Vitamin D Status and Cancer Incidence, Survival, and Mortality

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Abstract

Over the last several decades, extensive research on vitamin D and its role on cancer incidence, cancer survival (survival or mortality from cancer among individuals diagnosed with cancer), and cancer mortality (fatal cases occurring during the study period in an initially cancer-free population) has been conducted. A variety of study designs were implemented to explore vitamin D status, assessed by measuring sun exposure, vitamin D intake, and circulating 25-hydroxyvitamin D (25(OH)D) concentration. Although not many randomized controlled trials have examined the relationship between vitamin D and cancer incidence, observational studies have consistently shown a protective association between vitamin D and cancer incidence, especially for colorectal cancer. In addition, randomized controlled trials and most observational studies suggested that vitamin D plays a role in reducing cancer mortality. The potential benefit of vitamin D on cancer mortality may operate during the pre-diagnostic stages by affecting late-stage tumor progression and metastatic seeding, during the treatment phase by complementing or enhancing effects of therapies, or during the post-diagnostic stages. However, further studies are needed to confirm these conclusions, establish the optimal dosage and timing of vitamin D intakes for the most benefit, find which cancer types are affected, and understand the underlying mechanisms.

Keywords

Vitamin D · Vitamin D supplementation · Vitamin D intake · Sun exposure · Circulating 25(OH)vitamin D · Cancer incidence · Cancer survival · Cancer mortality · Epidemiology

Introduction

There have been numerous efforts in studying the relationship between sun exposure and cancer incidence, survival, and mortality. In the late 1930s, Peller and Stephenson reported higher rates of skin cancer (i.e., 8 times higher) but lower rates of other cancers among the US Navy personnel [1]. Peller and Stephenson suggested that sun exposure induced skin cancer, which consequently conferred immunity against other

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cancers. After several years, Apperly reported an association between latitude and cancer mortality rate in North America [2]. Here, he observed that individuals in high-latitude regions had higher rates of total cancer mortality when compared to those in low-latitude regions. He argued that the "relative immunity to cancer is a direct effect of sunlight [2]." Although the hypothesis that sun exposure may be beneficial against cancer had been proposed early, these observations supporting the hypothesis were ignored for nearly 40 years until a clear mechanism was proposed.

In the 1980s, Garland and Garland suggested that the possible benefits of sun exposure could be attributed to vitamin D [3]. They hypothesized that vitamin D was protective against colon cancer, based on the premise that most vitamin D in humans is made from exposure to solar ultraviolet-B (UV-B) radiation. While this study focused on colon cancer, the proposed protective role of vitamin D was later extended to cancers in breast [4], ovary [5], prostate [6, 7], and other multiple sites [8]. Subsequent laboratory studies supported potential anti-carcinogenic properties of vitamin D, including increased differentiation and apoptosis and inhibited proliferation, invasiveness, angiogenesis, and metastatic potential [9].

This chapter provides a review and synthesis of up-to-date epidemiologic evidence on the association between vitamin D and incidence, survival, and mortality for various cancers. After Garland and Garland's initial hypothesis, numerous epidemiologic studies have supported the protective role of vitamin D (or sun exposure) on different cancer sites. In this chapter, we first discuss epidemiologic studies that assessed the association between serum vitamin D levels and cancer incidence, survival, and mortality and then discuss vitamin D intake studies, including evidence from recent randomized controlled trial (RCT) data. We consider three endpoints: cancer incidence (newly onset cases diagnosed during the study period in an initially cancer-free population), cancer mortality (fatal cases occurring during the study period in an initially cancer-free population), and cancer survival (survival or mortality from cancer among individuals already diagnosed with cancer).

25-hydroxyvitamin D, Cancer Incidence, Survival, and Mortality

Many initial studies on this topic were ecological studies that examined population cancer incidence or mortality rates in relation to latitudes or regions that differ in UV-B radiation exposure [3–8]. These studies, in general, found that populations residing in regions of higher solar UV-B exposure generally had lower incidence and mortality rates of cancer. Similar findings were reported in Australia, China, France, Japan, and Spain, and at least 15 types of cancer, especially colorectal cancer, were shown to correlate with low sun exposure [10, 11]. An important limitation of ecological studies is that factors that are correlated with latitude or UV-B exposure may be the causal factors (confounders) rather than the UV-B exposure itself. However, the inverse association between regional solar UV-B exposure and cancers was not only observed in the United States but also in other regions such as Japan [12], China [13], and Spain [14]. The unlikelihood that potential confounders have similar relationships with solar UV-B exposure in all these different regions supports the hypothesis that the inverse association between UV-B exposure and cancers is causal.

While ecological studies examine exposure and outcome at the population level, case-control and cohort studies ("analytic epidemiologic studies") assess hypotheses at the individual level. Since more detailed information on covariates can be obtained in analytic studies, confounding is often better controlled for in case-control and cohort studies than ecological studies. In the recent 20 years, there have been numerous epidemiological studies (primarily cohort studies) assessing circulating 25-hydroxyvitamin D (25(OH)D) levels in relation to cancer risks. Since serum- or plasma-based studies provide the most definite evidence for the role of vitamin D in observational studies, we mainly review evidence from such study designs to assess relationships

between vitamin D and colorectal cancer, breast cancer, prostate cancer, and other cancers. Studies that measured 25(OH)D levels for individuals who were already diagnosed with cancer should be interpreted with caution because of the potential for reverse causation, which is, the cancer may lead to low levels of 25(OH)D rather than vice versa. For example, the cancer may cause pathophysiologic changes that lower 25(OH)D levels or lead to behaviors due to illness that reduce sun exposure.

Colorectal Cancer

Colorectal cancer has been studied the earliest and the most in relation to vitamin D, specifically vitamin D deficiency. In general, studies have consistently shown that low levels of 25(OH)D were associated with higher risks of colorectal cancer or adenoma.

Cancer Incidence

Studies that supported an inverse association between vitamin D and incidence of colorectal cancer were from various populations including the Nurses' Health Study (NHS) [15], the Health Professionals Follow-up Study [16], the Women's Health Initiative [17], the Japan Public Health Center-based Prospective Study [18], the European Prospective Investigation into Cancer and Nutrition Study (EPIC) [19], and the Multiethnic Cohort Study [20]. These are among the largest prospective cohort studies of cancer.

Meta-analyses also found evidence favoring a protective association. In a meta-analysis published in 2007, Gorham et al. reported that serum 25(OH)D levels of $\geq$33 ng/mL were associated with a 50% lower risk of colorectal cancer compared to that of relatively low values of $\leq$12 ng/mL[21]. From this evidence, the authors suggested that daily intake of 1000–2000 IU/day of vitamin D would reduce colorectal cancer incidence. In support of this, another meta-analysis published in 2011 showed that based on 2630 cases, the summary relative risk for a 10 ng/mL increase in serum 25(OH)D was 0.85 (95% confidence interval [CI]: 0.79 to 0.91) [22]. In a recent large pooling project of 17 cohorts with 5706 colorectal cancer cases and 7107 controls, deficient 25(OH)D levels of <30 nmol/L were associated with 31% higher colorectal cancer risk, compared to 25(OH)D levels of 50 to <62.5 nmol/L (95% CI: 1.05 to 1.62) [23]. Intriguingly, this study reported that the inverse association persisted up until 100 nmol/L; at 25(OH)D levels of $\geq$100 nmol/L, the risk did not decline further and was not statistically significant. The "effective" dosage of vitamin D that the authors suggested on reducing colorectal cancer risk was higher than doses conventionally recommended (optimal concentrations: 75–100 nmol/L[23]). Based on multiple studies and meta-analyses, it is very clear that there is an inverse association between circulating 25(OH)D levels and colorectal cancer risk. Individuals in the highest quartile of 25(OH)D level had approximately half the risk of colorectal cancer incidence compared to those in the lowest quartile. Statistical adjustment for potential confounding factors generally did not affect the estimates for 25(OH)D and cancer.

Cancer Survival

Previous studies have consistently found that higher circulating 25(OH)D levels were associated with better colorectal cancer survival and prognosis. In a prospective study of 1598 patients with stage I to III colorectal cancer, higher plasma 25(OH)D was significantly associated with better colorectal cancer survival [24]. To be specific, compared to patients in the lowest tertile of 25(OH)D, those in the highest tertile had a hazard ratio of 0.68 (95% CI: 0.50 to 0.90) for colorectal cancer-specific deaths (i.e., higher postoperative 25(OH)D levels were related to better survival). In this study, blood samples were collected postoperatively, and the median time to blood sampling was 105 days after the treatment of colorectal cancer. Since factors like acute illness, surgery, or postoperative recovery could affect vitamin D levels, the authors in this study created a variable describing time from definitive treatment to blood sampling. Furthermore, systematic reviews and meta-analyses supported the benefits of higher circulating

25(OH)D in prognosis and survival among colorectal cancer patients [25–27]. For colorectal cancer-specific deaths, the pooled hazard ratio for the highest versus the lowest category of circulating 25(OH)D levels was 0.65 (95% CI: 0.49 to 0.86) [27]. For overall, not cancer-specific deaths of colorectal cancer patients, the corresponding pooled hazard ratio ranged from 0.55 (95% CI: 0.33 to 0.91) [26] to 0.71 (95% CI: 0.55 to 0.91) [27]. It seems clear from the evidence that there is a strong inverse association between circulating 25(OH)D levels and colorectal cancer deaths among patients (i.e., higher circulating levels associated with better colorectal cancer survival). An important thing to note from these meta-analyses is that included studies had different times of blood collection. For example, one of the studies (included in the meta-analysis) showed that higher pre-diagnostic 25(OH)D levels were significantly associated with better survival among colorectal cancer patients (hazard ratio comparing highest quintile versus lowest quintile for cancer-specific deaths, 0.69; 95% CI: 0.50 to 0.93) [28]. However, the authors from this study warranted further studies investigating the potential effects of vitamin D levels before, at, and after colorectal cancer diagnosis and/or treatment.

Prostate Cancer

Along with colorectal cancer, prostate cancer appears to be a well-studied cancer through case-control and cohort studies. However, unlike colorectal cancer studies that showed a clear inverse association, prostate cancer incidence data have been equivocal.

Cancer Incidence

Although some studies [29–34] suggested a weak inverse association between circulating 25(OH)D levels and risk of prostate cancer, most studies [35–38] reported no association between vitamin D and prostate cancer risk. In particular, two studies [39, 40] that were conducted in Nordic countries (where 25(OH)D levels tend to be low due to high-latitude and low UV-B exposure) supported an inverse association. Even these studies remained inconclusive as one [40] of them noted a U-shaped risk of prostate cancer (i.e., an increased risk was observed not only when 25(OH)D level decreased from the reference but also when it increased from the reference). Recent large studies also did not find an association between 25(OH)D levels and prostate cancer risk. For instance, Ahn et al. found no statistically significant association between season-standardized serum 25(OH)D level and prostate cancer risk in a large prospective study [41]. Similarly, in a nested case-control study within the EPIC cohort (652 cases matched to 752 controls), the authors found no statistically significant association between 25(OH)D levels and prostate cancer risk (odds ratio for the highest versus the lowest quintile: 1.28; P for trend: 0.188).

Meta-analyses and Mendelian randomization study also showed mixed results regarding the association between 25(OH)D levels and prostate cancer incidence. A meta-analysis published in 2011 showed that based on 3956 cases, the summary relative risk for a 10 ng/mL increase in serum 25(OH)D was 0.99 (95% CI: 0.95 to 1.03) [22]. Such null association was confirmed in another meta-analysis [42]. A recent Mendelian randomization study also supported this and observed that there was no evidence of a causal association (odds ratio per 25 nmol/L increase: 1.00; 95% CI: 0.93 to 1.07) [43]. Mendelian randomization studies are those that utilize genetic variation in genes of known function (in this case, variation in 25(OH)D levels) to examine the presumed causal effect of exposure on disease. However, with a meta-analysis published in 2014 even suggesting a positive association between 25(OH)D level and prostate cancer risk [44], evidence on prostate cancer remains equivocal. Such discrepancies on the results of prostate cancer studies could potentially be attributed to differences in disease aggressiveness, which is critical to account for in prostate cancer epidemiology [45]. For example, in a recent study that aggregated 19 prospective studies (13,462 incident prostate cancer cases and 20,261 controls), a positive association between serum vitamin D

concentrations and total prostate cancer risk (odds ratio for highest versus lowest quintile: 1.22; 95% CI: 1.13 to 1.31) varied by disease aggressiveness [46]. Specifically, higher 25(OH)D levels were associated with increased risk of non-aggressive disease (odds ratio per 80 percentile increase: 1.24; 95% CI: 1.13 to 1.36) but not aggressive disease (odds ratio: 0.95; 95% CI: 0.78 to 1.15; aggressive disease defined as stage 4, metastases, or prostate cancer deaths). Therefore, although there were some studies suggesting a weak inverse association, studies on circulating 25 (OH)D levels and prostate cancer incidence have been inconclusive.

Cancer Survival and Mortality

The literature on prostate cancer survival and mortality in relation to vitamin D has also been inconsistent. Among studies that assessed post-diagnostic circulating 25(OH)D levels and prostate cancer deaths in patients, one found a significant protective association (relative risk: 0.16 for high levels of serum 25(OH)D versus low serum levels; 95% CI: 0.05 to 0.43 for cause-specific deaths) [47], but the others found no association [48, 49]. However, we noted that one of the studies that found no association had a short median follow-up (31 months) and only included men with stage IV prostate cancer [49]. Advanced cancers (e.g., stage IV prostate cancer) may be less influenced by vitamin D status and modifiable lifestyle factors in general. Not only post-diagnostic but also pre-diagnostic circulating 25(OH)D studies showed inconsistent results. One study found that higher pre-diagnostic plasma 25(OH)D was associated with improved prostate cancer prognosis [50]. To be specific, prostate cancer patients in the lowest 25(OH)D quartile were more likely to die from their cancer compared to those in the highest quartile (hazard ratio: 1.59; 95% CI: 1.06 to 2.39). In support of this, two survival analyses concluded that higher levels of pre-diagnostic serum 25(OH)D (e.g., above 85 nmol/L[51]) could improve survival in prostate cancer patients [51, 52]. On the other hand, results from a large cohort consortium (518 fatal prostate cancer cases and 2986 controls) showed that there was no statistically significant relationship between pre-diagnostic circulating 25(OH)D and fatal prostate cancer (odds ratio for extreme quartiles: 0.86; 95% CI: 0.65 to 1.14) [53]. Although it is suggestive that higher levels of serum 25(OH)Ds are associated with better prostate cancer prognosis and survival, further research is warranted.

Breast Cancer

Breast cancer is one of the cancers that has been studied much in relation to vitamin D. However, the results have been inconsistent, and in general, have not been supportive of an association.

Cancer Incidence

The evidence for breast cancer has been mixed. In a nested case-control study within the NHS cohort (701 breast cancer cases and 724 controls), women in the highest quintile of 25(OH)D had a relative risk of 0.73 (95% CI: 0.49 to 1.07), compared to those in the lowest quintile [54]. Although still statistically insignificant, the association was stronger for women who were 60 years old or older (relative risk: 0.57; 95% CI: 0.31 to 1.04). This result suggested that vitamin D could be an important factor, particularly for postmenopausal breast cancer. Interestingly, a recent study observed an inverse association between total baseline 25(OH)D and breast cancer risk (odds ratio: 0.87 per 10 ng/mL increase; 95% CI: 0.78 to 0.98) [55]. Here, the association remained similar when the analyses were restricted to postmenopausal women. However, this inverse association changed to a significantly positive association when the authors assessed second blood draw measures during follow-up and subsequent breast cancer risk (odds ratio: 1.17 per 10 ng/mL; 95% CI: 1.08 to 1.26). This finding, therefore, suggested that discrepant results among studies on vitamin D and breast cancer incidence may be due to temporal trends in vitamin D and potential reverse causation.

Findings from meta-analyses and Mendelian randomization study were mostly null. A meta-analysis by Gandini et al. reported a null association between 25(OH)D levels and breast cancer

risk among 5 prospective studies (summary relative risk: 0.97 for a 10 ng/mL increase; 95% CI: 0.92 to 1.03) [22]. In support of this, a more recent meta-analysis published in 2014 observed no statistically significant association between blood 25(OH)D levels and breast cancer incidence among 30 prospective studies (pooled relative risk: 0.92; 95% CI: 0.83 to 1.02) [56]. A recent Mendelian randomization study also suggested a null association, and that there was no evidence of a causal association (odds ratio per 25 nmol/L increase: 1.02; 95% CI: 0.97 to 1.08) [43]. Therefore, based on the studies of breast cancer risk in relation to circulating 25(OH)D levels, no clear association was found in general.

Cancer Survival

Many systematic reviews and meta-analyses supported that higher circulating 25(OH)D levels were associated with better breast cancer prognosis and survival [25–27, 57–59]. For example, a meta-analysis published in 2014 reported that low levels of 25(OH)D were significantly associated with higher risks of overall and breast cancer-specific deaths among breast cancer patients (hazard ratio for the highest versus the lowest tertile: 1.52, 95% CI: 1.22 to 1.88 and hazard ratio: 1.74, 95% CI: 1.23 to 2.40, respectively) [58]. Since studies with longer times from diagnosis to blood collection tend to report no association [57], the protective association seemed to be stronger for studies in which blood samples were drawn close to diagnosis. This may be because serum 25(OH)D concentrations could change from therapy or lifestyle modifications after the diagnosis or due to disease worsening [60]. For instance, the association of serum 25(OH)D levels and mortality was statistically significant only for patients whose blood samples were collected prior to chemotherapy [61].

Although there were many studies in support of an association, some studies on breast cancer treatment trials showed no association between 25(OH)D levels and breast cancer prognosis [62–64]. Since these were treatment trials, all these studies measured post-diagnostic 25(OH)D levels after they recruited the cases. One of the studies mentioned that they collected all the blood samples before treatment [63]. One explanation for the differences in the results between observational studies conducted in general cohorts and those in the context of treatment trials could be that trials had stricter inclusion criteria, which led the study population to be more homogeneous. Alternatively, it might be due to a potential that adjuvant therapies negated the adverse effect of low 25(OH)D levels. In addition, it should be noted that information on vitamin D supplementation was not available.

Other Cancer Types

Unlike colorectal, prostate, and breast cancers, other cancers have not been examined much in relation to vitamin D. Furthermore, some cancers are too rare to study in individual cohorts.

Cancer Incidence

There have been some studies that examined 25(OH)D levels and risks of cancers in various sites including skin, lung, and pancreas. In a recent study based on 217,244 individuals, there were significant positive associations between 25(OH)D levels and skin (both non-melanoma and melanoma), prostate, and hematological cancers but a significant inverse association for lung cancer [65]. One nested case-control study of blood 25(OH)D levels and pancreatic cancer risk was based on the cohort of male Finnish smokers (200 incident exocrine pancreatic cancer cases matched to 400 controls) [66]. In this study, higher vitamin D concentrations were associated with almost a threefold increased risk of pancreatic cancer, and the association remained significant even after excluding cases early in follow-up. However, since pancreatic cancer is rare, studying it in individual cohorts could result in relatively less statistical power. Therefore, the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP) was formed to address the role of circulating 25(OH)D in less common cancers [67]. The VDPP, a consortium of ten prospective cohort studies from the United States, Finland, and China, was used to examine the associations between 25(OH)D levels and the

risks of endometrial, kidney, ovarian, pancreatic, and upper gastrointestinal tract cancers and non-Hodgkin lymphoma. The total numbers of cases for each of the malignancies were 830 for endometrial cancer, 775 for kidney cancer, 516 for ovarian cancer, 952 for pancreatic cancer, 1065 for upper gastrointestinal cancers, and 1353 for non-Hodgkin lymphoma. In general, the results from the VDPP showed that there were no statistically significant associations between circulating 25(OH)D levels and risks of cancers mentioned above, except for increased pancreatic cancer risk at high levels ($\geq$ 100 nmol/L) of 25(OH)D [68–73]. However, such a potential positive association between vitamin D and pancreatic cancer incidence has not yet been entirely confirmed. For example, in a pooled analysis of nested case-control studies from 5 cohorts (451 cases and 1167 controls), higher circulating 25(OH)D levels were associated with a lower risk of pancreatic cancer, suggesting an inverse, not a positive, association [74].

Although there was no overall association between 25(OH)D levels and upper gastrointestinal and ovarian cancers in the VDPP, subgroup analyses and results from other studies deserve attention. For instance, there were racial differences in the association between 25(OH)D levels and gastrointestinal cancers. Among Asians, not Whites, lower concentrations of 25(OH)D (< 25 nmol/L) were associated with a lower risk of upper gastrointestinal cancers (odds ratio: 0.53; P for trend: 0.003) [69]. However, such positive association could possibly be attributed to reverse causation because one of the Asian cohorts (Shanghai Men's Health Study) had a short follow-up time of 1.7 years. Besides, undiagnosed cancers at baseline blood draw could have affected the 25(OH)D level. In the subgroup analysis by smoking status, concentrations of <25 nmol/L were associated with a decreased risk of upper gastrointestinal cancers among never smokers. Regarding ovarian cancer, a nested case-control study within the Finnish Maternity Cohort observed that having sufficient (> 75 nmol/L) serum 25(OH)D levels compared to insufficient serum 25(OH)D was associated with a decreased risk (odds ratio: 0.32; P-value: 0.03), suggesting an inverse association [75].

Cancer Survival and Mortality

Studies on overall cancer survival and mortality have generally found better prognosis and lower mortality for those with higher 25(OH)D levels. In a meta-analysis of 12 cohort studies, lower 25(OH)D levels were associated with more cancer deaths (pooled relative risk comparing bottom versus top thirds: 1.14; 95% CI: 1.01 to 1.29) [76]. This part of the meta-analysis assessed cancer mortality rather than cancer survival because eligible observational cohort studies included healthy participants at baseline. Similar findings were also reported for cancer survival among patients. A recent study with 4616 cancer cases (2884 died of their cancer during 28 years of follow-up) found that higher 25(OH)D levels were associated with better overall cancer survival (hazard ratio for the highest versus the lowest quintile: 0.76; 95% CI: 0.67 to 0.85) [77]. Here, cancer cases were drawn from the previous nested case-control studies of circulating 25(OH)D levels and cancer risk within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Fasting blood samples were collected at baseline (pre-diagnostic) and stored until analysis. This study also found that significant inverse associations were present for kidney cancer deaths among kidney cancer patients (hazard ratio: 0.59; 95% CI: 0.35 to 0.98) and melanoma deaths among melanoma patients (hazard ratio: 0.39; 95% CI: 0.20 to 0.78), but a significant positive association for lung cancer deaths among lung cancer patients (hazard ratio: 1.28; 95% CI: 1.02 to 1.61).

Studies on vitamin D in relation to lung cancer, lymphoma, melanoma, and pancreatic cancer prognoses, individually, are worthy of notice. For lung cancer, two studies in Norway (which collected serum samples within 90 days of cancer diagnosis) [78] and the United States (which collected samples at the time of diagnosis) [79] observed better survival for patients with higher circulating serum levels of 25(OH)D. However, this was not supported in a small Chinese study with 87 cases [80]. Besides, two studies on

advanced non-small-cell lung cancer did not find any significant association between post-diagnostic serum 25(OH)D levels and cancer survival [81, 82]. In a study of 500 Finnish men, pre-diagnostic serum 25(OH)D levels (median time from blood collection to diagnosis was 10 years) were also not significantly associated with lung cancer survival (hazard ratio comparing the highest to the lowest quartile: 1.18; 95% CI: 0.89 to 1.56) [83]. This study found suggestive associations between higher serum 25(OH)D and better survival from adenocarcinoma (hazard ratio: 0.64; 95% CI: 0.17 to 2.45) and small cell carcinoma (hazard ratio: 0.55; 95% CI: 0.21 to 1.45). However, these estimates were based on a relatively small number of cases and were not statistically significant. A similar null result was observed for lung cancer mortality as well as survival. In a study that analyzed 258 cases of lung cancer deaths, the authors found that there was no association between serum 25(OH)D levels and overall lung cancer mortality. They observed that among nonsmokers, $\geq$ 44 nmol/L versus <44 mol/L of serum 25(OH)D was associated with a decreased risk of lung cancer mortality (hazard ratio: 0.53; 95% CI: 0.31 to 0.92) [84]. Although there were many studies reporting null associations, there were some studies suggesting that higher circulating vitamin D levels could be associated with better lung cancer survival.

Although not many, some studies examined lymphoma, melanoma, and pancreatic cancer prognoses with respect to 25(OH)D levels. In the meta-analysis that showed significant inverse associations between 25(OH)D levels and colorectal and breast cancer deaths, higher 25(OH)D levels measured at or near the time of diagnosis were associated with better lymphoma outcomes (pooled hazard ratio for the highest versus the lowest quartile: 0.48; 95% CI: 0.36 to 0.64) [26]. Other studies also showed that higher 25(OH)D levels collected at or near diagnosis were associated with favorable prognosis in melanoma [85–87]. For pancreatic cancer, a study of 256 cases showed that baseline 25(OH)D levels were not associated with progression free or overall survival [88]. However, the authors of this study noted that baseline 25(OH)D levels in cancer patients might represent inadequate nutrition or limited outdoor activity due to the burden of cancer, instead of true steady state [89]. Also, since the median overall survival was very short (less than 6 months) and most of the cases had deficient (< 20 ng/mL; 44.5% of the cases) or insufficient (< 30 ng/mL; 22.5% of the cases) levels of vitamin D, it might have been hard to find an association. To sum up, 25(OH)D levels seem to be inversely associated with cancer deaths in general.

Vitamin D Intake Trials

As RCTs are considered to be a gold standard for epidemiologic evidence (i.e., a causal association), we discuss the results on trials of vitamin D intake and cancer incidence and mortality in this section. We are able to draw a causal inference in a well-designed RCT as issues on confounding will ideally be removed with effective randomization.

Randomized Controlled Trials (RCTs) of Vitamin D and Cancer Incidence

There are not many RCTs that have examined the relationship between vitamin D intake and cancer incidence. Since studies, in general, suffer from a lack of statistical power when examining specific cancers, some trials assessed the role of vitamin D supplements on total cancer incidence. In a meta-analysis summarizing these trials, the authors reported that vitamin D supplementation had no effect on total cancer incidence (summary relative risk: 1.00; 95% CI: 0.94 to 1.06; 4 RCTs with 4333 combined cases) [90]. However, they noted that this summary measure was based on relatively short duration (2–7 years of duration) and a limited dosage (400 to 1100 IU per day). A recent large randomized trial in the United States called the Vitamin D and Omega-3 Trial (VITAL) also found that vitamin D supplementation was not associated with a lower risk of invasive cancer [91]. VITAL was a randomized controlled study

of vitamin D at a dose of 2000 IU per day and omega-3 fatty acids at 1 g per day on cancer and cardiovascular disease among US men (≥ 50 years old) and women (≥ 55 years old). Among the total of 25,871 participants that were followed for a median of 5.3 years, 1617 were diagnosed with cancer (793 in the vitamin D group and 824 in the placebo group). The hazard ratio of the vitamin D group to the placebo group was 0.96, with a 95% CI of 0.88 to 1.06 (P = 0.47). In the VITAL study, supplementation of vitamin D also did not reduce the occurrences of colorectal, breast, and prostate cancers.

The results from VITAL were included in a new meta-analysis of cancer incidence [92]. This updated meta-analysis comprised 10 trials (6547 cases; 3–10 years of follow-up; 54–135 nmol/L of attained levels of circulating 25(OH)D in the intervention group). The summary RR was 0.98 (95% CI: 0.93 to 1.03; P = 0.42). The results remained null across subgroups tested, including even when attained 25(OH)D levels exceeded 100 nmol/L (RR: 0.95; 95% CI: 0.83 to 1.09; P = 0.48).

RCTs of Vitamin D and Cancer Mortality

Unlike the results on cancer incidence, results on cancer mortality tend to show an inverse association. In the meta-analysis mentioned above, the authors found that vitamin D supplementations significantly reduced total cancer mortality (summary relative risk: 0.88; 95% CI: 0.78 to 0.98; three RCTs with combined 1190 cases) [90]. This meta-analysis included RCTs on cancer mortality, not survival. Although only marginally significant, VITAL results also showed a protective association between vitamin D supplementations and cancer mortality (hazard ratio: 0.83; 95% CI: 0.67 to 1.02; 341 cancer deaths, with 154 in the vitamin D group and 187 in the placebo group) [91]. This association became stronger and significant in the analysis that excluded the first 2 years of follow-up, a pre-specified analysis (hazard ratio: 0.75; 95% CI: 0.59 to 0.96). It is common to exclude early years of follow-up in analyzing trials on diet and cancer because the effects of nutritional factors become clear only after a certain period of time, especially for slow-growing diseases like cancer. In an updated meta-analysis [92], five trials were included to study total cancer mortality. These studies entailed 1591 deaths over 3–10 years of follow-up. The summary RR for vitamin D compared to placebo was 0.87 (95% CI: 0.79 to 0.96; P = 0.005). This result was largely attributable to interventions with daily dosing, rather than infrequent bolus dosing. No statistically significant heterogeneity was observed by attained levels of circulating 25 (OH)D above or below 100 nmol/L.

Conclusions

Over the last several decades, vitamin D has received substantial interest in relation to the common cancers and less so for the rarer malignancies. For cancer incidence, a consistent inverse association has only been observed for colorectal cancer in observational studies. RCTs also have not supported a general effect of vitamin D on cancer incidence. Although these RCTs potentially provide more evidence for a causal association, there exist some important limitations. Trials with extended duration are warranted for studies on cancer incidence because long durations are often required to observe an effect. For example, epidemiologic evidence suggests that at least 10 years are needed for any influence of calcium or vitamin D to show on colorectal cancer occurrence [93]. Since most cancers generally arise through a multi-stage process that lasts for a long period of time, studies with relatively short duration may not capture the benefit of vitamin D on cancer risk, if there is any. In addition, in trials, it is difficult to choose a single "proper" or "effective" dosage that a susceptible population could benefit from. Therefore, although RCTs are generally considered as a gold standard, their results should still be interpreted with caution for issues mentioned above and other issues such as noncompliance.

In contrast to the studies on cancer incidence, both RCTs and many though not all observational studies suggest that vitamin D may play a role in

cancer mortality or survival. Approximately a 15% reduction in total cancer mortality was observed in those who were randomized to receive vitamin D supplements over placebo, and the VITAL study suggested that this effect size could increase over the duration of vitamin D use. Most of the follow-up time in the studies was less than 5 years. In VITAL, after excluding the first 2 years, the risk reduction was 25%. Benefits were seen even at fairly high doses of 2000 IU/day and when levels of >100 nmol/L were attained. While the reason for the divergent findings for incidence and mortality of total cancer is not apparent, plausible mechanisms exist for vitamin D operating at multiple stages of carcinogenesis. Vitamin D may decrease tumor invasiveness and propensity to metastasize, which may occur at the late stages of carcinogenesis. In the RCTs, which showed benefits on mortality, vitamin D administration generally started before cancer diagnosis, likely during the late stages of carcinogenesis and continued during and after diagnosis. Thus, the potential benefit for vitamin D status on cancer mortality could operate during the pre-diagnostic stages by affecting late-stage tumor progression (e.g., invasion) and metastatic seeding, during the treatment phase possibly by complementing or enhancing effects of therapies, or during the post-diagnostic stages. It is unclear if similar benefits could be conferred by beginning vitamin D treatment at the time of diagnosis because some of the effects of vitamin D could be occurring during the metastatic seeding phase in the pre-diagnostic period.

Almost 10 million cancer deaths were projected to occur in 2018 worldwide [94]. With increasing population size and aging, cancer incidence and mortality is likely to increase over time. The results from meta-analyses support that achieving circulating levels of 25(OH)D around 54–135 nmol/L may contribute to reducing cancer mortality. Although the optimal 25(OH)D level for prevention is not established, it is likely to be higher than 50 nmol/L, and currently, a substantial portion of the world's population is below even this threshold. The Endocrine Society recommends at least 1500–2000 IU/day intake of vitamin D to maintain the levels of 25(OH)D above 75 nmol/L [95]. Further studies are needed to confirm our conclusions, establish the optimal dose and timing of vitamin D intakes for prevention, find which cancer types are affected, and determine the underlying mechanisms of action.

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