ANTICANCER RESEARCH *26*: 2687-2700 (2006)

The Association of Solar Ultraviolet B (UVB) with Reducing Risk of Cancer: Multifactorial Ecologic Analysis of Geographic Variation in Age-adjusted Cancer Mortality Rates

WILLIAM B. GRANT[1] and CEDRIC F. GARLAND[2]

[1]Sunlight, Nutrition and Health Research Center (SUNARC), 2107 Van Ness Avenue, Suite 403B, San Francisco, CA 94109-2529; [2]Department of Family and Preventive Medicine and Member, Comprehensive Cancer Center, University of California, San Diego, 9500 Gilman Drive, 0631C, La Jolla, CA 93093, U.S.A.

Abstract. *Background: Solar ultraviolet B (UVB) irradiance and vitamin D are associated with reduced cancer mortality rates. However, the previous ecologic study of UVB and cancer mortality rates in the U.S.* (*Grant, 2002*) *did not include other risk factors in the analysis. Materials and Methods: An ecologic study was performed using age-adjusted annual mortality rates for Caucasian Americans for 1950-69 and 1970-94, along with state-averaged values for selected years for alcohol consumption, Hispanic heritage, lung cancer (as a proxy for smoking), poverty, degree of urbanization and UVB in multiple regression analyses. Results: Models were developed that explained much of the variance in cancer mortality rates, with stronger correlations for the earlier period. Fifteen types of cancer were inversely-associated with UVB. In the earlier period, most of the associations of cancer death rates with alcohol consumption (nine), Hispanic heritage (six), the proxy for smoking (ten), urban residence (seven) and poverty (inverse for eight) agreed well with the literature. Conclusion: These results provide additional support for the hypothesis that solar UVB, through photosynthesis of vitamin D, is inversely-associated with cancer mortality rates, and that various other cancer risk-modifying factors do not detract from this link. It is thought that sun avoidance practices after 1980, along with improved cancer treatment, led to reduced associations in the latter period. The results regarding solar UVB should be studied further with additional observational and intervention studies of vitamin D indices and cancer incidence, mortality and survival rates.*

Correspondence to: William B. Grant, Sunlight, Nutrition and Health Research Center (SUNARC), 2107 Van Ness Avenue, Suite 403B, San Francisco, CA 94109-2529, U.S.A. Tel: 415-776-5274, Fax: 415-776-5270, e-mail: wgrant@sunarc.org / www.sunarc.org

Key Words: Vitamin D, alcohol, Hispanic, poverty, urbanization, smoking.

There is an increasing awareness that deficiency of vitamin D is associated with an increased risk of internal cancer. UVB and/or vitamin D have been identified as a risk reduction factor for twelve types of cancer (1-11). Epidemiologic studies of the geographic distribution of these cancers have shown that indices of solar UVB (290-315 nm) irradiation have strong inverse correlations with cancer mortality rates. These and other studies found that vitamin D, through photosynthesis or oral intake, was an important cancer risk reduction factor. Observational studies of individuals also support the role of vitamin D in reducing the risk of cancer, including studies of 25-hydroxyvitamin D (25(OH)D) in stored sera and the subsequent rates of development of colorectal cancer (2, 11), studies of dietary and supplementary sources of vitamin D and the subsequent development of cancer (11), the association of vitamin D receptor (VDR) alleles with risk of cancer (12), the demonstration that many tissues are able to convert circulating 25(OH)D to the active hormone 1 α,25-dihydroxyvitamin D ($1,25(OH)_2D$) (13), and the elucidation of the mechanisms whereby vitamin D reduces the risk of cancer (14-16).

While ecologic and other observational studies have been used to make the link between UVB and cancer risk reduction, a number of other factors also affect the risk of cancer and the geographic distribution of cancer mortality rates. This study incorporated additional factors into the analysis in order to reduce the likelihood that the associations with solar UVB radiation could be confounded by other factors. This enabled a more accurate assessment of the independent association of UVB and vitamin D with reduced mortality rates of particular types of cancer. It also enabled examination of the contribution of other factors, including a proxy indicator of smoking, alcohol intake, degree of urbanization, Hispanic heritage, poverty and latitude. The U.S. is an appropriate country for the study of the effects of specific factors on cancer risk

Table I. *Cancer mortality rates for white Americans for the periods 1970-94 and 1950-69 (25).*

Cancer	Mortality rate, males, 1970-94 (deaths/100 k/year)	Mortality rate, females, 1970-94 (deaths/100 k/year)	Ratio males/females, 1970-94	Mortality rate, males, 1950-69 (deaths/100 k/year)	Mortality rate, females, 1950-69 (deaths/100 k/year)
All	209.47	135.88	1.54	184.46	136.94
Bladder	6.56	1.87	3.51	7.38	2.64
Breast	0.25	26.89	0.009	0.30	26.43
Cervical		3.22			7.87
Colon	20.13	14.97	1.34	17.79	17.55
Endometrial		3.72			6.46
Esophageal	4.80	1.24	3.87	4.34	1.11
Gallbladder	0.57	1.10	0.52		
Gastric	7.33	3.41	2.15	16.34	8.37
Hodgkin's	1.10	0.67	1.64	2.33	1.36
Laryngeal	2.49	0.42	5.93	2.67	0.25
Lung	69.40	23.93	2.90	39.25	6.57
NHL	7.03	4.76	1.48	5.05	3.38
Oral	3.99	1.41	2.83	4.80	1.17
Other, unspecified	14.50	10.00	1.45	11.70	10.00
Ovarian		8.38			8.84
Pancreatic	10.21	6.84	1.49	10.20	6.26
Prostate	22.01			20.15	
Rectal	4.40	2.54	1.73	8.18	5.20
Renal	4.90	2.24	2.19	3.99	2.07

since the relevant data on many environmental, geographic and behavioral risk factors are available.

Materials and Methods

Methods. The ecologic approach was used in this analysis (1, 3-6, 8, 17-20). Populations defined geographically by state were treated as entities, and average values for disease outcomes and potential influence factors for each state population were used. The strengths and limitations of the ecologic approach have been reviewed (21, 22). Generally, associations between suspected risk or protective factors and disease outcomes are examined. Once associations have been found, further analyses are conducted to determine whether the associations satisfy standard criteria for causality (23, 24).

Cancer mortality data. Age-adjusted, sex- and race-specific cancer mortality rates were obtained from the National Cancer Institute's *Atlas of Cancer Mortality in the United States* (25). State-averaged data for Caucasians for the periods 1950-69 and 1970-94, age-adjusted to the age distribution of the total U.S. population in 1970, were used. While data for approximately 500 state economic areas (SEAs) had been used in the previous analysis (6), it was deemed proper in this case to use state-averaged values since values for many of the additional risk factors were generally available only at the state level. However, it was possible to use SEA data for lung cancer mortality rates, the index used for the health effects of smoking. Table I presents age-adjusted mortality rates for each cancer analyzed in this study.

Indices for each factor in this study have been developed based on factors most likely to affect cancer risk and for which readily accessible data are available at the state level. Since it generally takes about 15-25 years for cancer due to diet to progress from initiation to detection or death (18-20, 26), a reliable data set for a year near the beginning of each period was generally sought for this work. It is noted that more accurate results would have been obtained using data for a much larger period, suitably averaged. However, it was decided that the use of one year would suffice in this work.

Solar UVB irradiance. Solar UVB irradiance for July was used as the primary surrogate for vitamin D variation in the population since it appears that UVB irradiance, especially in summer, is the strongest determinant of geographical variation in serum 25(OH)D in the U.S. and much of the world (27, 28).

DNA-weighted UVB data for July 1992, derived from total ozone mapping spectrometer (TOMS) measurements (29), were determined for each state. DNA-weighted UVB is defined as that portion of the UV reaching the Earth's surface that directly alters DNA. This spectral region peaks near 300 nm, which is very similar to the spectral region important for vitamin D production (52). UVB radiation is absorbed by ozone, and the ozone layer is thinner west of and over the Rocky Mountains (30), because the prevailing westerly winds push the lower stratosphere higher in that region. In addition, UVB is attenuated somewhat by molecular scattering, so the generally higher surface elevation west of and including the Rocky Mountains increases the amount of UVB reaching the surface. July UVB irradiance is highest in the Southwest, lowest in the Northeast, and there is a 5°- 8° shift of the iso-UVB lines between the two regions. This asymmetry is an important signature which can separate UVB from other factors such as UVA and visible radiation and temperature, which have latitudinal variations with much less asymmetry. (See the Appendix for more information on the UVB index.)

Table II. *Ranges of values of the variables used in this study for the 48 contiguous states plus DC. See the text for the data sources. Update using the latest data and including Hawaii.*

Factor	Minimum	Median	Mean	Maximum
Alcohol (ethanol), (gallons/year) 1960-2	0.38	1.96	2.09	5.56
Alcohol (ethanol), (gallons/year/person aged 21+years), 1970	1.71	3.02	3.13	7.94
Hispanic (%), 1970	0.3	1.3	3.5	37.4
Hispanic (%), 1980	0.5	1.8	4.3	36.6
Latitude	21.0	39.7	38.7	47.2
Lung cancer, CM, CF, 1970-94 (deaths/100 k/year)	33.4 10.2	69.7 23.3	68.3 23.1	88.0 37.6
Lung cancer, CM, CF, 1950-69 (deaths/100 k/year)	21.1 3.4	38.1 5.5	36.9 6.2	54.0 9.3
Poverty (%), 1969	7.2	12.5	14.9	35.4
Urbanization (%), 1960	35.0	63.0	62.9	100.0
Urbanization (%), 1970	32.0	66.5	66.4	100.0
UVB-July (kJ/m^2)	4.0	5.2	6.0	9.2

CM, Caucasian males; CF, Caucasian females.

While the TOMS DNA-weighted UVB index for July was convenient for use in this project, it is correlated with vitamin D production potential throughout the year at several locations, based on an analysis of ground-based measurements (31).

Another index for UVB was also examined, namely that of measurements made from 1970 to 1994 using the Robertson-Berger (RB) meter. There were 19 stations extending from Hawaii to Vermont, primarily located in urban regions in order to measure UVB in relation to human exposure. The annual values were averaged for each station, then used in a regression analysis with respect to latitude and surface elevation to generate values for 44 states. The states omitted from the tabulation were Alaska, Delaware, District of Columbia, Hawaii, Mississippi, New Jersey and West Virginia. The latitude explained 68% of the variance, latitude and elevation, 91%, and latitude, elevation and cloud cover, 97% (32, 33). It is noted that the spectral response of the RB meter was matched to the erythema action spectrum and, thus, had some sensitivity in the UVA range to about 325 nm. Since there were only stations in the high-elevation western states of New Mexico and Utah, the network had little sensitivity to differences in stratospheric ozone. Nonetheless, it seemed useful to consider this index in order to provide a check on the TOMS UVB data.

Latitude was also used as an index for serum 25(OH)D levels in winter in the case of prostate cancer.

Smoking. It generally takes 20-50 years for smoking to lead to adverse health effects such as lung cancer, but reliable data by state on smoking prevalence and quantity smoked were not available until the mid-1980s (34). Data on cigarette smoking prevalence by state could be used as one estimate of the effect of smoking on the risk of cancer. The number of states for which data on the prevalence of smoking were available increased from 15 in 1984 to 49 in 1992 (34). Linear regressions were run with lung cancer mortality rates for four years: 1985, 1987, 1988 and 2000. The results are given in Appendix Table A2.

An alternate index of the health effects of smoking are the lung cancer mortality rates for the two periods (25). About 87-89% of lung cancer cases for males and 78% for females in the U.S. can be attributed to smoking (35), and lung cancer mortality rates appear to be an index of long-term smoking in the population. It was recently shown that lung cancer death rates were a good index of tobacco smoke exposure for approximating non-lung cancer death rates in colored males (36, 37). The temporal variation of other cancers closely follows that of lung cancer, and variations in lung cancer accounted for 60-67% of the non-lung cancer mortality rates for this population. Since lung cancer mortality data are available by time period and gender, they were used in this study.

Alcohol consumption. For the period 1950-69, data on alcohol consumption (gallons of ethanol per capita of the drinking age population) for the period 1960-62 were obtained from the Center of Alcohol Studies, Rutgers University (38). Additional data, starting from 1970, were available from the National Institutes of Alcohol Abuse and Alcoholism (NIAAA) (39). The 1970 data were used for the period 1970-94, in view of the fact that alcohol consumption rates vary slowly, and the relative consumption rates stay relatively constant.

Hispanic heritage. Hispanic heritage is a known risk factor for several types of cancer (40-42). The category "Caucasian Americans" includes those of Hispanic heritage. The proportion of Caucasian Americans in each state considered Hispanic was included in the analysis. The values used here were for 1980, the earliest year that comprehensive data were available (43). It is noted that gastric cancer mortality rates were highest near the U.S. - Mexico border, where Hispanics tend to live. Nonetheless, using the fraction of those with Hispanic heritage for each state seemed to yield reasonable results in the analysis.

Degree of urbanization. The proportion of each state's population living in urban areas from 1940 to 1970 was obtained from Ref. 44. Definitions of urban and rural residence are given in Ref. 45. It was determined that urbanization data for 1960 yielded the highest regression result for the period 1950-69, while those for 1970 did likewise for the period 1970-94.

Poverty. Cancer rates are sometimes related to socioeconomic status (SES) (7, 46), which could be due to differences in medical care (47) or diet. For example, among those of lower SES, there was a higher prevalence of smoking (48) and, among those of higher SES, there was a greater intake of animal products in the diet (49). Caucasians of lower SES in 1965 had diets judged to be healthier than those of higher SES (50). It was also reported that men in the lower SES levels had lower cancer mortality rates than

those in higher SES levels until 1985. This was also true for women until 1995 (51). The index used for poverty in this study was the fraction of inhabitants living below the poverty line in 1969 (52).

Statistical analysis. The data were used in linear regression analyses using SPSS Version 13.0 (53). The square roots of the mortality rates were used in the analysis to reduce the effect of extreme values (54). The number of independent factors that can be used in a regression analysis is generally limited to about one for every ten data values. For most analyses, six factors were included in the analysis: alcohol consumption, Hispanic heritage, lung cancer, poverty, urbanization and UVB; for prostate cancer, latitude was also included. Including all factors, whether significant or not, yielded results for the significant factors adjusted for the insignificant factors. In the tables of results, values of beta (normalized coefficient) and *p* (significance) are reported for each factor, and the adjusted R^2, F (F-test statistic) and *p* are given for the model.

For a number of cancers, there were few deaths in some states during the 25- or 30-year periods. It was determined that when there were fewer than about 20 deaths, the uncertainty adversely affected the regression analysis. The two-standard deviation uncertainty for 20 events is 45%. However, the population of the state has also to be considered since few deaths for a large population could indicate a low rate, regardless of the number of deaths. The states omitted for various cancers and periods based on 20 deaths are given in Table A3. Hawaii generally had a sufficient number of deaths for many cancers in the period 1970-94, but not in the earlier period. Alaska generally did not qualify in the earlier period. Note that both Alaska and Hawaii were admitted to statehood in 1959, so would not necessarily be that similar to other states in the earlier period. In addition, at the high latitude of Alaska, generally above 60˚ N, there is so little UVB that residents must rely on sources other than solar UVB for vitamin D (55). Therefore, Alaska was omitted from the analysis. Note that it was important to retain in the data set all states that are representative of the country as a whole. This was not done in the earlier work (5), in part because the rates in several southwest states were much higher than could be explained by solar UVB irradiance. It is now thought that, for several cancers, the high rates were due to a high Hispanic population, a factor now included in the model.

A summary of the range of values is given in Table II, and the cross correlation coefficients in Table III. Note that many of the independent factors were highly cross-correlated. Such cross correlations were, however, thought to have a minimal effect on the results in most cases. One notable exception was for alcohol consumption and urban residence for women.

To check the results of ordinary linear regressions using SPSS, Poisson regression analyses were also performed by an independent analyst. Poisson regression is useful for analyzing rates or counts that follow a Poisson distribution. The models used corrected for overdispersion, *i.e.*, when the variance of the rate of interest is greater than its mean. Prior to statistical modeling, the predictor variables were first assessed for the presence of multicollinearity, although no evidence of this was found (all Pearson correlation coefficients were less than 0.8). In general, there was good agreement between the two statistical approaches, so only the results based on ordinary regressions were presented.

Results

Models were developed that explained the majority of the variance in cancer rates for individual cancers for males and females. In the earlier period, adjusted R^2 values were higher than 0.8 for all except lung, bladder, breast, colon (males), esophageal (males), laryngeal (males), oral (males), ovarian and rectal (males) cancer, falling to 0.2-0.3 for cervical, other (females) cancer and Hodgkin's lymphoma (males). The age-adjusted mortality rates for cancer for 15 sites were significantly inversely-correlated with July solar UVB irradiance (Table IV). The proxy measure of tobacco smoking was significantly correlated with ten types of cancer, alcohol with nine, urban residence with five, Hispanic heritage with six, and poverty with two. Alcohol consumption was inversely correlated with two cancer sites for females, urban residence with one each for males and females and poverty with six for males and two for females.

For the period, 1950-69, 14 types of cancer were significantly inversely-correlated with July solar UVB irradiance (Table V). Only breast, esophageal (males) and ovarian cancer had adjusted $R^2 > 0.8$. The proxy measure of tobacco smoking was significantly correlated with ten cancer sites, alcohol consumption with six, urban residence with seven, Hispanic heritage with four, poverty with four and latitude with one. Alcohol was inversely correlated with one cancer site for females, urban residence with one for females and poverty with three each for males and females.

Discussion

The results largely confirmed and extended the previous ecologic findings regarding the association between UVB radiation and cancer (5), but with added confidence since a number of additional factors had been included. The added factors generally confirmed the results of other studies for smoking (56-58), alcohol consumption (59-61), urban residence (62, 63) and Hispanic heritage (40-42).

Ultraviolet B irradiance. The results of this study seem largely to confirm the associations between UVB irradiance and cancer mortality rates reported previously (5). The additional cancers, for which an inverse association with UVB irradiance was identified for Caucasian Americans in this study, were cervical, gallbladder, laryngeal, pancreatic and oral cancer and Hodgkin's lymphoma, bringing the total to 16, counting prostate cancer.

However, the prostate cancer mortality rates were found to be most strongly correlated with increasing latitude and weakly with July UVB when both were included in the same regression model. The latitude is thought to be an index of winter or springtime vitamin D levels, since UVB irradiance decreases rapidly with latitude in winter and spring (30). For

Table III. *Cross-correlations between the risk and risk reduction factors used in this study.*

Table IIIa. *For the period 1970-94, omitting Alaska. A negative value for the adjusted r^2 indicates an inverse correlation.*

Factor	Hispanic, 1980 (adj. r^2, p)	Latitude (adj. r^2, p)	Lung cancer, M (adj. r^2, p)	Lung cancer, F (adj. r^2, p)	Poverty, 1969 (adj. r^2, p)	Urban, 1970 (adj. r^2, p)	UVB (adj. r^2, p)
Alcohol	0.00, 0.37	0.03, 0.11	–0.02, 0.18	0.11, 0.01	–0.14, 0.005	0.16, 0.002	0.00, 0.38
Hispanic		–0.06, 0.04	–0.08, 0.02	–0.02, 0.60	–0.02, 0.89	0.13, 0.005	0.30, *
Latitude			–0.11, 0.01	–0.06, 0.05	–0.24, *	–0.02, 0.60	–0.56, *
Lung ca., M				0.33, *	0.18, 0.001	–0.03, 0.11	–0.02, 0.86
Lung ca., F					–0.01, 0.52	0.01, 0.21	–0.01, 0.45
Poverty						0.17, 0.002	0.15, 0.003
Urban, 1970							0.00, 0.37

M, males; F, females; *$p<0.001$.

Table IIIb. *For the period 1950-69, omitting Alaska and Hawaii.*

Factor	Hispanic, 1970 (adj. r^2, p)	Latitude (adj. r^2, p)	Lung cancer, M (adj. r^2, p)	Lung cancer, F (adj. r^2, p)	Poverty, 1969 (adj. r^2, p)	Urban, 1960 (adj. r^2, p)	UVB (adj. r^2, p)
Alcohol	–0.01, 0.50	0.03, 0.11	0.16, 0.002	0.22, *	0.26, *	0.40, *	–0.02, 0.15
Hispanic		–0.07, 0.04	–0.02, 0.65	0.04, 0.10	–0.02, 0.68	0.07, 0.03	0.32, *
Latitude			–0.11, 0.01	–0.10, 0.01	–0.41, *	–0.02, 0.91	–0.53, *
Lung ca., M				0.68, *	–0.02, 0.66	0.26, *	–0.02, 0.77
Lung ca., F					–0.01, 0.54	0.26, *	–0.01, 0.57
Poverty						–0.27, *	0.20, 0.001
Urban, 1960							–0.02, 0.98

M, males; F, females; *$p<0.001$.

example, it is impossible to produce vitamin D from solar radiation in November through March in Boston (64). A U-shaped relationship between 25(OH)D and risk of prostate cancer was reported in a study in Nordic countries (65), with both low and high values being associated with increased risk, and confirmed in an ecologic study of U.S. states (66). It has been proposed that the metabolic products of 25(OH)D may explain the effect of higher levels of 25(OH)D (67). Additional interactions between vitamin D metabolites and prostate cancer are still being studied (68).

The mechanisms by which vitamin D reduces the risk of cancer incidence and mortality have been fairly well described. Vitamin D metabolites increase cell differentiation, suppress growth-stimulatory signals, potentiate growth-inhibitory signals and reduce cell proliferation, metastasis and angiogenesis (14-16, 69).

The beneficial effects of vitamin D are more strongly evidenced for the reduction of mortality rates than incidence rates. Several studies in Norway supported this statement. One study found that the diagnosis of breast, colon and prostate cancer in summer and fall was associated with the highest survival rate, 30% higher than for winter or spring, but no seasonality was observed in the incidence rates (70). A second study found that the survival rate for colon cancer was increased for a diagnosis in fall (71). A third found that the 18-month survival rate for Hodgkin's lymphoma was about 30% higher for discovery in fall compared to winter or spring (72). A recent study of the survival of men in Boston with early stage non-small cell lung cancer found that both operation in the summer and a high vitamin D status improved the survival rates (73). In addition, it was reported that the total vitamin D index was more highly correlated with cancer mortality rates than incidence rates in the Physicians' Health Study cohort (74). These cohort results, which were adjusted for confounding factors, strongly support the correlations found in this work. The analysis reported here also served as the basis for an analysis of cancer mortality rates for colored Americans, finding similar results to those given here (75).

It is possible that the use of the July UVB levels is not the most appropriate index since vitamin D produced during other periods is also beneficial. However, the results on cancer survival (70-74) and the review of epidemiologic studies of vitamin D and the risk of colorectal cancer (11) indicated that higher levels of vitamin D are important.

Table IV. *Beneficial associations of ultraviolet B irradiance and effects of other factors associated with age-adjusted mortality rates, standardized regression coefficients and selected cancers, United States, 1970-94. Statistically significant values are indicated in bold type.*

Cancer, gender, No.	UVB	Smoking	Alcohol, 1970	Urban, 1970	Hispanic, 1980	Poverty, 1969	Latitude	Adj. R^2, F, *p*
All less lung, M	**–0.54, ***	**0.60, ***	**0.31, 0.001**	0.12, 0.26	0.18, 0.10	**–0.27, 0.02**		0.71, 21, *
All less lung, F	**–0.82, ***	**0.35, 8**	0.15, 0.08	0.16, 0.07	**0.18, 0.04**	–0.06, 0.50		0.79, 31, *
Gastrointestinal								
Esophageal, M	**–0.50, ***	**0.44, ***	**0.45, ***	0.06, 0.43	0.11, 0.16	**–0.36, ***		0.84, 43
Esophageal, F	**–0.36, ***	**0.43, ***	**0.52, ***	0.04, 0.66	0.14, 0.19	0.05, 0.64		0.71, 21
Gastric, M	**–0.51, 0.003**	–0.03, 0.86	–0.04, 0.75	0.09, 0.54	**0.46, 0.006**	–0.27, 0.12		0.36, 5.5
Gastric, F	**–0.53, 0.004**	0.01, 0.96	0.02, 0.92	0.13, 0.41	**0.52, 0.003**	–0.08, 0.63		0.26, 3.8, 0.004
Colon, M	**–0.71, ***	**0.42, ***	0.02, 0.77	**0.33, 0.001**	0.15, 0.15	**–0.25, 0.03**		0.74, 24
Colon, F	**–0.76, ***	**0.31, 0.004**	–0.13, 0.28	0.10, 0.40	0.09, 0.45	–0.14, 0.26		0.58, 12
Rectal, M	**–0.75, ***	**0.29, 0.001**	**0.22, 0.005**	–0.04, 0.63	**0.31, 0.001**	**–0.38***		0.79, 32
Rectal, F	**–0.70, ***	**0.36, ***	0.02, 0.87	–0.04, 0.68	**0.23, 0.04**	**–0.30, 0.008**		0.68, 18
Gallbladder, M, 47 (>25)**	**–0.67, 0.001**	–0.05, 0.74	–0.04, 0.77	0.32, 0.07	**0.50, 0.005**	–0.003, 0.99		0.41, 6.2
Gallbladder, F	**–0.85, ***	**–0.20, 0.04**	**–0.25, 0.02**	–0.01, 0.92	**0.78, ***	–0.11, 0.35		0.64, 16
Pancreatic, M	**–0.46, 0.005**	**0.59, ***	0.15, 0.23	0.06, 0.66	**0.34, 0.03**	0.28, 0.10		0.41, 6.7
Pancreatic, F	–0.34, 0.06	**0.37, 0.008**	0.25, 0.11	0.06, 0.72	0.24, 0.15	0.08, 0.64		0.27, 4.0, 0.003
Female sites								
Breast, M, 37 (>33)	–0.41, 0.11	**0.58, 0.008**	**0.58, 0.008**	0.11, 0.59	–0.02, 0.92	–0.13, 0.68		0.42, 5.3, 0.001
Breast, M, 40 (>23)	**–0.71, 0.006**	0.26, 0.17	**0.48, 0.02**	0.17, 0.44	0.07, 0.73	0.19, 0.52		0.31, 4.0, 0.004
Breast, F	**–0.71, ***	0.10, 0.14	**0.26, 0.001**	**0.31, ***	0.11, 0.15	–0.13, 0.10		0.84, 43
Ovarian	**–0.60, ***	–0.09, 0.17	**0.26, 0.001**	0.11, 0.15	0.12, 0.13	**–0.37, ***		0.83, 41
Endometrial	**–0.73, ***	0.03, 0.73	–0.04, 0.71	0.16, 0.11	**0.20, 0.05**	**–0.33, 0.002**		0.73, 23
Cervical	**–0.46, 0.005**	**0.61, ***	–0.21, 0.12	**–0.31, 0.03**	0.23, 0.11	0.26, 0.07		0.44, 7.4
Urogenital								
Renal, M	**–0.65, ***	**0.33, 0.02**	0.09, 0.46	–0.25, 0.10	0.27, 0.10	–0.12, 0.47		0.40, 6.5
Renal, F	**–0.70, ***	–0.01, 0.97	0.12, 0.42	–0.21, 0.18	0.17, 0.26	0.06, 0.68		0.35, 5.5
Bladder, M	**–0.29, 0.007**	**0.57, ***	**0.32, ***	–0.13, 0.19	0.16, 0.11	**–0.69, ***		0.75, 26
Bladder, F	**–0.44, 0.001**	**0.55, ***	**0.26, 0.02**	–0.03, 0.77	0.10, 0.38	–0.11, 0.33		0.65, 16
Prostate	**0.38, 0.04**	**–0.29, 0.03**	**0.25, 0.03**	**–0.47, ***	–0.19, 0.13	**–0.36, 0.01**	**0.45, 0.01**	0.59, 11
Prostate	0.27, 0.12	–0.24, 0.06	**0.23, 0.03**	**–0.53, ***		**–0.37, 0.01**	**0.44, 0.02**	0.58, 12
Lymphomas								
Hodgkin, M	**–0.97, ***	–0.04, 0.75	–0.09, 0.45	**0.32, 0.02**	0.23, 0.11	**0.38, 0.02**		0.48, 8.4
Hodgkin, F, 50	**–0.88, ***	0.08, 0.46	0.05, 0.72	**0.39, 0.005**	0.07, 0.59	**0.32, 0.02**		0.51, 9.6
NHL, M	**–0.59, ***	0.07, 0.58	0.17, 0.16	**0.41, 0.004**	–0.15, 0.30	0.08, 0.58		0.49, 8.9
NHL, F	**–0.54, 0.001**	–0.09, 0.48	**–0.35, 0.01**	0.15, 0.30	–0.02, 0.87	–0.21, 0.17		0.40, 6.5
Miscellaneous								
Oral, M	–0.24, 0.09	**0.54, ***	**0.48, ***	**0.25, 0.05**		0.04, 0.80		0.53, 12
Oral, M	–0.23, 0.06	**0.54, ***	**0.48, ***	0.24, 0.07	0.02, 0.89	0.04, 0.81		0.52, 9.9
Oral, F	–0.26, 0.08	**0.38, 0.002**	**0.49, ***	0.01, 0.95	–0.22, 0.12	0.06, 0.68		0.46, 8.0
Oral, F	–0.26, 0.07	**0.38, 0.002**	**0.50, ***		–0.21, 0.10	0.06, 0.66		0.47, 9.8
Laryngeal, M	**–0.85, ***	**0.25, 0.02**	**0.49, ***	0.13, 0.17	0.06, 0.58	–0.05, 0.67		0.75, 21
Laryngeal, F, 47 (>17)	**–0.40, 0.01**	**0.42, ***	**0.46, ***	0.23, 0.08	0.11, 0.38	**0.35, 0.02**		0.58, 12
Other, M	0.22, 0.18	**0.65, ***	**0.32, 0.02**	–0.09, 0.58	0.05, 0.78	–0.10, 0.56		0.33, 5.1, 0.001
Other, F	0.09, 0.64	**0.46, 0.002**	0.17, 0.29	–0.12, 0.49	–0.04, 0.83	0.07, 0.70		0.18, 2.8, 0.02

*$p<0.001$; ** numbers in parentheses indicate the minimum number of deaths in 25 years required for inclusion in the analysis. No. is the number of states included, and was equal to 50 if not stated. M, males; F, females.

Table V. *Beneficial associations of ultraviolet B irradiance and effects of other factors associated with age-adjusted mortality rates, standardized regression coefficients and selected cancers, United States, 1950-69, as in Table IV.*

Cancer	UVB	Smoking	Alcohol, 1962	Urban, 1960	Hispanic, 1970	Poverty, 1969	Latitude	Adj. R^2, F, *p*
All less lung, M	**–0.65, ***	**0.28, 0.001**	0.15, 0.07	**0.36, 0.001**	0.06, 0.44	0.06, 0.51		**0.84, 42, ***
All less lung, F	**–0.85, ***	**0.24, 0.002**	0.04, 0.59	**0.28, 0.004**	0.12, 0.12	0.01, 0.91		**0.85, 45, ***
Gastrointestinal								
Esophageal, M	**–0.60, ***	**0.35, ***	**0.23, 0.01**	**0.37, 0.002**	0.09, 0.30	0.15, 0.12		**0.83, 40, ***
Esophageal, F, 48 (>17)	**–0.46, 0.009**	**0.65, ***	–0.06, 0.70	0.11, 0.55	0.01, 0.93	**0.38, 0.04**		**0.41, 6.5**
Gastric, M	**–0.73, ***	**–0.28, 0.04**	0.14, 0.31	0.17, 0.33	**0.43, 0.002**	–0.10, 0.54		**0.57, 11**
Gastric, F	**–0.84, ***	–0.18, 0.19	0.06, 0.67	0.10, 0.58	**0.60, ***	0.01, 0.97		**0.48, 8.3**
Colon, M	**–0.63, ***	**0.23, 0.004**	0.01, 0.90	**0.44, ***	–0.01, 0.91	–0.10, 0.26		**0.86, 51**
Colon, M	**–0.63, ***	**0.23, 0.001**		**0.44, ***		–0.10, 0.22		**0.87, 80**
Colon, F	**–0.70, ***	**0.24, 0.009**	–0.03, 0.75	**0.29, 0.01**	–0.02, 0.84	–0.12, 0.25		**0.78, 29**
Rectal, M	**–0.62, ***	**0.23, 0.004**	0.10, 0.21	0.17, 0.08	0.13, 0.10	**–0.29, 0.001**		**0.86, 50**
Rectal, F	**–0.65, ***	**0.23, 0.02**	0.17, 0.11	0.09, 0.45	0.14, 0.14	**–0.22, 0.05**		**0.76, 26**
Pancreatic, M	**–0.39, 0.02**	**0.53, 0.002**	0.16, 0.33	0.04, 0.86	0.16, 0.32	**0.41, 0.03**		**0.39, 6.0**
Pancreatic, F	**–0.74, ***	0.14, 0.32	**0.42, 0.007**	0.08, 0.63	**0.41, 0.004**	**0.40, 0.02**		**0.50, 8.9**
Female sites								
Breast	**–0.59, ***	–0.01, 0.83	**0.21, 0.005**	**0.38, ***	0.03, 0.67	**–0.17, 0.03**		**0.89, 63**
Ovarian	**–0.58, ***	–0.05, 0.49	0.16, 0.07	**0.25, 0.01**	0.10, 0.23	**–0.31, 0.001**		**0.83, 41**
Endometrial	**–0.67, ***	**0.34, 0.02**	**–0.54, 0.001**	0.24, 0.17	–0.03, 0.86	–0.10, 0.55		**0.46, 7.8**
Cervical	0.01, 0.96	**0.58, 0.001**	–0.11, 0.54	–0.32, 0.12	–0.10, 0.54	0.23, 0.23		**0.28, 4.1, 0.003**
Urogenital								
Renal, M	**–0.55, ***	–0.06, 0.51	**0.36, ***	0.08, 0.49	0.18, 0.07	**–0.27, 0.01**		**0.79, 31**
Renal, F	**–0.79, ***	–0.14, 0.27	0.23, 0.10	**–0.33, 0.04**	**0.39, 0.004**	–0.11, 0.47		**0.55, 11**
Bladder, M	**–0.32, 0.001**	**0.41, ***	**0.27, 0.003**	0.08, 0.48	0.04, 0.69	**–0.31, 0.002**		0.83, 40
Bladder, F	**–0.34, 0.02**	**0.49, ***	0.24, 0.09	0.17, 0.28	–0.19, 0.15	0.09, 0.52		0.59, 12
Prostate	0.02, 0.94	0.04, 0.86	0.12, 0.48	–0.27, 0.21	–0.14, 0.38	–0.10, 0.64	0.52, 0.09	**0.36, 4.9**
Prostate			0.13, 0.40	–0.26, 0.19	–0.15, 0.24	–0.11, 0.62	**0.48, 0.01**	**0.39, 7.2**
Lymphomas								
Hodgkin, M	**–0.39, 0.04**	0.003, 0.99	0.14, 0.42	0.02, 0.94	–0.09, 0.59	–0.19, 0.34		**0.29, 4.3, 0.002**
Hodgkin, F, 48 (>30)	**–0.70, ***	–0.05, 0.75	0.26, 0.10	0.09, 0.61	0.15, 0.28	0.04, 0.81		**0.46, 7.8**
NHL, M	**–0.66, ***	0.03, 0.82	–0.16, 0.27	**0.45, 0.02**	0.08, 0.57	–0.06, 0.70		**0.50, 9.0**
NHL, F	**–0.58, ***	–0.15, 0.27	0.09, 0.57	0.26, 0.13	**0.30, 0.04**	–0.19, 0.24		**0.49, 8.7**
Miscellaneous								
Laryngeal, M, 49 (>37)	**–0.33, ***	**0.61, ***	**0.22, 0.002**	**0.34, ***	–0.04, 0.50	**0.33, ***		**0.89, 68**
Laryngeal, F, 42 (>12)	–0.38, 0.09	**0.54, 0.001**	0.38, 0.06	–0.12, 0.63	–0.06, 0.71	**0.70, 0.002**		**0.47, 6.9, ***
Oral, M	**–0.30, 0.002**	**0.46, ***	0.10, 0.19	**0.57, ***	**–0.20, 0.03**	**0.33, 0.002**		**0.81, 36**
Oral, F, 48 (>30)	0.25, 0.14	**0.42, 0.005**	–0.03, 0.87	0.18, 0.32	**–0.39, 0.01**	**0.52, 0.004**		**0.44, 7.1**
Other, M	0.08, 0.59	**0.72, ***			–0.06, 0.62	**0.25, 0.04**		**0.54, 15**
Other, F	–0.02, 0.91	**0.49, 0.005**	0.11, 0.55	0.08, 0.71	–0.33, 0.07	0.35, 0.08		**0.21, 3.2, 0.01**

*$p<0.001$

The strength of the UVB correlation with cancer risk reduction was stronger for the earlier than the later period, as noted in the results section. It is proposed that increased concern about the adverse effects of solar UV irradiance led to changes in personal irradiance habits in the U.S. in the 1980s, resulting in a reduction in the amount of vitamin D produced from solar UVB irradiance. This hypothesis is supported by an analysis of the ratio of the breast cancer mortality rates for the two periods: an inverse correlation is found *vs*. latitude, ratio=1.46-0.01*latitude (adjusted $R^2=0.39$, $p<0.001$). At the same time, there was a positive correlation with latitude for the

Appendix

The TOMS UVB data were compared to ground-based measurements from the U.S. Department of Agriculture's (USDA) USDA UVB Monitoring and Research Program (116). There are approximately 30 UVB monitoring stations placed in rural locations throughout the U.S. Twenty-two of these stations are useful for comparison with the TOMS DNA-weighted UVB data. Plots of lamp-calibrated irradiances from the Erythemal UV Irradiance (derived from the UVB-1 Broadband, assuming 300 DU of ozone) were obtained and mean values estimated for July of a recent year. The data were then compared in a linear regression analysis. The results are given in Table A1. When all 22 stations were used, there were two outliers identified: Louisiana and Georgia, with the TOMS data much higher than the ground-based data. When those two states were omitted from the analysis, the regression model was considerably improved. The Louisiana station (LSU Central Research Station (Baton Rouge)) may be impacted by coastal clouds, while the Georgia site (Bledsoe Research Farm (Griffin)), may be affected by aerosols. Note, too, that the correlation was considerably weaker at 311.4 nm, as expected. Nonetheless, the TOMS data are very useful since they represent the only convenient UVB data set spanning the entire contiguous U.S.

Table A1.

	All 22 stations	GA, LA omitted
301 nm	0.62	0.82
305.5 nm	0.56	0.86
311.4 nm	0.31	0.50

GA, Georgia; LA, Louisiana.

Table A2. Linear regression results for cigarette smoking prevalence (117) vs. lung cancer for lung cancer mortality rates for Caucasian Americans in the period 1970-94

Race, Gender	Year, No.	Adjusted r^2, *p*
Caucasian, M	1985, 22	0.49, *
	1987, 32	0.55, *
	1988, 36	0.53, *
	1990, 44	0.41, *
Caucasian, F	1985, 22	0.33, 0.003
	1987, 32	0.24, 0.002
	1988, 36	0.26, *
	1990, 44	0.09, 0.027

*$p<0.001$; No. is the number of states with data.

Table A3. *States omitted from the analysis based on having 20 or fewer deaths in the period (25).*

Cancer	1950-69, M	1950-69, F	1970-94, M	1970-94 F
Breast	DE, DC, ID, MT, NV, NH, NM, SC, UT, VT, WY		DE, DC, HI, NH, ND, UT, VT, WY	
Endometrial		HI, WY		
Gallbladder			DC, HI,	
Hodgkin's				HI
Laryngeal		HI, ND, WY		
Oral		HI,		
Renal		CO, DE, HI, ID, MT, NV, NH, MN, ND, SD, UT, VT, WY		

F=female; M=male.

ratio of melanoma mortality rates for males for the two periods, ratio=0.60 +0.035*latitude (adjusted $R^2=0.39$, $p<0.001$). A separate manuscript on melanoma is in preparation (Grant *et al.*, in preparation).

In addition, work with the Surveillance, Epidemiology, and End Results (SEER) cancer data showed that there was a significantly increased survival rate for distant stage female breast cancer in the period 1973-79, which disappeared rapidly in the 1980s (76). The reduction of cancer survival rates in high UVB registries such as Hawaii was more pronounced than increased survival rates in low UVB registries. Similar findings were also made for several other cancers. Thus, the increased use of sunscreen and avoidance of midday solar UV irradiance, as well as improved medical treatment, seem to explain the changes.

Degree of urbanization. The degree of urbanization was found to be a significant risk factor for a number of cancers, most notably non-Hodgkin's lymphoma (NHL) in the later period and breast, colon, laryngeal and ovarian cancer in the earlier period. Urban residence could be an additional surrogate for reduction in solar UVB radiation. It is reasonable to assume that urban living is associated with reduced UVB exposure due to spending more time indoors, driving or riding in vehicles, and being shaded by buildings. However, urban residence was associated with increased alcohol consumption and smoking (77, 78), air pollution from vehicular and industrial emissions, and reduced UVB irradiance due to a lifestyle geared to indoor living and working. The amount of physical activity may also differ between urban and rural residents.

In a review of rates for 26 types of cancer in a number of countries, it was found that the rates for 23 types were higher in urban areas than in rural areas (62). Urban residence was found to be associated with increased cancer risk in a number of other studies (63).

Smoking. Smoking was found to be a significant independent risk factor for ten cancers for Caucasian Americans (Table IV). These correlations were in excellent agreement with those in the literature (56-58).

Alcohol consumption. The findings of this study regarding alcohol as an independent risk factor for nine cancers were in general agreement with the literature (79, 80). The correlations between alcohol consumption and cancer mortality rates for females did not always agree with those for males for the period 1970-94, with differences for NHL, other (unspecified) and rectal cancer. There are two reasons that probably explain this difference: alcohol consumption data are more appropriate for males since they drink more than females; men are several times more likely to engage in heavy drinking than women (81). In addition, alcohol consumption and urban residence are highly correlated (Table III).

Hispanic heritage. Hispanic heritage had a significant association with cancer of the gallbladder, ovary, rectum and stomach and weak, but significant, association with cancer of the pancreas and uterine corpus. These results are in general accordance with the findings reported for Hispanics in the U.S. (40-42). The stronger associations may either be due to environmental factors such as greater exposure to specific infectious agents and diet and/or to genetic factors (40-42).

Poverty. The economic status was found to be inversely-correlated with eight cancer sites for the period 1970-94, and four cancer sites for the period 1950-69. It was found to be strongly correlated with Hodgkin's lymphoma and weakly with laryngeal cancer (females only) for the later period, and with the larynx, oral cavity and pancreas for the earlier period. It was reported that, before the 1980s, those in lower SES levels had lower cancer mortality rates than those in the higher SES levels (51). More effort is required to evaluate this link and determine a likely cause. An initial hypothesis is that those who were poor spent more time outdoors and may have eaten fewer and simpler foods in the years that would affect the cancer rates (50). Another possibility is that the poor have higher rates of comorbidity and may die from other diseases rather than cancer (82-84).

Unmodeled risk factors. Other factors besides those considered in this study also affect cancer risk. It is noted that cancers such as breast, colon, rectum and NHL appear to have large, country-average mortality rates in comparison with international values, especially for developing countries (85), suggesting that there are factors associated with the lifestyle in the U.S. which are associated with cancer risk. In addition, improvements in cancer treatment and medical care in general are changing the geographic variation in cancer mortality rates.

Diet. It is possible that the high-energy, high-animal product diet prevalent in the U.S. explains much of the unmodeled portion of the mortality rates in this study. As found in ecologic multi-country studies, the animal product supply is highly correlated with cancers such as breast (17, 20), colon (17, 19), prostate (17, 18) and rectum (86). Obesity is also a risk factor for many types of cancer (87), and obesity is linked to the consumption of energy-dense foods (88).

The diet is estimated to account for approximately 30-50% of cancer deaths in the U.S. (89, 90), with higher fractions possible for several types of cancer, and with animal products playing an important role (17-20, 89-91). Data on the consumption of macro- and micronutrients for four regions of the U.S. for the period 1977-78 are available from the U.S. Department of Agriculture (92). These data indicate variations of 5-20% among the four regions. However, the data, which are survey data, are neither accurate enough nor sufficiently geographically specific for use in this study. Another way of evaluating the possible role of diet in explaining the geographic variation of cancer mortality rates in the U.S. is to consider the variations in cancer mortality rates in other countries. The highest breast, colon and prostate cancer rates are generally found in western developed countries, especially the Northern European ones, while the lowest cancer mortality rates in developed countries are generally found in Southeast Asia. The variation of dietary factors in the U.S. does not extend from Northern European in the Northeast to Southeast Asian in the Southwest. Thus, for the purpose of this study, the assumption that the diet was similar in all states seems reasonable.

Other factors. There are also several putative cancer risk-modifying factors which do not seem to explain much, if any, of the geographic variations in the cancer mortality rates. Reduced melatonin production associated with night shift work has been proposed to explain some of the risk of breast cancer (93). Blue or other visible radiation affects melatonin production. A melatonin effect would be linked to latitude, rather than the asymmetrical distribution associated with solar UVB for July. Industrial pollutants in the air and water could be associated with risk, but there are few regions with large amounts of industrial pollutants and none that stand out as being associated with increased cancer risk.

Premature cancer deaths in the U.S. The ecologic results presented here have been used to estimate that between 20,000 (6) and up to 50,000-60,000 cancer deaths annually in the U.S. can be considered premature due to insufficient UVB irradiance and vitamin D (94, 95). This represents about 10% of all U.S. cancer deaths. It was also estimated that between 1,000 and 3,000 I.U. (25-75 μg) of oral vitamin D intake per day in the absence of UVB irradiance would provide optimal protection against cancer (74, 96). While the geographic variation in cancer mortality rates is decreasing, a recent study reported a factor of two variation in five-year survival for non-small cell lung cancer (73).

Hepatocellular carcinoma (HCC). One cancer, HCC, has high mortality rates in the southeastern states. That might indicate a link to smoking; however, smoking has not been shown to have such a strong impact on rates of HCC as infections such as hepatitis, alcohol and aflatoxin (97). A more likely explanation is that the hot humid climate of the southeast encourages the growth of mold, which can result in the generation of aflatoxin (98). Given the high rate of HCC in the southeastern states related to unmodeled

factors, it was not possible in this ecologic study to investigate whether HCC is a vitamin D-sensitive cancer. However, other studies indicated such a connection (99).

Other diseases related to vitamin D. There is strong evidence that vitamin D sufficiency is a risk reduction factor for osteoporotic fractures, multiple sclerosis, type 1 diabetes mellitus, myopathy and end stage renal disease (95, 100-110). There is observational and/or other evidence that vitamin D sufficiency is a risk reduction factor for rheumatoid arthritis, tuberculosis and type 2 diabetes mellitus. Thus, if public health guidelines were modified to encourage people to obtain more vitamin D to reduce cancer risk, there would be public health benefits for a number of other diseases as well. The current scientific consensus is that between 1000 and 2000 IU of vitamin D per day is required for optimal health (74, 96), and that 4000 IU/day does not present a health problem (111).

Conclusion

The ecologic analysis presented in this paper provides additional strong support for the hypothesis that solar UVB radiation has significant inverse correlations with cancer at 15 sites, and that such associations were somewhat stronger decades ago than now. By confirming a number of other important risk-modifying factors for cancer mortality in models with high fractions of the variance explained, it seems unlikely that any unmodeled factors would explain the observed correlations with solar UVB. Solar UVB irradiance is a major source of vitamin D for most Americans and there are a number of papers presenting evidence that vitamin D reduces the risk of breast, colon, ovarian, prostate and rectal cancer and both Hodgkin's and NHL; the mechanisms are generally well described. The only major risk-modifying factor not included in this study was diet, which might explain 30-60% of the risk for a number of cancers (91, 92). However, since there appeared to have been very similar dietary patterns throughout the U.S. during the earlier study period (92), it is unlikely that differences in dietary factors could explain the geographic variations of cancer mortality rates. On the other hand, the increasing levels of obesity, which vary by state, are likely having an impact for the more recent data. Thus, it is concluded that solar UVB radiation, acting through the production of vitamin D, is an important risk reduction factor for most of the important forms of cancer.

It is hoped that these results will lead to further investigations into the role of vitamin D in the prevention and treatment of cancer, and that revised guidelines for UVB irradiance and vitamin D supplementation and fortification (107, 112-115) will be developed, in order to reduce the risk of cancer and provide numerous other health benefits.

References

1 Garland CF and Garland FC: Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol *9*: 227-231, 1980.

2 Garland C, Shekelle RB, Barrett-Connor E *et al*: Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet *1*: 307-309, 1985.

3 Garland FC, Garland CF, Gorham ED and Young JF: Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med *19*: 614-622, 1990.

4 Hanchette CL and Schwartz GG: Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. Cancer *70*: 2861-2869, 1992.

5 Lefkowitz ES and Garland CF: Sunlight, vitamin D, and ovarian cancer mortality rates in U.S. women. Int J Epidemiol *23*: 1133-1136, 1994.

6 Grant WB: An estimate of premature cancer mortality in the United States due to inadequate doses of solar ultraviolet-B radiation. Cancer *94*: 1867-1875, 2002.

7 Freedman DM, Dosemeci M and McGlynn K: Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med *51*: 257-262, 2002.

8 Mizoue T: Ecological study of solar radiation and cancer mortality in Japan. Health Phys *87*: 532-538, 2004.

9 Hughes AM, Armstrong BK, Vajdic CM *et al*: Sun exposure may protect against non-Hodgkin lymphoma: a case-control study. Int J Cancer *112*: 865-871, 2004.

10 Smedby KE, Hjalgrim H, Melbye M *et al*: Ultraviolet radiation exposure and risk of malignant lymphomas. J Natl Cancer Inst *97*: 199-209, 2005.

11 Grant WB and Garland CF: A critical review of studies on vitamin D in relation to colorectal cancer. Nutr Cancer *48*: 115-123, 2004.

12 Ingles SA, Garcia DG, Wang W *et al*: Vitamin D receptor genotype and breast cancer in Latinas (United States). Cancer Causes Control *11*: 25-30, 2000.

13 Zehnder D, Bland R, Williams MC *et al*: Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. J Clin Endocrinol Metab *86*: 888-894, 2001.

14 Studzinski GP, McLane JA and Uskokovic MR: Signaling pathways for vitamin D-induced differentiation: implications for therapy of proliferative and neoplastic diseases. Crit Rev Eukaryot Gene Expr *3*: 279-312, 1993.

15 Krishnan AV, Peehl DM and Feldman D: The role of vitamin D in prostate cancer. Rec Results Cancer Res *164*: 205-221, 2003.

16 Lamprecht SA and Lipkin M: Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. Nat Rev Cancer *3*: 601-614, 2003.

17 Armstrong B and Doll R: Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer *15*: 617-631, 1975.

18 Grant WB: An ecologic study of dietary links to prostate cancer. Altern Med Rev *4*: 162-169, 1999.

19 Grant WB: Dietary fiber and colorectal cancer. Townsend Lett *192*: 112-113, 1999.

20 Grant WB: An ecologic study of dietary and solar ultraviolet-B to breast carcinoma mortality rates. Cancer *94*: 272-281, 2002.

21 Morgenstern H: Ecologic studies. *In*: Rothman KJ, Greenland S (eds.). Modern Epidemiology, 2nd Edition. Lippincott, Philadelphia, pp. 459-480, 1998.

22 Greenland S: Ecologic *versus* individual-level sources of confounding in ecologic estimates of contextual health effects. Int J Epidemiol *30*: 1343-1350, 2001.

23 Hill AB: The environment and disease: association or causation? Proc R Soc Med *58*: 295-300, 1965.

24 Weed DL: Environmental epidemiology: basics and proof of cause-effect. Toxicology *181-182*: 399-403, 2002.

25 Devesa SS, Grauman DJ, Blot WJ, Pennello GA, Hoover RN and Fraumeni JF Jr: Atlas of Cancer Mortality in the United States, 1950-1994. NIH Publication No. 99-4564, 1999. http://cancer.gov/atlasplus/new.html (accessed October 26, 2005)

26 Tsuji K, Harashima E, Nakagawa Y, Urata G and Shirataka M: Time-lag effect of dietary fiber and fat intake ratio on Japanese colon cancer mortality. Biomed Environ Sci *9*: 223-228, 1996.

27 Holick MF: Photosynthesis of vitamin D in the skin: effect of environmental and life-style variables. Fed Proc *46*: 1876-1882, 1987.

28 Punnonen R, Gillespy M, Hahl M, Koskinen T and Notelovitz M: Serum 25-OHD, vitamin A and vitamin E concentrations in healthy Finnish and Floridian women. Int J Vitam Nutr Res *58*: 37-39, 1988.

29 Leffell DJ and Brash DE: Sunlight and skin cancer. Sci Am *275*: 52-53, 56-59, 1996. http://toms.gsfc.nasa.gov/ery_uv/dna_exp.gif (accessed October 26, 2005).

30 Lubin D, Jensen EH and Gies HP: Global surface ultraviolet radiation climatology from TOMS and ERBE data. J Geophys Res Atmos *103*: 26061-26091, 1998.

31 Kimlin MG: The climatology of vitamin D producing ultraviolet radiation over the United States. J Steroid Biochem Mol Biol *89-90*: 479-483, 2004.

32 Scotto J, Cotton G, Urbach F, Berger D and Fears T: Biologically effective ultraviolet radiation: surface measurements in the United States, 1974 to 1985. Science *239*: 762-764, 1988.

33 Scotto J, Fears TR, Fraumeni JF Jr, Solar Radiation. *In*: Schottenfeld D, Fraumeni JF Jr (eds.). Cancer Epidemiology and Prevention, 2nd Edition, Oxford University Press, New York, pp. 355-372, 1996.

34 Giovino GA, Schooley MW, Zhu BP *et al*: Surveillance for selected tobacco-use behaviors – United States, 1900-1994. MMWR CDC Surveill Summ *43*: 1-43, 1994.

35 Cresanta JL: Epidemiology of cancer in the United States. Prim Care *19*: 419-441, 1992.

36 Leistikow B: Lung cancer rates as an index of tobacco smoke exposures: validation against black male approximate non-lung cancer death rates, 1969-2000. Prev Med *38*: 511-515, 2004.

37 Leistikow BN and Tsodikov A: Cancer death epidemics in United States black males: evaluating courses, causation, and cures. Prev Med *41*: 380-385, 2005.

38 Hyman MM, Zimmermann MA, Gurioli C and Helrich A: Drinkers, Drinking, and Alcohol-Related Mortality and Hospitalizations; A Statistical Compendium [1980 Edition]. Center of Alcohol Studies, Rutgers University, New Burnswick, NJ, U.S.A.

39 Lakins NS, Williams GD, Li HY and Smothers BA: Surveillance Report #66: Apparent Per Capita Alcohol Consumption: National, State, and Regional Trends, 1977-2002. Washington, DC: NIAAA, 2004. http://pubs.niaaa.nih.gov/publications/surveillance66/CONS_02.pdf (accessed October 26, 2005)

40 Trapido EJ, Burciaga Valdez R *et al*: Epidemiology of cancer among Hispanics in the United States. J Natl Cancer Inst Monogr *18*: 17-28, 1995.

41 Canto MT and Chu KC: Annual cancer incidence rates for Hispanics in the United States: surveillance, epidemiology, and end results, 1992-1996. Cancer *88*: 2642-2652, 2000.

42 O'Brien K, Cokkinides V, Jemal A *et al*: Cancer statistics for Hispanics, 2003. CA Cancer J Clin *53*: 208-226, 2003.

43 Gibson C and Jung K: Historical census statistics on population totals by race, 1790 to 1990, and by Hispanic origin, 1970 to 1990, for the United States, regions, divisions, and states. Population Division. U.S. Census Bureau. Washington, DC 20233. Working Paper Series No. 56. 2002. (http://www.census.gov/population/www/documentation/twps0056.html (accessed October 26, 2005)

44 Urban and Rural Populations: 1900 to 1990. Source: 1990 Census of Population and Housing, "1990 Population and Housing Unit Counts: United States", (CPH-2); and 1980 PC80-1-1.http://www.census.gov/population/censusdata/urpop0090.txt (accessed October 26, 2005)

45 U.S. Department of Commerce. Geographic Areas Reference Manual, 1994. (http://www.census.gov/geo/www/garm.html, accessed October 26, 2005).

46 Krieger N, Quesenberry C Jr, Peng T *et al*: Social class, race/ethnicity, and incidence of breast, cervix, colon, lung, and prostate cancer among Asian, Black, Hispanic, and White residents of the San Francisco Bay Area, 1988-92 (United States). Cancer Causes Control *10*: 525-537, 1999.

47 Baquet CR and Commiskey P: Socioeconomic factors and breast carcinoma in multicultural women. Cancer *88*: 1256-1264, 2000.

48 Nilunger L, Diderichsen F, Burstrom B and Ostlin P: Using risk analysis in health impact assessment: the impact of different relative risks for men and women in different socio-economic groups. Health Policy *67*: 215-224, 2004.

49 Gordon NH: Socioeconomic factors and breast cancer in black and white Americans. Cancer Metastasis Rev *22*: 55-65, 2003.

50 Popkin BM, Siega-Riz AM and Haines PS: A comparison of dietary trends among racial and socioeconomic groups in the United States. N Engl J Med *335*: 716-720, 1996.

51 Singh GK, Miller BA, Hankey BF, Feuer EJ and Pickle LW: Changing area socioeconomic patterns in U.S. cancer mortality, 1950-1998: Part I – All cancers among men. J Natl Cancer Inst *94*: 904-915, 2002.

52 U.S. Census Bureau: Census Historical Poverty Tables. CPH-L-162. Persons by Poverty Status in 1969, 1979, and 1989, by State. (http://www.census.gov/hhes/poverty/census/cphl162.html, accessed October 26, 2005).

53 SPSS 13.0 Brief Guide: SPSS Inc., Chicago, 2004.

54 Guirgis HA, Lynch HT, Harris RE and Vandevoorde JP: Carcinoembryonic antigen (CEA) in the cancer family syndrome. Cancer *42*: 1574-1578, 1978.

55 Jablonski NG and Chaplin G: The evolution of human skin coloration. J Hum Evol *39*: 57-106, 2000.

56 Koop CE and Luoto J: "The Health Consequences of Smoking: Cancer". Overview of a report of the Surgeon General. Public Health Rep *97*: 318-324, 1982.

57 Sasco AJ: Tobacco and cancer: how to react to the evidence. Eur J Cancer Prev *1*: 367-373, 1992.

58 Thun MJ, Henley SJ and Calle EE: Tobacco use and cancer: an epidemiologic perspective for geneticists. Oncogene *21*: 7307-7325, 2002.

59 Salaspuro MP: Alcohol consumption and cancer of the gastrointestinal tract. Best Pract Res Clin Gastroenterol *17*: 679-694, 2003.

60 Poschl G, Stickel F, Wang XD and Seitz HK: Alcohol and cancer: genetic and nutritional aspects. Proc Nutr Soc *63*: 65-71, 2004.

61 Poschl G and Seitz HK: Alcohol and cancer. Alcohol Alcohol *39*: 155-165, 2004.

62 Doll R: Urban and rural factors in the aetiology of cancer. Int J Cancer *47*: 803-810, 1991.

63 Nasca PC, Mahoney MC and Wolfgang PE: Population density and cancer incidence differentials in New York State, 1978-82. Cancer Causes Control *3*: 7-15 1992.

64 Webb AR, Kline L and Holick MF: Influence of season and latitude on the cutaneous synthesis of vitamin D_3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. J Clin Endocrinol Metab *67*: 373-378, 1988.

65 Tuohimaa P, Tenkanen L, Ahonen M *et al*: Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer *108*: 104-108, 2004.

66 Grant WB: Geographic variation of prostate cancer mortality rates in the United States: implications for prostate cancer risk related to vitamin D. Int J Cancer *111*: 470-471, 2004.

67 Tuohimaa P, Tenkanan L, Ahonen M *et al*: Metabolism of 25-hydroxyvitamin D(3) may explain the u-shaped risk curve for prostate cancer. Int J Cancer *111*: 469, 2004.

68 Golovko O, Nazarova N and Tuohimaa P: Vitamin D-induced up-regulation of tumour necrosis factor alpha (TNF-alpha) in prostate cancer cells. Life Sci *77*: 562-577, 2005.

69 van den Bemd GJ and Chang GT: Vitamin D and vitamin D analogs in cancer treatment. Curr Drug Targets *3*: 85-94, 2002.

70 Robsahm TE, Tretli S, Dahlback A and Moan J: Vitamin D_3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). Cancer Causes Control *15*: 149-158, 2004.

71 Moan J, Porojnicu AC, Robsahm TE *et al*: Solar radiation, vitamin D and survival rate of colon cancer in Norway. J Photochem Photobiol B *78*: 189-193, 2005.

72 Porojnicu AC, Robsahm TE, Ree AH and Moan J: Season of diagnosis is a prognostic factor in Hodgkin's lymphoma: a possible role of sun-induced vitamin D. Br J Cancer *93*: 571-574, 2005.

73 Zhou W, Suk R, Liu G *et al*: Vitamin D is associated with improved survival in early-stage non-small cell lung cancer patients. Cancer Epidemiol Biomarkers Prev *14*: 2303-2309, 2005.

74 Giovannucci E: The role of vitamin D in cancer incidence and prevention. Am Assoc Cancer Res Annual Meeting, 2005.

75 Grant WB: Lower vitamin-D production from solar ultraviolet-B irradiance may explain some differences in cancer survival rates. J Natl Med Assoc *98*: 357-364, 2006.

76 Grant WB and Garland CF: Investigation of cancer incidence and survival rates in the U.S. with respect to solar ultraviolet-B irradiance using SEER data. Poster presented at Frontiers in Cancer Prevention Research, American Association for Cancer Research, Baltimore, October 26, 2005 (available at www.sunarc.org)

77 Lyon JL, Gardner JW and West DW: Cancer in Utah: risk by religion and place of residence. J Natl Cancer Inst *65*: 1063-1071, 1980.

78 Samet JM, Humble CG, Skipper BE and Pathak DR: History of residence and lung cancer risk in New Mexico. Am J Epidemiol *125*: 800-811, 1987.

79 Bagnardi V, Blangiardo M, La Vecchia C and Corrao G: A meta-analysis of alcohol drinking and cancer risk. Br J Cancer *85*: 1700-1705, 2001.

80 Bagnardi V, Blangiardo M, La Vecchia C and Corrao G: Alcohol consumption and the risk of cancer: a meta-analysis. Alcohol Res Health *25*: 263-270, 2001.

81 Caetano R and Clark CL: Trends in alcohol consumption patterns among whites, blacks and Hispanics: 1984 and 1995. J Stud Alcohol *59*: 659-668, 1998.

82 Schrijvers CT, Coebergh JW and Mackenbach JP: Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer *80*: 1482-1488, 1997.

83 Polednak AP: Poverty, comorbidity, and survival of colorectal cancer patients diagnosed in Connecticut. J Health Care Poor Underserved *12*: 302-310, 2001.

84 De Marco MF, Janssen-Heijnen ML, van der Heijden LH and Coebergh JW: Comorbidity and colorectal cancer according to subsite and stage: a population-based study. Eur J Cancer *36*: 95-99, 2000.

85 Ferlay J, Bray F, Pisani P and Parkin DM: GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide, Version 2.0. IARC CancerBase No. 5. Lyon, IARC Press, 2004. Available at http://www-dep.iarc.fr/ (accessed October 26, 2005)

86 Koo LC, Mang OW and Ho JH: An ecological study of trends in cancer incidence and dietary changes in Hong Kong. Nutr Cancer *28*: 289-301, 1997.

87 Calle EE and Thun MJ: Obesity and cancer. Oncogene *23*: 6365-6378, 2004.

88 Grant WB: The primary role of sweeteners in the body mass indexes of women from developing countries: implications for risk of chronic disease. Am J Clin Nutr *80*: 527-528, 2004.

89 Doll R and Peto R: The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst *66*: 1191-1308, 1981.

90 Donaldson MS: Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutr J *3*: 19, 2004.

91 World Cancer Research Fund in association with the American Institute for Cancer Research: Food, Nutrition and the Prevention of Cancer: A Global Perspective. Washington, DC, pp. 670, 1997.

92 Nutrition Monitoring Division, Human Nutrition Information Service, U.S. Department of Agriculture: Food and Nutrient Intakes: Individuals in Four Regions, Year 1977-78, Hyattsville, MD, Report No. I-3, 1985.

93 Megdal SP, Kroenke CH, Laden F, Pukkala E and Schernhammer ES: Night work and breast cancer risk: a systematic review and meta-analysis. Eur J Cancer *41*: 2023-2032, 2005.

94 Grant WB: Insufficient sunlight may kill 45,000 Americans each year from internal cancer. J Cos Dermatol *3*: 176-178, 2004.
95 Grant WB, Garland CF and Holick MF: Comparisons of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar UV irradiance for the United States. Photochem Photobiol *81*: 1276-1286, 2005.
96 Gorham ED, Garland CF, Garland FC *et al*: Vitamin D and prevention of colorectal cancer. J Steroid Biochem Mol Biol *97:* 179-194, 2005
97 Yu MC and Yuan JM: Environmental factors and risk for hepatocellular carcinoma. Gastroenterology *127*: S72-S78, 2004.
98 Bhatnagar D, Yu J and Ehrlich KC: Toxins of filamentous fungi. Chem Immunol *81*: 167-206, 2002.
99 Pourgholami MH and Morris DL: 1,25-Dihydroxyvitamin D_3 in lipiodol for the treatment of hepatocellular carcinoma: cellular, animal and clinical studies. J Steroid Biochem Mol Biol *89-90*: 513-518, 2004.
100 Holick MF: Vitamin D: a millenium perspective. J Cell Biochem *88*: 296-307, 2003.
101 Zittermann A: Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr *89*: 552-572, 2003.
102 Heaney RP: Long-latency deficiency disease: insights from calcium and vitamin D. Am J Clin Nutr *78*: 912-919, 2003.
103 Hayes CE, Nashold FE, Spach KM and Pedersen LB: The immunological functions of the vitamin D endocrine system. Cell Mol Biol (Noisy-le-grand) *49*: 277-300, 2003.
104 Plotnikoff GA and Quigley JM: Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc *78*: 1463-1470, 2003.
105 Holick MF: Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr *79*: 362-371, 2004.
106 Mosekilde L: Vitamin D and the elderly. Clin Endocrinol (Oxf) *62*: 265-281, 2005.
107 Calvo MS and Whiting SJ: Overview of the proceedings from Experimental Biology 2004 symposium: vitamin D insufficiency: a significant risk factor in chronic diseases and potential disease-specific biomarkers of vitamin D sufficiency. J Nutr *135*: 301-303, 2005.
108 Peterlik M and Cross HS: Vitamin D and calcium insufficiencies predispose for multiple chronic diseases. Eur J Clin Invest *35*: 290-304, 2005.
109 Grant WB and Holick MF: Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev *10*: 94-111, 2005.
110 Cantorna MT, Zhu Y, Froicu M and Wittke A: Vitamin D status, 1,25-dihydroxyvitamin D_3, and the immune system. Am J Clin Nutr *80*: 1717S-1720S, 2004.
111 Vieth R, Kimball S, Hu A and Walfish PG: Randomized comparison of the effects of the vitamin D_3 adequate intake *versus* 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutr J *3*: 8, 2004.
112 Raiten DJ and Picciano MF: Vitamin D and health in the 21st century: bone and beyond. Executive summary. Am J Clin Nutr *80*: 1673S-1677S, 2004.
113 Newmark HL, Heaney RP and Lachance PA: Should calcium and vitamin D be added to the current enrichment program for cereal-grain products? Am J Clin Nutr *80*: 264-270, 2004.
114 Hollis BW and Wagner CL: Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr *80*: 1752S-1758S, 2004.
115 Calvo MS, Whiting SJ and Barton CN: Vitamin D intake: a global perspective of current status. J Nutr *135*: 310-316, 2005.
116 Bigelow DS, Slusser JR, Beaubien AF and Gibson JH: The USDA Ultraviolet Radiation Monitoring Program. Bull Amer Meteorol Soc *79*: 601-605, 1998. http://uvb.nrel.colostate.edu/UVB/home_page.html (accessed October 26, 2005).
117 Giovino GA, Schooley MW, Zhu BP *et al*: Surveillance for selected tobacco-use behaviors – United States, 1900-1994. MMWR CDC Surveill Summ *43*: 1-43, 1994.

Received December 29, 2005
Accepted January 10, 2006