Null Results in Brief

Prospective Study of Solar Exposure, Dietary Vitamin D Intake, and Risk of Breast Cancer among Middle-aged Women

Hannah Kuper,[1] Ling Yang,[2,3] Sven Sandin,[4] Marie Lof,[4,5] Hans-Olov Adami,[4,6,7] and Elisabete Weiderpass[3,4,6,8]

[1]Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]Clinical Trial Service Unit and Epidemiological Study Unit, University of Oxford, Oxford, United Kingdom; [3]Samfundet Folkhalsan, Helsinki, Finland; [4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [5]Department of Clinical and Experimental Medicine, University of Linkoping, Linkoping, Sweden; [6]Cancer Registry of Norway, Oslo, Norway; [7]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and [8]Department of Community Medicine, University of Tromsö, Tromsö, Norway

Abstract

The relationship between solar exposure or dietary vitamin D intake and breast cancer risk has not been fully elucidated. These associations were studied within the Women's Lifestyle and Health Cohort Study, a cohort of 49,259 Swedish women ages 30 to 50 years at baseline (1991-1992). Women were asked about solar exposure and completed a food frequency questionnaire and were followed-up through linkages to national registries until December 2004. In the current analyses, 41,889 women were included, 840 of whom were diagnosed with breast cancer during follow-up. Breast cancer risk was not related to solar exposure variables, including sun sensitivity, annual number of sunburns, time spent on sunbathing vacations, or solarium use at any age period of exposure. There was also no association with dietary vitamin D intake or supplementary multivitamin use. These relationships were not modified after stratifying by estrogen or progesterone receptor status. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2558–61)

Introduction

Sunlight exposure is the major determinant of serum vitamin D levels. Biological data, and to a lesser extent, epidemiologic studies, suggest that vitamin D may protect from a range of cancers (1). The role of sunlight exposure in breast cancer etiology is, however, not clearly elucidated. Ecological studies show an inverse association with breast cancer risk (2-4), also evident in some case-control studies, although often limited to subgroups (2-7). The National Health and Nutrition Examination Survey cohort found an inverse association between breast cancer incidence and sunlight exposure (8). In contrast, cohort and case-control studies investigating the etiology of breast cancer have generally found no role for dietary vitamin D and conflicting evidence for serum levels of vitamin D metabolites (9).

Our aim was to assess the association between solar exposure and dietary or supplementary vitamin D intake with breast cancer risk within a cohort of middle-aged Swedish women.

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Requests for reprints: Hannah Kuper, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom. Phone: 44-20-7927-2622; Fax: 44-20-7958-8325. E-mail: hannah.kuper@lshtm.ac.uk

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Materials and Methods

The Women's Lifestyle and Health cohort was enrolled in 1991 to 1992. A sample of 96,000 women ages 30 to 49 y residing in the Uppsala Health Care Region were randomly selected from the Swedish Central Population Registry at Statistics Sweden and sent a survey questionnaire. The 49,259 women who returned a completed mailed questionnaire comprise the study cohort. Full details of the study are available (10).

The cohort was followed-up through linkages with the death register, register of population migration, and the national cancer register, using the individually unique national registration number assigned to all Swedish residents. Follow-up started from the date of receipt of the returned questionnaire and person-years were calculated until the primary diagnosis of breast cancer (based on International Classification of Diseases-7 code 170), date of emigration or death, or the end of follow-up (December 31, 2004), whichever came first. Women were excluded if they had a history of invasive cancer before enrollment (n = 1,213), had total energy intake outside of the 1% to 99% percentile (843), or lacked data on all solar exposure variables (26). The final study population included 47,177 women, and a complete data set for covariate variables was available for 41,889 women.

The average length of follow-up was 12.9 y (SD = 1.6), during which time 840 women were diagnosed with an

invasive breast cancer. Of these cases, 548 were estrogen receptor–positive and 159 estrogen receptor–negative, 463 progesterone receptor–positive and 234 progesterone receptor–negative, and the remainder were of unknown receptor status.

Solar exposure was assessed through self-report using the following variables as previously described in detail (10):

1. Sun sensitivity—the effect on the skin of acute sun exposure at the beginning of the summer, and long-lasting or chronic sun exposure.
2. History of sunburn (i.e., burned by the sun so severely that it resulted in pain or blisters that subsequently peeled) and sunbathing vacations at different ages (10-19, 20-29, 30-39, or 40-49 y).
3. Use of solarium at different ages (10-19, 20-29, 30-39, or 40-49 y).

The women also completed a self-administrated food-frequency questionnaire that covered the frequency of consumption and quantity of approximately 80 food items and beverages reflecting dietary habits during the preceding 6 mo. We used these data to calculate individual dietary intake of vitamin D. Women also reported the use of multivitamins.

We calculated hazard ratios (HR) with corresponding 95% confidence intervals (95% CI) using the Cox proportional hazards regression model. Models were adjusted for established breast cancer risk factors (see table footnotes), using the attained age as the time scale. Analyses were further stratified by hormone receptor status. We checked the proportional hazards assumption by evaluating the Schoenfeld residuals (11). With the available sample size, we would be able to identify a risk ratio of 1.24 with 95% confidence and 80% power, assuming 25% of the women were in the "exposed" group (e.g., lowest quartile for vitamin D intake) and 2% of the unexposed women were diagnosed with breast cancer during follow-up (average across cohort).

The study was approved by the Data Inspection Board in Sweden and by the regional Ethical Committee.

Results

Sun sensitivity measures were unrelated to risk of breast cancer (Table 1). We found no association of breast

Table 1. HRs and 95% CIs of breast cancer according to measures of sun sensitivity and vitamin D intake

Characteristics	No. of women (no. of cases)	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)*
Skin color after acute sun exposure at the beginning of summer			
Brown	9,671 (185)	Reference	Reference
Red	20,021 (401)	1.1 (0.9-1.3)	1.1 (0.9-1.3)
Red with pain and/or blisters	12,060 (253)	1.2 (1.0-1.5)	1.2 (1.0-1.4)
Skin color after long-lasting or chronic sun exposure			
Deep brown	6,761 (154)	Reference	Reference
Brown	25,725 (487)	0.8 (0.7-1.0)	0.8 (0.7-1.0)
Light brown/never brown	100 (2)	0.9 (0.2-3.8)	0.9 (0.2-3.6)
Hair color			
Dark brown, black	11,683 (237)	Reference	Reference
Brown	18,048 (363)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Blond	10,385 (197)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Red	1,310 (35)	1.4 (1.0-2.0)	1.4 (1.0-1.9)
Eye color			
Brown	5,616 (112)	Reference	Reference
Gray, green or mix	14,673 (292)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Blue	20,846 (423)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Body surface area = (weight$^{0.425}$ × height$^{0.725}$ × 0.007184) m^2			
≤1.61	10,335 (182)	Reference	Reference
1.62-1.69	10,291 (221)	1.2 (1.0-1.4)	1.3 (1.0-1.6)
1.70-1.78	10,316 (213)	1.1 (0.9-1.4)	1.2 (1.0-1.5)
≥1.79	10,947 (224)	1.1 (0.9-1.3)	1.3 (1.0-1.6)
Total number of asymmetric nevi >5 mm on legs			
0	33,406 (638)	Reference	Reference
1	4,170 (93)	1.2 (1.0-1.5)	1.2 (0.9-1.5)
2-6	2,674 (58)	1.1 (0.9-1.5)	1.1 (0.9-1.5)
≥7	440 (11)	1.4 (0.8-2.5)	1.4 (0.8-2.5)
Use of sun block cream			
Never use	3,625 (76)	Reference	Reference
Infrequently	17,083 (359)	1.0 (0.8-1.3)	1.0 (0.8-1.3)
About half of time	3,743 (66)	0.9 (0.7-1.3)	0.8 (0.6-1.2)
Almost always use	17,238 (335)	1.0 (0.7-1.2)	0.9 (0.7-1.2)
Dietary vitamin D			
Quartile 1	10,230 (210)	Reference	Reference
Quartile 2	10,539 (233)	1.1 (0.9-1.3)	1.1 (0.9-1.3)
Quartile 3	10,578 (203)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Quartile 4	10,542 (194)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
Multivitamin use			
Yes	35,683 (714)	Reference	Reference
No	6,206 (126)	1.1 (0.9-1.3)	1.0 (0.8-1.2)

*Adjusted for parity (nulliparous, 1, 2, 3, ≥4), age at first birth (<21, 21-24, ≥25 y), body mass index (<18.5, 18.5-24, ≥25 kg/m^2), age at menarche (<12, 13, ≥14 y), use of hormonal contraceptives (never or ever), consumption of alcohol (nondrinker,<1.7, 1.7-4.4, ≥4.4 units), breast-feeding (<6, 6-12, ≥12 mo), education (<10, 10-12, 13-15, ≥16 y), family history of breast cancer (yes or no), physical activity (very low or low, normal, high or very high), and smoking (never or ever).

Table 2. HRs and 95% CIs of breast cancer according to solar exposure during different age periods of exposure

Age period for exposure	Annual number of sunburns			Weeks per year spent on sunbathing vacations			Solarium use		
	Frequency	No. of women (no. of cases)	Multivariate HR (95% CI)*	Frequency	No. of women (no. of cases)	Multivariate HR (95% CI)*	Frequency	No. of women (no. of cases)	Multivariate HR (95% CI)*
10-19 y									
	Never	8,361 (160)	Reference	Never	14,670 (325)	Reference	Never	38,379 (759)	Reference
	≤1/y	20,031 (418)	1.1 (1.0-1.4)	1 wk/y	10751 (192)	0.9 (0.8-1.1)	Rarely	528 (14)	2.2 (1.3-3.8)
	≥2/y	10,994 (206)	1.1 (0.9-1.4)	2-3 wk/y	10,089 (193)	1.0 (0.9-1.2)	≥1 time/mo	263 (3)	0.9 (0.3-2.9)
				≥4 wk/y	4,034 (80)	1.1 (0.8-1.4)			
20-29 y									
	Never	6,516 (122)	Reference	Never	8,140 (170)	Reference	Never	30,564 (676)	Reference
	≤1/y	23,294 (485)	1.2 (0.9-1.4)	1 wk/y	13,850 (252)	0.9 (0.7-1.1)	Rarely	4,760 (55)	0.9 (0.7-1.3)
	≥2/y	10,318 (193)	1.1 (0.9-1.4)	2-3 wk/y	14,416 (311)	1.1 (0.9-1.3)	≥1 time/mo	4,384 (48)	1.0 (0.7-1.4)
				≥4 wk/y	4,054 (76)	1.0 (0.8-1.3)			
30-39 y									
	Never	10,479 (210)	Reference	Never	8,620 (167)	Reference	Never	19,814 (483)	Reference
	≤1/y	22,774 (465)	1.0 (0.8-1.1)	1 wk/y	13,323 (259)	1.0 (0.8-1.2)	Rarely	9,806 (162)	0.8 (0.7-1.0)
	≥2/y	5,494 (113)	1.0 (0.8-1.2)	2-3 wk/y	13,314 (292)	1.1 (0.9-1.3)	≥1 time/mo	9,363 (142)	0.8 (0.7-1.0)
				≥4 wk/y	3711 (86)	1.1 (0.9-1.5)			
40-49 y†									
	Never	7,335 (203)	Reference	Never	4,765 (119)	Reference	Never	7,770 (223)	Reference
	≤1/y	9,515 (282)	1.0 (0.9-1.3)	1 wk/y	6,126 (177)	1.1 (0.9-1.4)	Rarely	5,720 (156)	0.9 (0.7-1.1)
	≥2/y	1,590 (42)	0.9 (0.7-1.3)	2-3 wk/y	6,163 (177)	1.1 (0.8-1.4)	≥1 time/mo	5,816 (163)	0.9 (0.8-1.2)
				≥4 wk/y	1775 (56)	1.2 (0.9-1.6)			

*Adjusted for parity (nulliparous, 1, 2, 3, ≥4), age at first birth (<21, 21-24, ≥25 y), body mass index (<18.5, 18.5-24, ≥25 kg/m^2), age at menarche (<12, 13, ≥14 y), use of hormonal contraceptives (never or ever), consumption of alcohol (nondrinker,<1.7, 1.7-4.4, ≥4.4 units), breast-feeding (<6, 6-12, ≥12 mo), education (<10, 10-12, 13-15, ≥16 y), family history of breast cancer (yes or no), physical activity (very low or low, normal, high or very high), and smoking (never or ever).
†Restricted to women ages ≥40 at enrollment.

cancer with sun sensitivity of skin, hair or eye color, body surface area, or number of asymmetric nevi. Dietary or supplementary vitamin D intake and sun block use were also not associated with breast cancer risk.

Solar exposure variables were also unrelated to risk of breast cancer (Table 2). There was no relationship between annual number of sunburns, weeks per year spent on sunbathing vacations, or use of solariums, at any age period of exposure, with risk of breast cancer. A composite of exposure to these variables between ages 10 and 39 was also unrelated to risk of breast cancer (data not shown).

Using the same models, we analyzed estrogen-positive, estrogen-negative, progesterone-positive, and progesterone-negative cancers separately, but found no evidence of effect modification for the association of solar exposure or vitamin D with breast cancer risk (data not shown).

Discussion

We found no association between sun sensitivity, solar exposure (at any age period of exposure), or dietary vitamin D intake with risk of breast cancer in this large cohort of Swedish women. These findings are not consistent with some earlier studies (2-9), although previous inverse associations were generally weak and inconsistent, detectable mainly in subgroups. The inverse association reported in other studies may indicate a true causal relationship because vitamin D, whether the product of solar exposure or dietary intake, may protect from a range of types of cancer (1). Alternatively, recall bias may play a role, as most associations have been detected in case-control studies. Confounding may also bias the results of earlier studies as socioeconomic status may relate to both higher solar exposure and increased breast cancer risk.

The strengths of this study included its large size and prospective design, with complete follow-up of women through linkages to national registers. The main possible limitation is misclassification in the assessment of solar exposure and dietary vitamin D, which may have biased the results to the null. However, previous analyses from this study have shown a strong association between these solar exposure measures and risk of malignant melanoma (10), suggesting that the questionnaire items to assess solar exposure are appropriate. Detailed information was collected on known breast cancer risk factors to allow adjustment for confounding.

In conclusion, this large cohort study provides no support for the hypothesis that solar exposure or vitamin D reduces risk of breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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