Published in final edited form as:
Menopause. 2010 ; 17(6): 1152–1160. doi:10.1097/gme.0b013e3181e102d9.

Dietary vitamin D and calcium intake and mammographic density in postmenopausal women

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Abstract

Objectives—Dietary intake of vitamin D and calcium may be related to risk of breast cancer, possibly by affecting mammographic density. However, the few studies that have evaluated the association between these nutrients and mammographic density in postmenopausal women have had inconsistent results.

Methods—We conducted a cross-sectional analysis in 808 participants of the Mammogram Density Ancillary Study of the Women's Health Initiative. Mammographic percent density was measured using baseline mammograms taken prior to randomization of participants in the intervention trials. Vitamin D and calcium intake was assessed with a validated food frequency questionnaire and an inventory of current supplement use both completed at baseline.

Results—After adjustment for age, body mass index, regional solar irradiance and other factors, we did not find a relationship between vitamin D or calcium intake and mammographic density. Mean mammographic percent density in women reporting total vitamin D intakes of <100, 100-199, 200-399, 400-599, ≥600 IU/day were 5.8%, 10.4%, 6.2%, 3.8%, and 5.1%, respectively (P-trend = 0.67). Results in women reporting total calcium intake of <500, 500-749, 750-999, 1000-1199, and ≥1200 mg/day were 7.3%, 4.9%, 7.3%, 6.9%, and 7.l%, respectively (P-trend = 0.51). We did not observe effect modification by overall level of mammographic density or solar irradiance, but

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Conflict of interest: The University of North Carolina Breast Imaging Lab has contractual research agreements with General Electric, Sectra, VuComp, and Real Imaging.

supplemental vitamin D use was associated with lower density in younger women (P-interaction=0.009).

Conclusions—These findings do not support a relationship between dietary vitamin D or calcium intake and mammographic density in postmenopausal women. Additional studies should explore these associations in women of different ages and in relation to serum vitamin D levels.

Keywords

vitamin D; calcium; mammography; breast neoplasms; mammography

INTRODUCTION

Mammographic density has been identified as a strong predictor of breast cancer risk. Relative risks of breast cancer for women with high percent density (i.e., ≥ 50-75% fibro-glandular tissue) compared to those with relatively lower density (i.e., < 25%) have ranged from 2.0-6.0 in recent studies.[1,2] These associations appear to apply to both premenopausal and postmenopausal breast cancer. Given the consistency of evidence and the strong magnitude of the associations observed, mammographic density may be an intermediate biomarker of breast cancer and has been used as a surrogate endpoint for breast cancer risk in some studies.[1,3]

Some evidence suggests that vitamin D may be inversely related to risk of breast cancer.[4,5] *In vitro* studies indicate that vitamin D can inhibit cell proliferation and promote apoptosis and cell differentiation in breast tumor tissue.[6-8] Results from observational studies of vitamin D and breast cancer risk have been inconsistent. While some studies have found high dietary vitamin D intake and/or high 25-hydroxyvitamin D levels to be protective against risk of postmenopausal breast cancer,[9-15] others have reported a borderline association[16] or no association.[17-22] Studies in premenopausal women have more consistently reported an inverse relationship,[18,20,23,24] but overall results have also be inconclusive. A large randomized trial in the Women's Health Initiative, which compared daily intake of 1000 mg of elemental calcium plus 400 IU of vitamin D_3 per day to placebo, did not find that supplementation reduced risk of postmenopausal breast cancer over 7 years.[21] A second smaller trial of postmenopausal women reported that overall cancer incidence was significantly reduced after 4 years of supplementation with 1400-1500 mg of elemental calcium plus 1100 IU of vitamin D_3 per day, [2] but too few cases of breast cancer (n=19) occurred during follow-up to separately evaluate effect of intervention on this cancer.

Only a small number of studies have considered whether vitamin D and calcium intake may be related to breast cancer risk through a relationship to mammographic density. Results have been inconsistent, with inverse relationships between dietary vitamin D, 25-hydroxyvitamin D (25(OH)D) levels and/or calcium and postmenopausal mammographic density observed in some[26-30] but not all[31-36] studies. Results from these analyses have raised several interesting questions warranting further investigation. For example, it is not clear whether vitamin D and calcium from foods and from supplements are similarly related to mammographic density. In addition, factors such as regional solar irradiance, season, and duration of supplement use may modify this relationship and yet have been infrequently considered. Therefore, we conducted a cross-sectional analysis of the relationship between mammographic density and dietary vitamin D and calcium intake in the Women's Health Initiative, a diverse and well-characterized population of postmenopausal women.

METHODS

Study population

The Women's Health Initiative randomized clinical trials of postmenopausal hormones have been described in detail previously.[37-39] Briefly, between 1993 and 1998, women age 50-79 years of age were recruited through direct mailing campaigns and media awareness programs. Enrollments were made at 40 clinical centers throughout the US. Major ineligibility criteria for the trials included medical conditions likely to result in death within 3 years, previous history of breast or other cancers (except non-melanoma skin cancer), and conditions likely to interfere with adherence and retention, including alcoholism and dementia. Ultimately, 16,608 women who had not had a hysterectomy were randomized to 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate per day in a single table or a similar placebo (E+P trial). An additional 10,739 women without a uterus were randomized to 0.625 mg conjugated equine estrogen daily or a similar placebo (E-alone trial).

At baseline enrollment visits prior to randomization, participants completed questionnaires that assessed a variety of demographic, reproductive, behavioral and health factors. Participants were required to have evidence of a screening mammogram within 6 months prior to randomization or were referred for a screening mammogram before they were randomized. The study protocol was approved by institutional review boards at each participating institution.

WHI Mammogram Density study

The Mammogram Density Ancillary Study of the WHI hormone trial has been described in detail previously.[40] Briefly, this ancillary study enrolled women from both the E+P and E-alone trials to evaluate the effect of postmenopausal hormones on mammographic density. Fifteen of the 40 clinical centers agreed to participate. Women who had a baseline mammogram taken prior to randomization and at least one follow-up mammogram 1-2 years later were eligible to join. The WHI Clinical Coordinating Center identified eligible women and selected those for inclusion in this ancillary study using a stratified random sampling protocol, with the goal of enrolling equal numbers of non-Hispanic white, African American, Hispanic, and Asian American women. Among E+P trial participants, 214 of the 233 women sampled from those assigned to E+P and 223 of the 240 women sampled from those assigned to placebo agreed to join in the mammogram density study. Complete mammogram data showing no evidence of invasive breast cancer were received from 202 women assigned to E+P and 211 assigned to placebo. Among E-alone trial participants, 220 of the 234 women sampled from those assigned to E-alone and 238 of the 264 women sampled from those assigned to placebo agreed to join in the mammogram density study. Complete mammogram data showing no evidence of invasive breast cancer were received from 209 women assigned to E-alone and 226 assigned to placebo. Ultimately, 808 women were included in the present analysis.

Assessment of mammographic density

After receiving informed consent, mammograms from each participant were requested from their individual mammography provider, blinded as to participant identification, and then sent to the University of North Carolina for digitizing. Mammograms were taken within the 6 months prior to randomization for 805 (99.6%) women; for the other 3 (0.4%) women, the mean time between mammogram and randomization was 12 months.

Digitizing of films was performed on a Lumisys 85 laser digitizer with a maximum resolution of approximately 50 μm and 12-bit depth, with the digitizer recalibrated between sessions. A standard data-averaging method was used to convert raw image files to bitmap format for display and measurement of mammographic density. For each film, a unique serial number,

the date of exam, laterality and view were recorded. The technique used to assess mammographic density has been validated previously[41] and used a computer-assisted interactive thresholding technique with software from the Imaging Research Program (Sunnybrook Health Science Center, Toronto, Ontario, Canada).

Mammograms were sorted separately for 2 trained observers (CM, JP), who both reviewed all films. Inter-observer reliability for measuring percent density was assessed before the study began and found to be very high (i.e., intraclass correlation coefficients >0.92). Observers were blinded to participant identification, randomization status, the timing of the mammogram (baseline vs. follow-up), result from the other observer, and results of other mammograms from the same woman. The craniocaudal view of the right breast was used if available, otherwise the same view from the left breast was used. Investigators determined the breast edge and noncontinguous areas of mammographic density. The total area of breast and the total combined area of mammographic density were both calculated (pixels), and then the latter was divided by the former to calculate percent density. Each participant's density was then calculated as the mean of the estimates of percent density from the 2 readers.

Assessment of vitamin D and calcium intake and other factors

At their baseline clinic visit, participants completed a semiquantitative food frequency questionnaire (SFFQ) designed for the Women's Health Initiative and validated in this population.[42] Participants were asked to report their usual intake of 122 foods or food groups in the 3 previous months, with response options ranging from never or less than once per month to ≥2 times per day (≥6 times per day for beverages). Women were also asked to specify their usual portion size compared to a stated medium size serving for each food. Additional questions asked about usual cooking method, fats added during cooking, and usual intake of specific food groups.

Vitamin D and calcium intakes from food sources were calculated by multiplying the nutrient content of the specified portion size of each food (University of Minnesota Nutrient Coding Center nutrient database) by its frequency of consumption and summing the contributions of all foods. Nutrient intakes were adjusted for total energy intake, also measured by SFFQ, by the residual method.[43]

Information on the use of vitamin and mineral supplements, including those containing vitamin D and calcium, was also collected at the baseline clinic visit. Women were interviewed about their use of supplements by trained interviewers using a standard questionnaire. Participants were also asked to bring all supplements they were currently taking to their clinic interview, where the interviewer recorded the dose, frequency (pills per week), and duration (months and years) of use for multivitamins, multivitamin-mineral, and single supplements. Interviewers also directly recorded the ingredients of all supplements provided. Only supplements used once per week or more were recorded.

Study questionnaires completed during baseline visits were used to assess breast cancer risk factors, including age, race/ethnicity, previous use of hormone therapy and oral contraceptives, education, alcohol intake, participation in physical activity, history of smoking, and age at menarche. Weight and height were measured directly and used to calculate body mass index (weight (kg) / height (m) squared). Annual evel of solar irradiance in Langleys (gm-cal) per cm^2 at each clinical center was estimated using measurements from the US Weather Bureau and were adapted for use in the WHI.[44]

Statistical analysis

All analyses were based on mammograms collected at baseline before study participants were randomized to hormone therapy, dietary modification or calcium and vitamin D (i.e., CaD trial) interventions. We excluded from analysis 40 women with implausible calorie intake (<600 and >5000 kcal/day). Differences in mean total vitamin D and total calcium intake by participant characteristics at baseline were compared, along with p-values from F-tests in a linear model adjusted for age and ethnicity. The study population was divided into categories of nutrient intake (calcium and vitamin D), and to be consistent with previously published work,[40] we present arithmetic means. Since mammographic density of our sample was skewed, statistical tests were performed on the log scale across categories of nutrient intake using linear models. This analysis was repeated for vitamin D from food sources and supplements separately, and for the three aspects of calcium intake (i.e., total, and food and supplements separately). We also cross-classified participants by collapsed categories of vitamin D and calcium level, and assessed interaction between nutrients using a multiplicative interaction term in the multivariable model.

In addition to adjusting for age, we used multivariable analyses to adjust for factors determined to be important confounders of the nutrient -- mammographic density relationship and those that have been identified as confounders in previous studies in the literature. We evaluated three specific multivariable models. Model 1 was adjusted for factors associated with breast cancer, mammographic density and/or vitamin D and calcium intake. These included: age (models included categories of 50-59, 60-69, 70-79 years, and a continuous variable); race/ethnicity (Asian/Pacific Islander, Black, Hispanic; White not of Hispanic origin); duration of self-reported past hormone therapy use at baseline (0, <5, 5-<10, ≥10 years), education (school after high school); body mass index (models included categories of <25, 25-<30, ≥30 kg/m^2 and a continuous variable); alcohol intake (0, ≤1, >1 drink per day); hours per week of moderate-to-strenuous physical activity (tertiles); smoking status (never, former, current); age at menarche (≤12, 12-13, ≥14 years); parity (0, 1, 2, ≥3), family history of breast cancer (no, yes); Gail risk score (models included tertiles of score and a continuous variable), duration of oral contraceptive use (0, <5, 5-<10, ≥10 years), and total calories (models included tertiles of intake and a continuous variable). We adjusted for hormone treatment assignment (E+P, E+P placebo, E-alone, E-alone placebo) because, in addition to mammographic density, baseline vitamin D and calcium intake varied by treatment arm. We also adjusted for multivitamin use (no, yes) because previous studies have reported significant differences in behaviors related to vitamin D level and mammographic density in women who do and do not use multivitamins. Model 2 adjusted for all factors in model 1, and additionally, calcium and vitamin D were adjusted for the effects of the other nutrient, and nutrients from food sources were also adjusted for the effects of nutrients from supplements, and vice versa. Model 3 adjusted for all factors included in models 1 and 2, and in addition controlled for factors associated with endogenous vitamin D production including season of mammogram (winter, spring, summer, fall) and solar irradiance at each participant's WHI clinic location (<350, 350-< 400, ≥400 Langleys). Models 1 through 3 were weighted to account for sampling design. Weights are inversely proportional to the probability of being selected from the clinical trial into the Mammogram Density Ancillary Study and are estimated from a logistic regression model. Predictor variables included the sampling strata variables (i.e., race/ethnicity and hysterectomy status), age and prior hormone use.

We investigated whether the effects of vitamin D (total, dietary and supplemental) and calcium (total, dietary and supplemental) were modified by age, race/ethnicity, body mass index, smoking status, duration of supplement use, alcohol use, and solar irradiance at each participant's clinical center, as has been suggested by previous studies. Interactions were assessed using multiplicative interaction terms in multivariable models. Interactions with p-

values < 0.05 were judged to be statistically significant; two significant interactions were expected due to chance.

To evaluate whether a nutrient-density relationship was more evident in women with higher percent density, we classified women by overall category of mammographic percent density at baseline (<1%, 1 – 9%, ≥ 10%). Finally, we conducted a subanalysis excluding women reporting multivitamin use and those reporting hormone treatment at baseline.

RESULTS

Participant characteristics by mean total vitamin D and calcium intake are presented in table 1. Vitamin D and calcium intake were each significantly and positively associated with age, education, and physical activity level. Intakes of both nutrients varied significantly by race/ethnicity and by hormone trial. Vitamin D and calcium intakes were inversely related to level of solar irradiance, and calcium intake varied by smoking status.

In multivariable models adjusting for age, smoking and breast cancer risk factors (model 1), we did not observe a relationship between total intake of vitamin D and baseline mammographic density (table 2). Mean percent mammographic density by increasing categories of total vitamin D intake were 5.4%, 9.8%, 6.2%, 4.0% and 5.7%, respectively (P for trend = 0.96). Results from models further adjusted for calcium intake (model 2) and for Langleys and season of mammogram (model 3) were similar. We observed evidence of a modest positive association between vitamin D from food sources and mammographic density (P for trend = 0.05). Vitamin D supplement use was unrelated to mammographic density.

We did not find a relationship between mammographic percent density and total calcium intake, calcium from foods sources only or calcium from supplements (table 2). For example, mean mammographic percent density in women reporting total calcium intake of ≥1200 mg/day was 6.4% (95% CI = 4.7-8.1; P for trend = 0.42).

When total vitamin D and calcium intake were assessed together (table 3), we did not observe an interaction between nutrients (P for interaction = 0.99). Density was lowest in women reporting 200-399 IU/day of vitamin D and <750 mg/day of calcium (2.4%; 95% CI = 0.0–5.7), and highest in those reporting <200 IU/day of vitamin D and 750-1199 mg/day of calcium (10.5%; 95% CI = 7.2-13.8).

We stratified our participants by category of mammographic percent density at baseline to evaluate whether a nutrient-density relationship was more evident among women with higher mammographic density. Results are presented in table 4. Among women with density ≥10%, we did not find either vitamin D or calcium intake to be significantly associated with mean mammographic density. However, women taking vitamin D supplements had a modestly lower mammographic density (P=0.09).

We assessed whether the nutrient-mammographic density relationship was modified by several other factors. The effect of vitamin D supplement use was significantly modified by age (P-interaction = 0.009), with supplement use associated with lower density among women aged 50-59 (mean, 95% CI = 6.7, 3.5-9.8 for supplement users vs. 9.0, 6.7 – 11.3 for non-users), but not among older women. We did not observe evidence of effect modification by other factors, including body mass index, race/ethnicity, alcohol use, duration of supplement use, and solar irradiance (p-values all >0.05; results not shown). Furthermore, we did not find evidence that the vitamin D-mammographic density relationship varied by season of mammogram, and there was no seasonal variation in vitamin D intake, calcium intake, or mammographic density.

Results from analyses limited to women not reporting multivitamin use (n = 579) were similar to those of the main analysis; for example, mean percent mammographic density in women reporting total vitamin D intake of <100, 100-150, 150-199 and ≥200 IU/day were 4.9%, 9.5%, 6.3% and 5.3%, respectively (P for trend = 0.40). Mean percent mammographic density in women reporting total calcium intake of < 500, 500-749, 750-999 and ≥ 1000 mg/day were 7.6%, 6.2%, 9.4% and 5.9%, respectively (P for trend = 0.66). Results limited to women not reporting hormone therapy use at baseline (n = 755) were also virtually identical to the main analysis.

DISCUSSION

In our large population of postmenopausal women, we did not observe a relationship between dietary intake of vitamin D and calcium and mean mammographic percent density prior to randomization in the intervention trials. Adjustment for factors including solar irradiance and season of mammogram did not alter these findings.

While some previous studies have observed a relationship between these nutrients and postmenopausal mammographic density, results overall have been inconclusive. In a study of a population at high risk for breast cancer, Tseng and colleagues (2007)[30] reported a significant 50% lower risk of high breast density in women with high vitamin D intake (median = 737 IU/day) compared to those reporting the lowest intake (median = 164 IU/day). Higher vitamin D and/or calcium intake were also inversely related to high mammographic density in a two other studies.[26,27] In contrast, several other studies in a variety of other populations have not observed relationships between mammographic density and intake of vitamin D[28,31-33,35] or calcium[28,30-33,35] in postmenopausal women.

Inverse relationships between vitamin D, calcium and mammographic density have been more consistently observed in studies of premenopausal women.[28,31,32,35,45] Differences in finding by menopausal status may be in part due to the complex interplay between these nutrients and insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3). Evidence from laboratory studies suggests that vitamin D and calcium may interact with IGF-1 and IGFBP-3 through a variety of mechanisms,[46] many of which may affect breast cell proliferation and breast cancer development.[45] In a study of 771 premenopausal women, Diorio and colleagues (2006)[45] found that the inverse relationships between vitamin D and calcium and mammographic density was stronger in women with higher IGF-1 and IGFBP3 levels than in those with low levels. It is plausible that a relationship between vitamin D, calcium and mammographic density may be limited to premenopausal women, who have substantially higher levels of IGF-1 and IGFBP-3 than postmenopausal women.[46]

The mean mammographic density among participants in our population (weighted mean = 7.0%; SD = 9.5%) was considerably lower than in previous studies of postmenopausal women,[31,32] perhaps because our participants were somewhat older than women in other studies. Studies reporting the strongest relationship between density and vitamin D and/or calcium intake generally compared women with more extreme mammographic densities.[26,30] For example, Berube and colleagues (2004)[26] compared risk of having ≥ 70% of the breast with densities vs. ≤ 30%. Although we assessed this association after stratifying by mammographic density at baseline and did not find differences across categories, an effect of vitamin D and/or calcium on breast density may be evident only across a greater range of mammographic density than observable in our population. We did find evidence of significant effect modification by age, with vitamin D supplement use associated with lower density in women 50-59 but not in older women. This supports the hypothesis that an effect of vitamin D may exist only in younger women with higher overall densities.

Our study assessed the association between vitamin D from dietary or supplemental sources only and mammographic density, and did not directly take into consideration vitamin D produced by sunlight exposure. Plasma vitamin D metabolites, mainly 25(OH)D, have been related to breast cancer risk in several studies[10,12-14] but few studies have assessed whether 25(OH)D is related to breast density and results have been inconsistent.[34,53,36] For example, Knight and colleagues (2006)[34] did not find serum 25(OH)D levels to be inversely associated with mammographic density in a study of pre and postmenopausal women. Instead, density was non-significantly higher in women in the highest quartile of 25(OH)D levels (geometric mean percent mammographic density = 23.9%) compared to the lowest (21.6%; P = 0.59). Neither 25(OH)D nor 1,25-dihydroxyvitamin D levels were associated with mammographic density in a recent analysis in the postmenopausal women.[36] In contrast, Brisson and colleagues (2007)[47] observed a strong correlation between mean 25(OH)D levels and mean mammographic density in a population of premenopausal women, after taking into consideration seasonal variation in both 25(OH)D levels and mammographic density. In our population, we did not find that mammographic density or dietary vitamin D intake varied by season, and observed no evidence of effect modification by season. Additional studies evaluating the association between 25(OH)D levels and mammographic density in women of different ages are warranted.

Our study has several additional limitations. Levels of dietary vitamin D and calcium intake were relatively low in our population. Given the older ages of our participants, and the declines in subcutaneous vitamin D synthesis and dietary absorption with age,[48,49] intake may have been insufficient to detect an effect on mammographic density. It has been proposed that in the absence of sunlight exposure, vitamin D intake of 1700-2000 IU per day is necessary to achieve 25(OH)D levels of 75 nmol/L (30 ng/dL),[21] which may be needed to lower breast cancer risk.[50,51] While vitamin D and calcium intake levels in our study are comparable with those in some previous studies that have observed a relationship with mammographic density in premenopausal and younger postmenopausal women,[26,28,32] higher levels may be needed to modify mammographic density among older postmenopausal women.

The correlation between total vitamin D and total calcium intakes in our study was high (r for total calcium vs. vitamin D intake = 0.59, P < 0.001; r for calcium from foods vs. vitamin D from foods = 0.62, P < 0.001). This high correlation may have affected our ability to evaluate the independent effects of these two nutrients. However, when we categorized participants based on intake of both nutrients, we did not find clear evidence that either nutrient was independently associated with mammographic density. In addition, we were unable to evaluate the relationship between vitamin D and calcium and the total dense and non-dense area of the breast, which has been evaluated in some previous studies.[28,34]

CONCLUSIONS

In summary, we did not observe an association between dietary vitamin D or calcium intake and mammographic density in our diverse population of postmenopausal women. Additional studies are needed to further evaluate this relationship in premenopausal women, to consider the effects of plasma 25(OH)D levels, and to explore issues related to the timing of mammographic measurements with respect to vitamin D assessment.

Acknowledgments

The WHI program is funded by the National Heart, Lung and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, Anne McTiernan; (Medical Research Labs, Highland Heights, KY) Evan Stein; (University of California at San Francisco, San Francisco, CA) Steven Cummings.

Clinical Centers: (Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, TX) Aleksandar Rajkovic; (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (Brown University, Providence, RI) Charles B. Eaton; (Emory University, Atlanta, GA) Lawrence Phillips; (Fred Hutchinson Cancer Research Center, Seattle, WA) Shirley Beresford; (George Washington University Medical Center, Washington, DC) Lisa Martin; (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, OR) Yvonne Michael; (Kaiser Permanente Division of Research, Oakland, CA) Bette Caan; (Medical College of Wisconsin, Milwaukee, WI) Jane Morley Kotchen; (MedStar Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Northwestern University, Chicago/Evanston, IL) Linda Van Horn; (Rush Medical Center, Chicago, IL) Henry Black; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (State University of New York at Stony Brook, Stony Brook, NY) Dorothy Lane; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham, AL) Cora E. Lewis; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of California at Davis, Sacramento, CA) John Robbins; (University of California at Irvine, CA) F. Allan Hubbell; (University of California at Los Angeles, Los Angeles, CA) Lauren Nathan; (University of California at San Diego, LaJolla/Chula Vista, CA) Robert D. Langer; (University of Cincinnati, Cincinnati, OH) Margery Gass; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Hawaii, Honolulu, HI) J. David Curb; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Massachusetts/Fallon Clinic, Worcester, MA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ) Norman Lasser; (University of Miami, Miami, FL) Mary Jo O'Sullivan; (University of Minnesota, Minneapolis, MN) Karen Margolis; (University of Nevada, Reno, NV) Robert Brunner; (University of North Carolina, Chapel Hill, NC) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (University of Tennessee Health Science Center, Memphis, TN) Karen C. Johnson; (University of Texas Health Science Center, San Antonio, TX) Robert Brzyski; (University of Wisconsin, Madison, WI) Gloria E. Sarto; (Wake Forest University School of Medicine, Winston-Salem, NC) Mara Vitolins; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI) Michael Simon.

Source of Funding: The Women's Health Initiative program is funded by the National Heart, Lung and Blood Institute, National Institutes of Health, US Department of Health and Human Services. The Mammogram Ancillary Study was funded by the National Cancer Institute (CA7601704).

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Menopause. Author manuscript; available in PMC 2011 November 1.

Table 1

Demographic and behavioral characteristics of participants at baseline by total vitamin D and total calcium intakes, Women's Health Initiative Mammogram Density Study (n = 808).

		Total Vitamin D intake		Total calcium intake	
Characteristic	**n**	**Mean (SD)**	**P-value****	**Mean (SD)**	**P-value**
Age (years)			< 0.001		< 0.001
50 - 59	326	243 (203)		802 (457)	
60 - 69	312	290 (231)		925 (517)	
70 - 79	170	362 (253)		1039 (507)	
Ethnicity			< 0.001		< 0.001
White not of Hispanic origin	338	335 (241)		1044 (514)	
Black	312	233 (203)		700 (400)	
Hispanic	130	258 (213)		1002 (539)	
Asian/Pacific Islander	28	421 (257)		910 (371)	
School after High School			< 0.001		< 0.001
No	254	251 (208)		829(482)	
Yes	545	306 (237)		932 (504)	
Parity (number full term pregnancies)			0.55		0.14
0	84	301 (215)		980 (568)	
1	67	276 (220)		870 (441)	
2	162	292 (230)		881 (529)	
≥ 3	485	285 (234)		901 (486)	
Age at First Birth (years)*			0.41		0.05
<20	187	265 (228)		795 (492)	
20 – 29	386	302 (232)		952 (508)	
≥ 30	47	273 (219)		909 (484)	
Body Mass Index (kg/m^2)			0.78		0.02
< 25	167	333 (248)		1038 (520)	
25 - < 30	276	293 (244)		898 (503)	
≥ 30	362	258 (201)		838 (476)	
Alcohol Intake (drinks per day)			0.27		0.62
0	468	271 (220)		871 (485)	

Characteristic	n	Total Vitamin D intake Mean (SD)	Total Vitamin D intake P-value**	Total calcium intake Mean (SD)	Total calcium intake P-value
≤ 1	290	308 (244)		939 (516)	
> 1	50	301 (224)		935 (520)	
Smoking Status			0.68		0.01
Never	436	297 (231)		939 (502)	
Former	258	285 (236)		901 (514)	
Current	109	239 (179)		750 (426)	
Moderate-Strenuous Activity ≥ 20 minutes (episodes/week)			0.01		<0.001
0	168	246 (206)		775 (462)	
< 2	345	278 (216)		875 (448)	
2 – 3	101	324 (242)		991 (551)	
≥ 4	127	358 (279)		1121 (569)	
History of Benign Breast Disease			0.91		0.75
No	627	292 (233)		902 (500)	
Yes, 1 biopsy	76	289 (244)		937 (552)	
Yes, ≥ 2 biopsies	23	281 (232)		937 (406)	
Age at Menarche (years)			0.90		0.64
≤ 11	170	278 (215)		926 (490)	
12 – 13	415	289 (234)		900 (518)	
≥ 14	219	288 (232)		880 (472)	
Years since Menopause			0.74		0.61
< 5	125	251 (199)		848 (522)	
5 – 10	106	276 (213)		877 (469)	
10 – 15	110	305 (235)		926 (464)	
≥ 15	356	311 (249)		944 (533)	
Family History of Breast Cancer			0.84		0.70
No	659	282 (232)		895 (506)	
Yes	105	293 (206)		937 (473)	
Duration of Oral Contraceptive Use (years)			0.51		0.69
Non-user	461	292 (233)		920 (520)	
< 5	208	276 (235)		893 (485)	

Characteristic	n	Total Vitamin D intake		Total calcium intake	
		Mean (SD)	P-value**	Mean (SD)	P-value
5 – < 10	72	264 (199)		830 (474)	
≥ 10	67	305 (214)		855 (419)	
Duration of HT Use (years)			0.49		0.52
Non-user	566	284 (234)		889 (481)	
< 5	143	280 (217)		907 (553)	
5 – < 10	48	284 (204)		863 (495)	
≥ 10	51	334 (230)		1028 (535)	
Solar Irradiance (Langleys)			0.002		0.04
< 350	203	337 (242)		999 (487)	
350 - < 400	338	289 (230)		882 (528)	
≥ 400	267	244 (210)		847 (460)	
Season of Baseline Mammogram			0.21		0.46
Winter	195	265 (231)		880 (517)	
Spring	179	277 (205)		867 (460)	
Summer	215	302 (245)		910 (471)	
Fall	219	297 (230)		933 (539)	

* In women reporting a full term pregnancy (n = 620).

** P values from a linear model adjusting for age and ethnicity.

Table 2

Multivariable adjusted mean mammographic density at baseline by level of vitamin D and calcium intake in the Women's Health Initiative Mammogram Density Study (n = 808).

		Percent Density (95% Confidence Interval)			
Nutrient	**n**	**Age-adjusted**	**Model 1**	**Model 2**	**Model 3**
Total Vitamin D intake (IU/day)					
< 100	170	6.3 (4.6, 7.9)	5.4 (3.5, 7.3)	5.6 (3.4, 7.8)	5.8 (3.6, 8.0)
100 – 199	262	9.3 (7.2, 11.3)	9.8 (7.7, 12.0)	10.1 (7.9, 12.4)	10.4 (8.1, 12.6)
200 – 399	137	6.9 (5.1, 8.7)	6.2 (4.1, 8.2)	6.1 (3.9, 8.3)	6.2 (4.1, 8.3)
400 – 599	147	4.7 (3.5, 5.8)	4.0 (2.0, 6.1)	3.8 (1.7, 5.9)	3.8 (1.6, 6.0)
≥ 600	92	6.9 (4.7, 9.1)	5.7 (3.1, 8.3)	5.2 (2.2, 8.2)	5.1 (2.1, 8.1)
		P = 0.28	P = 0.96	P = 0.66	P = 0.67
Vitamin D from food sources (IU/day)					
< 100	249	5.8 (4.6, 7.1)	4.5 (3.1, 5.9)	4.5 (3.0, 6.1)	4.6 (3.0, 6.1)
100 – 150	236	6.8 (5.2, 8.4)	7.1 (5.5, 8.7)	7.2 (5.6, 8.8)	7.3 (5.6, 8.9)
150 – 199	139	10.2 (7.3, 13.0)	9.2 (6.8, 11.6)	9.2 (6.9, 11.6)	9.4 (7.1, 11.7)
≥ 200	184	6.2 (4.8, 7.6)	6.0 (4.4, 7.7)	6.1 (4.3, 7.8)	6.2 (4.5, 7.9)
		P = 0.11	P = 0.13	P = 0.06	P = 0.05
Vitamin D from supplements only					
No	563	7.8 (6.6, 9.0)	7.7 (5.9, 9.5)	7.7 (5.8, 9.5)	7.5 (5.8, 9.3)
Yes	285	5.9 (4.8, 7.0)	5.1 (3.2, 7.0)	5.1 (3.0, 7.1)	5.5 (3.5, 7.5)
		P = 0.15	P = 0.66	P = 0.97	P = 0.96
Total calcium intake (mg/day)					
< 500	155	7.0 (4.9, 9.1)	6.9 (4.8, 9.0)	7.2 (5.0, 9.3)	7.3 (5.1, 9.5)
500 – 749	235	5.8 (4.5, 7.1)	5.6 (4.2, 6.9)	4.9 (3.5, 6.4)	4.9 (3.4, 6.4)
750 – 999	168	8.4 (6.3, 10.5)	7.8 (5.8, 9.9)	7.4 (5.5, 9.3)	7.3 (5.5, 9.1)
1000 – 1199	82	6.8 (4.5, 9.1)	6.1 (3.5, 8.6)	6.5 (3.8, 9.3)	6.9 (4.1, 9.6)
≥ 1200	168	6.8 (5.2, 8.5)	6.4 (4.7, 8.1)	6.8 (4.9, 8.7)	7.1 (5.2, 9.0)
		P = 0.59	P = 0.42	P = 0.41	P = 0.51
Calcium from food sources (mg/day)					
< 500	210	6.9 (5.3, 8.4)	6.2 (4.6, 7.9)	6.6 (4.9, 8.2)	6.7 (5.0, 8.3)
500 – 649	194	5.8 (4.3, 7.3)	5.4 (3.7, 7.0)	5.0 (3.4, 6.6)	5.0 (3.4, 6.6)

		Percent Density (95% Confidence Interval)			
Nutrient	**n**	**Age-adjusted**	**Model 1**	**Model 2**	**Model 3**
650 – 799	140	7.1 (5.1, 9.1)	6.6 (4.5, 8.7)	6.2 (4.2, 8.2)	6.1 (4.1, 8.1)
≥ 800	264	7.7 (6.1, 9.2)	7.3 (5.8, 8.8)	7.4 (5.9, 9.0)	7.6 (6.1, 9.1)
		P = 0.60	P = 0.85	P = 0.85	P = 0.72
Calcium from supplements					
None	512	7.4 (6.2, 8.7)	7.0 (5.5, 8.5)	6.2 (4.9, 7.6)	6.3 (5.0, 7.6)
< 500	197	6.6 (5.1, 8.0)	6.4 (4.7, 8.2)	6.9 (5.2, 8.6)	7.1 (5.4, 8.7)
≥ 500	139	6.6 (4.8, 8.3)	5.9 (4.0, 7.7)	6.5 (4.6, 8.5)	6.6 (4.7, 8.6)
		P = 0.39	P = 0.48	P = 0.94	P = 0.95

Model 1 is adjusted for age, race/ethnicity, body mass index, age at menarche, parity, oral contraceptive use and duration, previous HT use/duration, HT trial randomization assignment, family history of breast cancer, education, alcohol intake, smoking, total calorie intake, physical activity, Gail risk, and use of multivitamins.

Model 2 is adjusted for all covariates in Model 1. In addition, vitamin D is adjusted for total calcium and vice-versa, and nutrients from food sources are adjusted for nutrient from supplemental sources and vice-versa.

Model 3 is adjusted for all covariates in Model 2 plus solar irradiation and season of mammogram.

Table 3

Multivariable adjusted mean mammographic density and 95% confidence intervals by total vitamin D and calcium intake at baseline, Women's Health Initiative Mammogram Density Study (n = 808).

	Vitamin D (IU)		
Calcium (mg)	< 200	200 - 399	≥ 400
< 750	7.5 (5.7, 9.2)	2.4 (0.0, 5.7)	2.8 (0.0, 5.7)
750 - 1199	10.5 (7.2, 13.8)	6.3 (3.9, 8.6)	4.0 (1.1, 6.9)
≥ 1200	7.3 (3.0, 11.5)	8.8 (3.9, 13.7)	4.5 (2.5, 6.5)
			P int = 0.99

Adjusted for covariates in Model 1: age, race/ethnicity, body mass index, age at menarche, parity, oral contraceptive use and duration, previous HT use/duration, HT trial randomization assignment, family history of breast cancer, education, alcohol intake, smoking, total calorie intake, physical activity, Gail risk, and use of multivitamins.

Table 4

Multivariable adjusted mean mammographic density by total vitamin D and calcium intake at baseline, stratified by category of percent density at baseline, Women's Health Initiative Mammogram Density Study (n = 808).

	Percent Density (95% Confidence Interval) by Category of Percent Density		
Nutrient	**< 1 % (n = 212)**	**1 - < 10% (n = 388)**	**≥ 10% (n = 208)**
Total Vitamin D intake (IU/day)			
< 100	0.5 (0.4, 0.6)	3.7 (2.8, 4.6)	18.1 (14.4, 21.8)
100 – 199	0.6 (0.4, 0.7)	4.5 (3.5, 5.6)	23.3 (20.2, 26.4)
200 – 399	0.4 (0.2, 0.5)	3.7 (2.9, 4.4)	19.8 (16.0, 23.6)
≥ 400	0.5 (0.4, 0.6)	3.6 (2.7, 4.6)	16.9 (12.3, 21.5)
	P = 0.16	P = 0.79	P = 0.67
Vitamin D from food sources (IU/day)			
< 100	0.5 (0.4, 0.6)	3.6 (2.9, 4.2)	17.0 (13.7, 20.3)
100 – 150	0.5 (0.4, 0.6)	4.4 (3.5, 5.2)	20.0 (17.4, 22.7)
150 – 199	0.5 (0.4, 0.6)	3.9 (3.0, 4.8)	22.6 (19.3, 25.9)
≥ 200	0.4 (0.3, 0.5)	3.7 (3.1, 4.3)	20.6 (17.1, 24.1)
	P = 0.26	P = 0.50	P = 0.15
Vitamin D from supplements only			
No	0.5 (0.4, 0.6)	3.8 (3.0, 4.5)	22.4 (19.1, 25.7)
Yes	0.5 (0.3, 0.6)	3.9 (3.1, 4.8)	17.1 (12.7, 21.4)
	P = 0.72	P = 0.91	P = 0.09
Total calcium intake (mg/day)			
< 500	0.5 (0.4, 0.6)	3.4 (2.6, 4.3)	20.5 (16.5, 24.4)
500 – 749	0.6 (0.5, 0.7)	4.2 (3.5, 5.0)	19.8 (16.0, 23.5)
750 – 999	0.5 (0.4, 0.6)	4.0 (3.2, 4.9)	21.8 (18.2, 25.4)
≥ 1000	0.4 (0.4, 0.5)	3.6 (3.0, 4.2)	19.5 (16.8, 22.2)
	P = 0.07	P = 0.66	P = 0.85
Calcium from food sources (mg/day)			
< 500	0.5 (0.4, 0.6)	4.0 (3.2, 4.9)	20.3 (16.7, 23.8)
500 – 649	0.5 (0.4, 0.6)	4.2 (3.5, 4.9)	19.1 (15.0, 23.1)
650 – 799	0.5 (0.3, 0.6)	3.1 (2.2, 4.0)	18.8 (15.2, 22.5)
≥ 800	0.5 (0.4, 0.6)	3.7 (3.2, 4.3)	21.6 (18.8, 24.4)
	P = 0.93	P = 0.48	P = 0.27
Calcium from supplements			
None	0.6 (0.5, 0.7)	3.9 (3.3, 4.5)	21.1 (18.6, 23.6)
< 500	0.4 (0.3, 0.5)	3.8 (3.0, 4.6)	20.2 (16.4, 24.1)
≥ 500	0.5 (0.3, 0.6)	3.7 (2.9, 4.6)	19.0 (16.0, 22.0)
	P = 0.97	P = 0.48	P = 0.17

Adjusted for covariates in Model 1: age, race/ethnicity, body mass index, age at menarche, parity, oral contraceptive use and duration, previous HT use/duration, HT trial randomization assignment, family history of breast cancer, education, alcohol intake, smoking, total calorie intake, physical activity, Gail risk, and use of multivitamins.