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Review

A Review of the Evidence Supporting the Vitamin D-Cancer Prevention Hypothesis in 2017

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Abstract. *The vitamin D–cancer prevention hypothesis has been evaluated through several types of studies, including geographical ecological studies related to indices of solar ultraviolet-B (UVB) dose (the primary source of vitamin D for most people), observational studies related to UVB exposure or serum 25-hydroxyvitamin D [25(OH)D] concentrations, laboratory studies of mechanisms, and clinical trials. Each approach has strengths and limitations. Ecological studies indirectly measure vitamin D production and incorporate the assumption that vitamin D mediates the effect of UVB exposure. Findings from observational studies with long follow-up times are affected by changing 25(OH)D concentrations over time. Most clinical trials have been poorly designed and conducted, based largely on guidelines for pharmaceutical drugs rather than on nutrients. However, three clinical trials do support the hypothesis. In general, the totality of the evidence, as evaluated using Hill's criteria for causality in a biological system, supports the vitamin D–cancer prevention hypothesis.*

The ultraviolet-B (UVB)–vitamin D–cancer hypothesis was first proposed based on a geographical ecological study of colon cancer mortality rates in the United States with respect to annual sunlight doses (1). Since then, researchers have undertaken considerable effort to understand how vitamin D affects the risk of many cancers. As of August 28, 2017, 7947 publications were listed at pubmed.gov, found by searching "vitamin D or vitamin D_3 or 25-hydroxyvitamin D and cancer" in the title/abstract. Several recent papers have reviewed the evidence (2-9). Some of the shortcomings noted include inconsistent findings from observational studies (6) and lack of supporting clinical trials (10). Despite 37 years and millions of dollars of research effort, the consensus on the importance of vitamin D status in reducing cancer risk and improving survival after initiation is still mixed. On one hand, supporters point to the large body of evidence including geographical ecological studies, observational studies, clinical trials, and an understanding of the mechanisms. On the other hand, doubters point to observational studies and clinical trials that failed to support the hypothesis as well as possible problems with some studies that did.

This paper reviews the epidemiological study results regarding UVB exposure and vitamin D and cancer risk along with the clinical trials of vitamin D supplementation and black-white disparities in cancer survival rates. The goal is to clarify how UVB exposure and vitamin D reduce cancer risk and increase survival after initiation through a narrative review.

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Background

Vitamin D's role in reducing cancer risk can be determined through a variety of approaches:

- Geographical ecological studies related to indices of solar UVB doses
- Observational studies related to 25-hydroxyvitamin D [25(OH)D] concentration
- UVB exposure or oral vitamin D intake (case–control, prospective, and cross-sectional)
- Genetic polymorphisms and mechanisms
- Clinical trials

Additional support also comes from comparing cancer survival rates between black and white Americans (11).

Geographical ecological studies. Geographical ecological studies use population-averaged data on cancer and its risk-

modifying factors, including a UVB index such as annual solar radiation (1,12) solar UVB in the summer (13), annual solar erythemal radiation (14), or latitude (15). Other factors often included are alcohol consumption, ethnic background, lung cancer rates (an index of both smoking and, less so, diet), socioeconomic status, and urban/rural residence (16). Although this approach is indirect in that it considers UVB exposure, factors related to solar exposure other than vitamin D production probably cannot explain the findings. According to one study in mice, UV exposure had a stronger effect in reducing progression of colorectal cancer tumors than oral vitamin D, both of which raised 25(OH)D concentrations by the same amount (17). However, no mechanism was proposed and no further studies along that line have been conducted.

Occupational UVB exposure studies. Studying occupational exposure to UVB is another way to assess how solar UVB exposure and, presumably, vitamin D status affect cancer risk. Such exposure would occur regularly for many years and would be much higher for people with predominantly outdoor occupations than for people with predominantly indoor occupations.

Observational studies. Observational studies offer another approach to determine whether vitamin D affects cancer risk. Three types of observational studies exist: case–control (CC), prospective or nested case–control (NCC), and cross-sectional. In CC studies, 25(OH)D concentrations are determined near the time of cancer diagnosis and compared with those of matched controls. Cross-sectional studies have the distinct disadvantage that enough time has generally passed since cancer diagnosis that serum 25(OH)D concentrations could have changed from those taken before diagnosis.

Genetic polymorphism studies. Because serum 25(OH)D concentrations change, researchers have sought alternative approaches to determine how vitamin D affects cancer risk. Most of vitamin D's action regarding cancer occurs through the hormonal metabolite of vitamin D, 1,25-dihydroxyvitamin D, affecting gene expression through activating vitamin D receptors (VDRs). Therefore, studies of cancer risk with respect to VDR polymorphisms can be useful.

Clinical trials. Clinical trials designed to show that vitamin D reduces cancer risk have largely been based on the pharmaceutical drug model: that the trial is the only source of the agent; and that there is a linear dose-response relationship. Unfortunately, that study model is not appropriate for vitamin D because vitamin D does not satisfy the two basic assumptions of drug trials: people obtain vitamin D from UVB exposure, diet, and supplements, and that the dose–response relationship is not linear. Serum 25(OH)D concentrations vary widely by individual for the same vitamin D supplement amount (18), in part because of different body mass indicies indices (19) and in part due to different baseline 25(OH)D concentrations. In addition, many of the trials enrolled people with relatively high baseline 25(OH)D concentrations or did not give high enough vitamin D doses to significantly change 25(OH)D concentrations along the health outcome–25(OH)D concentration relationship.

Results

Geographical ecological studies. For many cancers, mortality rates in the U.S.A. are lowest in the southwestern states and highest in the northeastern states (20). According to later ecological studies, 22 cancers have incidence or mortality rates inversely correlated with solar UVB doses in the U.S. for whites (which includes Hispanic heritage): bladder, breast, colon, endometrial, esophageal, gallbladder, kidney, laryngeal, liver, lung, oral, ovarian, pancreatic, pharyngeal, prostate, rectal, small intestine, thyroid, vulvar cancer, Hodgkin's lymphoma, leukemia, and non-Hodgkin's lymphoma (12, 13, 16, 21-23). For black Americans, the cancers include bladder, breast, colon, gastric, lung, ovarian, pancreas, and rectal (13, 139). Findings from ecological studies in the U.S. and several other midlatitude countries are reviewed in (2).

According to U.S.A. ecological studies conducted using cancer incidence rates after 1999, UV doses significantly inversely correlated with 14 cancers: bladder, brain, breast, colon, endometrial, hepatocellular carcinoma, lung, ovarian, pancreas, pleura, prostate, rectal, and thyroid cancer as well as non-Hodgkin's lymphoma (mainly diffuse large B-cell lymphoma) (12, 14, 22, 24). For cancer mortality rates, inverse correlations were evident only for bladder, endometrial, esophageal, lung, and ovarian cancer as well as leukemia and non-Hodgkin's lymphoma (12). However, researchers in two studies found no inverse correlations between solar UVB dose or exposure and incidence of breast cancer after 2000 (14, 22). As my letter to the editor regarding the Zamoiski study pointed out (25), the inverse correlation between solar UVB dose for July 1992 and breast cancer mortality rates for white women started to decrease in the 1980-1984 period, with a rapid decrease for 1990-1994. The decreases can be attributed to increased sun avoidance and use of sunscreen, increasing rates of obesity, and widespread screening and improved treatment for some of those cancers. Obesity lowers 25(OH)D concentrations, possibly through volumetric dilution (26). Several factors, including those mentioned as well as use of daily sunlight rather than solar UVB in summer, may explain why no inverse correlations were apparent for mortality rates for

breast, colon, gallbladder, oral cavity and pharynx, pancreas, rectal, stomach, and thyroid cancer (12).

Although ecological studies are generally adjusted for other cancer risk–modifying factors, they are generally considered to generate hypotheses rather than show causality. For example, the analysis may not include all relevant cancer risk–modifying factors. In addition, non–vitamin D effects of sunlight that affect cancer risk could be present. However, only one study, in mice, supports the role of non–vitamin D effects in the progression of cancer but not in its initiation (17).

Occupational UVB exposure studies. A study related to occupational UVB exposure was based on cancer incidence data for 2.8 million 30- to 64-year-old residents identified in censuses of 1960 to 1990 of five Nordic countries and followed up through cancer registries until about 2005 (27). The cases were assigned to one of 53 occupational categories or one group of economically inactive people. In the study, lip cancer standardized incidence ratio (SIR) less lung cancer SIR was the index chosen for personal long-term UVB exposure (28). Neither melanoma nor nonmelanoma skin cancer was judged to be an appropriate index of UVB exposure. Those cancers are linked to both UVA and UVB exposure, and occupational exposure is not a risk factor for melanoma (29). In fact, melanoma SIR was significantly inversely correlated with the UVB index for males, as was the nonmelanoma skin cancer SIR to a lesser extent. As expected, occupations with the highest expected outdoor work – farmers, forestry workers, and gardeners – had the lowest cancer SIRs. Occupations such as beverage workers, drivers, tobacco workers, and wait staff were at the high end. However, some people in those categories probably had cancer risk factors such as consuming alcohol and smoking in addition to lower 25(OH)D concentrations. For men, the UVB index was significantly inversely correlated with 14 internal cancers: bladder, breast, colon, gallbladder, kidney, laryngeal, liver, lung, oral, pancreatic, pharyngeal, prostate, rectal, and small intestine. For women, the same UVB index was inversely correlated with bladder, breast, and colon cancer. Because women generally wear lipstick, the UVB index developed for males was used for them.

Observational studies. Two recent papers reviewed the findings from observational studies on cancer incidence and mortality rates (6, 8). One paper concluded that reasonable evidence exists that prospective and NCC studies generally find higher 25(OH)D concentrations associated with reduced incidence of bladder, colorectal, and lung cancer, but results for breast and pancreas cancer were mixed (6). The other paper reported meta-analyses of cancer progression and mortality with respect to 25(OH)D concentration at time of diagnosis, with findings of significant reductions in progression for breast, hematological, skin, and overall cancer, and cancer-specific survival for breast, colorectal, gastric, hematological, kidney, liver, lung, ovarian, and overall cancer (8).

In NCC and prospective studies, 25(OH)D concentration in the blood is measured at enrollment. One problem with such studies is that 25(OH)D concentrations change with time because of seasonal variations in solar UVB doses and changes in diet, lifestyle, and supplementation. As a result, the observed effect of higher 25(OH)D concentration generally decreases with longer follow-up times, as shown for breast and colorectal cancer (3, 30) and all-cause mortality rate (31).

The CC study's primary advantage is that the values of the factors are obtained near the time of disease diagnosis. In general, that approach results in stronger associations between factor values and health outcomes. That proximity also is thought to be a disadvantage by many who assume that the disease state can affect the factor values. However, no studies have shown that having early-stage undiagnosed cancer affects 25(OH)D concentrations. Investigating the relationship between 25(OH)D concentration and breast cancer stage at time of diagnosis is one way to test whether 25(OH)D concentration changes as a result of cancer initiation and progression. From the abstract for one such study: "In fully adjusted logistic regression models, the ORs (95% [confidence intervals {CIs}]) for the association between vitamin D deficiency and Stage II and III cancers were 0.85 (0.59-1.22) and 1.23 (0.71-2.15), respectively (P_{trend}=0.59), compared to Stage I. This study confirms previous work regarding the correlates of 25(OH)D concentrations but does not provide support for an association between vitamin D status and breast cancer stage."(32). A later study in China supported those results (33). Because most breast cancer tumors are diagnosed at stages I and II, most CC studies should not be subject to a cancer effect on 25(OH)D concentration. Indeed, for breast cancer, the 25(OH)D concentration–incidence relations from 11 CC studies from seven countries are practically coincident; however, researchers conducting prospective studies with follow-up times longer than 3-4 y generally do not find a significant difference in incidence with respect to 25(OH)D concentration (3). Evidence was given that breast cancer quickly goes from undetectable to detectable. One supporting factor is that mammography is recommended annually. The other is that breast cancer has seasonal variations in incidence rates, higher in spring and fall than in summer and winter (34). The authors proposed that vitamin D reduces breast cancer risk in summer, whereas melatonin does so in winter. Thus, using CC studies to investigate how vitamin D status affects breast cancer incidence seems justified.

One overlooked problem regarding observational studies that useserum 25(OH)D concentrations is that animal

Table I. *Cancer incidence rates with respect to 25(OH)D concentrations from meta-analyses.*

Cancer	Type of study	N	Low, high 25(OH)D (nmol/L)	HR (95%CI) high *vs.* low 25(OH)D conc.	Reference
All	MA	7	Increase of 50	0.89 (0.81-0.97)	(40)
Bladder	MA, CC	3		0.70 (0.56-0.88)	(41)
Bladder	MA, NCC	5		0.80 (0.67-0.94)	(41)
Breast	MS, CC	5	Increase of 50	0.60 (0.54-0.67), p=0.001	(42)
Breast	MS, NCC	4	Increase of 50	0.92 (0.82-1.02), p=0.10	(42)
Breast	MA, Pr	14	Quantiles	0.92 (0.83-1.02)	(43)
Breast	MA, CC	11	<25, >125	0.23	(5)
Colorectal	MA	16	<13 *vs.* >125	0.4 (0.2-1.0)	(44)
Colorectal	MA	15	>50 *vs.* <50	0.67 (0.59-0.76)	(44)
Kidney	MA, NCC, Pr	9	Quantiles	0.79 (0.69-0.91)	(45)
Lung	MA, NCC	13	20 *vs.* 53	RR=0.88 (0.78-0.97)	(46)
Lung	MA	8	Quantiles	0.72 (0.61-0.85)	(47)
NHL	MA	9	Quantiles	OR=1.03 (0.84-1.26)	(48)
Ovarian	MA	10	Increase of 50	0.83 (0.63-1.08) p=0.17	(49)
Pancreatic	MA	9 (pub 2006-2012)	Quantiles	1.14 (0.90, 1.45)	(50)
Pancreatic	MA	5 (pub 2010-2015)	Quantiles	1.02 (0.68-1.57)	(51)
Prostate	MA, NCC	16	Quantiles	1.17 (1.08, 1.27)	(52)
Stomach	MA	7	Quantiles	0.92 (0.74-1.14), P_{trend}=0.43	(53)

CC: Case-control study; CI: confidence interval; CS: cancer specific; HR: hazard ratio; MA: meta-analysis; NCC: nested case-control study; NHL: non-Hodgkin's lymphoma; OR: odds ratio; Pr: prospective study; RR: relative risk; Vit D: oral vitamin D.

products such as meat, eggs, and fish are important dietary sources of vitamin D, sometimes in the form of 25(OH)D in meat. Meat eaters in the UK had mean 25(OH)D concentrations of 77 nmol/l, whereas vegans had 56 nmol/l (35). Meat consumption, especially of red and processed meat, is an important risk factor for many cancers (36, 37), as is egg consumption (38). However, fish consumption, a source of omega-3 fatty acids and vitamin D, reduces the risk of several cancers (36), including breast cancer (39). Because observational studies of 25(OH)D concentration and cancer seldom consider diet, it could play an important role in cancer risk, especially if dietary factors change during a long follow-up study. Diet also could be an important consideration in comparing populations with different dietary factors.

Despite observational studies' inherent problems, many have yielded significant inverse correlations between 25(OH)D concentration and cancer risk. Tables I, II, III, and IV present the most recent findings from observational studies regarding cancer incidence, progression, survival, and mortality rates with respect to 25(OH)D concentrations. Tables I and III present results for meta-analyses, and Tables II and IV for single studies for types of cancer for which meta-analyses have not been conducted. Meta-analyses report significant inverse correlations between serum 25(OH)D concentration and incidence of all, bladder, breast, colorectal, kidney, and lung cancer. Single studies report the same for brain (glioma), cervical, esophageal squamous-cell carcinoma, gastric adenocarcinoma, head and neck, larynx and hypopharynx, liver, oral cavity and gum, ovarian, and pancreatic cancer.

Negative observational studies. In several observational studies, either no correlation or a direct correlation was evident between serum 25(OH)D concentration and cancer incidence rates. A careful consideration of those studies' parameters indicates the presence of factors that call the results into question. Several of those studies are discussed here.

The Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP). The Vitamin D Pooling Project of Rarer Cancers (VDPP) combined data on cancer incidence with respect to baseline 25(OH)D concentration from 10studies from China, Finland, and the United States (81). The number of cancer cases varied from 775 for kidney cancer to 1353 for lymphoma. Median follow-up times varied from 2.1 to 10.8 y, with a median study time of 4.6 y. Results were given for endometrial, kidney, ovarian, pancreatic, and upper gastrointestinal (esophageal and gastric) cancer and for lymphoma. The only non-significant finding for six quantiles of 25(OH)D concentration was an increased risk for pancreatic cancer at the highest quantile. In other studies, reduced risk was evident for gastric (59), kidney (45), and ovarian cancer (82). Why no inverse correlations with respect to 25(OH)D concentration was present for those cancers in the VDPP study is unclear.

Table II. *Cancer incidence rates with respect to 25(OH)D concentrations from single studies.*

Cancer	Type of study	Follow-up period (y)	N cases, controls	Low, high 25(OH)D (nmol/L)	HR (95% CI) high *vs.* low 25(OH)D conc.	Reference
All	Trial	1-2		75 to 138, <75	0.65 (0.44-0.97)	(54)
Brain (glioma)	NCC	15 (med)	592, 1112	>66, >2 yr prior	OR=0.59 (0.38-0.91)	(55)
Cervical	CC	0	333, 1665	(Vit D) <162 IU/d *vs.* >291 IU/d	0.64 (0.43-0.94), P_{trend}=0.01	(56)
Endometrial	Pr	20 (max)	572, 572	Low, high quintiles	1.00 (0.73-1.36), P_{trend}=0.33	(57)
Esophageal SCC	CC	0	106, 108	<40, >70	0.37 (0.18-0.76), P_{trend}=0.007	(58)
Gastric adenocarcinoma	Retro	0	49, 49	Vitamin D <50	0.11 (0.05-0.20), p<0.0001	(59)
Head and neck	Pr	6.3 (mean)	350, 350	Doubling	0.70 (0.56-0.880, p=0.001	(60)
Hepatocellular carcinoma	Pr	6 (mean)	138, 138	Mean, 34 *vs.* 74	0.51 (0.26-0.99), p=0.04	(61)
Larynx and hypopharynx	Pr	6.3 (mean)	144, 144	Doubling	0.55 (0.39-0.78), p<0.001	(60)
Lymphoma, chronic lymphocytic	NCC	7.1 (mean), >2	161, 161	<43, >72	0.40 (0.18, 0.90), P_{trend}=0.05	(62)
Lymphoma, chronic lymphocytic	NCC	7.1 (mean)	202, 202	<43, >72	0.82 (0.43, 1.61), P_{trend}=0.86	(62)
Oral cavity and gum	Pr	6.3 (mean)	108, 108	Doubling	0.60 (0.43-0.87), p=0.005	(60)
Ovarian	CC	0	46, 106	<50.5	Area under ROC curve 0.81 (0.71-0.88)	(63)
Thyroid	Retro	0	212	<37.5, >37.5	0.50 (0.38, 0.93)	(64)
Vulvar	CC	0	24		Not significant	(65)

CC: Case–control study; FU: follow-up; HR: hazard ratio; IPRT: intratumoural periglandular reaction tumor; MA: meta-analysis; med, median; NCC: nested case–control study; NHL: non-Hodgkin's lymphoma; Pr: prospective study; Retro, retrospective; ROC: receiver operating characteristics; SCC: squamous-cell carcinoma; Vit D: oral vitamin D.

Table III. *Cancer survival with respect to 25(OH)D concentration at time of diagnosis from meta-analyses.*

Cancer	Study	N	Low, high 25(OH)D (nmol/L)	HR high *vs.* low 25(OH)D conc.	Reference
All (mortality)	MA, CS	16	Increase of 50	0.83 (0.71-0.96)	(40)
All, males (mortality)	MA, CS	16	Increase of 50	0.92 (0.65-1.32)	(40)
All, females (mortality)	MA, CS	16	Increase of 50	0.76 (0.60-0.98)	(40)
Breast	MA, OS	5	Fixed effects model	0.67 (0.56-0.79), p<0.001	(66)
Breast	MS, CS	4		0.58 (0.40-0.85)	(43)
Breast	MS, OS	6		0.61 (0.48-0.79)	(43)
Colorectal	MA, CS	4	Quintiles	POR=0.63, p<0.0001	(67)
Colorectal	MA, CS	3	Quartiles	0.65 (0.47-0.88)	(68)
Colorectal	MA, OS	5	Quartiles	0.55 (0.33-0.91)	(68)
Hematological	MA, RFS	12	Low 25(OH)D: 20 to 63	0.69 (0.59-0.80), p<0.001	(69)
Hematological	MA, OS	15	"	0.54 (0.45-0.65), p<0.001	(69)
Leukemia	MA, RFS	12	"	0.57 (0.44-0.75), p<0.001	(69)
Leukemia	MA, OS	12	"	0.46 (0.33-0.65), p<0.001	(69)
Lung	MA, OS	4	Quartiles	0.75 (0.30-1.86)	(68)
Lung	MA, CS survival	4		1.01 (0.87-1.18)	(47)
Lung	MA, CS mortality	3		0.38 (0.28-0.54)	(47)
Lymphoma	MA, RFS	12	Low 25(OH)D: 20 to 63	0.80 (0.65-0.98), p=0.04	(69)
Lymphoma	MA, OS	15	"	0.51 (0.39-0.68), p<0.001	(69)
Lymphoma	MA. CS	7	Quartiles	0.48 (0.36-0.64)	(68)
Lymphoma	MA. OS	7	Quartiles	0.50 (0.36-0.68)	(68)
Pancreatic	MA, OS	5	<50 *vs.* >75	0.62 (0.44-0.86), p=0.02	(70)
Pancreatic	MA, CS	5	Highest *vs.* lowest	0.81 (0.68-0.96)	(51)

HR: Hazard ratio; MA: meta-analysis; POR: pooled odds ratio; Pr: prospective study; RFS: recurrence-free survival.

Table IV. *Cancer progression or survival with respect to 25(OH)D concentration at time of diagnosis from individual studies.*

Cancer	Study	N cases, controls	Low, high 25(OH)D (nmol/L)	HR high *vs.* low 25(OH)D concn.	Reference
Bladder	Pr, OS	4126	<50 *vs.* >50	Mos. survived: 69.9 *vs.* 63.3	(71)
Bladder	Pr, OS	4126	25(OH)D tests: <3 *vs.* ≥3	Mos. survived: 90.6 *vs.* 39.7	(71)
Head and neck	Pr, OS (primarily CS)	87, 87	Doubling	0.71 (0.53-0.96), p=0.02	(60)
Kidney	Pr, CS	152,	Season-adjusted quartiles, median=43	0.70 (0.39-1.24), p=0.53	(72)
Kidney	Pr, OS	203,	Season-adjusted quartiles, median=43	0.59 (0.35-1.00), p=0.03	(72)
Liver	Pr	200	<25 *vs.* >25	0.50 (0.28-0.88), p=0.02	(73)
Lymphoma, follicular	SWOG, Pr, 5.4 y, PFS	183	<50, >50	1.97 (1.10-3.53)	(74)
Lymphoma, follicular	SWOG, Pr, 5.4 y, OS	183	<50, >50	4.16 (1.66-10.44)	(74)
Lymphoma, follicular	LYSA, Pr, 6.6 y, PFS	240	<25, >25	1.50 (0.93-2.42)	(74)
Lymphoma, follicular	LYSA, Pr, 6.6 y, OS	240	<25, >25	1.92 (0.72-5.13)	(74)
Melanoma					(75)
Ovarian	Pr, PFS	491, 650	Per 10	0.98 (0.93-1.03)	(76)
Ovarian	Pr, OS	435, 670	Per 10	0.93 (0.88-0.99)	(76)
Prostate	Pr, CS	1000	<20, >52	0.72 (0.52-0.99), P_{trend}=0.006	(77)
Prostate	Pr, CS	2282	<50, >50	1.20 (0.97-1.48)	(78)
Prostate	Pr, OS	2282	<50, >50	1.25 (1.05-1.50)	(78)
Stomach	Pr, OS	197	<50 *vs.* >50	0.59 (0.37-0.91), p=0.02	(79)
Thyroid		820	20, 58	1.72 (0.46, 6.41)	(80)

CaCo: Case–cohort; CS: cancer specific; HR: hazard ratio; LYSA: Lymphoma Study Association; MA: meta-analysis; OS: overall survival; PFS: progression-free survival; POR, pooled odds ratio; Pr: prospective study; Retro: retrospective; SWOG; Southwest Oncology Group.

Many studies examining the relation between cancer incidence and 25(OH)D concentration were conducted using results for participants in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. That randomized, double-blind, placebo-controlled primary prevention trial was undertaken to determine whether supplementation with α-tocopherol, β-carotene, or both would reduce the incidence of lung and other cancers in male smokers. A total of 29,133 men aged 50-69 y who smoked five or more cigarettes daily were randomly assigned to receive α-tocopherol (50 mg), β-carotene (20 mg), α-tocopherol and β-carotene, or a placebo daily for 5-8 y (median, 6.1 y) (83). Thus, the population may not be representative of most populations. A second problem was that cancer cases were ascertained up to 20 y after blood draw. Long follow-up times reduce the correlation between cancer incidence and 25(OH)D concentration (3). Two studies were reported for colon and rectal cancer. In the first one, with a follow-up period up to 8 y, an inverse correlation was found between 25(OH)D concentration and incidence of distal colon cancer and rectal cancer (84). In the second one, for the period 1999–2005, using 25(OH)D concentrations from 1985 to 1988, colon cancer cases were directly correlated with 25(OH)D concentration, whereas no correlation was found for rectal cancer (85). In a study with a follow-up period up to 16 y, a direct correlation was found for pancreatic cancer at the highest $25(OH)D_2$ plus $25(OH)D_3$ quantile (86). Thus, long follow-up time may have adversely affected the results.

A related study was conducted in the U.S. (87). One hundred eighty-four incident cases of pancreatic adenocarcinomas occurred between 1994 and 2006 (follow-up to 11.7 y; median, 5.4 y). Although no significant correlation was found between 25(OH)D concentration and incidence of pancreatic cancer, an effect was found depending on whether the participants lived in areas with low or high residential UVB doses: for people living in low-dose regions, "higher compared with lower 25(OH)D concentrations were positively associated with pancreatic cancer (compared with first quintile, the ORs for each respective quintile were 2.52, 2.33, and 4.03; 95% CI, 1.38-11.79), whereas among subjects with moderate to high residential UBV exposure, 25(OH)D concentrations were not associated with pancreatic cancer." The 25(OH)D concentrations reported in both that study and the Finnish study were a combination of $25(OH)D_2$ and $25(OH)D_3$. In a later study, adults living in the northern U.S. were more likely to have $25(OH)D_2$ concentrations than those living in the central and southern regions (88). Vitamin D_2 appears to have adverse effects, according to a review of vitamin D supplementation and mortality rate (89). Thus, the higher $25(OH)D_2$ concentrations in both the northern U.S. and

Finland may have contributed to the findings of direct correlations between 25(OH)D concentration and incidence of pancreatic cancer. For more discussion of pancreatic cancer (51, 90).

Esophageal cancer. In studies of esophageal and gastric cancer incidence in China, direct correlations with 25(OH)D concentration were evident for men but not women (91). The Chen study was conducted in LinXian. A later review noted that LinXian was a high-risk region for esophageal cancer and listed the following factors: drinking very hot and salted tea, boiled with milk; a diet rich in meat – especially salted, dry, and/or smoked meat – and dairy products; a diet poor in fresh fruit and vegetables; poor oral hygiene; and infection with human papillomavirus (92). Thus, studies conducted there should not be considered representative of outcomes expected elsewhere.

Prostate cancer. Findings for prostate cancer with respect to solar UVB doses and serum 25(OH)D concentration differ from those for many other cancers such as breast and colon. The geographical variation of prostate cancer mortality rate in the U.S.A. indicates highest rates in the northwest and lowest rates in the southeast, whereas most cancers have highest rates in the northeast and lowest rates in the southwest (20). One report links high sun exposure to increased risk (93). Some indication of a U-shaped relationship is evident between 25(OH)D concentration and incidence of prostate cancer, with both low and high concentrations associated with increased risk (94). A meta-analysis of 21 studies supported that finding (52). Part of the explanation may have to do with calcium. Higher intake of nonfat dairy and calcium is a risk factor (95). Vitamin D increases calcium absorption, but people with genetically reduced calcium absorption have a lower risk of prostate cancer (96).

Genetic polymorphism studies. According to a review of *VDR* polymorphism studies through the end of 2016, several studies have looked at the association of VDRs with incidence of breast, colorectal, esophageal, hepatocellular, lung, ovarian, prostate, renal, and thyroid cancer (97). However, the findings regarding specific cancers are sometimes contradictory and often limited in scope, precluding definitive conclusions. To date, only one *VDR* polymorphism has been found significantly associated with cancer progression in a meta-analysis, [Rs7975232 (ApaI)], and two with cancer survival [Rs7975232 (ApaI)] and [Rs1544410 (BsmI)] (8). None was significantly correlated with any specific cancer.

Mendelian randomization studies also have been used to assess whether vitamin D may be causally linked to reduced risk of various diseases. Such studies examine the correlations of genetic polymorphisms of genes responsible for circulating 25(OH)D concentrations: *CYP2R1*, the main 25-hydroxylase of vitamin D; *GC*, coding for the vitamin D–binding protein that transports 25(OH)D and other metabolites in blood; and *CYP24A1*, which 24-hydroxylates both 25(OH)D and the hormone (98). Mendelian randomization studies have offered support for vitamin D in reducing risk of colorectal cancer (99), risk of ovarian cancer (100, 101), and risk of all-cancer mortality rate (102).

Mechanisms. The mechanisms whereby vitamin D reduces cancer risk and increases survival are well known. They include effects on cellular differentiation, proliferation, and apoptosis as well as reduced angiogenesis around tumors and inhibition of metastasis (2, 7,9, 10, 103-105).

Clinical trials. Pharmaceutical drugs require placebo-controlled, double-blind clinical trials to assess efficacy and investigate short-term adverse effects. However, drug companies know how to engineer clinical trials to show beneficial effects while ignoring the findings regarding adverse effects – some of which may take years to uncover (106). Nutritional compounds such as vitamin D are not well suited for clinical trials because the pharmaceutical drug trial assumptions are not appropriate and vitamin D clinical trials have generally not supported observational studies that report beneficial effects of higher 25(OH)D concentrations (107).

Nonetheless, three vitamin D_3-plus-calcium clinical trials have shown beneficial effects in reducing cancer incidence. The first one involved postmenopausal women living in Nebraska who were given 1,100 IU/d of vitamin D_3 plus 1,450 mg/d of calcium, 1,450 mg/d of calcium, or placebo. "When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects ($p<0.03$). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 ($p=0.01$) and 0.532 ($p=0.06$), respectively. When analysis was confined to cancers diagnosed after the first 12 months, RR for the Ca + D group fell to 0.232 (95%CI: 0.09, 0.60; $p<0.005$) but did not change significantly for the Ca-only group."(108).

The second study was a reanalysis of results from the Women's Health Initiative, in which women in the treatment arm took 400 IU/d of vitamin D_3 plus 1500 mg/d of calcium."In 15,646 women (43%) who were not taking personal calcium or vitamin D supplements at randomization, CaD significantly decreased the risk of total, breast, and invasive breast cancers by 14-20% and nonsignificantly reduced the risk of colorectal cancer by 17%. In women taking personal calcium or vitamin D supplements, CaD did not alter cancer risk (HR: 1.06-1.26)." (109).

The third study again involved postmenopausal women living in Nebraska. This time they took 2000 IU/d of vitamin

D_3 plus 1500 mg/d of calcium or a placebo. In unadjusted Cox proportional hazards regression, the hazard ratio was 0.70 (95% CI=0.47-1.02; p=0.06) (54). However, as noted in an online supplement, women with 25(OH)D concentrations greater than 125 nmol/L at the most recent measurement before cancer diagnosis had significantly reduced cancer risk. Because the proposal did not state that the analysis would use 25(OH)D concentrations, the journal editors did not let those findings be reported in the print version of the study findings.

Those three studies were recently reviewed (5). That review pointed out that the most recent trail was near the limit of power to find a beneficial effect of vitamin D supplementation due primarily to a relatively high baseline 25(OH)D concentration (83 nmol/l) according to the 25(OHI)D concentration–breast cancer incidence relation determined from CC studies. That it failed by only one cancer case in the treatment arm was remarkable.

Two studies reported beneficial effects of vitamin D_3 supplementation for cancer patients. In one for men with low-grade prostate cancer, participants took 4000 IU/d of vitamin D_3 for a year. According to the report, "24 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." (110). Although the study used no control subjects, historical controls had a mean increased number of positive cores of about 1 over more than 18 months in comparison with a reduction of about 1.5 positive cores for the participants. The authors later reported, "These clinical results also suggest that robust and sustained vitamin D_3 supplementation can reduce prostate cancer–related health disparities in African-American men and that these health disparities are at least in part the result of widespread hypovitaminosis D within the African-American population." (111).

The other study looked at vitamin D_3 supplementation for colorectal cancer patients. Those taking 4,000 IU/d of vitamin D_3 had a median progression-free survival of 12.4 months, in comparison with 10.7 months for those taking 400 IU/d; log-rank p=0.03). "After multivariate adjustment for prognostic variables, HR was 0.66 (95%CI, 0.45-0.99; 2-sided p=0.04). In comparing HiVitD with LowVitD, RR was 58% *vs.* 63% (p=0.54) and disease control rate was 100% *vs.* 94% (p=0.05)." (112).

Robert Heaney outlined how vitamin D clinical trials could be conducted. The key points include the following: 1. Start with an understanding of the 25(OH)D concentration–health outcome relationship. 2. Measure 25(OH)D concentration of prospective participants and try to enroll those with concentrations near the low end of the relationship. 3. Give vitamin D_3 doses high enough to raise 25(OH)D concentrations to the upper part of the relationship. 4. Measure 25(OH)D concentration again during the trial to determine the success of the dosing and assess compliance (113).

Guidelines for designing vitamin D trials more likely to find beneficial effects were outlined in two recent papers (5, 114). It was suggested that all trial outcomes be related to 25(OH)D concentrations, measured several times during the trial, with adjustments in dosing to produce desired achieved concentrations (114).

Comparing cancer survival between black and white Americans. Another way to assess vitamin D's role in cancer is to examine the disparity in cancer survival rates between black and white Americans. In the period 2001-2004, black Americans older than 40 y had mean 25(OH)D concentrations between 35 and 43 nmol/L, whereas white Americans had mean concentrations around 63-65 nmo/L (115). On the assumption that cancer survival rates have the same relationship to 25(OH)D concentrations as for breast cancer incidence, black Americans would have 60% higher cancer mortality rates than white Americans, although that estimate is highly uncertain. According to a review of the journal literature, disparities are evident for 13 cancers after consideration of socioeconomic status, stage at diagnosis, and treatment in most cases: bladder, breast, colon, endometrial, lung, ovarian, pancreatic, prostate, rectal, testicular, and vaginal cancer; Hodgkin's lymphoma; and melanoma (11). Cancer-specific mortality rates for black Americans averaged about 25% higher than for white Americans. Of course, other lifestyle factors could also be involved. One concern is that black Americans have a different biologically available 25(OH)D concentration. That effect was believed to be a result of a different relation between total and free 25(OH)D due to a different effect of the vitamin D–binding protein (116). But a recent study dispelled that concern by showing nearly identical odds ratios for free and total 25(OH)D concentrations for colorectal cancer incidence for black Americans (117).

Summary table. Table V presents findings of ecological and observational studies regarding cancer incidence, survival, and mortality rates with respect to indices of solar UVB or 25(OH)D concentration, as well as results regarding disparities in cancer-specific survival rates between black and white Americans. The ecological study findings are taken from the review in (2). The occupational exposure results are primarily from an analysis of SIRs by occupation (28). The observational results for 25(OH)D concentrations are generally the latest meta-analysis. If no meta-analysis has been published, the most recent paper is used. The results for African Americans are from (11) along with results from later papers. The cancers are grouped into epithelial or hematopoietic (hematological) categories and arranged in descending order according to estimated incidences in 2002

Table V. *Summary table of significant inverse relationships regarding UVB dose, 25(OH)D concentration, on cancer incidence, survival, mortality rate or survival disparities for African Americans compared to white Americans.*

Cancer	U.S. cases, 2002 (118)	Ecologic, U.S.	Ecologic, other countries	Personal UVB or occupational exposure	25(OH)D incidence	25(OH)D progression, mortality	African American Survival
All		(2)	(2)	(28)		(8)	
Epithelial							
Breast	205,000	(2)	(2)	(28)	(5)	(8)	(11)
Prostate	180,000	(2)	(2)				(11)
Lung	169,200	(2)	(2)		(46)	(47)	(11)*
Colon	107,300	(2)	(2)	(28)	(44)	(8)	(11)
Bladder	56,500	(2)	(2)	(28)	(41)		(11)
Melanoma	53,600			(28)			(11)
Rectal	41,000	(2)	(2)		(44)	(8)	(11)
Kidney	31,800	(2)	(2)		(45)		
Pancreatic	30,300	(2)	(2)	(28), (119)		(70)	(11)*
Endometrial	30,300	(2)	(2)		(57)		(11), (120)
Oral cavity	28,900	(2)	(2)	(28)	(60)	(60)	
Ovarian	23,300	(2)	(2)	(121), (122)	(63)	(8)	(11)*
Stomach	21,600	(2)	(2)		(59)	(8)	
Thyroid	20,700	(2)	(2)		(64)		
Brain, CNS	17,000	(2)	(2)		(55)		
Liver	16,600	(24)		(28)	(61)	(8)	
Esophageal	13,100	(2)	(2)	(28), (123)	(58)	(60)	
Uterine cervix	13,000		(2)		(56)		(124)
Larynx	8,900	(2)		(28)	(60)	(60)	
Pharynx	8,600	(2)	(2)	(28)	(60)	(60)	
Testicular	7,500	(2)	(2)				(11)
Gallbladder	7,100	(2)	(2)	(28)			
Small intestine	5,300	(2)		(28)			
Vulvar	3,800	(2)					
Vaginal	1,000						(11)*
Hematological						(8)	
NHL	53,900	(2)	(2)	(125)	(48)		
Leukemia	30,800	(2)	(2)			(69)	
AML (myeloma)	10,000	(2)					
Hodgkin's	7,000	(2)					
NHL, T-cell	3,200				(48)		
Lymphoma, B-cell				(126)	(48)		

*Did not include all three factors, stage at diagnosis, treatment, and socioeconomic status; 25(OH)D: 25-hydroxyvitamin D; AML: acute myelogenous leukemia; CLL: chronic lymphocytic leukemia; CNS: central nervous system; NHL, non-Hodgkin's lymphoma; UVB: ultraviolet-B.

(118). That order is used because the likelihood of finding effects of UVB or vitamin D is expected to increase with the annual number of cases. As seen in the table, only one observational study reported findings for cancers with fewer than 8,000 cases/y.

Evident from that Table is that 17 of the epithelial cancers have combinations of inverse correlations of incidence or progression/mortality with respect to indices of solar UVB and 25(OH)D concentration. In addition, seven of those 17 also have studies reporting significantly poorer survival rates for black Americans than white Americans. The findings are less robust for hematological cancers, with little support for protective effects against cancer incidence. However, some studies report inverse correlations between serum 25(OH)D concentration at time of diagnosis and progression or survival.

Hill's criteria for causality. Another way to assess causality is to apply A. Bradford Hill's criteria for causality in a biological system (127). The criteria appropriate for vitamin D include strength of association, consistency, temporality, biological gradient (dose–response relationship), plausibility

Table VI. *Assessing the UVB–vitamin D–cancer hypothesis by using Hill's criteria for causality in biological systems (127).*

Criterion	How satisfied
Strength of association	Significantly reduced risk at $p<0.05$ for 25(OH)D concentrations for several cancers.
Consistency	Ecological studies in several midlatitude countries as well as occupational study in Nordic countries report similar inverse correlations between solar UVB indices and cancer incidence or mortality rates. Meta-analyses review several studies for cancer risk with respect to 25(OH)D concentration for several cancers.
Temporality	Prospective and NCC studies look at results later than when 25(OH)D concentration was measured. CC studies also can satisfy the temporality criterion if the concentration is representative of the history.
Biological gradient	Significant inverse correlations between 25(OH)D concentration and cancer incidence, progression, or mortality have been found for several cancers.
Plausibility	Mechanisms have been found explaining how vitamin D reduces incidence, progression, and metastasis.
Experiment	Clinical trials arguably support vitamin D supplementation's role in reducing cancer risk by comparing trial results with model calculations based on the 25(OH)D concentration–breast cancer incidence relationship.
Analogy	Ecological and observational studies on UVB dose or exposure since sun exposure may have other cancer risk–reducing effects. Observational studies of cancer risk and outcomes related to 25(OH)D concentration may be related to solar UV exposure, not vitamin D.
Confounding factors	Most ecological and observational studies adjust the findings for other risk-modifying factors.

(*e.g.*, mechanisms), coherence with generally known facts, and experiment (*e.g.*, clinical trial). Later authors added two more criteria: account for confounding factors and eliminate bias (128). Not all criteria need be satisfied, but the more that are, the stronger the case for causality. Hill's criteria have been applied to cancer for cancer in general (129) and breast cancer (130). Because several years have passed since those two analyses, a brief update is worthwhile. Table VI summarizes how the criteria are satisfied.

The way forward. Because clinical trials are considered the "gold standard" for determining causality, it behooves the vitamin D community to perform clinical trials that are very likely to succeed. The authors of several recent papers suggest how that can be done (5, 114). In addition, the results of several large-scale vitamin D clinical trials should be available in the next year or two. Although they may not have been ideally designed, they should nonetheless report reduced risk for cancer, especially among the black Americans in the Vitamin D and OmegA-3 (VITAL) trial (131).

Another factor to consider is more widespread use of CC studies in which 25(OH)D concentrations are measured near time of cancer diagnosis along with taking a recent history of supplement intake, dietary sources including meat (35), and sun exposure. Controls should be matched as well as possible, including time of blood draw.

While awaiting conclusive results on the role of UVB exposure and vitamin D in the risk of cancer incidence, progression, and mortality, individuals should consider sensible sun exposure and vitamin D_3 supplementation to raise serum 25(OH)D concentrations to above 100-125 nmol/l. That concentration was associated with significantly reduced cancer incidence in a clinical trial in Nebraska (54). Men who raise serum 25(OH)D concentrations that high may want to limit calcium supplementation to 500 mg/d. As discussed in a recent paper, little reliable evidence indicates that 25(OH)D concentrations below 250 nmol/l are associated with adverse health outcomes, other than for prostate cancer, falls and fractures when given high-dose monthly or annual bolus vitamin D doses, and heart failure (140). In a recent study, supplementing heart failure patients with 4,000 IU/d of vitamin D_3 increased the need for mechanical circulatory support implants (132). Most other studies reporting J- or U-shaped 25(OH)D concentration–health outcome relationships did not obtain a vitamin D supplementation history of the participants, and most participants with high 25(OH)D concentrations (higher than expected from solar UVB exposure) were probably taking vitamin D supplements, many starting only recently, perhaps because of osteoporosis concerns.

Many other health benefits are associated with higher 25(OH)D concentrations, including reduced risk of autoimmune diseases (133), diabetes mellitus type 2 (134), adverse pregnancy and birth outcomes (135), respiratory tract infections (136), and all-cause mortality rate (137). Whether vitamin D reduces risk of cardiovascular disease is still uncertain based on support from observational studies but not clinical trials (138). Thus, raising 25(OH)D concentrations in an effort to reduce cancer risk will yield additional benefits. The optimal 25(OH)D concentration is certainly above 75 nmol/l and more likely 100-150 nmol/l. Reaching those concentrations could take 1,000-5,000 IU/d of vitamin D_3 or a moderate amount of sensible sun exposure. The only way to ensure reaching the desired concentration is to have serum 25(OH)D concentration measured (18, 19).

Conclusion

The UVB–vitamin D–cancer hypothesis has considerable supporting scientific evidence from a variety of study types: geographical ecological, observational, and laboratory studies of mechanisms, as well as several clinical trials. At this time, the general public and individual physicians can spend more reasonable time in the sun and use vitamin D_3 to prevent and treat many cancers. Hopefully soon, the clinical evidence will be strong enough that health care systems and agencies will endorse vitamin D_3 supplementation as a way to prevent and treat cancer.

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