Nutrition 66 (2019) 166–172

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Vitamin D supplementation after malnutrition associated with time-related increase of cancer diagnoses: A cohort study of 389 patients with Wernicke-Korsakoff syndrome

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ARTICLE INFO

Article History:
Received 20 December 2018
Received in revised form 20 April 2019
Accepted 16 May 2019

Keywords:
Alcohol-related disorders
Neoplasms
Malnutrition
Vitamin D, Korsakoff syndrome

ABSTRACT

Objectives: Vitamin deficiencies may reflect less-than-optimal health in select populations. The aim of this study was to determine whether vitamin D supplementation (VDs) after malnutrition may be adversely related to cancer diagnoses in a selected group of patients with alcoholic Wernicke-Korsakoff syndrome (WKS).
Method: This was a retrospective cohort study of all patients admitted to Slingedael Korsakoff Center, from 1996 to 2018. The patients were subdivided into three predefined groups depending on differences in VDs: "early" supplementation, which started during or before the previous hospital admission, before the transfer to our center; "late" supplementation, which started later in our center; and "no" VDs received. Data collection involved patients' ages, sex, body mass index, skin type, baseline serum 25-hydroxyvitamin D concentrations if available, doses of cholecalciferol (vitamin D_3) supplementation, other vitamins, sun exposure, malnutrition, alcohol use, smoking, cognitive diagnoses, somatic comorbidity, cancer diagnoses, cause of death, and length of stay in Slingedael. New tumors (dependent variable) may have been diagnosed during VDs (exposed cases) or before the start of VDs, if any (unexposed cases).
Results: New cancers were diagnosed in 87 of 389 (22.4%) patients after median 3 y of follow-up (interquartile range, 1.1–5.8 y). In logistic regression analysis, age, smoking, and length of stay in log (y) showed odds ratios of 1.021, 2.74, and 1.68, respectively. The temporal relationship of VDs and cancer diagnosis was significant in VDs that started in the year leading up to the diagnosis (Wilcoxon signed-ranks test of positive ranks corresponding with supplementation and negative ranks corresponding with non-supplementation: Z score 2.54; $P = 0.011$).
Conclusion: VDs was time-related to cancer diagnosis in a cohort of patients with alcoholic WKS. The study may suggest the proliferation of cancer as an adverse effect of VDs, particularly in malnourished patients.

Introduction

In addition to its effect on calcium and phosphate homeostasis, vitamin D could be involved in gene expression and normal cell growth, in responses of the immune system such as antimicrobial and anti-inflammatory activity of various immune cells, and in beneficial antiproliferative effects on cancer cells [1–3]. The molecular mechanisms in the antiproliferative action of vitamin D, however, are largely unknown. In particular, it is difficult to understand how cell growth and anticancer effects of vitamin D, that is, both proliferative and antiproliferative effects, can occur simultaneously. According to the latest systematic review of the Cochrane library, there is no firm evidence that vitamin D supplementation (VDs) decreases or increases cancer occurrence in predominantly older community-dwelling women [4]. Other reviews, however, suggest that there could be a role for vitamin D in cancer risk reduction and therapy—while awaiting the results of future trials to determine the most favorable target concentrations of serum 25-hydroxyvitamin D [25 (OH)D] and when supplements should optimally be introduced [5].

Patients with nutritional deficiencies of any origin are at risk for Wernicke-Korsakoff syndrome (WKS) caused by thiamine deficiency.

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https://doi.org/10.1016/j.nut.2019.05.008
0899-9007/

In addition to alcoholism, WKS may occur in patients with dietary imbalance and a history of gastrectomy [6,7]. In clinical practice, initial WKS symptoms, such as drowsiness, confusion, and walking disability, usually develop within 2 wk before the subsequent hospital admission. Patients with WKS typically are treated with multiple vitamin supplements, including thiamine and other B vitamins, and variable vitamin C supplements, and vitamin D supplements in the form of cholecalciferol (vitamin D_3). Alcohol drinking can cause several types of cancer [8]. The objective of the present study was to determine whether VDs after malnutrition may be related to cancer diagnoses in a selected group of patients with alcohol-related WKS.

Vitamin deficiencies may reflect less-than-optimal health in selected populations. As for low serum 25(OH)D values, however, we wondered if these also might be a natural physiologic response to low food reserves that serve as a possible mechanism of growth inhibition thus preserving tissue homeostasis. Unfortunately, the relationship between diet composition, alterations in eating or fasting, and possible fluctuations of serum 25(OH)D concentrations or the active metabolite 1,25-dihydroxyvitamin D, have barely been discussed in the literature on vitamin D deficiency [9].

Methods

Study design

In a retrospective, descriptive cohort study, we included all patients admitted to Slingedael Korsakoff Center from August 1, 1996, to May 1, 2018. The study was approved by the Medical Ethics Review Committee of the Utrecht University Medical Center (UMC Utrecht), Utrecht city, The Netherlands. The Slingedael Korsakoff Center in Rotterdam, The Netherlands, is a long-term care facility for patients with WKS. The Korsakoff Center offers day care, observation and diagnosis, and specialized nursing home care. In June 2011, an institution-wide implementation of dietary VDs was introduced in the center in accordance with a former advice of the Health Council of The Netherlands regarding additional vitamin D in nursing home residents and people who have little or no exposure to sunlight. In the present study, we divided the patients into three predefined groups depending on differences in their VDs

- "Early" VDs, started before or during the hospital admission (within 4 wk from hospital admission date) previous to the transfer to our center;
- "Late" VDs, if started later, after admission to our center, and
- "No" VDs y VDs before or during admission to our center.

In early VDs, we chose to define the starting point of the follow-up as the first prescription of VDs, which usually coincided with the previous hospital admission before transfer to our center, but may have started at an earlier date. In the groups with late and no VDs, we defined the starting point of follow-up by the previous hospital admission before the transfer to our center. Reasons for not receiving VDs were categorized as followed:

- Serum 25(OH)D ≥50 nmol/L,
- Contraindications for VDs,
- Not started, physicians being cautious with supplementation,
- Observation period before June 2011, and
- Other reasons or reasons unknown.

Patient characteristics

Data collection involved sex, age, body mass index (BMI), and skin type (i.e., whether the patient was fair- or dark-skinned).

Clinical characteristics

Data involved baseline serum 25(OH)D concentrations (if available), doses of cholecalciferol (vitamin D_3) supplementation, and data on vitamin B and C supplements. Furthermore, we made an estimation of sun exposure based on daily outdoor activities in the patient's health care plan, if applicable (≤30 min/d, >30 min/d). Previous malnutrition was based on information from hospital discharge letters or general practitioners' reports on the patient's self-neglect and malnourishment, when the patient had not been eating well for the previous months, and sometimes not eating at all for several days or weeks. Alcohol use disorder was diagnosed according to DSM-5 criteria. In all patients, admission resulted in sustained remission of alcohol use. Korsakoff syndrome was diagnosed according to the DSM-5 criteria for major neurocognitive disorder of the confabulation-amnestic type [10]. In our center, the diagnosis was confirmed by extensive neuropsychological testing after ≥6 wk of sobriety. Tobacco smoking was based on qualitative data, whether the patients had been smoking before or during their stay in Slingedael. Somatic comorbidity was listed as follows: Barrett esophagus, liver cirrhosis, diabetes mellitus, chronic obstructive pulmonary disease (COPD), high blood pressure, myocardial infarction, peripheral artery disease, stroke, epilepsy, polyneuropathy, and other (e.g., osteoporosis, rheumatoid arthritis, or cerebellar atrophy). Furthermore, we described previous cancer diagnoses, death related to cancer or other causes, the total length of stay in our center, and dismissal of the patient (eg, to another long-term care facility or home).

Dependent variable: New cancer diagnosis

Diagnoses of new malignant neoplasms refer to diagnoses made during (intermittent) hospital admissions and outpatient consultations from cohort entry. The number of new cancers may include multiple primary cancers occurring in a single patient. The incidence rate does not include reoccurring cancer and the primary site reported is the site of origin and not the metastatic site.

Newly diagnosed cancer and VDs

The tumors may have been diagnosed during VDs (exposed cases) or before the start of VDs, if any (unexposed cases). First, we calculated the time difference between the date of cancer diagnosis and start of supplementation. Positive values indicate that VDs was started before a diagnosis of cancer was made. Negative intervals indicate non-supplementation at the time of cancer diagnosis. We used the end of follow-up as a substitute for "start of supplementation" in cancer diagnoses without any VDs during follow-up. Second, we calculated the length of vitamin D exposure before a diagnosis of cancer for different conditions of VDs, being used over a period ranging from >3 mo to >3 y before the diagnosis of cancer was made.

Statistical analysis

We used a logistic regression analysis for associations between newly diagnosed cancer (dependent variable) and patient and clinical characteristics (independent variables). Wilcoxon signed-ranks tests were done for the length of time of diagnosis date minus starting date of supplementation or end of follow-up in non-supplementation. The statistical analyses were conducted with SPSS, version 23 (IBM, Armonk, NY, USA).

Results

Patient and clinical characteristics

The cohort consisted of 316 men and 73 (18.8%) women, mean age 61.4 y (SD 9.1), BMI 22.9 kg/m^2 (SD 4.3). Alcohol misuse was described in all of the patients and a current or previous smoking habit in 79.8% patients. As for skin type, 355 (91%) patients had fair skin and 34 had dark skin. In 184 patients, sun exposure was estimated at <30 min/d, whereas sun exposure for 176 patients was estimated to be >30 min/d. No data was available for 38 patients. WKS was confirmed in 352 of 389 patients (90.5%) and other alcohol-related cognitive disorders or dementia in 37 (9.5%). Causes of death were related to cancer in 59 of 148 patients (39.9%) and infections in 39 of 148 patients (26.6%). Sudden death occurred in 11 patients, and other causes in 39 patients.

Newly diagnosed cancer

New malignant neoplasms were diagnosed in 87 of 389 patients (22.4%) after median 3 y of follow-up (interquartile range [IQR], 1.1–5.8 y). New double cancers were found in 11 of 389 patients. The cancer incidence rate was 4.9 new cancers per 100 person-years. For the three subgroups of patients with early, late, and no VDs, further details are shown in Table 1. Newly diagnosed cancers were bladder cancer (3), brain tumor (1), breast cancer (3), colon cancer (12), esophageal cancer (10), gynecologic cancer (2), laryngeal cancer (4), leukemia (2: amyloid light-chain-amyloidosis;

Table 1
Results in cohort of patients with WKS* in subgroups according to their VDs

		Early	Late	None
Patients		69	224	96
Age, y	Mean (SD)	63.4 (7.9)	60.7 (9.1)	61.4 (9.8)
BMI, kg/m^2, on admission	Mean (SD)	22.1 (4.1)	23 (4.3)	23.2 (4.5)
Number of disorders/patient†	Mean (SD)	2.7 (1.4)	2.3 (1.4)	2.4 (1.4)
Alcohol misuse (%)		(100)	(100)	(100)
Smoking habit (%)‡		54/69 (78)	184/222§ (83)	67/91§ (74)
25-hydroxyvitamin D				
Test data being available (%)‖		37 (54)§	64 (29)§	19 (20)§
Test results, nmol/L‖	Mean (SD)	21.8 (18)	26.9 (14.8)	39.7 (19.5)
First vitamin D prescription, y	Mean (SD)	Cohort entry	2.2 (2.8)	N/A
Reason no vitamin D therapy				
25-hydroxyvitamin D >50 nmol/L			1¶	3
Contraindications		1¶		
Not started				35
Observation before June 2011#				50
Other reasons; unknown		6¶	1¶	8
Follow-up				
Time before Slingedael, y	Mean (SD)	1.4 (1.6)	0.7 (1.1)	1 (2.4)
Length of follow-up, y	Mean (SD)	3.7 (2.9)	6.4 (4.6)	3 (3.5)
Follow-up, total, person-years		256.4	1424.4	283.6
Malignant neoplasms				
Previously treated	Tumors, n	10	20	7
Newly diagnosed	Tumors, n	17	64	17
of which double tumors		2	8	1
Tumors/100 patients, n		24.6	28.6	17.7
Diagnosis after start vitamin D		15/15	48/56	0/16

BMI, body mass index; VDs, vitamin D supplementation; WKS, Wernicke-Korsakoff syndrome.
Numbers are patient numbers, unless otherwise indicated.
*Or other alcohol-related cognitive disorders or dementia in 37 of 389 patients (9.5%).
†Range 0 to 7 of 11 predefined comorbid disorders.
‡Including currently and previously smoking.
§Missing data in the other patients.
‖Serum 25-hydroxyvitamin D concentrations being assessed at baseline before VDs, if applicable.
¶VDs was started but discontinued after mean 1.6 y of supplementation.
#In June 2011 an institution-wide implementation of dietary VDs was introduced.

monoclonal gammopathy of undetermined significance), liver cancer (2), lung cancer (23), lymphoma (3), oral cancer (12), oropharyngeal cancer (4), pharyngeal cancer (9), prostate cancer (3), skin cancer: basal cell/squamous cell (2), suspected abdominal cancer (2), and undifferentiated carcinoma (1).

Vitamin D prescriptions

The mean time from entry in the cohort to the first vitamin D prescriptions or end of follow-up in non-supplementation was 2.02 y (SD 2.89). The mean time from first vitamin D prescriptions to the end of follow-up was 3.05 y (SD 3.19). In early vitamin D prescriptions, the main regimes of VDs were oral cholecalciferol 400 to 800 IU/d and 5600 IU/wk, median 800 IU/d (IQR, 400–800 IU/d; 5600 IU/wk was counted as 800 IU/d, and 100 000 IU/3 mo as 1095 IU/d). Doses >880 IU were prescribed to 29 of 68 patients with early VDs. In Slingedael, supplementation was continued (or started) as oral 100 000 IU cholecalciferol once per 2 to 3 mo in 263 patients, 400 to 800 IU/d in 9 patients, and other doses in 12 patients. In 9 patients, VDs was started but discontinued after a mean 1.6 y of supplementation.

Newly diagnosed cancer and VDs

The distribution of cancers over time is shown in Figure 1. Previous VDs was found in 63 of the 87 patients with newly diagnosed tumors (Table 1). For different conditions of length of VDs (exposure) before cancer diagnosis, calculations are shown in Table 2. In these calculations, we randomly selected 42 = 63/1.51 patients with VDs and a diagnosis of cancer, correcting for the mean 1.51 times longer observation time with VDs.

Logistic regression analysis

The analysis is reported in Table 3 and Table 4.

Discussion

In this observational cohort study, the objective was to determine whether VDs is related to cancer diagnoses in a selected group of patients with alcohol-related WKS. Differences in time between the dates of tumor diagnosis and the starting point of VDs or the end of follow-up in non-supplementation were significant in supplementation that started ≤1 y before cancer diagnosis was made (i.e., to the disadvantage of cancer diagnosis and VDs). These assocations may suggest that introduction and length of VDs may relate to tumor risks.

Patients characteristics

Sex differences were not taken into account because of the relatively small group of women (sex ratio 5:1), which is a common finding in institutionalized patients with WKS. Nonlinearity of age and newly diagnosed cancer mainly depended on a higher estimation of tumors in the age group enclosing the mean age at admittance (Table 3). A suboptimal BMI (<18.5 kg/m^2) was related to higher cancer estimates compared with normal BMI, a lower estimate occurred in only 23 patients with BMI values >30 kg/m^2.

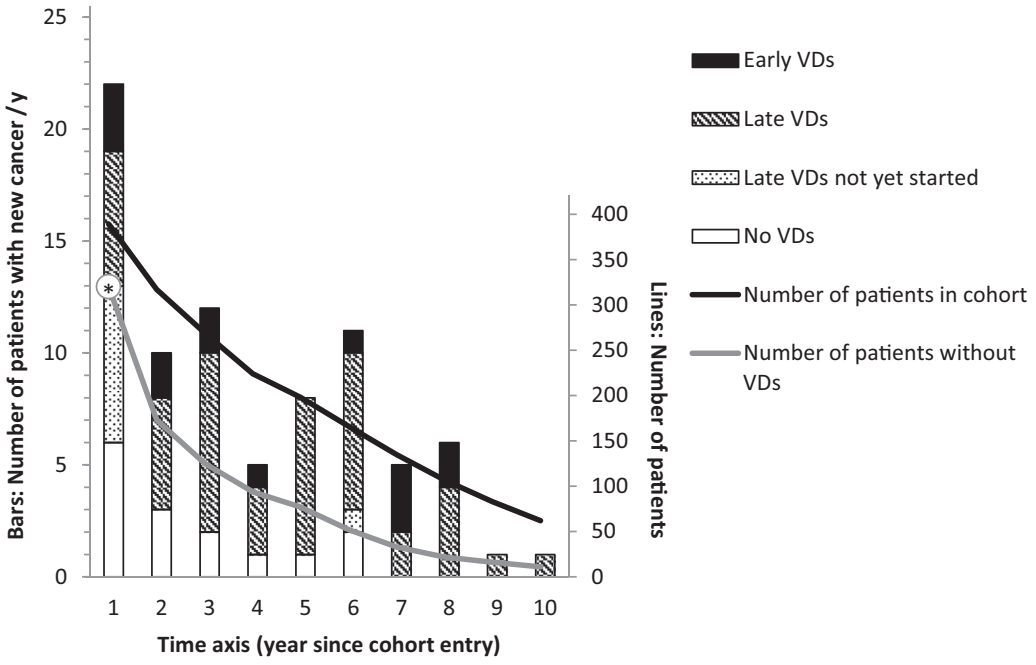

Fig. 1. Number of patients with newly diagnosed cancer per year since entry in cohort, divided into categories depending on their VDs. Early VDs started before or during hospital admission, whereas late supplementation started later at a variable length of time. Late VDs show whether patients had VDs at time of cancer diagnosis. No vitamin D supplementation involves patients who did not have any VDs. Secondary axis on the right side of the figure represents number of patients in the cohort during follow-up and number of patients not (yet) receiving VDs. *The starting point of the curve of initially 320 patients without VDs is projected at the bar height of 13 patients with newly diagnosed tumors without VDs. VDs, vitamin D supplementation.

Length of stay in Slingedael

Time-related bias may have occurred, which might have influenced the associations with the outcome of cancer diagnoses (e.g., by duration of admission and endpoints of observation). The vast majority of the patients did not receive help until the onset of an acute episode of vitamin B_1 (thiamine) deficiency resulted in admission. Other vitamin deficiencies including vitamin D deficiency, therefore, may co-occur with diagnostic findings such as newly diagnosed malignant tumors and a relatively high number of patients diagnosed in the first year of follow-up (Fig. 1). Furthermore, calculations based on the endpoints of observation—death, end of stay in Slingedael without follow-up, and end of the study—showed significant associations with cancer estimates (Table 3). These findings may be explained by differences in the proportions of patients with newly diagnosed cancer, respectively 68 of 148 (45.9%), 9 of 132 (6.8%), and 10 of 109 (9.2%) at the different endpoints of follow-up because of possible interdependent relations between a patient's previous cancer diagnosis and cause of death in patients admitted for long-term care.

Cancer in patients with alcohol-related WKS

For comparison, in the general population in The Netherlands, the overall cancer incidence was 286.8 persons per 100 000 (0.29%) in 2010 and adjusted for age-distribution (World Health Organization). In a study of 61 patients with WKS, main causes of death included cancer in 33.3%, median 5.3 y after the WKS diagnosis was made [11]. It is well known that combined alcohol use and smoking is associated with a high risk (up to 35 times compared with non-smoking non-drinkers) for developing malignant tumors of the oral cavity, pharynx, larynx, and esophagus [12]. The

Table 2
Wilcoxon signed-ranks tests*

Condition of VDs†, started at least since	Positive ranks	Sum of ranks‡	Negative ranks	Sum of ranks§	*Z*-score	*P*-value
No condition	42	1764	24	447	−4.21	<0.0001
3 mo	40	1702	26	509	−3.83	0.0001
6 mo	37	1639	29	572	−3.40	0.0007
1 y	32	1504	34	707	−2.54	0.011
1.5 y	28	1381	38	830	−1.76	0.078
2 y	25	1223	41	988	−0.75	0.45
3 y, before diagnosis	18	960	48	1251	−0.94	0.35

*Date of cancer diagnosis minus starting date of VDs (or end of follow-up in non-supplementation) for different conditions of length of VDs before cancer diagnosis. In case of identical dates, zero ranks were avoided by adding 1 d to the starting date of VDs. Positive ranks indicate that VDs was started before a diagnosis of cancer was made. Negative ranks indicate non-supplementation at the time of cancer diagnosis.
‡Sum of positive ranks.
§Sum of negative ranks.
†For different *conditions*, the starting date of vitamin D was changed to original date plus the extra time up to 3 y *before* the diagnosis of cancer. Calculations were based on newly diagnosed tumors in 24 non-supplemented patients and 42/63 randomly selected patients with VDs during follow-up, correcting for the mean 1.51 times longer observation time with VDs. Ranks, sum of ranks, and Z scores are means after ten iterative calculations. For double tumors, the date of the intial diagnosis was used.

Table 3
Logistic regression: Dependent variable new cancer (22.4%)

Variables in equation		B	SE	*P*-value	Exp (B)	95% CI for Exp (B)		Estimated new cancer (%)
Sex								
	Female	0.136	0.303	0.653	1.146	0.632	2.076	24.3
	Male*	-	-	-	-	-	-	21.9
Age, y								
	<55	−0.765	0.313	0.014†	2.151^{-1}	1.164^{-1}	3.968^{-1}	16.7
	55–65[a]	-	-	-	-	-	-	30.1
	>65	−0.674	0.290	0.020†	1.960^{-1}	1.112^{-1}	3.460^{-1}	18
BMI, kg/m^2								
	<18.5	0.224	0.341	0.512	1.251	0.641	2.443	29
	18.5–25[b]	-	-	-	-	-	-	24.8
	25–30	−0.775	0.371	0.037	2.169^{-1}	1.049^{-1}	4.484^{-1}	13
	>30	−0.431	0.570	0.450	1.538^{-1}	0.503^{-1}	4.717^{-1}	17
Status of malnutrition								
	Yes	0.352	0.410	0.391	1.421	0.637	3.172	23
	No data*	-	-	-	-	-	-	17
Smoking status								
	Yes	1.052	0.376	0.005†	2.863	1.369	5.988	25.6
	No or no data*	-	-	-	-	-	-	11
Number of comorbidities								
	< mean 2.4[c]	-	-	-	-	-	-	22.6
	> mean 2.4	−0.029	0.244	0.907	1.028^{-1}	0.638^{-1}	1.661^{-1}	22.1
s-25(OH)D	nmol/L	−0.003	0.014	0.849	1.003^{-1}	0.976^{-1}	1.031^{-1}	
VDs								
	None*	-	-	-	-	-	-	17
	Early	0.329	0.400	0.412	1.389	0.634	3.043	22
	Late	0.511	0.314	0.104†	1.667	0.900	3.086	25
LOS in Slingedael								
	0–2.5 y	−0.335	0.323	0.299	1.398^{-1}	0.743^{-1}	2.632^{-1}	18.8
	2.5–5	−0.226	0.373	0.544	1.253^{-1}	0.604^{-1}	2.604^{-1}	20.5
	5–7.5	0.241	0.357	0.499	1.273	0.632	2.562	29.2
	>7.5*	-	-	-	-	-	-	24.4
Log(time)‡	−2.56 to 1.34	0.518	0.212	0.015†	1.679	1.107	2.547	
Endpoint of follow-up-								
	Death	2.130	0.371	0.000	8.415	4.070	17.397	45.9
	Dismissal	−0.322	0.479	0.501	1.381^{-1}	0.540^{-1}	3.533^{-1}	6.8
	End of study*	-	-	-	-	-	-	9.2

Log, logarithm; LOS, length of stay; s-25(OH)D, laboratory result of serum 25-hydroxyvitamin D concentration at baseline; VDs, vitamin D supplementation. In case of negative B values (i.e., associations with lower estimates of new cancer) exp(B) is written as $(1/\exp(B))^{-1}$.
*Reference group: [a]Includes mean age of 61.4 y. [b]Normal, healthy weight. [c]Number of mean 2.4 somatic disorders/patient, range 0–7.
†Candidate variables used for entry in multiple logistic regression analysis.
‡Time = LOS in Slingedael Korsakoff center in years.

Table 4
Multiple logistic regression analysis

	Model 1			Model 2		Model 3			
Covariates	B	Exp(B)	*P*-value	B	*P*-value	B	*P*-value	H&L *P*-value	ROC: AUC (95% CI)
Age	0.025	1.025	0.082					0.351	0.634 (0.571–0.698)
Smoking	1.006	2.736	0.009						
Log(time)*	0.522	1.685	0.023						
Age				0.024	0.088			0.396	0.636 (0.573–0.700)
Smoking				0.999	0.010				
Log(time)*				0.399	0.418				
Early D				0.145	0.733				
Late D				0.180	0.638				
Early D by Log(time)†				0.238	0.737				
Late D by Log(time)†				0.055	0.926				
Age						0.024	0.091	0.559	0.637 (0.572–0.701)
Smoking						1.056	0.006		
Early D by Log(time)†						0.650	0.197		
Late D by Log(time)†						0.524	0.055		
(Constant)	−3.739		0.000	−3.878	0.000	−3.791	0.000		

AUC, area under curve; H&L, Hosmer and Lemeshow test; LOS, length of stay; ROC, receiver operating characteristic; VDs, vitamin D supplementation. Exp(B) = e^B = OR. The -2 Log likelihood of model 1 = 396.6, model 2 = 396.2, model 3 = 397.1.
*Time = LOS in Slingedael Korsakoff center in years.
†Covariate composed of Early (late) VDs by Log(time) = (Patient category in which VDs started Early (late) vs reference no VDs) × [Log(time) involving stay in Slingedael Korsakoff center in years].

percentage of 80% tobacco smokers in Slingedael corresponds to those reported in other studies of patients with WKS. In the general population, the incidence rates for oral cavity, pharyngeal, and laryngeal cancer were related to alcohol consumption. Furthermore, esophageal cancer showed two patterns: Squamous cell carcinoma was associated with alcohol consumption, whereas adenocarcinoma of the esophagus was unrelated to either alcohol or smoking. Glottis cancer and lung cancer were more closely associated with smoking [13].

Vitamin D status

A study of the association between dietary vitamin D intake and oral/pharyngeal cancer and esophageal SCC showed a high risk for these tumors among heavy consumers of alcohol and heavy current smokers, which was most pronounced in those with lower vitamin D intake [14]. However, overall dietary vitamin D intake was low, both in patients and controls, and neither sunlight exposure nor vitamin D status was taken into account. In a study of serum 25(OH)D and risk for esophageal and gastric cancer, no significant associations were found between these upper gastrointestinal tumors and serum 25(OH)D concentrations [15].

Vitamin D and food

Does vitamin D exhibit a regulatory function in proliferative processes in the body? In children receiving standard therapy for uncomplicated severe acute malnutrition, two doses of 200 000 IU cholecalciferol improved their mean weight-for-height and developmental parameters [16]. A marked circadian variation of serum vitamin D concentrations has been demonstrated in healthy volunteers and in postmenopausal women, but the reasons for these variations remained unclear. Serum 1,25-dihydroxyvitamin D [1,25 (OH)D] concentrations showed a diurnal rhythm with the lowest concentrations in the morning, followed by a rapid increase to a plateau during the day, with concentrations being 14% above the lowest concentrations [17]. A similar pattern of variation was found in serum 25(OH)D concentrations in 10 healthy volunteers,

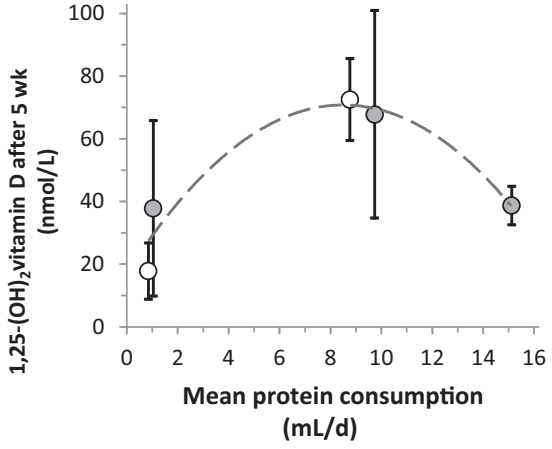

Fig. 2. Trend of serum 1,25-dihydroxyvitamin D concentration depending on food, protein, and alcohol consumption. Calculated from numbers of an animal study with isocaloric diets containing the same amount of vitamin D [20]. White dots: Diet contained 36% ethanol. Grey dots: Diet contained 0% ethanol. Mean protein consumption depends on the diet protein content and the amount of food consumed. Left side of figure: Two diets with 2% protein. The other diets contained 18% protein. To the far right of figure: Result of ad libitum-fed animals on the diet with 18% protein and 0% ethanol. After 5 wk, low mean serum 1,25-dihydroxyvitamin D concentrations were found in animals with low-protein diets and in ad libitum-fed animals. Whiskers represent SDs.

with peak concentrations (the acrophase) at 10:40 h and an increase of 27% compared with the lowest concentrations [18]. Although some studies reported vitamin D concentrations in Ramadan fasting [19], no data were found that addressed the possibility of a short-term decrease in vitamin D concentrations following fasting or starvation. In an animal study on metabolic effects of four isocaloric diets containing either 2 or 18% protein with or without 36% ethanol, a low-protein diet resulted in low mean serum 1,25(OH)D concentrations [20], although all diets contained identical amounts of vitamin D. A fifth group of ad libitum-fed animals also ended up with low mean vitamin D levels. The results show an inverted U-curve when the serum vitamin D concentrations on 5 wk follow-up are plotted against the daily protein intake (Fig. 2). The ad libitum-fed animals gained considerably in weight, which may explain their lower vitamin D concentrations after 5 wk of feeding [21]. The relation between body weight, body composition, and vitamin D status, however, is complex. Adverse associations between body weight and serum vitamin D concentrations, and differences in response to VDs, were found in several studies [22–24], including the aforementioned experimental study [20].

Strength and limitations

To our knowledge, this is the first direct indication that VDs after malnourishment might be associated with cancer diagnoses in patients with WKS. Because results in the cohort study may be prone to time-related bias, we accounted for differences of follow-up time (time-window bias) in supplementation and non-supplementation [25]. Although the study represented a large group of patients with WKS, from a perspective of cancer research the total number of patients was rather small. In malnourished alcoholic patients, self-neglect and other unhealthy behaviors, rather than the patients' individual vitamin D intake, are more likely to influence cancer risk. Data on various factors were collected retrospectively and this may have affected the quality of the data in some respect. Information bias may have occurred in the retrieval of data from heterogeneous sources (i.e., patient charts, electronic patient records, practitioner reports, and hospital discharge letters). Owing to lack of detailed data, no further analysis could be made of the severity of baseline vitamin D deficiencies. If vitamin D prescriptions were started in a previous ambulatory setting, the patient's medication adherence may not have been as certain as during hospital admission and after stay in our center. The majority of the study population had a lean BMI, which may have limited the ability to generalize the results to other populations where obesity is common and a contributing factor to morbidity.

Conclusion

VDs was time-related to cancer diagnoses in a cohort of patients with alcoholic WKS. The temporal relationship of VDs and cancer diagnosis was significant ($P < 0.05$) to the disadvantage of cancer diagnoses and VDs that started in the year leading up to the diagnosis. VDs and diagnostic findings of newly diagnosed malignant tumors may have occurred together by selection bias in self-neglecting patients. Our findings may be considered hypothesis generating regarding possible adverse consequences of VDs in malnourished patients, such as those with WKS. Although the results have to be interpreted with considerable caution, we suggest that in patients with alcoholic WKS, their already increased risk for tumor growth may be enhanced by VDs, either when started early in daily dosages or later as intermittent high-dose supplementation. Notwithstanding the retrospective design of the study, we suggest that in patients with WKS extensive or intermittent high-dose VDs be postponed until the patient is no longer malnourished.

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