

Prospective study of ultraviolet radiation exposure and risk of cancer in the United States

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Ecologic studies have reported that solar ultraviolet radiation (UVR) exposure is associated with cancer; however, little evidence is available from prospective studies. We aimed to assess the association between an objective measure of ambient UVR exposure and risk of total and site-specific cancer in a large, regionally diverse cohort [450,934 white, non-Hispanic subjects (50–71 years) in the prospective National Institutes of Health (NIH)-AARP Diet and Health Study] after accounting for individual-level confounding risk factors. Estimated erythemal UVR exposure from satellite Total Ozone Mapping Spectrometer (TOMS) data from NASA was linked to the US Census Bureau 2000 census tract (centroid) of baseline residence for each subject. We used Cox proportional hazards models adjusted for multiple potential confounders to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for quartiles of UVR exposure. Restricted cubic splines examined nonlinear relationships. Over 9 years of follow-up, UVR exposure was inversely associated with total cancer risk ($N = 75,917$; highest versus lowest quartile; HR = 0.97, 95% CI = 0.95–0.99; p -trend < 0.001). In site-specific cancer analyses, UVR exposure was associated with increased melanoma risk (highest versus lowest quartile; HR = 1.22, 95% CI = 1.13–1.32; p -trend < 0.001) and decreased risk of non-Hodgkin's lymphoma (HR = 0.82, 95% CI = 0.74–0.92) and colon (HR = 0.88, 95% CI = 0.82–0.96), squamous cell lung (HR = 0.86, 95% CI = 0.75–0.98), pleural (HR = 0.57, 95% CI = 0.38–0.84), prostate (HR = 0.91, 95% CI = 0.88–0.95), kidney (HR = 0.83, 95% CI = 0.73–0.94) and bladder (HR = 0.88, 95% CI = 0.81–0.96) cancers (all p -trend < 0.05). We also found nonlinear associations for some cancer sites, including the thyroid and pancreas. Our results add to mounting evidence for the influential role of UVR exposure on cancer.

Key words: ultraviolet radiation, cancer, vitamin D, prospective

Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio; NASA: National Aeronautics and Space Administration; NHL: non-Hodgkin's lymphoma; NIH: National Institutes of Health; OR: odds ratio; TOMS: Total Ozone Mapping Spectrometer; UVR: ultraviolet radiation

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Ecologic studies suggest that exposure to solar ultraviolet radiation (UVR) may protect against risks of several cancers,¹ including colorectal, prostate and female breast cancers, and subsequent epidemiologic studies also showed associations with these cancer sites^{2–4} and others such as non-Hodgkin's lymphoma (NHL).⁵ The beneficial effects of sunlight against cancer may be due to vitamin D⁶; solar UV-B exposure contributes to ~90% of serum vitamin D levels.⁷ Some studies suggest that high levels of dietary or circulating serum vitamin D are associated with lower cancer risk; however, the results are inconsistent.⁸ In addition to vitamin D, UVR exposure may affect health due to other mechanisms.⁹

Existing evidence is derived mostly from ecologic studies, which lack individual-level covariates and have frequently relied on geographic location such as latitude^{10,11} as surrogate for sunlight exposure. Estimated ground-level UVR exposure (erythemal dose) from the Total Ozone Mapping Spectrometer (TOMS) dataset of the National Aeronautics and Space Administration (NASA) has been widely used in recent studies^{3,12} to better estimate potential UVR exposure. Few studies with individual-level data on UVR exposure and covariates have been conducted in diverse regions.

Here, we used the TOMS UVR estimates to prospectively examine the association between ambient residential UVR

exposure and total and site-specific incident cancer risk in the National Institutes of Health (NIH)-AARP Diet and Health Study. We assessed the associations between a historically available objective measure of ambient UVR exposure and incident cancer in a large, regionally diverse population after accounting for individual lifestyle and other potentially confounding risk factors.

Material and Methods

Study population

The NIH-AARP Diet and Health study has been described elsewhere.¹³ Briefly, between 1995 and 1996, a self-administered questionnaire was mailed to 3.5 million AARP members aged between 50 and 71 years and residing in six US states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) and two metropolitan areas (Atlanta and Detroit). The study was approved by the National Cancer Institute Institutional Review Board. This questionnaire elicited information on demographic characteristics, health-related behaviors and dietary intake, and 566,399 completed the questionnaire in satisfactory detail and consented to be in the study. Subsequently, two more questionnaires were administered during follow-up. We excluded proxy-responders (15,760), subjects with cancer prior to baseline (51,234), those with calorie intake of more than two interquartile ranges from the median (4,417) and those who were missing age information (46). We excluded those who self-identified as any race or ethnicity other than white, non-Hispanic or had missing race/ethnicity information (43,445). We also excluded participants for whom we did not have geocoded baseline residence (563). The resulting cohort included 450,934 participants: 272,796 men and 178,138 women.

Follow-up and case ascertainment

The follow-up for incident cancer spanned from the day of study entry until diagnosis of cancer, death, loss to follow-up (those who moved out of the cancer catchment area) or the current end of incident cancer follow-up (December 31, 2006). Cancer cases were identified by probabilistic record linkage with cancer registries in the original eight states or metropolitan areas and two additional states (Arizona and Texas)¹⁴; cancers were identified by anatomic site and histologic code of the International Classification of Disease for Oncology, 3rd edition (ICD-O).

UVR exposure assessment

The NASA TOMS database (<http://toms.gsfc.nasa.gov>) provided daily information on a noon-time ground-level erythemal estimate on a 1° latitude by 1.25° longitude grid between 1978–1993 and 1996–2005. We assigned the ground-level erythemal exposure for each participant in the study by deterministic linkage of the census tract centroid of the residence at baseline to the closest point on the TOMS grid using ArcView 9.3 (Esri, Redlands, CA); the census tract for each subject was assigned spatially, based on the longitude and latitude coordinates from

geocoding residential address. The erythemal exposure was averaged across all available measured days in the month of July because summer is when surface UVR is strongest, noise factors such as clouds and aerosols are not as influential¹⁵ and when the TOMS UVR data are in better agreement with ground-based data.¹⁶ We used both continuous and quartiles of the erythemal exposure, defined as joules per square meter (J/m²).¹⁷

Covariate assessment

Additional exposure variables were derived from information provided in the baseline questionnaire, which included a 124-item food frequency questionnaire.¹³ Sex and age at baseline (used as a continuous variable) were self-reported. Body mass index (BMI) was calculated from self-reported baseline height and weight and was used as a continuous variable. Intakes of fruits, vegetables, red meat and white meat were expressed as servings per day as defined by the US MyPyramid equivalents database. Alcohol consumption was measured as drinks per day. We also categorized tobacco smoking, education and two physical activity variables (usual routine physical activity throughout the day and vigorous physical activity). For each subject, we assigned the median household income for the 2000 census tract as a proxy measure of socioeconomic status. For all covariates, missing indicator variables were used for those who had missing values.

Statistical analysis

We first examined the cross-sectional association between ambient residential UVR exposure and self-reported history of nonmelanoma skin cancer (assessed in 2004–2006 follow-up questionnaire) in a subset of the study participants ($n = 251,703$) to verify that our measure of UVR exposure was valid. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). This exploratory data analysis revealed the presence of residual spatial correlation in logistic regression models to explain nonmelanoma skin cancer. We considered generalized additive models with a smoothed term that was a function of spatial coordinates using thin plate regression splines.¹⁸ We fitted models with the smoothed term based on longitude and latitude separately and together. Longitude alone was statistically significant without explaining the effect of UVR exposure (UVR exposure was related to longitude and latitude). We used this longitude function as the residual variation adjustment term in models for total cancer risk as well as organ-specific cancer risk. However, we noted that the term for residual spatial correlation was significant in only 22% of the models and did not substantially change the main effect estimates. Therefore, we omitted the spatial correlation term in all models presented here.

We used a Cox proportional hazards model adjusted for multiple potential confounders (listed in Table 1) considered important *a priori* to estimate hazard ratios (HRs) and 95% CI per quartile of UVR exposure. Trends were measured based on the ordinal quartiles. We also examined the

Table 1. NIH-AARP Diet and Health Study cohort characteristics

	Cohort	July erythemal exposure (J/m ²) ¹			
		≤186.3	>186.3–236.8	>236.8–253.7	>253.7
<i>N</i>	450,934	118,344	105,843	106,356	120,391
Male, <i>n</i> (%)	272,796 (60.50)	73,937 (62.48)	64,481 (60.92)	63,362 (59.58)	71,016 (58.99)
Age at entry, mean (SD)	62.07 (5.38)	61.84 (5.44)	61.88 (5.41)	62.05 (5.34)	62.46 (5.30)
BMI (kg/m ²), mean (SD)	27.05 (4.78)	27.44 (4.86)	26.98 (4.71)	26.97 (4.80)	26.79 (4.71)
Calories intake (kcal/day), mean (SD)	1,836 (795)	1,879 (803)	1,855 (802)	1,803 (783)	1,805 (791)
Alcohol (drinks per day), mean (SD)	0.94 (2.41)	0.85 (2.27)	0.84 (2.28)	1.00 (2.46)	1.06 (2.61)
Fruit (servings per day), mean (SD)	1.16 (0.79)	1.18 (0.79)	1.11 (0.76)	1.16 (0.78)	1.20 (0.81)
Vegetables (servings per day), mean (SD)	1.14 (0.58)	1.13 (0.56)	1.09 (0.55)	1.15 (0.59)	1.18 (0.62)
Red meat (servings per day), mean (SD)	1.12 (0.69)	1.14 (0.69)	1.14 (0.67)	1.10 (0.69)	1.10 (0.71)
White meat (servings per day), mean (SD)	0.65 (0.56)	0.65 (0.56)	0.61 (0.52)	0.66 (0.55)	0.69 (0.60)
Smoking² (%)					
Never	34.69	35.92	35.24	34.79	32.89
Former, ≤ 20 cigarettes per day	26.31	26.20	26.22	26.32	26.48
Former, > 20 cigarettes per day	21.81	20.83	21.09	22.17	23.10
Current, ≤ 20 cigarettes per day	8.61	8.78	8.63	8.30	8.68
Current, > 20 cigarettes per day	5.11	4.61	5.41	5.03	5.42
Education² (%)					
High school or less	25.43	32.48	27.46	20.39	21.17
Technical/some college	33.16	29.13	31.97	35.04	36.52
College	18.97	17.24	19.40	20.06	19.33
Postgraduate	20.02	18.90	18.75	22.12	20.38
Physical activity throughout the day² (%)					
Sit during day, not much walking	7.89	8.13	7.17	8.22	7.98
Sit much of day, walk fair amount	32.32	32.71	30.46	33.46	32.55
Stand/walk a lot, no lifting	37.61	34.78	37.50	38.58	39.62
Lift/carry light loads	17.48	19.47	19.63	15.47	15.40
Heavy work	2.88	2.86	3.39	2.68	2.63
Vigorous physical activity² (%)					
Never	4.22	4.76	4.19	3.86	4.04
Rarely	13.42	15.00	13.16	12.63	12.77
1–3 per month	13.59	14.78	13.69	13.25	12.64
1–2 per week	21.73	22.61	22.43	21.39	20.55
3–4 per week	26.88	25.35	27.25	27.69	27.36
>5 per week	19.46	16.74	18.54	20.52	21.99
Census tract median household income, mean (SD)	54,477 (23,585)	60,458 (24,826)	49,598 (19,538)	57,022 (26,431)	50,640 (21,172)

¹The July erythemal exposure was calculated as the averaged exposure across all available measured days in the month of July between 1978–1993 and 1996–2005. ²Because of missing data, percentages do not total 100%. Abbreviation: BMI, body mass index.

possibility of nonlinear relationships between UVR exposure and select cancers nonparametrically using restricted cubic splines.¹⁹ All tests of statistical significance were two sided.

All analyses were conducted using the software packages R (<http://www.r-project.org/>) and SAS 9.2 (SAS Institute, Cary, NC). Graphs were made using GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA). We present both age-

and multivariate-adjusted effect estimates. We interpreted $p < 0.05$ and 95% CIs excluding 1 as statistically significant.

Results

Table 1 presents the characteristics of the 450,934 participants by UVR exposure quartiles (176.1–186.3, >186.3–236.8, >236.8–253.7 and >253.7–289.5 J/m²). The UVR

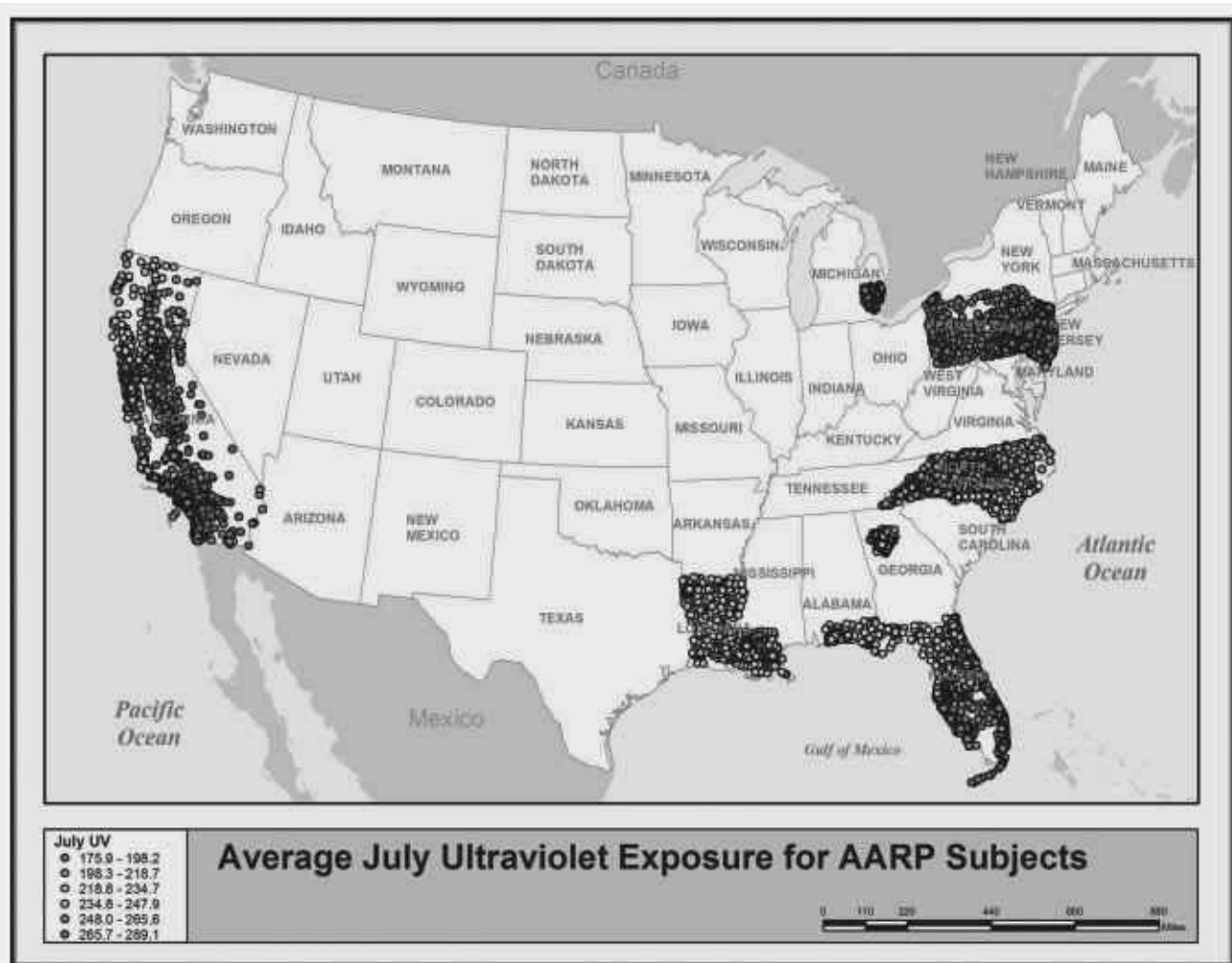


Figure 1. Map of ambient residential UVR exposure of participants in NIH-AARP Diet and Health Study cohort. Ground-level erythemal exposure for each participant was assigned by linking the census tract centroid of the self-reported residence at baseline to the closest point on the TOMS grid. The census tract for each subject was assigned spatially based on the longitude and latitude coordinates from geocoding residential address. The erythemal exposure was averaged across all available measured days in the month of July. The units are defined as joules per square meter (J/m^2).

exposure and the location of the participants are shown in Figure 1. Among the nonmelanoma skin cancer subset, ambient residential UVR exposure as a continuous variable was significantly associated with an increased nonmelanoma skin cancer risk (OR = 1.25, 95% CI = 1.22–1.28).

In the complete cohort, during a mean follow-up of 9.07 years (standard deviation 2.92 years), 75,917 incident cancer diagnoses were ascertained. When all cancers were combined, we found that the highest quartile of UVR exposure was inversely associated with total cancer risk (multivariate-adjusted HR = 0.97, 95% CI = 0.95–0.99). Because of the known adverse effect of UVR on melanoma risk, we excluded melanoma cases ($n = 5,052$), and the inverse association remained; we also excluded the large number of prostate cancer cases ($n = 21,439$), and the inverse association remained, although was nonsignificant; the inverse association remained after the exclusion of both melanoma and prostate cancer cases (data not shown).

The age-adjusted estimates are given in Supporting Information Table S1, and the multivariate-adjusted estimates for the associations between ambient residential UVR exposure and site-specific cancer risk are listed by ICD-O code in Table 2. We found that ambient residential UVR exposure was significantly associated with an increased risk of melanoma and other nonepithelial skin cancers, and the association was monotonic.

The highest quartile of UVR exposure was significantly associated with decreased risks of NHL (including diffuse large B-cell lymphoma and T-cell lymphomas) and squamous cell lung cancer and cancers of the colon, pleura, prostate, kidney and bladder. In addition to these cancer sites, pancreatic and thyroid cancers and lung adenocarcinoma also had p -trend < 0.05.

As a sensitivity analysis, we examined the association between UVR exposure and total cancer and site-specific

Table 2. The multivariate HR and 95% CI¹ for cancer by site² in relation to ambient resident UVR exposure

ICD-O Code	Cancer site	Cases	July erythemal exposure (J/m ²) ³				p-trend
			≤186.3	>186.3–236.8	>236.8–253.7	>253.7	
C00.0–C00.9	Lip	101	1.00	1.17 (0.62–2.19)	1.97 (1.13–3.43)	1.28 (0.71–2.33)	0.079
C00.0–C06.9	Oral	745	1.00	0.90 (0.72–1.12)	1.17 (0.96–1.44)	1.10 (0.90–1.35)	0.079
	Non-Hodgkin's lymphoma (total)	2,731	1.00	0.97 (0.87–1.08)	0.95 (0.85–1.05)	0.82 (0.74–0.92)	0.002
	Diffuse large B-cell lymphoma	1,059	1.00	1.05 (0.89–1.25)	1.06 (0.90–1.25)	0.80 (0.67–0.96)	0.005
C02.4, C09.8, C09.9,	Follicular lymphoma	577	1.00	0.87 (0.69–1.09)	0.77 (0.60–0.97)	0.85 (0.68–1.07)	0.161
C11.1, C14.2, C37.9, C42.2, C77.0–C77.9	Chronic lymphocytic leukemia/small lymphocytic lymphoma	237	1.00	0.92 (0.63–1.33)	0.95 (0.66–1.37)	0.99 (0.70–1.41)	0.964
	Other B cells	451	1.00	1.08 (0.84–1.40)	1.07 (0.82–1.38)	0.85 (0.65–1.11)	0.252
	T cell	188	1.00	0.76 (0.51–1.14)	0.83 (0.57–1.22)	0.61 (0.41–0.93)	0.200
C09.0–C13.9	Pharynx	318	1.00	1.19 (0.86–1.65)	1.18 (0.84–1.64)	1.26 (0.91–1.73)	0.547
C15.0–C15.9	Esophageal adenocarcinoma	607	1.00	0.90 (0.72–1.13)	0.99 (0.79–1.24)	0.92 (0.73–1.14)	0.732
	Esophageal squamous cell carcinoma	190	1.00	0.84 (0.56–1.26)	0.94 (0.64–1.39)	0.63 (0.41–0.95)	0.114
C16.0–C16.9	Stomach	827	1.00	0.79 (0.65–0.97)	0.96 (0.79–1.16)	0.96 (0.79–1.15)	0.126
C17.0–C17.9	Small intestine	220	1.00	0.99 (0.69–1.44)	0.77 (0.52–1.14)	0.91 (0.63–1.31)	0.555
C18.0–C18.9, C26.0	Colon	5,133	1.00	0.98 (0.91–1.06)	0.96 (0.89–1.04)	0.88 (0.82–0.96)	0.011
C20.9	Rectum	1,912	1.00	0.90 (0.79–1.02)	0.86 (0.75–0.98)	0.90 (0.80–1.02)	0.113
C22.0, C22.1	Liver	498	1.00	1.16 (0.90–1.50)	1.02 (0.79–1.33)	1.18 (0.92–1.52)	0.444
C23.9	Gall bladder	105	1.00	0.56 (0.32–1.00)	0.71 (0.42–1.22)	0.76 (0.46–1.26)	0.233
C25.0–C25.9	Pancreas	1,598	1.00	0.91 (0.79–1.05)	0.79 (0.68–0.91)	0.95 (0.83–1.09)	0.009
C30.0–C30.1, C31.0–C31.9,	Lung (total)	9,103	1.00	0.97 (0.91–1.03)	1.02 (0.96–1.08)	1.03 (0.97–1.09)	0.270
C32.0–C32.9, C34.0–C34.9,	Lung (adeno)	3,766	1.00	0.87 (0.79–0.95)	0.94 (0.86–1.03)	0.98 (0.90–1.07)	0.013
C38.4, C33.9, C38.1–C38.3, C38.8, C39.0, C39.8, C39.9	Lung (squamous)	1,861	1.00	0.92 (0.80–1.05)	1.02 (0.90–1.16)	0.86 (0.75–0.98)	0.030
	Lung (other)	4,118	1.00	1.07 (0.98–1.17)	1.06 (0.97–1.16)	1.11 (1.01–1.21)	0.159
C32.0–C32.9	Larynx	595	1.00	0.75 (0.59–0.95)	0.89 (0.71–1.12)	0.94 (0.76–1.17)	0.096
C38.0, C47.0–C47.9, C49.0–C49.9	Soft tissue including heart	280	1.00	1.61 (1.14–2.27)	1.29 (0.90–1.84)	1.38 (0.97–1.95)	0.057
C38.4	Pleura	203	1.00	0.61 (0.41–0.90)	0.72 (0.50–1.05)	0.57 (0.38–0.84)	0.014
C42.0, C42.1, C42.4	Leukemia	1,524	1.00	0.91 (0.79–1.05)	0.91 (0.79–1.05)	1.03 (0.90–1.18)	0.196
C42.1	Myeloma	783	1.00	1.20 (0.99–1.47)	1.11 (0.91–1.36)	0.94 (0.76–1.15)	0.066
C44.0–C44.9	Melanoma and other nonepithelial skin cancer	5,052	1.00	1.04 (0.95–1.13)	1.10 (1.02–1.19)	1.22 (1.13–1.32)	<0.001
C50.0–C50.9	Breast	8,681	1.00	0.99 (0.93–1.05)	1.05 (0.99–1.12)	1.03 (0.97–1.09)	0.198
C54.0–C54.9, C55.9	Uterus	1,467	1.00	0.99 (0.85–1.15)	1.00 (0.87–1.16)	1.01 (0.88–1.17)	0.991
C56.9	Ovary	648	1.00	1.14 (0.92–1.42)	0.92 (0.74–1.16)	0.93 (0.75–1.17)	0.209
C61.9	Prostate	21,439	1.00	0.94 (0.91–0.98)	0.96 (0.92–0.99)	0.91 (0.88–0.95)	<0.001
C64.9, C65.9	Kidney	1,923	1.00	0.93 (0.82–1.05)	0.88 (0.77–1.00)	0.83 (0.73–0.94)	0.030
C67.0–C67.9	Bladder	4,124	1.00	0.88 (0.81–0.96)	0.87 (0.80–0.95)	0.88 (0.81–0.96)	0.003
C69.0–C69.9	Eye	151	1.00	1.42 (0.88–2.29)	1.14 (0.70–1.88)	1.53 (0.96–2.42)	0.256
C71.0–C71.9	Brain	709	1.00	0.85 (0.68–1.06)	1.02 (0.83–1.25)	0.96 (0.78–1.18)	0.376
C73.9	Thyroid	536	1.00	0.93 (0.73–1.18)	0.69 (0.54–0.89)	0.87 (0.69–1.09)	0.026

¹Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated using Cox regression models adjusted for the following covariates: age at baseline, sex, BMI, caloric intake, intake of fruit, vegetables, red and white meat, alcohol consumption, tobacco smoking, education, physical activity and median household income. ²Cancer sites with less than 100 cases are not shown here. ³The July erythemal exposure was calculated as the averaged exposure across all available measured days in the month of July between 1978–1993 and 1996–2005. Histology codes for Esophageal adenocarcinoma: 8140, 8142, 8144, 8261, 8310, 8480, 8481, 8570, 8260, 8263 and 8490; esophageal squamous cell carcinoma: 8041, 8070, 8071, 8072 and 8074. Cancers of the breast, uterus and ovary were restricted to females; prostate cancer was restricted to males.

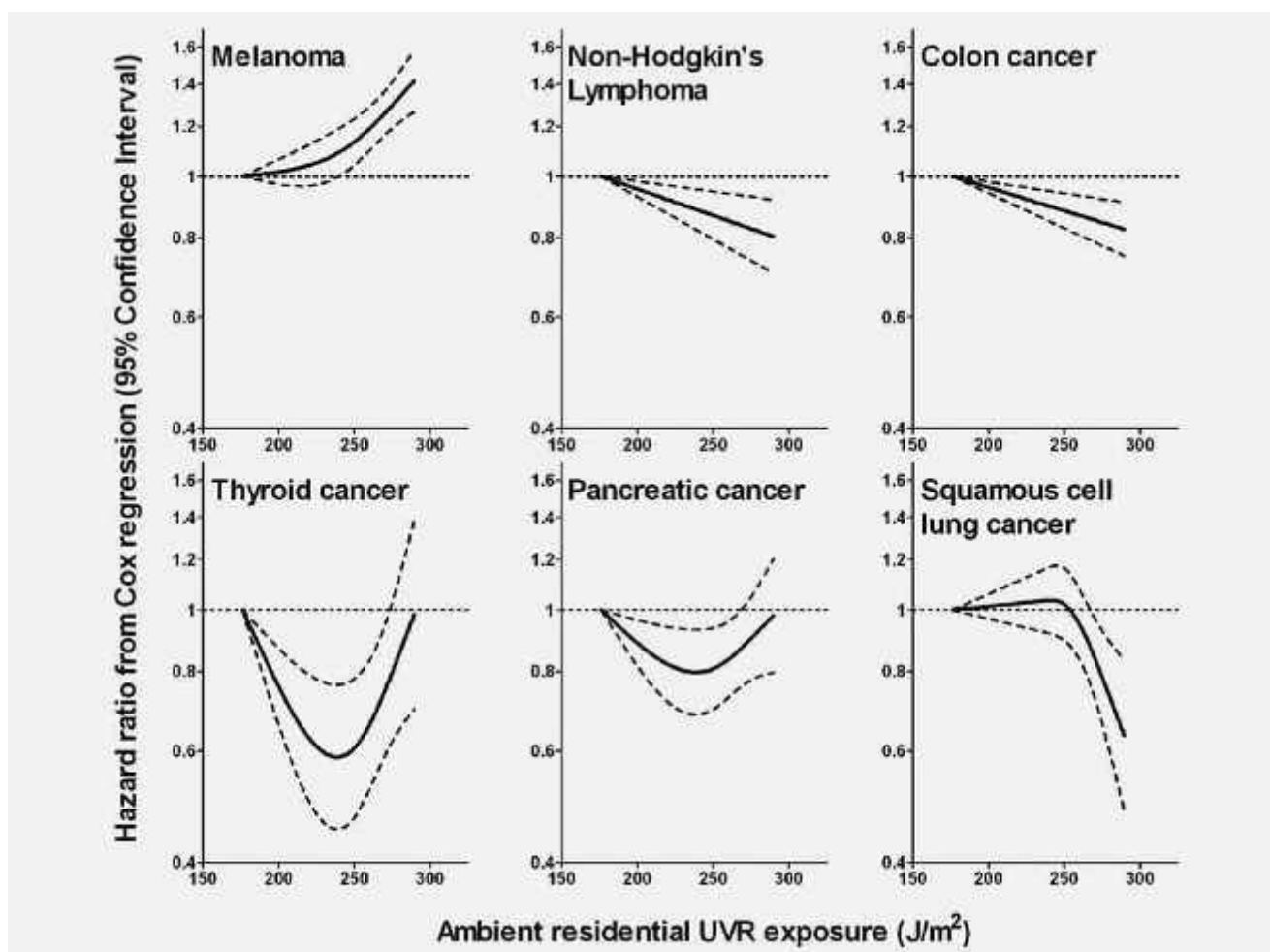


Figure 2. Restricted cubic spline analysis of UVR exposure and risk of selected site-specific cancers. Monotonic associations were observed for NHL and colon cancer. Nonlinear associations were observed for melanoma, thyroid cancer, pancreatic cancer and squamous cell lung cancer.

cancer risks in subjects residing in California because residents had a wide range of UVR exposure and also comprised a large number of cancer cases. Although effect estimates were similar to those found for the original cohort, they were less precise (data not shown).

Our analysis of UVR exposure in quartiles suggested potential nonlinear relationships. For example, for pancreatic and thyroid cancers, the third quartile was significantly associated with decreased risk, but the highest quartile was not significant.

Therefore, we examined the possibility of nonlinear associations. Using cubic spline analysis, we estimated a nonlinear association between UVR exposure with squamous cell lung cancer, thyroid cancer and pancreatic cancer risks. Figure 2 shows the estimated splines for some site-specific cancers. The spline analyses were concordant with our quartile analyses presented in Table 2.

Discussion

We examined total and site-specific cancer risk in relation to ambient residential UVR exposure in a large prospective

study in the United States. We found a significant inverse association with total cancer risk. This association may in part be driven by the inverse association found for prostate cancer (28% of cases). These results should be interpreted with caution as the small effect sizes reflect the greatly varied risk patterns for individual cancers and are mainly driven by the large number of total cancer cases.

In the analyses of individual cancer sites, we found a positive association with melanoma risk and an inverse association with risk of incident cancers at several sites, including NHL, colon, squamous cell lung, pleura, prostate, kidney and bladder. We also found nonlinear associations between UVR exposure and risk of pancreatic, thyroid and squamous cell lung cancers. We detected several different patterns of association between the range of UVR exposure and cancer risk, which suggest that different biological mechanisms may be responsible for these associations. In this section, we discuss some of these cancer outcomes in the context of relevant previous studies and also assess the limitations and strengths of our study.

Although the association with other cancers is less clear, it is well established that sunlight or UVR exposure contributes to risk of melanoma²⁰ and nonmelanoma skin cancer.²¹ As expected, we found a significantly increased risk with incident melanoma in our cohort. We had self-reported history of nonmelanoma skin cancer in only a subset, and indeed, in a cross-sectional subset analysis, ambient residential UVR exposure was significantly associated with increased nonmelanoma skin cancer risk. This statistically significant positive association strongly supported using the erythemal exposure from the TOMS dataset to assess ambient residential UVR exposure in relation to cancer outcomes in the NIH-AARP Diet and Health study cohort.

Many studies on UVR exposure and cancer risk have focused on NHL and cancers of the colon, prostate and female breast. We found inverse associations with risk of NHL and cancers of the colon and prostate, but not the breast.

Worldwide, the incidence of NHL has been increasing, and increased sunlight exposure has been proposed to be partly responsible.^{5,22} Ecological and observational studies have suggested that geographic residence and self-reported UVR exposure behaviors, respectively, may be positively^{5,23} or negatively^{5,24} correlated with NHL incidence. Although inconsistent,⁵ most studies have found an inverse association,²⁵ and our prospective study, which controlled for potential confounders, contributes additional evidence. Some studies have suggested that this inverse association may be due to a mechanism independent of vitamin D.^{26,27}

UVR exposure was significantly associated with a monotonic decreased colon cancer risk. Previous ecologic and observational studies^{3,28,29} of sun exposure suggest a similar association. Our study, along with others that examined dietary or circulating vitamin D,^{30–32} adds support to the hypothesis that vitamin D is associated with colon cancer risk.

Our finding of a significant association between ambient residential UVR exposure and decreased prostate cancer risk is consistent with the hypothesis that sun exposure may be inversely associated with prostate cancer risk^{1,33,34}; prostate cancer showed an inverse association at each quartile level and an apparent dose response. Mounting epidemiologic evidence on sun exposure supports this hypothesis,² although results from less informative studies of dietary vitamin D and studies of circulating vitamin D are generally nonsupportive, with some studies even suggesting an increased prostate cancer risk in those with the highest serum vitamin D values.³⁵

We found a significant nonlinear association between ambient residential UVR exposure and pancreatic cancer risk. UVR exposure may play a role independent of vitamin D, as an adverse effect was apparent in a large consortia analysis of circulating vitamin D and pancreatic cancer risk.³⁶ Further studies on UVR exposure and pancreatic cancer are warranted; assessment of populations with a wide range of personal UVR exposure or circulating serum vitamin D may help future studies to clarify the molecular mechanisms of these associations.

Unlike previous studies,^{4,37} we found no association between UVR exposure and breast cancer risk. Studies of vitamin D and breast cancer produced mixed results.^{38,39} We did find significant associations between UVR exposure and risk of squamous cell carcinoma and adenocarcinoma of the lung and cancers of the pleura, kidney, bladder and thyroid. These associations have not been the focus of previous studies of UVR exposure and may be interesting for future explorations.

This study has several limitations. First, we did not have information on sun-related behaviors, such as sunscreen use or time spent outdoors. Ambient residential UVR exposure was calculated for each participant based on residence at baseline, and the spatial resolution of UVR exposure was limited in the TOMS dataset to grids of 1° latitude by 1.25° longitude, which represents about 111 km north to south and between 75 and 101 km east to west depending on latitude. Participants were assigned the same erythemal exposure if they lived within the same grid. However, the use of the TOMS dataset provides some improvement over estimates based on latitude, and location of residence is more objective compared to measures of self-reported sun exposure behaviors. The dataset takes into account a variety of environmental factors that affect erythemal exposure, including cloud cover and automobile exhaust. Averaging the TOMS-estimated exposures over longer periods of time improves the agreement with measured ground-level UVR,¹⁶ and we used the TOMS-estimated exposures over several years. However, a known limitation of the TOMS estimate is the underestimation of the effect of aerosols,⁴⁰ which is a very important consideration in the northeastern US and could bias our results toward the null.

Another limitation is that although the NIH-AARP Diet and Health Study is a large study, it is not geographically representative of the US population for UVR exposure. We used only the residence at baseline and did not consider population mobility; moreover, we could not take into account seasonal migrations of subjects, that is, time spent in winters or summers in locations other than their residence at baseline, and migrating individuals may adopt different behaviors at alternative residences. We also do not have data on occupation or leisure time spent outdoors. The UVR at baseline may not be representative of early life sun exposure, and the etiologically relevant exposure periods are unknown; in addition, our results may not be generalizable to younger age groups.

Incomplete control for confounders may have influenced our results. Cancer screening practices and unaccounted cancer site-specific confounders may result in residual confounding. Regional variations exist for viruses and organisms linked with cancer, including hepatitis infection and liver cancer.⁴¹ We excluded all participants who did not self-identify as “white, non-Hispanic” (~8% of the cohort, thus representing very small numbers of cancer events); however, our racial grouping of the remaining participants does not

sufficiently account for important regional ethnic variations as well as geographically variable degrees of racial mixing, all of which may reflect potential genetic and lifestyle factors that may be linked to UVR and cancer risk. In addition, we had no information on the range of skin pigmentation or skin types. Our results may not be generalizable to other racial/ethnic groups.

There are several strengths to our study. We used a very large prospective cohort, which avoided reverse causation, of participants with regional diversity and a large range of UVR exposures. We used an objective measure of exposure estimated from a residential address obtained prior to case ascertainment and valid classification of incident outcomes. A major advantage of our study compared to ecologic studies is that in our models, we adjusted for a large number of potential confounders, including individual-level BMI, tobacco use and physical activity, although their inclusion did not substantially change the risk estimates. Moreover, dietary habits throughout the United States may vary, and we adjusted for food intake in dietary categories such as fruits, vegetables and meats.

Although UVR exposure and cancer risk may be explained through various mechanisms,⁹ several studies suggest that the molecular actions of vitamin D contribute to cancer prevention,⁴² and therefore, exposure to solar UVR radiation, which results in the cutaneous synthesis of most of the vitamin D in the human body, is important. Geographic location, particularly latitude used in several studies, is limited in determining vitamin D production,⁴³ and indeed, even individuals in high UVR environments may not have sufficient levels of circulating vitamin D.⁴⁴ We used the TOMS dataset, which is an improvement over several studies to better estimate ground-level erythemal exposure and also broadly encompasses the UV-B region (280–320 nm) that is responsible for the production of vitamin D.⁴⁵ However, the TOMS dataset captures the UV-A (320–400 nm) wavelengths as well and does not consider the differences between UV-A and UV-B radiation wavelengths in their ability to initiate DNA damage, cell signaling pathways and immune alterations.⁴⁶ The TOMS dataset also does not consider human body geometry or that age decreases the ability to produce vitamin D⁴⁷; therefore, additional conversion factors may be needed to estimate more accurately the vitamin D production-relevant UVR exposures.⁴⁸ Moreover, we could neither

adjust for vitamin D supplementation, which was uncommon in the mid-1990s,⁴⁹ nor estimate dietary vitamin D intake in our cohort, although dietary intake is not as well correlated with serum vitamin D as sunlight exposure.⁵⁰ Moreover, UVR exposure may be a proxy or marker of some other risk factor for cancer.

In summary, our results add to mounting evidence for the influential role of UVR exposure on cancer. We found that ambient residential UVR exposure was inversely associated with total cancer risk. We also observed that this measure of UVR exposure was associated with differential risks of some site-specific incident cancers and that several different patterns of association were evident in the data. Future studies may account for cumulative exposures through residential history, develop new techniques to capture individual exposures or further examine associations with cancer sites that have not been previously well studied.

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