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Review

Roles of Solar UVB and Vitamin D in Reducing Cancer Risk and Increasing Survival

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Abstract. *The present article reviews existing scientific evidence in support of the ultraviolet-B (UVB)–vitamin D–cancer hypothesis, now being in its 35th year. Literature evidence comes from geographical ecological and observational studies, two successful clinical trials, and an understanding of how vitamin D reduces risk of and increases survival from cancer. Each approach has its strengths and limitations, and considering findings from all of these approaches yields the best conclusions. There exist over 15 types of cancer for which UVB exposure and/or 25-hydroxyvitamin D [25(OH)D] concentrations have been found associated with reduced risk. The optimal 25(OH)D concentration for preventing and surviving cancer appears to be above 75-100 nmol/l. There exists mounting evidence that individuals with higher 25(OH)D concentration at the time of cancer diagnosis have better cancer-specific and overall survival rates, suggesting that cancer-affected people should raise their 25(OH)D concentrations.*

The first epidemiological study linking vitamin D to reduced risk of cancer mortality was an ecological study of colon cancer mortality rates with respect to annual mean daily solar radiation in the United States (1). The brothers Cedric and Frank Garland noticed a pronounced geographic variation in colon cancer rates (highest in the cloudy northeast, lowest in the sunny southwest), found a significant inverse correlation with respect to solar radiation, and hypothesized that vitamin D production provided the mechanism to reduce cancer risk. They later added breast cancer (2) and ovarian cancer (3) to the list, and Schwartz added prostate cancer (4). I added 10 more types of cancer in 2002 (5). Several observational studies analyzed cancer incidence and/or mortality rates with respect to circulating 25-hydroxyvitamin D [25(OH)D] concentrations (6-9). Also, two randomized controlled trials (RCTs) found reduced incidence rates of cancer with vitamin D and calcium supplementation (10, 11).

According to the National Library of Medicine's PubMed database, more than 10,400 publications since 1980 have included "cancer" and "vitamin D" or "25-hydroxyvitamin D" in their title or abstract. Several reviews have discussed the understanding of the roles of UVB and vitamin D in preventing or treating cancer (12-17).

The present article reviews evidence showing that higher UVB exposure and 25-hydroxyvitamin D [25(OH)D] concentrations are associated with lower cancer incidence and mortality rates as well as increased survival after diagnosis of cancer.

Types of Studies

There exist several types of studies used to assess the roles of UVB exposure and/or vitamin D on incidence and/or survival of cancer. The primary ones are geographical ecological, observational, clinical, and mechanism studies. Each has its advantages and disadvantages. Thus, considering all types of studies leads to the best conclusions regarding the roles of UVB exposure and vitamin D in reducing risk of cancer. Table I summarizes the important advantages and disadvantages of each. Results from each type of study are examined in the rest of this review article.

Ecological studies of cancer incidence and mortality rates. Ecological studies of cancer incidence and/or mortality rate were the first to find the beneficial effects of solar UVB exposure in reducing cancer risk. The paper credited with proposing the ultraviolet-B (UVB)–vitamin D–cancer hypothesis is one by the brothers Cedric and Frank Garland. Their study linked annual solar radiation to reduced colon cancer mortality rates (1). However, a 1974 study published

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Table I. *Advantages and disadvantages of types of studies used to evaluate the roles of UVB exposure and/or vitamin D and cancer incidence and/or mortality rates*

Type of study	Advantages	Disadvantages
Geographical ecological	Large number of cases; many risk-modifying factors can be included; data are largely available.	Mainly useful for single midlatitude countries; in multi-country studies, diet plays a the most important role (18) and 25(OH)D concentrations do not vary much by country (19). The mechanisms associated with UVB doses may be unrelated to vitamin D (20).
Observational	Case-control	25(OH)D concentrations at time of diagnosis are most strongly linked to cancer incidence (21). Concern that the disease state may affect the 25(OH)D concentration (22). They are subject to selection bias (23).
Cohort or nested case-control	25(OH)D concentrations precedes cancer incidence.	Long follow-up times lead to attenuated findings (24). Some participants may have started taking vitamin D supplements shortly prior to enrollment (25), thereby leading to misclassification.
Cross-sectional	Large number of cases are included.	Cannot establish causality.
Clinical	Ensures that vitamin D intake explains the findings.	Most clinical trials to date have not been properly designed (26).
Mechanisms	They provide support for the role of vitamin D in reducing risk of cancer.	

in a Japanese University Journal revealed a strong inverse correlation between incidence of stomach cancer and annual hours of sunshine at various locations. But it also found comparable inverse correlations with respect to concentrations of calcium sulfate in rivers. According to the abstract, "The sunshine duration may be concerned with calcium absorption through its action of vitamin D production on skin" (27). However, probably owing to the title and the fact that it was published in a university journal, it has received no citations as of this writing.

I have reviewed geographical ecological studies of cancer incidence and/or mortality rates with respect to solar UVB doses (14, 28). Ecological studies have many advantages: the large number of cases; the large range of UVB doses in larger mid-latitude countries; and, since people generally live in the same region for many years, UVB doses are a reasonable proxy for vitamin D concentrations. From my perspective, single-country geographical ecological studies are ideally suited for studying the role of UVB and vitamin D in cancer risk. On one hand, populations in single countries are generally relatively homogeneous in diet, religion (which can affect clothing style), ethnic background and skin pigmentation, alcohol consumption, and smoking. If not, the geographical variations can generally be characterized by suitable indices such as lung cancer rates for the adverse health effects of smoking or ethnic background for skin pigmentation (29).

The most comprehensive ecological studies were performed in the United States (5, 29) (30), Japan (31), China (32), Spain (33), and France (34). The study in Spain used latitude and non-melanoma skin cancer mortality rates by province as indices of solar UVB doses and exposure. A study based on latitude as a proxy for cosmic rays in Australia found inverse correlations for breast, colorectal, ovarian, and prostate cancer, as well as leukemia (35). Observational studies from Australia with respect to latitude as a proxy for solar UVB doses found inverse correlations for non-Hodgkin's lymphoma (NHL) (36) and for esophageal (37), ovarian (38), and pancreatic cancer (39). For esophageal cancer, lower latitude was associated with a reduced risk for esophageal adenocarcinoma and esophagogastric junction adenocarcinoma but not esophageal squamous cell carcinoma (37). Overall, ecological studies support the role of solar UVB–and by extension vitamin D–in reducing mortality rates of 19 types of cancer: bladder, breast, colon, endometrial, esophageal, gallbladder, gastric, lung, oral/pharyngeal, ovarian, pancreatic, prostate, rectal, renal, thyroid, vulvar cancer, Hodgkin's lymphoma, NHL, and leukemia. The evidence is stronger for more common cancers (14). Although these studies used UVB indices such as latitude, which may also be correlated with other factors such as temperature, the UVB index in the United States is not highly correlated with latitude. Rather, the index is asymmetrical with highest UVB doses in summer in the southwest and lowest in the northeast (40), due to higher surface elevation and thinner stratospheric ozone layer in the west and higher aerosol burden and cloud cover in the northeast.

The beneficial effects of UVB exposure and vitamin D were proposed based on the latitude dependence of prostate cancer mortality rate in the U.S. (4). However, observational studies report that both low and high 25(OH)D concentrations are associated with similar risk (41). Evidence also exists to associate high UVB doses with increased risk of prostate cancer. A recent study in Australia found an increased risk of prostate cancer for men living in regions of higher UVB exposures (42). Many cancers, such as breast and colon, have strong evidence for beneficial effects of solar UVB exposure and vitamin D (43). In the U.S., mortality rates for such cancers are highest in the northeast and lowest in the southwest. By contrast, prostate cancer mortality rates are highest in the northwest and lowest in the southeast, whereas lung cancer rates are highest in the southeast. Mapping shows that the average life expectancy for white males in 1997-2001 was ~65-73 years in the southeast and ~76-80 years in the northwest (44). That finding supports the idea that men who die from prostate cancer live longer, a fact that could be due, in part, to having higher 25(OH)D concentrations.

The data used to carry out ecological studies of cancer mortality rate in the United States are available at http://ratecalc.cancer.gov/ratecalc/archivedatlas/ and http://ratecalc.cancer.gov/.

Two geographical ecological studies found stronger correlations with cancer mortality rates than cancer incidence rates with respect to indices of solar UVB doses. One was in the United States (30), the other in China (32). The study in China was extended to examine the effect of UVB dose on cancer survival rates by calculating one minus the mortality-to-incidence ratio (45). Increased survival rates were found for all cancer and cancers of esophagus, stomach, and bladder in both sexes together and breast cancer in women.

Cancer incidence with respect to 25(OH)D concentration. Although geographical ecological studies offer strong support for the role of solar UVB exposure in reducing mortality risk from many types of cancer, the evidence from observational studies with respect to 25(OH)D concentrations or vitamin D supplementation has been less supportive. Substantial agreement exists that 25(OH)D concentrations are inversely correlated with incidence of colorectal cancer (46). For breast cancer, both prospective (23) and case-control studies (21) found significant inverse correlations. However, no statistically significant associations were observed in European prospective studies and for premenopausal women, respectively (23). For prostate cancer, either no correlation generally occurs (46) or a slight positive correlation appears with respect to high *versus* low 25(OH)D concentration (24). As to other types of cancer, the Vitamin D Pooling Project found no inverse correlation between 25(OH)D concentrations and incidence of six rarer types of cancer: endometrial, esophageal, gastric, kidney, NHL, ovarian, and pancreatic cancers (47). That finding may have been due to the small number of cases and long (9 years) follow-up periods, during which time 25(OH)D concentrations changed (24). A recent meta-analysis found a 12% (95% confidence interval [CI]=3%-22%) reduction of lung cancer incidence with respect to 25(OH)D concentrations for an increase from 20 to 50 nmol/l (48). Another meta-analysis found a relative risk of 0.83 (95% CI=0.77-0.90; $p<0.001$) for high *versus* low 25(OH)D concentration (49).

The situation regarding breast cancer observational studies is as follows: case–control studies always find an inverse correlation between 25(OH)D and incidence, but prospective studies with a mean follow-up after blood draw of longer than 3 years generally do not (21). In a meta-analysis of 11 case–control studies from seven countries (Australia, Germany, Iran, Mexico, Shanghai, the United States, and the UK), the values of relative risk for breast cancer incidence with respect to 25(OH)D concentration overlaid each other very well, rapidly decreasing in incidence from 15 to 40 nmol/l, then more slowly out to approximately 80 nmol/l. Critics of the case–control studies raise the possibility of reverse causality–that the disease state may affect the 25(OH)D concentration. A recent article discussed this possibility (22). That article noted that cancer begins some time before it is diagnosed and has physiological effects that may lead to behavioral and dietary changes, possibly affecting 25(OH)D concentrations at time of diagnosis. The physiological effects of 25(OH)D concentrations on cancer were discussed, but they seem to be minor. However, reverse causality seems unlikely for several reasons. First, in at least one study in that meta-analysis, 25(OH)D concentrations were measured up to a year before diagnosis. Secondly, the shape of the relation between breast cancer incidence risk and 25(OH)D concentration is similar to that for breast cancer and colorectal cancer with prospective studies included (6). Third, although 25(OH)D concentrations may be lower at diagnosis for stage III and IV breast cancer, most breast cancers are diagnosed at stages I and II; moreover, stage at diagnosis had little effect on cancer survival with respect to 25(OH)D concentration near the time of diagnosis (50). Finally, strong evidence indicates that breast cancer develops rapidly (21), and since 25(OH)D concentrations change with time (24, 51), it is not surprising that prospective studies do not find an inverse correlation between 25(OH)D and breast cancer incidence.

Another way to look at the effect of solar UVB exposure and cancer incidence is to use the "predicted vitamin D level" approach that Giovannucci introduced with the Health Professionals Follow-up Study (52). In this approach, a regression model of 25(OH)D concentration is based on 25(OH)D concentration measurements with respect to such factors as oral vitamin D intake, geographical location, skin pigmentation, and leisure time in the sun for some individuals in a cohort. Those findings are then applied to the entire cohort. The approach found significant inverse correlations between

predicted vitamin D and five cancers (colorectal, esophageal, oral/pharyngeal, pancreatic cancer, and leukemia) and found non-significant inverse correlations for six other types (bladder, kidney, lung, prostate [advanced], and stomach cancer as well as NHL) (52). Later use of this approach also found a significant inverse correlation for pancreatic cancer (53).

Two recent observational studies found no significant inverse correlations between 25(OH)D concentrations and cancer incidence but did for cancer mortality rates. The study in Australia involved elderly women with a median follow-up time of 10 years. Excess death rates were found for 25(OH)D concentrations below 64 nmol/l. For a 30-nmol/l drop in 25(OH)D, the mortality rate increased by 30% (54). In the ESTHER study in Germany, which had a 10-year follow-up period, the relative risk for all-cancer incidence was 1.10 (95% CI=0.93-1.30), whereas the relative risk for all-cancer mortality was 1.25 (95% CI=0.96-1.62) (55). Although the long follow-up periods in those two studies would be expected to reduce the vitamin D effect (24), the fact that the effect was stronger for mortality rate than incidence rate supports the idea that vitamin D has a greater impact on cancer progression and mortality than on cancer incidence.

There have been reports that higher 25(OH)D concentrations are associated with increased risk of pancreatic cancer (56, 57). The first study was from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a cohort study of Finnish male smokers followed-up to 16.7 years. The studies based on this cohort are often at odds with others such as the finding that pre-diagnostic 25(OH)D concentration was not associated with colon or rectal cancer incidence except for colon cancer when the data were analyzed in a season-specific manner, in which case the highest three 25(OH)D quartiles were associated with a significant increased risk compared to the lowest quartile (58). In the second study, 25(OH)D concentration was associated with increased risk of pancreatic cancer in regions of the U.S. with low UVB doses but not in the rest of the U.S.A. likely reason for this finding is that those with higher 25(OH)D concentrations likely started supplementing with vitamin D later in life, perhaps with vitamin D_2 rather than vitamin D_3. A recent analysis of several million 25(OH)D assays by Quest Diagnostics between 2007 and 2009 found that in the northern states, those with 25(OH)D concentrations >125 nmol/l were very likely to have supplemented with vitamin D2 (25). A recent meta-analysis of all-cause mortality rate with respect to vitamin D supplementation found that vitamin D_3 supplementation was associated with a 11% (95% CI=1%-20%) reduction in all cause mortality rate but that vitamin D_2 supplementation was associated with a 4% (95% CI=–3%-11%) increase in mortality rate (15).

UVB exposure. Observational studies have also examined UVB exposure. Several reported reduced risk of breast cancer for women who had higher UVB exposure, some in early life (59-62), others later in life (63, 64). Evidence is mounting that risk of breast cancer starts accumulating when people are in their teens and twenties (9).

Observational studies have also found inverse correlations between UVB exposure and risk of several other cancers. Many studies reported inverse correlations for incidence of lymphoma, especially NHL, with respect to solar UVB exposure (36, 65-70). Similar findings have also emerged for endometrial (71) and pancreatic cancer (39). However, a meta-analysis of studies examining 25(OH)D and the incidence of NHL found no significant correlation (72).

A study of cancer incidence in Nordic countries with respect to solar UV exposure was made using cancer incidence data by occupation. A total of 1.4 million male cancer cases and 1.36 female cancer cases occurred in 54 occupational categories from 1960 to 2005 (73). In this study, the amount of solar UVB exposure was calculated as the incidence rate of lip cancer less incidence rate of lung cancer for males; neither melanoma nor non-melanoma skin cancer was found to be a useful UVB exposure index (74). That index was significantly inversely correlated with melanoma and non-melanoma skin cancer for males, and lip cancer was also significantly inversely correlated with melanoma for males. Lip cancer for females did not yield a good index, probably because women wear lipstick. That UVB index was significantly inversely correlated with 14 types of cancer for males and 4 for females (bladder, beast, colon, and corpus uteri). The occupations with the lowest all-cancer rates were farming (standard incidence rate [SIR]=0.83), forestry (SIR=0.84), gardening (SIR=0.85), and teaching (SIR=0.88); occupations with the highest all-cancer rates were waiting tables (SIR=1.48), bartending (SIR=1.27), tobacco industry workers (SIR=1.23), and military service at sea (SIR=1.22). Three occupations with the lowest all-cancer SIRs involve working outdoors, whereas three with the highest all-cancer SIRs involve indoor work. Smoking rates probably also contribute to the findings. All the types of cancer inversely correlated with this UVB index are also linked to reduced incidence and/or mortality rates in geographical ecological studies with respect to indices of solar UVB doses (14).

One possible confounding factor is physical activity, a considerable part of outdoor occupations. As of 2010, strong epidemiological evidence existed that physical activity reduced risk of breast, colon, and endometrial cancer, with weaker evidence for lung, ovarian, and prostate cancer (75). Physical activity was more strongly inversely correlated with colon cancer than with rectal cancer in the U.S. (76), whereas smoking is a greater risk for rectal cancer than colon cancer (77). In the Nordic study, the inverse correlation of the UVB index in a linear analysis was nearly the same for colon and rectal cancer. More recently, strong evidence was also found for physical activity reducing risk of esophageal cancer (78). In the Nordic study, the UVB index was not correlated with

esophageal cancer in a multiple linear regression analysis with lung cancer, although it was inversely correlated with several other smoking-related cancers. Lifetime vigorous-intensity physical activity was inversely associated with NHL risk in a study in Canada (79). In the Nordic study, the UVB index was not significantly correlated with NHL. A reason might be that the ratio of UVA to UVB intensity is higher in Nordic countries than at lower latitudes, and UVA seems to increase risk of NHL by affecting the immune system (80). A recent U.S. study associated physical activity indoors or outdoors with a modest increase in 25(OH)D concentration, apparently with an effect partly independent of solar UVB exposure. People with the highest activity level had 25(OH)D concentration of 63 nmol/l, whereas those with the lowest activity level had a concentration of 55 nmol/l (81). According to the 25(OH)D concentration–incidence rate relation for breast cancer from case–control studies, that would make a 5% difference in NHL incidence rates (21). However, some indoor occupations, such as waiting tables, may involve considerable activity walking back and forth between the kitchen and the tables. Thus, whereas physical activity reduces risk of several cancers, it appears to play only a modest role in the Nordic study and does not seem to detract from the interpretation of a protective effect of UVB exposure.

Racial disparities. The U.S. has pronounced black–white racial disparities in cancer incidence, mortality and survival rates (82). Because black Americans have 25(OH)D concentrations about 60% of those of white Americans (83), one can reasonably expect that this difference may explain much of the cancer disparity between races (84). In fact, my 2012 article outlined the evidence that the black–white disparities in cancer survival rates were probably due to differences in 25(OH)D concentrations (84). Many of the observational studies reporting such disparities for 13 cancers found unexplained racial disparities averaging 25% after considering socioeconomic status, stage at diagnosis, and treatment–similar to what was expected on the basis of differences in 25(OH)D concentrations. Although black Americans have stronger bones than many white Americans, the reason is probably due to differences in such things as a calcium economy that adapted to a hot, dry environment. There is no expectation that anything similar would apply to cancer.

Cancer Survival

Effects of season on diagnosis and survival. Since 25(OH)D concentrations are higher in summer than in winter (85), one might expect people diagnosed with cancer in summer to have better short- to intermediate-term survival rates than people diagnosed in winter. The first evidence for this effect was reported for breast, colon, and prostate cancer in Norway (86). Hodgkin's lymphoma was added later (87). A UK study replicated the results for breast cancer, also adding lung cancer (88). A review of the Norwegian studies showed a 15%-25% reduced risk of death within 36 months of diagnosis for breast, colon, prostate cancer, and Hodgkin's lymphoma for summer *versus* winter diagnosis (89). More recently, season of recurrence, but not season of diagnosis, were shown to affect survival for ovarian cancer in China, where "median progression-free survival of patients with recurrence month from April to November and December to March was 20 and 8 months, respectively ($p<0.001$)" (90).

A study in Finland found that mortality rates for brain tumors during the 2 months after surgery during the darkest 4 months of the year were much higher (ratio=1.7 [95% CI=1.1-2.3]) than for other months (91). Most of these patients had stage II-IV gliomas.

On the other hand, a recent paper from Italy examined the effect of season on the effectiveness of chemotherapy and survival on patients with newly-diagnosed metastatic colorectal cancer (92). The 1,601 patients were diagnosed with Stage I (12%), Stage II (27%), Stage III (27%), and Stage IV (56%). The COSINOR analysis of response rate to adjuvant chemotherapy varied from 43% in winter to 32% in summer. The COSINOR analysis of probability of progression at six months varied from 82% in winter to 76% in summer. The COSINOR analysis of survival probability at one year varied from 82% in winter to 78% in summer. The authors suggested a number of factors that might explain the findings including changes in 25(OH)D concentrations and folate destruction by UVB in summer. However, the link to vitamin D was considered unlikely since most people diagnosed with Stage IV colorectal cancer are vitamin D-insufficient (93) and patients are advised to limit sun exposure. Not considered were seasonal variations in gene expression, which has been found to be quite pronounced (94). This study found peaks and valleys in January and July, which corresponds more closely with photoperiod than 25(OH)D concentration, with peak and valley in the UK in September and March (85). Vitamin D supplementation can also correct reductions in 25(OH)D concentrations arising from chemotherapy (95).

Randomized controlled trials for cancer prevention. Articles regarding findings on vitamin D and cancer often call for RCTs of vitamin D supplementation. RCTs would serve two purposes: to check whether vitamin D reduces cancer risk and to determine whether vitamin D supplementation has any adverse effects.

Two RCTs found a beneficial effect of vitamin D-plus-calcium supplementation in reducing cancer risk. The first was conducted at Creighton University, involving 1,179 community-dwelling post-menopausal women living in rural areas of Nebraska (10). Participants were assigned, over 4 years, to take 1,450 mg/d of calcium, 1,450 mg/d of calcium

Table II. *Meta-analyses, high vs. low 25(OH)D concentration.*

Cancer	N, #	Incidence	Overall survival (OS)	Cancer-specific mortality (CSM)	Disease-free (recurrence-free) survival (DFS)	Reference
All	17		0.80 (0.70-0.90)			(15)
Breast	6 (OS), 4 (CSM)		0.63 (0.51-0.77)	0.65 (0.44-0.98)	0.42 (0.29-0.62)	(8)
	6 (OS), 4 (CSM)	0.92 (0.83-1.02)	0.61 (0.48-0.79)	0.58 (0.40-0.85)		(97)
	5 (CSM)			0.56 (0.41-0.61)		(98)
Colorectal	5(OS),					
3 (CSM)		0.55 (0.33-0.91)	0.65 (0.47-0.88)		(8)	
	4 (CSM)			0.63 (0.52-0.75)		(99)
Hematological	7 (OS), 2643		0.54 (0.45-0.65)		0.69 (0.59-0.83)	(100)
Lung	4 (OS), 1 (CSM)		0.75 (0.30-1.86)	0.18 (0.11-0.29)	0.92 (0.64-1.33)	(8)
Lymphoma	7 (OS), 7 (CSM)		0.48 (0.36-0.64)	0.50 (0.36-0.68)	0.80 (0.65-0.98)	(8)

N, Number of studies; #, number of patients.

plus 1,100 IU/d of vitamin D_3, or a placebo. Baseline 25(OH)D concentrations were 72 nmol/L, and people taking vitamin D plus calcium increased their 25(OH)D concentration to 96 nmol/L. Between the end of years 1 and 4, participants taking calcium had a non-significant 41% (95% CI=73%-104%) lower incidence of cancer, whereas those taking calcium plus vitamin D had a significant reduction of 77% (95% CI=18%-80%). The second successful trial was the Women's Health Initiative, as shown in a re-analysis of data. That study was conducted over 7 years and had participants take 1 g of calcium and 400 IU/d of vitamin D_3 or a placebo. For women who had not taken vitamin D or calcium supplements before entering the study, supplementation with calcium plus vitamin D significantly decreased risk of total, breast, and invasive breast cancers by 14%-20% and nonsignificantly reduced risk of colorectal cancer by 17%. (11).

Most vitamin D trials conducted to date have been poorly designed. The most common flaws are using too little vitamin D, not measuring baseline and achieved 25(OH)D concentrations, and not enrolling people with relatively low 25(OH)D concentrations. Vitamin D trials should seek to evaluate the 25(OH)D concentration–health outcome relations determined from observational or other studies. As seen for breast cancer, risk rises rapidly for 25(OH)D concentrations below 40 nmol/L but drops slowly at concentrations above 50 nmol/L (21). A recent meta-analysis of vitamin D trials with respect to biomarkers of inflammation found that half the trials with baseline 25(OH)D concentration below 48 nmol/L found significant reductions in biomarkers of inflammation; however, only a quarter of those with baseline concentrations above 50 nmol/L did (96). Heaney outlined the guidelines for nutrient trials that apply to vitamin D trials (26). The important criteria for vitamin D include starting with an understanding of the 25(OH)D concentration-health outcome of interest, measuring 25(OH)D concentrations of prospective participants, only enrolling those with low concentrations, giving sufficient vitamin D in the treatment arm to raise 25(OH)D concentrations significantly along the 25(OH)D concentration-health outcome relation, and measuring achieved 25(OH)D concentration.

While the evidence that vitamin D reduces risk of cancer is supported by ecological and observational studies and two RCTs, the evidence that would be most convincing would be the successful completion of a clinical trial finding that cancer incidence is significantly reduced with vitamin D supplementation. Hopefully, some of the ongoing trials will make such a finding.

Observational studies of survival after diagnosis of cancer. A growing number of studies have looked at survival rates after diagnosis of cancer. As Table II shows, for cancers with sufficient prospective studies of survival after diagnosis, the overall and cancer-specific survival rates are significantly better for high *versus* low 25(OH)D concentration at time of cancer diagnosis. Disease-free survival rates were also significantly better for three of the types, but not for lung cancer.

For cancers with only one to three prospective studies of survival after diagnosis, certain evidence exists that higher 25(OH)D concentrations are associated with significantly better overall survival, cancer-specific survival, and/or disease-free survival: gastric cancer (101), head and neck cancer (102, 103), melanoma (104), ovarian cancer (105), prostate cancer (50), and renal cancer (106). Results for all but ovarian and renal cancer are tabulated in two articles (8, 9). Table III summarizes the findings from many of these studies.

A recent study from Finland involving 670 deaths (209 from cancer) of elderly men found that serum 25(OH)D concentration was significantly correlated with death only for those with dietary intake of magnesium less than 414 mg/d (112). A study in Poland found from measurements of 25(OH)D concentration at several times after cancer

Table III. *Prospective studies, high vs. low 25OHD, for cancers or papers not included in meta-analyses in Table I.*

Cancer	Incidence	Overall survival	Cancer-specific mortality	Disease-free survival	Reference
Colon					(50)
Colorectal		0.70 (0.55-0.89	0.68 (0.50-0.90)		(93)
		0.61 (0.38-0.98)			(107)
Gastric					(108)
Head & neck		0.85 (0.57-1.28)			(102)
Melanoma		0.72 (0.54-0.96)*		0.72 (0.56-0.96)*	(109)
		0.85 (0.70-1.04)**		0.77 (0.63-0.96)**	
Ovarian		0.69 (0.51-0.93)			(105)
Prostate					(50)
			0.63 (0.42-0.94)		(110)
Renal cell	0.82 (0.68-0.99)***				(111)
		0.57 (0.34, 0.97)			(106)
Upper aerodigestive tract					(103)

*for January to March; **for July to September; ***for a doubling of 25(OH)D concentration

Table IV. *Mechanisms by which vitamin D affects cancer incidence, progression, and metastasis.*

Stage	Mechanism	Reference
Incidence	Cellular prodifferentiation, antiproliferative, and proapoptotic effects	(17)
	Prodifferentiation	(114)
	Antiproliferation by suppressing Wnt/β-catenin signaling pathway by up-regulating key tumor suppressor genes such as E-cadherin	(115)
	Reduces secretion of inflammatory cytokines	(116)
	Reduces inflammation	(96)
Progression	Antiangiogenesis: reduces expression of the vascular endothelial growth factor	(117)
	Regulates cancer-associated autophagy (digestion of cellular debris or accumulated damagedorganelles)	(14)
Metastasis	Maintains cell–cell adhesion by controlling E-cadherin and other adhesion components	(13)
	Inhibits secretion of matrix metalloproteinases 2 and 9, whichdegrade components of the extracellular matrix	(118)
	Maintains calcium ion homeostasis in the blood	(119, 120)

diagnosis that if 25(OH)D concentration rose above 40 nmol/l at any time, there was a profound difference in disease outcomes (113).

Mechanisms of vitamin D affecting cancer incidence, progression, and metastasis. Studies have identified several mechanisms that mediate vitamin D's effect on cancer incidence, progression, and metastasis. Several recent papers reviewed the mechanisms whereby vitamin D reduces risk of cancer and its progression (13). Table IV gives an overview of the mechanisms of vitamin D affecting cancer.

Vitamin D generally works by influencing gene expression through the action of $1,25(OH)_2D$ though vitamin D receptors (VDRs). VDRs have several alleles, with polymorphisms that have different associations with the most common cancers (121-123), providing additional evidence that vitamin D affects risk of cancer.

While $1,25(OH)_2D$ works through VDRs to fight cancer, the organs that develop cancer convert circulating 25(OH)D to $1,25(OH)_2D$ (124). Thus, high concentrations of $1,25(OH)_2D$ are not in the blood; if they were, risk of hypercalcemia would increase.

One vitamin D mechanism not widely discussed is the reduction of cancer cachexia (CC), that is characterized by systemic inflammation, weight loss, body-fat atrophy, and muscle wasting (125). Up to 50% of cancer patients suffer from CC (126) and up to 30% may die from it (127). Several mechanisms associated with CC involve cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor-α (126). A review discusses the role of various chemokines, cytokines, and other factors that play a role in cancer networks (128). Vitamin D affects many of these factors, especially those associated with inflammation (96, 129). A recent paper reviewed the role of vitamin D in reducing CC (130). IL-6

seemed to be a key mediator of muscle wasting in CC. IL-6 is one cytokine that vitamin D suppresses. A vitamin D supplementation study with colorectal cancer patients showed that precise effect, albeit non-significantly in a 6-month trial with 800 IU/d of vitamin D_3 (131). Although no studies appear to directly address vitamin D' s role in reducing risk of CC, it may explain some of the beneficial effects of 25(OH)D concentrations in survival, and increasing 25(OH)D concentrations would reduce risk of CC.

Treating cancer with vitamin D. Given the strong inverse correlations of cancer survival and mortality rates with respect to UVB dose or exposure and 25(OH)D concentrations, one would expect that raising 25(OH)D concentrations in persons diagnosed with many types of cancer would improve survival rates. To investigate this possibility, I searched PubMed, using search terms treatment, vitamin D, cancer, survival. I herein discuss the articles with beneficial effects.

A trial in which 44 men with low-grade prostate cancer were given 4,000 IU/d of vitamin D_3 for 1 year showed that "No adverse events associated with vitamin D(3) supplementation were observed. No significant changes in PSA levels were observed. However, 24 out of 44 subjects (55%) showed a decrease in the number of positive cores or decrease in Gleason score; five subjects (11%) showed no change; 15 subjects (34%) showed an increase in the number of positive cores or Gleason score." (132).

A Harvard researcher who has published 27 papers on vitamin D wrote, "Prospective observational studies suggest that higher vitamin D levels are associated with lower risk of incident CRC (colorectal cancer) as well as improved survival in patients with established CRC, and randomized clinical trials are desperately needed to establish causality. Moreover, there remains a great need to improve prognosis for patients with CRC, and investigating vitamin D as a potential therapeutic modality is an attractive option in regards to safety and cost, particularly in this era of expensive and often toxic anti-neoplastic agents" (133).

Vitamin D was also associated with decreased risk of recurrence among estrogen receptor–positive, but not estrogen receptor–negative, tumors ($p_{interaction}$=0.01) (134). Similar results were found in a study in Florida in which breast cancer patients received 10,000 IU/wk of vitamin D_3. Vitamin D use was associated with improved disease-free survival (hazard ratio, 0.36; 95% CI=0.15-0.88; p=0.03), but not overall survival (135).

A study from the Czech Republic noted that "Insufficient vitamin D plasma levels are found in 20-60% of cancer patients at diagnosis" and "it should become standard-of-care to examine 25- hydroxyvitamin D serum levels and correct vitamin D insufficiency in cancer patients" (136).

Other benefits of vitamin D relevant to cancer patients. Results primarily from observational studies showed that low 25(OH)D concentrations are correlated with poorer health outcomes, including cardiovascular disease (137), diabetes mellitus (138), and all-cause mortality rate (139). Several recent reviews summarize the beneficial effects of vitamin D (140-142). For colorectal cancer patients in particular, vitamin D supplementation has been found to increase quality of life also taking calcium supplements (143).

Concerns regarding vitamin D supplementation. Hypercalcemia in cancer patients can be due to parathyroid hormone–related protein secreted by cancer cells (144). Bisphosphonates are used to treat bone metastasis from breast cancer (145). But use of bisphosphonates leads to vitamin D deficiency (146). However, in lymphoma, the macrophages can produce $1,25(OH)_2D$, which leads to hypercalcemia (147). Thus, most cancer patients should have no concern about risk of hypercalcemia when using vitamin D supplements to raise 25(OH)D concentrations. That was shown to be the case in a 4-month trial in Canada in which breast cancer patients with bone metastasis were given 10,000 IU/d of vitamin D_3 plus 1,000 mg/d of calcium (146). During this trial, 25(OH)D concentrations were raised from a mean value of 72 nmol/L to 155 nmol/L, and the mean number of pain sites decreased from 3.2 to 2.0. Two patients developed hypercalcemia, but the cause was primary hyperparathyroidism, which vitamin D supplementation unmasked.

Discussion

A limited number of trials show the benefits of UVB exposure or vitamin D supplementation in preventing or treating cancer. However, an alternative method can be used to evaluate the evidence obtained to date: Hill's criteria for causality in a biological system (148). The Hill criteria relevant for UVB, vitamin D, and cancer include the following: Strength of association; Consistent findings in different populations; Temporality; Biological gradient (dose–response relation); Plausibility (*e.g.*, mechanisms); Coherence (no serious conflict with known natural history and biology); Experiment (*e.g.*, RCT); Analogy.

Confounding factors should also be accounted for (149). Not all criteria need be satisfied to claim causality; however, the more they are, the stronger the case. Researchers have evaluated these criteria for cancer in general (150) and breast cancer in particular (151). Readers of this article can evaluate how well they think the criteria have been satisfied now.

One other test of a good hypothesis is the extent to which predictions made based on the hypothesis are found consistent with the hypothesis. The original hypothesis by Cedric and Frank Garland was that solar UVB reduced cancer risk by stimulating production of vitamin D (1). Many studies since then have supported this hypothesis, including other ecological studies, observational studies, mechanism studies, two RCTs,

and the consideration of black–white cancer disparities in the United States. Although not all studies support the hypothesis, enough do that it should be considered largely verified. In addition, design flaws often limited failed studies' ability to find beneficial effects of UVB or 25(OH)D concentration.

Conclusion

Evidence is abundant that UVB exposure, vitamin D intake, and 25(OH)D concentrations are inversely correlated with many cancers. The evidence is not perfect, and the findings of ostensibly similar studies do not always agree. However, when one considers the results as a whole, a much greater likelihood exists that UVB and vitamin D do reduce the risk of many cancers and increase survival rates once cancer is diagnosed. Health officials and medical systems will probably wait for more definitive vitamin D trials before recommending that people use vitamin D supplementation to reduce the risk of and treat cancer, in part because officials rely heavily on RCTs to make such decisions. However, on the basis of existing evidence, physicians and patients can add vitamin D supplementation to the other modalities used to prevent and treat cancer.

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