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Lifetime exposure to ultraviolet radiation and the risk of multiple sclerosis in the US radiologic technologists cohort study

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Abstract

Background: Low exposure to ultraviolet radiation (UVR) from sunlight may be a risk factor for developing multiple sclerosis (MS). Possible pathways may be related to effects on immune system function or vitamin D insufficiency, as UVR plays a role in the production of the active form of vitamin D in the body.

Objective: This study examined whether lower levels of residential UVR exposure from sunlight were associated with increased MS risk in a cohort of radiologic technologists.

Methods: Participants in the third and fourth surveys of the US Radiologic Technologists (USRT) Cohort Study eligible ($N = 39{,}801$) for analysis provided complete residential histories and reported MS diagnoses. MS-specialized neurologists conducted medical record reviews and confirmed 148 cases. Residential locations throughout life were matched to satellite data from NASA's Total Ozone Mapping Spectrometer (TOMS) project to estimate UVR dose.

Results: Findings indicate that MS risk increased as average lifetime levels of UVR exposures in winter decreased. The effects were consistent across age groups <40 years. There was little indication that low exposures during summer or at older ages were related to MS risk.

Conclusion: Our findings are consistent with the hypothesis that UVR exposure reduces MS risk and may ultimately suggest prevention strategies.

Keywords: Epidemiology, ultraviolet radiation, vitamin D

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Introduction

The geographic distribution of multiple sclerosis (MS) prevalence and incidence suggests etiologic roles for environmental factors.[1] Studies conducted in the United States, Australia, and New Zealand have found increasing MS prevalence with increasing latitude;[2,3] a large meta-analysis of 650 MS prevalence estimates indicates a consistent association on a global scale.[4] Latitude is strongly correlated with amount and intensity of sunlight, which may explain the inverse correlation frequently observed in epidemiologic studies.[5,6] In addition, MS risk declines among people who migrate from high-risk to low-risk areas.[7] This decline is more evident when migration occurs during childhood, a possible indication of the importance of early sun exposure for the risk of MS.[7]

The mechanistic relationship between low exposure to ultraviolet radiation (UVR) and MS has not been fully elucidated, although it may be through immune system effects or through vitamin D insufficiency. UVR from sunlight is a major contributor to the synthesis of biologically active vitamin D. Vitamin D deficiency has been previously implicated in increased risk of MS.[5]

Several studies have examined the risk of MS and UVR exposure, based on exposure assessment methods ranging from quantitative measures from satellite data[8–12] to proxy measures for sun exposure.[13–18] There is epidemiological evidence suggesting that low exposure to ambient UVR during early life may be associated with MS[12,13] and earlier symptom onset.[15] We

conducted a study within a well-characterized U.S. nationwide prospective cohort to assess the quantitative relations between exposure to UVR over the lifetime and subsequent risk of developing MS.

Methods

Study population

The study population was drawn from the U.S. Radiologic Technologists (USRT) study, a large prospective cohort composed of radiologic technologists residing throughout the U.S. and certified by the American Registry of Radiologic Technologists for at least 2 years between 1926 and 1982. Self-administered questionnaires were mailed to participants during four time periods (1983–1989, 1994–1998, 2003–2005, and 2012–2013). Previous publications describe the cohort in more detail,[19–21] and the study website (http://radtechstudy.nci.nih.gov/) provides further information on the extensive health studies completed to date. Eligibility requirements for the current analysis include completion of the third and fourth questionnaires with complete data (N = 39,801). The third questionnaire elicited information on lifetime residential history that was required for UVR dosimetry, time spent outdoors in summer on weekends and weekdays during age periods throughout life, history of sunburns, sun skin sensitivity characteristics, and demographic, health, and lifestyle questions. Participants were asked about prior diagnoses of MS, including year of diagnosis, on both questionnaires. Participants were followed up from completion of the third survey until diagnosis of MS or completion of the fourth survey (2012–2013).

Human Subjects Review Boards at the University of Minnesota (Minneapolis, MN), the National Cancer Institute (Bethesda, MD), Boston University, the University of Washington, and the University of California, San Diego approved the study.

Diagnostic confirmation of MS

Self-reported diagnoses of MS were confirmed by retrieving medical records for review by study neurologists. Participants reporting a diagnosis were contacted to secure consent and appropriate Health Insurance Portability and Accountability Act of 1996 (HIPAA) documentation to obtain relevant medical records. The request was sent initially as a letter and followed up by telephone in instances of non-response. Requests were forwarded to the physician or medical facility where the participant was diagnosed or treated, with follow-up telephone calls as needed to prompt a response or clarify the treating physician and facility and year of diagnosis. All medical records were reviewed to verify information pertaining to the diagnosis of MS, screened to ensure irrelevant records were not included, and de-identified prior to review.

A panel of study neurologists with clinical expertise in MS (G.A.S., A.W., G.M.F., and K.W.T.) conducted independent, blinded reviews of medical records for the McDonald MS diagnostic criteria,[22–24] including clinical and laboratory presentation, brain or spinal magnetic resonance imaging (MRI), results from cerebrospinal fluid (CSF), visually evoked potential (VEP), and assessments using the Expanded Disability Status Scale (EDSS).[25] The assessment included evaluating clinical presentation of the course of disease (relapse history, insidious, or secondary progression) and symptoms (visual, gait, bladder/bowel, brain stem, cerebral, cerebella, sensory, other) by chart review to indicate possible diagnosis of MS. Medical records of each case were reviewed independently by two neurologists. If they did not reach the same diagnosis, the record was sent to a third tiebreaker neurologist to reach a consensus review. Final diagnoses were determined as consistent with definite MS (e.g. evidence of clinical and/or MRI progression), possible MS, not MS, or unknown. The year of MS diagnosis was abstracted from the record of confirmed cases.

There were 569 self-reported cases of MS in the USRT Cohort Study. Table 1 summarizes the outcome of locating, contacting, and validating the medical records to confirm diagnoses of each self-reported case. Approximately 22% did not respond to requests to release medical records, 27% refused to release, 3% denied reporting MS, and 1% were deceased, or otherwise unable to confirm (6%). Medical records were successfully obtained for 40% (n = 228) of self-reported cases. Missing or incomplete address data required for UVR exposure assessment led us to exclude 25 MS cases. Among the remaining 203 records, study neurologists were able to reach consensus reviews of "definite MS" for 148 cases, "not MS" for 8 cases, "possible MS" for 24 cases, and 5 cases were "unknown." In addition, there were 18 records where there was no consensus for the diagnosis; these participants were excluded from the analysis. All analyses therefore focused on the 148 definite MS cases (additional details are provided in Supplemental Table 1).

Assessment of UVR exposure

Estimates of UVR exposure at specific age intervals were derived by linking residential information with

Table 1. Enrollment and ascertainment of cases.

	n	%
Outcome for cases contacted for confirmation in MS study (*n* = 569)		
Medical records obtained	228	40
Refused to release medical record	154	27
No response to request for medical record	127	22
Unable to validate self-reported MS	52	9
Deceased	8	1
Outcome of medical record review (*n* = 228)		
Diagnosis classified as "definite MS"	148	65
Medical records excluded		
Missing or incomplete data for UVR assessment[a]	25	11
No consensus for diagnosis	18	8
Diagnosis classified as "not MS"	8	4
Diagnosis classified as "unknown"	5	2
Diagnosis classified as "possible MS"	24	11

MS: multiple sclerosis; UVR: ultraviolet radiation.
[a]Participant medical records were reviewed for diagnostic confirmation concurrently to conducting UVR exposure assessments. As a result, some cases (*n* = 25; 24 definite MS cases and 1 possible MS case) were excluded due to incomplete or missing residential information to spatially locate and match to satellite data for UVR exposure.

satellite data from NASA's Total Ozone Mapping Spectrometer (TOMS) project.[26] For each participant, questionnaires ascertained the city, state, and country of their longest residence during five age ranges: 0 to 12, 13 to 19, 20 to 39, 40 to 64, and >65 years old. In addition, they were asked the average number of hours spent in the sun from 9:00 a.m. to 3:00 p.m. on a typical weekday and weekend day in the summer for each of the age ranges. Each residential address was located geographically to the primary post office serving that city using Google's geocoding service.[27] The data were geographically matched to the closet grid of TOMS data, which include estimates of daily erythemal exposure (J/m^2) in 1.25° × 1.00° grids for most of the planet from 11/1978 to 8/2005. Pre-11/1978 and post-8/2005 doses were estimated by extrapolating data backward using the 1978 estimate and forward using the 2005 estimate.

During the winter months, there is reduced UVR in many areas of the country, while in summer, UVR is higher and also believed to be sufficient for vitamin D production.[28] Using TOMS data, we analyzed average UVR erythemal exposure data separately for winter (December through February), for summer (June through August), and as an annual measure (an average of all months) to characterize UVR exposure over a year. Exposure to ambient UVR was averaged annually for each ages ⩽12, 13 to 19, 20 to 39, and 40 to 64 years old, and was combined to estimate lifetime averages. We also analyzed time spent outdoors during summer, calculated as a weighted average from reported hours per day on weekdays and weekends (<1, 1–2, 3–5, and 5+ hours), and as a combined variable with ambient UVR exposure. Time spent outdoors was weighted as 0.1 hour if participants reported "0," since it is unlikely that individuals spent zero time outside, and midpoints for the remaining categories (1.5, 4, and 5.5 hours). Exposure categories were based on quartiles of the distribution of doses for the USRT study population during the age period 20 to 39 years, the time closest and prior to the age at diagnosis for MS.

Statistical methods

We estimated risk of MS in relation to lifetime and age-specific UVR exposures, in which the cohort's follow-up for MS began at dates of birth since participants could report earlier diagnoses when completing the third survey. Follow-up ended at diagnosis dates for cases and at fourth survey completion for non-cases. Multivariable Cox regression models with attained age as the time variable were used to calculate the associations between MS and UVR exposures. Relative risk estimates, hazard ratios (HRs), and 95% confidence intervals (CIs) were estimated assessing UVR exposure in a time-dependent fashion while controlling for covariates, including birth cohort (<1945, 1945–1950, 1950–1955, and >1955), race (White, non-White), sex (male, female), smoking (never/ever), and baseline body mass index (BMI) (<18.5, 18.5–24.9, 25–29.9, and >30), as reported on the first or

second survey. Categorical values were modeled as continuous to examine dose–response trends.

Results

The study population was predominately (>90%) female, Caucasian, and non-Hispanic (Table 2). The mean age at diagnosis for MS was 44 years old (standard deviation (SD) = 10.4). Cases were more likely to have ever smoked compared to non-cases (56.8% vs 48.6%). Cases were slightly more likely to have a healthy BMI compared to non-cases (70.3% vs 65.2%) and somewhat less likely to be classified as obese (6.1% vs 8.1%) (Table 2).

When ambient UVR exposure was examined as a lifetime average, there was a strong trend for increasing risk of MS with decreasing ambient UVR exposure during winter months but not in summer months (Table 3). The association for ambient winter UVR (but not summer) by age-specific period was consistent, particularly for the lowest exposure category (<22 J/m^2) compared to the highest (>49 J/m^2), for ages less than 40 years old (HR = 1.59 (<12 years old), HR = 1.55 (13–19 years old), and HR = 1.57 (20–39 years old)). When we adjusted for all other age-specific periods in each individual analysis, we found attenuation of the estimates (data not shown).

As expected, participants tended to report more time spent outdoors at younger ages and less time at older ages. Compared to 5+ hours/day, spending less than 1 hour/day at ages <12 years old (HR = 1.02, 95% CI: 0.55–1.92) and ages 13 to 19 years old (HR = 1.31, 95% CI: 0.65–2.62) did not show an association with risk of MS. Less than 1 hour/day spent outdoors in summer was shown to have a non-significant increased risk of MS at ages 20 to 39 (HR = 1.92, 95% CI: 0.59–6.20) and 40 to 64 (HR = 1.71, 95% CI: 0.42–7.05), as compared to 5+ hours/day. Results were similar when time spent outdoors was combined with ambient summer UVR into a weighted UVR measure. For <12 years old, 65% of non-cases and 68% of MS cases reported >3 hours per day spent outdoors in summer. In contrast, by ages 20 to 39 years old, 79% of non-cases and 68% of case reported <3 hours per day spent outdoors in summer. For sun susceptibility factors, we did not see any differences in risk of MS related to eye color, hair color, and complexion, skin reaction to first sun or skin reaction to repeated sun exposure (data not shown).

Discussion

Our findings add to the growing body of evidence that low exposure to UVR is a risk factor for MS. This association is especially prominent for very low UVR exposures, particularly when estimated as a lifetime average. Although UVR exposure in the summer months is believed to be sufficient for vitamin D production, in winter months some areas of the country have substantially reduced UVR exposure, thus increasing the risk of vitamin D deficiency.[28] Our findings supported this assessment by observing stronger inverse associations for ambient winter UVR than for ambient summer UVR.

A major strength of the current study was the ability to examine UVR exposure with quantitative measures, with wide variability across a large geographic area (United States), and at critical time points in life, particularly early in life. A summary of studies most pertinent to our study is available (Supplemental Table 2). Linking satellite data and residential history as in the current study and others[14] has been described by Canadian investigators as a superior exposure measure to using latitude in studies of MS.[29] Unlike latitude and other geographic surrogates for UVR, the NASA TOMS data are collected on a daily basis with global coverage, providing actual estimates of seasonal and average annual UVR exposure.[26] The exposure estimate incorporates levels of atmospheric ozone, cloud cover, and the relationship (distance and angle) of the sun to the location, given the terrain (altitude) and time of year. Each of these factors affects the amount of UVR that reaches the surface of the earth and can result in differences between regions at the same latitude. For example, persistent cloud cover that occurs in some regions reduces UVR, and atmospheric chemical processes can affect levels of ozone and protection it can provide in others.[26]

Some studies using satellite sources of UVR data have been ecologic in nature[8,11] or had limits in sample size and geographic scope.[10] Comparable studies examining UVR exposure across lifetime have found MS to be more strongly related to estimated UVR levels than to latitude.[9–11] A study in Australia examined an early indicator of possible MS (first demyelinating event), used the NASA TOMS UVR data and other measures to estimate sun exposure starting at age 6, and found higher levels of past, recent, and accumulated exposure were each associated with reduced risk of a first event.[14] Other studies of childhood and adolescent measures for UVR exposure found evidence that low exposure to ambient UVR may be associated with MS[12,13] and studies have consistently found month of birth to influence the risk of MS, particularly in areas with low sunlight exposure compared to areas with high sunlight exposure.[16]

The mechanistic pathway between UVR and MS has not been fully elucidated, although there are several

Table 2. Selected demographic characteristics of study population, USRT Cohort Study (first and second questionnaires).

Characteristic	MS cases ($n=148$)		Non-cases ($n=39,653$)	
Gender				
Male	11	7.4%	7635	19.3%
Female	137	92.6%	32,018	80.7%
Birth year				
<1930	0	0.0%	1067	2.7%
1930–1935	1	0.7%	1674	4.2%
1935–1940	4	2.7%	3212	8.1%
1940–1945	19	12.8%	5513	13.9%
1945–1950	31	20.9%	8635	21.8%
1950–1955	51	34.5%	10,991	27.7%
>1955	42	28.4%	8561	21.6%
Race				
White	146	98.6%	38,145	96.2%
Non-White	2	1.4%	1508	3.8%
Ethnicity				
Non-Hispanic	147	99.3%	38,746	97.7%
Hispanic	1	0.7%	826	2.1%
Missing	0	0.0%	81	0.2%
Education				
High school or vocational school	5	3.4%	1521	3.8%
College or graduate school	55	37.2%	19,073	48.1%
2-year hospital Rad Tech Program	76	51.4%	19,004	47.9%
Missing	12	8.1%	55	0.1%
Smoking				
Never	64	43.2%	20,341	51.3%
Ever	84	56.8%	19,262	48.6%
Missing	0	0.0%	50	0.1%
Baseline BMI				
Underweight (<18.5)	8	5.4%	1434	3.6%
Healthy (18.5–24.9)	104	70.3%	25,868	65.2%
Overweight (25–29.9)	26	17.6%	8666	21.9%
Obese (>30)	9	6.1%	3218	8.1%
Missing	1	0.7%	467	1.2%

USRT: US Radiologic Technologists; MS: multiple sclerosis; BMI: body mass index.

possible explanations for the consistently observed association. While vitamin D serum levels were not measured in the current study, low UVR exposure can be considered a reasonable proxy for vitamin D deficiency. There is biological support for associations between vitamin D deficiency and increased risk of MS. Vitamin D targets nervous system tissues, regulating important neurotrophic factors in the brain, and also exerts effects on the differentiation and functioning of immune cells.[30] An animal model of MS, experimental autoimmune encephalomyelitis (EAE), can be strongly inhibited by the biologically active form of vitamin D ($1,25(OH)_2D$), whereas vitamin D deficiency results in increased susceptibility.[31,32] UVR may have an effect on the immune system independent from its role in vitamin D production in the body. Experimental studies have demonstrated the suppression of EAE by UVR independent of vitamin D production,[33,34] indicated that vitamin D deficiency suppresses EAE incidence and severity,[35] and indicated that deletion of the *VDR* gene may actually protect against EAE.[36] The release of secondary mediators following absorption of UVR by photoreceptors can result in suppressed cell-mediated immunity.[33] Impairment of natural defense mechanisms could have a negative effect on certain health effects, such as skin cancer, but may be beneficial in preventing MS, an autoimmune disease.

Table 3. Risk of MS and ambient UVR exposure by age-specific period and season.

Age	Ambient winter UVR	No. of cases	HR	95% CI	Ambient summer UVR	No. of cases	HR	95% CI	Ambient annual UVR	No. of cases	HR	95% CI
Lifetime average	<22	44	2.00	1.21–3.30	<185	45	1.25	0.77–2.03	<103	39	1.50	0.91–2.49
	22–31	46	1.80	1.10–2.95	185–195	33	0.96	0.57–1.61	103–112	40	1.22	0.74–2.01
	31–49	34	1.34	0.79–2.26	195–232	44	0.85	0.52–1.38	112–141	44	1.09	0.67–1.78
	>49	24	Ref.		>232	26	Ref.		>141	25	Ref.	
	p-trend		0.004		*p*-trend		0.15		*p*-trend		0.03	
<12	<22	56	1.59	0.95–2.67	<185	56	1.18	0.73–1.90	<103	52	1.26	0.78–2.06
	22–31	41	1.17	0.68–2.00	185–195	40	0.88	0.53–1.46	103–112	46	0.93	0.57–1.53
	31–49	31	1.10	0.63–1.93	195–232	28	0.71	0.41–1.23	112–141	26	0.69	0.39–1.20
	>49	20	Ref.		>232	24	Ref.		>141	24	Ref.	
	p-trend		0.02		*p*-trend		0.30		*p*-trend		0.09	
13–19	<22	55	1.55	0.94–2.57	<185	52	1.19	0.73–1.96	<103	50	1.46	0.88–2.44
	22–31	40	1.13	0.67–1.93	185–195	41	0.98	0.59–1.64	103–112	44	1.07	0.64–1.81
	31–49	32	1.12	0.64–1.94	195–232	32	0.88	0.51–1.50	112–141	33	1.04	0.6–1.80
	>49	21	Ref.		>232	23	Ref.		>141	21	Ref.	
	p-trend		0.03		*p*-trend		0.45		*p*-trend		0.16	
20–39	<22	44	1.57	0.97–2.53	<185	43	1.05	0.67–1.65	<103	43	1.32	0.84–2.08
	22–31	40	1.35	0.83–2.21	185–195	37	1.03	0.65–1.63	103–112	38	1.02	0.64–1.62
	31–49	34	1.24	0.75–2.05	195–232	30	0.79	0.49–1.29	112–141	31	0.89	0.54–1.45
	>49	27	Ref.		>232	35	Ref.		>141	33	Ref.	
	p-trend		0.05		*p*-trend		0.65		*p*-trend		0.24	
40–64	<22	35	1.31	0.79–2.15	<185	32	1.15	0.68–1.94	<103	31	1.38	0.81–2.35
	22–31	23	0.87	0.50–1.51	185–195	19	0.85	0.47–1.55	103–112	25	1.03	0.59–1.81
	31–49	17	0.68	0.37–1.24	195–232	27	1.01	0.58–1.74	112–141	23	0.94	0.53–1.67
	>49	28	Ref.		>232	25	Ref.		>141	24	Ref.	
	p-trend		0.61		*p*-trend		0.87		*p*-trend		0.74	

MS: multiple sclerosis; UVR: ultraviolet radiation; HR: hazard ratio; CI: confidence interval; USRT: US Radiologic Technologists.
All analyses adjusted for birth cohort (<1945, 1945–1950, 1950–1955, and >1955), race (White, non-White), and sex (male, female). Cox proportional hazards analysis using attained age as timescale. Exposure categories based on the distribution of doses for the USRT study population during the age period 20–39 years, the time closest, and prior, to the age at diagnosis for MS. Participants missing UVR data for one or more addresses are excluded. Categorical values modeled as continuous for trend tests. Results not shown for ages 65+ because only one MS case diagnosed during that period. UVR in units of J/m^2.

We also acknowledge several study limitations. There may be some survival bias as the population had to survive through the fourth survey to be included in the analysis. MS is estimated to shorten life expectancy by 5 to 10 years.[37] Thus, it is unlikely that many cases did not survive until their outcome was assessed. Although our ability to generate quantitative UVR exposure estimates is a strength of the study, some extrapolation of the UVR data was required because satellite data are not available for all years. However, variability of UVR exposure in a given location is primarily a function of season and is fairly stable across spans of several years. The data are still the most complete and accurate information available for the study period. There also may have been some error in reporting one address over a defined age period when a participant may have lived at more than one residence. In addition, we did not have data on serum vitamin D levels measured over time to corroborate the assumption that the association between UVR and MS may be a function of vitamin D levels. We also did not have data on sun protection behaviors. We mitigated misclassification confirming self-reported diagnoses of MS by conducting independent medical record reviews for a consensus diagnosis. We also did not have information on MS symptom onset dates. Initial symptoms may have limited mobility and time spent outdoors in the time periods leading up to diagnosis and may explain the observed results of that analysis. Personal time spent outdoors also relied on participant's recall, was restricted to summer, and reported by age-specific period as typical over many years.

This study provides supporting evidence that lower average lifetime exposure to low levels of UVR can increase subsequent risk of MS. These results are generalizable to adult women and men living and working across the United States. Future studies of UVR and MS should evaluate the reproducibility of the findings, incorporate multiple sources of vitamin D exposure, and consider susceptibility factors, such as genetic markers, to elucidate pathogenesis mechanisms and identify susceptible subgroups.

Declaration of Conflicting Interests

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