

Review

Ecological Studies of the UVB–Vitamin D–Cancer Hypothesis

WILLIAM B. GRANT

Sunlight, Nutrition, and Health Research Center, San Francisco, CA, U.S.A.

Abstract. *Background/Aim:* This paper reviews ecological studies of the ultraviolet-B (UVB)–vitamin D–cancer hypothesis based on geographical variation of cancer incidence and/or mortality rates. *Materials and Methods:* The review is based largely on three ecological studies of cancer rates from the United States; one each from Australia, China, France, Japan, and Spain; and eight multicountry, multifactorial studies of cancer incidence rates from more than 100 countries. *Results:* This review consistently found strong inverse correlations with solar UVB for 15 types of cancer: bladder, breast, cervical, colon, endometrial, esophageal, gastric, lung, ovarian, pancreatic, rectal, renal, and vulvar cancer; and Hodgkin's and non-Hodgkin's lymphoma. Weaker evidence exists for nine other types of cancer: brain, gallbladder, laryngeal, oral/pharyngeal, prostate, and thyroid cancer; leukemia; melanoma; and multiple myeloma. *Conclusion:* The evidence for the UVB–vitamin D–cancer hypothesis is very strong in general and for many types of cancer in particular.

Ecological studies based on geographical variation of cancer incidence and/or mortality rates have made important contributions to the ultraviolet-B (UVB)–vitamin D–cancer hypothesis. This process began when the hypothesis was first proposed on the basis of viewing the map of colon cancer mortality rates for the U.S. and realizing that the mortality rates were correlated with annual sunlight doses (1). The Garland group proposed that because vitamin D production was the most important physiological effect of sunlight for humans, vitamin D probably provided the mechanism linking sunlight to reduced risk of cancer. Later ecological studies by the Garland group added breast (2) and ovarian (3) cancer to the list. Other groups inversely correlated prostate cancer and

non-Hodgkin's lymphoma (NHL) with solar UVB indices (4, 5). The total number of UVB-sensitive types of cancer was increased to 15 in 2002 (6). This study was extended in 2006 by including other cancer risk-modifying factors (7, 8). Other studies have reviewed the status of ecological studies of UVB, vitamin D, and cancer as of the end of 2008 (9, 10).

A related study is that of personal UVB irradiance and risk of cancer. Reviewing the field, Rhee and colleagues (11) found that significant inverse correlations were reported for breast, colon, ovarian, prostate, and rectal cancer as well as NHL.

Another approach is to examine the risk of internal cancer after diagnosis of nonmelanoma skin cancer (NMSC). In fact, the first paper suggesting that sunlight might reduce the risk of cancer used this approach (12). Investigating this approach, several studies found it to be a moderately useful index of solar UVB irradiance primarily in sunnier countries (13-15). However, studies found significant inverse correlations in the Netherlands between diagnosis of NMSC and incidence of colorectal (16) and prostate (17) cancer. Those who developed NMSC in Michigan had higher serum 25-hydroxyvitamin D [25(OH)D] levels at the time of the first visit from those who sought osteoporosis- or low bone-density-related advice from 1997 to 2001 (18).

The UVB–vitamin D–cancer hypothesis has also been studied using observational studies of cancer incidence with respect to serum 25(OH)D levels. Studies found significant inverse correlations for breast and colorectal cancer (19-21). Some reports also exist for other types of cancer, such as esophageal (22), oral/pharyngeal (22), ovarian (23), and pancreatic cancer (22, 24), as well as leukemia (22). However, the Vitamin D Pooling Project found no reduced risk of cancer incidence for seven rare types of cancer (25). The likely reason for failure to find an inverse correlation between prediagnostic serum 25(OH)D level and cancer incidence is the long follow-up times involved, 6.63 years. Two studies reported inverse relations for the first few years of follow-up, followed by a direct correlation (26, 27). A recent paper addressed this problem, showing that the serum 25(OH)D level measured at time of enrollment, loses predictive power with increasing follow-up time for breast cancer (28).

Correspondence to: William B. Grant, Sunlight, Nutrition, and Health Research Center, P.O. Box 641603, San Francisco, CA 94164-1603, U.S.A. E-mail: wgrant@infionline.net

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Table I. Parameters of studies included in this review.

Country	Outcome	Years	Vitamin D index	Confounding factors	Reference
Australia	Mortality	1968-2002	GeV (latitude)		31
	Mortality	1968-85	Latitude		32
China	Mortality	1978	Latitude, temperature	Diet, <i>H. pylori</i> , iodine, lung cancer,	33
	Incidence, mortality	1990-92	TOMS UVB (305 nm)	Smoking	34
France	Incidence, mortality	1998-2000	Latitude	Diet	30
Japan	Mortality		Latitude, temperature	Diet, smoking	35
	Mortality	2000	Latitude	Diet, per capita income	36
	Mortality	1998-2002	Annual global solar radiation, temp		37
Spain	Mortality	1978-92	Latitude, NMSC	Smoking	38
United States	Mortality	1950-69, 1970-94	July UVB from TOMS (305 nm)	Alcohol, Hispanic heritage, poverty, smoking, urban residence	7
	Incidence	1998-2002	Annual erythemally weighted UVB from TOMS	Age, air quality, alcohol, exercise, income, outdoor occupation, poverty, urban/rural	8
	Mortality	1993-2002	"	"	8
	Mortality	1950-69, 1970-94	July UVB	Alcohol, Hispanic heritage, poverty, smoking, urban residence	39
California	Mortality	1950-64	July UVB, NMSC	Smoking	Grant, submitted

This review examines the ecological studies of cancer incidence and/or mortality rate with respect to solar UVB indices in order to determine how strong the evidence is for various types of cancer, compared to results from other selected studies, and discusses the lessons learned about the use of ecological studies of solar UVB irradiance and disease outcome.

Materials and Methods

Articles on using the ecological approach to study the UVB–vitamin D–cancer hypothesis were sought through the National Library of Medicine’s (www.PubMed.gov), with some additional ones found through Google Scholar (www.scholar.google.com). Search terms included *cancer*, *ecological*, *ultraviolet*, and *vitamin D*. Representative papers were chosen for inclusion in this review. Those chosen were either single-country studies that carried out analyses for several types of cancer or multicountry studies using more than 100 countries and risk-modifying factors in addition to solar UVB indices.

Three U.S. studies were included in the analysis. Two included additional risk-modifying factors (7, 8); the other used solar UVB, NMSC, and lung cancer mortality rates (Grant, CCC, submitted).

Single-country ecological studies for cancer in Australia, China, France, Japan, and Spain were found. The data from France were incidence and mortality rate data for the 21 continental regions for 1998-2000 (29). The regressions were recalculated with respect to latitude for the present article; they differ slightly from the values reported in (30) because latitude rather than the square of latitude was used.

Table I presents the parameters of the various single-country ecological studies. Most studies used mortality rate data, but three also used incidence rate data. The years of the data ranged from

1950-64/5 to 1998-2002. The UVB indices included latitude, temperature, annual solar radiation, and satellite-determined UVB doses for July or the entire year. The study from Australia used cancer mortality rate data for six states and one territory along with an index highly correlated with latitude: dose of cosmic ray neutrons (31, 40). Most studies included other risk-modifying factors such as alcohol consumption, diet, smoking, and socioeconomic status.

This review also includes nine multicountry studies from the Garland group (41-49). These studies were based on cancer incidence rates in 2002 for 107-175 countries. The UVB indices included latitude, stratospheric ozone, cloud cover, and anthropogenic aerosols. These studies also included other risk-modifying factors such as smoking and dietary factors, as deemed appropriate.

Representative results from other studies were also found through www.PubMed.gov. Studies were chosen to illustrate points being made. Some results agree with the ecological studies, but the discussion also includes some that do not.

Results

Table II summarizes findings regarding U.S. cancer incidence and mortality rates. The types of cancer are ordered by the higher mortality rate for males or females in the U.S. for 1970-94 (50) because as the mortality rate declines, obtaining statistically significant results becomes progressively harder (39). At least one study found a statistically significantly reduced risk for 18 types of cancer: bladder, brain, breast, colon, endometrial, esophageal, gallbladder, gastric, ovarian, pancreatic, prostate, rectal, renal, thyroid, and vulvar cancer; Hodgkin’s lymphoma and NHL; and multiple myeloma.

Table II. Comparison of ecological studies of cancer incidence and mortality rates, United States.

Cancer	MR	U.S. (7) M Mortality 1970-94 (β , p, adj. R ²)	U.S. (7) F Mortality (β , p, adj. R ²)	U.S. (8) M Incidence, mortality (High vs. low latitude) (RR)	U.S. (8) F Incidence, mortality (High vs. low latitude) (RR)	California (Grant, submitted) 1950-64 M NMSC, latitude (β , p; β , p)
All, males	209.5					-0.69, *; 0.47, 0.009
All, females	135.9					
Lung	69.4					-0.38, 0.11; -, -
Breast	26.9		-0.71, 0.006, 0.84	-, -	1.06, 1.15	
Colorectal	24.5					
Prostate	22.0			1.20, 1.17		-0.62, 0.005; -, -
Colon	20.1	-0.71, *, 0.74	-0.76, *, 0.58	1.11, 1.27	1.14, 1.24	-0.64, 0.002; 0.47, 0.01
Pancreatic	10.2	-0.46, 0.005, 0.41	-0.34, 0.06, 0.27	1.09, 1.06	1.17, 1.11	
Leukemia	8.8			1.09, 1.07	1.15, 1.09	
Ovarian	8.4		-0.60, *, 0.83		1.03 ns, 1.09	
Gastric	7.3	-0.51, 0.003, 0.36	-0.53, 0.004, 0.26	1.42, 1.31	1.27, 1.26	-0.45, 0.003;
0.79, *						
NHL	7.0	-0.59, *, 0.49	-0.54, 0.001, 0.40	1.08, 1.12	1.09, 1.15	-0.54, 0.02; -, -
Bladder	6.6	-0.29, 0.007, 0.75	-0.44, 0.001, 0.65	1.13, 1.24	1.15, 1.21	-0.54, 0.02; -, -
Brain	5.2			1.08, 0.91	1.07, 0.86	-0.62, 0.004; -, -
Renal	4.9	-0.65, *, 0.40	-0.70, *, 0.35	1.09, 1.12	1.17, 1.20	-0.35, 0.06; -, -
Esophageal	4.8	-0.50, *, 0.84	-0.36, *, 0.71	1.27, 1.36	1.08 ns, 1.21	-, -; 0.51, 0.02
Rectal	4.4	-0.75, *, 0.79	-0.70, *, 0.68	1.27, 1.53	1.14, 1.37	-0.48, 0.009; 0.48, 0.007
Oral, pharyngeal	4.0	-0.24, 0.09, 0.53	-0.26, 0.07, 0.47	0.77, 0.79	0.83, 0.73	-, -; -, -
Endometrial	3.7		-0.73, *, 0.73		1.49, 1.52	
Liver	3.3			1.01 ns, 0.88	1.05 ns, 0.85	
Cervical	3.2		-0.46, 0.005, 0.44		0.84, 0.89	
Myeloma	3.1			1.19, 1.16	1.22, 1.16	-0.66, 0.002; -, -
Melanoma	3.0			0.72, 0.70	0.78, 0.83	0.46, 0.03; -0.57, 0.008
Laryngeal	2.5	-0.85, *, 0.75		0.87, 1.04 ns	0.80, 0.96 ns	
Gallbladder	1.1		-0.67, 0.001, 0.64	1.13 ns, 1.58	1.86, 1.98	
Hodgkin's	1.1	-0.97, *, 0.48	-0.88, *, 0.51	1.16, 1.14	1.19, 1.25	
Thyroid	0.4			1.05 ns, 1.00	1.10, 1.30	
Vulvar	0.3				1.18, 1.93	

*: $p < 0.001$; -, -: no results; MR: mortality rate, deaths/100,000/year in the U.S., 1970-94 (50); ns: not statistically significant.

Table III presents the results for the other single-country studies. At least one study found a statistically significantly reduced risk for 14 types of cancer: brain, breast, colon, endometrial, esophageal, gallbladder, gastric, ovarian, pancreatic, prostate, and rectal cancer; Hodgkin's lymphoma; melanoma; and multiple myeloma.

Tables IV and V give the findings from the multicountry studies. The solar UVB indices (aerosols, cloud cover, and/or UVB) are significantly correlated with five types of cancer for both males and females: bladder, brain, lung, renal cancer and leukemia, and one only for males, pancreatic cancer. According to Bernoulli's principle ($p < 0.05/n$, where n is the number of variables), the results for UVB for females for breast, endometrial, and pancreatic cancer are not statistically significant.

Discussion

Hill's criteria for causality in a biological system can be used to assess the evidence in support of the UVB–vitamin D–cancer hypothesis based on ecological studies. Several of these criteria can be evaluated using ecological studies: strength of association, consistency, biological gradient, accounting for confounding factors, and analogy (53). Those that cannot, include plausibility (mechanisms), temporality, and experimental verification; however, other approaches can be used to assess those criteria. The discussion includes such information when appropriate. The types of cancer are discussed in approximate order of the apparent strength of UVB and vitamin D in reducing risk.

Table III. Comparison of ecological studies of cancer incidence and mortality rates, other single countries. For Spain, the UVB factor with the highest r value from Ref. 38 is shown.

Cancer	Japan	Spain (38)	Spain (38)	China (39) ^a	China (39) ^a	France (30)	France (30)	Australia ^b
		M (r) (p<0.05)	F (r) (p<0.05)	M Incidence, mortality (+10 units UVB) (ratio) UVB) (ratio)	F Incidence, mortality (+10 units UVB) (ratio)	M, F Incidence (R ² , p)	M, F Mortality (R ²)	(40) M, F (r)
All, males				1.09, 0.96		0.73, *	0.63, *	
All, females					1.05, 0.96; (33)	0.58, *	0.58, *	
Lung			NMSC -0.31	1.07, 0.90; (33)	1.01*, 0.85	0.48, NS	0.54, NS	
Breast			NMSC -0.38		1.12, 0.95	-,; 0.31, 0.005	-,; 0.39, 0.001	-0.82
Colorectal				0.84, 0.98*	G; 0.96, 0.96	0.22, 0.02; 0.40, 0.001	0.20, 0.39	-0.77, -0.78
Prostate				(33)*		0.38, 0.002	0.44, 0.001	-0.24
Colon	(36)	NMSC -0.30	NMSC -0.31					
Pancreatic	(36-38)	Lat 0.55	Lat 0.40					-0.88 (32)
Leukemia	(53)			0.98*, 0.98*	1.05*, 1.02*			0.12,* -0.08*
Ovarian			NMSC -0.51					-0.81
Gastric	(36)	Lat 0.41	Lat 0.46	0.84, 0.97 (33)	0.89, 0.97 (33)			-0.77, -0.73
NHL		NMSC -0.32	NMSC -0.63					
Bladder				1.02*, 0.93	0.89, 0.97			
Brain		NMSC -0.31	Lat 0.58					
Esophageal	(36)	NMSC -0.30		0.76, 0.93; (33)	G; 0.68, 0.91	0.71, *; NS	0.63, *; 0.37, 0.002	
Rectal	(36)	Lat 0.61	NMSC -0.35	(33)*				
Endometrial + cervical							0.37, 0.002	
Endometrial						0.48, *		
Liver				1.26, 0.97	1.11, 0.95			
Cervical					0.87, 1.11; (33)	0.31, 0.005		
Myeloma			NMSC -0.45					
Melanoma	(52) (males)		NMSC -0.43					
Gallbladder	(36)	NMSC -0.31						
Hodgkin's			NMSC -0.47					
Thyroid		NMSC -0.35	Lat 0.48					

*:p<0.001; -, -: no data; ^adata reported are for Ref. 39: (33) means that Ref. 33 made a similar finding; ^bdata reported are for Ref. 40: finding for pancreatic cancer from Ref. 32; lat: latitude; NMSC: non-melanoma skin cancer; NS, not significant.

Specific Types of Cancer

Those with strong evidence.

Colon cancer: Colon cancer was the first type of cancer for which research identified an inverse correlation between

solar UVB dose and mortality rate (1). Many ecological and observational studies have since supported this finding (20, 21). Observational studies indicate increasing serum 25(OH)D levels out to above 100 nmol/l can significantly reduce risk (54).

Table IV. Summary of multicountry studies—males.

Cancer type	No. of countries	First factor (t, p)	Second factor (t, p)	Third factor (t, p)	Fourth factor (t, p)	R ²	Reference
Bladder (M, F)	111	Health expenditure 8.11, <0.0001	UVB -3.46, 0.0007			0.49	(46)
		Cigarettes 3.89, 0.0002	UVB -2.45, 0.02			0.38	
Brain	107	UVB -4.11, <0.0001	Animal energy 2.61, 0.01	Fish -2.37, 0.02	Over-weight 2.03, 0.04	0.74	(48)
Leukemia	138	Health expenditure 4.01, 0.0001	UVB -3.37, <0.001	Animal energy 2.44, 0.02		0.61	(49)
Lung	111	Cigarettes 8.63, <0.001	UVB -3.08, 0.003	Aerosols 2.84, 0.005	Cloud cover 2.02, 0.05	0.78	(44)
Lung (contribution to R ²)	111	Cigarettes 0.71, <0.001	UVB 0.04, 0.003	Aerosols 0.02, 0.005	Cloud cover 0.01, 0.05	0.78	(44)
Pancreatic	104	Alcohol 6.49, <0.001	UVB -2.68, <0.01	Cigarettes 2.63, <0.01	Sugar 1.23, 0.22	0.76	(47)
Renal	175	Animal energy 5.38, <0.0001	UVB -3.68, 0.0003	Clouds 3.03, 0.003		0.73	(42)

Rectal cancer: The findings for rectal cancer are similar to those for colon cancer, and the two types of cancer are often studied together (20, 21, 54).

Breast cancer: Breast cancer was the second type of cancer for which research identified a beneficial effect of solar UVB (2). Case–control studies have supported the role of vitamin D in reducing risk on the basis of serum 25(OH)D levels at time of diagnosis. However, many nested case–control studies (NCCS) found no inverse correlation of breast cancer incidence with respect to prediagnostic serum 25(OH)D level. As the follow-up period increases, the odds/risk ratio tends closer to unity (28). One study found an inverse correlation with serum 25(OH)D for follow-up times up to 10 years, no correlation for 10–15 years, and then a direct correlation for 15–20 years (26). Breast cancer is a rapidly growing cancer on the basis of seasonal peaks of diagnosis in spring and fall (55), and as follow-up time increases, the serum 25(OH)D level at time of diagnosis becomes progressively less meaningful. With this understanding of

Table V. Summary of multicountry studies—females.

Cancer type	No. of countries	First factor (t, p)	Second factor (t, p)	Third factor (t, p)	Fourth factor (t, p)	R ²	Reference
Brain	107	UVB -4.60, <0.0001	Animal energy 1.49, 0.14	Over-weight 1.34, 0.17		0.63	(48)
Breast	107	Animal energy 4.69, <0.01	UVB -2.05, 0.04	Alcohol 1.72, 0.08		0.81	(45)
Endometrial	107	Health expenditure 4.16, <0.0001	Over-weight 2.93, 0.004	Animal energy 2.68, 0.01	UVB -2.30, 0.02	0.73	(43)
Leukemia	138	Health expenditure 3.18, 0.002	UVB -2.54, 0.01	Animal energy 1.94, <0.05		0.51	(49)
Lung	111	Cigarettes 9.51, <0.001	UVB -3.82, 0.0002	Aerosols 2.87, 0.005	Cloud cover 2.28, 0.02	0.78	(44)
Lung (contribution to R ²)	111	Cigarettes 0.66, <0.001	UVB 0.08, 0.0002	Aerosols 0.02, 0.005	Cloud cover 0.01, 0.02	0.78	(44)
Ovarian	175	Ozone 3.40, <0.001	UVB -3.14, 0.002	Fertility rate -2.57, 0.01		0.49	(41)
Pancreatic	104	Alcohol 4.08, <0.0001	Sugar -2.32, <0.001	UVB -2.32, 0.02	Cigarettes 1.60, 0.11	0.64	(47)
Renal	175	Animal energy 5.66, <0.0001	Clouds 3.43, 0.0008	UVB -1.82, 0.04		0.68	(42)

why NCCS may not support the UVB–vitamin D–cancer hypothesis for breast cancer, the evidence for a beneficial role of UVB and vitamin D is very strong.

Gastric cancer: Inverse correlations with solar UVB were found for all the U.S. ecological studies and all the other single-country studies including France, on the basis of a second set of data for 1993–97 not reported (56). *Helicobacter pylori* is a declining risk factor for gastric cancer, and some evidence exists that vitamin D strengthens the immune system response to *H. pylori* infection (57). In addition, the stomach is part of the gastrointestinal tract, and excellent evidence exists that vitamin D reduces the risk of colorectal cancer; the evidence for esophageal cancer is very good. Thus, the evidence that UVB and vitamin D reduce the risk of gastric cancer is strong.

NHL: All the U.S. ecological studies and the study in Spain (females) found inverse correlations between UVB indices and NHL mortality rates. Very good evidence from a pooled analysis of case-control studies indicates that personal UV irradiance is associated with reduced risk of NHL (58). The fact that NHL mortality rates are highest in the Midwest (50) implicates farming as a risk factor (59). A prospective study of those diagnosed with NHL in Iowa and Minnesota found improved survival rates for those with diffuse large B-cell lymphoma and T-cell lymphoma; these types of NHL represented 45% of all patients (60).

Hodgkin's lymphoma: Two U.S. studies and one single-country study (Spain, females) found inverse correlations between a solar UVB index and incidence and/or mortality rates of Hodgkin's lymphoma. Epstein-Barr virus (EBV) is a risk factor for Hodgkin's lymphoma, and vitamin D reduces the risk of EBV infection (61). Hodgkin's lymphoma incidence rates are highest in spring (62). Those diagnosed with Hodgkin's lymphoma in summer in Norway survive longer than those diagnosed in winter (63).

Bladder cancer: All the U.S. studies found an inverse correlation between solar UVB and bladder cancer mortality rate, as did a study in China. A study in New Hampshire found a significant inverse correlation between vitamin D intake and incidence of bladder cancer (64). A NCCS with about a 15-year follow-up period found a significantly reduced risk of bladder cancer for male smokers in Finland with lower serum 25(OH)D at time of enrollment (65).

Endometrial cancer: Two of the U.S. studies and the study from France found inverse correlations between solar UVB indices and endometrial cancer. A NCCS in Sweden found a significant inverse correlation between use of sunbeds and incidence of endometrial cancer (66). That article suggested that raising vitamin D levels in winter explained the association.

Ovarian cancer: Five of the ecological studies reviewed here found an inverse correlation between solar UVB and ovarian mortality rate. A death certificate study in the U.S. found risk of ovarian cancer reduced with respect to solar UVB doses at place of residence and physical activity but not with respect to indoor/outdoor occupation (67). A meta-analysis of 10 observational studies, mostly NCCS, found a summary relative risk of 0.83 (95% confidence interval, 0.63-1.08) for an increase of 25(OH)D by 20 ng/mL ($p=0.16$) (68). A recent NCCS reported an inverse correlation between serum 25(OH)D level at time of enrollment with up to a 6.4-year mean follow-up to diagnosis of ovarian cancer (69). Thus, the evidence that UVB and vitamin D reduce the risk of ovarian cancer is reasonably strong.

Pancreatic cancer: Pancreatic cancer was found to be inversely correlated with solar UVB in two U.S. studies and in studies in Australia, Japan, and Spain, as well as in the multicountry study for males but not significantly for females. Pesticides are a risk factor for pancreatic cancer (69) and may account for the higher mortality rate for pancreatic cancer in the Midwest. Chemical pollutants emitted by industrial plants may account for the high mortality rate in Louisiana (70). Smoking is an important risk factor for pancreatic cancer, which may mask some of the UVB effect in the United States because of an imperfect index of smoking (lung cancer mortality rates).

Studies have inversely correlated vitamin D with both oral vitamin D intake (24) and serum 25(OH)D (22). Studies that found a direct correlation with serum 25(OH)D level were NCCS with long follow-up times (16.5 years (71) and 6.63 years (25)), which has been identified as a significant problem (28). Thus, reasonable evidence exists that UVB and vitamin D reduce the risk of pancreatic cancer, but further research to confirm this link is necessary.

Esophageal cancer: All the U.S. and single-country studies—except Australia, for whom there are no data—reported inverse correlations with respect to UVB indices for esophageal cancer. Re-examining the regression analysis in (7), it appears that there is no correlation with lung cancer, the index of smoking, in the analysis for males. Without lung cancer in the analysis, only July UVB and alcohol consumption were significant risk-modifying factors with the same impact but different signs, explaining 70% of the variance for males. For females, lung cancer appears to be a risk factor, based on higher mortality rates in the states on the west coast, the Gulf of Mexico, and the Atlantic Ocean. However, some of the lung cancer rates along the coast could be due to ship building activities involving asbestos (72). Omitting lung cancer, alcohol consumption and UVB explained 64% of the variance, with alcohol being much more important than UVB.

Five observational studies found conflicting results between vitamin D indices and risk of esophageal cancer. The first, a NCCS with a 5.25 year follow-up period in China, found a direct correlation between prediagnostic serum 25(OH)D level with incidence of esophageal squamous cell carcinoma (ESCC) for males but not females (73). ESCC is the most common type of esophageal cancer in Asia and southern Europe. The second, a cross-sectional study in Linxian, China, found a direct correlation between serum 25(OH)D and squamous dysplasia, a common precursor for ESCC, for both males and females (74). The third, a pair of case-control studies in Italy, found an inverse correlation between oral vitamin D intake and incidence of esophageal cancer (75). The fourth, a pooled NCCS, found no correlation between serum 25(OH)D level and incidence of esophageal cancer with a mean follow-up time of 6.63 years (25). The fifth, a

case–control study in Ireland, found a direct correlation between oral vitamin D intake and esophageal adenocarcinoma (76). Esophageal adenocarcinoma accounts for over half of esophageal cancers in the U.S. Some problems with these studies include that the oral intake studies had low intake levels, less than 400 IU/d, which is generally too low to have an impact on any health outcome other than rickets, and that five and six years of follow-up may be too long to rely on a single serum 25(OH)D level (27, 28). It is thought that the ecological studies provide stronger results regarding the role of vitamin D in the risk of esophageal cancer, but these observational studies provide some doubt.

Lung cancer: Ecological studies of UVB and lung cancer risk are hampered because of the limited information on smoking rates several decades before the periods of the lung cancer rate data. The multicountry study used cigarette sales data for 1980–82 for lung cancer incidence rates in 2002. The UVB indices including clouds and anthropogenic aerosols contributed 10%–15% to the regression-adjusted R^2 value. However, serum 25(OH)D levels can predict survival in early-stage non-small cell lung cancer (77). A recent review summarized the evidence that vitamin D reduces the risk of lung cancer (78).

Cervical cancer: Two studies (7, 33) found inverse correlation between solar UVB indices and cervical cancer mortality (7, 34), and two studies in China and France found inverse correlation with cervical cancer incidence rate (30, 34). Smoking is an important risk factor for cervical cancer (79), complicating the ecological studies. Because the other U.S. study compared only northern with southern states (8), and lung cancer rates are much higher in the south than in the north (50), this may have limited that study's ability to find an inverse correlation with respect to solar UVB. A case–control study in Japan found a significantly reduced risk of cervical neoplasia with increasing oral vitamin D intake (80).

Renal cancer: All the U.S. studies and the multicountry study, but none of the other single-country studies, found inverse correlations with the UVB index. In the U.S., the highest rates of renal cancer mortality rate are met in the Midwest. Pesticides used in agriculture might account for the high rates in the Midwest. However, a study to address this question found no correlation with pesticide use in four wheat-growing Midwest states (81). Evidently, other factors such as diet are more important in affecting the risk for renal cancer than is vitamin D.

Vulvar cancer: One U.S. study inversely correlated a vitamin D index with vulvar cancer incidence and mortality rates (8). Because the geographical variation of vulvar cancer mortality

rates in the U.S. has the typical vitamin D–sensitive cancer pattern (high in the Northeast, low in the Southwest), it seems likely that vitamin D reduces the risk for vulvar cancer.

Those with Limited Evidence

Gallbladder cancer: Two U.S. studies (7, 8), one in Japan (36), and one in Spain (38) found inverse correlations between UVB indices and gallbladder cancer incidence and/or mortality rate. Because this is a rare type of cancer, little additional evidence exist regarding vitamin D's role in risk.

Brain cancer: Two of the U.S. studies (7, 8), the study in Spain (38), and a multicountry study (48) found inverse correlations with UVB indices. However, inspection of the geographical variation of brain cancer mortality rate in the U.S. (50) indicates that rates are low in the Northeast and Southwest but high in the Southeast, Midwest, and Northwest. The high rates in the Southeast could be related to diet or smoking, whereas the high rates in the Midwest could be related to farming (82).

Multiple myeloma: Two of the U.S. studies and the study in Spain found inverse correlations between the solar UVB indices and multiple myeloma mortality rates. However, the Midwest seems to be the U.S. region with the highest mortality rates, rather than the Northeast, suggesting that agricultural pesticides may be responsible. A review of studies in the U.S. found farmers at increased risk of multiple myeloma, with microorganisms, solvents, and pesticides possible contributing factors (83). A study in Minnesota found that at time of diagnosis, the fraction with deficient serum 25(OH)D levels increased progressively as the stage at diagnosis increased (84).

Leukemia: Only two studies, one in the U.S. (8) and a study in China (34), found inverse correlations between solar UVB and leukemia mortality rate. An ecological study in China found an inverse correlation between annual solar UVB doses and leukemia incidence and mortality rates in rural regions but found an increased risk in urban regions (34). Those living in rural regions are much more likely to spend significant time outdoors, possibly by working in agriculture. Thus, this study offers evidence of a beneficial effect of UVB irradiance in reducing the risk of leukemia.

As with several other types of cancer, the highest rates are in the Midwest U.S. Farming is an important risk factor for leukemia (85). The NCCS with respect to a serum 25(OH)D level index found a statistically significant inverse correlation for male health professionals (22). The failure of other studies to confirm these two findings indicates that the beneficial effect of vitamin D on all leukemia types is weak. However, some types of leukemia may exist for which the effect is strong.

Prostate cancer: Two U.S. studies as well as studies in Australia and France found inverse correlations with the solar UVB indices. However, the geographical variation of prostate cancer mortality rate in the U.S. is much different from that of the vitamin D-sensitive types of cancer such as breast, colon, and rectal; for one thing, there is a more pronounced latitudinal increase, and for another, the highest mortality rates are in the Northwest and lowest in the Southeast, whereas for the other cancers, the highest rates are in the Northeast and lowest in the Southwest (50). The latitudinal finding led to a study suggesting that viral infections were involved (86). However, there is little support for this hypothesis. The observation that prostate cancer has a different geographical variation than commonly accepted vitamin D-sensitive types of cancer such as breast, colon, ovarian, and rectal cancer led to the discovery that prostate cancer mortality rates in the U.S. were highly correlated with ethnic background (87). In addition, African-Americans have about twice the prostate cancer mortality rate as white-Americans (50). Latitude is also an index of prevalence of apolipoprotein E-4 (APOE4) for those living in their ancestral homelands. In the U.S., those with Northern European ancestry are more likely to live at higher latitudes, while those with Southern European or Hispanic ancestry are more likely to live at lower latitudes. In a multicountry ecological study for 102 non-African countries in which APOE4 allele prevalence, diet (cereals/grains), and *per capita* gross domestic product were included, the model explained 67% and 56% of the variance for prostate cancer incidence and mortality rates, respectively, with APOE4 prevalence accounting for about one-third (88). This study does not prove that APOE4 is a risk factor for prostate cancer, but does show that there are other possible explanations for the geographical variation of prostate cancer rates. Note that nearly all studies of prostate cancer incidence with respect to prediagnostic serum 25(OH)D level have reported no correlation (21, 28). One study reporting a U-shaped relationship was an NCCS with a follow-up period of 15-17 years (89). However, some evidence indicates that higher serum 25(OH)D levels are associated with increased cancer-specific and all-cause survival after diagnosis of prostate cancer (90).

Laryngeal cancer: The two U.S. studies found different results for laryngeal cancer with respect to solar UVB indices (7, 8). When the Midwest states are omitted, UVB is associated with reduced risk for females but not for males. Smoking is an important risk factor for laryngeal cancer. Whether vitamin D reduces risk is not clear.

Thyroid cancer: One U.S. study and the study in Spain found inverse correlations between the UVB indices and thyroid cancer incidence or mortality rates. However, in the U.S., this was only the case for females. Vitamin D receptor alleles affect thyroid cancer prognosis (91, 92).

Melanoma: Only one study found an inverse correlation between a UVB index and melanoma mortality rates, that for females in Spain. Other evidence indicate that vitamin D (93) and sun exposure (94) reduce the risk of melanoma. Another mechanism of UV irradiance in reducing risk of melanoma is the generation of elastosis (95).

Oral/pharyngeal cancer: Two of the U.S. studies found inverse correlations between solar UVB indices and oral/pharyngeal cancer, but none of the single-country studies did. An NCCS from Harvard found a statistically significant relative risk of about 0.3 for male health professionals with respect to a vitamin D index (22).

General comments: The strength of the association of a solar UVB index with cancer outcome is affected to some extent by the relative roles of vitamin D from the UVB doses and the values of the other risk-modifying factors. Sometimes, the indices used for the effect of smoking might mask the effect of solar UVB, such as for cervical and pancreatic cancer.

The advantages of the ecological approach include the many cases available, the many datasets available for ecological studies, that publicly available information is generally available for confounding factors, that designing 'experiments' is easy, and that data from many periods are available. In contrast to other epidemiological study types such as case-control studies and NCCS, the UVB-vitamin D index generally covers many years of life, with an emphasis on the later years of the case patients unless they moved shortly before dying. Moreover, ecological studies entail minimal time and cost.

Ecological studies use indices of solar UVB doses, which can be considered an indirect measure of vitamin D. Vitamin D production is the only factor proposed to explain the findings. UV irradiance is an important risk factor for development of basal cell carcinoma and squamous cell carcinoma (13-15). A registry study found significant inverse correlations between those diagnosed with NMSC in sunnier countries and three types of internal cancer in a statistically significant manner (liver and gallbladder, pancreatic, and prostate) and six types of cancer in a nonsignificant manner (bladder, colon, gastric, ovarian, rectal, and renal), but not in less sunny countries (13). It was suggested that in sunnier countries, people were able to expose more body surface area (15). A recent study found that those diagnosed with NMSC in Detroit, Michigan, had higher prediagnostic serum 25(OH)D levels (18).

Dental caries are inversely correlated with solar UVB doses and vitamin D. Several studies starting in 1865 found tooth loss and dental caries inversely correlated with summertime solar UVB doses (96). Vitamin D induces production of cathelicidin, which reduces the burden of oral bacteria that

cause dental caries (96). Thus, this disease provides an analogous result to the findings for the cancer in (7).

Two ecological studies reported results for both cancer incidence and mortality rates with respect to solar UVB indices (8, 34). One reason for the finding that inverse correlations between solar UVB doses and cancer mortality rate than incidence rate, is that more risk-modifying factors might affect cancer incidence than affect cancer survival. Mechanisms of vitamin D that affect survival include reduced risk of angiogenesis and metastasis (97).

Other Risk-modifying Factors

Three additional ecological studies of cancer in the United States were also carried out, examining the possible role of other risk-modifying factors on cancer mortality rates. One tested the hypothesis that wintertime vitamin D levels were important in the risk of some types of cancer, owing to higher rates of viral infections in winter that might be related to cancer risk, such as demonstrated for Hodgkin's lymphoma and multiple sclerosis (86). Cancer types with a higher risk associated with latitude or temperature in January included bladder, gastric, prostate, testicular, and thyroid cancer; Hodgkin's lymphoma; and NHL. There is limited evidence that viral infections play a role regarding risk for prostate cancer (98). It also appears that prostate cancer may be related to ethnic background in general and APOE alleles in particular, with APOE4 associated with higher risk (88). Working as a farmer seems to be a risk factor for Hodgkin's lymphoma (99) and NHL (59, 100), which could explain some of the elevated levels at higher latitudes. *H. pylori*, rather than viruses, is an important risk factor for gastric cancer. Recent evidence exists that maternal EBV infections are associated with increased risk of testicular cancer in offspring (101). Limited evidence also exists for a role of EBV infection in the risk of thyroid cancer (102). However, for these and the other cancer types, the viral infection hypothesis as proposed is probably not valid.

A second study examined the possible role of dietary iron and zinc in affecting the risk of cancer mortality rates in the United States (103). Data on iron and zinc were available only for four large regions. Iron was associated with increased risk for 10 types of cancer, whereas zinc inversely correlated with 12 types of cancer. Because the iron and zinc values were obtained from dietary factors, the findings could be related to other components of such dietary factors. Later work found an increased risk of endometrial cancer from dietary iron intake (104) and colorectal cancer from heme iron from meat (105), as well as evidence that zinc protects against cancer (106). No effect of dietary iron was reported for bladder cancer (107), in agreement with the ecological study.

A third ecological study investigated the possible role of air pollution in cancer risk (108). The index used was an acid

deposition map for the United States for 1985. The acidity level was highest in the Northeast and lowest in the West. Coal-fired power plants are an important source of acid rain in the Northeast. Cancer types having elevated risk with respect to acid deposition instead of summertime solar UVB doses included cervical, laryngeal, lung, nasopharyngeal, and oral cancer. Smoking is an important risk factor for all types of cancer. Black carbon and aromatic hydrocarbons are an important component of both cigarette smoke and combustion products of coal, diesel fuel, and wood, but not gasoline or oil. Aromatic hydrocarbons adsorb to black carbon and are associated with increased risk of cancer (109). It was assumed that the acid deposition index was a measure of black carbon and aromatic hydrocarbons in the air breathed in the various states. Acid deposition was also associated with seven other types of cancer along with solar UVB. The cross-correlation coefficient between acid deposition and solar UVB dose was 0.37 ($p=0.01$), so some of the correlations found, could be due to overlap between the two indices. Nonetheless, this study offers hypothesis-generating evidence that air pollution plays a role in cancer in general. Air pollution is an important risk factor for lung cancer and cardiovascular disease (110).

Hill's Criteria for Causality

As discussed in 2009 (111), Hill's criteria were generally satisfied for breast and colorectal cancer, with good evidence for 10 other types of cancer: bladder, esophageal, gallbladder, gastric, ovarian, rectal, renal, and uterine corpus cancer, as well as Hodgkin's and NHL. The findings discussed here support these findings and add cervical and vulvar cancers to the list.

Vitamin D Pooling Project

The Vitamin D Pooling Project study found no correlation between prediagnostic serum 25(OH)D and incidence of six rare cancer sites: endometrial, esophageal, gastric, kidney, NHL, and ovarian cancers (25). However, a direct correlation was found with pancreatic cancer (25). The evidence from ecological studies supports a beneficial role of UVB irradiance and vitamin D for all of these types of cancer. As noted earlier, the long follow-up time, 6.63 years, probably explains why inverse correlations were not found.

U-Shaped Relationship with 25(OH)D

Several NCCS found direct or U-shaped relations between cancer incidence rates and the prediagnostic serum 25(OH)D level (71, 89, 112). Ecological studies can be used to look for similar findings. In the U.S., as summertime UVB dose increases, cancer mortality rates and dental caries rates decrease rapidly at first and then meet a plateau at higher doses (6, 91). The flattening at higher doses could be due either to a saturation of the beneficial effect of vitamin D (54), or to people spending less time in the sun because of the heat.

Summary and Conclusion

Ecological studies of cancer incidence and mortality rates give some of the strongest evidence that solar UVB is associated with reduced risk of many types of cancer. The results are reasonably consistent between different cancer types and countries. No mechanism other than vitamin D production has been proposed to explain the effect of UVB irradiance on reducing cancer risk. One barrier to adopting the UVB–vitamin D–cancer hypothesis is that observational studies, generally NCCS, have reported inconsistent results with respect to serum 25(OH)D levels. As discussed here and elsewhere, an important problem in using NCCS is that because of the long follow-up periods after enrollment and serum collection, the 25(OH)D level determined from serum draw at time of enrollment loses predictive value beyond 3-7 years of follow-up. Policy-makers also seem to be waiting for a definitive randomized controlled trial (RCT) of vitamin D to provide convincing evidence that vitamin D reduces cancer risk (113). The only RCT investigating cancer incidence with respect to vitamin D that used sufficient vitamin D (1100 IU/d) to produce an effect, found a 77% reduction in all-cancer incidence rates between the ends of the first and fourth years (114). Many problems are associated with RCTs, including cost and time involved; the availability of few cases for rarer types of cancer; poor compliance; other sources of vitamin D, both oral and from UVB irradiance; that the beneficial effect of vitamin D depends on serum 25(OH)D level in the absence of oral intake (54); and that no uniform relationship exists between oral vitamin D intake and serum 25(OH)D level (115). Waiting for a definitive RCT may subject countless people to needless cancer and other chronic and infectious diseases. Based on observational studies, it was calculated that if serum 25(OH)D levels were raised globally from a mean value of about 54 nmol/l to 110 nmol/l, life expectancies could be increased by two years (116).

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