An Estimate of Premature Cancer Mortality in the U.S. Due to Inadequate Doses of Solar Ultraviolet-B Radiation

William B. Grant, Ph.D.

Independent Researcher, Newport News, Virginia.

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Address for reprints: William B. Grant, Ph.D., 12 Sir Francis Wyatt Place, Newport News, VA 23606-3660; Fax: (757) 864-7790, E-mail: wbgrant@infi.net

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BACKGROUND. There are large geographic gradients in mortality rates for a number of cancers in the U.S. (e.g., rates are approximately twice as high in the northeast compared with the southwest). Risk factors such as diet fail to explain this variation. Previous studies have demonstrated that the geographic distributions for five types of cancer are related inversely to solar radiation. The purpose of the current study was to determine how many types of cancer are affected by solar radiation and how many premature deaths from cancer occur due to insufficient ultraviolet (UV)-B radiation.

METHODS. UV-B data for July 1992 and cancer mortality rates in the U.S. for between 1970–1994 were analyzed in an ecologic study.

RESULTS. The findings of the current study confirm previous results that solar UV-B radiation is associated with reduced risk of cancer of the breast, colon, ovary, and prostate as well as non-Hodgkin lymphoma. Eight additional malignancies were found to exhibit an inverse correlation between mortality rates and UV-B radiation: bladder, esophageal, kidney, lung, pancreatic, rectal, stomach, and corpus uteri. The annual number of premature deaths from cancer due to lower UV-B exposures was 21,700 (95% confidence interval [95% CI], 20,400–23,400) for white Americans, 1400 (95% CI, 1100–1600) for black Americans, and 500 (95% CI, 400–600) for Asian Americans and other minorities.

CONCLUSIONS. The results of the current study demonstrate that much of the geographic variation in cancer mortality rates in the U.S. can be attributed to variations in solar UV-B radiation exposure. Thus, many lives could be extended through increased careful exposure to solar UV-B radiation and more safely, vitamin D3 supplementation, especially in nonsummer months. ***Cancer* 2002;94: 1867–75.** © *2002 American Cancer Society.*

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There are large geographic variations in cancer mortality both in the U.S and abroad.[1–4] Mortality rates for bladder, breast, colon, corpus uteri, ovarian, and rectal carcinomas generally are twice as high in the northeast U.S. compared with the southwest U.S. for both white and black Americans. A number of other types of malignancy, such as kidney carcinoma and non-Hodgkin lymphoma (NHL) have less pronounced latitudinal gradients in the U.S.

The most important risk factors for many types of cancer are environmental,[5,6] with diet or lifestyle choices such as smoking generally accepted as playing the largest role. However, differences

in dietary or smoking habits do not appear to explain the geographic distributions of cancer mortality in the U.S. except in a few limited cases. For the U.S. during 1977–1978, it was found that large-scale dietary patterns in the 4 quadrants of the U.S. varied by < 10–20%,[7] seemingly minimizing the role of diet in explaining the geographic distribution of the 6 cancer types noted earlier. Indeed, a recent investigation of the geographic distribution of the mortality rate for bladder carcinoma in the U.S. concluded that diet could not explain the distribution.[8] Diet and lifestyle may play a role in the geographic distribution of lung carcinoma and liver carcinoma, for which mortality rates are highest in the southeast U.S. among white Americans. Smoking is a risk factor for lung carcinoma, and alcohol, aflatoxin from peanuts,[6] and infectious diseases are risk factors for liver carcinoma.[6] Individuals living in southeastern states in the U.S. may possess more of these risk factors than those residing in other regions. Mortality rates for gastric carcinoma are nearly double for white Americans living in northern states compared with those living in southeastern states.[1] Mortality rates due to gastric carcinoma in the southwest are nearly as high as in the northern states, most likely due to a high Hispanic population, a group that is included in the white American classification, and the fact that components of the Mexican diet (such as hot peppers) are risk factors for gastric carcinoma.[9] Pesticides and other manmade chemicals have been implicated as risk factors for cancer, but exposure to these agents does not appear to explain the geographic distribution of cancer mortality in the U.S.[10]

There have been reports that inverse correlations exist between exposure to solar radiation and the development of carcinoma of the breast,[2,3,11,12] colon,[13] NHL,[14,15] ovary,[16] and prostate.[17,18] One explanation for the geographic distribution of mortality for these malignancies in the U.S. is that solar ultraviolet (UV)-B radiation (280–320 nanometers [nm]) exposure reduces the risk of cancer through photoinitiation of vitamin D production. Vitamin D, or its analogues, have been shown to play a number of roles in cell biology (such as increasing differentiation and reducing proliferation) that appear to reduce the risk of some tumors, such as prostate carcinoma.[19]

The goal of the current study was to determine additional malignancies for which UV-B a risk reduction factor and how many Americans die prematurely each year from cancer due to insufficient UV-B radiation.

MATERIALS AND METHODS

Data Collection

The work presented herein is an ecologic study of cancer mortality rates in the U.S. with respect to solar UV-B exposure. The cancer mortality data were taken from the Atlas of Cancer Mortality,[1] in which age-adjusted rates for white and black Americans separated by gender are given by county (n = 3053) and state economic area (SEA) (n = 506) for the periods 1950–1969 and 1970–1994. SEAs are individual counties or groups of counties that are relatively homogeneous with respect to various demographic, economic, and cultural factors. The original cancer data were obtained from the National Center for Health Statistics, whereas population estimates were obtained from the Census Bureau. The SEA data for the period 1970–1994 were used in the current study, although the 1950–1969 data showed similar geographic distributions.

Two solar UV-B indices and data sets were used in the current study. The primary data set used for the current analysis was the DNA-weighted UV-B radiation exposure map obtained by using the Total Ozone Mapping Spectrometer (TOMS).[20,21] TOMS is a space-based instrument that yields UV data for the entire country with a 1-degree × 1.25-degree grid spacing. The July 1992 TOMS data, posted at the TOMS website, was used.[20] The color images were digitized to yield average values for each SEA or population center within the SEAs, including major urban areas. The color contour interval was 0.75 kilojoule (kJ)/m^2, with a noontime average range in the U.S. of 3.4–10 kJ/m^2. The location of the SEA can be determined to approximately 33–50% of a contour or approximately 0.3–0.4 kJ/m^2. This represents approximately 10% of the dose at the lower exposures and 4% at the higher exposures. However, the TOMS estimate of UV-B radiation apparently underestimates the reduction due to aerosols,[22] which is a very important consideration in the northeastern U.S.

In addition to the TOMS data, UV-B data obtained from ground-based UV-B monitoring stations operated by the U.S. Department of Agriculture (USDA) also were used.[23,24] This network has 26 stations in rural locations in the U.S., 24 of which were in operation by 1999. The UV-B data were determined as follows: 1) the earliest year on or after 1997 for which July data were available was found; 2) a week's worth of data were obtained from the website in graphic form; 3) the value for that week was the highest midday value that was unaffected by clouds; and 4) the mean value for the 4 weeks was determined. If clouds affected the data for the entire week, the correspond-

ing week of the next year was used instead. This approach emphasizes the contributions of solar zenith angle, station elevation, ozone, and typical aerosol loading of the atmosphere. The relative uncertainty of each determination was estimated to be < 0.1. From the 24 stations, 9 stations were identified that when removed, resulted in an increase in the regression coefficient (r) for male colon carcinoma in July. The stations removed often were in coastal or border regions where they could have been subjected to influences such as clouds or recent immigration. The remaining 15 stations were used in analyses for July and early September.

Exclusion Criteria

A number of malignancies take 15–25 years to develop,[25,26] so if the population growth came via immigration, those who immigrated could not be expected to have experienced the same UV-B exposure as long-term residents. Because it was important in the current analysis that a large fraction of those living in the state had lived there a number of years, states with large population increases ($> 25\%$) between 1980–1990 (Alaska, Arizona, California, Florida, and Nevada) were omitted from the analysis.[27] These states had cancer mortality rates that were much higher than neighboring states or demonstrated large changes in mortality rates between 1950–1969 and 1970–1994.[1] A secondary exclusion criterion used was whether there were large increases in cancer mortality rates between the two periods. Hawaii was eliminated based on this criterion. The omitted states, based on both criteria, comprised approximately 20% of the white American mortality cases for the primary malignancies.

For white Americans, the data were of sufficient numbers that the remaining 466 SEAs could be used. However, for black Americans, this was not the case due to low populations in many SEAs. It was found that good statistical results could be obtained by applying 2 criteria to the data for black Americans: 1) the average population in a SEA during the 25-year period was > 1100, and 2) there were at least 2 cases of mortality during the period. For black Americans, only 10% of the cases were omitted from the analysis by applying the criteria for states and data values.

Data Analysis

To assess the role of solar UV-B radiation as a protective factor against cancer, an estimate was made of the number of lives that were lost prematurely (i.e., due to cancer but which were preventable or delayed with sufficient solar UV-B radiation). To make the calculations, the following steps were taken:

1. Regression analyses were performed using the available data. Second-order regressions were used when the values did not demonstrate a linear decrease of mortality with increasing UV-B dose. Second-order regressions reflected the fact that in the southwest U.S., mortality did not increase linearly with dose, perhaps due to a larger proportion of Hispanics being included in the "white American" category.
2. The minimum mortality rate was determined from the regression analysis as the value that corresponded to the maximum UV-B dose for which at least one mortality rate value was near the mean.
3. The number of cases for each SEA was multiplied by the mortality rate for that SEA minus the value determined in Step 2, and the values were summed. This step yielded the variance for the analysis.
4. A multiplicative factor was formed from the variance divided by total number times r^2 in which r is the regression coefficient. The use of r^2 is in accordance with the general rule that a statistical regression explains the fraction r^2 of the variance.
5. The numbers determined in Step 3 were multiplied by the factor in Step 4. The resulting value was considered to represent the number of premature deaths that could be attributed to insufficient UV-B.
6. The 95% confidence interval (95% CI) was calculated in the same manner as above.

In addition, an estimate of the number of premature cancer deaths due to insufficient UV-B radiation was made using multicancer aggregate data. For white Americans, the sum of cancers for which significant inverse correlations between UV-B radiation and cancer was used; for black Americans, all cancers were included. The difference between the two groups arises partly because lung carcinoma is correlated highly with UV-B for white Americans but is correlated inversely with UV-B for black Americans, and partly because the statistics for many malignancies in black Americans do not reach significance due to limited data. Summing the values improves the statistical quality of the data and takes advantage of the fact that if people do not die from one type of cancer, they may die from another. In this case, there are connections between the various malignancies in the form of diet, lifestyle, and solar UV-B radiation.

RESULTS

The statistical results for the TOMS DNA-weighted UV-B data are shown in Tables 1 and 2 and Figures 1 to 5. A total of 11 cancer types, 8 for men and 9 for women, were found to have statistically significant (P

TABLE 1A
Premature Mortality From Malignancy Due to Insufficient UV-B Radiation (White Americans; 466 SEAs)

Malignancy	Gender	r	Max UV	Mortality rate		Deaths	
				Max UV	Ave	Annual	Premature (95% CI)
Bladder	M	−0.57	9.5	4.00	6.56	6290	800 (690–900)
	F	−0.40	9.0	1.43	1.87	2830	100 (80–120)
Breast	F	−0.67	9.3	19.7	26.9	33,500	4000 (3660–4180)
Colon	M	−0.62	9.4	13.9	20.1	19,400	2370 (2140–2600)
	F	−0.63	9.8	10.2	15.0	21,200	2630 (2370–2910)
Esophagus	M	−0.54	9.6	3.20	4.80	4660	470 (400–530)
Kidney	M	−0.29	10.0	4.37	4.90	4480	45 (30–60)
	F	−0.37	9.4	1.91	2.24	2960	70 (50–90)
NHL	M	−0.41	10.0	5.86	7.03	6850	200 (160–240)
	F	−0.38	10.0	4.03	4.76	6410	160 (120–190)
Ovary	F	−0.63	9.4	6.33	8.38	10,500	1010 (890–1110)
Prostate	M	−0.32	10.0	20.4	22.0	20,900	170 (120–220)
Rectum[a]	M	−0.69	9.4	2.37	4.40	4250	960 (750–1160)
Rectum	F	−0.63	8.2	1.24	2.54	3570	740 (660–800)
Stomach[a]	M	−0.57	7.2	5.71	7.33	7090	510 (590–550)
	F	−0.48	6.7	2.47	3.41	4830	240 (210–260)
Uterus (corpus)	F	−0.58	9.4	2.57	3.72	5000	550 (490–610)
Total, males						69,400	5530 (4880–6260)
Total, females						87,800	9500 (8530–10,270)
Total, males and females						157,000	15,030 (13,410–16,530)

UV: ultraviolet; SEA: state economic area; r: regression coefficient; Max: maximum; Ave: average; 95% CI: 95% confidence interval; M: male; F: female; NHL: non-Hodgkin lymphoma.
[a] Second order regression.
The P value was < 0.001 in all cases.

TABLE 1B
Premature Mortality from All UV-B-Sensitive Malignancies Due to Insufficient UV-B Radiation (white Americans)

Malignancy	r	Max UV	Mortality rate		Deaths	
			Max UV	Ave.	Annual	Premature (95% CI)
Males						
Bladder, colon, esophagus, kidney NHL, prostate	−0.70	9.4	49.8		68,200	7570 (7080–8290)
Stomach (2nd order)	−0.57	7.2	5.71	7.33	7090	510 (590–550)
Total					75,300	8080 (7670–8840)
Females						
Bladder, breast, colon, kidney, NHL, ovary, rectum, uterus	−0.76	9.4	48.0		86,000	13,400 (12,500–14,300)
Stomach (2nd order)	−0.48	6.7	2.47	3.41	4830	240 (210–260)
Total					87,200	13,640 (12,710–14,560)
Total, males and females						21,720 (20,380–23,400)

UV: ultraviolet; r: regression coefficient; Max: maximum; Ave: average; 95% CI: 95% confidence interval; NHL: non-Hodgkin lymphoma.
$P < 0.001$ in all cases.

< 0.001) inverse correlations with DNA-weighted UV-B radiation for white Americans (Table 1). For black Americans, statistically significant results ($P < 0.001$) were found for a total of six cancers, four for males and three for females (Table 2). The regression analysis results for the individual malignancies indicate that approximately 15,000 white and 700 black Americans annually died prematurely from cancer between 1970–1994 due to insufficient UV-B radiation. However, when the mortality rates for all malignancies found to have a strong inverse relation with UV-B for white Americans were combined into one statistical

TABLE 2
Premature Mortality from Malignancy Due to Insufficient UV-B Radiation (black Americans)

Malignancy	No.	r	Max UV	Mortality rate		Deaths	
				Max UV	Ave.	Annual	Premature (95% CI)
Males							
Bladder	300	−0.33	10.0	3.70	5.44	470	16 (9–22)
Colon[a]	339	−0.34	8.9	19.1	21.6	1920	28 (17–42)
Lung	321	−0.32	10.0	76.9	94.1	8570	240 (180–330)
Rectum	287	−0.29	8.9	3.23	4.45	399	8 (6–12)
Total, males						11,400	292 (212–406)
Females							
Breast	336	−0.30	10.0	23.4	28.6	3640	60 (42–77)
Lung (2nd order)	325	−0.48	9.0	19.8	23.9	2960	110 (44–176)
Pancreas	327	−0.33	9.6	8.56	9.72	1230	5 (1–9)
Total, females						7830	361 (176–558)
Total, males and females						19,200	653 (388–964)
Males, all cancers	351	−0.48	9.6	160		26,600	790 (620–950)
Females, all cancers	332	−0.47	8.8	139		20,300	560 (440–690)
Totals, males and females						46,800	1350 (1060–1640)

UV: ultraviolet; r: regression coefficient; Max: maximum; Ave: average; 95% CI: 95% confidence interval.
[a] Second order regression.
The *P* value was 0.001 for ovarian carcinoma and < 0.001 in all other cases.

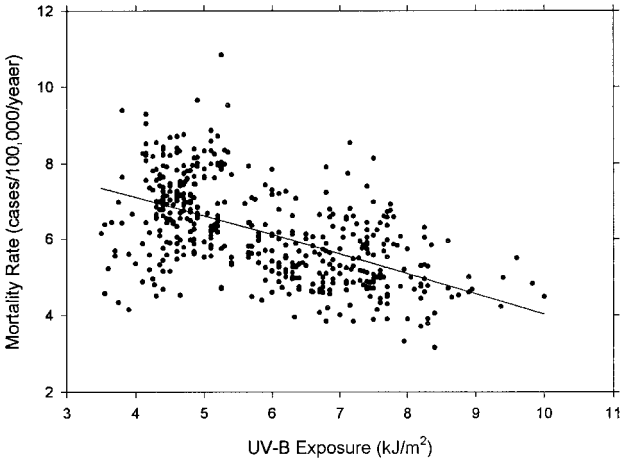

FIGURE 1. Annual mortality rates for bladder carcinoma in white males (1970–1994) versus DNA-weighted ultraviolet (UV) radiation for July 1992 from the Total Ozone mapping Spectrometer (TOMS).

analysis with the mortality rate for gastric carcinoma (which was treated separately due to the increased rate in the southwest attributed to dietary differences), the total premature cancer mortality rate was approximately 21,700 (Table 1b). Likewise, when all malignancies were combined into one analysis for black Americans, the total premature cancer mortality rate was approximately 1400 (Table 2). Asians and other ethnic groups, with a population in 1980 of 5.3 million,[28] could be expected to have a total premature cancer mortality rate of 500 (95% CI, 400–600), assuming the same rate as for white Americans, for a total of 23,600 (95% CI, 21,900–25, 700) premature annual cancer deaths (to my knowledge there are no available cancer mortality data for Asian Americans).

A similar analysis was performed[29] using UV-B data for July and the first 2 weeks of September from ground-based UV-B monitoring stations maintained by the USDA.[23,24] Statistically significant results ($P < 0.014$) were found for eight cancers in males and eight cancers in females (Table 3). A comparison of the data for the first 2 weeks of September with the month of July showed that the r value for the 8 cancers in males increased an average of 0.03, whereas that for all cancers summed increased by 0.07; for females, the mean increase was 0.02 whereas for the sum, the increase was 0.03.

DISCUSSION

The findings of the current study demonstrate that cancer mortality rates are correlated inversely with local solar UV-B doses for 13 types of cancer. These results confirm and extend previous findings regarding the relation between solar radiation and cancer mortality. The total number of annual premature cancer deaths estimated here, 23,600, is lower than the estimate of 32,000 based on 33% of colon and breast carcinoma rates.[30] This estimate considered all mortality rates above the high-UV-B region minimum for breast and colon carcinoma to be premature. Making the same assumption here would yield values of

TABLE 3
Premature Mortality from Malignancy Due to Insufficient UV-B Radiation (White Americans; USDA UV-B values)[26]

	Males		Females	
	July	September	July	September
Malignancy	r, *P* value	r, *P* value	r, *P* value	r, *P* value
Bladder	−0.65,0.001	−0.79,[a]	−0.70,0.004	−0.74,0.002
Breast			−0.64,0.011	−0.68,0.005
Colon	−0.80,[a]	−0.84,[a]	−0.80,[a]	−0.81,[a]
Esophagus	−0.64,0.011			
Kidney	−0.67,0.007	−0.65,0.009	−0.73,0.002	−0.73,0.002
NHL	−0.70,0.004	−0.78,[a]	−0.72,0.002	−0.76,0.001
Ovary			−0.69,0.004	−0.70,0.003
Prostate	−0.44,0.061	−0.63,0.012		
Rectum	−0.83,[a]	−0.86,[a]	−0.75,0.001	−0.78,[a]
Uteri, corpus	−0.64,0.010	−0.68,0.006		
Vulva			−0.47,0.087	−0.42,0.014
UV-B sensitive cancers, less gastric carcinoma	−0.85,[a]	−0.92,[a]	−0.84,[a]	−0.87,[a]

UV: ultraviolet; USDA: United States Department of Agriculture; r: regression coefficient; NHL: non-Hodgkin lymphoma.
[a] $P < 0.001$.

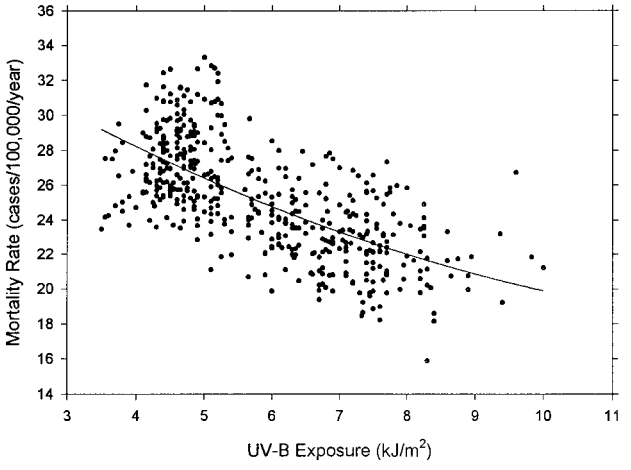

FIGURE 2. Annual mortality rates for breast carcinoma in white females (1970–1994) versus DNA-weighted ultraviolet (UV) radiation for July 1992 from the Total Ozone mapping Spectrometer (TOMS).

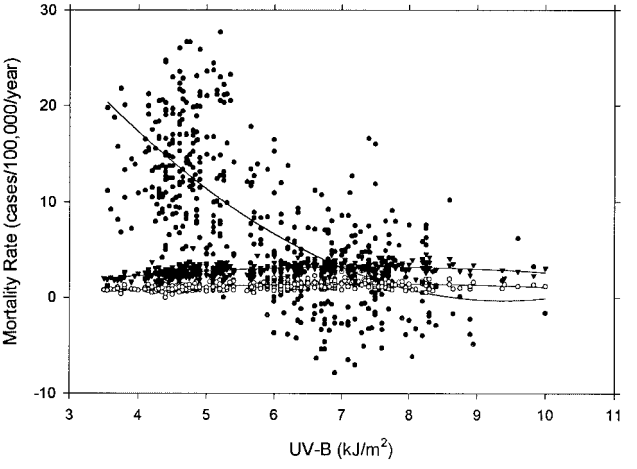

FIGURE 3. Mortality rates for melanoma and other skin cancers and the variance of ultraviolet (UV) B-sensitive malignancies (less gastric carcinoma) versus July 1992 UV-B radiation in white males. A value of 54.3 cases/100,000/year was subtracted from the rates for UV-B-sensitive malignancies. The solid dots represent UV-B-sensitive malignancies, the solid triangles represent melanoma, and the circles represent other skin cancer mortality rates.

41,000 for white Americans, 6000 for black Americans, and 1000 for Asians.

The higher magnitude of the regression results using USDA UV-B data for early September is most likely due to the greater ratio of photoproduction in southern states than in the northeastern states than in July. For example, it has been shown that wintertime UV-B levels in Boston are insufficient to promote vitamin D3 synthesis in skin.[31]

The most likely mechanism whereby solar UV-B radiation provides protection against cancer is through production of vitamin D. Many organs have been shown to convert the inactive form of vitamin D, 25-$(OH)_2D_3$, to the active, cancer-reducing form, 1,25$(OH)_2D_3$.[32,33] This ability has been shown for prostate carcinoma[32] and for malignancies of the brain, colon, lymph nodes, pancreas, placenta, and skin.[33] Serum levels of 1,25$(OH)_2D_3$, obtained between 1964–1971, were found to be correlated inversely with prostate carcinoma,[34] breast carcinoma,[35] and colon carcinoma.[36,37] Further supporting a role for vitamin D in protection from cancer is the finding that genetic

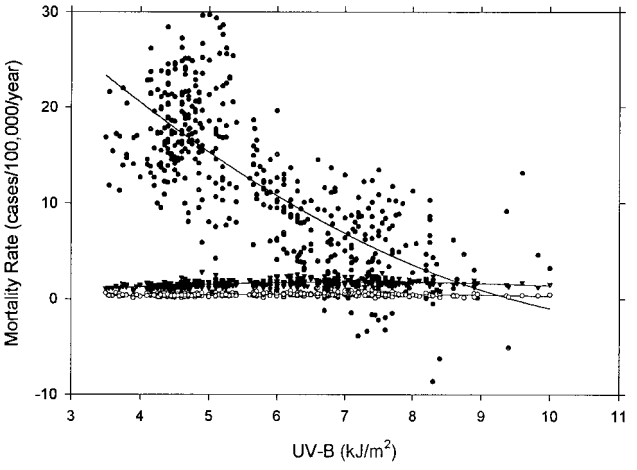

FIGURE 4. Mortality rates for melanoma and other skin cancers and the variance of ultraviolet (UV)-B-sensitive malignancies (less gastric carcinoma) versus July 1992 UV-B radiation in white females. A value of 48.0 cases/100,000/year was subtracted from the rates for UV-B-sensitive malignancies. The solid dots represent UV-B-sensitive malignancies, the solid triangles represent melanoma, and the circles represent other skin cancer mortality rates.

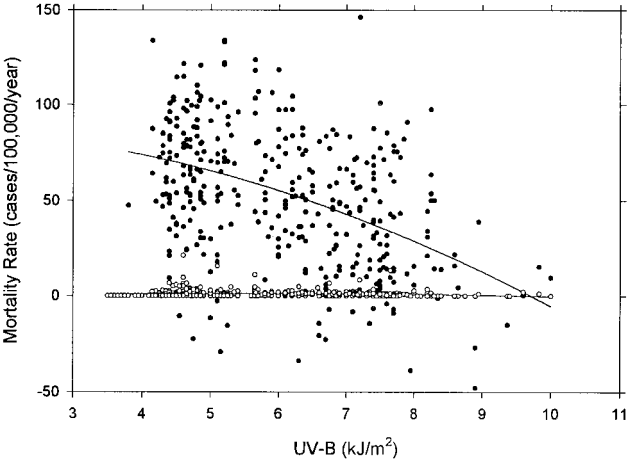

FIGURE 5. Mortality rates for melanoma and other skin cancers and the variance of ultraviolet (UV)-B-sensitive malignancies (less gastric carcinoma) versus July 1992 UV-B radiation in black males. A value of 244 cases/100,000/year was subtracted from the rates. The solid dots represent UV-B-sensitive malignancies, the solid triangles represent melanoma, and the circles represent other skin cancer mortality rates.

polymorphisms in the vitamin D receptor are associated with different mortality rates for breast,[38] colon,[39,40] prostate,[41] and rectal carcinomas.[42] The addition of vitamin D to cells from prostate carcinoma,[43] colon carcinoma,[34] melanoma,[44] NHL,[45] ovarian carcinoma,[46] and renal carcinoma[47] decreases the proliferation of these cells or induces differentiation in other cell types such as colonic HT 29 cells[48] and endometrial carcinoma cell lines.[49]

Previous studies examining the effect of solar UV-B on malignancy used other measures of solar radiation including average annual solar radiation and SO_2[2,12] and haze.[11] Although these studies provided useful findings, the measure of solar radiation was not optimized for vitamin D production. The wavelength reported to be most effective in converting cholesterol to vitamin D is 295–300 nm,[50] but all the UV-B range (280–320 nm) is reported to be effective.[51] Although there are a number of spectrally weighted UV exposure curves in the UV-B spectral region (UV-B, DNA, and erythemal [sunburning]),[52] none is exactly weighted for vitamin D production. The DNA-weighted UV-B curve (centered at 300 nm with a 5–10-nm bandwidth) from the TOMS date appears to be a better approximation than the erythemally weighted curve (peaked at 300 nm but extending to 340 nm) because it is a better approximation of the vitamin D photoproduction-weighted UV-B spectrum.

Because the current report is an ecologic study, confounding factors and limitations of the data may play a role in the results.[5] 1) the study analyzes solar UV-B radiation data from only 2 months and no information is available regarding dietary sources of vitamin D; 2) individuals do not have personal exposure to UV-B that is directly proportional to regional UV-B exposures; 3) the detection and treatment of cancer varies between individuals; and 4) unmodeled risk factors for cancer may vary somewhat around the country. All these factors, to the extent that they differ by geographic region, will act primarily to reduce the correlations between cancer mortality rates and solar UV-B radiation exposure. Garland et al.[12] also addressed potential confounding factors such as diet and socioeconomic factors with respect to sunlight and breast carcinoma and found that these factors could not explain their findings.

Lung carcinoma most likely has the greatest contribution from unmodeled confounding factors. Smoking is the highest risk factor for lung carcinoma, but exposure to asbestos, radon, and other airborne carcinogens play a role, along with diet.[53] Although the higher mortality rates from lung carcinoma reported in the southeast U.S. for white Americans are not surprising because the majority of the tobacco in the U.S. is grown in the south and the smoking rates tend to be higher there,[54,55] the lower rates of lung carcinoma mortality reported for black Americans in the southeast states compared with the states to the north are surprising. The finding that there is a strong inverse correlation between lung carcinoma mortality rates and solar UV-B radiation for this group, if indeed

related to a protective effect of solar UV-B radiation, most likely is associated with a nearly uniform rate of smoking among black Americans throughout the eastern U.S. This finding awaits further investigation.

CONCLUSIONS

Inverse correlations were found between UV exposure and cancer mortality rates for 13 cancer types in the U.S. Approximately 23,600 Americans died annually between 1970–1994 from malignancies associated with insufficient solar UV-B radiation. These results indicate, and are supported for some malignancies through epidemiologic studies of serum vitamin D and cancer, that cancer incidence and mortality rates in the U.S. and elsewhere could be reduced significantly by increased UV-B exposure or supplementary vitamin D consumption, especially in the northeastern U.S. Because this is a hypothesis article, it is hoped that the current study will form the basis for further investigations using case–control or cohort approaches.

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