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Ultraviolet radiation exposure and breast cancer risk in the Nurses' Health Study II

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Background: Ultraviolet (UV) radiation exposure, the primary source of vitamin D for most people, may reduce breast cancer risk. To date, epidemiologic studies have shown inconsistent results.

Methods: The Nurses' Health Study II is a U.S. nationwide prospective cohort of female registered nurses. A UV exposure model was linked with geocoded residential address histories. Early-life UV exposure was estimated based on the state of residence at birth, age 15, and age 30. Self-reported breast cancer was confirmed from medical records. Time-varying Cox regression models adjusted for established breast cancer risk factors were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: From 1989 to 2013, 3,959 invasive breast cancer cases occurred among 112,447 participants. Higher UV exposure during adulthood was not associated with invasive breast cancer risk overall (adjusted HR comparing highest to lowest quintile = 1.00; 95% CI = 0.90, 1.11, P for trend = 0.64) or according to estrogen receptor (ER) status. There were suggestive inverse associations between ER- breast cancer and early-life UV exposure at birth (adjusted HR = 0.94; 95% CI = 0.88, 1.01 per interquartile range increase [15.7 mW/m²]), age 15 (adjusted HR = 0.96; 95% CI = 0.89, 1.04 per 18.0 mW/m²), and age 30 (adjusted HR = 0.90; 95% CI = 0.82, 1.00 per 27.7 mW/m²).

Conclusions: Ambient UV exposure during adulthood was not associated with risk of invasive breast cancer overall or by ER status. However, we observed suggestive inverse associations between early-life UV exposure and ER- breast cancer risk.

Introduction

Solar ultraviolet B (UV-B) radiation (280–315 nm) is the primary source of vitamin D for most humans, as UV-B penetrates the skin and converts 7-dehydrocholesterol to previtamin D₃ and

subsequently vitamin D₃.^{1,2} UV-B irradiance is hypothesized to impact breast carcinogenesis through resultant increases in circulating levels of 25-hydroxyvitamin D (25(OH)D) and availability of this substrate in the epithelial tissues of the terminal ductal lobular unit of the breast.³ Although experimental studies have demonstrated biological plausibility in vitamin D inhibiting cell proliferation and inducing apoptosis in breast cancer cells,^{4–7} results from previous population-based research examining the association between ambient UV exposure and breast cancer risk have been inconsistent, showing both inverse and null associations.^{8–14} A potential limitation of previous epidemiologic studies that could have contributed to mixed findings has been the use of relatively coarse-scale UV exposure measures. For example, studies have linked geographic variables (e.g., Census tracts and cities) with National Aeronautics and Space Administration (NASA) Total Ozone Mapping Spectrometer (TOMS) UV satellite images (spatial resolution is approximately 100 km²)^{8,10,11,13} and estimated UV during adulthood based on state at birth and state of longest residence.¹² Although several of these studies showed no association between UV exposure and breast cancer,^{8,10–13} UV has been observed to exhibit substantial spatial and temporal variability;^{15,16} improved exposure

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What this study adds

Consistent with previous epidemiologic studies, this U.S. nationwide prospective cohort study showed that ambient ultraviolet (UV) radiation exposure during adulthood was not associated with invasive breast cancer risk. However, there were suggestive inverse associations between early-life UV exposure and estrogen receptor-negative breast cancer, which warrants further investigation as UV exposure during early life, a critical period regarding breast morphogenesis and differentiation, may be more relevant to breast carcinogenesis compared to exposure later in life. Strengths of this study included a high spatiotemporal resolution UV exposure assessment using updated geocoded residential addresses, examination of breast cancer subtypes, and extensive evaluation of potential confounding and effect modification.

assessment for ambient UV with increased spatiotemporal resolution may reduce measurement error. The objective of this study was to examine the association between ambient UV exposure and breast cancer incidence in a prospective cohort of U.S. women using biennially updated geocoded residential address histories and a high spatiotemporal resolution UV exposure model.

Methods

Study population

The Nurses' Health Study II (NHSII) is an ongoing U.S. nationwide prospective cohort study of 116,429 female registered nurses aged 25–42 years at baseline in 1989.¹⁵ Participants originally resided in California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas. As of the mid-1990s, participants lived in all 50 states and Washington, D.C. Self-administered questionnaires were completed biennially to ascertain information regarding incident disease, medical history, diet, lifestyle factors, and health behaviors. Response rates for each questionnaire cycle are $\geq 90\%$.¹⁵ We excluded women who were missing exposure information due to residence outside of the contiguous US (where the UV exposure model was not available) or with prior diagnoses of other cancers (except nonmelanoma skin cancer). The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Participants provided implied consent through returning questionnaires and informed consent for release of medical records and collection of tissue specimens.

Assessment of outcome

Invasive breast cancer cases were identified through self-report on biennial questionnaires. Deaths were reported by family members, U.S. Postal Service, or ascertained from the National Death Index. A medical record review was conducted to confirm breast cancer cases and abstract information regarding tumor characteristics. As 99% of breast cancer cases were confirmed via medical record review, self-reported cases without medical record confirmation were also included in the analysis. We also examined breast cancer subtypes defined by hormone receptor status based on tissue microarrays (TMAs) constructed at the Dana-Farber/Harvard Cancer Center Tissue Microarray Core Facility. Three 0.6 mm diameter cores from tumor tissue samples were inserted into TMA blocks. Immunohistochemical staining for markers including estrogen receptor (ER) was performed on 5 μm paraffin sections cut from TMA blocks. Immunostained TMA sections were reviewed under a microscope and visually scored for ER positivity as determined by any nuclear staining ($\geq 1\%$).^{16,17} If TMA information was unavailable, hormone receptor status was based on the medical record or pathology report.

Exposure assessment

Participant residential address histories updated every 2 years beginning in 1989 (Figure 1A) were geocoded to the street or ZIP Code level and spatially joined to a high spatiotemporal resolution erythemal UV exposure model (Figure 1B)¹⁸ in a geographic information system using ArcMap 10.5.1 (Esri, Redlands, California). Erythemal UV incorporates UV-A and UV-B wavelengths (the latter is involved in cutaneous vitamin D production) and weights these wavelengths based on their relative effectiveness to induce erythema on white skin.^{19,20} Shorter UV-B wavelengths are weighted more in the erythemal

UV calculation. The UV model was developed by applying area-to-point residual kriging to downscale NASA erythemal UV satellite remote sensing images from the TOMS and Ozone Monitoring Instrument satellite sensors.¹⁸ The UV model also incorporated information on established predictors of UV including aerosol optical depth, cloud cover, elevation, ozone, and latitude.^{18,21} The UV model predicts average July noon-time erythemal UV irradiance (mW/m^2), spanning the contiguous US, with a spatial resolution of 1 km^2 and an annual temporal resolution that varied over time for each year from 1980 to 2015. Model cross-validation demonstrated high predictive performance, showing positive percent relative improvements in mean absolute error (0.6%–31.5%) and root mean square error (3.6%–29.4%) in UV exposure prediction compared to using TOMS or Ozone Monitoring Instrument satellite images only.¹⁸ For each participant, UV exposure during adulthood was calculated as a time-varying cumulative average, where UV exposure from previous years was averaged and this average was updated every 2 years over the course of follow-up.

In secondary analyses, we examined UV exposure during early life. We lacked street address information for participant residences before cohort inception. Therefore, to estimate ambient UV exposure in early life, we linked the self-reported state of residence at birth, age 15, and age 30, with the UV exposure model using geographic information system. The UV model was aggregated to the state level, where UV raster cell centroids intersecting a given state were averaged to calculate a mean state UV exposure value. For California residents, participants reported living in Northern or Southern California; UV exposure was estimated using established boundaries.²² For participants who were born, age 15, or age 30 in years on or before 1980, we used the UV model estimates from 1980 (earliest available year). For participants who were born, age 15, or age 30 in years after 1980, we used the UV model in the concurrent year.

Additional covariates

Individual-level data on variables including breast cancer risk factors were collected from biennial questionnaires (or every other questionnaire for diet and physical activity). Area-level variables, such as population density (to account for rural/urban differences in environmental exposures and access to health care), were ascertained by linking each participant's locational information with Census tract-level data from the U.S. Census Bureau. Fine particulate matter air pollution $<2.5 \mu\text{m}$ in diameter ($\text{PM}_{2.5}$) and coarse PM air pollution between 2.5 and 10 μm in diameter ($\text{PM}_{2.5-10}$) exposures at each residential address were estimated by linking geocoded addresses with validated spatiotemporal exposure models.²³

Statistical analysis

Person-time accrued from June 1989 until the end of follow-up in May 2013, incidence of invasive breast cancer or other cancer (excluding non-melanoma skin cancer, but including in situ breast cancer), death, or loss to follow-up, whichever occurred first. Time-varying Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between UV exposure and incidence of invasive breast cancer. All models were stratified by age and questionnaire period. UV exposure was examined using quintiles (or tertiles for early-life UV exposure) and continuously per interquartile range (IQR) increase. The IQR for UV exposure during adulthood was 30.0 and 15.7 mW/m^2 (birth), 18.0 mW/m^2 (age 15), and 27.7 mW/m^2 (age 30) for early life. Tests for trend were calculated using the median value of each quintile of exposure. Cubic regression splines were used to test for deviations from linearity. The missing indicator method was used to account for any missing covariates.

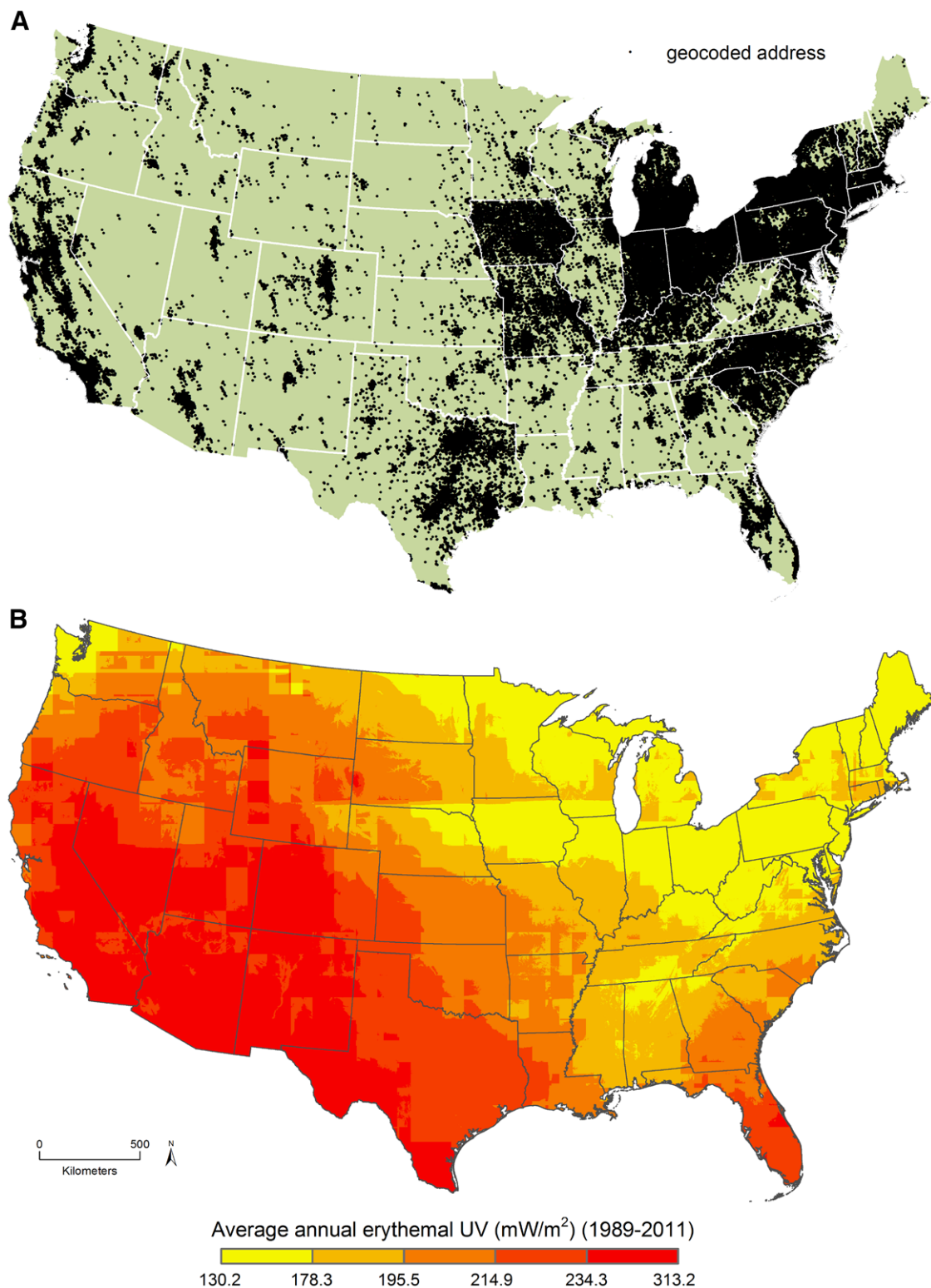


Figure 1. (A) NHSII participant geocoded residential addresses (1989–2011) and (B) the spatiotemporal UV exposure model (1989–2011).

The following established and suspected breast cancer risk factors were included in multivariable models a priori: age, race, family history of breast cancer, personal history of biopsy-confirmed benign breast disease, age at menarche, parity, age at first birth, lactation, menopausal status and hormone use (among postmenopausal women only), height, body mass index (BMI) at age 18, change in BMI since age 18, physical activity, adult alcohol consumption, total vitamin D intake (from diet and supplements), individual-level socioeconomic status (SES)

(i.e., personal income, marital status, and living arrangements), area-level SES (i.e., Census tract median home value and median income), and population density. We also evaluated potential confounding by oral contraceptive use, screening mammography, smoking status, alcohol consumption at age 15 and 18, Alternate Healthy Eating Index diet score,²⁴ $PM_{2.5}$, $PM_{2.5-10}$, and sun exposure, sensitivity, and protection measures (number of sunburns from ages 15–20; hair color; sunscreen use as a teenager; time in direct sunlight during summer months, winter

months, high school/college, and ages 25–35; reaction to sun; and tanning booth use during high school/college, ages 25–35, and as an adult). However, as these variables did not change the effect estimate for UV exposure (i.e., $\geq 10\%$ change in the HR), they were not included in the final model. We present results from a basic model, a parsimonious model, and a fully adjusted model.

We explored potential effect modification by race, menopausal status, BMI, physical activity, total vitamin D intake, $PM_{2.5}$, $PM_{2.5-10}$, U.S. Census Bureau region of residence (i.e., Northeast, Midwest, West, and South), sun exposure, sensitivity, and protection measures, and residential mobility. These variables have exhibited differential associations with either UV or subgroups of the population with higher risk or susceptibility for breast cancer.^{11,21,25,26} Effect modification was assessed by conducting stratified analyses using continuous UV exposure. Tests for interaction were performed by adding interaction terms to the model and using likelihood ratio tests to determine statistical significance. All statistical analyses were conducted using SAS (SAS Institute, Cary, North Carolina).

Results

Table 1 shows population characteristics of the 112,447 participants included in the analysis overall and by quintiles of cumulative average UV exposure over follow-up. Participants were on average 45.4 ± 8.3 years of age, consumed an average of 385.0 ± 211.0 IU/day of vitamin D from diet and supplements, and were mostly white, premenopausal, married, parous, and never-smokers. The majority of participants over the course of follow-up resided in the Northeast and Midwest regions of the United States, and experienced at least one sunburn from ages 15 to 20 years. Women residing in areas with higher UV levels were more likely to live in the Western or Southern United States, to be nonwhite, never-smokers, nulliparous, have higher individual-level income, and live in areas with a higher Census tract median home value and income. Women in high-UV areas were also more likely to have had at least three sunburns from ages 15 to 20 years, spend ≤ 1 hour/week in direct sun during the summer months but ≥ 5 hours/week during the winter months, and to have ever moved during follow-up.

During 2,497,437 person-years of follow-up from 1989 to 2013, 3,959 invasive breast cancers occurred ($n = 2,368$ ER+; $n = 585$ ER-). Higher levels of UV exposure during adulthood were not associated with invasive breast cancer risk overall (adjusted HR comparing highest to lowest quintile = 1.00; 95% CI = 0.90, 1.11; P for trend = 0.64), or with ER+ and ER- breast cancer subtypes in multivariable models (Table 2). Results from the basic model adjusted for age and race did not substantially change after adjustment for SES factors in parsimonious models, or after additional adjustment for established breast cancer risk factors, total vitamin D intake, and population density in fully adjusted models. We did not observe any statistically significant deviations from linearity. Similar null results were observed when examining UV exposure continuously (Table 2) and in analyses among premenopausal women (see Supplemental Material, Table S1; <http://links.lww.com/EE/A49>) and postmenopausal women (see Supplemental Material, Table S2; <http://links.lww.com/EE/A49>).

There were no statistically significant differences in the association between UV exposure and invasive breast cancer risk by race, menopausal status, BMI, physical activity, total vitamin D intake, $PM_{2.5}$, $PM_{2.5-10}$, region of residence, and sun exposure, sensitivity, and protection measures (see Supplemental Material, Table S3; <http://links.lww.com/EE/A49>). Similar null results were observed among participants who never moved compared to those who ever-moved during follow-up (see Supplemental Material, Table S4; <http://links.lww.com/EE/A49>).

Although we did not observe associations between early-life UV exposure and invasive breast cancer risk overall, we did observe suggestive inverse associations with ER- breast cancer (Table 3). IQR increases in UV at birth (adjusted HR = 0.94; 95% CI = 0.88, 1.01 per 15.7 mW/m²), age 15 (adjusted HR = 0.96; 95% CI = 0.89, 1.04 per 18.0 mW/m²), and age 30 (adjusted HR = 0.90; 95% CI = 0.82, 1.00 per 27.7 mW/m²) were associated with slight decreases in ER- breast cancer risk.

Discussion

In this nationwide prospective analysis of US women, we did not observe an association between ambient UV exposure during adulthood and invasive breast cancer risk overall or according to subtypes defined by ER status. These results are consistent with several previous epidemiologic studies demonstrating null associations between UV and breast cancer.^{8–14} We also observed suggestive inverse associations between early-life UV exposure and ER- breast cancer.

Vitamin D derived from sun exposure is hypothesized to protect against breast cancer through mechanisms related to apoptosis, inhibition of cell proliferation, metastasis, and the synthesis and biological actions of estrogens.⁶ Breast tissue contains 1- α -hydroxylase, an enzyme required for production of the active vitamin D metabolite (1,25(OH)₂D) from circulating 25(OH)D.⁶ Locally synthesized 1,25(OH)₂D can bind to vitamin D receptors, which are present in breast epithelium and thus play a role in regulating gene expression.²⁷ Yet population-based studies examining vitamin D using blood, diet, self-reported sun exposure, and residence-based ambient UV measures have demonstrated inconsistent results with breast cancer risk.

Higher blood levels of circulating 25(OH)D have been associated with both inverse and null associations with breast cancer risk, where effect estimates ranged from 0.55 to 0.99.^{28–32} For example, a meta-analysis of 24 prospective cohort and nested case-control studies with 31,867 breast cancer cases found that higher levels of 25(OH)D in blood were not statistically significantly associated with breast cancer risk (pooled relative risk (RR) = 0.92; 95% CI = 0.83, 1.02).³⁰ Although some observational studies and randomized controlled trials have shown that higher levels of vitamin D intake (dietary and/or supplemental) are associated with decreased risk for breast cancer, the majority of studies have not been associated with breast cancer risk (pooled RRs ranging from 0.91 to 1.11).^{28,30,33,34} Randomized controlled trials of vitamin D supplementation at a dose of 400 IU/day combined with calcium supplementation (1,000 mg/day) or 2,000 IU/day did not significantly reduce breast cancer risk compared to the placebo group.^{35,36}

Previous prospective and retrospective studies assessing self-reported sun exposure and time spent outdoors have been mixed.^{8,9,11–14,37–40} In a retrospective case-control study in Ontario, Canada, >21 hours per week spent outdoors during ages 40–50 years compared to ≤ 6 hours per week was associated with a 16% lower risk for breast cancer (adjusted odds ratio [OR] = 0.74; 95% CI = 0.61, 0.88).¹³ There was an inverse association between frequent recreational sun exposure (adjusted RR = 0.66; 95% CI = 0.44, 0.99) and occupational sun exposure (adjusted RR = 0.64; 95% CI = 0.41, 0.98) and breast cancer risk in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study.¹² In contrast, sun exposure (i.e., sunburns, sunbathing vacations, and tanning booth use) was not associated with breast cancer risk in the Women's Lifestyle and Health Cohort Study in Sweden.³⁷ Time spent outdoors during early- and adult-life was not associated with breast cancer risk in the United States Radiologic Technologists (USRT) study.¹¹ However, time spent outdoors during the summer, other seasons, or year round was positively associated with postmenopausal breast cancer risk in the

Table 1
Age-adjusted characteristics of 112,447 NHSII women over follow-up from 1989 to 2013 by cumulative average UV quintile

	Overall	UV quintile 1 (<166.6 mW/m^2)	UV quintile 2 (≥ 166.6 – 173.7 mW/m^2)	UV quintile 3 (≥ 173.7 – 182.9 mW/m^2)	UV quintile 4 (≥ 182.9 – 209.9 mW/m^2)	UV quintile 5 (≥ 209.9 mW/m^2)
Person-years (n)	2,497,437	500,327	500,537	503,207	500,037	493,329
Cumulative average UV (mW/m^2) (mean \pm SD)	186.4 \pm 28.2	159.6 \pm 12.2	168.9 \pm 6.9	177.6 \pm 4.8	193.2 \pm 9.0	233.8 \pm 17.4
Age (years) (mean \pm SD)	45.4 \pm 8.3	45.4 \pm 8.2	45.3 \pm 8.3	45.2 \pm 8.3	45.1 \pm 8.3	46.1 \pm 8.2
White (%)	96	97	96	97	96	91
Family history of breast cancer (%)	11	10	11	11	10	11
Personal history of biopsy-confirmed benign breast disease (BBD) (%)	17	17	18	17	17	16
Menopausal status and hormone use (%)						
Premenopausal	67	68	68	67	66	66
Never users	5	6	6	6	4	4
Past users	11	11	10	11	11	11
Current users	8	7	6	7	9	10
Missing	9	9	10	9	10	9
Age at menarche (years) (mean \pm SD)	12.4 \pm 1.4	12.4 \pm 1.4	12.4 \pm 1.4	12.4 \pm 1.4	12.4 \pm 1.4	12.4 \pm 1.5
Parity and age at first birth (%)						
Nulliparous	17	17	16	16	16	21
1–2 children <25	14	14	14	15	16	13
1–2 children ≥ 25 – 30	19	20	19	20	20	18
1–2 children ≥ 30	13	12	12	12	12	15
3+ children <25	11	12	12	13	11	8
3+ children ≥ 25 – 30	10	11	11	11	9	8
3+ children ≥ 30	2	2	2	2	2	2
Missing	13	12	13	12	14	14
Breastfeeding (%)						
Never	13	15	14	14	13	8
Ever	55	55	54	56	54	55
Missing	11	11	11	11	12	11
Oral contraceptive (OC) use (%)						
Never	12	14	14	12	9	10
Past	73	72	71	73	75	74
Current	7	6	6	6	7	7
Missing	9	8	9	8	9	9
Height (in) (mean \pm SD)	64.9 \pm 2.6	64.8 \pm 2.6	64.8 \pm 2.6	64.9 \pm 2.6	64.9 \pm 2.6	64.9 \pm 2.7
BMI (kg/m^2) at age 18 (mean \pm SD)	21.2 \pm 3.2	21.3 \pm 3.2	21.3 \pm 3.2	21.4 \pm 3.2	21.2 \pm 3.2	21.0 \pm 2.9
Current BMI (kg/m^2) (mean \pm SD)	25.5 \pm 4.9	25.6 \pm 5.0	25.6 \pm 4.9	25.6 \pm 4.9	25.5 \pm 5.0	25.0 \pm 4.8
Smoking status (%)						
Never	65	64	63	63	64	69
Past	25	25	26	26	25	23
Current	9	10	10	10	10	7
Alternate Healthy Eating Index (AHEI) (mean \pm SD)	53.6 \pm 10.8	52.8 \pm 10.7	52.8 \pm 10.7	53.1 \pm 10.8	53.3 \pm 10.7	56.0 \pm 10.7
Total vitamin D intake (IU/day) (mean \pm SD)	385.0 \pm 211.0	382.9 \pm 207.3	382.7 \pm 206.4	384.0 \pm 207.1	374.9 \pm 206.1	401.1 \pm 227.2
Adult alcohol consumption (g/day) (mean \pm SD)	3.2 \pm 5.2	2.9 \pm 4.7	2.9 \pm 4.8	3.2 \pm 5.1	3.2 \pm 5.3	3.6 \pm 6.0
Physical activity (MET hours/week) (mean \pm SD)	19.8 \pm 27.9	20.1 \pm 28.2	19.7 \pm 28.4	19.8 \pm 27.2	18.9 \pm 27.0	20.5 \pm 28.8
Census tract median home value ($\$10,000$) (mean \pm SD)	16.3 \pm 12.1	14.8 \pm 9.9	15.7 \pm 11.6	13.8 \pm 7.9	13.9 \pm 9.1	23.4 \pm 17.1
Census tract median income ($\$$) (mean \pm SD)	63,655 \pm 23,808	63,610 \pm 23,807	64,518 \pm 24,431	61,948 \pm 20,378	60,418 \pm 22,067	67,880 \pm 27,187
Individual-level income $> \$100,000$ (%)	21	20	21	20	20	25
Married (%)	56	58	56	57	55	53
Living alone (%)	7	7	7	7	7	8
Region of residence (%)						
Northeast	33	45	51	48	21	0
Midwest	32	51	42	36	30	2
West	15	0	0	1	7	68
South	19	4	6	15	43	30
Cumulative average $\text{PM}_{2.5}$ ($10 \mu\text{g/m}^3$) (mean \pm SD)	1.5 \pm 0.3	1.6 \pm 0.3	1.6 \pm 0.3	1.5 \pm 0.3	1.4 \pm 0.3	1.4 \pm 0.5
Cumulative average $\text{PM}_{2.5-10}$ ($10 \mu\text{g/m}^3$) (mean \pm SD)	1.1 \pm 0.5	0.9 \pm 0.3	0.9 \pm 0.3	0.8 \pm 0.3	1.0 \pm 0.3	1.6 \pm 0.6
Population density (population/ mi^2) (mean \pm SD)	3,767 \pm 10,848	3,979 \pm 12,766	5,991 \pm 18,221	2,731 \pm 6,893	1,866 \pm 3,255	4,310 \pm 4,973
No. sunburns from ages 15–20 (%)						
0	35	37	36	35	34	34
1	21	22	22	22	21	19
2	17	17	17	17	18	17
≥ 3	26	24	24	25	28	30
Hair color (%)						
Black	3	2	3	2	3	6
Blonde	14	13	13	14	14	15
Brown	66	69	68	68	65	61
Red	3	3	3	3	4	3
Missing	14	12	13	13	15	15

(Continued)

Table 1
(Continued)

	Overall	UV quintile 1 (<166.6 mW/ m ²)	UV quintile 2 (≥166.6–173.7 mW/ m ²)	UV quintile 3 (≥173.7–182.9 mW/m ²)	UV quintile 4 (≥182.9–209.9 mW/m ²)	UV quintile 5 (≥209.9 mW/m ²)
Sunscreen use as teenager (%)						
Not in sun	2	2	2	2	2	2
<50%	66	67	66	67	65	64
≥50%	12	13	13	12	12	12
Missing	20	18	19	19	21	21
Time in direct sun during summer months (%)						
≤1 hour/week	16	16	15	15	17	19
2–4 hours/week	32	32	31	32	31	32
≥5 hours/week	23	24	24	24	22	20
Missing	29	28	30	29	31	29
Time in direct sun during winter months (%)						
≤1 hour/week	36	41	39	39	34	26
2–4 hours/week	26	24	25	25	26	31
≥5 hours/week	8	6	7	7	9	13
Missing	30	28	30	29	31	30
Time in direct sun during high school/college (%)						
≤1 hour/week	5	5	5	5	5	5
2–4 hours/week	23	23	22	23	23	22
≥5 hours/week	42	43	43	43	41	42
Missing	30	29	30	29	31	30
Time in direct sun from ages 25–35 (%)						
≤1 hour/week	6	6	6	6	6	7
2–4 hours/week	29	29	28	29	29	29
≥5 hours/week	35	36	36	37	34	34
Missing	30	29	30	29	32	30
Reaction to sun (%)						
No reaction or some redness	53	53	53	53	54	53
Burn or painful burn	47	47	47	47	46	47
Tanning booth use during high school/college (%)						
None	64	65	64	64	62	64
1–2 times/year	3	3	3	3	3	3
≥3 times/year	3	3	3	4	4	3
Missing	30	28	30	29	31	30
Tanning booth use from ages 25–35 (%)						
None	57	58	57	56	54	59
1–2 times/year	5	5	5	6	6	5
≥3 times/year	8	8	8	9	9	6
Missing	30	29	30	29	31	30
Tanning booth use during adulthood (%)						
None	60	59	59	58	58	64
1–2 times/year	3	3	3	3	3	2
≥3 times/year	8	9	8	9	8	4
Missing	30	29	30	29	31	30
Ever-moved Census tract (%)	79	72	76	80	81	85

Women's Health Initiative Observational Study.⁸ These inconsistent findings may be related to recall bias from self-reported measures and/or assessing different measures of sun exposure (e.g., time spent outdoors versus sunburns) that may not adequately capture vitamin D status.

Ambient UV exposure is a proxy measure of long-term vitamin D status as solar UV-B is the primary source for vitamin D in most people.⁴¹ Approximately 90% of circulating levels of vitamin D come from solar UV-B.⁴¹ Ambient UV exposure has also been predictive of colorectal cancer risk.^{10,42} In this study, we were able to reconstruct historical ambient UV exposure through linking a spatially- and temporally-varying UV exposure model with biennially updated residential addresses geocoded to the street or ZIP Code level starting in 1989. Although the UV exposure assessment in our study was an improvement compared to several previous studies that were limited to using coarse geographic variables (e.g., region of residence, city, study clinic), baseline address only, and/or low-resolution UV exposure models, our null results were comparable to the majority of previous studies examining ambient UV exposure during adulthood and breast cancer incidence.^{8–13,40}

In particular, several epidemiologic studies examining UV exposure using NASA TOMS UV satellite images have shown no association with breast cancer risk.^{8,10,11,13} Specifically, UV exposure based on the city of residence in Canada was not associated with breast cancer risk (n = 3,101 cases; adjusted OR = 0.99; 95% CI = 0.83, 1.18).¹³ UV exposure estimated using the study clinic was not associated with postmenopausal breast cancer risk in Women's Health Initiative Observational Study (n = 2,535 cases).⁸ UV exposure from baseline residential Census tracts was not associated with breast cancer risk in the NIH-AARP Diet and Health Study (n = 8,681 cases; adjusted HR = 1.03; 95% CI = 0.97, 1.09).¹⁰ Average lifetime combined UV, a measure incorporating UV estimated using the city of residence and the daily number of hours spent outdoors, was not associated with breast cancer risk in USRT (n = 716 cases; adjusted HR = 0.85; 95% CI = 0.67, 1.08), although participants were exposed to relatively lower levels of UV in the USRT study compared to NHSII.¹¹ In a study using an exposure model interpolated to a spatial resolution finer than 2.5° (≥276 km),⁴³ UV exposure based on municipalities of residence was not associated with breast cancer risk in the Norwegian Women and Cancer Study

Table 2
Associations between cumulative average UV exposure during adulthood and breast cancer risk in NHSII from 1989 to 2013
(n = 112,447)

Outcome ^a	Cases (n)	Person-years (n)	Basic ^b HR (95% CI)	Parsimonious ^c HR (95% CI)	Fully adjusted ^d HR (95% CI)
Invasive breast cancer					
UV quintile 1	790	500,327	Referent	Referent	Referent
UV quintile 2	821	500,537	1.05 (0.95, 1.15)	1.05 (0.95, 1.16)	1.05 (0.95, 1.16)
UV quintile 3	760	503,207	0.97 (0.88, 1.07)	0.98 (0.88, 1.08)	0.96 (0.87, 1.06)
UV quintile 4	755	500,037	0.98 (0.89, 1.09)	1.00 (0.90, 1.11)	0.98 (0.88, 1.08)
UV quintile 5	833	493,329	1.03 (0.93, 1.14)	1.04 (0.94, 1.15)	1.00 (0.90, 1.11)
<i>P</i> for trend			0.86	0.79	0.64
Continuous UV (per IQR increase) ^e	3,959	2,497,437	1.00 (0.97, 1.04)	1.01 (0.97, 1.05)	0.99 (0.96, 1.03)
ER+					
UV quintile 1	460	500,642	Referent	Referent	Referent
UV quintile 2	504	500,847	1.10 (0.97, 1.25)	1.10 (0.97, 1.25)	1.10 (0.97, 1.25)
UV quintile 3	445	503,493	0.98 (0.86, 1.11)	0.98 (0.86, 1.12)	0.97 (0.85, 1.10)
UV quintile 4	445	500,346	1.00 (0.88, 1.14)	1.02 (0.89, 1.16)	0.99 (0.87, 1.13)
UV quintile 5	514	493,626	1.09 (0.96, 1.24)	1.07 (0.94, 1.22)	1.03 (0.90, 1.17)
<i>P</i> for trend			0.45	0.71	0.73
Continuous UV (per IQR increase) ^e	2,368	2,498,954	1.02 (0.97, 1.06)	1.01 (0.96, 1.06)	0.99 (0.95, 1.04)
ER−					
UV quintile 1	120	500,972	Referent	Referent	Referent
UV quintile 2	127	501,188	1.09 (0.85, 1.40)	1.10 (0.85, 1.41)	1.10 (0.86, 1.42)
UV quintile 3	115	503,788	0.98 (0.75, 1.26)	0.98 (0.76, 1.27)	0.97 (0.75, 1.25)
UV quintile 4	112	500,631	0.96 (0.74, 1.25)	0.98 (0.76, 1.27)	0.97 (0.75, 1.26)
UV quintile 5	111	493,973	0.93 (0.72, 1.21)	0.98 (0.75, 1.29)	0.98 (0.74, 1.28)
<i>P</i> for trend			0.31	0.58	0.54
Continuous UV (per IQR increase) ^e	585	2,500,552	0.97 (0.89, 1.07)	1.00 (0.90, 1.10)	1.00 (0.90, 1.10)

^aUV quintile 1: <166.6 mW/m²; quintile 2: ≥166.6–173.7 mW/m²; quintile 3: ≥173.7–182.9 mW/m²; quintile 4: ≥182.9–209.9 mW/m²; quintile 5: ≥209.9 mW/m².

^bAdjusted for age and race.

^cAdditionally adjusted for Census tract median home value, Census tract median income, marital status, living arrangements, and individual-level income.

^dAdditionally adjusted for family history of breast cancer, personal history of biopsy-confirmed BBD, age at menarche, parity, age at first birth, lactation, menopausal status and hormone use (among postmenopausal women only), height, BMI at age 18, change in BMI since age 18, physical activity, adult alcohol consumption, total vitamin D intake, and population density.

^eAn IQR increase in cumulative average UV is 30.0 mW/m².

(n = 948 cases; adjusted RR = 1.17; 95% CI = 0.95, 1.44).⁹ Studies assessing UV exposure in addition to other sun exposure-related variables (e.g., time spent outdoors, sunscreen use, skin color, tanning booth use, sunburns) showed inverse and null associations.^{8,11,13,43} In particular, UV exposure was not associated with breast cancer risk in studies that adjusted for time spent outdoors.^{8,11,13} There was also little evidence of an association when considering ER/PR status.⁸ In contrast to these studies suggesting no association, studies that have shown inverse associations between UV exposure and breast cancer have been ecological or used relatively coarser geographic variables to link UV exposure data compared to studies showing null results.⁴⁴ For example, there was an inverse association between higher UV exposure based on the region of residence at baseline and breast cancer risk in the French E3N cohort (n = 2,871 cases; adjusted HR = 0.91; 95% CI = 0.82, 0.99).⁴⁰

In our study, we observed a suggestive inverse association between early-life UV exposure and ER− breast cancer. UV exposure during early life, a critical period regarding breast morphogenesis and differentiation during which the breast is highly sensitive to various influences, may be more relevant to breast carcinogenesis compared to UV exposure later in life as an adult.⁴⁵ For example, atomic bomb radiation exposure during ages 10–19 years was associated with higher than expected breast cancer incidence compared to women exposed during adulthood.⁴⁶ Exposure to radiation treatment for tuberculosis was associated with higher risk for breast cancer mortality, with the highest risk observed among those exposed between ages 10–14 years.⁴⁷ Further, several epidemiologic studies have shown inverse associations between early-life UV exposure from self-report. Spending >21 hours/week outdoors during ages 10–19 years (adjusted OR = 0.71; 95% CI = 0.60, 0.85) and 20–39 years (adjusted OR = 0.64; 95% CI = 0.53, 0.76) was associated with a lower risk for breast cancer.¹³ Although the

residence-based early-life UV exposure measures in that study showed no association with breast cancer, the authors noted limited exposure variability in Ontario, Canada.¹³ In another study conducted in Ontario, higher outdoor activity episodes (for at least 30 minutes between 9 AM and 5 PM at least once per month from June to August) during ages 20–29 years were associated with a lower risk for breast cancer (adjusted OR = 0.65; 95% CI = 0.50, 0.85).⁴⁸ Among wives of Agricultural Health Study participants, at least 1 hour of sun exposure per day 10 years before enrollment (60.3% of participants were aged <50 years at enrollment) was associated with a decreased risk for breast cancer (adjusted HR = 0.8; 95% CI = 0.6, 1.0); this inverse association was also observed with ER+ but not ER− breast cancer.¹⁴ Sunbathing vacations between ages 10 and 29 years as well as tanning booth use between ages 10 and 39 years were associated with decreased risks for breast cancer in the Swedish Women's Lifestyle and Health Cohort.³⁹ In our study, the early-life UV exposure measures were based on the state of residence and are subject to exposure misclassification. Further, the range for early-life UV exposure was lower than for cumulative average UV exposure during adulthood. Future research assessing UV earlier in life before adulthood, such as from menarche to first pregnancy,⁴⁹ and potential differential effects by breast cancer subtype is warranted.

These analyses include several limitations. We did not have information on variables affecting personal UV exposure including time spent outdoors, clothing for sun protection, and seeking shade. However, we were able to account for several sun exposure, sensitivity, and protection measures collected from questionnaires. For example, results stratified by time in direct sun during summer as well as winter months were similarly null. However, there may be residual confounding as these measures may not adequately capture UV exposure-related behaviors. We also adjusted for physical activity, which is a proxy for time

Table 3
Associations between early-life UV exposure according to state at birth, age 15, and age 30 and breast cancer risk in NHSII

Outcome ^a	Cases (n)	Person-years (n)	Basic ^b HR (95% CI)	Parsimonious ^c HR (95% CI)	Fully adjusted ^d HR (95% CI)
Invasive breast cancer					
UV at birth					
UV tertile 1	873	527,563	Referent	Referent	Referent
UV tertile 2	1,335	763,853	1.03 (0.95, 1.12)	1.04 (0.95, 1.13)	1.04 (0.95, 1.13)
UV tertile 3	965	578,424	1.00 (0.92, 1.10)	1.01 (0.92, 1.11)	0.99 (0.90, 1.08)
P for trend			0.83	0.85	0.49
Continuous UV (per IQR increase) ^e	3,173	1,869,840	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)	0.99 (0.97, 1.02)
UV at age 15					
UV tertile 1	870	526,425	Referent	Referent	Referent
UV tertile 2	1,312	756,440	1.02 (0.94, 1.12)	1.03 (0.95, 1.12)	1.03 (0.95, 1.13)
UV tertile 3	991	586,974	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)	0.99 (0.90, 1.08)
P for trend			0.99	0.99	0.52
Continuous UV (per IQR increase) ^e	3,173	1,869,840	1.00 (0.97, 1.02)	1.00 (0.97, 1.03)	0.99 (0.96, 1.02)
UV at age 30					
UV tertile 1	1,033	619,994	Referent	Referent	Referent
UV tertile 2	1,111	648,144	1.11 (1.02, 1.21)	1.11 (1.02, 1.22)	1.10 (1.01, 1.20)
UV tertile 3	1,029	601,702	1.08 (0.99, 1.18)	1.08 (0.98, 1.18)	1.05 (0.95, 1.15)
P for trend			0.34	0.34	0.78
Continuous UV (per IQR increase) ^e	3,173	1,869,840	1.01 (0.98, 1.05)	1.01 (0.97, 1.05)	1.00 (0.96, 1.03)
ER+					
UV at birth					
UV tertile 1	547	527,857	Referent	Referent	Referent
UV tertile 2	824	764,337	1.01 (0.90, 1.12)	1.01 (0.91, 1.13)	1.02 (0.91, 1.13)
UV tertile 3	571	578,802	0.95 (0.84, 1.07)	0.94 (0.83, 1.06)	0.92 (0.81, 1.03)
P for trend			0.26	0.19	0.07
Continuous UV (per IQR increase) ^e	1,942	1,870,996	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	0.99 (0.96, 1.02)
UV at age 15					
UV tertile 1	531	526,735	Referent	Referent	Referent
UV tertile 2	813	756,906	1.03 (0.93, 1.15)	1.04 (0.93, 1.16)	1.04 (0.93, 1.16)
UV tertile 3	598	587,355	1.00 (0.89, 1.12)	0.99 (0.88, 1.11)	0.96 (0.85, 1.08)
P for trend			0.73	0.59	0.25
Continuous UV (per IQR increase) ^e	1,942	1,870,996	1.00 (0.97, 1.03)	0.99 (0.96, 1.03)	0.99 (0.95, 1.02)
UV at age 30					
UV tertile 1	638	620,354	Referent	Referent	Referent
UV tertile 2	659	648,582	1.10 (0.98, 1.24)	1.10 (0.99, 1.24)	1.09 (0.97, 1.22)
UV tertile 3	645	602,061	1.14 (1.02, 1.27)	1.13 (1.00, 1.27)	1.09 (0.97, 1.22)
P for trend			0.05	0.09	0.30
Continuous UV (per IQR increase) ^e	1,942	1,870,996	1.04 (1.00, 1.09)	1.03 (0.99, 1.08)	1.02 (0.97, 1.07)
ER-					
UV at birth					
UV tertile 1	135	528,258	Referent	Referent	Referent
UV tertile 2	194	764,900	0.98 (0.79, 1.23)	0.99 (0.80, 1.24)	1.00 (0.80, 1.25)
UV tertile 3	139	579,207	0.94 (0.74, 1.19)	0.97 (0.76, 1.23)	0.96 (0.75, 1.22)
P for trend			0.60	0.77	0.69
Continuous UV (per IQR increase) ^e	468	1,872,365	0.94 (0.88, 1.01)	0.95 (0.88, 1.02)	0.94 (0.88, 1.01)
UV at age 15					
UV tertile 1	145	527,118	Referent	Referent	Referent
UV tertile 2	181	757,482	0.86 (0.69, 1.07)	0.87 (0.69, 1.08)	0.88 (0.70, 1.09)
UV tertile 3	142	587,765	0.87 (0.69, 1.10)	0.89 (0.71, 1.13)	0.89 (0.70, 1.12)
P for trend			0.43	0.59	0.49
Continuous UV (per IQR increase) ^e	468	1,872,365	0.96 (0.89, 1.03)	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)
UV at age 30					
UV tertile 1	168	620,803	Referent	Referent	Referent
UV tertile 2	167	649,042	0.97 (0.77, 1.21)	0.97 (0.77, 1.22)	0.96 (0.77, 1.21)
UV tertile 3	133	602,521	0.79 (0.62, 1.00)	0.81 (0.63, 1.03)	0.79 (0.62, 1.01)
P for trend			0.04	0.07	0.04
Continuous UV (per IQR increase) ^e	468	1,872,365	0.90 (0.82, 0.99)	0.91 (0.82, 1.01)	0.90 (0.82, 1.00)

^aFor UV exposure at birth and age 15—UV tertile 1: <164.6 mW/m²; tertile 2: ≥164.6–170.9 mW/m²; tertile 3: ≥170.9 mW/m². For UV exposure at age 30—UV tertile 1: <170.9 mW/m²; tertile 2: ≥170.9–186.5 mW/m²; tertile 3: ≥186.5 mW/m².

^bAdjusted for age and race.

^cAdditionally adjusted for Census tract median home value, Census tract median income, marital status, living arrangements, and individual-level income.

^dAdditionally adjusted for family history of breast cancer, personal history of biopsy-confirmed BBD, age at menarche, parity, age at first birth, lactation, hormone use (among postmenopausal women only), height, BMI at age 18, change in BMI since age 18, physical activity, adult alcohol consumption, total vitamin D intake, and population density.

^eAn IQR increase in UV is 15.7 mW/m² for birth, 18.0 mW/m² for age 15, and 27.7 mW/m² for age 30.

spent outdoors. Exposure measurement error may have impacted study results as ambient UV exposure was estimated using geocoded residential addresses, which did not account for time-activity patterns around the workplace, outdoor

recreational locations, or other locations. There may be low variability in time spent outdoors and ambient UV exposure in this study population,⁵⁰ contributing to the null results. Further, early-life UV exposure was based on the state of residence, likely

leading to exposure misclassification error as UV levels vary within states. The generalizability of our results may be limited, as participants were predominantly white. Vitamin D insufficiency is more prevalent in black women, who are characterized by increased melanin that absorbs UV and reduces vitamin D production in the skin.²⁶

Strengths of this study include a high spatiotemporal resolution UV exposure assessment. Ambient UV was objectively estimated by linking biennially updated geocoded residential addresses with a validated UV exposure model that is, to date, the highest spatially and temporally resolved model of its kind spanning the contiguous US. Residence-based UV exposure is a strong predictor of plasma 25(OH)D levels.⁵¹ Given the long follow-up period of over 24 years, we were able to examine a large number of breast cancer cases as well as breast cancer subtypes defined by ER status. Using the wealth of information collected from NHSII questionnaires as well as linkages of geocoded addresses to large-scale objective databases such as the U.S. Census Bureau, we were able to evaluate potential confounding and effect modification using time-varying information on many different known and suspected breast cancer risk factors, sun exposure, sensitivity, and protection (e.g., sunburns; reaction to the sun; hair color, sunscreen use; time in direct sunlight; and tanning booth use), and other sources of vitamin D including dietary and supplemental vitamin D intake.

Conclusions

Results from this large prospective cohort study of US women do not support the hypothesis that higher ambient UV exposure during adulthood reduces the risk of invasive breast cancer overall or by ER status. Early-life UV exposure may be inversely associated with ER- breast cancer.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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