VITAMIN D IN ONCOLOGY

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INTRODUCTION

Studies in vitro and in vivo demonstrated that the physiologically active vitamin D metabolite (1,25(OH)D or calcitriol), which exerts its action via the vitamin D Receptor (VDR), has antiproliferative effects in various cell types and was found to regulate the expression of tumor-related genes, mediate inhibition of cell growth, adhesion, migration, metastases and angiogenesis. Furthermore, a number of epidemiologic showed inverse associations of cancer incidence with high 25-hydroxycholecalciferol (25(OH)D). However, observational studies suffer from reverse causation bias and intervention studies did not confirm these associations. Discrepancies with randomised clinical trials (RCTs) suggest that low 25(OH)D could be just a marker of ill health. Inflammatory processes involved in disease occurrence and clinical course would reduce 25(OH)D, which would explain why low vitamin D status (measured by 25OHD) is reported in a wide range of disorders.

More convincing results were found for mortality, in fact evidence comes not only from observational studies but also from clinical trials. A meta-analysis of observational studies showed a nonlinear relationship of overall mortality risk with increasing circulating 25(OH)D, with optimal concentrations around 30-35 ng/ml. A meta-analysis of randomized clinical trials in healthy subjects showed that current doses of vitamin D supplements are associated with a significant decrease in overall mortality for vitamin D_3 supplementation, whereas no association with vitamin D_2 supplementation was found.

Recent evidence suggests to investigate the link of vitamin D with cancer survival and mortality, identifying this topic as one of the most promising area of research.

OBSERVATIONAL STUDIES

A meta-analysis of cohort studies (1) showed that people with high baseline 25(OH)D were at significant decreased risk of cancer deaths. Summary risk estimates were: Summary Relative Risk (SRR) = 0.91 (95% CI: 0.85-0.98) and 0.69 (95% CI: 0.61-0.78) for primary prevention cohorts (participants not selected on the basis of pre-existing chronic disease) and secondary prevention cohorts (pre-existing baseline conditions) respectively, adjusting for several potential confounding factors. Subgroup analyses indicated that the inverse associations of 25(OH)D with cancer specific mortality were significantly stronger in the populations with low prevalence of vitamin D supplement use (< 10%).

In an individual-patients pooled analysis of 8 cohorts studies a consistent increase in mortality was observed for subjects with 25(OH)D concentrations below 40 nmol/L. The prevalence of 25(OH)D concentrations below 40 nmol/L was estimated to be about 20%. No clear linear relationship between 25(OH)D and cancer mortality (2) was demonstrated, however in a previous pooled analysis a significant association with cancer mortality was observed among subjects with a history of cancer (risk ratio = 1.70 (95% CI: 1.00-2.88)) (3).

A mendelian pooled analysis of the UK Biobank evaluated whether genetically predicted 25(OH)D concentrations are associated with cancer mortality summarising data of 438 870 healthy subjects and 6998 cancer-specific deaths. Results showed that genetically low plasma 25(OH)D concentrations were not associated with cancer mortality (4). More consistent results suggesting inverse association of 25(OH)D with cancer mortality were found by meta-analyses for patients with some specific cancer sites: Pancreas, Breast, Lung, Prostate, Colorectal and Haematological (Table I). Some single cohort studies also found a significant decreased cancer mortality risk for the upper aerodigestive tract and Gastric cancer (Table II).

Since sun exposure is a recognised risk factor for melanoma, the commonly given advice to melanoma patients to reduce their sun exposure after diagnosis could further exacerbate their vitamin D insufficiency. In fact, in a pro-

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TABLE I.
Recent meta-analysis on 25OHD and survival/cancer mortality.

	Cancer sites	First author, Publication year	N. studies	No. subjects	Endpoint	Summary Risk estimate (95%CI)	Contrasts
Meta-analysis	Pancreas	Zhang, 2017	8	2166	Mortality	0.81 (0.68-0.96)	High *vs* low
	Breast	Hu, 2018	6	5984	Overall survival	0.67 (0.56-0.79)	Highest with lowest
	Lung	Huang, 2017	8	2166	Overall survival	0.80 (0.59-1.08)	High *vs* low
		Feng, 2017	4	17919	Mortality	0.76 (0.61-0.94)	High *vs* low
			5		Overall survival	1.01 (0.88-1.16)	High *vs* low
	Prostate	Song, 2018	7	7808	Overall survival	0.91 (0.87-0.97)	20 nmol/L increase
	Colorectal	Maalmi, 2018	11	7718	Overall survival	0.67 (0.57-0.78)	Highest with lowest
	Hematological	Wang, 2015	7	2643	Overall survival	0.54 (0.45-0.65)	Normal *vs* low
	Any	Chowdhury, 2014	17	120735	Mortality	0.80 (0.70-0.91)	High *vs* low
Pooled-analysis any		Ong, 2018*		6998	Mortality	0.97 (0.84-1.11)	20 nmol/L increase
		Gaksch, 2017	8	26916	Mortality	0.79 (0.60-1.04)	> 100 *vs* 75-99 nmol/L
		Schöttker, 2014	8	26018	Mortality	0.60 (0.35-1.00)	Top *vs* bottom quintiles

* Mendelian randomisation.

spective cohort of 1171 melanoma patients the variation of 25(OH)D from baseline was found associated with risk of relapse: an increased risk was found with a reduction and an increase in 25(OH)D (5). Patients who did not change their habitudes and had sunny holidays after melanoma diagnosis likely correspond to the reference category of no change in 25(OH)D in the study by Saiag et al. (5). In a cohort of 691 melanoma patients we found that the risk of melanoma recurrence was significantly lower in patients who had holidays in the sun after melanoma diagnosis avoiding sun exposure during peak hours (6). Furthermore, sunny holidays before melanoma diagnosis were found to be significantly associated with lower Breslow thickness, the main prognostic factor of melanoma. Number of weeks of sunny holidays was also significantly and inversely associated with thickness in a dose-dependent manner (6).

A big prospective cohort of 1,042 melanoma patients after a median follow-up time of seven years showed that low vitamin D was significantly associated with worse melanoma prognostic factors (high tumor thickness, ulcerated tumor and advanced melanoma stage). Multivariable hazards ratios confirmed a significant reduced risk of relapse, overall survival and melanoma specific survival for increasing values of 25OHD (7), adjusting for markers of inflammation.

RANDOMIZED CLINICAL TRIALS

Few RCTs investigated effect of vitamin D supplementation on cancer mortality or survival in cancer patients (Table III).

The Cochran collaboration in 2014 reviewed 18 clinical trials and showed that Vitamin D_3 (cholecalciferol), given singly (with no calcium), is associated with decreased cancer mortality and all-cause mortality, even if limitations were outlined due to low statistical power and risk of attrition bias (8).

A nationwide, randomized, placebo-controlled trial (VITAL), with vitamin D_3 at a dose of 2000 IU per day, conducted on 25,871 participants, showed overall no results on all main endpoints such as cancer incidence. However when first 1-2

TABLE II.
Cohort studies on 25OHD and survival/cancer mortality for cancer sites.

Cancer site	First author, PY	Country	No. subjects	Risk estimate (95% CI)	Contrasts*
Melanoma	Fang, 2016			0.71 (0.55-0.93)	> 20 *vs* < 20
Upper aerodigestive tract	Gugatschka, 2011	Austria	88	0.89 (0.83-0.97)	> 10 *vs* < 10
Gastric	Ren, 2012 (NHANES)	China	197	0.59 (0.37-0.91)	≥ 50 *vs* < 50
Head and neck	Meyer, 2011	Canada	522	0.85 (0.57-1.28)	> 78 *vs* < 48

PY: publication year; * ng/mL.

TABLE III.
Randomised clinical trial (CRT) on vitamin D and survival/cancer mortality.

Study design	Cancer site	First author, PY	Arms	N. trials	Endpoint	N. deaths	HR (95% CI)
RTC	Breast	Chlebowski, 2008	Vitamin D + calcium Placebo	1	Mortality	46	0.99 (0.55-1.76)
Meta-analysis of RCT	Prostate	Shahvazi, 2019	Vitamin D *vs* control	3	Survival	477	1.05 (0.81-1.36)
RTC	Any	Trivedi, 2003	Vitamin D Placebo	1	Mortality	63	0.86 (0.61-1.20)
RTC	Any	Wactawski-Wende, 2006; Brunner, 2011	Vitamin D + calcium Placebo	1	Mortality	744	0.90 (0.77-1.05)
RTC	Any	Avenell, 2011 (RECORD)	Vitamin D Calcium Vitamin D+ Calcium Placebo	1	Mortality	329	0.85 (0.68-1.06)
Meta-analysis of RCT	Any	Keum, 2019	Vitamin D *vs* control	5	Mortality	1591	0.87 (0.79-0.96)

PY: publication year.

years of follow-up were excluded to take into account of latency effect, a significant decreased risk of cancer death was estimated for vitamin D arm *vs* placebo: Hazard Ratio (HR) = 0.75 (95% CI: 0.59-0.96) (9).

A randomized, double-blind trial in 155 lung cancer patients, who received vitamin D supplements (1,200 IU/day) for 1 year after surgery or placebo, found overall no results. However, selecting patients with early-stage adenocarcinoma with low 25(OH)D, vitamin D supplementation was found to be significantly associated with 63% decrease risk of death (HR = 0.37; 95% CI: 0.15-0.95) (10)

A randomised clinical trial in 417 digestive tract cancer patients assessed the effect of vitamin D (2000IU/d) versus placebo on relapse free survival (AMATERASU trial). Overall no effect was found, however in patients with medium baseline serum 25(OH)D levels (between 20 and 40 ng/mL), supplementation was found to be associated with a significant decreased risk of relapse (HR = 0.46; 95% CI, 0.24-0.86). No association was found for the patients with 25(OH)D below 20 ng/mL. The dose of vitamin D could have been insufficient to increase vitamin D levels in that subgroup (11).

The SUNSHINE study, a phase 2 randomised clinical trial of 139 advanced/metastatic colorectal cancer patients, assessed the efficacy of high-dose vitamin D3 vs standard dose (+standard chemotherapy): 8,000 IU/d for 14 days, then 4,000 IU a day thereafter versus 400 IU/d during all cycles. Multivariable analysis showed a significant reduced risk of relapse: HR = 0.64 (95%CI: 0-0.90). The effect of high-dose vitamin D3 on progression-free survival appeared to be greater among patients with a lower BMI, more metastatic sites and KRAS wild-type cancers (p = 0.04, p = 0.02 and p = 0.04 respectively for interaction). Furthermore, vitamin D was associated with fewer grade 3 or higher diarrhea events (12).

In 2019 a meta-analysis summarised 5 clinical trials and included 1591 cancer deaths. The 25(OH)D levels attained was between 54 and 135 nmol/l in the intervention group and the summary risk estimate indicated a significant reduced risk of cancer death: SRR = 0.87 (95% CI: 0.79-0.96), with no heterogeneity. Interestingly the effect was largely attributable to interventions with daily dosing (as opposed to infrequent bolus dosing). No statistically significant heterogeneity was observed by attained levels of circulating 25(OH)D (13).

DISCUSSION

Findings from observational studies constitute suggestive pieces of evidence of a relationship between vitamin D and cancer survival and mortality but they are insufficient to establish causality. Main results of RCTs showed overall no effect on cancer mortality and survival, however subgroup analyses are suggestive and strong enough to consider that RCTs may not have correctly addressed the question. Several issues were raised on the validity of the conclusions. First of all, RCTs included study participants irrespective of their 25(OH)D level and may thus have failed to detect significant treatment effects in vitamin D deficient individuals. The doses used in the majority of trials are ordinary doses of vitamin D supplements as for the prevention of fractures and we do not know the exact dose that could be effective for cancer mortality and survival.

A particular case is the one of melanoma patients. Given that ultraviolet exposure is a recognized risk factor for melanoma, a common advice after melanoma diagnosis is to stop sun exposure. Thus, the UK melanoma guidelines recommend checking vitamin D levels in all melanoma patients at diagnosis and offer supplementation if necessary. However, there are some concerns that oral supplementation of vitamin D may not be as

efficient as limited controlled sun exposure and more studies are needed in this area.
Obese subjects are usually vitamin D deficient because of "trapping" of the vitamin D parent compound, cholecalciferol, in adipose tissue. Moreover obesity is inversely associated with physical activity that is positively associated with 25OHD among people with normal- and overweight BMI but not in people with obese BMI. The association between physical activity and vitamin D status has often been attributed to physical activity being a surrogate for sun exposure; however, in the few studies in which both estimates are adjusted for sun exposure, the physical activity-vitamin D relationship persisted (14).
It has also been speculated that immune-modulating ability of vitamin D could offer indications for a novel application in cancer patients receiving immunotherapy, to reinforce the anti-tumoral response and to prevent and/or limit the onset of immune related adverse events (15).
Evidence from RTCs do not allow definitive answers but it raises the hypothesis that combination therapy is required for cancer survival/mortality. New RCTs should be organized in particular in this setting because we need more information on dose of vitamin D supplementation, per specific cancer sites and stages, and to assess the benefits in patients with low vitamin D status at baseline. New studies should also take into account BMI and have good follow-up of all participants, in order to reduce attrition bias, better evaluate compliance and the effect of vitamin D on cancer therapy toxicity.

Conflicts of Interest

The author declare no conflict of interest.

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