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Vitamin D and Cancer Survival: Does Vitamin D Supplementation Improve the Survival of Patients with Cancer?

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Abstract

Purpose of Review Clinical evidence suggesting the beneficial effects of vitamin D on survival of patients with cancer has been accumulating. Recent articles were thoroughly reviewed to determine if there is enough evidence to conclude that vitamin D supplementation improves survival of patients with cancer.

Recent Findings Meta-analyses of observational studies showed that higher blood 25-hydroxyvitamin D levels in patients with cancer at a variety of sites were associated with lower cancer-specific and overall mortalities. Moreover, meta-analyses of randomized clinical trials (RCTs) also suggested that vitamin D supplementation improved the survival of patients with cancer. However, each RCT used in these meta-analyses, as well as very recent RCTs, e.g., the SUNSHINE and the AMATERASU trial, did not show statistical significance in the primary results.

Summary For now, compelling evidence that vitamin D supplementation effectively improves survival of patients with cancer is lacking. Thus, confirmatory RCTs are still obligatory for the future.

Keywords Mortality · Vitamin D3 · 25-hydroxyvitamin D · Prognosis · Relapse-free survival · Meta-analysis

Introduction

According to a report by the International Agency for Research on Cancer, 17 million new cancer cases occurred and 9.6 million people died from cancer in 2018 [1], suggesting that more than half of patients with cancer die from cancer progression. Recently, immune-checkpoint inhibitors have emerged and achieved impressive success in cancer treatment, but only a subset of patients derive clinical benefit [2], and a reasonable number of patients have adverse events [3]. More importantly, the cost of cancer care has been increasing rapidly with the emergence of these immune-checkpoint inhibitors [4]. Thus, vitamin D supplementation, which is much less toxic and much more cost-effective, deserves continued exploration for patients with cancer.

Vitamin D is synthesized from 7-dehydrochoresterol under the skin exposed to sunlight, and is taken through diet, or a supplement, and it is metabolized in the liver to 25-hydroxyvitamin D (25[OH]D), a biomarker of vitamin D status. The 25(OH)D is further activated in the kidneys by 1αhydroxylase to 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), which facilitates calcium absorption and is associated with bone health. In addition, most tissues, as well as cancers, have both 1αhydroxylase to convert blood 25(OH)D to 1,25(OH)2D and vitamin D receptors (VDR), a steroid hormone nuclear receptor that regulates a variety of genes within a cell, by which vitamin D is hypothesized to prevent cancer relapse and progression through inhibiting cell proliferation, angiogenesis, and metastasis, while inducing apoptosis and differentiation [5]. Indeed, clinical evidence suggesting the

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beneficial effects of vitamin D on cancer survival has been accumulating. Recent articles within 5 years were thoroughly reviewed to determine whether further evidence is needed to prove that vitamin D supplementation improves the survival of patients with cancer.

Colorectal Cancer

In terms of relationships between 25(OH)D and cancer survival, colorectal cancer is one of the most researched malignant neoplasms. A previous meta-analysis of observational studies [6] and its updated meta-analysis [7] showed improved survival with higher blood 25(OH)D levels in patients with colorectal cancer. The hazard ratio (HR) for all-cause death was 0.68 (95% confidence interval (CI) 0.55 to 0.85), and that for cancer-specific death was 0.67 (95% CI 0.57 to 0.78) in patients with higher blood 25(OH)D levels compared to those with lower levels [7] (Table 1). These findings for colorectal cancer survival were further verified in prospective cohort studies including 1016 patients with stage III colon cancer receiving adjuvant chemotherapy [8]. The highest quintile of predicted 25(OH)D score was associated with significantly improved hazard for disease recurrence or death (HR, 0.62; 95% CI, 0.44–0.86) and for all-cause death (HR, 0.55; 95% CI, 0.38–0.80), and this benefit appeared consistent across molecular tumor characteristics, including microsatellite instability and *KRAS*, *BRAF*, *PIK3CA*, and *TP53* mutation status [8]. Similarly, another study with two cohorts, which both included over 1600 patients with stages I to III colorectal cancer undergoing curative surgery, showed an association between higher 25(OH)D tertile and a reduced risk of colorectal cancer death (HR, 0.69; 95% CI, 0.46 to 0.91), as well as all-cause death (HR, 0.68; 95% CI, 0.50 to 0.85), independent of C-reactive protein as a marker of the systemic inflammatory response [9].

In 2019, a double-blind, phase II, randomized, clinical trial (RCT) of 139 patients with advanced or metastatic colorectal cancer receiving mFOLFOX6 plus bevacizumab chemotherapy to determine the effect of vitamin D supplementation on progression-free survival was reported [10••]. In this SUNSHINE trial, the median progression-free survival with high-dose vitamin D3 (Loading dose of 8000 IU/d for cycle 1 followed by 4000 IU/d for subsequent cycles) was 13.0 months vs. 11.0 months with standard-dose vitamin D3 (400 IU/d for all cycles), with no statistically significant difference [10••]. The authors commented that this finding warrants further evaluation because of the small sample size and its phase II nature. Following the results of the SUNSHINE trial, a larger, multicenter, randomized, double-blind, phase III trial is ongoing (NCT04094688, ClinicalTrials.gov identifier).

In summary, results regarding colorectal cancer and vitamin D were considered to be opposite; high blood 25(OH)D levels were significantly associated with longer survival in observational studies, whereas progression-free survival in the RCT was not significantly improved by vitamin D supplementation without multivariate adjustment. Discrepancies between observational studies and the RCT suggest that higher blood 25(OH)D levels can be confounded largely by healthy lifestyles.

Lung Cancer

In meta-analyses of observational studies, higher blood 25(OH)D levels were associated with better non-small cell lung cancer prognosis: an increase of 4 ng/mL in blood 25(OH)D was associated with a 7% reduction in non-small cell lung cancer mortality [11] (Table 1), and low blood 25(OH)D levels were significantly correlated with poor overall survival [12]. In an RCT conducted at university-affiliated hospitals in Japan, results suggested that vitamin D3 supplementation (1200 IU/d) improved both relapse-free survival and overall survival in a subgroup of patients with early-stage lung adenocarcinoma and lower blood 25(OH)D levels, but not in the total study population [13••].

In summary, the evidence mentioned above is suggestive but does not prove that vitamin D supplementation has beneficial effects on survival of patients with lung cancer.

Breast Cancer

In a meta-analysis of 6 prospective cohort studies including a total of 6092 patients with breast cancer, high blood 25(OH)D levels were significantly associated with low breast cancer mortality (relative risk (RR), 0.58; 95% CI, 0.40 to 0.85), as well as overall mortality (RR, 0.61; 95% CI, 0.48 to 0.79) [14] (Table 1). Another meta-analysis of 6 studies including 5984 patients showed a similar inverse association between high blood 25(OH)D levels and overall survival, with a linear dose-response [15]. This protective effect of blood 25(OH)D levels for breast cancer survival was verified in a population-based prospective cohort study; blood 25(OH)D levels were lower in women with advanced-stage tumors than in early-stage, the lowest in premenopausal women with triple-negative breast cancer, and women with the highest tertile compared with the lowest tertile of blood 25(OH)D levels had better overall survival with adjustment for clinical prognostic factors (HR, 0.72; 95% CI, 0.54 to 0.98) [16].

In summary, in breast cancer, observational studies indicated that lower blood 25(OH)D levels could predict a poor prognosis. However, an RCT of vitamin D supplementation to investigate the effect in patients with breast cancer as the primary endpoint has not yet been reported.

Table 1 Meta-analyses of observational studies

First author (year)	# Study	# Participants	Outcomes	HR[*1]	95% CI[*2]	Journal	Ref.
Colorectal cancer							
Maalmi H (2014)	5	2330	Overall survival highest vs. lowest blood 25(OH)D levels	0.71	0.55–0.91	Eur J Cancer	6
			Cancer-specific survival highest vs. lowest blood 25(OH)D levels	0.65	0.47–0.82		
Maalmi H (2018)	11	7718	Overall survival highest vs. lowest blood 25(OH)D levels	0.68	0.55–0.85	Nutrients	7
			Cancer-specific survival highest vs. lowest blood 25(OH)D levels	0.67	0.57–0.78		
Lung cancer							
Feng Q (2017)	4	NA[*3]	Cancer mortality per 4 ng/mL increment of blood 25(OH)D levels	0.93	0.88–0.96	Medicine (Baltimore)	11
	5	NA[*3]	Cancer survival per 4 ng/mL increment of blood 25(OH)D levels	1.04	0.91–1.17		
Huang JD (2017)	5	1501	Unadjusted cancer mortality for low blood 25(OH)D levels	1.30	1.08–1.55	Bull Cancer	12
	8	2166	Adjusted cancer mortality for low blood 25(OH)D levels	1.25	0.93–1.67		
Breast cancer							
Kim Y (2014)	6	6092	Overall survival highest vs.lowest blood 25(OH)D levels	0.61	0.48–0.79[*3]	Br J Cancer	14
			Cancer-specific survival highest vs. lowest blood 25(OH)D levels	0.58	0.40–0.85[*3]		
Hu K (2018)	6	5984	Overall survival highest vs. lowest blood 25(OH)D levels	0.67	0.56–0.79	Integr Cancer Ther	15
			Overall survival per 4 ng/mL increment of blood 25(OH)D levels	0.88	0.84–0.93		
Prostate cancer							
Song ZY (2018)	7	7807	All-cause mortality per 8 ng/mL increment of blood 25(OH)D levels	0.91	0.84–0.98	Endocr Connect	17
			Cancer-specific mortality per 8 ng/mL increment of blood 25(OH)D levels	0.91	0.87–0.97		
Hematologic malignancy							
Wang W (2015)	7	2643	Overall survival low vs. normal blood 25(OH)D levels	1.85	1.54–2.23	Cell Physiol Biochem	19
			Relapse-free survival low vs. normal blood 25(OH)D levels	1.45	1.25–1.70		
Pancreatic cancer							
Zhang X (2017)	5	1613	Cancer mortality high vs. low blood 25(OH)D levels	0.81	0.68–0.96	Oncotarget	32
All cancers							
Han J (2019)	16	101,794	Cancer mortality highest vs. lowest blood 25(OH)D levels	0.81	0.71–0.93[*3]	Nutrients	35

*[1] Hazard ratio

*[2] Confidence interval

*[3] Not available

*4 Relative Risk, not Hazard Ratio

Prostate Cancer

In a meta-analysis of 7 cohort studies including a total of 7807 patients with prostate cancer, an increment of 8 ng/mL in the blood vitamin D level was associated with reduction in prostate cancer-specific mortality (HR, 0.91; 95% CI, 0.87 to 0.97), as well as all-cause mortality (HR, 0.91; 95% CI, 0.84 to 0.98) [17] (Table 1). In contrast, another meta-analysis of 3 RCTs with 1273 prostate cancer patients given vitamin D supplementation (including oral vitamin D3 4 μg once to three times per 1 cycle chemotherapy and doxercalciferol 10 μg/d) showed that total mortality was not significantly different between the vitamin D and placebo groups (RR, 1.05, 95% CI, 0.81 to 1.36), although the heterogeneity among trials was high [18].

In summary, whether there is a beneficial association of vitamin D with prostate cancer survival remains controversial.

Hematologic Malignancy

A meta-analysis of 7 prospective cohort studies including 2643 patients with hematological cancer suggested that lower blood 25(OH)D levels, compared with normal blood 25(OH)D levels, were significantly associated with both poor relapse-free survival (HR, 1.45, 95% CI, 1.25 to 1.70) and poor overall survival (HR, 1.85, 95% CI, 1.54 to 2.23) [19] (Table 1).

In B cell lymphoma, two prospective cohort studies including patients with follicular lymphoma who received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy plus an anti-CD20 antibody or chemotherapy plus rituximab demonstrated an association between vitamin D deficiency and a poor prognosis [20]. Similar findings were also shown in patients with diffuse large B cell lymphoma treated with CHOP plus rituximab [21], and in patients with follicular lymphoma with other than rituximab-containing treatment [22]. About myeloid malignancies, in a retrospective study including patients with hematologic malignancies undergoing allogeneic transplantation, 25(OH)D deficiency (< 20 ng/mL) before allogeneic transplantation was significantly associated with a higher relapse rate (HR, 2.55; 95% CI, 1.21 to 5.39), and this finding was validated in another independent cohort [23].

In a post hoc analysis of the Woman's Health Initiative RCT of calcium and vitamin D supplementation (400 IU daily), a protective association between the intervention and cancer-specific mortality was found in lymphoid malignancies (HR, 0.46; 95% CI, 0.24 to 0.89), but not in overall hematologic malignancy (HR, 0.77; 95% CI, 0.53 to 1.11) [24].

In summary, high blood 25(OH)D levels and vitamin D supplementation appeared to be associated with a better prognosis in patients with hematologic malignancies, but results in each disease were not always consistent. An RCT investigating vitamin D supplementation is ongoing (NCT 02553447 ClinicalTrials.gov identifier).

Melanoma

In two cohort studies including 2182 and 1042 patients, respectively, with melanoma, a dose-dependent protective effect of high blood 25(OH)D levels at diagnosis on melanoma-specific death was observed [25, 26]. In contrast, in another prospective cohort study including 1171 patients and a post hoc analysis of an RCT including 341 patients with melanoma, blood 25(OH)D levels at diagnosis were not associated with risk of relapse, death, or both [27, 28].

In summary, whether there is an association between high blood 25(OH)D levels and improved survival outcomes is still controversial. A multicenter, phase III trial of monthly bolus vitamin D supplementation to improve relapse-free survival, including patients with surgically resected stage IB-III, is ongoing [29] (NCT01748448, ClinicalTraials.gov identifier).

Other Cancers

Inverse associations between vitamin D and cancer survival were also reported in a variety of other cancer sites, but recent articles regarding the following cancer sites were examined: head and neck, esophageal, pancreatic, kidney, and ovarian cancers. A prospective cohort study including 434 patients with head and neck cancer showed the inverse trend between total vitamin D intake and recurrence (Q4 vs. Q1: HR, 0.47; 95% CI, 0.20 to 1.10) [30]. In a prospective cohort study including 303 patients with esophageal cancer, vitamin D supplement use was associated with longer disease-free survival (HR, 0.61; 95% CI, 0.38 to 0.98) [31]. In patients with pancreatic cancer, a meta-analysis of five cohort studies including a total of 1613 patients showed that high blood 25(OH)D levels were inversely associated with pancreatic cancer-specific mortality (HR, 0.81; 95% CI, 0.68 to 0.96) [32] (Table 1). For urological cancers other than prostate cancer, a prospective cohort study including 630 patients with renal cell carcinoma indicated that blood 25(OH)D levels at diagnosis were inversely associated with all-cause mortality (HR, 0.57; 95% CI, 0.34 to 0.97) [33]. For gynecological cancer, in an observational study including 670 patients with ovarian cancer, higher blood 25(OH)D levels at diagnosis were significantly associated with better survival (HR, 0.93; 95% CI, 0.88 to 0.99 per 4 ng/mL) [34].

In summary, associations between vitamin D intake or high blood 25(OH)D levels and prolonged survivals were reported only in observational studies among patients with cancers at other sites, and they remain to be confirmed through RCTs.

All Cancers

Regarding vitamin D and cancer mortality, four meta-analyses including tens of thousands of participants, were presented in 2019. One meta-analysis of 16 prospective cohort studies including more than 100,000 patients demonstrated that higher blood 25(OH)D levels were not significantly associated with cancer incidence, but significantly associated with decreased risk of cancer-specific death: HR, 0.81; 95% CI, 0.71 to 0.93 [35] (Table 1). Three meta-analyses of RCTs, each of which included more than 70,000 participants, reported almost the same results that vitamin D3 supplementation (ranged from 400 IU/d to 3279 IU/d) significantly reduced the risk of

cancer-specific death: HR, 0.87; 95% CI, 0.79 to 0.96 [36•]; HR, 0.87; 95% CI, 0.79 to 0.95 [37]; and HR, 0.84; 95% CI, 0.74 to 0.95 [38•], even though each individual RCT had a null result (Table 2). In contrast, 25(OH)D or vitamin D supplementation was not significantly associated with the risk of cancer incidence [36•, 37]. Moreover, another meta-analysis found that vitamin D supplementation was not associated with all-cause mortality, cardiovascular mortality, or non-cancer, non-cardiovascular mortality, but only with significant risk reduction in cancer-cause mortality [38•].

In summary, all four meta-analyses reported in 2019 suggested that vitamin D may reduce cancer mortality by more than 10%. .

Randomized Clinical Trials

Recent RCTs of vitamin D supplementation given post diagnosis including the SUNSHINE trial among patients with advanced or metastatic colorectal cancer [10••], the AMATERASU trial involving patients with digestive tract cancers from the esophagus to the rectum [39••], and another trial involving patients with non-small cell lung cancer [13••], did not show significant differences in progression or relapse-free survival (RFS) between vitamin D and placebo in the primary results. However, results of these RCTs are not necessarily considered negative. For example, the SUNSHINE trial [10••], as well as the AMATERASU trial [39••], indeed showed a beneficial association with adjustment, and the AMATERASU trial [39••] and the other trial [13••] suggested that vitamin D was effective in subgroups of patients with baseline blood 25(OH)D levels between 20 and 40 ng/mL and with early-stage lung adenocarcinoma with lower blood 25(OH)D levels (< 20 ng/mL), respectively.

In the recent VITAL study [40••], a large primary prevention trial, vitamin D3 supplementation (2000 IU/d) given prediagnostically did not lower the risk of cancer incidence in middle-aged and older adults, but it showed a non-significant, but marginal, risk reduction in cancer mortality: HR, 0.83; 95% CI, 0.67 to 1.02. Furthermore, a post hoc analysis showed a significant reduction if events occurring within the first year of randomization were excluded (HR, 0.79; 95% CI, 0.63 to 0.99) and if the first 2 years were excluded (HR, 0.75; 95% CI, 0.59 to 0.96).

In the four RCTs mentioned above, there were no significant differences between the vitamin D and placebo group with respect to incident diagnoses of hypercalcemia, kidney stones, or others [10••, 13•, 39••, 40••].

In summary, each of the four RCTs cited above did not result in a significant difference in any primary analysis, but results were significant on exploratory analyses. For now, we have no compelling evidence that vitamin D is effective for reducing relapse, progression, and death in patients with cancer. Thus, confirmatory RCTs are needed to evaluate whether vitamin D supplementation reduces the risk of relapse or death in a large number of patients with a longer follow-up period [41].

Future Directions

Because beneficial effects of vitamin D have been reported for a variety of cancer sites, target molecules of vitamin D can be relatively common across cancers at all primary sites, e.g., p53 tumor suppressor, vitamin D receptor (VDR), 25(OH)D levels at baseline, and anti-tumor immunity.

The p53 gene is the most frequently mutated gene in about half of cancers, the majority of which are missense and signaling of which may have cross-talk with vitamin D signaling [42]. We thus conducted a post hoc analysis of the AMATERASU trial of postoperative oral vitamin D3 supplementation (2000 IU/day) in 417 patients with stages I to III digestive tract cancer from the esophagus to the rectum who underwent curative surgery [39••] by investigating p53-positivity on immunohistochemistry with high sensitivity for missense mutations in p53 gene [43]. It was found that, in a subgroup of patients with p53-positive cancer ($n = 226$), 5-year relapse-free survival was 79% in the vitamin D group, which was significantly higher than the 57% in the placebo

Table 2 Meta-analyses of randomized clinical trials

First author (year)	# study	# Participants	Cancer Incidence RR[*1] (95%CI[*2])	# Study	# Participants	Cancer Mortality RR[*1] (95% CI[*2])	Journal	Ref.
Keum N (2019)	10	83,362[*3]	0.98 (0.93–1.03)	5	77,504[*3]	0.87 (0.79–0.96)	Ann Oncol	36
Zhang X (2019)	10	81,362	0.99 (0.94–1.03)	7	77,653	0.87 (0.79–0.95)	Biosci Rep	37
Zhang Y (2019)	NA[*4]	NA[*4]	NA[*4]	52	75,454	0.84 (0.74–0.95)	BMJ	38

*[1] Risk ratio

*[2] Confidence interval

*[3] By calculation

*[4] Not available

group (HR, 0.52; 95% CI, 0.31 to 0.88), whereas in the subgroup of patients with p53-negative cancer, 5-year relapse-free survival in the vitamin D group vs. placebo group was 72% vs. 84%. Effect modification by p53-positivity was significant ($P = 0.02$ for interaction) [44••].

VDR is also widely expressed in most cell types, as well as cancer cells. In the post hoc analysis of the AMATERASU trial, vitamin D supplementation significantly reduced the risk of relapse or death in the highest level of VDR expression determined by immunohistochemistry (HR, 0.30; 95% CI, 0.09 to 0.96) [44••], although the significance of VDR expression for cancer survival was controversial in observational studies [45, 46]. In addition, five single nucleotide polymorphisms of vitamin D receptor (VDR) have been intensively researched: rs2228570 (Fok*I*); rs1544410 (Bsm*I*); rs731236 (Taq*I*); rs7975232 (Apa*I*); and rs11568820 (Cdx2) [47]. In a meta-analysis of 21 observational studies, the Bsm*I* variant was associated with overall survival (HR, 1.40; 95% CI, 1.05 to 1.75), and Apa*I* was associated with progression-free survival (HR, 1.29; 95% CI, 1.02 to 1.56). The Fok*I* variant was associated with overall survival in lung cancer patients (HR, 1.29; 95% CI, 1.0 to 1.57) [48]. However, significant associations were not seen between vitamin D supplementation and each subgroup of SNPs of VDR in the AMATERASU trial, although some trends were observed in a couple of SNPs [39••].

In the AMATERASU trial, relapse-free survival was improved in a pre-specified subgroup with middle (20–40 ng/mL) but not low (< 20 ng/mL) blood total 25[OH]D levels [39••], which was contrary to our expectations. Vitamin D supplementation (2000 IU/day, the same dose as in the AMATERASU and VITAL trials) prevented cancer incidence only when the blood 25(OH)D levels were between 30 and 55 ng/mL (HR, 0.65; 95% CI, 0.44 to 0.97) [49]. In contrast, vitamin D supplementation was effective in the subgroup of patients with early-stage lung adenocarcinoma and with lower 25(OH)D levels (< 20 ng/mL) [13••]. Thus, effect modification by baseline levels of 25(OH)D is still uncertain. Recently, the landscape in the assessment of vitamin D status has started changing from total 25(OH)D to bioavailable 25(OH)D, which is not bound to vitamin D binding protein (DBP), but bound to albumin or existing as the free form [50]. Because DBP has 1000 times stronger affinity to 25(OH)D than albumin, cancer cells take-up DBP-bound 25(OH)D poorly, but they can easily take-up albumin-bound 25(OH)D and also free 25(OH)D, i.e., bioavailable 25(OH)D [51]. Indeed, black Americans had lower concentrations of total 25(OH)D and DBP-bound 25(OH)D than white Americans, resulting in similar concentrations of estimated bioavailable 25(OH)D, which may explain, at least in part, the paradox of why black Americans have lower total 25(OH)D but rather higher bone mineral density than white Americans [52]. Thus, bioavailable 25(OH)D may be a more appropriate marker of vitamin D insufficiency than total 25(OH)D. Indeed, a prospective cohort study including 1031 patients with hepatocellular carcinoma showed that the highest vs. lowest quartile of bioavailable 25(OH)D levels was associated with improved liver cancer-specific mortality (HR, 0.69; 95% CI, 0.51 to 0.93) and all-cause mortality (HR, 0.71; 95% CI, 0.53 to 0.94) [53].

Not only direct effects of vitamin D on cancer cells, but indirect effects through inducing anti-cancer immunity may be plausible. Vitamin D supplementation was demonstrated to prevent acute respiratory infection [54] and asthma exacerbations requiring treatment with systemic corticosteroids [55], in individual participant's data meta-analysis, probably through modulating immune function. In the Nurses' Health Study and Health Professionals Follow-up Study, the beneficial effect of the postdiagnosis 25(OH)D score on colorectal cancer-specific mortality was enhanced in cases with a negative/low peritumoral lymphocytic reaction [56], which remains unproven by RCTs.

We also conducted post hoc analyses of the AMATERASU trial to explore the effects of vitamin D supplementation on survival by histopathological characteristics. In patients with poorly differentiated adenocarcinoma, 5-year relapse-free survival of patients supplemented with vitamin D was 91%, which was significantly better than the 63% of those with placebo (HR, 0.25; 95% CI, 0.08 to 0.78; P for interaction = 0.02). Similarly, 5-year overall survival was 92% in the vitamin D group, which was significantly better than the 72% of the placebo group (HR, 0.25; 95% CI, 0.07 to 0.94; P for interaction = 0.01) [57•]. Why vitamin D supplementation was effective in digestive tract cancer patients with poorly differentiated adenocarcinoma is unknown. While there were no significant effects, a trend toward significant effects on survival was observed in the signet-ring cell carcinoma subgroup, which is classified as an undifferentiated type together with poorly differentiated adenocarcinoma [57•]. Therefore, it is possible that the effect of vitamin D may be related to the degree of differentiation of a tumor. In fact, a clinical pilot trial indicated that vitamin D might increase differentiation in the normal colorectal mucosa of patients with colorectal adenoma [58].

However, the subgroup analyses described above may increase the probability of type I error due to multiple comparisons. Thus, the findings must be considered exploratory and interpreted with caution.

Conclusions

Since the early 1990s, much evidence has been accumulated regarding vitamin D and cancer survival. In the last 5 years, many meta-analyses of observational studies of each cancer site have been published to demonstrate inverse associations between blood 25(OH)D levels and cancer-specific mortality

or overall mortality, especially in patients with colorectal cancer and breast cancer (Table 1). In 2019, three meta-analyses of RCTs of all cancer sites (Table 2) reported that vitamin D supplementation given pre-diagnostically reduced only the risk of total cancer mortality by 13% to 16%, but not risks of cancer incidence, all-cause mortality, cardiovascular mortality, or other mortality. Thus, there already exists the meta-analyses of RCTs with homogeneity, indicating that vitamin D supplementation may improve the prognosis of patients with cancer. However, each RCT used in the meta-analysis, as well as recent RCTs, the SUNSHINE trial by Ng et al. [10••], the AMATERASU trial by Urashima et al. [39••], and another trial by Akiba et al. [13••], did not show statistically significant results. Discrepancies between the results of these 3 RCTs and the meta-analyses of RCTs suggest that more patients with cancer should be followed-up for a longer time to evaluate the effects of vitamin D supplementation on their survival as the next RCT.

At present, we have not yet obtained compelling evidence that vitamin D supplementation effectively improves survival of patients with cancer. Thus, confirmatory RCTs are still mandatory for the future.

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Compliance with Ethical Standards

Conflict of Interest Taisuke Akutsu, Hikaru Kitamura, Shoko Himeiwa, Shinto Kitada, Tatsuya Akasu, and Mitsuyoshi Urashima declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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