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Review

Review of Recent Advances in Understanding the Role of Vitamin D in Reducing Cancer Risk: Breast, Colorectal, Prostate, and Overall Cancer

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Abstract. *This article is a narrative review of recent epidemiological findings regarding ultraviolet-B (UVB) dose or exposure, serum 25-hydroxyvitamin D [25(OH)D] concentrations, vitamin D supplementation, and genetic variations in 25(OH)D concentration for incidence, survival, and mortality rates of overall and breast, colorectal, and prostate cancer. According to ecological studies, solar UVB doses are inversely correlated with incidence/mortality rates for about 20 cancer types. Observational studies support a role of higher 25(OH)D concentrations in reducing risk of breast and colorectal cancer incidence and mortality rates but, for prostate cancer, in increasing incidence rates while reducing mortality rates. Mendelian randomization studies offer little support for vitamin D in reducing cancer risk. Their primary limitation is that they only investigate small variations in genetically predicted 25(OH)D concentration near the population mean value. The secondary analyses from the VITAL clinical trial indicated significant reductions from 2000 IU/d of vitamin D_3 supplementation in all-cancer incidence and mortality rates for selected subgroups. Thus, Hill's criteria for causality in a biological system are now largely satisfied for supporting the claim that vitamin D reduces the risk of cancer incidence and death.*

The ultraviolet-B (UVB)–vitamin D–cancer hypothesis was proposed approximately 40 years ago (1). As of August 25, 2019, 25,105 publications were listed at PubMed.gov with "cancer" and "vitamin D" or "vitamin D_3" or "25-hydroxyvitamin D" or "25-hydroxyvitamin D_3" in the title or abstract. Thus, one might expect that the hypothesis would be widely accepted and included in clinical practice. Unfortunately, that is not the case.

Researchers use several types of evidence to examine the role of UVB irradiance and vitamin D in the risk of cancer incidence, progression, and mortality. The types of evidence include geographical ecological studies; observational studies related to UVB radiation, oral vitamin D intake, and serum 25-hydroxyvitamin D [25(OH)D] concentrations; randomized controlled trials (RCTs) of vitamin D supplementation; studies of genetic allele polymorphisms affecting 25(OH)D concentrations; and mechanisms. Each type has strengths and limitations. Thus, all types of studies should be considered when assessing how UVB exposure and vitamin D affect cancer risk.

This article is a narrative review of the evidence supporting the hypothesis, with suggestions on how the evidence can be strengthened.

A literature search was conducted at https://www.ncbi.nlm.nih.gov/pubmed/ and https://scholar.google.com/ by using search terms "cancer", "ultraviolet", "vitamin D", "25-hydroxyvitamin D", "ecological", "case–control", "breast", "colorectal", "prostate", and "Mendelian randomization".

Ecological Studies

Ecological studies treat populations in geographically defined regions as entities and use statistical methods to compare disease outcomes averaged for each region, with risk-modifying factors also averaged for each region. For cancer, incidence or mortality rates are compared with indices for vitamin D production that can be annual solar radiation dose (1), summertime UVB dose (2, 3), or latitude in countries with flat terrain (4). Because many factors affect cancer risk, values for other risk-modifying factors should

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also be used. An ecological study of cancer mortality rates for White people in the United States included indices for alcohol consumption, Hispanic heritage, socioeconomic status (poverty), smoking (lung cancer mortality rates), and urban/rural residence (3). Lung cancer mortality rates integrate decades of the adverse effects of smoking and so are better indices than recent smoking rates. However, they also are affected by diet, with meat consumption an important risk factor (5). Ecological studies are best performed in single midlatitude countries with large UVB dose gradients as well as relatively homogeneous populations or data for the various ethnic groups. A summary of single-country ecological studies of UVB and cancer mortality rates is presented in (6). Lower UVB dose has been linked to about 20 cancers. Unfortunately, ecological studies of cancer risk are becoming much harder to conduct because of rising rates of obesity, reduced UVB exposure owing to concerns about skin cancer and melanoma, and improved cancer treatment. For example, U.S. breast cancer mortality rates have shown little geographic variation since the 1990s (7).

It was noted that prostate cancer mortality rates have a different geographical distribution in the United States than most types of cancer for which UVB exposure is associated with reduced risk. Prostate cancer rates are highest in the northwest and lowest in the southeast (8). After Tuohimaa *et al*. reported a U-shaped relationship between baseline 25(OH)D concentration and prostate cancer incidence (9), I pointed that difference out and suggested it supported their finding (10). More recently, a study in Australia reported that high sun exposure was associated with increased prostate cancer incidence (11). The reason for the increased risk will be discussed here later.

Breast cancer mortality rates exhibited geographic variations with respect to U.S. solar UVB doses for 1950-69 and 1970-94 in a manner similar to that for colon and rectal cancer (2, 3, 8). However, breast and rectal cancer mortality rates for white males and females near the West Coast were slightly higher in California and Nevada than for most other western states, which was not the case for colon cancer for White males and females. Breast and rectal cancer protection may require higher 25(OH)D concentration than colon cancer.

Prospective Observational Studies of Cancer Incidence Related to Serum 25(OH)D Concentration

The more common approach to testing the UVB–vitamin D–cancer hypothesis is to enroll people in a cohort study; measure various parameters, including serum 25(OH)D concentration; and monitor participants for several years. Such prospective studies strongly support the role of vitamin D in reducing risk of colorectal and lung cancer (Table I). However, they offer little support for vitamin D's role in reducing risk of breast cancer (Table II). The reasons for the difference are that 25(OH)D concentrations vary with time and that breast cancer can develop rapidly. Mammography is recommended every 1-2 years, in contrast to sigmoidoscopy or colonoscopy for colorectal cancer screening, which is recommended every 10 years. A review of the well-documented seasonal variation of breast cancer incidence (higher in spring and fall) suggested that vitamin D protected against breast cancer in summer and that melatonin did so in winter (12). The longer the follow-up time, the lower the odds ratio of cancer *versus* 25(OH)D concentration that will be found for breast and colorectal cancer (13) and for all-cause mortality rate (14).

On the basis of the shortcomings of prospective studies for 25(OH)D and breast cancer, it was proposed that case–control studies of 25(OH)D concentration near time of diagnosis be used to evaluate the role of vitamin D in reducing breast cancer risk (22). When findings of breast cancer odds ratio *versus* 25(OH)D concentration from 11 studies from seven countries are plotted over each other, the data points overlap well and show a power-law fit (13, 16). The results agree well with those from an observational study using pooled data from two vitamin D clinical trials and one open-label observational study in which serum 25(OH)D concentration was measured every 6 months (21).

The use of case–control studies to evaluate the role of vitamin D in reducing cancer risk has been criticized on the basis that having cancer may affect the serum 25(OH)D concentration. A study involving children aged 2-35 months living in Nepal reported that 25(OH)D concentration during the acute phase of pneumonia and after recovery did not change significantly, remaining near 32 ng/ml (23). A study of 374 breast cancer patients in Korea indicated that median serum 25(OH)D concentration changed from 12.9 to 10.5 ng/ml after neoadjuvant chemotherapy (24). Other studies cited in that article did not report significant changes in 25(OH)D with neoadjuvant chemotherapy with pathologic complete response. More importantly, in a study of newly diagnosed patients with colorectal cancer in the San Francisco Bay Area with a median 25(OH)D concentration of 27.0 ng/ml at baseline, researchers found that for patients who did not receive vitamin D supplementation during chemotherapy, the median change from baseline to 6 months was –0.7 ng/ml (–19.4 to 51.7) for the 58 patients treated with chemotherapy and 1.6 ng/ml (–6.4 to 33.2) for the 19 patients who did not receive chemotherapy (25). Thus, the assumption that undiagnosed cancer affects serum 25(OH)D concentration seems invalid which supports the use of case–control studies in determining the 25(OH)D concentration–cancer incidence relationship for cancer.

Table I. *Cancer incidence related to serum 25-hydroxyvitamin D [25(OH)D] concentration according to meta-analyses.*

Cancer type	Number of studies	Conditions	Number of participants	25(OH)D (ng/ml)	RR (95% CI)	Reference
Breast	24	Prospective	31,867	High *vs.* low	0.92 (0.83-1.02)	15
Breast	11	Case-control studies		<10 *vs.* >40	~5.4 (±4.4)	13, 16
Breast	29	Case-control studies		High *vs.* low	0.66 (0.57-0.76)	17
	14	Cohort studies		High *vs.* low	0.92 (0.83-1.01)	17
Colorectal	17	<2 Years of follow-up	949	Per 10	0.82 (0.67-1.00)	18
		≥2-5 Years of follow-up	1,493		0.78 (0.69-0.89)	
		>5 Years of follow-up	3,077		0.90 (0.81-0.99)	
		US	3,016		0.84 (0.79-0.90)	
		Outside US	2,690		0.91 (0.81-1.01)	
		BMI <25 kg/m^2	2,310		0.83 (0.77-0.90)	
		BMI >25 kg/m^2	3,293		0.89 (0.82-0.96)	
		Low physical activity	1,472		0.89 (0.80-0.99)	
		High physical activity	1,318		0.81 (0.73-0.90)	
Prostate	19	Prospective		High *vs.* low	1.15 (1.06-1.24)	19
				Per 10	1.04 (1.02-1.06)	19

CI: Confidence interval; BMI: body mass index; RR: risk ratio.

Pooled Analysis from Vitamin D Supplementation Studies

Two articles reported pooled analyses of cancer incidence for women taking vitamin D supplements either in RCTs (21, 26) or voluntarily. In the first of those studies, involving 2,304 women, the hazard ratio (HR) for all-cancer incidence for >40 *versus* <20 ng/ml was 0.33 [95% confidence interval (CI)=0.12-0.90] (27). In the second study, involving 5,038 women, the rate ratio for breast cancer for those with >60 *versus* <20 ng/ml was 0.18 (p=0.02) (21).

On the basis of those studies, the serum 25(OH)D concentration for cancer prevention and treatment should be at least 40 ng/ml. Few adverse effects occur for 25(OH)D concentrations below 100 ng/ml. The observational studies that suggested adverse effects for 25(OH)D concentrations above about 60 ng/ml were largely determined to have enrolled some people who had begun vitamin D supplementation only shortly before entering the study and thus were put in the wrong 25(OH)D category (28). A recent study of high-dose vitamin D supplementation showed that higher vitamin D doses, up to 10,000 IU/d, reduced bone mass density slightly over a 3-year period but not bone strength at either the radius or tibia (29).

Observational Studies of Cancer Survival or Mortality Rates

A growing number of studies have examined survival or mortality rates *versus* 25(OH)D concentration for people with cancer. Such studies usually measure serum 25(OH)D concentration near the time of diagnosis and then monitor individuals for many years, looking at cancer-specific and overall survival or death rates. Inverse correlations between 25(OH)D concentration and cancer-specific survival have been found for several cancer types (see Tables III and IV).

RCTs of Cancer Incidence

RCTs are generally considered the strongest evidence regarding the efficacy and safety of a medical agent or procedure. However, vitamin D is a nutrient rather than a drug. Most vitamin D RCTs have been based on the guidelines for pharmaceutical drugs. The two basic assumptions for such trials are that the trial is the only source of the agent and that a linear dose–response relationship exists. Neither assumption is satisfied for vitamin D. Robert Heaney was the first to point out that RCTs for nutrients should be conducted differently for nutrients than for drugs (35). The most important consideration for vitamin D is that trials be based on 25(OH)D concentrations, not vitamin D dose, because all outcomes are related to 25(OH)D concentrations directly and vitamin D intake indirectly. The recommendations regarding vitamin D were recently extended: start with an understanding of the 25(OH)D concentration–health outcome relationship; measure baseline 25(OH)D concentrations and try to enroll those with values near the low end of the relationship; supplement with enough vitamin D_3 to increase 25(OH)D concentrations to where the relationship no longer increases; measure achieved 25(OH)D concentration one or more times during the trial; base outcomes on 25(OH)D concentrations, not vitamin D_3 dose (36). So many vitamin D RCTs have failed – not just for cancer but for many other health outcomes – because the

Table II. *Breast cancer incidence on the basis of 25-hydroxyvitamin D [25(OH)D] concentration from single prospective studies.*

Cohort	Follow-up period (years)	Conditions	Cases/controls, n	25(OH)D (ng/ml)	RR (95% CI)*	Reference
Nurses' Health Study	Up to 10	Winter blood draw	712/703	>32.7 *vs.* <17.5	1.10 (0.75-1.60)	20
		Summer blood draw	783/799	>32.7 vs.<17.5	0.66 (0.46-0.94)	20
Lappe RCTs, Grassroots Health	Median 4.0		77/4961	>60 *vs.* <20	0.29 (0.05-0.82), p=0.03	21

CI: Confidence interval; ca/co: cases/controls; EPIC: European Prospective Investigation into Cancer and Nutrition; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation. *Multivariate adjusted.

Table III. *Survival after diagnosis of breast cancer with respect to serum 25-hydroxyvitamin D [25(OH)D] concentrations from a single prospective study (follow-up period of 8 years) (30).*

Conditions	Cases/total, n	25(OH)D (ng/ml)	Cancer-specific survival	Overall survival
All participants, fully adjusted	88/1045	>25.1 *vs.* <16.8	RR=0.85 (95% CI=0.55-1.33), p_{trend}=0.53	
Fully adjusted	176/1045	>25.1 *vs.* <16.8		RR=0.72 (95% CI=0.54-0.98), p_{trend}=0.03
Premenopausal		>25.1 *vs.* <16.8	HR=0.37 (95% CI=0.15-0.93)	HR=0.45 (95% CI=0.21-0.96)

CI: Confidence interval; HR: hazard ratio; RR: risk ratio.

participants had relatively high baseline 25(OH)D concentrations and the vitamin D dose was too low to produce much change in health outcome.

Recently, the results of the VITamin D and OmegA-3 TriaL (VITAL) for cancer were published (37). Participants in the treatment arm were given 2,000 IU/d of vitamin D_3 for a mean period of 5.3 years. Based on intention to treat the entire group, the HR for cancer incidence was 0.96 (95% CI=0.88-1.06) and for cancer death, 0.83 (95% CI=0.67-1.02). However, in the secondary analyses, several significant reductions in cancer were apparent: For participants with body mass index (BMI) <25 kg/m^2, HR=0.76 (95% CI=0.63-0.90); for Black people, HR=0.77 (95% CI=0.50-1.01); for cancer death, omitting the first year of data, HR=0.79 (95% CI=0.63-0.99). The trial had some limitations: The mean baseline 25(OH)D concentration for those who provided measurements was 31 ng/ml. The vitamin D dose was limited to 2000 IU/d. All participants were permitted to take 600-800 IU/d of vitamin D, and compliance was not 100%. Given those limitations and strengths, the secondary analyses provide strong evidence that vitamin D reduces risk of both cancer incidence and death. A letter to the editor pointed out that the secondary analyses from that RCT as well as one on progression from prediabetes to diabetes mellitus should be accepted as demonstrating beneficial effects of vitamin D supplementation (38). The response letter did not disagree, but it pointed out that neither article gave any guidance on the matter (39). Secondary analyses may often be ignored because if results from enough subgroups are analyzed, some analyses are likely to report significant results. Here, both BMI and Black ethnicity are well known to affect serum 25(OH)D concentrations.

Mendelian Randomization (MR) Studies

MR studies look at several alleles of genes that affect serum 25(OH)D concentrations to genetically predict concentrations in participants with or without the health outcome of interest. The genes of interest may include *CYP24A1, CG, DHCR7*, and *CPY2R1*. The alleles examined for those genes may affect 25(OH)D concentrations by about 1 ng/ml each (40). Because variations in alleles only affect the total 25(OH)D concentration by a small amount, many participants are generally used, up to 100,000 or more. Although in principle MR studies should provide reliable evidence regarding whether 25(OH)D concentration is causally linked to reduced risk of cancer, such findings have been reported only for all-cancer mortality rate (41) and ovarian cancer incidence (40). An MR analysis using data from the UK Biobank for 438,870 White participants aged 36-73 years, including 46,155 cancer cases and 6998 cancer deaths, did not show a significant correlation between the predicted 25(OH)D concentration based on using five 25(OH)D genetic markers and either cancer incidence or mortality rate (42). However, for 76 MR studies of cancer risk through October 31, 2017, a few

Table IV. *Survival after cancer diagnosis related to 25-hydroxyvitamin D [25(OH)D] concentration from meta-analyses.*

Cancer type	Cases/total, n*	25(OH)D (ng/ml)	Cancer-specific survival, RR (95% CI)	Overall survival, RR (95% CI)	Reference
Breast	194/2,636	High *vs.* low	0.57 (0.38-0.84)		31
	622/4,413			0.62 (0.49-0.78)	
Breast	1,024/9,984	High *vs.* low	Not given	0.67 (0.56-0.79)	32
Colorectal	1,594/6,366	High *vs.* low	0.67 (0.57-0.78)		33
	2,330/10,718	High *vs.* low		0.68 (0.55-0.78)	
Prostate	No data/7,808	Per 8 ng/ml	0.91 (0.87-0.97), p=0.02	0.91 (0.84-0.98), p=0.01	34

*Total: Which is more than in the low and high quantiles; CI: confidence interval; RR: risk ratio.

reported alcohol consumption, BMI, height, telomere length, and hormonal exposures as factors likely to contribute to cancer causation (43).

A major problem with MR studies is that genetic variations in 25(OH)D concentration are with respect to population mean concentrations. One recent study reported that a genetic risk score, derived using five single-nucleotide polymorphisms of vitamin D status, was associated with circulating 25(OH)D (mean±standard deviation=27±10 ng/ml; 23±17 ng/ml in the lowest *versus* 30±11 ng/ml in the highest quintile of genetic risk score) (44). Another article regarding breast and prostate cancer that failed to show a significant correlation between genetically determined variations in breast and prostate cancer with respect to 25(OH)D concentration admitted that nonlinear effects of vitamin D could not be excluded (45). As shown for breast cancer, risk changes more rapidly below 20 ng/ml than above 20 ng/ml (16). A recent article on the MR study stated (46): "Furthermore, the relationship between the 25(OH)D level and the risk of diseases may be nonlinear. As shown by previous studies, vitamin D supplementation only shows treatment effects among individuals with baseline 25(OH)D levels of no more than (12 ng/ml). When all participants were analysed irrespective of their baseline 25(OH)D levels, there was no treatment effect. Thus, the effect of 25(OH)D on health outcomes may differ by baseline serum 25(OH)D level. Considering the potential divergent 25(OH)D levels of the UK population, it is possible that we missed the true association between 25(OH)D levels and diseases among individuals of certain 25(OH)D levels".

Another MR study published around the same time supported that statement. For the Copenhagen data sets, the HR for a 10-ng/ml increase in the MR genetically determined 25(OH)D concentration and cancer mortality rate was 0.97 (95% CI=0.94-1.10; p=0.06), whereas the HR for 10 ng/ml of serum 25(OH)D concentration was 0.93 (95% CI=0.88-0.98) (47). However, the HRs for 25(OH)D quartiles 1-4 were 1.00, 0.86 (95% CI=0.78-0.94), 0.87 (95% CI=0.78-0.96), and 0.79 (95% CI=0.71-0.89), respectively (p_{trend}=9.7×10^{-5}). Thus, MR studies should not be relied on to determine whether the role of vitamin D in cancer is causal.

Mechanisms

The mechanisms whereby vitamin D reduces risk of cancer incidence, progression, and metastasis are well known. What is known about these mechanisms is not reviewed here but several reviews on the topic are available (6, 48-52).

Prostate Cancer

A higher serum 25(OH)D concentration is associated with increased risk of prostate cancer incidence (19). High solar UVB exposure is also linked to increased risk of prostate cancer incidence (11) and mortality (53). The U.S. geographical variation of prostate cancer mortality rate is different from that for most vitamin D-sensitive cancer types such as breast and colonic (8). That distribution was hypothesized to support the U-shaped 25(OH)D relationship for prostate cancer incidence (10) first reported by Tuohimaa *et al.* (9). In my opinion, the reason for increased risk of prostate cancer for higher 25(OH)D concentrations and UVB exposure is that vitamin D increases absorption of dietary calcium, and calcium is a risk factor for prostate cancer (54). A recent study reported that calcium intake was a significant risk factor for aggressive prostate cancer for African Americans (55). A preclinical study in France demonstrated that a diet high in calcium dose-dependently accelerated the progression of early-stage prostate tumors and that dietary vitamin D prevented this effect (56).

Vitamin D Treatment of Patients With Cancer

Because higher solar UVB doses and 25(OH)D concentrations are generally associated with better cancer survival rates and lower cancer mortality rates, one could expect that vitamin D supplementation would reduce risk of

Table V. *Update on "Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps, and Challenges" (63).*

Problem	Current understanding	Reference
Link between 25(OH)D and breast cancer is complex and not resolved.	Because breast cancer can develop rapidly, case–control studies provide better information than do prospective studies.	13
25(OH)D concentration has both positive and negative relationships with prostate cancer.	Increased calcium absorption seems to explain the reason for the direct correlation between 25(OH)D and prostate cancer incidence.	55
Observational studies of incidence of several other cancers do not show reduced incidence with higher 25(OH)D.	Because ecological studies in single midlatitude countries report similar inverse correlations between solar UVB doses and cancer incidence, and because most types of cancer are epithelial, the most likely explanation is that observational studies were affected by changes in serum 25(OH)D with long follow-up times.	22, 13
Supplementation trials have not supported the role of vitamin D in reducing cancer risk.	The VITAL study showed that 2000 IU/d of vitamin D_3 can reduce cancer incidence and death for selected subpopulations.	37, 38
	Pooled results from studies including women taking vitamin D_3 supplements have shown that raising 25(OH)D to above 60 ng/ml significantly reduces risk of all-cancer and breast cancer incidence rates.	21, 27
Mendelian randomization studies do not support a role of vitamin D in reducing cancer risk.	Mendelian randomization studies are sensitive to small 25(OH)D variations near the mean of the population studied. They are not sensitive to low and high concentrations, as in observational studies.	47
Of the relatively few investigations of vitamin D biochemical status and cancer risk in Black populations, most have been retrospective case–control analyses, making their interpretation challenging because of issues related to reverse causality.	As discussed here, reverse causality is an assumption not proven to apply to case–control analyses regarding 25(OH)D concentration and cancer incidence.	

cancer death. That appears to be the case. A study in Ireland reported that for 5,417 women aged 50-80 years diagnosed with breast cancer during 2001-2011 and monitored for up to 11 years, the 2,581 who started taking vitamin D supplements after breast cancer diagnosis had a 20% reduced risk of cancer-specific mortality (HR=0.80, 95% CI=0.64-0.99; p=0.048) (57). For those who started taking vitamin D supplements within 6 months of diagnosis, the reduction increased to 49% (HR=0.51, 95% CI=0.34-0.74; p<0.001).

A meta-analysis of 12 RCTs with 428 cancer deaths out of 22,793 participants in the vitamin D treatment arms and 511 cancer deaths out of 22,785 controls reported the risk ratio for death in the treatment arm of 0.84 (95% CI=0.74-0.95) (58).

Hill's Criteria for Causality

A. Bradford Hill outlined the criteria for causality in a biological system in his 1965 address to the British Medical Society (59). The criteria applicable to vitamin D and cancer include strength of association, consistency of observations, temporality (exposure must precede outcome), biological gradient, plausibility, coherence with known facts, experiment (*e.g.* RCT), and analogy. Later, "other scientific considerations include study designs, statistical tests, bias, confounding, and measurement issues" were added (60). Two articles reviewed the evidence for causality for UVB exposure/vitamin D and reduced risk of cancer on the basis of the original Hill criteria (61, 62). Both concluded that all relevant criteria were satisfied except perhaps experimental verification. That criterion has now been satisfied with the secondary analyses of results of the VITAL study (37, 38) as well as the open-label vitamin D studies of all-cancer (27) and breast cancer (21) incidence, for which the higher 25(OH)D concentrations were largely the result of vitamin D supplementation. In addition, support for the other criteria have been strengthened on the basis of more recent studies, such as those discussed here.

An article was published in 2017 with the title "Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps, and Challenges" (63). The problems those authors identified together with newer information are summarized in Table V. Better understandings now exist, based on articles they overlooked or that were published later.

Summary and Conclusion

This review describes results from ecological studies of UVB dose and cancer risk, observational studies of 25(OH)D concentrations and UVB exposure and cancer risk, open-label vitamin D supplementation studies of cancer risk, observational studies of survival after cancer with respect to baseline 25(OH)D concentrations, RCTs of vitamin D

supplementation and cancer risk, MR studies, and vitamin D treatment of cancer. Overall, UVB exposure and higher 25(OH)D concentrations are associated with reduced risk of cancer incidence and mortality, with few exceptions. Although RCTs are generally regarded in medical circles as being required to prove effectiveness and lack of important adverse effects for any treatment, RCTs with vitamin D are difficult to conduct, and most have been poorly designed and carried out. Nonetheless, the VITAL study reported significantly reduced risk of all-cancer incidence and mortality rates in secondary analyses. Scientifically, Hill's criteria for causality in a biological system are more appropriate, and two analyses using Hill's criteria published before the VITAL study results reported that those criteria were largely satisfied. This article also showed why MR studies are inappropriate for examining the causal role of vitamin D in reducing cancer risk. On the basis of those findings, medical practice should embrace and public health advice should encourage use of vitamin D to reduce cancer risk and increase survival rates after diagnosis.

Conflicts of Interest

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