Short Communication

Sun Exposure and Prostate Cancer Risk: Evidence for a Protective Effect of Early-Life Exposure

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Abstract

Mounting experimental and epidemiologic evidence supports the hypothesis that vitamin D reduces the risk of prostate cancer. Some evidence suggests that prostate cancer risk may be influenced by sun exposure early in life. We analyzed data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study to examine associations of prostate cancer risk with early-life and adult residential sun exposure and adult sun exposures that were assessed through self-report, physician report, and dermatologic examination. We used solar radiation in the state of birth as a measure of sun exposure in early life. Follow-up from 1971 to 1975 (baseline) to 1992 identified 161 prostate cancer cases (102 nonfatal and 59 fatal) among non-Hispanic white men for whom sun exposure data were available. Significant inverse associations were found for men born in a region of high solar radiation (relative risk, 0.49, 95% confidence interval, 0.27-0.90 for high versus low solar radiation), with a slightly greater reduction for fatal than for nonfatal prostate cancer. Frequent recreational sun exposure in adulthood was associated with a significantly reduced risk of fatal prostate cancer only (relative risk, 0.47; 95% confidence interval, 0.23-0.99). These findings suggest that, in addition to sun exposure in adulthood, sun exposure in early life protects against prostate cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1283–6)

Introduction

Mounting experimental and epidemiologic evidence supports the hypothesis that vitamin D reduces the risk of prostate cancer (1, 2). The major source of vitamin D is casual exposure to sunlight, which accounts for ~90% of serum levels of 25(OH)D, the main circulating metabolite of vitamin D (3). In the United States, prostate cancer mortality rates are inversely correlated with solar radiation levels, with the highest rates found in the Northeast (4, 5). Recently, several studies reported inverse associations with prostate cancer risk in relation to residential sun exposure (6), self-reported sun exposure (7), a sun exposure index based on skin pigmentation measurements (8), serum levels of 25(OH)D (9, 10), and composite score based on multiple predictors of serum levels of 25(OH)D (11). Additionally, high residential sun exposure has been associated with significantly increased survival (12) and decreased mortality from prostate cancer (13).

Although data are sparse, some evidence suggests that prostate cancer risk may be influenced by sun exposure early in life (6, 7). Most previous studies have focused on the effect of sun exposure during adulthood, and the effect of sun exposure in early life has been little explored. We examined the effect of early-life versus adult sun exposure on prostate cancer risk in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study, a nationwide prospective study of men spanning a wide range of residential sun exposure.

Materials and Methods

Study Population. NHANES I was conducted from 1971 to 1975 in a probability sample of the noninstitutionalized U.S. population. Adults ages 25 to 74 years, including 5,811 men, were recontacted for follow-up interviews conducted in 1982 to 1984, 1986 to 1987, and 1992 as part of the NHANES I Epidemiologic Follow-up Study (14). Baseline data were obtained through an in-person interview and a dermatologic examination, including information on residential history and sun-induced skin damage. The first follow-up interview conducted in 1982 to 1984 collected information on self-reported recreational and occupational sun exposure.

Of 5,811 male NHANES I participants, 306 (5.3%) were lost or declined participation in follow-up. Information on various health outcomes, including prostate cancer, was collected through interviews with surviving individuals or proxy respondents. A total of 249 men were identified who were diagnosed with or died from prostate cancer during the follow-up period. Of these, 52 were non-white and were excluded in this analysis. The remaining 197 white prostate cancer cases included 73 self-reports only, 32 self-reports confirmed by hospital records, 48 self-reports confirmed by death certificates, 19 identified through hospital records only, and 25 identified through death certificates. Analyses were based on 161 non-Hispanic white cases and 3,367 non-Hispanic white noncases for whom information on sun exposure was available.

Statistical Analysis. We examined prostate cancer risk in relation to solar radiation in state of birth, as a proxy measure of early-life sun exposure, and several measures of sun exposure in adulthood, including solar radiation in the state of longest residence, and sun exposure assessed by self-report, physician report, and dermatologic examination. Each U.S. state of residence was assigned an average solar radiation level as described elsewhere (15), and solar radiation in each state was classified as low, medium, or high based on the approximate

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tertile distribution. The first follow-up interview in 1982 to 1984 collected information on self-reported recreational and occupational sun exposure rated as never, rare, occasional, or frequent. In the dermatologic baseline examination, sun-induced skin damage was rated as absent, minimal, moderate, or severe, and physician-assessed sun exposure was rated as unimpressive, moderate, or considerable. We used Cox proportional hazard regression modeling to estimate relative risks (RR) and 95% confidence intervals (95% CI), adjusting for age only, because in a previous analysis of the NHANES I follow-up data (6), we found no evidence of confounding by family history of prostate cancer, fat intake, or calcium intake. Because the influence of vitamin D may be different on early-stage versus advanced disease, we did analyses for all prostate cancer cases combined and stratified analyses for nonfatal and fatal cases. For cases, person-years of follow-up were estimated from the year (midpoint of June 30) of the NHANES I interview to the year of prostate cancer incidence, defined as the year of first hospital admission related to prostate cancer, the year of the self-reported diagnosis for prostate cancers without hospital record confirmation, and the year of death for prostate cancers confirmed by death certificate only. For men without prostate cancer, the person-years of follow-up were estimated from the year of the NHANES I interview to the year of last interview, if alive, or to the year of death, if deceased.

Results

As reported previously (6), high residential sun exposure was associated with reduced prostate cancer risk (Table 1). Lower risks were found among men born in a state of high solar radiation (RR, 0.52; 95% CI, 0.33-0.81) and among men whose longest residence was in a state of high solar radiation (RR, 0.59; 95% CI, 0.39-0.88). An inverse association with high early-life solar radiation remained after adjustment for adult solar radiation (odds ratio, 0.49; 95% CI, 0.27-0.90) and was present for both nonfatal and fatal prostate cancer. Conversely, the inverse association with solar radiation at the longest residence was greatly weakened after adjustment for solar radiation at birth, and no association remained for nonfatal prostate cancer. A nonsignificant inverse association was found for fatal prostate cancer only.

The majority of men born in a particular solar radiation region (i.e., low, medium, and high) reported the longest residence in the same solar radiation region. The proportions were 91%, 80%, and 91% for men born in low, medium, and high solar radiation regions, respectively. Compared with men who were born and lived the longest in a low solar radiation region, those born and with longest residence in a high solar radiation region had a 48% lower risk (RR, 0.52; 95% CI, 0.32-0.83), and those born and with longest residence in a medium solar radiation region had an intermediate risk (RR, 0.69; 95% CI, 0.46-1.05; data not shown). When we classified solar radiation at birth and longest residence as high versus low (above or below the median), we found stronger associations with residential sun exposure for fatal than for nonfatal prostate cancer (Table 1). A significant risk reduction was found for men with fatal prostate cancer with both early-life and adult residence in a region of high solar radiation (RR, 0.34; 95% CI, 0.18-0.66 for high versus low solar radiation).

Associations with other sun exposure variables in adult life are shown in Table 2. Frequent recreational sun exposure was associated with significantly reduced risk of fatal prostate cancer (RR, 0.47; 95% CI, 0.23-0.99). A nonsignificant reduction in risk also was found for men whose usual sun exposure was rated as ''considerable'' by study physicians (RR, 0.62; 95% CI, 0.32-1.20). Nonfatal prostate cancer was not associated with physician-assessed or self-reported sun exposure in adulthood.

Discussion

Among several measures of sun exposure examined in this prospective study, high residential solar radiation in the state of birth, a proxy measure for early-life sun exposure, was associated with reduced prostate cancer risk. Among men born in a region of high solar radiation, risk was reduced by 51%, with a slightly greater risk reduction noted for fatal than for nonfatal prostate cancer. Among men with frequent recreational sun exposure, risk of fatal prostate cancer was reduced by 53%. Although limited by small numbers, the influence of sun exposure seemed stronger on fatal than nonfatal prostate cancer.

The finding of reduced risk associated with early-life sun exposure is consistent with results from a case-control study conducted in England where several indicators of childhood sun exposure, including sun burns and sunbathing, were inversely associated with prostate cancer risk (7). However, it

Table 1. Residential sun exposure in early life and in adulthood in relation to risk of nonfatal and fatal prostate cancer

	Nonfatal and fatal cases				Nonfatal cases		Fatal cases	
	n	Person-years	RR (95% CI)*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)
Solar radiation in state of birth †, ‡								
Low	78	20,098	1.0	1.0§	44	1.0§	34	1.0§
Medium	47	15,817	0.75 (0.52-1.07)	0.73 (0.48-1.09)	33	0.85 (0.52-1.40)	14	0.57 (0.28-1.14)
High	25	12,773	0.52 (0.33-0.81)	0.49 (0.27-0.90)	20	0.59 (0.29-1.21)	5	0.31 (0.09-1.03)
Solar radiation in state of longest residence †								
Low	86	21,887	1.0	1.0‖	43	1.0‖	34	1.0‖
Medium	41	14,835	0.72 (0.50-1.05)	0.90 (0.58-1.38)	29	1.07 (0.63-1.81)	12	0.70 (0.32-1.50)
High	33	14,591	0.59 (0.39-0.88)	0.80 (0.44-1.49)	25	1.02 (0.49-2.13)	7	0.49 (0.15-1.59)
Solar radiation in state of birth vs solar radiation in state of longest residence †								
Low vs low	82	22,210	1.0		47	1.0	35	1.0
Low vs high	8	2,055	0.87 (0.42-1.79)		4	0.78 (0.28-2.17)	4	1.00 (0.36-2.82)
High vs low	5	1,920	0.54 (0.22-1.33)		3	0.60 (0.19-1.93)	2	0.46 (0.11-1.93)
High vs high	55	22,162	0.66 (0.47-0.93)		43	0.89 (0.59-1.34)	12	0.34 (0.18-0.66)

NOTE: Solar radiation classified according to tertile distribution.
* Adjusted for age (continuous).
† Solar radiation classified according to tertile distribution.
‡ Analysis excludes foreign-born men.
§ Adjusted for age and solar radiation in state of longest residence (continuous).
‖ Adjusted for age and solar radiation in state of birth (continuous).

Table 2. Sun exposure in adulthood and risk of nonfatal and fatal prostate cancer

	Nonfatal and fatal cases			Nonfatal cases		Fatal cases	
	n	Person-years	RR (95% CI)*	*n*	RR (95% CI)*	*n*	RR (95% CI)*
Physician-assessed sun exposure							
Unimpressive	44	14,798	1.0	27	1.0	17	1.0
Moderate	63	21,610	0.85 (0.58-1.25)	39	0.87 (0.54-1.43)	24	0.81 (0.44-1.51)
Considerable	53	15,598	0.78 (0.52-1.17)	35	0.89 (0.53-1.47)	18	0.62 (0.32-1.20)
Physician-assessed skin damage induced by sun exposure							
None	35	22,461	1.0	25	1.0	10	1.0
Minimal	48	13,625	1.18 (0.76-1.84)	28	1.07 (0.62-1.86)	20	1.42 (0.66-3.04)
Moderate to severe	78	16,387	1.13 (0.75-1.71)	49	1.16 (0.70-1.94)	29	1.13 (0.55-2.34)
Self-reported recreational sun exposure							
Never or rare	18	4,453	1.0	8	1.0	10	1.0
Occasional	32	15,453	0.79 (0.44-1.40)	23	1.19 (0.53-2.66)	9	0.45 (0.18-1.12)
Frequent	102	40,027	0.92 (0.55-1.52)	77	1.46 (0.70-3.02)	25	0.47 (0.23-0.99)
Self-reported occupational sun exposure							
Never or rare	42	18,803	1.0	29	1.0	13	1.0
Occasional	25	12,377	0.93 (0.57-1.53)	18	0.95 (0.53-1.71)	7	0.88 (0.35-2.21)
Frequent	86	28,750	1.05 (0.73-1.52)	62	1.11 (0.72-1.73)	24	0.89 (0.45-1.74)
Self-reported occupational or recreational sun exposure							
Both never, rare or occasional	35	14,246	1.0	21	1.0	14	1.0
One frequent	47	22,574	0.80 (0.52-1.24)	36	1.02 (0.60-1.75)	11	0.46 (0.21-1.02)
Both frequent	70	23,058	1.05 (0.70-1.58)	51	1.28 (0.77-2.13)	19	0.70 (0.35-1.40)

*Adjusted for age (continuous).

is contrary to our recent report from a California-based case-control study, in which we did not find an association with residential solar radiation at birth or before age 20 years for advanced (8) and localized[3] prostate cancer. There are important differences in the residential histories of the two populations. In the NHANES I cohort, large proportions (80-91%) of men remained in the solar radiation region where they were born, whereas, in the case-control study, all men eventually moved to California, a state with high solar radiation, and large proportions of cases (75%) and controls (75%) spent 40 or more years in a high solar radiation region before the interview. Unlike the NHANES I follow-up study, the case-control study did not include any men with lifelong low residential sun exposure.

Our present findings, showing the importance of early-life sun exposure, and those from studies of adult sun exposure, are not necessarily in conflict. For example, because many case-control studies found a damaging effect of sunburns early in life on risk of melanoma, it had been widely believed that susceptibility to melanoma was restricted to a ''critical period'' in early life. However, subsequent studies have shown that after controlling for sunburns early in life, sunburns during adulthood also confer increased risk (16). Although based on small numbers, our findings suggest similarly that the window of opportunity for sunlight to alter prostate cancer risk is not restricted to adulthood. Although most epidemiologic studies have focused on the role of sunlight/vitamin D exposure in adulthood, it is biologically plausible that exposure to vitamin D in early life also may contribute to reduced risk. In particular, it is known that neonatal prostate cells express VDR [the receptor for $1,25(OH)_2D$, the hormonal form of vitamin D] and that early-life exposure of rats to high levels of $1,25(OH)_2D$ results in alterations in the cellular composition of the prostate gland (17). For example, whereas the ratio of epithelial to stromal cells in the normal rodent prostate is 5:1, prepubertal rats exposed to pharmacologic doses of $1,25(OH)_2D$ developed prostate glands that were composed predominantly of stromal cells (18). Because epithelial cells are the targets of carcinogenesis in the prostate, a reduction in the epithelial cell population is one mechanism whereby exposure to vitamin D in early life could reduce prostate cancer risk.

Stratification of the analysis by nonfatal and fatal prostate cancer suggests that recent adult sun exposure may be more important for fatal than nonfatal prostate cancer. Similarly, in our California-based case-control study, a sun exposure index based on skin pigmentation measurements was associated with reduced risk of advanced (8) but not localized prostate cancer.[3] These findings are consistent with experimental studies that show that $1,25(OH)_2D$ inhibits prostate cancer cell invasion (19) and metastasis (20) and warrant future studies that distinguish between the effects of sun exposure on early-stage versus advanced/fatal prostate cancer.

[3] E.M. John, J. Koo, G.G. Schwartz, unpublished data.

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