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Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps, and Challenges

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There has been substantial enthusiasm recently regarding the potential role of vitamin D in the primary and secondary prevention of cancer. Laboratory studies demonstrate a range of anticarcinogenic effects for vitamin D compounds, but human studies have yielded little consistent evidence supporting a protective association. Higher circulating levels of vitamin D (i.e., 25-hydroxyvitamin D or 25(OH)D) appear to be associated with reduced risk of colorectal and bladder malignancies, but higher risk of prostate and possibly pancreatic cancers, with no clear association for most other organ sites examined. Despite there being no official institutional recommendations regarding the use of vitamin D supplements for cancer prevention, screenings for vitamin D deficiency and vitamin D supplement use have increased substantially over the past decade. These widespread practices demonstrate that population sociobehavioral changes are often adopted before scientifically well-informed policies and recommendations are available. This review critically examines the currently available epidemiologic literature regarding the associations between circulating 25(OH)D, vitamin D supplementation, and vitamin D-related genetic variation and cancer risk and mortality, with a particular emphasis on prospective studies. We identify several important gaps in our scientific knowledge that should be addressed in order to provide sufficient reproducible data to inform evidence-based recommendations related to optimal 25(OH)D concentrations (and any role for vitamin D supplementation) for the primary and secondary prevention of cancer. With few exceptions, such recommendations cannot be made at this time.

genetics; incidence; mortality; neoplasms; prospective studies; vitamin D

Abbreviations: CI, confidence interval; *CYP2R1*, cytochrome P450 family 2 subfamily R member 1 gene; *CYP24A1*, cytochrome P450 family 24 subfamily A member 1 gene; *DHCR7*, 7-dehydrocholesterol reductase gene; *GC*, group-specific component gene; HR, hazard ratio; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; RR, relative risk; *RXRA*, retinoid X receptor α gene; SNP, single nucleotide polymorphism; USPSTF, US Preventive Services Task Force; *VDR*, vitamin D receptor gene.

INTRODUCTION

In recent years, there has been a great deal of enthusiasm regarding the potential role of vitamin D in the primary and secondary prevention of cancer. Vitamin D is an unusual micronutrient in that its bioavailability derives from not only diet and supplement use but also biosynthesis in the skin in response to exposure to solar ultraviolet B radiation. Based on the latter, early ecological studies were conducted that suggested that low vitamin D status explained the elevated rates of some cancers in populations living at higher latitudes (1). The primary circulating form of vitamin D is 25-hydroxyvitamin D (25(OH)D), which is considered the best indicator of an individual's vitamin D status in that it integrates vitamin D from all sources (2). 25(OH)D is converted to the hormonally active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), by 1α-hydroxylase (2, 3) in the kidney and other organs that express the enzyme. It is thought that this locally available $1,25(OH)_2D$ is the basis of vitamin D preventive effects for multiple cancers (2, 4). Vitamin D has a well-established role in calcium homeostasis and bone health, but laboratory studies have demonstrated that $1,25(OH)_2D$ also has many canonically anticarcinogenic actions, including antiinflammation, antiangiogenesis, and proapoptosis (2, 4). Despite such substantial experimental evidence, human studies of vitamin D and cancer have yielded little consistent evidence of a protective

association, and there are no formal (i.e., institutional) recommendations for vitamin D supplementation for cancer prevention (5). Nonetheless, screening for vitamin D deficiency and vitamin D supplement use has increased dramatically since the early 2000s.

In this article, we review the literature regarding vitamin D and cancer risk and mortality, the current recommendations regarding vitamin D status and supplementation, and the research gaps and inconsistencies that need to be addressed. Studies of circulating 25(OH)D, vitamin D-related genetic variation, and clinical trials of vitamin D supplementation are examined because, as discussed above, 25(OH)D is the best summary measure of vitamin D status, and vitamin D supplementation could be implemented for primary or secondary prevention of cancer if clear protective associations warranted. Because several factors related to a healthy lifestyle (i.e., body mass index, physical activity, smoking, diet, and use of other supplements) have been correlated with circulating 25(OH)D (6), we present the most fully adjusted risk estimates available from each study. Moreover, given that studies differ with respect to the directionality of the reported vitamin D comparisons (i.e., either lower or higher categories used as referent), we present here risks for higher versus lower vitamin D status. Throughout the review and tables, studies making this comparison have their original 95% confidence intervals presented, whereas those requiring recalculation of reciprocal risk estimates do not have the confidence intervals reported here. In addition, some studies reported units of 25 (OH)D in ng/mL while others reported in nmol/L; we have converted all studies to nmol/L for ease of comparison.

VITAMIN D AND CANCER RISK

Table 1 summarizes findings regarding the associations between cancer risk and blood concentrations of 25(OH)D, vitamin D supplementation trials, and vitamin D-related genetic variation.

Blood concentrations of 25(OH)D

Colorectum. Perhaps the strongest consensus for an inverse association between 25(OH)D and cancer risk exists for colorectal cancer. Four meta-analyses published in 2011 concluded that higher serum/plasma levels of 25(OH)D are associated with lower risk of both colon and rectal cancer (7–10) (Table 1). They each included the same 9 prospective studies, with the exception of the analysis of Lee et al. (8) that also included their own original data. Ma et al. (9) reported inverse summary associations for overall colorectal cancer, as well as by anatomical subsite comparing the highest with the lowest quantile of each study. With the addition of their original data, Lee et al. (8) found that the association was inverse for both colon and rectal cancer, but being somewhat stronger for rectal cancer. Inverse associations of similar magnitudes were shown by Touvier et al. (10) for colon and rectal cancer per 100-IU/L increase in circulating 25(OH)D, whereas Gandini et al. (7) reported a similar inverse association for colorectal cancer per 25-nmol/L increase in circulating 25(OH)D but did not examine colon and rectal cancer separately. Two subsequent individual studies also found inverse colorectal cancer associations (11, 12), and 1 other study suggested an increased risk with a higher level of vitamin D for colon cancer (13).

Breast. Studies of circulating 25(OH)D and risk of breast cancer have been far less consistent compared with colorectal cancer (Table 1). A recent review of 8 studies by Shao et al. (14) concluded that higher circulating concentrations of 25(OH)D were associated with a lower risk of breast cancer incidence. Whether blood samples were collected before or after cancer diagnosis in the studies was not taken into consideration, however (14). Two meta-analyses that pooled retrospective and prospective studies separately found that the inverse association with breast cancer was restricted to the retrospective studies, with a null association for the prospective studies (7, 15). Yin et al. (15) reported an inverse association for 5 retrospective studies and no association for 4 prospective studies; Gandini et al. (7) had similar findings. These analyses highlight the importance of prospective analyses with blood collected years in advance of diagnosis and treatment, and they suggest that the earlier, retrospective studies may have been subject to biases, particularly reverse causality.

Three more recent meta-analyses focused solely on prospective studies of 25(OH)D and breast cancer risk and showed some associations in specific population subgroups. Kim and Je (16) included 14 studies in their meta-analysis and reported no association comparing the highest and lowest categories of circulating 25(OH)D. Meanwhile, Bauer et al. (17) conducted a dose-response meta-analysis and found a nonlinear inverse association among postmenopausal women only. The meta-analysis of Wang et al. (18) included 14 studies and found an inverse association particularly in studies of postmenopausal women and those conducted in North America. Of 2 subsequent prospective studies, 1 conducted in a multiethnic population of postmenopausal women showed an inverse association among white women but no other racial group (19), and the other reported no association (menopausal status was not considered) (20). These findings suggest that the relationship between 25(OH)D and risk of breast cancer is complex and may differ by menopausal status and possibly race.

Prostate. Prostate cancer is 1 malignancy for which the cumulative evidence points to a positive (i.e., harmful) association with vitamin D status (Table 1). A recent meta-analysis of 21 studies concluded that men with elevated serum levels of 25(OH)D had a higher risk of developing cancer of the prostate than did men with lower serum levels of 25(OH)D (21). Sixteen of the 21 studies showed positive associations, and the finding was similar when restricted to the prospectively conducted studies (odds ratio (OR) = 1.17, 95% confidence interval (CI): 1.08, 1.27) or to studies conducted in the United States and Europe (OR = 1.15, 95% CI: 1.03, 1.29; OR = 1.21, 95% CI: 1.04, 1.40, respectively). The analysis did not consider disease aggressiveness, however, and 2 more recent studies suggest that the association does differ by aggressiveness, 1 reporting a possible U-shaped relation with plasma 25(OH)D that was stronger for high-grade disease (22) and the other indicating that higher levels of 25(OH)D might be associated with an increased risk of low-grade, but a decreased risk of high-grade, disease (23).

Table 1. Vitamin D and Cancer Risk

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI
		Circulating 25(OH)D			
Colorectal					
Lee, 2011 (8)	Meta-analysis	10 studies	Highest vs. lowest quantile		
	Prospective only		Colorectal	0.66	0.54, 0.81
			Colon	0.77	0.56, 1.07
			Rectum	0.50	0.28, 0.88
Gandini, 2011 (7)	Meta-analysis, retrospective ($n = 1$), and prospective	9 studies	Per 25-nmol/L increase (colorectal)	0.85	0.79, 0.91
Ma, 2011 (9)	Meta-analysis	9 studies	Highest vs. lowest quantile		
	Prospective only		Colorectal	0.67	0.54, 0.80
			Colon	0.62	0.46, 0.81
			Rectum	0.61	0.43, 0.79
Touvier, 2011 (10)	Meta-analysis, prospective only	9 studies	Per-100 IU/L increase		
			Colorectal	0.96	0.94, 0.97
			Colon	0.95	0.92, 1.00
			Rectum	0.95	0.86, 1.05
Weinstein, 2011 (13)	Nested case-control		≥75 vs. 50 to <75 nmol/L		
		239 colon	Colon	1.44	0.49, 4.26
		192 rectal	Rectum	0.76	0.28, 2.07
Chandler, 2015 (11)	Nested case-control	274 colorectal	Quartile 4 vs. quartile 1 (colorectal)	0.45	0.25, 0.81
Weinstein, 2015 (12)	Nested case-control	476 colorectal	Quintile 5 vs. quintile 1 (colorectal)	0.60	0.38, 0.94
Breast					
Yin, 2010 (15)	Meta-analysis, retrospective ($n = 5$), and prospective	9 studies	Per 50-nmol/L increase		
			Overall	0.73	0.60, 0.88
			Retrospective	0.59	0.48, 0.73
			Prospective	0.92	0.82, 1.04
Gandini, 2011 (7)	Meta-analysis, retrospective ($n = 5$), and prospective	10 studies	Per 25-nmol/L increase		
			Overall	0.89	0.81, 0.98
			Prospective	0.99	0.95, 1.03
Shao, 2012 (14)	Meta-analysis, retrospective ($n = 4$), and prospective	8 studies	Highest vs. lowest quantile (overall)	0.55	0.38, 0.80
Bauer, 2013 (17)	Meta-analysis, prospective only	9 studies	Per 12.5-nmol/L increase		
			Premenopausal	0.99	0.97, 1.04
			Postmenopausal		
			<67 nmol/L	1.01	0.98, 1.04
			67–85 nmol/L	0.88	0.79, 1.97
			>85 nmol/L	1.03	0.94, 1.12
Wang, 2013 (18)	Meta-analysis, prospective only	14 studies	Highest vs. lowest quantile (overall)	0.84	0.75, 0.95
Kim, 2014 (16)	Meta-analysis, prospective only	14 studies	Highest vs. lowest quantile (overall)	0.92	0.83, 1.02
Kim, 2014 (19)	Nested case-control	707	Per 50-nmol/L increase (white women)	0.43	0.23, 0.80
Skaaby, 2014 (20)	Cohort	159	Per 10 nmol/L increase (overall)	1.02	0.96, 1.09
Prostate					
Xu, 2014 (21)	Meta-analysis, retrospective ($n = 1$), and prospective	21 studies	Highest vs. lowest quantile		
			Overall	1.17	1.05, 1.30
			Prospective	1.17	1.08, 1.27

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI
Schenk, 2014 (23)	Nested case-control	1,695	Quartile 4 vs. quartile 1		
			Overall	1.10	0.90, 1.35
			Gleason 2–6 score	1.21	0.97, 1.52
			Gleason 7 score	1.09	0.78, 1.52
			Gleason 8–10 score	0.55	0.32, 0.94
Kristal, 2014 (22)	Nested case-cohort	1,731	Gleason ≥7 vs. quintile 1		
			Quintile 2	0.63	0.45, 0.90
			Quintile 3	0.66	0.47, 0.92
			Quintile 4	0.79	0.56, 1.10
			Quintile 5	0.88	0.63, 1.22
Bladder					
Zhang, 2015 (24)	Meta-analysis, retrospective ($n = 3$), and prospective	7 studies	Highest vs. lowest quantile	0.75[c,d]	
Zhao, 2016 (25)	Meta-analysis, retrospective ($n = 3$), and prospective	7 studies	>75 vs. <25 nmol/L	0.68	0.49, 0.86
Lung					
Zhang, 2015 (27)	Meta-analysis, prospective only	9 studies	Highest vs. lowest quantile	0.83	0.77, 0.90
Chen, 2015 (26)	Meta-analysis, retrospective ($n = 3$), and prospective	13 studies	Per 10-nmol/L increase	0.95	0.91, 0.99
Ovary					
Yin, 2011 (28)	Meta-analysis, prospective only	10 studies	Per 50-nmol/L increase	0.83	0.63, 1.08
Pancreas					
Stolzenberg-Solomon, 2010 (29)	Pooled study, prospective only	8 studies	100 vs. 50–75 nmol/L	2.12	1.23, 3.64
Wolpin, 2012 (30)	Pooled study, prospective only	5 studies	Quintile 5 vs. quintile 1	0.67	0.46, 0.97
Melanoma and skin					
Caini, 2014 (31)	Meta-analysis, retrospective ($n = 3$), and prospective	16 studies	Highest vs. lowest quantile		
			Melanoma	1.46	0.60, 3.53
			Nonmelanoma	1.64	1.02, 2.65
Kidney					
Gallicchio, 2010 (34)	Pooled study, prospective only	8 studies	75 to <100 vs. 50 to <75 nmol/L	1.19	0.78, 1.83
Afzal, 2013 (37)	Cohort	55	Per doubling	0.75[c,d]	
Muller, 2014 (38)	Nested case-control	560	Per doubling	0.82	0.68, 0.99
Non-Hodgkin lymphoma					
Purdue, 2010 (35)	Pooled study, prospective only	10 studies	75 to <100 vs. 50 to <75 nmol/L	1.15	0.91, 4.16
Endometrial					
Zeleniuch-Jacquotte, 2010 (36)	Pooled study, prospective only	7 studies	75 to <100 vs. 50 to <75 nmol/L	1.00	0.71, 1.42
Upper gastrointestinal					
Abnet, 2010 (33)	Pooled study, prospective only	8 studies	75 to <100 vs. 50 to <75 nmol/L	1.17	0.79, 1.75
			Vitamin D Supplementation Trials		
Bjelakovic, 2014 (39)	Cochrane Systematic Review		Intervention vs. placebo		
		18 studies	Overall cancer	1.00	0.94, 1.06
		5 studies	Lung	0.86	0.69, 1.07
		7 studies	Breast	0.97	0.86, 1.09
		5 studies	Colorectal	1.11	0.92, 1.34
		2 studies	Pancreas	0.91	0.57, 1.46
		1 study	Prostate	1.41	0.68, 2.95
		1 study	Uterus	0.82	0.07, 9.04

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI
		1 study	Ovary	1.51	0.06, 36.86
		1 study	Esophagus	0.50	0.19, 1.33
		1 study	Stomach	0.75	0.31, 1.77
		1 study	Liver	0.44	0.14, 1.44
		Vitamin D-Related Genes[e]			
*VDR Fok*I					
Gnagnarella, 2014 (42)	Meta-analysis		*ff* vs. *FF*		
		77 studies	Overall cancer	1.08	1.01, 1.16
		16 studies	Prostate	1.04	0.94, 1.16
		14 studies	Breast	1.05	0.90, 1.22
		16 studies	Colorectal	1.05	0.84, 1.31
		5 studies	Skin	1.24	1.01, 1.54
		6 studies	Ovary	1.20	1.02, 1.41
		3 studies	Kidney	0.94	0.57, 1.54
		15 studies	Other sites	1.18	0.85, 1.63
Deschasaux, 2015 (57)	Nested case-control	209	*ff* vs. *FF* (tobacco-related cancer)	1.87	1.08, 3.23
*VDR Bsm*I					
Raimondi, 2014 (43)	Meta-analysis		*BB* vs. *bb*		
		73 studies	Overall cancer	0.93	0.89, 0.98
		18 studies	Prostate	0.95	0.85, 1.07
		16 studies	Breast	0.98	0.91, 1.05
		13 studies	Colorectal	0.89	0.80, 0.98
		6 studies	Skin	0.87	0.70, 1.08
		5 studies	Ovary	1.01	0.79, 1.29
		3 studies	Kidney	0.61	0.19, 1.92
		3 studies	Non-Hodgkin lymphoma	1.08	0.78, 1.49
		9 studies	Other sites	0.83	0.57, 1.21
VDR Cdx2					
Serrano, 2016 (44)	Meta-analysis		*gg* vs. *GG*		
		18 studies	Overall cancer	1.12	1.00, 1.25
		5 studies	Prostate	1.09	0.76, 1.64
		3 studies	Breast	1.22	0.70, 2.12
		5 studies	Colorectal	1.24	0.94, 1.63
		3 studies	Skin	1.05	0.15, 7.60
		4 studies	Other sites	0.96	0.68, 1.36
*VDR Taq*I					
Serrano, 2016 (44)	Meta-analysis		*tt* vs. *TT*		
		64 studies	Overall cancer	0.98	0.90, 1.07
		17 studies	Prostate	0.94	0.78, 1.12
		11 studies	Breast	1.00	0.89, 1.12
		8 studies	Colorectal	1.43	1.30, 1.58
		6 studies	Skin	1.01	0.71, 1.45
		3 studies	Ovary	1.04	0.78, 1.38
		17 studies	Other sites	0.88	0.78, 1.00
Reimers, 2015 (55)	Case-control	967	*TT* vs. *CC* (breast)	0.74	0.56, 0.98

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI
*VDR Apa*I					
Serrano, 2016 (44)	Meta-analysis		*aa* vs. *AA*		
		36 studies	Overall cancer	1.06	0.95, 1.19
		9 studies	Prostate	1.00	0.74, 1.36
		8 studies	Breast	0.96	0.80, 1.15
		5 studies	Colorectal	1.21	0.82, 1.78
		3 studies	Skin	1.16	0.72, 1.89
		3 studies	Ovary	0.90	0.47, 1.71
		8 studies	Other sites	1.13	0.78, 1.64
VDR rs11574143					
Ahn, 2009 (58)	Nested case-control	749	Risk allele carriers vs. WT in men with low 25(OH)D (prostate cancer)	2.49	1.51, 4.11
VDR haplotypes					
Karami, 2009 (56)	Hospital-based case-control	777	Kidney		
			G-A-C vs. G-A-T haplotype	1.25	1.04, 1.51
			A-G-C vs. G-A-T haplotype	1.29	1.10, 1.52
CYP24A1 rs6068816					
Reimers, 2015 (55)	Case-control	967	*TT* vs. *CC* (breast)	0.28	0.10, 0.76
RXRA rs7861779					
Deschasaux, 2015 (57)	Nested case-control	209	*TT* or *CT* vs. CC (tobacco-related cancers)	1.60	1.07, 2.38
Karami, 2009 (56)	Hospital-based case-control	777	C-G vs. G-A haplotype (kidney)	1.35	1.11, 1.66
Mendelian randomization					
Mondul, 2013 (65)	Pooled study	7 studies	High vs. low 25(OH)D genetic score (aggressive prostate cancer)	1.52[c,d]	
Gilbert, 2015 (50)	Nested case-control	1,275	High vs. low 25(OH)D genetic score (high-grade prostate cancer)	1.32[c,d]	

Abbreviations: CI, confidence interval; *CYP24A1*, cytochrome P450 family 24 subfamily A member 1 gene; 25(OH)D, 25-hydroxyvitamin D; *RXRA*, retinoid X receptor α gene; *VDR*, vitamin D receptor gene; WT, wild type.

[a] Prospective studies are those where blood was collected prior to diagnosis with cancer. Retrospective studies are those where blood was collected from cases after diagnosis. Numbers of each type of study are shown in parentheses.

[b] For meta-analyses or pooled studies, sample size is the number of studies included. For individual studies, the number of cases is shown.

[c] Denotes study statistical significance.

[d] Because studies differ with respect to the directionality of the reported vitamin D comparisons (i.e., either lower or higher categories used as referent), we present here risks for higher versus lower vitamin D status. Studies making this comparison have their original 95% confidence intervals included, whereas those that require recalculation (e.g., reversal) of the risk estimates do not have the confidence intervals reported here.

[e] Only meta-analyses or individual studies with significant findings are included in this section of the table.

Bladder. Two meta-analyses that each included 7 individual studies found that higher circulating levels of 25(OH)D were associated with a lower risk of bladder cancer (24, 25) (Table 1). The study by Zhang et al. (24) reported a pooled odds ratio for highest versus lowest 25(OH)D categories of 0.75 that was statistically significant. The other by Zhao et al. (25) used a network meta-analysis approach to pool data from the 7 studies in order to examine absolute rather than relative values of 25(OH)D in relation to bladder cancer risk, and they concluded that only concentrations >75 nmol/L conferred "protection." These data demonstrate a fairly consistent inverse association between vitamin D status and bladder cancer risk, and a threshold effect is possible that warrants further study.

Lung. Two meta-analyses of circulating 25(OH)D and risk of lung cancer with slightly different inclusion criteria were recently published showing inverse associations (26, 27) (Table 1). Zhang et al. (27) included only prospective studies and found a statistically significantly lower lung cancer risk comparing the highest with lowest categories of circulating 25(OH)D. Chen et al. (26) similarly concluded that there was a 5% reduction in lung cancer risk per 10-nmol/L increment in 25(OH)D; they also found that there was a nonlinear association such that the lower risk occurred at 25(OH)D concentrations around 53 nmol/L. They also examined but found no evidence of interactions with various factors including sex and method of 25(OH)D measurement.

Ovary. One meta-analysis of 10 prospective studies of circulating vitamin D and ovarian cancer suggested a reduced risk for higher levels of 25(OH)D (Table 1) (28). The finding was not statistically significant, however.

Pancreas. Two separate analyses pooling data from multiple cohorts examined the association between circulating 25(OH)D and risk of pancreatic cancer (Table 1). Stolzenberg-Solomon et al. (29) analyzed participants from 8 cohorts in the Vitamin D Pooling Project of Rarer Cancers and found no risk association with lower concentrations of 25(OH)D but a 2-fold increased risk of pancreatic cancer for individuals with the highest concentrations. In contrast, Wolpin et al. (30) showed higher concentrations of 25(OH)D to be associated with a lower risk of pancreatic cancer in a pooled analysis of 5 prospective studies. Thus, the relationship between circulating 25(OH)D and risk of pancreatic cancer remains unclear.

Melanoma and other skin cancers. The relation between circulating 25(OH)D and skin cancer is complex, as exposure to ultraviolet radiation from the sun is both a source of circulating 25(OH)D and a well-established risk factor for the malignancy. A recent meta-analysis concluded that higher levels of 25(OH)D are associated with an increased risk of nonmelanoma skin cancer. There was also a suggestion that higher levels of 25(OH)D were associated with an increased risk of cutaneous melanoma, although the results were not statistically significant (31) (Table 1). Disentangling the detrimental effects of skin exposure and any potential protective effects of higher vitamin D status will continue to be challenging for future studies.

Other cancers. In 2010, the Vitamin D Pooling Project of Rarer Cancers reported its pooled data from 10 prospective cohort studies examining the association between circulating 25(OH)D and the following cancers: endometrial, kidney, ovarian, pancreatic, upper gastrointestinal, and non-Hodgkin lymphoma (32). Data from this project for ovarian (28) and pancreatic (29) cancers were discussed above, and 25(OH)D was not associated with any of the other organ sites (Table 1) (33–36). Other than publication of findings from the Vitamin D Pooling Project of Rarer Cancers, there have been few prospective studies of these malignancies, except for 2 studies of kidney cancer that reported an inverse association per doubling of circulating 25(OH)D (OR = 0.75, statistically significant (37); OR = 0.82, 95% CI: 0.68, 0.99) (38). Thus, most prospective data regarding 25(OH)D and risk of these rarer cancers point to a null association.

Vitamin D supplementation trials

A recent Cochrane Systematic Review combined the results of 18 controlled trials that tested vitamin D supplementation versus placebo or no intervention (Table 1) (39). The meta-analysis found no effect on overall cancer incidence (relative risk (RR) = 1.00, 95% CI: 0.94, 1.06), a finding that was robust in several sensitivity analyses taking into account factors including the risk of bias in the trials and the inclusion of participants with low baseline vitamin D status (39). They also examined site-specific cancers, finding no evidence of preventive efficacy for any of the malignancies, including lung cancer (5 trials), breast cancer (7 trials), colorectal cancer (5 trials), pancreatic cancer (2 trials), and prostate, uterine, ovarian, esophageal, gastric, and liver cancer (1 trial each). The findings do not support the hypothesis that vitamin D supplementation is likely to impact cancer incidence. The review did, however, point out that most of the trials had been conducted in community-dwelling elderly women and were originally designed to examine bone health outcomes. It also highlighted the need for additional trials in younger participants, men, and people with low vitamin D status, as well as longer trial supplementation periods and higher vitamin D dosages (39).

Vitamin D-related genes

The association between vitamin D-related genetic variants and cancer risk has been investigated, particularly with respect to the vitamin D receptor gene (*VDR*) and the 5 single nucleotide polymorphisms (SNPs) identified with known functional effects on receptor affinity for vitamin D (*Fok*I, *Bsm*I, *Taq*I, *Apa*I, and *Cdx*2). More recently, analyses of the genes associated with vitamin D synthesis, transport, and metabolism (e.g., 7-dehydrocholesterol reductase gene (*DHCR7*), cytochrome P450 family 2 subfamily R member 1 gene (*CYP2R1*), group-specific component gene (*GC*), cytochrome P450 family 27 subfamily B member 1 gene (*CYP27B1*), cytochrome P450 family 24 subfamily A member 1 gene (*CYP24A1*), and retinoid X receptor α gene (*RXRA*)) have been conducted, based in part on genome-wide association studies of circulating 25(OH)D (40, 41). Because there are a plethora of underpowered null genetic studies that have varied considerably in terms of design, analysis, and statistical tests used, it is difficult to succinctly summarize their results. Thus, only meta-analyses or individual studies with significant findings have been included in the tables (Tables 1 and 2).

Comprehensive meta-analyses have summarized investigations of the associations between the 5 *VDR* SNPs discussed above and cancer risk (Table 1) (42–44). For all of the polymorphisms, the genotype denoted as the wild type is the genotype associated with enhanced *VDR* activity through various biological mechanisms, such as increased receptor expression or affinity for vitamin D (45). Included in the meta-analysis of the *Fok*I polymorphism were 77 studies that showed the *ff* versus *FF* genotype to be associated with an increased risk of overall cancer (42). When specific cancer sites were examined, the *ff* genotype was associated with an increased risk of skin and ovarian cancers (42). Seventy-three studies included in the meta-analyses of the *Bsm*I variant revealed that the *BB* versus *bb* *Bsm*I genotype was associated with a lower risk of overall cancer, with the strongest associations for colorectal cancer (43). For *Cdx*2, the *gg* versus *GG* genotype was associated with an increased risk of overall cancer, but with no statistically significant association with any specific cancer site (44). Although *Taq*I and *Apa*I were not associated with risk of overall cancer, *Taq*I *tt* versus *TT* was associated with an increased colorectal cancer risk (44). Studies published after these meta-analyses have been largely null (46–54) (data not shown in Table 1), with a few studies finding associations between variation in *VDR* and risk of breast (55), renal (56), and tobacco-related cancers (57) (Table 1). Interestingly, 1 study found an association

Table 2. Vitamin D and Cancer Mortality

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI[c]
		Circulating 25(OH)D			
Overall cancer mortality					
Yin, 2013 (71)	Meta-analysis of prospective cohorts of cancer-free individuals	13 studies	Per 50-nmol/L increase	0.83	0.71, 0.96
			Women	0.76	0.60, 0.98
			Men	0.92	0.65, 1.32
Chowdhury, 2014 (67)	Meta-analysis of prospective cohorts	12 studies	Highest vs. lowest tertile	0.88[d]	
Schottker, 2014 (70)	Meta-analysis of prospective cohorts	8 studies	Highest vs. lowest quintile		
			With a history of cancer		0.59[d,e]
			No history of cancer		0.97[e]
Afzal, 2014 (73)	Pooled analysis of prospective cohorts	2 studies	Per 20-nmol/L increase		0.89[d,e]
El Hilali, 2016 (74)	Prospective cohort	144 cancer deaths	>75 nmol/L vs. 3 lower categories	Nonsignificant HRs: range, 0.91–1.25	
Khaw, 2014 (75)	Prospective cohort	3,121 cancer deaths	Per 20 nmol/L increase	0.94	0.89, 1.00
Colorectal					
Maalmi, 2014 (79)	Meta-analysis, prospective cohorts (2 studies) and blood collected from cancer patients after diagnosis (3 studies)	5 studies	High vs. low category	0.65	0.49, 0.86
Afzal, 2014 (73)	Pooled analysis of prospective cohorts	330 colorectal cancer deaths	Per 20-nmol/L increase		0.95[e]
Wesa, 2015 (82)	Blood collected after diagnosis of stage IV colorectal cancer	153 deaths (any cause)	≥75 nmol/L vs. <75 nmol/L	0.61	0.38, 0.98
Zgaga, 2014 (83)	Blood collected after diagnosis of stage I–III colorectal cancer	363 colorectal cancer deaths	Highest vs. lowest tertile	0.68	0.50, 0.90
Breast					
Maalmi, 2014 (79)	Meta-analysis, all blood collected from cancer patients after diagnosis	5 studies	High vs. low category	0.58	0.38, 0.84
Huss, 2014 (81)	Prospective cohort	99 breast cancer deaths	Tertile 1 vs. tertile 2	2.46	1.38, 4.37
			Tertile 3 vs. tertile 2	1.99	1.14, 3.49
Lung					
Afzal, 2014 (73)	Pooled analysis of prospective cohorts	624 lung cancer deaths	Per 20-nmol/L increase		0.78[d,e]
Anic, 2014 (80)	Prospective cohort of cancer-free individuals	428 lung cancer deaths	Highest vs. lowest quartile	1.18	0.89, 1.56
Ovary					
Walentowicz-Sadlecka, 2012 (84)	Blood collected from cancer patients after diagnosis	Overall survival	25(OH)D > 25 nmol/L	45[f]	
			25(OH)D < 25 nmol/L	28[f]	
Merkel cell carcinoma					
Samimi, 2014 (85)	Blood collected from cancer patients after diagnosis	19 Merkel cell carcinoma deaths	≥50 nmol/L vs. <50 nmol/L		0.19[e]

Table continues

Table 2. Continued

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI[c]
Pancreas					
Cho, 2013 (86)	Blood collected from cancer patients after diagnosis	82 deaths (any cause)	≥50 nmol/L vs. <50 nmol/L		
			All patients		$P = 0.30$
			Stage I or II		$P = 0.71$
			Stage III or IV		$P = 0.0019$
Prostate					
Holt, 2013 (87)	Blood collected from cancer patients after diagnosis	95 prostate cancer deaths	50–127 nmol/L vs. <30 nmol/L		0.83[e]
Gupta, 2015 (88)	Blood collected after diagnosis of stage IV prostate cancer	46 deaths (any cause)	>80 nmol/L vs. <50 nmol/L		0.71[e]
Brändstedt, 2016 (89)	Prospective cohort	169 prostate cancer deaths	Highest vs. lowest quartile	0.61	0.37, 1.01
Mondul, 2016 (90)	Prospective cohort of cancer-free individuals	362 prostate cancer deaths	Highest vs. lowest quintile	0.72	0.52, 0.99
Shui, 2012 (91)	Prospective cohort	114 prostate cancer deaths	Highest vs. lowest quartile	0.43	0.24, 0.76
Shui, 2015 (92)	Pooled analysis of 5 prospective cohorts	518 prostate cancer deaths	Highest vs. lowest quartile	0.86	0.65, 1.14
		Vitamin D Supplementation Trials			
Trivedi, 2003 (93)	100,000 IU of vitamin D every 4 months	135 overall cancer deaths	Vitamin D supplement vs. placebo	0.86	0.61, 1.20
		18 colon cancer deaths		0.62	0.24, 1.60
		21 respiratory cancer deaths		0.89	0.38, 2.09
Brunner, 2011 (94)	400 IU of vitamin D (and 1,000 mg of calcium) daily	662 cancer deaths	Vitamin D supplement vs. placebo	0.90	0.77, 1.05
Avenell, 2012 (95)	800 IU of vitamin D (and/or 1,000 mg of calcium) daily	329 cancer deaths	Vitamin D supplement vs. no vitamin D supplement	0.85	0.68, 1.06
Bjelakovic, 2014 (39)	Cochrane Systematic Review	4 trials (including the 3 above); 1,192 cancer deaths	Intervention vs. placebo or no intervention	0.88	0.78, 0.98
Buttigliero, 2011 (98)	Meta-analysis of advanced prostate cancer patients	3 trials		1.07	0.93, 1.23
Jeffreys, 2015 (99)	Linkage to prescription medication database for vitamin D prescriptions prior to cancer diagnosis	2,103 deaths among breast cancer patients		0.78	0.70, 0.88
		1,726 deaths among colorectal cancer patients		0.90	0.78, 1.04
		2,756 deaths among lung cancer patients		1.09	0.98, 1.22
		1,151 deaths among ovarian/uterine cancer patients		0.89	0.73, 1.07

Table continues

Table 2. Continued

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI[c]
Lewis, 2016 (100)	Vitamin D supplementation assessed after diagnosis of stage II colorectal cancer	71 total deaths (any cause)	Vitamin D supplement users vs. nonusers	0.77	0.37, 1.58
		Vitamin D-Related Genes[g]			
Vitamin D pathway genes (*VDR, GC, CYP27B1, CYP27A1, CYP2R1, CYP24A1, RXRA*)					
Shui, 2012 (91)	Nested case-control	68 deaths	28 *VDR* SNPs (prostate)		0.01[h]
			5 *CYP27A1* SNPs (prostate)		0.02[h]
			92 Total pathway SNPs (prostate)		0.006[h]
*VDR Bsm*I					
Orlow, 2016 (106)	Population-based case-control	254 deaths	rs1544410 *BB* vs. *bb* (melanoma)	0.79	0.64, 0.96
Anic, 2012 (109)	Clinic-based case-control	248 deaths	rs1544410 dominant model (glioma, high grade)	1.34	1.01, 1.77
*VDR Taq*I					
Perna, 2013 (102)	Population based case-control	48 deaths	rs731236 *tt* vs. *TT* (breast)	3.0	1.1, 8.1
Liu, 2011 (105)	Hospital based case-control	311 deaths (any cause)	rs731236 *AG* + *AA* vs. *GG* (non-small cell lung)	1.49	1.07, 2.08
Orlow, 2016 (106)	Population-based case-control	254 deaths	Melanoma	0.81	0.67, 0.99
*VDR Apa*I					
Obara, 2007 (108)	Hospital-based case-control	Unspecified[i]	*AA* vs. *Aa* + *aa* (kidney)	3.3	1.01, 10.6
VDR tag SNPs					
Holt, 2010 (103)	Population-based case-control	57 deaths	rs3782905 *GG* vs. *CC* (prostate)	3.0	1.2, 7.7
Orlow, 2016 (106)	Population-based case-control	254 deaths	Melanoma	0.80	0.65, 0.98
Holt, 2010 (103)	Population-based case-control	57 deaths	rs11168314 *TT* vs. *CC* (prostate)	2.8	1.1, 7.3
VDR other					
Orlow, 2016 (106)	Population-based case-control	254 deaths	rs4760674 *AA* vs. *CC* (melanoma)	1.22	1.01, 1.47
			rs2239182 *AA* vs. *GG* (melanoma)	1.25	1.05, 1.49
			rs7305032 *GG* vs. *AA* (melanoma)	1.22	1.01, 1.48
			rs7299460 *TT* vs. *CC* (melanoma)	0.80	0.66, 0.97
			rs12370156 *CC* vs. *TT* (melanoma)	1.19	1.00, 1.41
CYP24A1 tag SNPs					
Holt, 2010 (103)	Population-based case-control	57 deaths	rs2296241 *AG* + *GG* vs. *AA* (prostate)	0.5	0.3, 0.9
			rs2585428 *AG* + *AA* vs. *GG* (prostate)	2.0	1.1, 3.8

Table continues

Table 2. Continued

First Author, Year (Reference No.)	Study Design[a]	Sample Size[b]	Comparison/Outcome	Risk Estimate	95% CI[c]
			rs6022999 *AG* + *GG* vs. *AA* (prostate)	2.2	1.1, 4.2
Anic, 2012 (109)	Clinic-based case-control	248 deaths	rs6013897 per allele *A* (glioma, high grade)	0.79	0.63, 0.98
			rs6013897 recessive model (glioma, high grade)	0.54	0.30, 0.96
CYP27B1 tag SNPs					
Holt, 2010 (103)	Population-based case-control	57 deaths	rs3782130 *CG* + *GG* vs. *CC* (prostate)	0.5	0.3, 0.9
			rs4646537 *AC* + *CC* vs. *AA* (prostate)	2.3	1.0, 5.5
DHCR7 and *CYP2R1*					
Afzal, 2014 (73)	Prospective cohort	2,839 deaths	rs7944926 and rs11234027 (*DHCR7*); rs10741657 and rs12794714 (*CPY2R1*): allele score associated with 20-nmol/L increase (overall)		0.70[d,e]
GC					
Yin, 2016 (107)	GWAS: hospital-based case-control and nested case-control	143 deaths	rs12512631 per effect allele *C* (melanoma)	0.66	0.51, 0.86
RXRA					
Yin, 2016 (107)	GWAS: hospital-based case-control and nested case-control	143 deaths	rs7850212 per effect allele *A* (melanoma)	0.38	0.22, 0.68

Abbreviations: CI, confidence interval; *CYP2R1*, cytochrome P450 family 2 subfamily R member 1 gene; *CYP24A1*, cytochrome P450 family 24 subfamily A member 1 gene; *CYP27A1*, cytochrome P450 family 27 subfamily A member 1 gene; *CYP27B1*, cytochrome P450 family 27 subfamily B member 1 gene; *DHCR7*, 7-dehydrocholesterol reductase gene; *GC*, group-specific component gene; GWAS, genome-wide association study; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D; *RXRA*, retinoid X receptor α gene; SNP, single nucleotide polymorphism; *VDR*, vitamin D receptor gene.

[a] Prospective cohorts collected blood at baseline and followed subjects for mortality outcomes. Unless specified to be among cancer-free individuals, some individuals may have previously had cancer; however, these are not studies of cancer patients, and we assume that the majority of blood was collected prior to cancer diagnosis. Studies among cancer patients are sometimes described as "prospective" because they collect blood and then follow patients for mortality outcomes; however, in these studies, blood was collected from cases after a cancer diagnosis, and this is so noted. Only meta-analyses providing a quantitative pooled estimate or individual studies not included in a meta-analysis or review are included in this table.

[b] For meta-analyses or pooled studies, sample size is the number of studies included. For individual studies, the number of deaths is shown.

[c] For studies without reported confidence intervals, *P* values are shown.

[d] Denotes study statistical significance.

[e] Because studies differ with respect to the directionality of the reported vitamin D comparisons (i.e., either lower or higher categories used as referent), we present here risks for higher versus lower vitamin D status. Studies making this comparison have their original 95% confidence intervals included, whereas those that require recalculation (e.g., reversal) of the risk estimates do not have the confidence intervals reported here.

[f] Median survival time in weeks.

[g] Only meta-analyses or individual studies with significant findings are included in this section of the table.

[h] Global *P* from kernel machine analysis adjusted for 25(OH)D.

[i] Unspecified number of deaths; only lists cause-specific survival (time from surgery to death from renal cell carcinoma) among 135 patients.

between variation in *VDR* and risk of prostate cancer, but only among men with low levels of circulating 25(OH)D (58) (Table 1).

Several studies have attempted to comprehensively study variation in other vitamin D-related genes, but most have been null, particularly after adjustment for multiple comparisons (46, 48, 49, 52, 53, 55, 58–61). One study found an increased risk of renal cell carcinoma associated with a particular haplotype of *RXRA* (56). Studies using a candidate SNP approach have found individual SNPs in vitamin D-related genes to be associated with several cancers, but these findings have not been replicated in the more comprehensive studies (51, 54, 57, 62) (data not shown in Table 1).

Genome-wide association studies have identified SNPs in 4 key genes related to circulating 25(OH)D (*DHCR7*, *CYP2R1*, *GC*, and *CYP24A1*) that have been examined in relation to risk of cancer, an analytical approach referred to as Mendelian randomization. Studies of breast and colorectal cancer have found no association between these SNPs and risk of disease (63, 64) (data not shown in Table 1). By contrast, of 2 studies of prostate cancer, 1 showed an increased risk of aggressive disease with more SNPs associated with higher levels of 25(OH)D (65), and the other found an increased risk of high-grade disease (50) (Table 1).

VITAMIN D AND CANCER MORTALITY

Table 2 summarizes the information on the associations between cancer mortality and blood concentrations of 25(OH)D, vitamin D supplementation trials, and vitamin D-related genetic variation. Many reviews have summarized these data, and some of these are included in the Discussion section below. However, only meta-analyses providing a quantitative pooled estimate or individual studies not included in these reviews or meta-analyses are included in Table 2.

Blood concentrations of 25(OH)D

Studies of varying designs have examined 25(OH)D and cancer mortality/survival and are included in several reviews and meta-analyses (66–71). Cohort studies of overall and cause-specific (including cancer) mortality measured 25(OH)D in blood samples collected years prior to diagnosis, whereas clinical investigations of patients report site-specific cancer mortality in relation to 25(OH)D measured after diagnosis, and in some cases after treatment.

Overall cancer. Pilz et al. (66) concluded that the association between vitamin D and cancer mortality was inconsistent, differing among the 9 studies reviewed, including 1 study with a U-shaped relationship (72). In a meta-analysis that included 13 studies, Yin et al. (71) calculated a relative risk of 0.83 (95% CI: 0.71, 0.96) for overall cancer mortality for every 50-nmol/L increase in 25(OH)D (Table 2). They observed significant heterogeneity among the studies, however, and noted that the inverse association was restricted to women (71). Chowdhury et al. (67) reported a statistically significant lower risk of cancer mortality for a higher baseline level of 25(OH)D in a meta-analysis of 12 prospective cohorts. These 3 analyses incorporated many of the same primary studies, although there are some differences. In a consortium study of 1 US and 7 European cohorts, Schöttker et al. (70) reported lower cancer mortality for higher 25(OH)D, but only among participants with a history of cancer (RR = 0.59, significant CI), suggesting possible reverse causality. Afzal et al. (73) reported significantly lower cancer mortality with higher prediagnostic vitamin D status in 2 Danish cohorts (pooled hazard ratio (HR) = 0.89), but no association was found in a Dutch cohort (74) or in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort (75).

Site-specific cancer. Higher 25(OH)D status in cancer patients at the time of diagnosis has generally been reported in reviews to be associated with improved survival for most malignancies examined, although not all findings have been statistically significant. Although some of the associations are null, none of the individual studies indicated poorer survival with higher 25(OH)D (66–69). The sites examined include the breast ($n = 8$), colorectum ($n = 5$), stomach ($n = 1$), lung ($n = 3$), prostate ($n = 2$), and head/neck ($n = 2$), as well as lymphoma/leukemia ($n = 4$) and melanoma ($n = 1$) (66–69) (data not shown in Table 2). The majority of studies included in these reviews measured 25(OH)D in patients after cancer was diagnosed. Only 3 studies measured 25(OH)D in prediagnostic blood samples, and these found similar reduced risks of total, colorectal cancer, and prostate cancer mortality with higher levels of 25(OH)D (76–78).

On the basis of 5 studies for each site, Maalmi et al. (79) conducted a meta-analysis of colorectal and breast cancer survival and reported lower overall and disease-specific mortality with higher vitamin D status (colorectal-cancer HR = 0.65, 95% CI: 0.49, 0.86; breast cancer HR = 0.58, 95% CI: 0.38, 0.84) (Table 2). 25(OH)D was measured in blood samples taken after diagnosis for all of the breast cancer studies and 3 of the 5 colorectal cancer studies (79).

Other subsequently published data are more mixed in their findings and conclusions. For example, higher prediagnostic vitamin D status was associated with significantly lower lung cancer mortality in the 2 Danish cohorts (Table 2) (73), but not with colorectal cancer mortality (73), and lung cancer mortality was not related to 25(OH)D in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (80). A U-shaped relationship was observed for prediagnostic 25(OH)D and breast cancer mortality in the Swedish Malmo cohort (81). On the basis of blood samples taken after diagnosis, a higher level of 25(OH)D was associated with a lower colorectal cancer mortality (82, 83), ovarian cancer mortality (84), and Merkel cell carcinoma mortality (although not significant) (85). Higher postdiagnostic 25(OH)D status was also associated with significantly improved pancreatic cancer survival in 1 study (86).

Vitamin D measured after diagnosis was not associated with prostate cancer mortality in 2 studies (87, 88); however, higher prediagnostic 25(OH)D status was associated with lower prostate cancer mortality in the Swedish Malmo cohort (HR = 0.61, 95% CI: 0.37, 1.01) (89) and the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort (HR = 0.72, 95% CI: 0.52, 0.99) (90) (Table 2). Higher prediagnostic levels of 25(OH)D were also associated with a lower risk of fatal prostate cancer in the Health Professionals Follow-up Study (OR = 0.43, 95% CI: 0.24, 0.76) (91), but

this was not supported by a larger study using data from the Breast and Prostate Cancer Cohort Consortium (92).

Vitamin D supplementation

Very few studies have reported on vitamin D supplementation and either overall or site-specific cancer survival. Three randomized controlled trials of supplementation reported nonsignificantly lower overall cancer mortality with vitamin D supplementation (93–95) (Table 2), 1 of which also reported no effect on colon and respiratory cancer mortality (93). These trials were not powered for cancer mortality outcomes, however (96). A Cochrane Systematic Review calculated that vitamin D supplementation was associated with reduced cancer mortality (RR = 0.88, 95% CI: 0.78, 0.98) on the basis of the 3 above trials plus data from a fourth study (97) but concluded that the finding could be due to chance (39).

A meta-analysis of 3 randomized controlled trials of vitamin D supplementation in patients with advanced prostate cancer found no effect on survival (Table 2). The studies were heterogeneous, however, with 1 indicating a significant benefit for supplementation and a second "confirmatory" study showing significant harm (98).

In a study from the United Kingdom examining patients with breast, colorectal, lung, ovarian, or uterine cancers, prediagnostic vitamin D supplement prescriptions were associated with significant reduction in breast cancer mortality (Table 2), nonsignificant mortality reductions for colorectal, ovarian, and uterine cancer, and somewhat greater mortality for lung cancer (99). In patients with stage II colorectal cancer, vitamin D supplementation as assessed by interview after diagnosis was not associated with recurrence or mortality (100).

Vitamin D-related genes

Vitamin D genetic variants have also been studied with respect to cancer mortality and survival, particularly for the vitamin D receptor gene, *VDR*, with more recent analyses of genes associated with vitamin D synthesis, transport, and metabolism (e.g., *DHCR7*, *CYP2R1*, *GC*, *CYP27B1*, and *CYP24A1*). In some instances, the genetic associations were consistent with those observed for circulating 25(OH)D.

A low vitamin D genetic score of *DHCR7* and *CYP2R1* was associated with a lower overall cancer mortality in a pooled analysis of 3 large Danish cohorts (73) (Table 2).

A combined study of 2 German cancer cohorts (ESTHER II and VERDI) found no significant association between the *VDR* polymorphisms *Fok*I, *Cdx*2, *Taq*I, and *VDR*-5132 and colorectal cancer mortality (101), and the European Prospective Investigation into Cancer and Nutrition cohort also showed no association with *VDR* or the calcium-sensing receptor gene (*CASR*), even though a higher level of prediagnostic 25(OH)D was related to lower mortality (77) (data not shown). By contrast, the ESTHER II and VERDI analyses showed an association between *VDR Taq*I and breast cancer mortality, but not other *VDR* variants (102) (Table 2).

Variants in *VDR*, *CYP27B1*, and *CYP24A1* have been significantly associated with lower prostate cancer mortality in 1 study (although not after adjustment for multiple comparisons) (103) (Table 2), while another clinical study of men receiving androgen deprivation therapy showed no outcome differences across *VDR* genotypes (104) (data not shown in Table 2). A pathway analysis of vitamin D variants (including *VDR*, *CYP27B1*, *GC*, *CYP27A1*, *CYP2R1*, *CYP24A1*, and *RXRA*) and lethal prostate cancer in the Health Professionals Follow-up Study found significant associations, particularly for *VDR* and *CYP27A1*, that were independent of baseline plasma 25(OH)D (Table 2) (91). By contrast, a similar larger analysis in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium found no association between fatal prostate cancer and vitamin D-related variants (92) (data not shown in Table 2).

The *VDR Taq*I and *Bsm*I variants have been associated with survival in non-small cell lung cancer patients (105), and an international multicenter case-control study consortium (the Genes, Environment, and Melanoma (GEM) Study) found significant associations with melanoma mortality for 8 common *VDR* variants (106) (Table 2). Mortality was also associated with the vitamin D binding protein gene, *GC*, and *RXRA* in the Nurses' Health Study and Health Professionals Follow-up Study (107) (Table 2). *VDR* polymorphisms in *Apa*I have also been related to renal cell carcinoma mortality (108) and *Bsm*I to high-grade glioma mortality (109) (Table 2).

VITAMIN D AND CANCER IN BLACK POPULATIONS

Relative to other racial/ethnic groups, populations of African ancestry (hereafter referred to as "black") are known to be at higher risk for low vitamin D status (110, 111). They also experience higher incidence and/or mortality rates for several malignancies, including breast, colorectal, and prostate (112). Although it is known that the lower circulating 25(OH)D level in black populations results from the greater melanin pigmentation in darker skin reducing solar ultraviolet B radiation-related cutaneous vitamin D synthesis (113), the reasons for the racial disparities in cancer incidence and mortality have yet to be elucidated (112). Vitamin D has therefore been proposed to explain some of the racial disparities in cancer risk (114–116) and mortality (117–119). Of the relatively few investigations of vitamin D biochemical status and cancer risk in black populations, however, most have been retrospective case-control analyses, making their interpretation challenging because of issues related to reverse causality. Here, we summarize the available research regarding vitamin D status and cancer risk in black populations (Table 3).

Blood concentrations of 25(OH)D

Studies examining circulating 25(OH)D in relation to cancer risk in black populations have focused primarily on prostate cancer, with a few analyses looking at other malignancies.

Prostate. Studies to date on circulating vitamin D and prostate cancer risk in black men include retrospective, hospital-based, case-control (120–122), and cross-sectional analyses (123, 124). Among the prospective evaluations in black men, the number of cases has been relatively small (n = 91–250), contributing to imprecise risk estimates and inconsistent findings across studies (22, 125, 126) (Table 3).

One of the first investigations of vitamin D status and cancer risk in blacks found that prospectively measured 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) was inversely associated

Table 3. Circulating Vitamin D and Cancer in Black Populations

First Author, Year (Reference No.)	Study Design	Sample Size	Comparison/Outcome	Risk Estimate	95% CI
Prostate					
Corder, 1993 (125)	Nested case-control	90 cases	1,25(OH)D (quartile 4 vs. quartile 1 of 25(OH)D) (overall)	0.15[a,b]	
Park, 2010 (126)	Nested case-control	136 cases	≥75 nmol/L vs. <50 nmol/L (overall)	0.97[d]	
Beyene, 2014 (122)	Hospital-based case-control	91 cases	Serum 25(OH)D (continuous, overall)	0.89[e]	
Murphy, 2014 (123)	Cross-sectional	168 cases	≥50 nmol/L vs. <50 nmol/L (biopsy, overall)	0.41[c,d]	
Kristal, 2014 (22)	Case-cohort	250 cases	≥75 nmol/L vs. <37.5 nmol/L		
			Overall	0.86	0.51, 1.44
			Gleason 2–6 score	1.04	0.52, 2.10
			Gleason 7–10 score	0.47	0.19, 1.18
Jackson, 2015 (120)	Hospital-based case-control	224 cases	Tertile 3 vs. tertile 1 (overall)	2.47	1.20, 4.90
Paller, 2015 (121)	Hospital-based case-control	90 cases	>75 nmol/L vs. ≤75 nmol/L (overall)	0.29	0.08, 1.03
Steck, 2015 (124)	Cross-sectional	519 cases	Tertile 3 vs. tertile 1 (high aggressive)	1.46	0.89, 2.39
Layne, 2017 (127)	Nested case-control	226 cases	Quartile 4 vs. quartile 1		
			Overall	0.73	0.40, 1.33
			Gleason ≥7 score	1.16	0.43, 3.14
			Gleason <7 score	0.59	0.27, 1.30
Breast					
Janowsky, 1999 (128)	Hospital-based case-control	21 cases	1,25(OH)D Quartile 4 vs. quartile 1 (overall)	2.0[d]	
Kim, 2014 (19)	Nested case-control	106 postmenopausal cases	Overall		
			25(OH)D2 (>0 nmol/L vs. 0 nmol/L)	0.29	0.12, 0.70
			25(OH)D3 (per 50-nmol/L increase)	1.61	0.83, 3.11
			25(OH)D (per 50-nmol/L increase)	1.16	0.63, 2.16
Colorectal					
Woolcott, 2010 (129)	Nested case-control	45 cases	Per doubling	0.68[f]	0.51, 0.92
Cancer mortality					
Freedman, 2010 (130)	Prospective cohort	98 deaths (women), 146 deaths (men)	≥80 nmol/L vs. <37.5 nmol/L		
			Total cancer (women)	1.84	0.76, 4.45
			Total cancer (men)	1.28	0.59, 2.80
Kritchevsky, 2012 (131)	Prospective cohort	101 deaths	≥75 nmol/L vs. <25 nmol/L (total cancer)	0.63[d]	

Abbreviations: CI, confidence interval; 1,25(OH)D, 1,25-hydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D2, ergocalciferol; 25(OH)D3, cholecalciferol.

[a] Analyzed together with 91 white cases.

[b] No 95% confidence interval provided, but indicated to exclude 1.0.

[c] Denotes study statistical significance.

[d] Because studies differ with respect to the directionality of the reported vitamin D comparisons (i.e., either lower or higher categories used as referent), we present here the risks for higher versus lower vitamin D status. Studies making this comparison have their original 95% confidence intervals included, whereas those that require recalculation (e.g., reversal) of the risk estimates do not have the confidence intervals reported here.

[e] No 95% confidence interval provided; global $P = 0.47$.

[f] No exact race-specific risk estimates presented; $P_{interaction}$ by race/ethnicity = 0.46.

with prostate cancer risk, particularly among men in the lowest quartile of 25(OH)D (125). The association was evident in older men and similar to the association observed for whites ($P_{interaction} = 0.5$). More recently, the Multiethnic Cohort reported no association between plasma 25(OH)D and risk in black men (126) (Table 3). Black men in the study had the highest prostate cancer incidence and the lowest circulating concentration of 25(OH)D, compared with the other racial/ethnic groups (126). The Selenium and Vitamin E Cancer Prevention Trial found a significant inverse trend in the association for plasma 25(OH)D in black men, but only for high-grade, Gleason score 7–10 cancers ($P_{trend} = 0.048$) (22). Our own nested case-control analysis of black men in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial showed nonsignificant risk associations between serum 25(OH)D and overall prostate cancer (inverse) and aggressive disease (positive). In addition, there was a significant inverse association with nonaggressive disease (global $P = 0.03$), although the association comparing the extreme quartiles of vitamin D was not statistically significant (Table 3) (127).

Breast. A hospital-based case-control study found that pretreatment levels of 25(OH)D and $1,25(OH)_2D$ were not associated with risk in black women (128). Plasma 25(OH)D and postmenopausal breast cancer risk were also examined in the Multiethnic Cohort, finding lower average total 25(OH)D and $25(OH)D_3$ concentrations and a higher $25(OH)D_2$ concentration in black versus white women, with only $25(OH)D_2$ being inversely associated with risk in black women (19) (Table 3).

Colorectum. In the Multiethnic Cohort, there was a significant inverse trend in the association between plasma 25(OH)D and colorectal cancer risk (129) (Table 3). A similar risk estimate was observed among blacks, although it was nonsignificant ($P_{interaction}$ by race/ethnicity = 0.46) (128).

Overall cancer. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted in 1988–1994, Freedman et al. (130) found nonsignificant positive associations between higher versus lower prediagnostic 25(OH)D and overall cancer mortality in non-Hispanic black men ($P_{trend} = 0.70$) and women ($P_{trend} = 0.32$). Additionally, adjustment for continuous 25(OH)D in analyses of categorical vitamin D levels did not attenuate the elevated risk of overall cancer mortality in non-Hispanic blacks compared with non-Hispanic whites (without adjustment, RR = 1.37, 95% CI: 1.08, 1.73; continuous 25(OH)D adjusted, RR = 1.44, 95% CI: 1.15, 1.81) (Table 3).

The Health, Aging, and Body Composition Study, a prospective cohort study of community-dwelling men and women, reported a significant association between higher levels of serum 25(OH)D and lower all-cause mortality in blacks ($P_{trend} < 0.001$) but no trend in the association with cancer mortality in this group ($P_{trend} = 0.27$) (131) (Table 3).

HEALTH POLICY: VITAMIN D AND CANCER RISK AND PREVENTION

Current expert recommendations versus population trends

Despite notable examples to the contrary, such as the increased risk of lung cancer associated with β-carotene supplementation in smokers (132), there exists a common misconception that, at worst, nutritional supplements will do nothing to reduce cancer risk and that, if taking some is beneficial, taking more is likely better. Given that dietary supplements are widely available and actively promoted to the public, their highly prevalent use for disease prevention demonstrates that population behavioral changes are often adopted before official policies and recommendations that are well informed by the totality of scientific data are made.

In 2011, the Institute of Medicine, now called the National Academy of Medicine of the National Academies of Sciences, Engineering, and Medicine, issued an updated *Dietary Reference Intakes for Calcium and Vitamin D* (5). The recommendations concerning vitamin D were based on an assumption of minimal sun exposure (as supporting increased ultraviolet B exposure would put individuals at risk of skin cancer) and were aimed at maintaining blood concentrations of 25(OH)D in the 50–75-nmol/L range. This target was chosen on the basis of evidence that 50 nmol/L meets the needs of 97% of the population with respect to bone health, not necessarily for the prevention of cancer, as the report concluded that there was insufficient evidence to link higher vitamin D status with any benefit for other health outcomes. It should also be noted that the report's recommendations were intended for healthy populations, and it provided no particular guidance with respect to individuals already diagnosed with cancer. The US Preventive Services Task Force (USPSTF), which develops recommendations for clinical preventive services, currently gives a rating of "I" to screening for vitamin D deficiency in adults as well as to the use of vitamin D supplements for the prevention of cancer (133, 134). It defines this rating as follows: "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults" "(I statement)" (133, p. 133). Indeed, although vitamin D has long been considered to be critical for maintaining adequate bone health, the USPSTF currently recommends the use of vitamin D supplements only for the prevention of fractures in community-dwelling adults ≥65 years of age who are at increased risk of falls. For all other groups, the rating is either "I" or "D," the latter of which is a recommendation against (i.e., "discourages") the use of the supplements (135).

Despite the absence of any such recommendation in favor of supplementation or screening the general population for low vitamin D status, both behaviors and practices have increased dramatically in recent years. One study conducted in the United Kingdom found that the number of requests for vitamin D blood testing increased 11-fold from 2007 to 2012 (136), and data from the National Health and Nutrition Examination Survey demonstrate that vitamin D supplement use has nearly doubled over the past 3 decades in the US population, particularly in men and women aged 60 years or more (women ≥60 years: 30% in 1988–1994, 56% in 2003–2006; men ≥60 years: 24% in 1988–1994, 44% in 2003–2006) (137).

Current state of vitamin D cancer research and next steps

Part of the enthusiasm for vitamin D in the prevention of cancer is the fact that if it is truly protective, then an effective

intervention is readily available and easy to implement; that is, the "chemopreventive" approach. Vitamin D supplements are relatively inexpensive, generally safe, easy for people to use, and readily available over the counter. The increasing use of vitamin D supplements in the US population discussed above shows clearly that the public is receptive to this theoretically beneficial behavior. Yet several knowledge gaps exist in the current scientific literature that limit the implementation of recommendations for or against use of vitamin D for the prevention of 1 or more cancers.

As mentioned, official institutional recommendation statements to date have concluded that the evidence regarding vitamin D and cancer is inconsistent or insufficient to assess the balance of benefits and harms. It seems clear from the currently available research reviewed here that vitamin D does not have a strong protective influence on the risk of most malignancies. Furthermore, it is well known that cancer is not 1 disease and that risk factors and etiologies differ by organ site on the basis of endogenous and exogenous exposures, underlying biology, and genetics. This is supported by the vitamin D-cancer risk literature cited, with vitamin D appearing to be protective for some cancers (notably, colorectal and bladder), possibly increasing the risk for others (e.g., prostate and pancreas), and having no apparent, or an inconsistent, association with the majority of organ sites. It may also be that the vitamin D association is different for cancer incidence and mortality for some organ sites, on the basis of underlying tissue biology and whether vitamin D may be impacting tumor initiation or promotion at a given site. Notably, there is accumulating support for this in prostate cancer where a higher vitamin D concentration appears to increase the risk of its diagnosis but may provide benefit for more aggressive disease and prostate cancer survival.

This highlights the critical need for larger and more detailed studies of individual organ sites, with particular attention to specific cancer subtypes. There are, for example, important distinctions between such clinically relevant subgroups, including hormone receptor status in breast cancer, histological subtypes of non-Hodgkin lymphoma and ovarian, lung, and gastric cancers, and disease aggressiveness in prostate cancer. Interestingly, 1 recent study found that a higher vitamin D status was more beneficial for colorectal tumors having greater lymphocytic infiltration (138), supporting the view expressed in a recent commentary that substantially greater attention is needed with respect to organ site-specific biological mechanisms (139). The current literature also suggests that there may be other important factors that interact with vitamin D status, such as menopausal status in breast cancer (17), sex in colorectal cancer (140), and circulating vitamin D binding protein in prostate cancer (141). Relevant to the latter observation, studies have begun to pay more attention to the measurement of 25(OH)D by examining the role of free versus total vitamin D in cancer etiology, with free 25(OH)D appearing to be more important for some cancer sites and total 25(OH)D appearing to be more important for others (12, 80, 141–143). Although laboratory analyses have recently been developed to directly measure free 25(OH)D, to date these studies have estimated free 25(OH)D by measuring total 25(OH)D and vitamin D binding protein and estimating the free fraction by using mass action equations or the 25(OH)D: vitamin D binding protein molar ratio (144). This has presented some challenges for studying vitamin D binding protein and free 25(OH)D in black populations, as one of the most widely used assays for vitamin D binding protein does not measure the predominant circulating vitamin D binding protein isoform in blacks (145). Attention to these dimensions in future studies will be critical for the conduct of informative and reproducible research in the field.

It is also very clear that more research is needed with regard the role of vitamin D in cancer survival. As described above, substantial research has been conducted regarding the role of genetic variation in *VDR* in cancer risk and mortality, and some recent studies have examined variation in other vitamin D-related genes with respect to these outcomes. In addition to continuing to explore these non-*VDR* vitamin D-related genetic associations with cancer, there may be important interactions between vitamin D status and vitamin D-related genetic variation that have not yet been fully elucidated but deserve evaluation.

Observational studies with prospectively collected blood samples, germline DNA, and, ideally, tumor tissue samples, will be required to conduct these nuanced investigations that will be necessary to adjudicate the apparent inconsistencies in the vitamin D-cancer research literature. Large cancer chemoprevention trials of vitamin D are ongoing, most notably the Vitamin D and Omega-3 (VITAL) trial that has randomized women and men to 2,000 IU/day of vitamin D (plus 1 g of fish oil) or placebo, and should be completed before 2020 (146). Given that the trial is powered to test the preventive efficacy for overall cancer and major cardiovascular disease events combined, it is likely to have insufficient statistical power to definitively examine individual cancer sites and provide conclusive evidence for benefit (or harm). This limitation will be compounded with regard to cancer subtypes and exploration of subgroup-specific effects (e.g., supplementation interactions with sex, menopausal status, and specific tumor histologies). One means by which to address these issues is the pooling of data from multiple observational studies to collectively achieve large sample sizes. The Pooling Project of Circulating Biomarkers and Breast and Colorectal Cancer Consortium is 1 such ongoing effort comprising data from 21 prospective studies of circulating 25(OH)D that is examining the association with these 2 commonly diagnosed malignancies (147). Results from these and other pooled investigations should help to provide a consensus for some of the questions and inconsistencies discussed here, and they may identify subgroups of individuals who would benefit from increased vitamin D status more than others. In particular, the association between vitamin D and cancer in black men and women, and whether this association differs from that in white individuals, warrants substantially increased attention from the scientific community. Whether the well-documented lower vitamin D status in blacks contributes to the racial disparities in cancer incidence and mortality in the United States should be more aggressively investigated through new and larger studies in this population.

One other important gap preventing the establishment of clear guidelines with respect to vitamin D and cancer is the inconsistency of laboratory assays for vitamin D (148). This

weakness is cited by the USPSTF as one of the reasons that screening for vitamin D deficiency received an "I" rating (133). There are many different laboratory assay methods available for measuring circulating 25(OH)D, and the accuracy of these methods varies. In the existing literature, results are frequently reported comparing the highest with the lowest quantiles of circulating 25(OH)D within a study. However, both the laboratory methods used and the distribution of circulating 25(OH)D and, therefore, the cutpoints for these quantiles vary from study to study. This makes comparison across investigations and establishing optimal recommended blood concentrations, or supplementation dosages of vitamin D, for cancer prevention challenging if not outright difficult. Several aforementioned meta-analyses attempt to use dose-response methods to take into account the absolute concentrations of 25 (OH)D in individual studies and, in some cases, nonlinear associations are suggested (17, 26). The Vitamin D Standardization Program is an ongoing collaborative effort led by the National Institutes of Health Office of Dietary Supplements to standardize the laboratory measurement of vitamin D status in both research and clinical settings, using standard reference materials available from the National Institute of Standards and Technology (149). This program has developed a reference measurement system to establish worldwide standardization of 25(OH)D assays, including a certification program for clinical laboratories, the use of National Institute of Standards and Technology standards as "trueness" controls, and statistical procedures for standardizing 25(OH)D values from completed studies. Future investigations should incorporate 1 or more of these methods and resources in order to both facilitate cross-study comparisons and maximize the usefulness of research data for the potential establishment of cutpoints for vitamin D deficiency and sufficiency with respect to cancer risk and survival.

Despite extensive research on vitamin D and cancer risk, important gaps in our knowledge exist with respect to cancer survival, tumor subtypes, interactions between vitamin D and other factors including genetic variation, and vitamin D and cancer risk in black populations. We do not believe there is currently sufficient new information to support a meaningful update to the recommendations from the National Academy of Medicine of the National Academies of Sciences, Engineering, and Medicine or the USPSTF. Addressing these gaps should provide the new data needed to help inform evidence-based recommendations for or against the use of vitamin D supplements for primary and secondary cancer prevention that cannot be made at this time. Until then, and with few exceptions, the scientific community remains unable to make evidence-based recommendations related to optimal 25(OH)D concentrations or for or against the use of vitamin D supplementation for primary or secondary prevention of any cancer site.

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