An Inter-Method Reliability Study Comparing Interview Information on Sunlight, Tanning Beds, Food, and Supplement Exposures with Serum 25-Hydroxy Vitamin D Levels

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Abstract

Background: We developed a questionnaire designed to capture the vitamin D related exposures of sunlight, tanning bed use, dietary intake, and supplement use, and used an inter-method reliability approach to compare the study method (self-reported information on vitamin D related exposures nearest the blood draw) with serum 25-hydroxy vitamin D (25(OH)D) levels.

Methods: This inter-method reliability study included 512 control women from a population-based, case-control study in Alberta, Canada. All women self-reported data on food/supplement intake (average µg/day), sun exposure (cumulative hours/year), and tanning bed exposure (cumulative hours/year) and provided fasting serum samples, measured in duplicate with a DiaSorin immunoassay for 25(OH)D levels. The correlation between participant characteristics and 25(OH)D are described. We used multivariable robust regression to estimate the percent of variation in 25(OH)D explained by our variables of interest.

Results: Food intake, sun exposure, and tanning bed exposure had positive and significant correlations with 25(OH)D levels of a similar magnitude (Spearman r= 0.17 to 0.19). Supplement intake (average µg/day, Spearman r= 0.44) had the strongest positive correlation. In both crude and adjusted models (adjusted for age, body mass index, race, smoking, oral contraceptive use, and menopausal status/hormone therapy), we consistently found that food explained 3.1%, supplements 18.9%, sunlight 2.2%, and tanning bed use 3.0% of the variation in 25(OH)D levels, and all variables combined explained 27.5% - 36.0% of the total variation. Conclusions: These results suggest that our comprehensive dietary and light exposure questionnaire may be a reasonable proxy measure of vitamin D status in the recent past when either 25(OH)D measurements or serum samples are not available for study participants.

Introduction

Vitamin D is an essential nutrient for the human body with reference intakes established by the United States (US) National Academy of Medicine, most recently updated for bone health in 2010(1). However, unlike other nutrients, it is also synthesized in the skin in response to exposure to ultraviolet B (UVB) radiation (e.g., from sunlight). While vitamin D sufficiency is closely tied with bone health(1), it has also been linked to a number of other disease states from cancer(2) to autoimmune disorders(3) to dementia(4). Along with direct measurement of circulating 25-hydroxy vitamin D (25(OH)D) levels, surveys and questionnaires are often used to estimate vitamin D related exposures such as sunlight exposure, tanning bed use, dietary intake, and supplement use. From both a public health and research standpoint, it is important to consider the relative contribution of these vitamin D related exposures to circulating 25(OH)D levels on an individual level. Such knowledge can be used to develop predictive models for the public concerning vitamin D related exposures that can achieve sufficient vitamin D status while minimizing any harms such as from UVB radiation; many such models have been published (e.g., (5–15)). Alternatively, for research purposes, it is useful to evaluate if questionnaire responses, specifically designed to capture vitamin D related exposures, are correlated with circulating 25(OH)D levels.

We developed a questionnaire designed to capture self-reported adult life-time vitamin-D related sun, tanning bed, diet, and supplement exposures for a case-control study(16). Retrospective serum samples from age 20 years forwards for our study participants were not available, but we did have a serum samples as well as self-reported vitamin D related exposures near to the reference date, i.e., an assigned month/year for controls that had the same distribution as the diagnosis dates of ovarian cancer cases. Using an inter-method reliability approach(17) we

compared the study method (self-reported information on vitamin D related exposures nearest the blood draw) with serum 25(OH)D levels in the control women only from a population-based, case-control ovarian cancer study in Alberta, Canada.

Methods

Study population and data collection

The study population was derived from Alberta control participants who participated in the Ovarian Cancer in Alberta and British Columbia (OVAL-BC) Study, described previously(18). Briefly, in accordance with the Canada Health Act, Alberta has a publicly administered and funded health care systems ensuring eligible residents access to medically necessary hospital and health care services. All residents register for coverage and the control women were randomly identified through this provincial health roster from September 2005 through June 2011. These participants were: 1) Alberta residents; 2) age 40–79 years; 3) English-speaking; and, 4) able to complete the telephone interview. Consent was obtained in a two-step process. In the first step, 1,514 eligible women were contacted and 604 (40%) provided active consent for release of their contact information to the study team. In the second step, 519 (86%) of the 604 women provided signed, informed consent, completed the telephone interview and provided a fasting blood sample (two 6 ml red top/serum tubes).

Information on risk factors was ascertained up to the time point of the reference date (month/year) that was assigned for controls as part of the case-control study design(18). The telephone interview was extensive and included personal health history, reproductive and menstrual history, exogenous hormone use, family history of cancer, physical activity patterns (for a subset of women only), adult lifetime caffeine and alcohol consumption, smoking habits, demographic characteristics and adult height and weight at each decade from age 20 years onward. Additionally, four vitamin D related exposures over adult life were ascertained(16) and are described below. For the purposes of this analysis, we used the most recently reported exposures relative to the reference date.

Vitamin D related exposures

For specified ages at ten-year age intervals (20, 30, etc.) through age 70 years women were queried about: calendar year during each age, place of residence, job title or school attended, number of days per week on and off work/school. Although Canada is generally north of 49^0N, study participants could have lived at any inhabited latitude and were not required to reside in Canada all of their adult lives for this study. Considering both the southern and northern hemispheres, and the sun exposure therein, we used 42^0N, 42^0S, the Tropic of Cancer and the Tropic of Capricorn, to split the two hemispheres into five regions: north (> 42^0N), mid-north (Tropic of Cancer to 42^0N), equator (Tropic of Cancer to Tropic of Capricorn), mid-south (Tropic of Capricorn to 42^0S, and south (> 42^0S). Women were asked about the amount of sunlight exposure received on average on week days and weekend days from 9:00 am to 5:00 pm between April 1 and September 30 when residing in the north region. Similarly, the amount of sunlight exposure for winter sun holidays/seasonal residences between October 1 and March 31 that occurred in the mid-north, equator or mid-south regions were also recorded. If a woman resided in the mid-north, equator or mid-south regions sunlight exposure was collected for the entire year. If multiple patterns of sunlight exposure occurred at a given age (because of job changes, moves, etc.) each distinct pattern was recorded separately. The cumulative hours of relevant sun exposure per individual was summed over the entire year. For this analysis, we used sunlight exposure for the most recent exposure age (i.e., 40, 50, 60, etc. years of age) that preceded the reference age. For example, for a woman who was 53 years at reference date, her most recent sun

exposure was based on the calendar year when she turned 50 years of age. Because blood samples were always collected after the reference date, there was a variable amount of time between the reported sunlight exposures and the date of blood draw. On average this varied by 4.2 years.

Participants also provided information on the consumption of foods/beverages that were vitamin D fortified (all types of milk, margarine)(19) or naturally contain vitamin D (tuna, salmon, oysters, sardines, eggs), and supplements (multivitamins, vitamin D tablets with/without calcium, cod liver oil capsules or liquid) in the last 12 months and for specified ages at ten-year age intervals (20, 30, etc.) through age 70 years. The dietary interview, which we developed specifically to estimate vitamin D intake, was based on the Canadian adaptation of the National Cancer Institute's (NCI) Diet History Questionnaire (20–22) with slight modifications for our specific foods (e.g., salmon and tuna were asked separately, not as a general fish category). Vitamin D content in food was based on Health Canada nutrient data(23). To estimate average daily dietary vitamin D exposure for each study participant, we summed reported vitamin D intakes (in µg per day) for each food in the 12 months prior to the reference date. For each food item, average daily vitamin D intake was derived as: (consumption frequency per day) x (portion size in grams) x (vitamin D content per 100 grams of food). For supplements, women provided the frequency for each supplement used, and for vitamin D pills/capsules or cod liver oil capsules an estimate of the vitamin D content per tablet/capsule (< 100 international units [IU]/<2.5 micrograms [µg], 100–199 IU/2.5–4.9 µg, 200–399 IU/5.0- 9.9 µg, ≥ 400 IU/>10 µg), and the teaspoons of liquid cod liver oil taken. Multivitamins were assigned a vitamin D value of 400 IU/10 µg given that the majority of our data was collected before late 2010 when new recommendations were published and supplement formulations changed(1). Cod liver oil liquid was assigned 100 IU/2.5 µg per gram of oil(24). For each supplement category, average daily vitamin D intake was derived as: (consumption frequency per day) x (vitamin D content) and then summed over all categories of supplements.

To avoid small, sporadic exposures in tanning bed use, women had to have at least 12 exposures in one year since they turned 20 years of age to be considered a tanning bed user. For women who answered affirmatively, lifetime use was ascertained by recording the age started and stopped and hours of exposure per week or month for each pattern of tanning. For this analysis, the cumulative hours of tanning bed exposure per woman was summed during the 12 months prior to the reference date.

Serum 25(OH)D levels

Serum samples were available for 512 of the 515 women who completed the interview. Serum was aliquoted from fasting blood samples and stored in -80^{0}C freezers. Serum concentrations of total 25(OH)D were measured in duplicate (in different batches) across seven batches between June 9–28, 2016 at Calgary Laboratory Services® (CLS, Calgary, Alberta) using the DiaSorin immunoassay analyzer, LIAISON® XL(25). CLS is a participating member of the Vitamin D External Quality Assessment Scheme (DEQAS)(26) for external validation of total 25(OH)D. The reliability between the duplicate serum 25(OH)D measurements was estimated by the intra-class correlation coefficient (ICC) for absolute agreement using a two-way random effects model. We observed an ICC of 0.94, which is in the excellent range, indicating a high degree of agreement between duplicate measurements. We used the average value of the duplicate serum measurements for each woman in all analyses. All 25(OH)D concentrations are reported in nmol/L (to convert to ng/ml, multiply by 0.4006).

Statistical analysis

The final study population consisted of the 512 women for whom we had interview information and blood samples available. We plotted the distribution of serum 25(OH)D levels, overall and by age and by season. Characteristics of women and the associated 25(OH)D levels are described as well as the p-value for a difference in group means within each characteristic. P-values were calculated using t tests for comparison of two groups and one-way analysis of variance F tests for comparison among three or more groups. Food intake was evaluated both as a continuous variable and grouped in tertiles: low (0.17–2.80 μg/day), medium (2.81–5.07 μg/day) and high (5.08–20.30 μg/day). Supplement intake was also evaluated as a continuous variable and grouped in tertiles: low (0.0-3.18 μg/day), medium (3.19-15.00 μg/day) and high (15.01–42.50 μg/day). Tanning bed hours and sunlight hours (which included sun holiday hours) were evaluated as continuous variables. We calculated Pearson and Spearman correlation coefficients (r) between serum 25(OH)D levels and food intake, supplement intake, sunlight exposure, and tanning bed exposure. For modeling, we initially used linear least squares regression but outliers violated the assumption of normally distributed residuals. To best accommodate the effects of outliers we performed multivariable robust regression to examine the association between covariates and serum 25(OH)D levels and to estimate the percent of variation in serum 25(OH)D levels that can be explained by food intake, supplement intake, sun exposure, and tanning bed exposure in crude and adjusted models. We implemented M-estimation with Huber weighting in the robust regression (27) to produce estimates of the regression slopes that are robust to outliers by down-weighting the contribution of outliers. Final models were adjusted for age, body mass index (BMI), race, smoking, oral contraceptive (OC) use, and menopausal status/hormone therapy, all which had a borderline to highly statistically significant relationship with serum 25(OH)D levels. We were unable to adjust for physical activity because this was only available for a subset of the women. We also explored interactions by age, BMI, and OC use in white women only using likelihood ratio tests comparing the full model including the interaction term to the reduced model without (Supplemental Table 1). The categories of menopausal status and hormone therapy (HT) use were too sparse to evaluate interactions. All analyses were performed using R Studio version 1.0.136(28). All statistical tests were two-tailed and the significance level was set at $\alpha = 0.05$.

Results

Among this sample of women aged 40–79 years in Alberta, 25(OH)D serum concentrations were normally distributed with a mean of 69.6 nmol/L (standard deviation [SD] = 23.04) and median of 69.7 nmol/L (interquartile range [IQR] = 29.6) (Fig. 1). Mean serum 25(OH)D concentrations were over 60.0 nmol/L in all age groups and varied little, with no significant differences between age groups (Table 1). Mean concentrations were over 60 nmol/L in all seasons of blood draw, but was significantly higher in summer (72.7 nmol/L) than in winter (64.3 nmol/L) ($p < 0.01$).

Table 1
Characteristics and 25(OH)D concentrations in women.

Characteristic		N	%	25(OH)D serum levels (nmol/L)				p-value for difference in group means
				Median	Q1, Q3	Mean	SD	
Age (years)	40–49	108	21.1	66.7	51.5, 83.5	67.6	26.3	0.35
	50–64	269	52.5	68.9	53.8, 83.1	69.2	22.5	
	65–79	135	26.4	72.5	59.7, 84.5	71.8	21.2	
Race	White	477	93.2	70.7	55.2, 83.9	70.0	23.1	0.09
	Non-White /Unknown	35	6.8	64.1	47.0, 76.5	63.4	22.0	
Education	University	209	40.8	71.1	54.6, 84.3	69.8	22.9	0.96
	Vocational School	135	26.4	70.7	53.8, 83.2	69.8	23.8	
	High School or less	167	32.6	67.8	53.6, 83.2	69.1	23.1	
	Unknown	1	< 1.0					
BMI (kg/m^2)	< 25	250	48.8	73.9	59.4, 85.8	73.6	22.5	< 0.01
	25–30	150	29.3	70.6	55.8, 84.3	71.2	23.2	
	>=30	112	21.9	59.5	43.5, 72.6	58.5	20.6	
Smoking	Never	260	50.8	68.4	54.5, 82.3	69.4	21.8	< 0.01
	Former	217	42.4	71.6	57.5, 85.7	71.9	23.9	
	Current	35	6.8	53.9	39.4, 76.1	56.5	22.23	

*: peri/post = perimenopausal and postmenopausal

†: based on n = 262 women with physical activity information; percentages presented used 262 as the denominator.

: median value = 358 hours/year

Characteristic		N	%	25(OH)D serum levels (nmol/L)				p-value for difference in group means
				Median	Q1, Q3	Mean	SD	
Alcohol								
Beer	No	294	57.4	69.0	54.0, 83.7	69.3	23.3	0.71
	Yes	218	42.6	70.9	54.0, 83.4	70.0	22.8	
Hard liquor	No	216	42.2	70.8	54.5, 84.3	69.4	21.2	0.90
	Yes	296	57.8	68.8	53.6, 84.3	69.7	24.4	
Wine	No	202	39.5	66.0	49.6, 83.1	66.4	23.3	0.21
	Yes	308	60.2	71.5	57.4, 84.0	71.6	22.8	
	Unknown	2	< 1.0	79.0	74.8, 83.3	79.0	12.0	
Oral contraceptive use (years)	No	73	14.3	64.5	46.0, 76.7	64.2	20.5	< 0.01
	< 5	244	47.7	67.1	54.5, 81.4	67.9	21.1	
	>= 5	195	38.1	73.80	56.7, 89.1	73.6	25.6	
Parity	0	55	10.7	69.0	56.1, 84.5	72.1	24.3	0.24
	1	50	9.8	64.6	48.9, 78.6	64.9	28.1	
	2	225	44.0	71.2	56.8, 84.5	71.3	21.9	
	>= 3	182	35.6	68.7	50.8, 83.2	68.0	22.4	
Breastfeeding (months)	Never	152	29.7	68.3	53.1, 82.7	68.5	23.4	0.28

*: peri/post = perimenopausal and postmenopausal

†: based on n = 262 women with physical activity information; percentages presented used 262 as the denominator.

: median value = 358 hours/year

Characteristic		N	%	25(OH)D serum levels (nmol/L)				p-value for difference in group means
				Median	Q1, Q3	Mean	SD	
	< 10	197	38.5	69.0	51.8, 84.3	68.5	23.2	
	>= 10	163	31.8	71.1	57.3, 84.5	71.9	22.5	
Menopausal status and hormone use	Premenopausal	138	26.9	69.8	53.3, 84.1	69.0	25.5	< 0.01
	Peri-Post*/no HT	224	43.7	67.1	52.0, 79.2	67.6	22.3	
	Peri-Post/ E-only	52	10.2	63.8	50.1, 79.1	64.1	20.0	
	Peri-Post/ Other combination	98	19.1	78.2	65.8, 89.9	77.7	20.7	
Physical activity † (minutes/week)	< 60	169	64.5	71.5	54.0, 86.8	71.8	25.1	0.05
	>=60	93	35.5	78.4	64.8, 91.1	78.0	23.0	
Vitamin D in Food (µg/day)	Low (0.17–2.80)	171	33.4	66.2	47.5, 80.6	65.3	25.3	< 0.01
	Medium (2.81–5.07)	170	33.2	68.6	55.8, 82.0	69.5	22.1	
	High (5.08–20.30)	171	33.4	72.8	60.3, 86.7	73.9	20.8	
Vitamin D Supplement (µg/day)	Low (0.00-3.18)	170	33.2	56.2	44.5, 70.7	57.4	21.2	< 0.01
	Medium (3.19-15.00)	190	37.1	71.5	57.2, 84.2	71.0	20.9	
	High (15.01–42.50)	152	29.7	78.9	67.6, 91.8	81.4	20.9	
Tanning bed (hours/year)	Never	479	93.6	68.9	53.6, 82.5	68.3	21.9	< 0.01
	Yes, 0.65-61.00	33	6.4	89.0	67.6, 95.7	88.4	30.6	

*: peri/post = perimenopausal and postmenopausal

†: based on n = 262 women with physical activity information; percentages presented used 262 as the denominator.

: median value = 358 hours/year

Characteristic		N	%	25(OH)D serum levels (nmol/L)				p-value for difference in group means
				Median	Q1, Q3	Mean	SD	
Sun exposure (hours/year)	≤ 358 hours □	255	49.8	66.0	50.7, 80.6	66.4	23.5	< 0.01
	> 358 hours	257	50.2	73.7	58.7, 85.3	72.7	22.2	
By time between blood draw and reported sunlight exposure (years)	0–1	125	24.4	73.9	56.8, 84.6	71.8	22.7	0.46
	2–5	204	39.8	67.9	54.4, 83.5	68.7	21.8	
	6–10	183	35.7	68.6	53.1, 82.8	69.1	24.6	
*: peri/post = perimenopausal and postmenopausal								
†: based on n = 262 women with physical activity information; percentages presented used 262 as the denominator.								
□: median value = 358 hours/year								

Mean 25(OH)D concentrations varied significantly across a number of participant characteristics (Table 1). Higher mean 25(OH)D levels were found in women with BMI of 25 kg/m^2 or less, among never/former smokers, among women reporting use of OCs for five or more years, among those who reported higher intake of vitamin D related foods and vitamin D supplements, and in those with greater sunlight exposure and any tanning bed use (Table 1). Additionally, peri/postmenopausal women who used estrogen plus progesterone and other combinations of hormones had a higher mean serum concentration than the other women classified by menopausal status and hormone use. Physical activity was only available for a subset of the women, but among this subset, women with an average of 60 or more minutes of physical activity per week had higher mean 25(OH)D concentrations than those with lower levels of activity.

The correlations between dietary and light exposures and 25(OH)D levels are shown in Table 2. Overall food intake (average μg per day; Pearson r = 0.13 and Spearman r = 0.17), sun exposure (cumulative hours per year; Pearson r = 0.16 and Spearman r = 0.19), and tanning bed exposure (cumulative hours per year; Pearson r = 0.25 and Spearman r = 0.17) were all positively related to 25(OH)D levels. The strongest positive correlations were noted for supplement intake (average μg per day; Pearson r = 0.42 and Spearman r = 0.44) and hours per year tanning bed use among those who used tanning beds (Pearson r = 0.47 and Spearman r = 0.47). Because there could be up to 10 years between the reported sun exposure and the blood draw, we looked at correlations by this lag time. Not surprisingly, higher correlations were noted for a small lag time (0–1 years, Pearson r = 0.26 and Spearman r = 0.28) than for a longer lag time (6–10 years, Pearson r = 0.06 and Spearman r = 0.10).

Table 2
Correlation of dietary and light exposures with 25(OH)D concentrations in women.

	N	%	Mean	SD	Median	Q1, Q3	Pearson r	p-value	Spearman r	p-value
Food* (µg/day)	512	100.0	4.5	3.0	3.9	2.2, 6.1	0.19	< 0.01	0.17	< 0.01
Supplement* (µg/day)	512	100.0	11.3	10.3	10.0	0.7, 17.9	0.42	< 0.01	0.44	< 0.01
Sun exposure (hrs/year)	512	100.0	406.7	278.1	358.2	217.0, 540.0	0.16	< 0.01	0.19	< 0.01
Time between blood draw and reported sun exposure (years)	125	24.4	376.9	311.9	320.4	172.9, 540.0	0.26	< 0.01	0.28	< 0.01
0–1	204	39.8	413.1	261.2	360.0	231.4, 540.0	0.21	< 0.01	0.21	< 0.01
2–5	183	35.7	419.8	272.0	360.0	233.7, 547.8	0.06	0.425	0.10	0.17
6–10										
Tanning table*,† (hrs/year)	512	100.0	0.5	3.3	0.0	0.0, 0.0	0.25	< 0.01	0.17	< 0.01
Users only	33	6.5	7.2	11.0	3.3	2.2, 8.7	0.47	< 0.01	0.47	< 0.01

*: in the last 12 months;

†: n = 479, no tanning exposure

The estimated variation in 25(OH)D levels that is explained by light and dietary exposures as captured in our questionnaire are shown in Table 3. We built three models. The first, model 1, included just the light and dietary exposures by themselves. Model 2 was further adjusted for age, BMI, and race; these characteristics are well known to be associated with 25(OH)D levels. Model 3 was further adjusted for OC use, smoking, and menopausal status and hormone use; these characteristics were identified as associated with 25(OH)D levels in this study. As expected, the total R^2, or the percent of variation in 25(OH)D levels explained by the light and dietary exposures, as captured in our study, increased with the total number of variables modeled, explaining an estimated 27.5% – 36.0% of the variation in 25(OH)D levels. There was minimal variation in β-coefficients between models for each light and dietary exposure (approximately 3.1% for food; 18.9% for supplements; 2.2% for sunlight; and, 3.0% for tanning beds) indicating a consistent relationship with 25(OH)D levels that was independent of the adjustment variables in this study population of women.

Table 3

Variation in 25(OH)D serum concentrations that is explained by light and dietary exposures as captured in the OVAL-BC questionnaire.

		Food (µg/day)		Supplement (µg/day)		Sunlight exposure	Tanning (hrs/year)
		Medium	High	Medium	High	Per 100 hours	Any tanning
Model 1 *		2.2	6.5	12.1	22.8	1.2	15.0
	(95% CI)	(-2.0, 6.3)	(2.4, 10.7)	(8.0, 16.2)	(18.5, 27.1)	(0.6, 1.8)	(8.1, 21.9)
	Partial R^2	3.2%		18.9%	2.4%		2.9%
	Multiple R^2	27.5%					
Model 2 †		2.4	6.7	12.1	22.5	1.1	14.3
	(95% CI)	(-1.7, 6.4)	(2.6, 10.7)	(8.1, 16.2)	(18.2, 26.8)	(0.5, 1.7)	(7.6, 21.1)
	Partial R^2	3.2%		18.9%	2.2%		3.0%
	Multiple R^2	33.1%					
Model 3 ‡		1.6	5.7	11.5	20.9	1.2	14.1
	(95% CI)	(-2.5, 5.8)	(1.6, 9.8)	(7.5, 15.6)	(16.4, 25.4)	(0.6, 1.8)	(7.2, 20.9)
	Partial R^2	3.0%		18.8%	2.2%		3.0%
	Multiple R^2	36.0%					

*: model 1: food + supplement + sun exposure + tanning hours

†: model 2: model 1 + age + BMI + race (categories for adjustment as shown in Table 1)

‡: model 3: model 2 + OC use + smoking + menopausal status and hormone use (categories for adjustment as shown in Table 1)

Supplemental Table 1

Evaluation of possible interaction of food intake, supplement intake, sunlight exposure, and tanning bed exposure with age, body mass index (BMI), and oral contraceptive use associated with serum 25(OH)D concentrations in white women only.

	Food (ug/day) *		**Supplements (ug/day) ***		**Cumulative Sunlight (hrs/yr) †, ‡**	**Tanning Bed (hrs/yr) *,†**
	Medium (2.81, 5.07)	High (5.08, 20.30)	Medium (3.19–15.00)	High (15.01–42.50)	Per each 100 hours	Any use, previous year
	β_1 (95%CI)	β_2 (95%CI)	β_1 (95%CI)	β_2 (95%CI)	β (95%CI)	β (95%CI)
Age (years) §						
<50	3.5 (-3.0, 9.9)	7.6 (1.2, 14.0)	11.4 (4.9, 17.9)	20.9 (14.1, 27.8)	1.2 (0.3, 2.1)	11.8 (5.2, 24.5)
50–64	-0.7 (-8.4, 6.9)	5.3 (-2.7, 13.2)	10.79 (2.8, 18.8)	23.4 (15.3, 31.5)	0.6 (-0.6, 1.7)	7.7 (-6.9, 22.4)
≥65	3.0 (-6.0, 12.0)	1.8 (-7.2, 10.8)	15.3 (6.5, 24.1)	21.1 (11.9, 30.4)	1.7 (0.3, 3.0)	15.5 (0.8, 30.2)
p-interaction	0.63		0.77		0.66	0.57
BMI (kg/m^2) ‖						
<25	-3.2 (-13.7, 7.2)	7.6 (-2.5, 17.8)	6.2 (-3.8, 16.2)	22.5 (10.8, 34.1)	0.8 (-0.7, 2.4)	9.6 (-4.4, 23.6)
25–29	3.0 (-2.5, 8.5)	5.7 (0.1, 11.2)	13.5 (8.0, 18.9)	21.6 (15.8, 27.3)	1.7 (0.9, 2.6)	14.3 (5.8, 22.8)
≥30	2.1 (-7.0, 11.2)	1.9 (-7.2, 11.0)	11.9 (1.9, 21.9)	20.8 (11.3, 30.4)	0.3 (-0.9, 1.6)	20.2 (-1.0, 40.3)
p-interaction	0.74		0.33		0.20	0.75

*: in the previous year

†: hrs/yr = hours per year

‡: sun exposures in the year closest to year of blood draw

§: results adjusted for BMI and oral contraceptive use

‖: results adjusted for age and oral contraceptive use

**: results adjusted for age and BMI

	Food (ug/day) *		Supplements (ug/day) *		Cumulative Sunlight (hrs/yr) †, ‡	Tanning Bed (hrs/yr) *,†
Oral contraceptive use**						
None	11.1 (-1.6, 23.8)	10.6 (-2.6, 23.8)	10.1 (-2.5, 22.7)	25.6 (12.0, 39.1)	0.6 (-1.5, 2.6)	-12.0 (-51.3, 27.4)
< 5 years	-1.5 (-9.2, 6.2)	3.6 (-3.8, 11.0)	13.5 (6.3, 20.8)	25.5 (17.3, 33.6)	1.5 (0.5, 2.5)	16.3 (6.7, 25.8)
≥5 years	1.5 (-4.3, 7.2)	5.4 (-0.5, 11.3)	12.6 (6.4, 18.9)	19.0 (13.2, 24.9)	1.0 (0.1, 2.0)	12.2 (1.1, 23.2)
p-interaction	0.49		0.16		0.17	0.22
*: in the previous year						
†: hrs/yr = hours per year						
‡: sun exposures in the year closest to year of blood draw						
§: results adjusted for BMI and oral contraceptive use						
||: results adjusted for age and oral contraceptive use						
**: results adjusted for age and BMI						

Supplemental Table 2

Variation in 25(OH)D serum concentrations that is explained by light and dietary exposures among women who did not use supplements (n = 93) as captured in the OVAL-BC questionnaire.

		Food (µg/day)		Sunlight exposure	Tanning (hrs/year)
		Medium	High	Per 100 hours	Any tanning
Model 1 *		10.3	7.0	1.4	11.8
	(95% CI)	(0.4, 20.2)	(-3.2, 17.1)	(0.01, 2.8)	(-9.3, 32.8)
	Partial R^2	4.3%		6.5%	1.5%
	Multiple R^2	12.3%			
Model 2 †		11.1	6.5	1.0	9.7
	(95% CI)	(1.9, 20.2)	(-2.9, 15.8)	(-0.3, 2.3)	(-9.7, 29.2)
	Partial R^2	4.3%		5.6%	1.5%
	Multiple R^2	27.9%			
Model 3 □		11.8	7.4	1.1	8.4
	(95% CI)	(2.3, 21.4)	(-2.5, 17.2)	(-0.2, 2.4)	(-12.4, 29.1)
	Partial R^2	5.2%		6.0%	1.6%
	Multiple R^2	40.6%			

*: model 1: food + supplement + sun exposure + tanning hours

†: model 2: model 1 + age + BMI + race (categories for adjustment as shown in Table 1)

□: model 3: model 2 + OC use + smoking + menopausal status and hormone use (categories for adjustment as shown in Table 1)

In an exploratory analysis, we also assessed possible interactions between food intake, supplement intake, sunlight exposure, and tanning bed exposure and age, BMI, and OC use in relation to serum 25(OH)D concentrations, in white women only (Supplemental Table 1). Non-whites were excluded from this analysis due to small numbers. While there was some variation across the categories, our results suggest that dietary and sunlight exposures as captured in our questionnaire have the same relationship with 25(OH)D concentrations across all levels of age, BMI, and OC use, although this result is possibly a function of limited sample size.

We also assessed food intake, sunlight exposure and tanning bed exposure among the 93 women who reported no vitamin D supplement use (Supplemental Table 2). In these women, both food and sunlight exposure explained

more of the variation in 25(OH)D levels (~ 5% and ~ 6%, respectively) than in the models that included women who used supplements (~ 3% and ~ 2%, respectively).

Discussion

We found that mean 250H-D concentrations varied significantly across the levels of consumption of foods containing vitamin D, sunlight exposure, and any tanning bed exposure as ascertained by our vitamin D-specific questionnaire. We observed positive and significant correlations of a similar magnitude (Spearman r = 0.17 to 0.19) for all of these factors. Stronger positive and significant correlations were noted for vitamin D supplement use and among the small percentage of women who reported tanning bed use. The reported dietary and light exposures captured by our questionnaire accounted for up to 36% of the variation in serum 25(OH)D levels in this analysis. There was a consistent relationship with the variation in 25(OH)D levels explained by food consumption (~3.1%), supplements (~18.9%), sunlight (~2.2%), and tanning bed use (~3.0%) in both crude and adjusted models.

Dietary/supplement and light exposures may be important in chronic disease risk. However, such analyses often rely on recalled information that is almost certainly imperfect. Although the interpretation of the strength of effect sizes is influenced by the biological and clinical context, if we use Cohen's conventions for a small (R^2 = 2%), medium (R^2 = 13%), and large (R^2 = 26%) strength of association(29), our results suggest that reported diet, sunlight, and tanning bed use have a small level of association and that supplements have a medium to large level of association with 25(OH)D levels. Combined, these variables have a large effect (27.5% – 36.0%) on 25(OH)D levels. Presumably, 25(OH)D levels can also be influenced by environmental factors (e.g., exact latitude, cloud or tree cover, ground surface reflectivity, time of day) to personal influences (e.g., sunscreen use, clothing, hats, standing versus sitting) to activation/absorption and metabolic variation of vitamin D between individuals. Thus, given the imperfect measures of recalled diet and light exposures, and the many other factors that can contribute to vitamin D status, the four variables we assessed in our questionnaire explained a substantial amount of variation in 25(OH)D levels in this population of women.

As expected 25(OH)D serum concentrations were normally distributed with a range from 10.1 to 182.5 nmol/L in this, mainly white (93.2%) population-based sample of English-speaking women in Alberta. As others have recently reported(30, 31), circulating 25(OH)D concentrations were not lower in the oldest age group in our population of women. In this population, 80% of women had mean 25(OH)D concentrations of 50 nmol/L or greater which is considered a sufficient level, at least for bone health(32, 33). Of the 20% of women below 50 nmol/L, only 4.1% were vitamin D deficient at < 30 nmol/L. While the majority of Albertans speak English at home or identify it as their "mother tongue"(34), non-English speakers were excluded in this study and may have different 25(OH)D levels than presented here due to diet, lifestyle factors, or skin pigmentation.

Another limitation of this study is that we only had physical activity data for a subset of women (n = 262), but among these women physical activity was significantly related to 25(OH)D levels. We therefore repeated the analysis presented in Table 3 for this subset of women and adjusted for physical activity. The results were very similar to those reported in the final model in Table 3 without adjustment for physical activity, with the partial R^2 for supplements again being the highest (about 18.5%). These results again imply that there is a consistent relationship between 25(OH)D levels and the diet and light variables as measured in our questionnaire regardless of adjustment for other covariates.

There is substantial variation in the ascertainment of vitamin D related foods across studies. We attempted to capture all major sources of vitamin D from food in our study and only included those foods that were consumed

by at least 5% of the population in our previous reliability study(16). Yogurt was not found to be a major source of vitamin D from food but yogurt made with vitamin D fortified milk became more common during our study. In another study in Alberta(35), about 20% of breast cancer cases reported consuming yogurt in a 2010 questionnaire and at least half of their consumption was yogurt made with vitamin D fortified milk. Daily consumption of such yogurt could increase vitamin D from food by approximately 1.2 μg per day. This implies that we probably under-estimated vitamin D intake from food for some participants, particularly for the latter years of our study, and this could have contributed to the relatively low correlation of 25(OH)D levels with food.

Among the small proportion of women who reported tanning bed use there was a moderate correlation with 25(OH)D levels. Tanning beds mainly emit UV-A radiation, but there is a small, variable amount of UV-B that can trigger the production of vitamin D. While a comprehensive picture of total light (e.g., UV) exposures, including tanning bed use, is important in research studies, tanning beds are associated with an increased risk for skin cancer (36) and their use as a targeted source for vitamin D is highly controversial.

Outdoor sunlight exposures explained a consistent but small level of the variation in serum 25(OH)D levels. Correlations were similar between food and sunlight with respect to 25(OH)D levels, suggesting that our sunlight ascertainment in the recent past performed at the same level as dietary exposure of vitamin D. Furthermore, when we stratified by lag time, we found the highest correlation with a short lag time (0–1 years, $r = 0.26$), one that exceeded the correlation with the past year's diet ($r = 0.19$). These results suggest that our ascertainment of sunlight is a useful measurement in assessing putative vitamin D exposure, even in a population at that resided predominantly in the north region where UV-B intensity is only sufficient for cutaneous vitamin D production for about half of the year(37). It should be noted that we did not collect sun screen use. In our pilot study, we collected this information but women had a difficult time recalling past use accurately, could not recall the sun protection factor (SPF) used, and confused "suntan lotion" with sun screen based on the reported years of use.

We could not directly assess vitamin D related exposures in the distant past because we did not have distant past serum samples for 25(OH)D measurement. However, we did find that our questionnaire measures of recalled diet and light exposures in the more recent past had significant positive correlations with 25(OH)D levels. Given the imperfect measures of recalled diet and light exposures, and the many other factors that can contribute to vitamin D status, the four variables we assessed in our questionnaire explained a substantial amount of variation in 25(OH)D levels in this population of women in Alberta. These results suggest that our comprehensive dietary and light exposure questionnaire is a reasonable proxy measure of vitamin D status for exposures in the recent past when either 25(OH)D measurements or serum samples are not available for study participants.

Conclusions

The reported dietary and light exposures captured by our questionnaire accounted for up to 36% of the variation in serum 25(OH)D levels. There was a consistent relationship with the variation in 25(OH)D levels explained by food consumption (~3.1%), supplements (~18.9%), sunlight (~2.2%), and tanning bed use (~3.0%) in both crude and adjusted models. These results suggest that our comprehensive dietary and light exposure questionnaire may be a reasonable proxy measure of vitamin D status in the recent past when either 25(OH)D measurements or serum samples are not available for study participants.

Abbreviations

25(OH)D
serum 25-hydroxy vitamin D
US
United States
UVB
ultraviolet B
OVAL-BC Study
Ovarian Cancer in Alberta and British Columbia Study
NCI
National Cancer Institute
DEQAS
Vitamin D External Quality Assessment Scheme
ICC
intra-class correlation coefficient
r
Pearson and Spearman correlation coefficients
BMI
body mass index
OC
oral contraceptive
HT
hormone therapy
SD
standard deviation
95% CI
95% Confidence Interval
Q1, Q3
Q1 = the median of the lower half of the data; Q3 = the median of the upper half of the data.

Declarations

Ethics approval and consent to participate:

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Health Research Ethics Board of Alberta. Written informed consent was obtained from all participants.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and/or analyzed during the current study are not publicly available due to compromising individual privacy, but are available from the corresponding author on reasonable request.

Competing interest:

Not applicable

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Authors' contributions:

Formulated the research question: LSC, XG, NB, NL, LL

Designed the study: LSC, XG, NB, NL, LL

Data/Biospecimen Collection: LSC, XG, NL

Analyzed the data: LSC, XG, LL

Wrote or critically reviewed the submitted manuscript: LSC, XL, XG, NB, NL, LL, CP

References

1. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. Ross CA, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington DC: Institute of Medicine of the National Academies, National Academies Press; 2010.
2. IARC Working Group. Vitamin D and Cancer. Lyon. France: International Agency for Research on Cancer; 2012.
3. Gallone G, Haerty W, Disanto G, Ramagopalan SV, Ponting CP, Berlanga-Taylor AJ. Identification of genetic variants affecting vitamin D receptor binding and associations with autoimmune disease. Hum Mol Genet. 2017;26(11):2164–76. DOI:.
4. Feart C, Helmer C, Merle B, Herrmann FR, Annweiler C, Dartigues JF, et al. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. Alzheimers Dement. 2017;13(11):1207–16. DOI:.
5. Touvier M, Deschasaux M, Montourcy M, Sutton A, Charnaux N, Kesse-Guyot E, et al. Determinants of vitamin D status in Caucasian adults: influence of sun exposure, dietary intake, sociodemographic, lifestyle, anthropometric, and genetic factors. J Invest Dermatol. 2015;135(2):378–88. DOI:.
6. Greene-Finestone LS, Berger C, de Groh M, Hanley DA, Hidiroglou N, Sarafin K, et al. 25-Hydroxyvitamin D in Canadian adults: biological, environmental, and behavioral correlates. Osteoporos Int. 2011;22(5):1389–99. DOI:.
7. Rabenberg M, Scheidt-Nave C, Busch MA, Rieckmann N, Hintzpeter B, Mensink GB. Vitamin D status among adults in Germany–results from the German Health Interview and Examination Survey for Adults (DEGS1). BMC Public Health. 2015;15:641. DOI:.
8. Chan J, Jaceldo-Siegl K, Fraser GE. Determinants of serum 25 hydroxyvitamin D levels in a nationwide cohort of blacks and non-Hispanic whites. CCC. 2010;21(4):501–11. DOI:.

9. Millen AE, Bodnar LM. Vitamin D assessment in population-based studies: a review of the issues. Am J Clin Nutr. 2008;87(4):1102 s-5s.1102 s-5s.
10. Greenfield JA, Park PS, Farahani E, Malik S, Vieth R, McFarlane NA, et al. Solar ultraviolet-B radiation and vitamin D: a cross-sectional population-based study using data from the 2007 to 2009 Canadian Health Measures Survey. BMC Public Health. 2012;12:660. DOI:.
11. Bertrand KA, Giovannucci E, Liu Y, Malspeis S, Eliassen AH, Wu K, et al. Determinants of plasma 25-hydroxyvitamin D and development of prediction models in three US cohorts. Br J Nutr. 2012;108(10):1889–96. DOI:.
12. Lucas RM, Ponsonby AL, Dear K, Valery PC, Taylor B, van der Mei I, et al. Vitamin D status: multifactorial contribution of environment, genes and other factors in healthy Australian adults across a latitude gradient. J Steroid Biochem Mol Biol. 2013;136:300–8. DOI:.
13. Freedman DM, Cahoon EK, Rajaraman P, Major JM, Doody MM, Alexander BH, et al. Sunlight and other determinants of circulating 25-hydroxyvitamin D levels in black and white participants in a nationwide U.S. study. Am J Epidemiol. 2013;177(2):180–92. DOI:.
14. Kuhn T, Kaaks R, Teucher B, Hirche F, Dierkes J, Weikert C, et al. Dietary, lifestyle, and genetic determinants of vitamin D status: a cross-sectional analysis from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Germany study. Eur J Nutr. 2014;53(3):731–41. DOI:.
15. Kimlin MG, Lucas RM, Harrison SL, van der Mei I, Armstrong BK, Whiteman DC, et al. The contributions of solar ultraviolet radiation exposure and other determinants to serum 25-hydroxyvitamin D concentrations in Australian adults: the AusD Study. Am J Epidemiol. 2014;179(7):864–74. DOI:.
16. Cook LS, Moon BL, Dong Y, Neilson HK. Reliability of self-reported sun exposure in Canadian women and estimation of lifetime exposure to vitamin D from sun and diet. Public Health Nutr. 2014;17(4):747–55. DOI:.
17. Armstrong BK, White E, Saracci R. Principles of Exposure Measurement. New York: Oxford University Press; 1992.
18. Cook LS, Leung AC, Swenerton K, Gallagher RP, Magliocco A, Steed H, et al. Adult lifetime alcohol consumption and invasive epithelial ovarian cancer risk in a population-based case-control study. Gynecol Oncol. 2016;140(2):277–84. DOI:.
19. Canadian Food Inspection Agency. Reference Information: Foods to Which Vitamins, Mineral Nutrients and Amino Acids May or Must be Added Ottawa, Canada: Government of Canada; [updated May 11, 2018]; cited 2019. Available from: .
20. Csizmadi I, Kahle L, Ullman R, Dawe U, Zimmerman TP, Friedenreich CM, et al. Adaptation and evaluation of the National Cancer Institute's Diet History Questionnaire and nutrient database for Canadian populations. Public Health Nutr. 2007;10(1):88–96. DOI:.
21. U.S. National Cancer Institute. Diet History Questionnaire (Archive Version) 2017 [updated 2019, Dec 11]. Available from: .
22. U.S. National Cancer Institute. Changes Between DHQ I & DHQ II 2017 [updated 2019, Dec 4]. Available from: .
23. Health Canada. Nutrient Data 2017 [updated 2016, June 3]. Available from: .
24. United States Department of Agriculture Agricultural Research Service. National Nutrient Database for Standard Reference Release 28 2016 [updated May 2016]. Available from: .
25. DiaSorin. Liaison [Available from: .

Figures

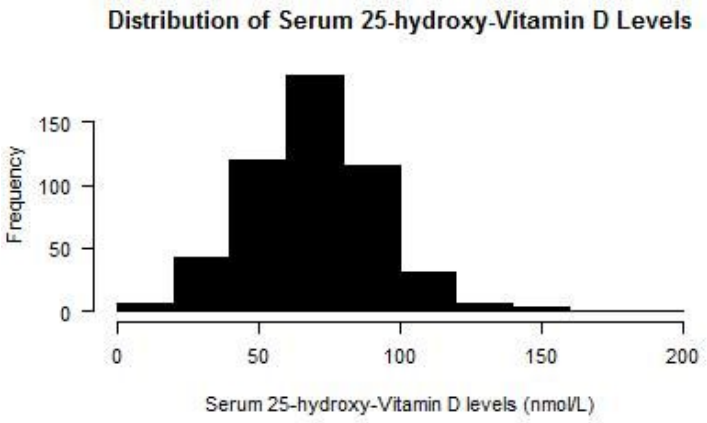

Figure 1

Distribution of 25(OH)D serum levels, women, Alberta, 2005-2011.