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Residential sunlight exposure is associated with a decreased risk of prostate cancer☆

Esther M. John[a], Darlene M. Dreon[a], Jocelyn Koo[a], Gary G. Schwartz[b,*]

[a] *Northern California Cancer Center, Union City, CA 94587, USA*
[b] *Departments of Cancer Biology and Public Health Sciences, Wake Forest Comprehensive Cancer Center, Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157, USA*

Abstract

The possibility that exposure to sunlight reduces the risk of clinical prostate cancer has been strongly suggested by ecologic data. However, data on prostate cancer risk in relation to sunlight exposure in individuals are sparse. We analyzed data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study in order to test the hypothesis that residential sunlight exposure reduces the risk of prostate cancer. We identified 153 men with incident prostate cancer from a cohort of 3414 white men who completed the baseline interview and dermatologic examination in 1971–1975 and were followed up to 1992. We used Cox proportional hazards modeling to estimate relative risks (RR) and 95% confidence intervals (CI) for measures of residential sunlight exposure, adjusting for age, family history of prostate cancer, and dietary intake of fat and calcium. Residence in the South at baseline (RR = 0.68, CI = 0.41–1.13), state of longest residence in the South (RR = 0.62, CI = 0.40–0.95), and high solar radiation in the state of birth (RR = 0.49, CI = 0.30–0.79) were associated with significant and substantial reductions in prostate cancer risk. These data support the hypothesis that sunlight exposure reduces the risk of prostate cancer and have important implications for prostate cancer prevention.

Keywords: Prostate cancer; Vitamin D; Sunlight; Epidemiology

1. Introduction

In 1992, Hanchette and Schwartz [1] published data on ultraviolet radiation and prostate cancer mortality rates for 3073 counties of the contiguous US. They demonstrated significant inverse correlations between the availability of sunlight, the major source of Vitamin D, and mortality rates from prostate cancer among white men (see Figs. 1 and 2). They interpreted these data to suggest that Vitamin D acts to maintain the normal phenotype of prostate cells. The same year, Miller et al. [2] demonstrated specific high-affinity receptors for the hormonal form of Vitamin D ($1,25(OH)_2D$) in the LNCaP human prostate cancer cell line and showed that $1,25(OH)_2D$ promoted the differentiation and inhibited the proliferation of these cells. Since then, research by many investigators has established that prostate cells respond to $1,25(OH)_2D$ by a promotion of differentiation and an inhibition of proliferation, invasiveness, and metastasis [3–7].

The ecologic data strongly supported the hypothesis that exposure to sunlight reduces the risk of prostate cancer [8]. However, because these correlations were based on group-level data, they did not demonstrate that sunlight exposure reduces prostate cancer risk among individuals. Moreover, these data presented an interpretive dilemma, i.e., although serum levels of 25-hydroxyvitamin D (25-OHD) are strongly dependent on exposure to sunlight, at physiological levels, 25-OHD is inert. Conversely, serum levels of the active hormone, $1,25(OH)_2D$, are tightly regulated and are not correlated with systemic levels of 25-OHD [9]. How, then, could exposure to sunlight reduce the risk of prostate cancer?

In 1998, Schwartz et al. [10] showed that normal human prostate cells (as well as some cancerous cell lines) possess 25-OHD-1α-hydroxylase (1-OHase) and synthesize $1,25(OH)_2D$ intracellularly from 25-OHD. Moreover, we showed that physiologic levels of 25-OHD exert anti-proliferative effects on prostate cells that possess this enzyme [11,12] (Fig. 3). These data provide the mechanism through which sunlight exposure could reduce the risk of prostate cancer among individuals. We analyzed data from a large, prospective epidemiologic study, the First National

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* Corresponding author. Tel.: +1-336-716-7446; fax: +1-336-716-5687.
E-mail address: gschwart@wfubmc.edu (G.G. Schwartz).

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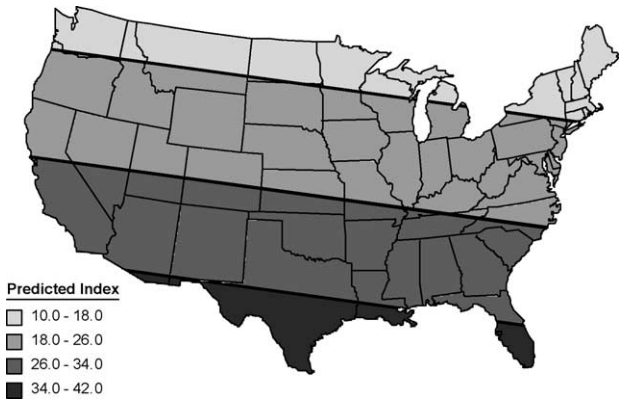

Fig. 1. Trend surface analysis of ultraviolet radiation in contiguous US counties (from [1]; reprinted by permission of Wiley–Liss Inc., a subsidiary of John Wiley and Sons Inc.).

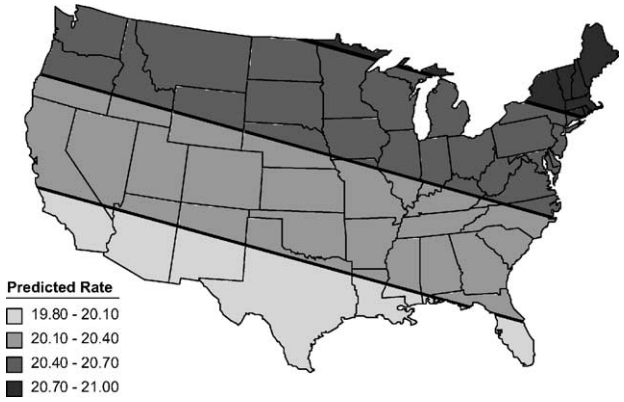

Fig. 2. Trend surface analysis of age-adjusted prostate cancer mortality in white men 1970–1979 in contiguous US counties (from [1]; reprinted by permission of Wiley–Liss Inc., a subsidiary of John Wiley and Sons Inc.).

Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study, in order to test the hypothesis that residential sunlight exposure reduces the risk for prostate cancer in individuals.

2. Materials and methods

NHANES I was conducted from 1971 to 1975 in a probability sample of the non-institutionalized United States population. Adults, aged 25–74, including 5811 men, were recontacted and interviewed in 1982–1984, 1986–1987, and 1992 as part of the NHANES I Epidemiologic Follow-up Survey (NHEFS). The baseline in-person interview collected information on demographic background, medical history, lifestyle factors, dietary intake in the past 24 h, and supplement use. In addition, laboratory tests and medical examinations were performed, including a dermatologic examination. The follow-up interviews conducted with surviving individuals or proxy respondents questioned about various health outcomes, including prostate cancer.

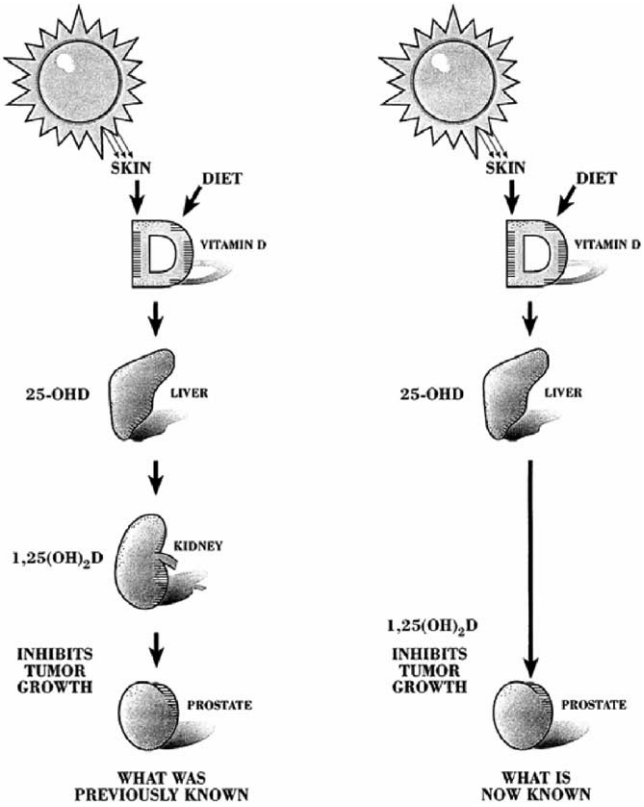

Fig. 3. Current understanding of the synthesis and effects of $1,25(OH)_2D$ on prostate cells. The synthesis of $1,25(OH)_2D$ begins with the cutaneous production of Vitamin D after exposure to sunlight or after Vitamin D is obtained from the diet. To become biologically active, Vitamin D must undergo two hydroxylations. The first hydroxylation occurs in the liver at the 25th carbon, forming 25-OHD. The second hydroxylation occurs in the kidney at the 1α position, forming $1,25(OH)_2D$, the hormonally active metabolite. $1,25(OH)_2D$ exhibits prodifferentiating, anti-proliferative and anti-metastatic effects on prostate cells [2–7]. In addition to the kidney, the prostate synthesizes $1,25(OH)_2D$ intracellularly from 25-OHD [10].

From the interview, dietary assessment, and dermatological examination we derived several Vitamin D exposure variables, described in detail elsewhere (John et al. [13]). Among these were residential sun exposure variables, including region of residence at baseline (South, West, Midwest, Northeast); state of longest residence and length of residence in that state; and state of birth. Since geographic latitude is an important determinant of cutaneous Vitamin D synthesis following sun exposure, we assigned each state an average solar radiation level, and classified each state as low, medium, or high based on the tertile distribution.

The analytic cohort included 3414 white men without a prior history of prostate cancer who completed the baseline interview, 24-h dietary recall, and dermatological examination. A total of 153 men with prostate cancer were identified. Of these, 65 were self-reports confirmed by hospital records or death certificates, 33 were identified through hospital records or death certificates only, and 55 were self-reports only.

Table 1
Residential sun exposure and prostate cancer risk among white men: First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971–1975 to 1992

	Prostate cancer cases	Age-adjusted RR (95% CI)	Multivariate-adjusted RR (95% CI)[a]
Region of residence[b]			
Northeast	37	1.0	1.0
Midwest	42	1.08 (0.69–1.68)	1.05 (0.66–1.67)
West	46	0.92 (0.60–1.42)	0.94 (0.60–1.48)
South	28	0.66 (0.41–1.08)	0.68 (0.41–1.13)
Solar radiation at longest residence[c]			
Low	80	1.0	1.0
Medium	41	0.80 (0.55–1.16)	0.81 (0.55–1.21)
High	30	0.58 (0.38–0.88)	0.62 (0.40–0.95)
Solar radiation at place of birth			
Low	79	1.0	1.0
Medium	46	0.75 (0.52–1.08)	0.75 (0.51–1.09)
High	23	0.48 (0.30–0.76)	0.49 (0.30–0.79)

[a] Adjusted for age, family history of prostate cancer, fat intake, calcium intake.
[b] Northeast: Maine, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, and Pennsylvania; Midwest: Ohio, Illinois, Indiana, Michigan, Wisconsin, Minnesota, Iowa, and Missouri; West: Washington, Oregon, California, Nevada, New Mexico, Arizona, Texas, Oklahoma, Kansas, Nebraska, North Dakota, South Dakota, Idaho, Utah, Colorado, Montana, and Wyoming; South: Delaware, Maryland, District of Columbia, West Virginia, Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, and Arkansas.
[c] Low: Maine, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island, New York, Pennsylvania, Ohio, Michigan, Minnesota, and Washington.

We used Cox proportional hazard regression modeling to estimate relative risks (RR) and 95% confidence intervals (CI) for prostate cancer risk in relation to residential sun exposure. Age-adjusted analyses were based on 153 prostate cancer cases and 3261 men without prostate cancer.

We assessed confounding by known and suspected risk factors for prostate cancer and adjusted the relative risk estimates for age, family history of prostate cancer in first-degree relatives, and dietary intake of fat and calcium. Since family history was ascertained in the first follow-up interview in 1982–1984, the multivariate analyses were based on 144 cases.

3. Results

Age-adjusted and multivariate adjusted relative risks for prostate cancer from residential sun exposure are shown in Table 1. Residence in the South at baseline (RR = 0.68, CI = 0.41–1.13), state of longest residence in the South (RR = 0.62, CI = 0.40–0.95), and high solar radiation in the state of birth (RR = 0.49, CI = 0.30–0.79) were associated with significant and substantial reductions in the risk for prostate cancer.

4. Discussion

These data, from a large, representative sample of the non-institutionalized US population, indicate that higher lifetime solar exposure is associated with a significantly decreased risk of prostate cancer. Our findings, particularly those regarding a protective effect of high solar radiation in the state of birth (RR = 0.49, CI = 0.30–0.79) are consistent with our previous ecologic data which demonstrated an approximate halving of the risk of prostate cancer for men in the Southern-most US [2] (Figs. 1 and 2). To our knowledge, this is the first prospective study of sunlight exposure and risk of prostate cancer in individuals.

This study has several important methodologic strengths, including the population-based design of NHANES I, the prospective follow-up, thereby reducing the potential for differential recall bias, and the large sample size with minimal loss to follow-up (5.3%), thus reducing potential selection bias. These data are consistent with a recent case–control study from the UK in which cases with prostate cancer reported significantly less solar exposure than did control patients with benign prostatic hyperplasia [14] and with a nested case–control study of prostate cancer in relation to prediagnostic levels of 25-OHD among participants in the Helsinki Heart Study (Finland) [15].

Our findings have important implications for prostate cancer prevention. Our analyses suggest that solar exposure early in life may be important in determining risk of subsequent prostate cancer (i.e., in primary prevention). However, because many cells from cancerous human prostates retain the ability to synthesize $1,25(OH)_2D$ [16], it is possible that sunlight exposure also could retard the progression of existing prostate cancer (i.e., secondary prevention). Future studies on the timing of sunlight exposure in relation to risk of prostate cancer are warranted.

References

[1] C.L. Hanchette, G.G. Schwartz, Geographic patterns of prostate cancer mortality: evidence for a protective effect of ultraviolet radiation, Cancer 70 (1992) 2861–2869.

[2] G.J. Miller, G.E. Stapleton, J.A. Ferrara, M.S. Lucia, S. Pfister, T.E. Hedlund, P. Upadhya, The human prostate carcinoma cell line LNCaP expresses biologically active specific receptors for 1α,25-hydroxyvitamin D_3, Cancer Res. 52 (1992) 515–520.
[3] G.G. Schwartz, M.-H. Wang, M. Zhang, R.K. Sing, G.P. Siegal, 1α,25-Dihydroxyvitamin D (calcitriol) inhibits the invasiveness of human prostate cancer cells, Cancer Epidemiol. Biomarkers Prev. 6 (1997) 727–732.
[4] B.L. Lokeshwar, G.G. Schwartz, M.G. Selzer, K.L. Burnstein, S.-H. Zhuang, N.L. Block, L. Binderup, Inhibition of prostate cancer metastasis in vivo: a comparison of 1,25-dihydroxyvitamin D (calcitriol) and EB 1089, Cancer Epidemiol. Biomarkers Prev. 8 (1999) 241–248.
[5] T.C. Polek, N.L. Weigel, Vitamin D and prostate cancer, J. Androl. 23 (2002) 9–17 (review).
[6] G.G. Schwartz, Prostate cancer and Vitamin D: from concept to clinic. A 10-year update, in: A.W. Norman, R. Bouillon, M. Thomasset (Eds.), Vitamin D Endocrine System, University of California Press, 2000, pp. 445–452.
[7] X.-Y. Zhao, D. Feldman, The role of Vitamin D in prostate cancer, Steroids 66 (2001) 291–300.
[8] G.G. Schwartz, B.S. Hulka, Is Vitamin D deficiency a risk factor for prostate cancer (hypothesis)? Anticancer Res. 10 (1990) 1307–1311.
[9] R.W. Chesney, J.F. Rosen, A.J. Hanstra, C. Smith, K. Mahaffey, H.F. DeLuca, Absence of seasonal variations in serum concentrations of 1,25-dihydroxyvitamin D despite a rise in 25-hydroxyvitamin D in summer, J. Clin. Endocrin. Metab. 53 (1981) 139–143.
[10] G.G. Schwartz, L.W. Whitlatch, T.C. Chen, B.L. Lokeshwar, M.F. Holick, Human prostate cells synthesize 1α,25-hydroxyvitamin D_3 from 25-hydroxyvitamin D_3, Cancer Epidemiol. Biomarkers Prev. 7 (1998) 391–395.
[11] T.C. Chen, G.G. Schwartz, K.L. Burnstein, B.L. Lokeshwar, M.F. Holick, The in vitro evaluation of 25-hydroxyvitamin D_3 and 19-nor-1α,25-dihydroxyvitamin D_2 for prostate cancer therapy, Clin. Cancer Res. 6 (2000) 901–908.
[12] A. Barreto, G.G. Schwartz, R. Woodruff, S.D. Cramer, 25-Hydroxyvitamin D_3, the prohormonal form of 1,25-dihydroxyvitamin D_3, inhibits the proliferation of primary prostatic epithelial cells, Cancer Epidemiol. Biomarkers Prev. 9 (2000) 265–270.
[13] E.M. John, G.G. Schwartz, D.M. Dreon, J. Koo, Vitamin D and breast cancer risk: The NHANES Epidemiologic Follow-up Study, 1971–1975 to 1992, Cancer Epidemiol. Biomarkers Prev. 8 (1999) 309–406.
[14] D. Bodiwala, C.J. Luscopmbe, M.E. French, S. Liu, M.F. Saxby, P.W. Jones, et al., Susceptibility to prostate cancer: studies on interactions between UVR exposure and skin type, Carcinogenesis 24 (2003) 711–717.
[15] M.H. Ahonen, L. Tenkanen, L. Teppo, M. Hakama, P. Tuohimaa, Prostate cancer risk and prediagnostic serum 25-hydroxvitamin D levels (Finland), Cancer Causes Control 11 (2000) 847–852.
[16] L.W. Whitlatch, M.V. Young, G.G. Schwartz, J.N. Flanagan, K.L. Burnstein, B.L. Lokeshwar, et al., 25-Hydroxyvitamin D-1α-hydroxylase activity is diminished in human prostate cancer cells and is enhanced by gene transfer, J. Steroid Biochem. Mol. Biol. 81 (2002) 135–140.