of women was recruited without reference to breast density, season or 25(OH)D levels, and measurements of breast density were made without knowledge of 25(OH)D and vice versa. The principal limitation of this study is its cross-sectional nature. Cross-sectional studies are generally not well suited to examine issues such as lag time. Current findings provide an incentive to elaborate studies with stronger designs that could better evaluate the issue of lag time in the association of changes in 25(OH)D with those in breast density. The possibility of residual confounding cannot be completely excluded. Availability of information on many potential confounders does reduce concerns about confounding. However, some biological phenomena other than 25(OH)D vary with season, and these could perhaps explain findings. For instance, seasonal variations of melatonin levels that can affect cellular proliferation (25) have been reported. Moreover, addition of IGFBP-3 in the model reduced the strength of the association of breast density with season. However, the *IGFBP-3* gene has a vitamin D responsive element, and in laboratory studies, vitamin D can increase IGFBP-3 expression (26-29). Thus, IGFBP-3 may be in the causal pathway of 25(OH)D to breast density and perhaps should not be considered a confounding factor. Finally, observed seasonal variations of breast density, if real, may be generalizable only to premenopausal women of European descent with low skin pigmentation and living at high latitudes. Whether other premenopausal women, women of other racial/ethnic backgrounds, or postmenopausal women experience seasonal variations in breast density needs to be assessed.

In conclusion, this study provides some support for the idea that circulating vitamin D is inversely related to breast density among premenopausal women. Future studies of the relation of variations in vitamin D status to variations in breast density should take lag time into account.

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