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ORIGINAL PAPER

# UV, latitude, and spatial trends in prostate cancer mortality: All sunlight is not the same (United States)

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**Abstract**
*Objective* We showed previously that Caucasian mortality rates from prostate cancer for 1970–1979 are significantly inversely correlated with ultraviolet (UV) radiation. We now present the analysis of prostate cancer mortality data over a 45-year period (1950–1994) in order to examine the persistence of this pattern. Furthermore, because vitamin D synthesis does not occur during winter months at latitudes higher than 40° N, we examined this relationship above and below 40° N latitude.
*Methods* We used trend surface and linear regression analyses to characterize the relationship between prostate cancer mortality and UV radiation for U.S. counties at northern and southern latitudes.
*Results* For U.S. Caucasians, prostate cancer mortality rates at the county and SEA levels followed a significant north–south spatial trend that is the inverse of UV radiation. We found significant inverse correlations between UV radiation and prostate cancer mortality at all time points over this 45-year period. These correlations were significantly more pronounced at locations north of 40° N latitude.
*Conclusions* Our analyses confirm and extend our findings that the geographic distribution of prostate cancer mortality is the inverse of that of UV radiation. This effect is strongest in counties north of 40° N latitude, where vitamin D synthesis is limited to non-winter months. These findings add additional support for the hypothesis that vitamin D insufficiency increases risk for prostate cancer.

**Keywords** Prostate cancer · Vitamin D · Sunlight · Epidemiology · Ultraviolet radiation

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## Introduction

Interest in vitamin D among cancer epidemiologists, biologists and clinicians is currently experiencing an enormous renaissance. This renaissance is the result of two related discoveries: the first is the recognition that beside its ''classical'' role in regulating mineral homeostasis, the hormonal form of vitamin D controls the differentiation and proliferation of many cell types that possess vitamin D receptors (VDRs) [1]. The second is that many non-classical cells, such as prostate cells, synthesize the vitamin D hormone from its prohormone, the serum levels of which are largely determined by exposure to sunlight. These discoveries suggest that sunlight may play key roles in the natural history of many cancers, in processes ranging from cancer prevention to survival [2–4].

To understand how sunlight/vitamin D could prevent cancer, it is important to recall the synthesis of vitamin D metabolites. The synthesis of $1,25(OH)_2D$ begins with the production of vitamin $D_3$ (cholecalciferol) after 7-dehydrocholesterol in the skin is exposed

to ultraviolet (UV) radiation (wavelength 290–315 nm). Although vitamin D can be obtained from the diet, the measured contribution of diet to serum vitamin D levels in the U.S. is small (approximately 10%) [5, 6]. To become biologically active, vitamin D undergoes two hydroxylations: the first occurs in the liver, forming 25-Hydroxyvitamin D (25-OHD), the prohormone and major circulating form of vitamin D; the second occurs at the 1 $\alpha$ position, forming $1,25(OH)_2D$, the hormonal form of vitamin D [7]. Until recently, the synthesis of $1,25(OH)_2D$ was thought to occur exclusively in the kidney, although local production of $1,25(OH)_2D$ had also been described in placenta and in keratinocytes [8]. However, in 1998, Schwartz et al. demonstrated that the normal prostate hydroxylates 25-OHD to $1,25(OH)_2D$, where the hormone functions locally to control growth and differentiation [9, 10]. The implications of this discovery for prostate cancer prevention are profound; they imply that greater sunlight exposure, which results in higher serum levels of 25-OHD, should result in a greater synthesis of $1,25(OH)_2D$ within prostate cells and to a reduced risk of prostate cancer [11, 12].

Because the majority of vitamin D comes from cutaneous exposure to UV radiation, in 1992, we examined annual UV radiation for U.S. counties and county-level mortality rates from prostate cancer and reported that prostate cancer mortality rates were significantly inversely correlated with UV radiation [13]. These findings were not apparent from inspection of conventional (i.e., chloropleth) county-wide maps of cancer mortality. These maps have stimulated several analytic epidemiologic studies of sunlight exposure and prostate cancer risk, the results of which largely support a protective effect of sunlight exposure (see [14] for a review). However, several important questions about the relationship of prostate cancer mortality rates to UV radiation remain. For example, our analyses in 1992 used data from only a single decade, 1970–1979, and whether the striking inverse relationship between mortality rates and UV radiation has been constant over time is unknown. Mortality data for more than four decades recently have become available and now enable us to answer this question. Moreover, we now appreciate that the cutaneous synthesis of vitamin D is threshold-related. For example, Webb et al. showed that irradiation of 20 $mJ/cm^2$ is required to convert 7-dehydrocholesterol into vitamin D in vitro [15]. This was confirmed in human subjects in vivo by Matsuoka et al. who showed that an irradiation threshold of 18 $mJ/cm^2$ was required in order to induce the production and release of vitamin $D_3$ into the circulation [16]. This work has important public health implications because at approximately 40° N latitude (e.g., the location of cities like Philadelphia, Boston, etc.), the accumulated UVB daily irradiation from November to February is below the critical threshold of 20 $mJ/cm^2$. Thus, for 1/3 of the year, sunlight exposure north of 40° N latitude does not induce vitamin D synthesis. This suggests that the effects of ultraviolet radiation on prostate cancer should differ above and below 40° N latitude.

This paper analyzes prostate cancer mortality data over a 45-year period in order to examine the persistence of the north–south trend in prostate cancer mortality. Additionally, we examine the relationships between prostate cancer mortality and UV radiation north and south of 40° N latitude in order to test the hypothesis that the effect of latitude is greater in the North, where vitamin D synthesis is limited to the non-winter months.

## Data and methods

We used trend surface analysis to determine whether the north–south trend in prostate cancer mortality for white males was present systematically over a 45-year period and compared these trends to geographic patterns of ultraviolet radiation. We also used linear regression analysis to characterize the relationship between mortality and UV radiation for all counties in the continental U.S. Both methods were then used to examine rates north and south of 40° N latitude.

Data on ultraviolet radiation, in the form of the UV Index, were obtained from the National Oceanic and Atmospheric Administration (NOAA). The UV Index (UVI) is a standardized way of reporting UV information to the public that is derived from satellite observations, cloud cover data, and atmospheric pressure and temperature forecasts [17]. It is computed daily for 58 cities in the U.S. These data can be interpolated to produce a forecast of UV intensity at the earth's surface for any location in the country. Values range from 0 to 16, with higher values indicating the intensity of skin-damaging solar radiation. We used the 1995 average annual UV Index for the 55 cities in the contiguous U.S, as full-year data were not available for earlier years.

The UV Index includes the ''sunburning'' or ''erythemally weighted'' UV, which includes both UVB, which induces vitamin D synthesis, and UVA (400–320 nm), which contributes to erythema but does not induce vitamin D synthesis. Over a wide range of ozone amounts and solar zenith angles, McKenzie et al. showed that there is a simple relationship

between the UV Index and $UVB_{280–315\ nm}$, given by the equation $UVB_{280–315\ nm}$, in units of $W\ m^{-2}$, $= 18.9 \times UVI$. Using 2,395 individual measurements the correlation observed between measured UVB and erythemally weighted UV was 0.948 [18].

We analyzed white male cancer mortality rates using two geographic units of analysis: counties and state economic areas (SEAs), which are aggregations of several counties. Data for Black males are too sparse for national-level analyses. We obtained mortality rate data from the National Cancer Institute (NCI), which standardized these rates to the 1970 U.S. population standard using the direct method [19]. County rates were available for two time periods: 1950–69 and 1970–94. Rates for SEAs were available for all five-year periods from 1950–1994. The NCI dataset contains rates for 3,053 counties in the continental United States. For both study time periods some counties had sparse values, which can result in unstable rates due to small numbers. We used NCI's criteria for defining a rate as ''unstable'' and treated these as missing values. This resulted in a total of 2,573 counties for the 1950–69 analysis and 2,850 counties for the 1970–94 analysis. Very few of the 505 SEAs had unstable rates during any of the five-year study periods.

It is often necessary to smooth data for the visualization and/or confirmation of geographic patterns that otherwise may be obscured by random variation [20]. Trend surface analysis, also known as ''global polynomial interpolation,'' is a smoothing method that produces a modeled surface and identifies broad, overall patterns in geographic data. We used trend surface analysis to determine whether the north–south trend in prostate cancer mortality for Caucasians was present systematically and compared these trends to geographic patterns of ultraviolet radiation.

A ''trend'' is ''any large-scale systematic change that extends smoothly and predictably from one map edge to the other'' [21]. Trend surface analysis is a regression analysis characterized by the general formula:

$$z = f(x,y)$$

where $z$ is the magnitude of an attribute (e.g., prostate cancer mortality rate), $x$ and $y$ are spatial coordinates (e.g., longitude and latitude) and $f$ is a function. Typically, trend surface analysis uses a polynomial function and fits this to the data using least-squares regression. The result is an equation that describes the overall trend of the attribute and is used to predict a new value for each surface location. The new value is then mapped. A coefficient of determination, $r^2$, describes how well the estimated trend explains the observed data. Thus, trend surface analysis resembles linear regression analysis but with an added dimension, geographic location.

The simplest trend uses a linear equation. The result can be envisioned as an inclined plane that lies over the observed data points. Higher order trends (i.e., quadratic, cubic, etc.) produce higher $r^2$ values but are computationally more complex.

Several imitations of trend surface analysis have been described [22]. Chief among these is that when these techniques are used for hypothesis generation, it may be difficult to develop hypotheses to explain the complex surfaces that result from higher order trends. Secondly, trend surface analysis is most appropriate when the data points are distributed evenly across a map (i.e., on a rectangular grid), as highly clustered data may yield spurious results. Additionally, analysis of the residuals from trend surface analysis can be hindered by spatial autocorrelation.

We used the Geostatistical Analyst extension of ESRI's ArcGIS software (Environmental Systems Research Institute, Redlands, CA) to compute and map spatial trends in UV radiation and prostate cancer mortality. Although we computed trends at several orders, we focused on linear (first order) trends because these explain almost all (96%) of the spatial variation in UV radiation. Moreover, our rationale for producing these trends was not to generate hypotheses, but to evaluate an hypothesis that was proposed previously [23]. Although the spatial distribution of data points across our map area (i.e., county centroids) was not even, the large sample size ($n$ = 3,053) minimizes concern about data distribution, as all areas in the 48 contiguous states were well-represented.

## Results

Table 1 shows the results of the trend surface analyses. The $r^2$ values do not characterize the relationship between UV radiation and mortality; rather, they indicate how well the modeled surface fits the original data.

As expected, the first order trend surface map of the UV Index, using values from 55 cities, depicted a strong southwest to northeast trend, dependent on both latitude and cloud cover (Fig. 1). This trend is nearly identical to the trend we produced in 1992 using a different index, the UV Count [24, 25].

First-order trend surface maps of county-level mortality data for the two study periods, 1950–69 and 1970–94, are shown in Fig. 2. Both maps depict a general north to south trend, with a slightly elevated

**Table 1** Results of trend surface analyses for UV radiation and prostate cancer mortality

| Variable | Geographic unit | Time period | Trend order | *n* | *r* | $r^2$ | *p* value |
|---|---|---|---|---|---|---|---|
| UV index | City | 1995 | 1 | 55 | 0.96 | 0.93 | < 0.0001 |
| Prostate cancer mortality | County | 1950–69 | 1 | 2,573 | 0.18 | 0.03 | < 0.0001 |
| Prostate cancer mortality | County | 1970–94 | 1 | 2,850 | 0.30 | 0.09 | < 0.0001 |
| Prostate cancer mortality | County | 1970–94 | 4 | 2,850 | 0.41 | 0.17 | < 0.0001 |
| Prostate cancer mortality | County | 1970–94 | 7 | 2,850 | 0.44 | 0.19 | < 0.0001 |
| Prostate cancer mortality | County | 1970–94 | 10 | 2,850 | 0.47 | 0.22 | < 0.0001 |
| Prostate cancer mortality | SEA | 1950–54 | 1 | 495 | 0.25 | 0.06 | < 0.0001 |
| Prostate cancer mortality | SEA | 1955–59 | 1 | 497 | 0.25 | 0.06 | < 0.0001 |
| Prostate cancer mortality | SEA | 1960–64 | 1 | 500 | 0.25 | 0.06 | < 0.0001 |
| Prostate cancer mortality | SEA | 1965–69 | 1 | 502 | 0.27 | 0.07 | < 0.0001 |
| Prostate cancer mortality | SEA | 1970–74 | 1 | 501 | 0.23 | 0.05 | < 0.0001 |
| Prostate cancer mortality | SEA | 1975–79 | 1 | 502 | 0.35 | 0.12 | < 0.0001 |
| Prostate cancer mortality | SEA | 1980–84 | 1 | 504 | 0.40 | 0.16 | < 0.0001 |
| Prostate cancer mortality | SEA | 1985–89 | 1 | 505 | 0.42 | 0.18 | < 0.0001 |
| Prostate cancer mortality | SEA | 1990–94 | 1 | 505 | 0.31 | 0.09 | < 0.0001 |

surface in the northwestern U.S. The two trends are nearly identical except that, overall, observed and predicted rates and the $r^2$ value in the latter time period are higher.

For state economic areas, where geographic precision is lower, but rates are more stable, the most notable result is the persistence of the general north–south trend across all time periods (Fig. 3).

Higher order trends, which use more complex polynomial equations, produce a closer fit between observed data and predicted rates, i.e., they explain more of the spatial variation in the data. At some point, the $r^2$ value begins to plateau as successive trends and higher orders offer ''diminishing returns.'' Table 1 contains information about higher order trend surface analyses performed on the 1970–94 county data. The results of the 10th order trend, which explains 22% of the spatial variation in prostate cancer mortality, are mapped in Fig. 4. The spatial patterns confirm those identified by previous geographic studies [26, 27].

In addition to the trend surface analyses, we regressed county level prostate cancer mortality rates for three time periods on both winter and summer UV Index values for January and July (respectively). Results of these regression analyses are shown in Table 2. These analyses demonstrate significant negative correlations using January and July UV data at all time points. The correlations in January and in July do not differ appreciably from one another.

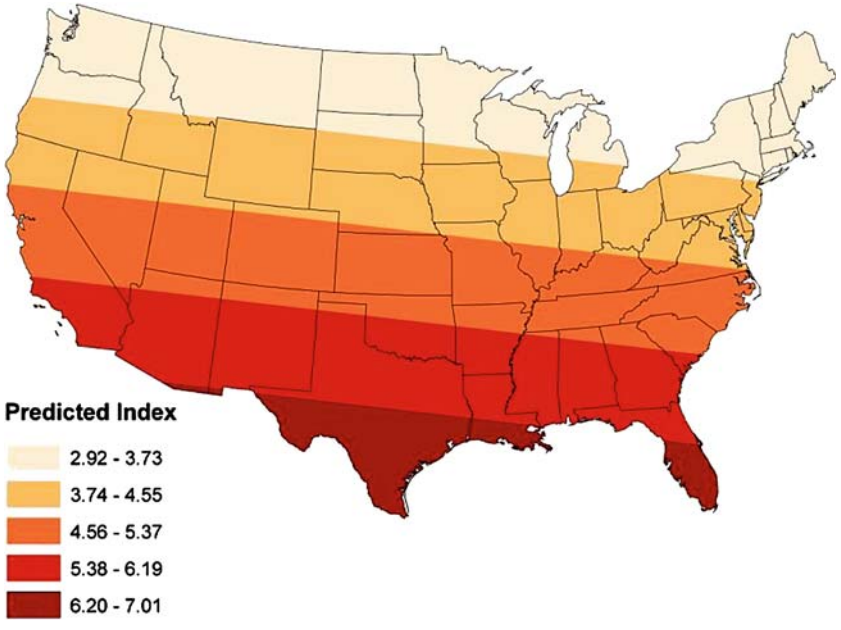


**Fig. 1** First order trend surface map of annual UV radiation

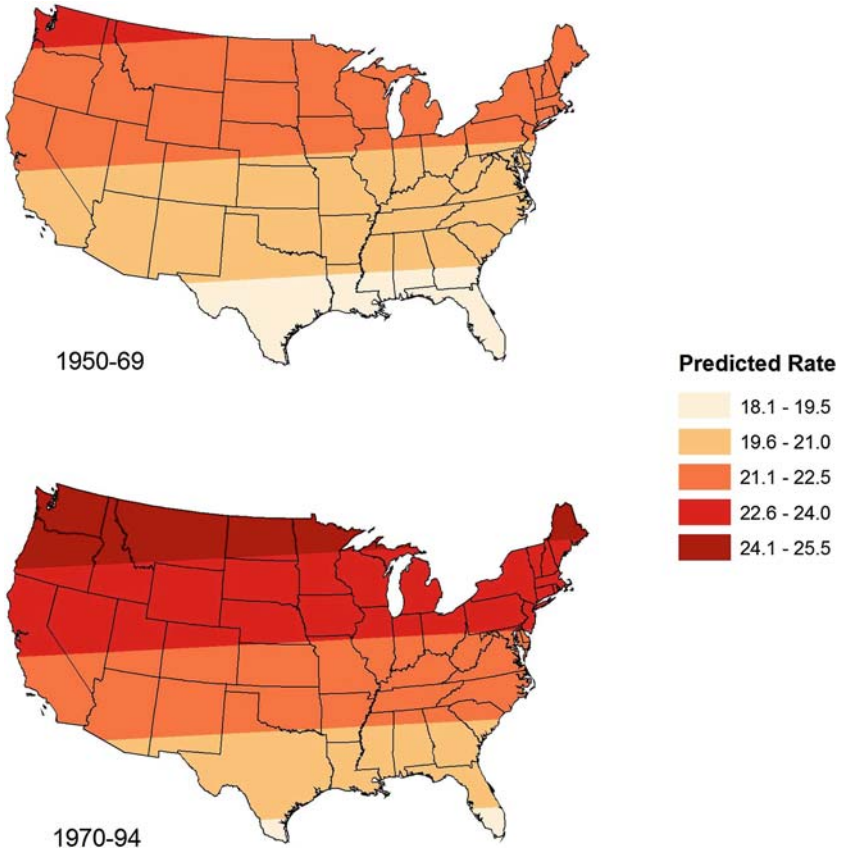


**Fig. 2** First order trend surface maps of prostate cancer mortality by county, white males, 1950–69 and 1970–94

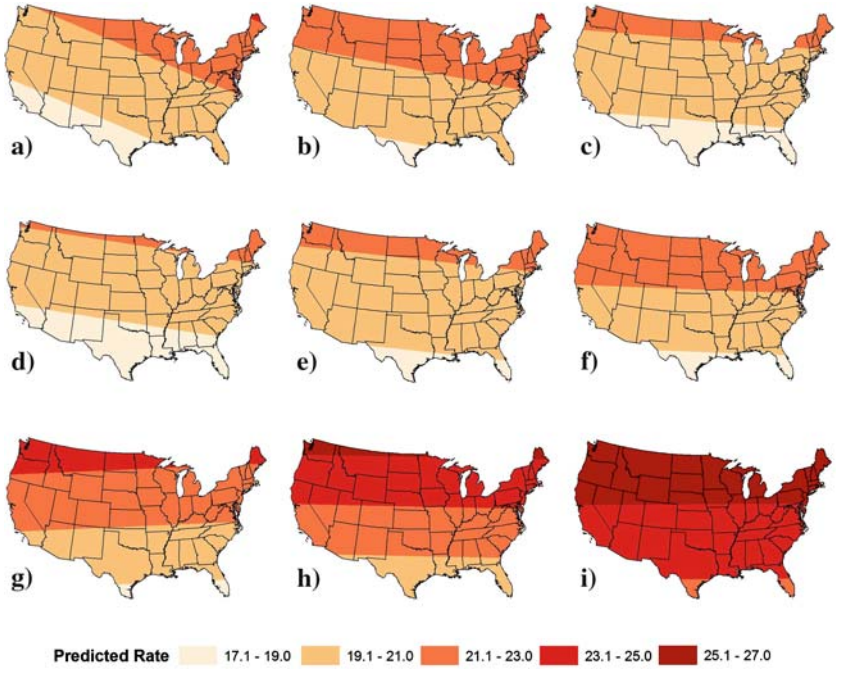


**Fig. 3** First order trend surface maps of prostate cancer mortality by state economic area, white males, for nine five-year time periods: (**a**) 1950–54, (**b**) 1955–59, (**c**) 1960–64, (**d**) 1965–69, (**e**) 1970–74, (**f**) 1975–79, (**g**) 1980–84, (**h**) 1985–89, and (**i**) 1990–94

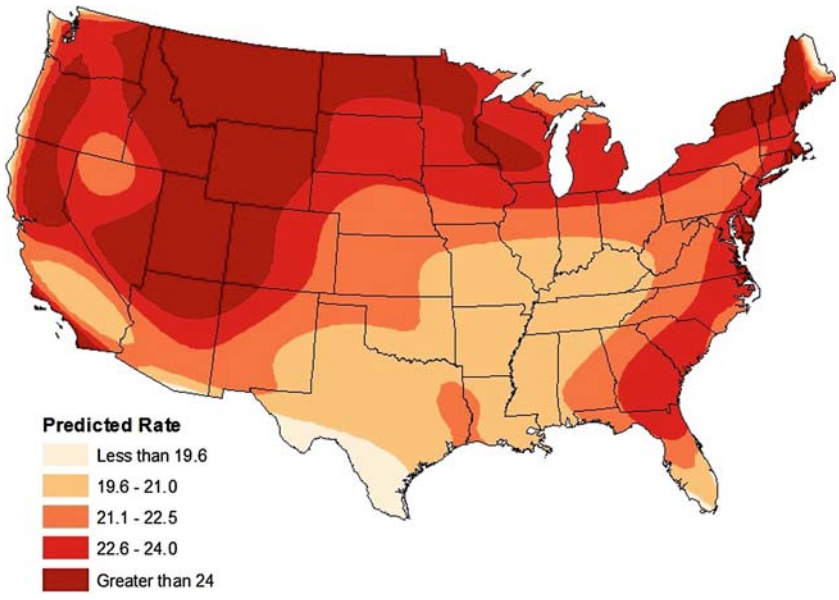


**Fig. 4** Tenth order trend surface map of prostate cancer mortality by county, white males, 1970–94

We next focused on the 1970–1994 time period in order to determine possible differences between the northern and southern U.S. (Table 3). Using the interpolated UV index values for all continental U.S. counties yielded an $r^2$ value of 0.055 ($p < 0.0001$). The $r^2$ value for northern counties ($r^2 = 0.03$, $n = 1074$) was much higher than for southern counties ($r^2 = 0.0001$, $n = 1776$). The latter was not statistically significant; i.e., a significant inverse correlation between prostate cancer mortality and UV radiation was observed for latitudes north of 40° N only.

Separate linear trend surface analyses for the northern and southern counties of the U.S. both depict the general north–south trend identified for the nation as a whole (Fig. 5). The $r^2$ values for these trends are shown in Table 4. Although significant trends were observed in the North ($r = 0.27$, $p < 0.001$) and in the South ($r = 0.06$, $p = 0.009$), it is apparent that the trend in the North explains more of the spatial variation in the data than the trend for the South.

**Table 2** Results of regression analyses: UV radiation and county prostate cancer mortality, January and July

| Year | $r$ | $r^2$ | $p$ | $n$ |
|---|---|---|---|---|
| *January* | | | | |
| 1950–69 | –0.19 | 0.03 | <0.001 | 2573 |
| 1970–94 | –0.28 | 0.08 | <0.001 | 2850 |
| 1950–94 | –0.30 | 0.09 | <0.001 | 2949 |
| *July* | | | | |
| 1950–69 | –0.15 | 0.02 | <0.001 | 2573 |
| 1970–94 | –0.25 | 0.06 | <0.001 | 2850 |
| 1950–94 | –0.26 | 0.07 | <0.001 | 2949 |

We tested the hypothesis that the effects of latitude were equal in the North and South using the Fisher $Z$-transformation, a test used to determine whether two correlations have different strengths [28]. The two correlations are transformed using the following formula:

$$\mathrm{Zf} = 1/2 * \ln((1 + R)/(1 - R))$$

The difference is computed with the formula,

$$z = (\mathrm{Zf1} - \mathrm{Zf2})/\mathrm{SQRT}(1/(\mathrm{N1} - 3) + 1/(\mathrm{N2} - 3))$$

which is approximately Standard Normal distributed and is used to determine the level of significance. Results are shown in Table 5.

The results indicate that the correlation coefficients for northern counties are negative and significant ($p < 0.0001$). That is, the effects of latitude are more pronounced in the North, where vitamin D synthesis is limited to non-winter months, than in the South, where vitamin D synthesis occurs year-round. This is confirmed visually by the steepness of the trend for northern counties (Fig. 5).

**Table 3** Results of regression analyses: UV radiation and prostate cancer mortality, northern and southern counties

| Unit | $n$ | $r$ | $r^2$ | $p$ value |
|---|---|---|---|---|
| County | 2,850 | –0.23 | 0.06 | <0.0001 |
| County, North | 1,074 | –0.16 | 0.03 | <0.0001 |
| County, South | 1,776 | 0.01 | 0.0001 | 0.7044 |

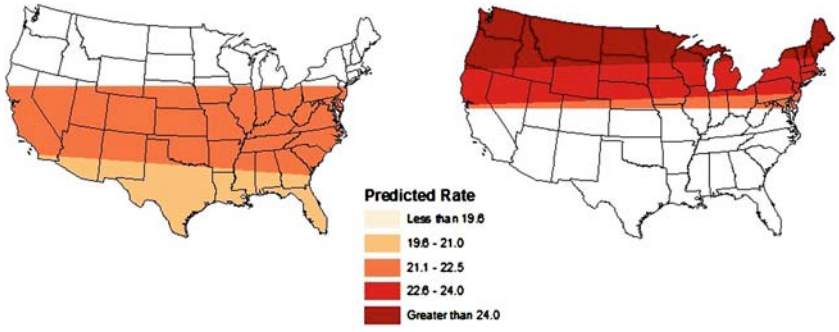


**Fig. 5** First order trend surface maps of prostate cancer mortality by county, white males, 1970–94, north and south of 40° N latitude

## Discussion

Using high quality data estimates for ultraviolet radiation and prostate cancer mortality rates for U.S. Caucasians from 1950 to 1994, we demonstrated that prostate cancer mortality at both the level of the county and the SEA followed a significant north–south trend that is essentially the inverse of UV radiation. These findings confirm and extend the findings from our original trend surface analyses demonstrating that the geographic distribution of prostate cancer among U.S. Caucasians is inversely related to the distribution of ultraviolet light. Moreover, we found that these trends are significantly more pronounced N of 40° N latitude.

To our knowledge, this is the first report to demonstrate that the relationship between UV radiation and cancer mortality in the U.S. is stronger in counties N of 40° N latitude. There are several possible explanations for this finding. One explanation is that more severe vitamin D insufficiency, e.g., serum levels of 25-OHD less than 20 ng/ml, which is known to be more prevalent at northern latitudes, may be a more potent cause of prostate cancer mortality than are milder forms of vitamin D insufficiency [29]. This interpretation is consistent with the seroepidemiologic literature on prostate cancer, which has generally found that serum levels of 25-OHD are associated with an increased risk of prostate cancer when the cutpoint for vitamin D insufficiency is relatively low [30].

**Table 4** Results of trend surface analyses of prostate cancer mortality for counties north and south of 40° N latitude

| Geographic unit | Time period | $n$ | $r$ | $r^2$ | $p$ value |
|---|---|---|---|---|---|
| County, North | 1970–94 | 1,074 | 0.27 | 0.07 | $<0.0001$ |
| County, South | 1970–94 | 1,776 | 0.06 | 0.004 | 0.0087 |

**Table 5** Comparison of correlations, North and South, regression and trend surface analyses

| Method | Northern $r$ ($n$ = 1074) | Southern $r$ ($n$ = 1776) | $p$ value |
|---|---|---|---|
| Regression | –0.16 | 0.01 | $<0.0001$ |
| Trend surface | 0.27 | 0.06 | $<0.0001$ |

The size of the correlation between the actual prostate cancer mortality rates and those predicted by the linear (north–south) trend surface varied by geographic unit and time period, ranging from 0.18 to 0.42. *r*-squared values were generally higher for state economic areas than for counties, a phenomenon that has been well-documented when data aggregation operates via the dependent variable [31]. The values of *r*-squared observed for the largest dataset, 1970–1994 (counties), suggests that approximately 9% of age-adjusted prostate cancer mortality rates ($0.09 \times 30{,}000$ deaths per year = 2,700 deaths per year) are explicable by a trend that mirrors that of UV radiation.

It is important to consider whether the inverse relationship of prostate cancer mortality rates and UV radiation could be explained by alternative hypotheses (e.g., confounding). Other than geographic latitude, the set of established risk factors for prostate cancer includes increased age, Black race, and family history of prostate cancer. Risk factors that are less well-established include obesity, low selenium, and high dietary calcium.

These data were age-adjusted and were restricted to Caucasians, precluding confounding by age and race. Since less than 10% of prostate cancer is believed to have important hereditary causes [32], confounding by family history is unlikely to have influenced these results. Alternately, geographic trends in prostate cancer mortality could result from systematic trends in other variables, including the accuracy of death certification, and/or differences in stage of disease presentation, utilization rates of curative therapy, migration and survival. For example, based on ecological data at county and state levels, Jemal et al. suggested that 10–30% of the geographic variation in prostate cancer

mortality rates may be due to variations in access to medical care [33]. Unfortunately, the sizeable numbers of cases reported as unstaged make this assessment difficult with ecological data. Additionally, it is conceivable the northern excess of fatal prostate cancer might reflect systematically later presentation of cancer in the North. Another possibility is that curative therapies (e.g., radical prostatectomy) might be utilized less frequently in the North.

These possibilities seem unlikely for several reasons. First, because advanced prostate cancer is not difficult to diagnose, the accuracy of its certification at death is unlikely to vary systematically by geographic region. Analyses of outcome data for patients undergoing radical prostatectomy from the Surveillance Epidemiology and End Results (SEER) program indicates both overall and disease-specific survival rates do not differ across the U.S. [34]. Indeed, although the utilization of these therapies has increased in recent years, prostatectomy rates are highest in northern locations in the U.S., such as San Francisco and Seattle (i.e., a trend contrary to the mortality pattern). Thus, the north–south trends in mortality do not seem to be explicable by obvious differences in reporting practices or survival.

Positive effects for low selenium, a trace element, and prostate cancer have been reported in several epidemiologic studies [35]. However, selenium measurements in forage crops have not detected deficiencies in the northern U.S. [36].

Greater intake of milk and/or calcium have been associated with an increased risk of prostate cancer in some, but not all observational studies [37]. Conversely, this association has not been confirmed in a randomized trial of calcium supplementation, in which men receiving calcium had a slightly reduced risk of prostate cancer [38]. Because this is an ecologic study, we are unable to control for confounding by individual-level factors such as milk or selenium consumption. However, for such confounders to have materially influenced our results, the distribution of such factors, in space and/or time, should be relatively consistent over the 45-year time span represented by these mortality data. For example, although milk is a major source of calcium, data from four representative samples of the U.S. population, the Nationwide Food Consumption Surveys, show that milk consumption among all age groups has declined from 1977 to 2001 [39].

Similarly, obesity has been found to modestly increase risk of prostate cancer in several studies [40]. In this regard, we note that national data show that the prevalence of obesity in men is highest in South Atlantic states [41]. Thus, confounding effects due to obesity, if any, are likely to have diminished the correlations observed in these data.

Another potential confounder is migration. The latency period for clinical prostate cancer is believed to be 20 years or more, suggesting that migration may have an important effect on geographic patterns of mortality. During the time periods covered by our analyses, the Northeast and Midwest regions (''Rust Belt'') experienced substantial population losses to the South and West (''Sun Belt'') [42]. Assuming that the major protective effects of UV exposure occur sometime prior to migration (as indicated by the NHANES analysis by John et al. [43], below), the effect of these migrations would be to dilute the observed correlations between prostate cancer mortality and UV exposure Rogerson et al. [44] reported a higher than expected increase in prostate cancer mortality in south-central states from 1990 to 1998, a finding that might be influenced by Sun Belt migration. However, a recent geographical study indicates that the protective effect of sunlight on prostate cancer mortality persists even after controlling for migration [45].

The data from the present study are at the level of the group, e.g., county, and thus do not address the question of sunlight exposure and risk of prostate cancer at the level of the individual. At least five epidemiologic studies have examined the risk of prostate cancer in relation to exposure to ultraviolet (UV) radiation, and their results are consistent with a protective effect of sunlight exposure. For example, Luscombe and colleagues compared 210 men with prostate cancer in the United Kingdom to 155 men with benign prostatic hypertrophy (non-cancer controls) on various measures of lifetime sunlight exposure [46]. A high sunbathing score was significantly protective for prostate cancer (OR = 0.83, 95% CI = 0.76–0.89). Conversely, a low exposure to ultraviolet radiation was associated with a significantly increased risk (OR = 3.03, 95% CI = 1.59–5.78). Multiple sunburns during childhood were significantly inversely associated with a reduced risk of prostate cancer (OR = 0.18, 95% CI = 0.08–0.38).

An important methodological issue in retrospective studies such as Luscombe's is recall bias. Due to the popularization of the sunlight/prostate cancer story in the lay press [e.g., 47], many men with prostate cancer may underestimate their actual exposures to UV radiation, leading to a bias in support of the hypothesis.

Four studies that circumvent this problem are those of Friedman et al., Weinrich et al., and two studies by John et al. Freedman et al. conducted a death certificate-based case–control study of mortality from prostate cancer in association with exposure to sunlight

[48]. Cases were deaths from cancer between 1984 and 1995 in 24 states. Controls were deaths from causes other than cancer and other diseases thought to involve sunlight exposure. Residential exposure to sunlight was classified by state of residence at birth and at death. These authors found that high residential exposure to sunlight was associated with a significantly decreased risk of fatal prostate cancer (OR = 0.90, 95% CI = 0.87–0.93). Because exposure to sunlight was classified from information on the death certificate, this study is unlikely to be influenced by recall bias.

Weinrich et al. measured the association between self-reported solar exposure and an abnormal serum prostate specific antigen (PSA) among men attending a prostate cancer screening program. Frequent sun exposure (3 or more times per week) was associated with a 55% reduction in the odds of an abnormal PSA, after adjustment for age, education, and income (R = 0.45, 95% CI = 0.21–0.97) [49].

John et al. analyzed data from the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study in order to test the hypothesis that sunlight exposure reduces the risk of developing prostate cancer [43]. One hundred and fifty-three (153) men with incident prostate cancer were identified from a cohort of 3,414 white men who completed the dermatologic examination and were followed until 1992. Age-adjusted relative risks (RR) and 95% confidence intervals (CI) were estimated for various measures of sunlight exposure using Cox proportional hazards. The data were adjusted for the confounding effects of education, income, body mass index (BMI), height, alcohol consumption, smoking, physical activity, energy intake, and intake of fat and calcium. State of longest residence in the South (RR = 0.58, CI = 0.38–0.88, $p < 0.01$), and high solar radiation in the state of birth (RR = 0.48, CI = 0.30–0.76, $p < 0.01$) were associated with substantial and significant reductions in the risk of prostate cancer. The prospective design of this study precludes the possibility of recall bias.

In a very recent study, John et al. conducted a population-based case–control study of advanced prostate cancer among men from the San Francisco Bay area [30]. Interview data were collected on lifetime sun exposure for 450 Caucasian cases and 455 Caucasian controls. Using a reflectometer, skin pigmentation was measured at 2 sites: the upper underarm (a measure of sun-unexposed skin) and the forehead (a measure of sun-exposed skin). A halving of the risk of prostate cancer was seen for men with high sun exposure as determined by reflectometry (OR = 0.51, 95% CI = 0.33–0.80). Reductions in risk were also observed among men with high occupational outdoor activity. The use of skin reflectometry adds important objective evidence for the effects of solar radiation that cannot be the result of reporting bias.

In contrast to studies of solar exposure, which have been consistently positive, the results of serologic epidemiologic studies on serum 25-OHD and risk of prostate cancer have been inconsistent. One explanation for this discrepancy is that the studies of solar exposure have often included lifetime measurements of vitamin D exposure. Conversely, the serological studies use a single vitamin D measurement at varying timepoints whose relevance to the natural history of prostate cancer is unknown [14].

Using data from Scandinavia, primarily Norway, Tuohimaa reported that both low and high levels of serum 25-OHD were associated with an increased risk of prostate cancer [50]. Similar findings for 25-OHD have not been reported by other investigators. If it were true that high levels of 25-OHD increased the risk for prostate cancer, then southern areas of the U.S., whose residents are known to have high levels of 25-OHD, should have high prostate cancer mortality rates and there should be a ''U'' shape to the mortality trend surfaces. Our analyses of 45 years of mortality data confirm significant first-order linear trends from north to south at every five year interval examined. These findings do not support the existence of higher mortality rates in the South. We also performed higher order trend-surface analyses (4th, 7th, and 10th orders), none of which indicated a trough at mid-latitudes. Similarly, three recent analyses using different geographic techniques, viz., spatial smoothing and the spatial scan statistic [20, 26, 27] confirm the northern excess in prostate cancer mortality among U.S. Caucasians and do not support a ''U-shaped'' relationship.

It is not yet clear at what age(s) vitamin D deficiency poses the greatest risk for prostate cancer, although the results of the NHANES analyses by John et al., which found a 48% reduction in risk for men born in a southern state, clearly suggest that exposure early in life may be important. Future geographic studies of prostate cancer risk in relation to migration would be valuable in clarifying this issue.

In conclusion, our research demonstrates that trend surface analyses can play important roles in revealing informative patterns in the otherwise dizzying array of countywide cancer mortality rates. Our analyses confirm that the geographic distribution of prostate cancer mortality among Caucasians is the inverse of that of UV radiation and demonstrate that this effect is strongest in counties N of 40° N latitude, where the synthesis of vitamin D is limited to non-winter months.

Additional research on the benefits of vitamin D supplementation on risk of prostate cancer, particularly for men who reside at northern latitudes, is warranted.

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