Research Article

Cancer Epidemiology, Biomarkers & Prevention

Joint Effects of Dietary Vitamin D and Sun Exposure on Breast Cancer Risk: Results from the French E3N Cohort

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Abstract

Background: Ecological studies have suggested that vitamin D production through ultraviolet (UV) solar irradiance could reduce breast cancer (BC) risk. Although studies restricted to dietary vitamin D intake have provided inconsistent results, little is known about the relationship between pre- and postmenopausal BC and combined intakes from diet, supplements, and sun exposure.

Methods: Cox proportional hazards regression models evaluated the association between vitamin D intakes, mean daily ultraviolet radiation dose (UVRd) at the place of residence and risk of BC among 67,721 women of the French E3N cohort. All analyses were stratified on menopausal status taking into account important confounders including calcium consumption.

Results: During 10 years of follow-up, a total of 2,871 BC cases were diagnosed. Dietary and supplemental vitamin D intakes were not associated with BC risk; however, in regions with the highest UVRd, postmenopausal women with high dietary or supplemental vitamin D intake had a significantly lower BC risk as compared with women with the lowest vitamin D intake (HR = 0.68, 95% CI: 0.54–0.85, and HR = 0.57, 95% CI: 0.36–0.90, respectively).

Conclusion: Our results suggest that a threshold of vitamin D exposure from both sun and diet is required to prevent BC and this threshold is particularly difficult to reach in postmenopausal women at northern latitudes where quality of sunlight is too poor for adequate vitamin D production.

Impact: Prospective studies should further investigate associations between BC risk, vitamin D status and sunlight exposure. *Cancer Epidemiol Biomarkers Prev; 20(1); 187–98. ©2011 AACR.*

Introduction

Experimental studies have shown anti-carcinogenic properties of vitamin D (1, 2) through regulation of proliferation, differentiation, and apoptosis of breast cells *in vitro* and *in vivo*. Yet, evidence from observational studies that examined the association between breast cancer (BC) risk and vitamin D dietary intakes remains inconclusive (3–6), while among those that specifically assessed vitamin D serum concentrations (7–10), several case–control studies nested in prospective cohorts (8, 11) described a decreasing BC risk with increasing vitamin D concentrations.

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Solar ultraviolet radiation B (UVB) irradiation (280–315 nm) provides 50% to 90% of the circulating vitamin D through cutaneous conversion of 7-dehydrocholesterol (12), the remaining coming from the diet, especially dairy foods and fish, or from dietary supplements.

Vitamin D from skin solar irradiation and diet is first metabolized in the liver into 25-hydroxyvitamin D [25(OH)D]—the relevant serum biomarker to assess a patient's vitamin D status—and then undergoes a second hydroxylation in the kidney and other cells such as breast cells, into 1,25 dihydroxyvitamin D [1,25$(OH)D_2$], the active biological form, tightly regulated by serum hormone, and calcium levels (12).

Discrepant results on the effects of vitamin D intakes on BC may be related to the tight calcium–vitamin D interrelation (5) or on heterogeneous intakes across countries due to different levels of food fortification, supplementation (13, 14), or sun exposure (15, 16).

Although ecological studies have supported an inverse association between UV-vitamin D and BC mortality or incidence (17), only very few studies explored simultaneous associations between vitamin D dietary intakes and UV exposure, and BC risk (18–20), while taking into

account dietary calcium intakes (20). Furthermore, limited evidence suggests that the association between vitamin D intakes and BC risk may differ by menopausal status (21, 22), although others did not find such effect modification (23, 24).

The objectives of the present study were to evaluate the relationship between BC risk and overall vitamin D intakes from diet and UV solar exposure in the large French E3N (Etude Epidémiologique auprès des femmes de l'Education Nationale) cohort taking into account calcium intakes and menopausal status.

Material and Methods

The E3N cohort

E3N is a prospective cohort initiated in 1990 that includes 98,995 French women born between 1925 and 1950 and insured by a health insurance plan mainly covering teachers (25). Participants, who provided written informed consents for external health follow-up through the health insurer, completed biennial self-administered questionnaires sent from 1990 to 2008 on medical and gynaecological history, menopausal status, and a variety of lifestyle characteristics. The study was approved by the French National Commission for Data Protection and Privacy.

Identification of participants with breast cancer

Occurrence of cancer was self-reported in each questionnaire, and a small number of cancers were further identified from the insurance files or information on causes of death obtained from the National Service on Causes of Deaths. The pathology report, used to confirm the diagnosis of invasive BC (our primary outcome), was obtained for 93% of declared BC cases. We also included participants who reported a BC diagnosis but for whom pathology reports had not been obtained, because the proportion of false-positive self-reports was low (<5%).

Dietary data

A validated 208-item diet history questionnaire administered between 1993 and 1995 assessed the previous year usual diet; it was available for 74,524 participants (26).

We estimated the average daily vitamin D, calcium, and energy intakes using a food composition table derived from the updated French national database (27).

Information on vitamin D and calcium supplement use was extracted from questions on treatment/prevention of osteoporosis and on dietary supplementation.

Place of residence and mean daily UV dose solar irradiance estimates

Data on region of residence was assessed for all participants at baseline, and linked to a database containing mean daily ultraviolet radiations doses (UVRd in kJ/m^2/day) in French departments obtained from the Joint Research Centre of the European Commission. UVRd were estimated by a satellite-derived mapping algorithm (28). In brief, the database covers the period from January 1, 1984 to August 21, 2003, with UVRd maps covering Europe with a spatial resolution of 0.05°. UVRd is obtained by interpolation in a validated look-up table (LUT) using the UVspec code (29) of the radiative transfer model package (version 13), the entries of which are solar zenith angle, total column ozone amount, cloud liquid water thickness, near-surface horizontal visibility, surface elevation, and UV albedo. Both satellite (Meteosat, the European geostationary meteorological satellite) and nonsatellite (synoptic observations, meteorological model results, digital elevation model) data are exploited to assign values to the influencing factors. UVRd is constructed by numerical integration of the dose rate estimated at half-hourly intervals from, and including, the local solar noon (for each pixel from the full resolution satellite images).

The quality of the satellite-derived estimates has been assessed at several sites in Europe with usually good r.m.s (relative difference between the satellite estimates and the measured ground erythemal daily doses) and small bias (<3%; ref 28).

For the present study, UVRd estimated over spring and summer seasons were used as the primary surrogate for vitamin D variation in the population since it appears that UVB irradiance, especially in summer, is the strongest determinant of geographical variation in serum 25(OH)D in the United States and much of the world (30). Quartiles of UVRd were thus estimated to categorize the study women (<2.4/2.4–2.5/2.5–2.7/>2.7 kJ/m^2/day; Fig. 1) as well as tertiles of latitude of residence, that is, Northern (>49°N), Central (46–49°N), and Southern (<46°N).

Information on region of residence was assessed in 1990 (first questionnaire), at baseline (diet questionnaire), and at the end of follow-up. In addition, birth place, data on skin complexion, recreational physical activity, and usual sunburn resistance were also requested at inclusion. No data were available on individual sunlight exposure.

Definition of menopause

Information on menopausal status was requested in each questionnaire. Women were considered postmenopausal if they had had 12 consecutive months without menstrual periods (unless due to hysterectomy), had undergone bilateral oophorectomy, had ever used menopausal hormone therapy (MHT), or self-reported that they were postmenopausal. Age at menopause was defined as age at the last menstrual period (if the latter occurred before any MHT use, and if amenorrhea was not due to hysterectomy), age at bilateral oophorectomy, or, in decreasing order of priority, self-reported age at menopause, age at start of MHT, or age at start of menopausal symptoms. Women whose age at menopause could not be determined were considered menopausal at age 47 if menopause was surgical and otherwise at age 51, the median ages for surgical and natural menopause, respectively, in the cohort.

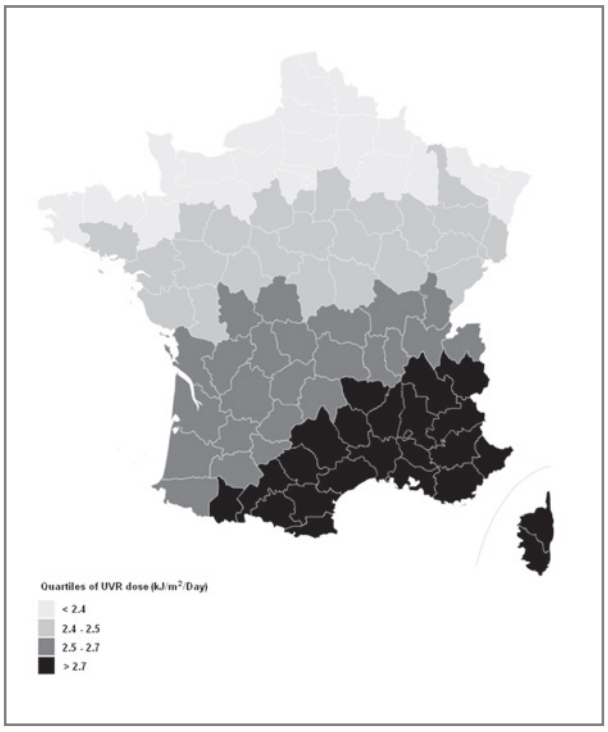

Figure 1. Average daily UVR dose (kJ/m^2/day) estimated during spring and summer seasons across French departments. French E3N Cohort.

Statistical analysis

Participants contributed person-years of follow-up from the date they completed the 1993 dietary questionnaire to the date of diagnosis of pre- or postmenopausal invasive BC as first primary cancer, date of diagnosis of another cancer, date of death, or July 2005, whichever came first. Among the 74,524 women with dietary data, women with extreme values (in the bottom 1% or top 1%) of the ratio between energy intake and energy required (computed after taking into account age, weight and height) were excluded (n = 1,339). In addition, 4,654 women who had reported cancer diagnosis before responding to the dietary questionnaire and 810 women with unavailable subsequent follow-up information were excluded. We finally studied 67,721 women.

To take into account the correlation between vitamin D and energy intakes (r = 0.40, $P < 0.0001$), we calculated the residuals of the linear regression of vitamin D intakes on energy intake from food (excluding energy from alcohol) and added corresponding mean vitamin D intake as a constant, according to the regression–residual method (31). We then categorized the obtained energy-adjusted vitamin D intakes into tertiles according to the distribution observed in the E3N study population. Women taking vitamin D supplements during follow-up were considered in a fourth separate category. Baseline characteristics of the participants were examined by tertiles of energy-adjusted total dietary and supplement vitamin D intakes and by quartiles of UVRd at the place of residence; P values for differences in characteristics across tertiles were calculated using the global 2-sided chi-square test (for nominal variables), the 2-sided Mantel–Haenszel chi-square test (for ordinal variables), or the 2-sided Wald chi-square test (for continuous variables in the linear regression on vitamin D intakes).

Hazard ratios (HR) and 95% confidence intervals (CI) were obtained for each tertile of dietary vitamin D intake plus a vitamin D supplement category, quartile of UVRd, and tertile of latitude, compared with the lowest category by using Cox's proportional hazards model stratified by 5-year-interval birth cohorts with the women's age as the time scale.

Known risk factors for BC and potential confounders were included in the final models, which were therefore adjusted for body mass index (BMI) before and after menopause (<20/20–25/>25 kg/m^2, considered as a time-dependent variable), physical activity at baseline (in metabolic task per hour in a week; <34/34–46/46–62/>62 Met-h/week), menopausal status (time-dependent), age at menopause (<47/47–54/>54 years among postmenopausal women), age at menarche, number of full-term pregnancies, previous use of oral contraceptives (ever/never), use of MHT (never/current/past/unknown, time-dependent variable, among postmenopausal women only), mean dietary calcium intakes (<868.4/868.4–1,092.5/>1,092.5 mg/day), current use of calcium supplement (yes/no, time-dependent variable), alcohol intake (g/day), total energy intake without alcohol (kcal/day), university degree (yes/no), previous family history of BC (yes/no), previous history of personal benign breast disease (ever/never, time dependent variable), previous mammography (yes/no, time-dependent variable), sun burn resistance (low/medium/high), and skin complexion (very fair/fair/medium/dark/very dark). Smoking status (current/ex/never-smoker; time-dependent variable), personal history of diabetes or thyroid disease (yes/no, time-dependent variables), and bone mineral densitometry exams (ever/never, time dependant variable) were not retained in the final model because they did not improve the model fit by the $P <$ 0.05 criterion.

For time-dependent covariates, data recorded in questionnaires i and earlier was used to prospectively categorize women for the period that followed (i.e., between questionnaire i and questionnaire j, where j was the next completed questionnaire).

Multivariate analyses on vitamin D consumption were stratified by menopausal status and additionally adjusted for UVRd in region of residence; HRs for quartiles of UVRd were also computed by adjusting for tertiles of dietary and supplemental vitamin D. We evaluated separately the associations between vitamin D and calcium intakes and BC risk within strata of vitamin D and calcium, respectively. We also investigated the consumption of foods or food groups that were the main contributors to vitamin D intakes in the study population. Although UVRd estimation was not available before

1984, we examined a possible differential effect of UVR childhood exposure by performing sensitivity analyses among women who were born in regions belonging to the same UVRd quartiles than at baseline. Additional analyses were computed by excluding women who moved between regions from 1990 until the beginning of the study (in 1993) or during the follow-up. Finally, we conducted stratified analyses on women whose diagnosis was close to or far from exposure assessment (according to median duration of follow-up until BC diagnosis).To test for trend, the median value for each quintile of UVRd or dietary vitamin D intakes was used as a continuous variable. Trends for dietary intakes were performed while excluding the supplement category because we did not have information on doses. To test for interactions, we included a cross-product term of the median value of intake for each tertile of vitamin D intake and a separate category for vitamin D supplements separately, and the pre-specified categories of stratification, that is, menopausal status, quartiles of UVRd, tertiles of calcium plus calcium supplementation. Log-likelihood tests were used to investigate potential interactions. All *P* values were 2 tailed. We used the SAS statistical software (Version 9.02) for data analysis. Results were presented as mean, standard deviation (SD) for continuous variables and N (%) for categorical variables.

Results

A total of 2,871 incident primary invasive BC were diagnosed (618 were premenopausal and 2,253 postmenopausal) in 67,721 women including in the analysis during 711,523 person-years of follow-up (mean duration = 10.4 years, SD, 2.4). The age range was 41.8 to 72.0 (mean age = 52.8 years, SD, 6.6) at baseline, and 43.9 to 78.8 (mean age = 59.2 years, SD, 7.0) at BC diagnosis. The distribution of baseline characteristics by tertiles of energy-adjusted vitamin D plus supplement and by quartiles of residential UVRd is provided in Table 1.

Median vitamin D intake was 96 IU/day (or 2.4 μg/day, 10th–90th percentile range: 52–172 IU/day) and median intake in energy-adjusted tertiles ranged from 64 to 143 IU/day. With regard to the contributions from different foods, 45.5% dietary vitamin D originated from fish and seafood, 16.1% from eggs, 11.0% from dairy products, 10.4% from oils and margarine, 6.5% from cakes, 5.1% from meat, 1.2% from breakfast cereals, and 4.2% from other miscellaneous foods.

Women with higher dietary vitamin D intakes had higher calcium intakes and were more likely to be overweight (BMI >25 kg/m^2), to use current MHT, and to report a previous mammography. Women with vitamin D supplements were older, mostly postmenopausal, had higher calcium consumption, a mean consumption of dietary vitamin D of 104 UI, SD = 48 UI, mostly took concomitantly calcium supplement intakes; they were more likely to have higher physical activity and to use MHT at baseline.

As compared with areas of lower sun exposure, women in areas with high sunlight exposure were older, had the lowest alcohol intakes, higher calcium consumption, and used more frequently calcium supplementation; the proportion of postmenopausal women was highest; women also declared to have the highest resistance to sun burn and the highest level of physical activity.

Vitamin D intake from either diet or supplements was not associated with overall, pre- or postmenopausal BC risk (Table 2). Dietary and supplemental vitamin D intakes were not associated with BC risk: third versus first tertile 0.94 (95% CI: 0.86–1.03); *P* for trend = 0.1; and supplement versus first tertile 0.90 (95% CI: 0.72–1.12). Considering other cutoffs for dietary vitamin D intake (<60; 60–120; 120–180; >180 IU/day) led to similar results.

There was no association between BC risk and any of the main food contributors to dietary vitamin D and calcium, in tertiles (data not shown).

Living in the regions with the highest UVRd (>2.7 kJ/m^2/day) was associated with a statistically significant decreased BC risk as compared to women with the lowest UVRd (HR = 0.91, 95% CI: 0.82–0.99, *P* for trend across quartiles = 0.06), especially in postmenopausal women (HR = 0.92, 95% CI: 0.82–0.98; *P* for trend = 0.05). Results were similar when considering residential latitudes. Compared to women living in Northern latitudes (>49°N), women in Southern latitudes (<46°N) had a significantly decreased BC risk (HR = 0.90, 95% CI: 0.82–0.98, *P* for trend = 0.02). The association was borderline significant in postmenopausal women (HR = 0.90, 95% CI: 0.81–1.00, *P* for trend = 0.06).

Since dietary vitamin D and calcium intakes were correlated (Pearson's $r = 0.28$, $P < 0.0001$), we evaluated the combined effect of calcium and vitamin D intakes (using tertiles of dietary intakes and additional categories for supplements) on the risk of BC. We did not observe any significant association between BC risk and calcium intake, nor with vitamin D over any stratum of calcium intake (data not shown).

There was no correlation between UVRd and dietary vitamin D intake ($r = -0.06$, $P < 0.0001$) nor between dietary vitamin D and calcium or alcohol intake. The association between vitamin D and BC risk was not significantly modified by age at menarche, age at menopause, BMI, alcohol, current use of MHT, family history of BC, history of benign breast disease, physical activity or dietary and supplement intake of calcium.

We observed a significant interaction between UVRd and dietary vitamin D intake in post ($P = 0.02$) but not in premenopausal women ($P = 0.4$). Relative risks of BC for each level of vitamin D intake and UVRd are presented in Table 3, taking as the reference both low dietary vitamin D and low UV exposure. There was no clear linear dose–response relationship in the joint associations between UVRd and vitamin D intakes, and BC risk, but BC risk was significantly decreased in women with both high UV exposure and the highest dietary (>113 IU/day) or supplemental vitamin D intakes (HR = 0.73, 95% CI:

Table 1. Baseline characteristics by tertiles of energy-adjusted vitamin D, vitamin D supplement, and quartiles of UVR dose at place of residence (n = 67,721) E3N cohort 1993 to 2005

	Vitamin D dietary intakes, IU/d % or mean (SD)				Mean daily UVR doses, kJ/m^2/d % or mean (SD)			
Baseline characteristics	**< 80**	**80–113**	**> 113**	**Supplement**	**< 2.4**	**2.4–2.5**	**2.5–2.7**	**> 2.7**
N	21,362	21,431	21,367	3,561	17,189	15,946	17,926	16,660
Age, y	52.7 (6.8)	52.4 (6.5)	52.8 (6.5)	54.3 (6.8)	52.5 (6.7)	52.4 (6.6)	52.8 (6.7)	53.3 (6.6)
Age at menarche, y	12.9 (1.4)	12.8 (1.4)	12.7 (1.4)	12.8 (1.4)	12.8 (1.4)	12.8 (1.4)	12.7 (1.4)	12.7 (1.4)
BMI								
<20	18.5	15.4	12.0	13.3	14.4	15,0	16.4	16.5
20–25	65.1	64.6	63.1	65.2	63.0	64.8	64.4	65.0
>25	16.4	20.0	24.9	21.5	22.6	20.2	19.2	18.5
Number of full-term pregnancies	2.0 (1.1)	2.0 (1.1)	2.0 (1.1)	1.9 (1.2)	2.0 (1.2)	2.1 (1.1)	2.0 (1.1)	2.0 (1.1)
Postmenopausal%	53.8	53.2	56.2	71.1	53.2	53.2	55.2	59.5
Age at menopause								
<47	13.4	13.3	14.2	16.7	13.4	13.2	13.8	14.6
47–52	59.6	59.7	60.2	57.3	60.7	60.7	58.8	58.7
>52	27.0	27.0	25.6	26.0	25.9	26.1	27.4	26.7
University degree, %	85.9	86.3	86.0	86.9	85.9	86.5	85.8	86.3
First degree relative with breast cancer, %	11.9	11.5	11.5	11.8	11.4	12.1	11.1	12.0
History of benign breast disease, %	26.2	26.7	25.8	27.0	26.4	25.9	26.1	26.4
Previous mammography, %	32.6	33.4	35.7	33.6	34.2	35.0	34.8	35.2
Ever oral contraceptive use, %	39.7	42.1	40.9	39.4	41.1	41.9	40.4	38.8
Use of postmenopausal MHT, %								
Never	70.8	69.1	66.7	56.8	68.7	67.5	69.2	67.4
Current	18.3	20.3	21.8	25.7	20.7	21.5	19.6	20.1
Past	10.9	10.6	11.5	17.5	10.6	11.0	11.2	12.5
Dietary variables								
Alcohol intake, g/d	9.9 (1.3)	11.3 (1.4)	12.5 (1.5)	10.0 (1.3)	12.3 (1.5)	12.2 (1.4)	10.2 (1.3)	10.9 (1.5)
Mean dietary calcium intake, mg/d	1,006.1 (315.1)	1,015.3 (298.4)	1,038.2 (302.7)	1,050.5 (330.8)	1,012.5 (313.2)	1,009.5 (297.4)	1,020.2 (301.5)	1,043.7 (315.1)
Mean dietary vitamin D intake, IU/d	60 (16)	96 (8)	156 (44)	104 (48)	108 (48)	108 (48)	104 (47)	100 (48)
Total energy intake without alcohol, kcal/d	2,139.6 (557.8)	2,025.9 (543.9)	2,110.2 (569.7)	2,067.9 (552.9)	2,098.0 (563.9)	2,103.1 (558.7)	2,097.8 (553.8)	2,063.9 (558.9)
Calcium supplement use, %[a]	17.0	16.2	16.3	78.3	18.6	18.4	19.8	22.2

(Continued on the following page)

Table 1. Baseline characteristics by tertiles of energy-adjusted vitamin D, vitamin D supplement, and quartiles of UVR dose at place of residence (n = 67,721) E3N cohort 1993 to 2005 (Cont'd)

	Vitamin D dietary intakes, IU/d % or mean (SD)				Mean daily UVR doses, kJ/m^2/d % or mean (SD)			
Baseline characteristics	**< 80**	**80–113**	**> 113**	**Supplement**	**< 2.4**	**2.4–2.5**	**2.5–2.7**	**> 2.7**
Sun-related variables								
UVR dose exposure (kJ/m^2/day)	2.6 (0.3)	2.6 (0.3)	2.5 (0.3)	2.6 (0.3)	2.3 (0.1)	2.4 (0.04)	2.6 (0.07)	2.9 (0.1)
Latitude for region of residence	46.8 (2.2)	47.0 (2.2)	47.1 (2.2)	46.8 (2.2)	49.3 (0.7)	48.4 (0.4)	46.1 (1.1)	44.0 (0.8)
Sunburn resistance								
Low	28.2	28.1	27.8	27.1	29.2	29.4	27.1	26.4
Medium	50.4	49.6	49.0	50.7	50.5	50.1	49.8	48.4
High	21.4	22.3	23.2	22.2	20.3	20.5	23.1	25.2
Skin complexion								
Fair	1.0	1.1	1.2	0.8	1.3	1.2	1.0	0.9
Medium	58.8	58.4	57.9	59.2	61.4	60.8	56.7	54.8
Dark	38.7	39.2	39.3	38.4	36.1	36.7	40.7	42.3
Very dark	1.5	1.3	1.6	1.6	1.2	1.3	1.6	1.9
Recreational physical activity, METs-h/wk								
<34	23.3	24.2	25.3	21.0	26.1	25.5	24.1	20.6
34–46	24.3	25.0	24.5	23.7	25.9	24.8	23.8	23.7
46–62	26.8	26.4	25.8	26.1	25.8	26.3	26.4	26.8
>62	25.6	24.4	24.4	29.2	22.2	23.4	25.7	28.9

Table 2. HRs of breast cancer according to: tertiles of energy-adjusted vitamin D and supplement intakes, quartiles of UVR dose exposure and latitudes at the region of residence (n = 67,721) E3N cohort 1993 to 2005

		Entire Population			Premenopausal			Postmenopausal		
	Median value	Person-Years	Cases	HR[a] (CI 95%)	Person-Years	Cases	HR[a] (CI 95%)	Person-Years	Cases	HR[a] (CI 95%)
Vitamin D, IU/d[b]										
< 80	64.4	230,702	927	(Reference)	48,676	212	(Reference)	182,026	715	(Reference)
80–113	96	228,375	947	1.02 (0.93–1.11)	48,649	199	0.92 (0.76–1.12)	179,726	748	1.04 (0.94–1.16)
>113	143.2	224,915	887	0.94 (0.86–1.03)	44,391	203	1.03 (0.85–1.25)	180,524	684	0.92 (0.83–1.02)
Supplemented	unknown	27,531	110	0.90 (0.72–1.12)	1,195	4	0.68 (0.25–1.87)	26,336	106	0.91 (0.73–1.14)
P value for trend				0.13			0.9			0.08
Mean daily UVR dose exposure at place of residence, kJ/m^2[c]										
< 2.4	2.3	182,934	756	(Reference)	37,024	168	(Reference)	145,910	588	(Reference)
2.4–2.5	2.4	177,040	707	1.01 (0.91–1.12)	36,515	162	1.06 (0.85–1.31)	140,525	545	0.99 (0.88–1.11)
2.5–2.7	2.6	178,854	746	0.95 (0.86–1.06)	37,154	169	1.01 (0.81–1.25)	141,700	577	0.94 (0.84–1.05)
>2.7	3.0	172,695	662	0.91 (0.82–0.99)	32,218	119	0.85 (0.67–1.08)	140,477	543	0.92 (0.82–0.98)
P value for trend				0.06			0.2			0.05
Latitudes at place of residence[c]										
>48.6°N	49.0	234,174	896	(Reference)	45,638	173	(Reference)	188,536	723	(reference)
45.8–48.6°N	47.4	238,435	964	0.98 (0.90–1.08)	48,221	221	1.01 (0.83–1.21)	190,214	743	0.98 (0.88–1.08)
< 45.8° N	44.0	238,914	1,011	0.90 (0.82–0.98)	49,052	224	0.89 (0.73–1.09)	189,862	787	0.90 (0.81–1.00)
P value for trend				0.02			0.2			0.06

[a]Adjusted for menopausal status (time dependent), BMI (<20/20–25/>25 kg/m^2), physical activity in 1993 (in Met-h/week; <34/34–46/46–62/>62), age at menopause (<47/47–54/>54 years among postmenopausal women only), age at menarche, parity (number of full-term pregnancies), previous use of oral contraceptives (ever/never), use of menopausal hormone therapy (never, current, past, unknown, time-dependent variable, among postmenopausal women only), daily calcium intake (< 868.4/868.4–1,092.5/>1,092.5 mg/day), current use of calcium supplement (yes, no, time-dependent variable), alcohol intake (g/day), total energy intake without alcohol (kcal/day), university degree (yes/no), previous family history of breast cancer (yes/no), previous personal history of benign breast disease (ever, never, time-dependent variable), previous history of mammographic exam (yes, no, time-dependent variable), sun bum resistance (low, medium, high), skin complexion (very fair, fair, medium, dark, very dark).

[b]HR were adjusted for the same covariates as [a] plus vitamin D dietary [<80/80–113/>113 (IU/day)] and supplement intakes.

[c]HR were adjusted for the same covariates as [a] plus UVR dose exposure at place of residence (<2.4/2.4–2.5/2.5–2.7/> 2.7 kJ/m^2/day).

Table 3. HRs of breast cancer according to tertile of energy-adjusted vitamin D and supplement intakes, quartiles of UVR dose exposure at the region of residence ($n = 67,721$) E3N cohort 1993 to 2005.

	Vitamin D dietary intakes, IU/d											
	< 80			80–113			> 113			Supplement		
UV dose exposure, kJ/m^2/d	Person-Years	Cases	HR[a] (CI 95%)	Person-Years	Cases	HR[a] (CI 95%)	Person-Years	cases	HR [a] (CI 95%)	Person-Years	Cases	HR[a] (CI 95%)
Entire population												
< 2.4	58,032	230	(reference)	58,644	248	0.91 (0.76–1.09)	59,156	248	0.86 (0.72–1.03)	7,102	30	0.88 (0.60–1.29)
2.4–2.5	54,158	203	0.89 (0.73–1.07)	59,202	244	0.99 (0.82–1.18)	57,053	238	0.92 (0.76–1.10)	6,627	22	0.72 (0.47–1.12)
2.5–2.7	58,299	243	0.85 (0.71–1.02)	57,189	236	0.88 (0.73–1.05)	55,849	232	0.89 (0.74–1.07)	7,517	35	1.00 (0.70–1.43)
> 2.7	60,213	251	0.88 (0.74–1.05)	53,340	219	0.91 (0.75–1.09)	52,857	169	0.73 (0.60–0.90)	6,285	23	0.63 (0.41–0.96)
Postmenopausal women												
< 2.4	46,809	182	(reference)	44,692	186	0.86 (0.70–1.06)	47,602	191	0.81 (0.66–0.99)	6,807	29	0.87 (0.59–1.28)
2.4–2.5	42,250	149	0.81 (0.65–1.02)	47,393	193	0.98 (0.80–1.20)	44,558	182	0.86 (0.70–1.05)	6,324	21	0.70 (0.45–1.10)
2.5–2.7	44,537	183	0.80 (0.65–1.04)	44,326	180	0.83 (0.68–1.02)	45,320	179	0.83 (0.68–1.02)	7,517	35	1.01 (0.71–1.46)
> 2.7	48,430	201	0.86 (0.70–1.05)	43,315	189	0.94 (0.77–1.15)	43,044	132	0.68 (0.54–0.85)	5,688	21	0.57 (0.36–0.90)
Premenopausal women												
< 2.4	11,223	48	(reference)	13,952	62	1.08 (0.74–1.57)	11,554	57	1.05 (0.72–1.55)	295	1	0.63 (0.09–4.54)
2.4–2.5	11,908	54	1.19 (0.81–1.75)	11,809	51	0.99 (0.67–1.47)	12,495	56	1.15 (0.78–1.69)	303	1	0.68 (0.09–4.96)
2.5–2.7	13,762	60	1.03 (0.70–1.51)	12,863	56	1.03 (0.70–1.52)	10,529	53	1.13 (0.76–1.66)	0	0	-
> 2.7	11,783	50	0.95 (0.64–1.41)	10,025	30	0.71 (0.45–1.12)	9,813	37	0.97 (0.63–1.49)	597	2	1.57 (0.38–6.44)

[a]Adjusted for menopausal status (time dependent), BMI (<20/20–25/>25 kg/m^2), physical activity in 1993 (in Met-h/week; <34/34–46/46–62/>62), age at menopause (<47/47–54/>54 years among postmenopausal women), age at menarche, parity (number of full-term pregnancies), previous use of oral contraceptives (ever/never), use of menopausal hormone therapy (never, current, past, unknown, time-dependent variable, among postmenopausal women only), daily calcium (<868.4/868.4–1,092.5/>1,092.5 mg/day), current use of calcium supplement (yes, no, unknown; time-dependent variable), alcohol intake (g/day), total energy intake without alcohol (kcal/day), university degree (yes/no), previous family history of breast cancer (yes, no), previous personal history of benign breast disease (ever, never, time-dependent variable), previous history of mammographic exam (yes, no, time-dependent variable), sun burn resistance (low, medium, high), skin complexion (very fair, fair, medium, dark, very dark).

0.60–0.90; and HR = 0.63, 95% CI: 0.41–0.96, respectively). The association was restricted to postmenopausal women (corresponding HRs = 0.68, 95% CI: 0.54–0.85 and 0.57, 95% CI: 0.36–0.90, respectively).

Based on UVRd quartile distribution (Fig. 1), analyses excluding participants who lived in regions in a different UVR exposure quartile than in 1990 (2%) or who moved before the end of follow-up (3%) provided similar results (data not tabulated). Analyses restricted to women who were born in regions in the same UVRd quartile than their residence at baseline (57%) showed similar BC risk figures, although results were no longer statistically significant (e.g., in postmenopausal women born and living in regions in the upper quartile of UVRd, HRs were 0.75, 95% CI: 0.56–1.01 for dietary vitamin D and 0.76, 95% CI: 0.44–1.32 for supplement intake as compared with those with the lowest intakes born in regions with low sun exposure). Finally, previous analyses stratified on women whose BC diagnosis was close to dietary exposure assessment (<6.3 years corresponding to median duration of follow-up until BC diagnosis) or far from it (>6.3 years) provided consistent BC risk reduction, and no differences were found between point estimates of these 2 groups (data not shown).

Discussion

In this French prospective cohort, with low dietary vitamin D, dietary and supplement vitamin D intakes alone were not associated with the risk of pre- or postmenopausal BC, while high dietary and supplemental vitamin D intakes are associated with a reduced BC risk in women living in areas with higher UV exposure. Although, our results do not support a linear dose–response relationship of both UVR dose and dietary vitamin D on BC risk, our findings suggest that a threshold of vitamin D exposure is required to prevent BC; this minimal amount is likely to vary with individual ability to metabolize or synthesize vitamin D from both sources.

As previously described (3–6, 9), evidence from observational studies on the relationship between vitamin D intake and BC risk is inconsistent. Some observational studies did not describe a decreased risk of BC with increasing vitamin D intakes (20, 32, 33), whereas others support such a relationship (19, 21, 23, 34–37), in either postmenopausal (24, 37), or premenopausal women (22, 34).

Only few observational studies (20–22, 34, 35, 38) examined the joint effect of dietary calcium and vitamin D intakes with discrepant conclusions; consistently to previous findings, we found no significant interaction between calcium and vitamin D intakes (21, 22, 34, 35) and analyses stratified on these 2 nutrients demonstrated that they did not confound each other. Our inconclusive results may be due to low intakes of both nutrients in France as compared to the United States. In the United States, fortification of foods, especially dairy products and margarines, with vitamin D and calcium has been common practice for a long time (13, 14), while it is still restricted to very few products in France. Indeed a recent meta-analysis (6) concluded to a significant decrease in BC risk only in women with vitamin D intakes over 10 μg/day (400 IU), a threshold that is difficult to reach in Western European countries without supplementation. Vitamin D dietary intakes from foods only were indeed particularly low in our population in comparison to North American populations [median intakes of vitamin D from diet only were 145 IU in women from the Women's Health Initiative trial (39) and 245 IU in the Women's Health Study (21), while only 96 IU in our population]. These low intakes may explain in part the absence of association in our study between overall vitamin D intake from diet and BC risk. Thus, as suggested by our results, diet alone seems unable to provide an adequate amount of vitamin D.

Regarding vitamin D from UV exposure, previous ecological studies (15, 40–42) described a significant inverse association between increased UVRd exposure and BC risk. It is noteworthy that we observed some inverse association between BC risk and a combination of high vitamin D dietary intakes and high UV solar irradiation, despite the fact that our population resides north of 41° latitude (Corsica); indeed, in most parts of France, sun exposure is sufficient for vitamin D production no more than 4 months a year (12), and over half of the year, most of the skin is covered up. High doses (>400 UI/day) of vitamin D supplements have been associated with BC risk reduction (35) but other observational or intervention studies (20) failed to show any association with lower doses of vitamin D supplements. Thus, in situations of low sun exposure, vitamin D dietary intakes may not provide sufficient amounts of vitamin D to observe any association with BC. In our population, the proportion of supplement users was small, and vitamin D intake from dietary sources was too low to compensate for the seasonal variations of vitamin D status at northerly latitudes where quality of sunlight is often too poor for adequate vitamin D production (43). However, we cannot exclude some other mechanism than vitamin D synthesis to account for the observed association between higher UVRd exposure and decreased BC risk.

Results from the first NHANES Epidemiologic study also suggested a stronger BC risk associated with vitamin D dietary intake in women living in areas with high solar radiation (19). In the opposite, others (20) found that the decrease in postmenopausal BC with high dietary vitamin D intake was confined to women living in American States with low UV index (P for interaction between dietary vitamin D and UV index = 0.05). Although apparently discrepant, these results suggest that both dietary and UV-produced vitamin D are of importance to ensure doses sufficient for controlling health hazards, the interaction between dietary and UV production depending on the level of each of these components, that is, level of dietary and supplement intake, and level of UVRd.

In France, both the Suvimax study (44) in over 1,500 women and a case–control study nested among 1,908 women of the E3N cohort (8) showed a south–north gradient of mean serum 25(OH)D concentrations with the highest levels in Southern regions and the lowest ones in Northern regions. Studies that examine 25(OH)D serum concentration (45) in relation to BC risk are of particular importance because 25(OH)D is a far more reliable indicator of the vitamin D status, less prone to misclassification bias, than dietary vitamin D intake. Our previous results found a decreased risk of BC with 25 (OH)D concentrations above 27 ng/mL as compared with the lowest tertile, under 20 ng/mL (8). 25(OH) vitamin D3 serum concentration has been described to be mainly determined by sunlight exposure (12), whereas in our sample we observed no significant correlation between 25 (OH)D and dietary or supplement vitamin D intake (8). Thus the most likely explanation for our present results of an inverse association between residential UVRd and BC risk is through vitamin D photosynthesis and consequently circulating 25(OH)D concentration, making more of this substrate available to the epithelial tissues of the terminal ductal lobular unit of the breast (9); when a sufficient vitamin D level is secured through UV exposure, variations in dietary intake may become of importance; in the opposite, when the underlying level of vitamin D photosynthesis is low, variations in dietary intake are insufficient to make any difference in disease risk.

The above-discussed associations in our study were confined to postmenopausal women. The likelihood of vitamin D deficiency increases with age, as intestinal absorption of vitamin D decreases (46), renal production of $1,25(OH)_2D$, the metabolically active form of vitamin D, may be impaired, and production of vitamin D by the skin declines, with the 7-dehydrocholesterase content of the skin being halved after 70 years of age (47). Moreover, after menopause, estrogen deficiency seems to reduce activation of vitamin D and the expression of the vitamin D receptor (48) resulting in increased risk of vitamin D deficiency in older and postmenopausal women (48, 49). However, since previous results from our nested case–control study were stronger in younger than in older women (8), our present results may be due to reduced power in premenopausal women. Alternatively we can hypothesize that vitamin D variation is more strongly related to UV exposure in the place of residence in older women, while place and duration of holidays, as well as other factors (duration of outdoors sports), which we could not consider in our study may be stronger determinants of the vitamin D level in younger women.

Strengths and limits

The prospective design of this study and the small number of women lost to follow-up limits the possibility of recall bias and selection bias as explanations for our results. Although residual confounding may be present, the minimal variation in our point estimates before and after adjustment for several recognized risk factors for BC reduces this possibility. In addition, we validated the dietary assessment tool, which proved reliable (26).

Previous data demonstrated that sunlight exposure measured by geographic proxies such as region of residence is reflective of the vitamin D status (18, 19, 42). Solar irradiance at the place of residence was assessed by satellite UVR dose calculation, and was thus unbiased, whereas self-declared data on sunbathing habits and outdoor sun exposure provided by sunlight exposure questionnaires may provide imprecise estimates of vitamin D status (50).

Furthermore, although results were of the same magnitude when analyses were stratified on latitude of residence, disparities between UV doses across French regions at same latitudes have been previously observed (28). Thus, use of UV doses may have reduced possible exposure misclassification. In addition, we adjusted for skin complexion, recreational physical activity, usual sunburn resistance, which are additional important predictors of the vitamin D status (14, 51, 52).

At last, our population was mainly composed of sedentary women living at latitudes above 43° where there is a minimal production of vitamin D in the skin during the winter; few women moved regions after inclusion in the study, and sensitivity analyses excluding women who moved between regions before and during the follow-up led to similar results. Thus, we can hypothesize that mean summer and spring UVR dose provided a good indicator of sunlight exposure.

Nevertheless, this study has some limitations. First, we only used a single dietary assessment and thus we could not estimate long-term effects of vitamin D dietary intake in early life as suggested by some studies (22, 23, 32) despite heterogeneous results. Some participants may also have changed their diets through follow-up resulting in some misclassification of exposure, which, though nondifferential, would have weakened the observed associations. In addition, analyses conducted on participants born in regions from same quartile of UVRd than at baseline failed to provide clear evidence of an early benefit of sun exposure on BC risk reduction. However, we can hypothesize that these findings may be due in some parts, to a lack of power and also unavailable estimation of UVRd in early life.

Second, we had no reliable information on doses of vitamin D supplements. However, taking account of vitamin D supplement intake did not affect the observed associations between dietary vitamin D and BC risk, since we considered supplementation as a fourth separate category, which was prospectively updated. This may have limited a potential misclassification bias. Moreover, updating the information on supplement use at each questionnaire could have put more emphasis on short-term effects of high vitamin D doses (53) than a single measurement at baseline.

Third, although adjustment was made for a number of risk factors for BC in the multivariate analyses, we cannot

exclude the possibility that within the main dietary sources of vitamin D and calcium, other nutrients could counteract potential benefits of vitamin D and calcium on BC risk (54). However, models using tertiles of the main food contributors of dietary vitamin D in the population one at a time did not demonstrate any association of these foods with BC risk.

Last, we used UVR dose that only corresponds to a proxy of UVB estimation. Nevertheless, UVR doses were estimated during summer months according to previous work (30) to attenuate the difference between UVB and effective UVR to synthesize vitamin D. Indeed, it has been shown that exposure of the body, in a bathing suit, to 1 minimal erythemal dose (MED; i.e., slight redness of the skin) is equivalent to taking between 10,000 and 25,000 IU of vitamin D orally (12).

Conclusion

In conclusion, based on this large population-based study of French women living above latitude 41°, our findings support a protective effect of sun exposure on the risk of BC and suggest that benefits of vitamin D dietary intakes on BC risk are modulated by UV exposure.

Considering that, in France, mean vitamin D dietary intake is low, and 25(OH)D serum concentrations are mostly below the 30 ng/mL recommended threshold (8), our results suggest that an increase in overall vitamin D intake should be encouraged by food and health agencies, possibly through fortification of foods.

Further investigations are warranted to improve assessment of UVR exposure and its correlation with the vitamin D status. Prospective studies should further investigate the associations between BC risk, vitamin D status, and sunlight exposure, while also considering the risk of cutaneous melanoma, examining different UVR exposure, and vitamin D intake thresholds.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Ethical approval

This study was approved by the ethics review board of the Inserm-U1018 research team.

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