Low Serum Levels of 25-Hydroxyvitamin D Predict Fatal Cancer in Patients Referred to Coronary Angiography

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Abstract

Accumulating evidence suggests that vitamin D may protect against cancer, but results from epidemiologic studies are inconclusive so far, and other studies looking into the prospective association of total cancer mortality and serum 25-hydroxyvitamin D [25(OH)D] levels, which are considered to be the best indicator of vitamin D status, are scarce. We measured 25(OH)D and 1,25-dihydroxyvitamin D in 3,299 patients from the Ludwigshafen Risk and Cardiovascular Health study. The baseline examination was done between July 1997 and January 2000 and included a fasting blood sampling in the morning before coronary angiography. During a median follow-up period of 7.75 years, 95 patients died due to cancer. After adjustment for possible confounders, the Cox proportional hazard ratio (95% confidence interval) of the fourth 25(OH)D quartile was 0.45 (0.22-0.93) when compared with the first quartile and the hazard ratio per increase of 25 nmol/L in serum 25(OH)D concentrations was 0.66 (0.49-0.89). We found no association between serum 1,25-dihydroxyvitamin D levels and fatal cancer. In summary, our data suggest that low levels of 25(OH)D are associated with increased risk of fatal cancer in patients referred to coronary angiography and that the maintenance of a sufficient vitamin D status might therefore be a promising approach for the prevention and/or treatment of cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(5):1228–33)

Introduction

Vitamin D exerts various anticarcinogenic effects, and epidemiologic studies have largely but not consistently shown that hypovitaminosis D is associated with an increased risk for cancer (1-7). Cholecalciferol that is hydroxylated to 25-hydroxyvitamin D [25(OH)D] in the liver mainly originates from the skin where UV-B radiation induces the conversion from 7-dehydrocholesterol to cholecalciferol (8). Several studies have shown that the intensity of UV-B radiation is inversely associated with cancer mortality and that survival rates for cancers diagnosed in summer were significantly higher than for those diagnosed in winter (1-4). In the elderly, dietary vitamin D intake becomes a more important determinant of 25(OH)D serum levels because outdoor activities and sun exposure are usually reduced and the capacity of the skin to produce cholecalciferol is decreased (9). In the Health Professionals Follow-up Study, variables, such as nutritional intake of vitamin D, skin pigmentation, geographic residence, physical activity, sunlight exposure, and adiposity, which is associated with reduced 25(OH)D concentrations presumably due to vitamin D deposition in the adipose tissue, were included in a statistical model to predict serum 25(OH)D levels in 47,800 men (10). In that study, it was calculated that an increment of 25 nmol/L in serum 25(OH)D concentrations was associated with a 17% reduction in the incidence of cancer, a 29% reduction in total cancer mortality, and a 45% reduction in digestive system cancer mortality (10). Furthermore, case-control studies have largely shown that serum 25(OH)D levels are reduced in patients with different types of cancer, particularly in colorectal and breast cancer (1-4). For prostate cancer, there exist inconsistent results that may be explained by low 1α-hydroxylase activity of prostate cancer cells (1). By contrast, other types of cancer cells (e.g., colorectal cancer cells) display a high degree of local intracellular conversion from 25(OH)D to the more active form 1,25-dihydroxyvitamin D [1,25(OH)2D; ref. 1]. Recently, data from the Third National Health and Nutrition Examination Survey (NHANES-III), which included 16,818 persons ages ≥17 years, were published, addressing for the first time the question of a prospective association between serum 25(OH)D levels and cancer mortality (5). Although low serum 25(OH)D levels were associated with an increased risk of deaths due to colorectal cancer in this study, the authors found no such association for total cancer mortality (5). Thus, the contribution of a poor vitamin D status to total cancer mortality remains inconclusive and warrants further investigations. To extend the current knowledge on this

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issue, we examined the prospective association between serum 25(OH)D levels and cancer mortality in a cohort of 3,316 patients from southwest Germany, who were routinely referred to coronary angiography at baseline.

Materials and Methods

Study Population. The Ludwigshafen Risk and Cardiovascular Health (LURIC) study was designed to evaluate cardiovascular risk factors and includes 3,316 study subjects that were all routinely referred to coronary angiography at a single tertiary care center (Ludwigshafen General Hospital) in southwest Germany (13). Inclusion criteria were the availability of a coronary angiogram, German ancestry, and a stable clinical condition, except of an acute coronary syndrome. Exclusion criteria were any acute illness other than acute coronary syndrome and any chronic disease where noncardiac disease predominated. Importantly, patients with a history (evidence) of malignancy within the past 5 years were also excluded and there was thus no patient enrolled in the study that had known advanced cancer. Baseline examinations, which have been published in detail previously (13), were done between July 1997 and January 2000. Each study subject had a single blood draw in the morning before coronary angiography. All study participants gave their written informed consent and the study was approved by the Ethics Committee at the ''Ärztekammer Rheinland-Pfalz.''

Measurements of Covariates. Retinol was measured with the high-performance liquid chromatography method of Aebischer et al. (14). Patients with a stenosis of at least 20% in at least 1 of 15 coronary segments were diagnosed as having coronary artery disease. Diabetes mellitus was defined according to the American Diabetes Association criteria (15). Weight and height were measured while subjects were barefoot and wearing light clothes, and body mass index was calculated as weight divided by height squared (kg/m^2). Patients were asked to grade their beer and wine consumption into never, sometimes, regularly, and often, and we used a questionnaire with a scoring system ranging from 1 to 11 that was used to categorize the patients according to their physical activity level into ''below average'' (score 1-4), ''average'' (score 5-7), and ''above average'' (score $\geq$8).

Analysis of Vitamin D Metabolites. Measurements of serum 25(OH)D levels were done by radioimmunoassay (DiaSorin Antony, France) with an intraassay and interassay coefficient of variation of 8.6% and 9.2%, respectively. In 100 randomly chosen samples, we measured 25(OH)D by liquid chromatography-tandem mass spectrometry with isotopically labeled internal standard and two fragments *m/z* 401.4/382.2 (quantifier) and 401.4/365.3 (qualifier). The 25(OH)D values obtained by liquid chromatography-tandem mass spectrometry and radioimmunoassay showed a highly significant correlation ($r = 0.875$; $P < 0.001$), and there was no marked systematic difference in absolute 25(OH)D concentrations between both methods (data not shown). Serum concentrations of 1,25(OH)2D were analyzed by radioimmunoassay (Nichols Institute Diagnostika) on a Berthold LB2014 multicrystal counter.

Table 1. Baseline characteristics of controls and patients with fatal cancer

	Controls	Fatal cancer
n	3,162	95
Females (%)	30.5	23.2
Age (y)	62.5 ± 10.6	68.1 ± 8.4
Body mass index (kg/m^2)	27.5 ± 4.1	27.0 ± 3.9
Physical activity level		
Below average (%)	25.6	41.8
Average (%)	54.2	46.2
Above average (%)	20.2	12.1
Active smokers (%)	19.7	21.1
Beer consumption		
Never (%)	48.6	39.8
Sometimes (%)	32.6	39.8
Regularly (%)	18.6	20.4
Often (%)	0.2	0.0
Wine consumption		
Never (%)	38.2	44.2
Sometimes (%)	35.2	32.6
Regularly (%)	26.4	22.1
Often (%)	0.2	1.1
Retinol (μmol/L)	1.98 ± 0.58	1.81 ± 0.54
Coronary artery disease (%)	78.3	87.2
Diabetes mellitus (%)	31.8	35.8
25(OH)D (nmol/L)	43.8 ± 24.3	36.9 ± 17.8
z value for 25(OH)D	0.01 ± 1.00	-0.30 ± 1.01
1,25(OH)2D (pmol/L)	91.0 ± 36.4	91.9 ± 36.7
z value for 1,25(OH)2D	0.00 ± 1.00	0.07 ± 0.88

Ascertainment of Fatal Cancers. Information on vital status was obtained from local person registries. Death certificates were reviewed for the classification of the causes of death. This was done by two experienced physicians who were blinded to any data of the study subjects, except of the information obtained from the death certificates. Fatal cancer was coded for deceased persons whose death was judged to be mainly attributed to cancer. In the case of a disagreement concerning the classification of a specific cause of death, it was discussed and the final decision was made by one of the principle investigators of the LURIC study (W.M.).

Statistical Analysis. We formed quartiles according to the 25(OH)D and 1,25(OH)2D concentrations of the whole study cohort. To account for the seasonal variation of vitamin D, we also formed quartiles based on the 25(OH)D and 1,25(OH)2D concentrations from each month of blood draw (16-20). Similarly, we calculated *z* values for 25(OH)D and 1,25(OH)2D according to the means and SDs from their concentrations within each month of blood draw. These *z* values are based on logarithmically transformed values because 25(OH)D and 1,25(OH)2D showed a skewed distribution. Cox proportional hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated for vitamin D quartiles by using the first quartile as the reference and for quartiles as a linear variable. HRs for fatal cancer were also calculated for *z* values, for the SDs of logarithmically transformed 25(OH)D and 1,25(OH)2D concentrations, and per increment of 25 nmol/L in 25(OH)D serum levels. In addition, we also present the HRs per increment of 11.8 nmol/L, which is the estimated increase in 25(OH)D concentrations achieved by supplementation of 400 IU vitamin D_3 in the Women's Health Initiative. We calculated unadjusted HRs, age- and

sex-adjusted HRs, and HRs adjusted for age, sex, body mass index, active smokers, exercise tertiles, beer and wine consumption, diabetes mellitus, and retinol. We adjusted for retinol because it was suggested to antagonize vitamin D effects by competing with 1,25(OH)2D for binding to the retinoid X receptor (1). $P < 0.05$ was considered statistically significant and the SPSS 15.0 statistical package (SPSS) was used.

Results

Values for 25(OH)D and 1,25(OH)2D were available in 3,299 study subjects. We excluded 18 patients that were lost during follow-up and 24 deceased persons for whom we could not obtain the death certificates so that our final study cohort consisted of 3,257 persons. Unadjusted baseline characteristics for patients with fatal cancer and for controls, which include survivors and patients that died due to causes other than cancer, are shown in Table 1. The baseline data (unadjusted) are also presented according to 25(OH)D quartiles that are based on the values of the entire study cohort (Table 2). Apart from this, we observed a seasonal variation of 25(OH)D with the lowest median concentrations obtained from blood samples drawn in February (26.0 nmol/L) and the highest from those drawn in August (56.4 nmol/L).

After a median follow-up time of 7.75 years, 736 persons died, including 95 deaths due to cancer. Among these the three most common cancer sites were those of the lung ($n = 24$), colon ($n = 13$), and pancreas ($n = 11$). Cox proportional HRs for fatal cancer according to quartiles of 25(OH)D and per SD and z value are depicted in Table 2. All statistical models showed that higher 25(OH)D levels were associated with significantly reduced risk for fatal cancer with approximately a bisection of the HRs in the fourth when compared with the first quartile (Table 3). The age- and sex-adjusted HR (with 95% CI) per increment of 25 nmol/L in 25(OH)D serum levels was 0.67 (0.52-0.88) and the fully adjusted HR (according to model 2 in Table 3) was 0.66 (0.49-0.89). Accordingly, the age- and sex-adjusted HR per increment of 11.8 nmol/L was 0.83 (0.73-0.94) and remained significant in the fully adjusted model with a HR of 0.82 (95% CI, 0.71-0.95). Interestingly, only one patient died due to cancer among the 336 study subjects (10% of the entire study cohort) with 25(OH)D levels above 75 nmol/L. Seven deaths due to cancer were recorded during the first 15 months of follow-up, but exclusion of these seven deceased patients from our analyses did not materially alter our results [fully adjusted HR for fatal cancer in the first quartile when compared with the fourth 25(OH)D quartile (based on the values of the entire study cohort): 0.43 (95% CI, 0.20-0.92)]. There was no significant interaction between 25(OH)D and sex and the proportionality of hazards was tested with log-minus-log survival and partial (Schönfeld) residuals versus survival plots and found valid. The age- and sex-adjusted HR for the fourth 1,25(OH)2D quartile was 1.00 (0.56-1.79) and the association between 1,25(OH)2D and fatal cancer remained nonsignificant in all other statistical models (data not shown).

Discussion

In this study, we have shown that low concentrations of serum 25(OH)D but not 1,25(OH)2D levels were prospectively associated with an increased risk of fatal cancer in a cohort of 3,299 patients who were scheduled for coronary angiography. The association between 25(OH)D and cancer mortality remained significant after adjustment for possible confounders and in different statistical models.

Several lines of evidence indicate that specific cancer sites are associated with a poor vitamin D status. To the

Table 2. Baseline characteristics according to quartiles of 25(OH)D

	1st quartile	2nd quartile	3rd quartile	4th quartile
Females (%)	42.4	29.9	23.8	24.9
Age (y)	64.8 ± 11.1	63.2 ± 10.7	61.8 ± 10.1	60.7 ± 10.0
Body mass index (kg/m^2)	27.5 ± 4.6	27.7 ± 4.1	27.7 ± 3.9	27.1 ± 3.6
Physical activity level				
Below average (%)	38.1	27.2	20.6	18.4
Average (%)	53.9	58.3	55.0	48.3
Above average (%)	8.0	14.5	24.4	33.3
Active smokers (%)	23.5	19.2	16.0	19.8
Beer consumption				
Never (%)	55.8	51.2	43.3	42.5
Sometimes (%)	29.0	31.3	38.3	33.2
Regularly (%)	15.0	17.3	18.4	23.9
Often (%)	0.1	0.3	0.0	0.4
Wine consumption				
Never (%)	48.8	40.3	33.5	30.2
Sometimes (%)	31.9	33.5	38.5	36.9
Regularly (%)	18.8	26.0	27.8	26.0
Often (%)	0.5	0.3	0.1	0.0
Retinol (μmol/L)	1.85 ± 0.65	1.97 ± 0.55	2.01 ± 0.57	2.07 ± 0.54
Coronary artery disease (%)	83.1	76.7	76.9	77.1
Diabetes mellitus (%)	40.6	34.9	29.8	22.0
25(OH)D (nmol/L)	18.1 ± 4.7	32.4 ± 4.0	48.0 ± 5.3	76.3 ± 20.7
z value for 25(OH)D	-1.22 ± 0.67	-0.22 ± 0.45	0.36 ± 0.42	1.11 ± 0.49
1,25(OH)2D (pmol/L)	72.6 ± 28.8	86.1 ± 32.9	98.7 ± 35.3	108.0 ± 37.9
z value for 1,25(OH)2D	-0.45 ± 1.02	-0.09 ± 0.99	0.20 ± 0.90	0.38 ± 0.86

Table 3. Cox proportional HR (95% CI) for fatal cancer according to quartiles, SD and *z* values of 25(OH)D serum levels

	Quartiles and SD based on 25(OH)D concentrations of the entire study cohort			Quartiles and *z* values based on 25(OH)D concentrations within each month of blood draw		
	3,257 patients at risk with 95 deaths due to cancer					
	Quartiles/SD	HR (95% CI)	*P*	Quartiles/*z* value	HR (95% CI)	*P*
Unadjusted	1st (<25.5)*	1.00 reference		1st (<38.0)*	1.00 reference	
	2nd (25.5-39.0)	0.86 (0.51-1.44)	0.567	2nd (18.8-56.0)	0.47 (0.27-0.82)	0.008
	3rd (39.1-57.5)	0.71 (0.41-1.22)	0.212	3rd (25.8-71.5)	0.51 (0.30-0.87)	0.014
	4th (>57.5)	0.42 (0.22-0.79)	0.007	4th (>38.0)	0.44 (0.25-0.87)	0.004
	Per quartile	0.77 (0.64-0.93)	0.005	Per quartile	0.77 (0.64-0.92)	0.005
	Per SD†	0.74 (0.60-0.93)	0.010	Per *z* value‡	0.71 (0.57-0.90)	0.004
Model 1§	1st (<25.5)*	1.00 reference		1st (<38.0)	1.00 reference	
	2nd (25.5-39.0)	0.86 (0.51-1.46)	0.862	2nd (18.8-56.0)	0.47 (0.27-0.83)	0.009
	3rd (39.1-57.5)	0.74 (0.42-1.28)	0.281	3rd (25.8-71.5)	0.53 (0.30-0.91)	0.021
	4th (>57.5)	0.47 (0.25-0.90)	0.023	4th (>38.0)	0.49 (0.28-0.88)	0.017
	Per quartile	0.80 (0.66-0.97)	0.021	Per quartile	0.80 (0.66-0.97)	0.021
	Per SD	0.73 (0.59-0.90)	0.003	Per *z* value	0.70 (0.57-0.86)	0.001
Model 2‖	1st (<25.5)	1.00 reference		1st (<38.0)	1.00 reference	
	2nd (25.5-39.0)	0.87 (0.50-1.52)	0.628	2nd (18.8-56.0)	0.61 (0.34-1.08)	0.091
	3rd (39.1-57.5)	0.73 (0.40-1.32)	0.293	3rd (25.8-71.5)	0.54 (0.30-0.98)	0.044
	4th (>57.5)	0.45 (0.22-0.93)	0.032	4th (>38.0)	0.51 (0.26-0.99)	0.048
	Per quartile	0.79 (0.64-0.98)	0.028	Per quartile	0.79 (0.64-0.98)	0.029
	Per SD	0.75 (0.60-0.93)	0.010	Per *z* value	0.72 (0.57-0.90)	0.004

*Range of values of 25(OH)D concentrations in nmol/L.
†SD of logarithmically transformed 25(OH)D levels.
‡*z* values were calculated according to the mean and SD of logarithmically transformed 25(OH)D concentrations within each month of blood draw.
§Model 1 adjusted for age and sex.
‖Model 2 adjusted for age, sex, body mass index, active smokers, retinol, exercise tertiles, beer and wine consumption, and diabetes mellitus.

best of our knowledge, there exists only one study reporting on the association between serum 25(OH)D levels and total cancer mortality (5), whereas a second study that analyzed such an association was based on predicted serum 25(OH)D concentrations (10). Our main result of a 34% risk reduction of fatal cancer per increase of 25 nmol/L in serum 25(OH)D levels is close to the 29% reduction of cancer mortality reported by Giovannucci et al. (10), who used predicted serum 25(OH)D concentrations in the Health Professionals' Follow-up Study. However, the results of these two studies appear to be contradictory to the negative findings reported in the NHANES-III (5). Reasons for these divergent results remain hypothetically but may be due to differences in the study populations and designs. One obvious major difference relates to the fact that in the LURIC study cohort, only Caucasian patients from a single geographic area (southwest Germany) were included and that all study participants were referred to coronary angiography (13). By contrast, the NHANES-III enrolled a representative population sample of the United States, including various ethnic groups from different regions within the United States (5). In that study, blood collections in southern latitudes were done from November to March and in northern latitudes from April to October. In this context, it is important to note that due to varying UV-B exposure, serum 25(OH)D levels show a seasonal variation that is greater in northern than in southern latitudes and that is attenuated in blacks when compared with Whites (5, 16-20). Therefore, a careful consideration of the month (season) of blood sampling for given geographical areas seems mandatory for interpretation of the results. To address that issue, we formed in addition to conventional quartiles that were based on the serum 25(OH)D values of the entire study cohort and that showed a gradual increase of fatal cancer risk from the highest to the lowest quartile (Table 3), also quartiles and *z* values, which were based on serum 25(OH)D concentrations from each month of blood draw. Using these latter quartiles, we found that the risk of fatal cancer was comparable in the highest three quartiles, with a significantly increased HR in the first (lowest) quartile (Table 3). This suggests that the association between low vitamin D levels and the risk of fatal cancer is rather weak over a broad range of 25(OH)D levels but steeply increases in patients with severe vitamin D deficiency. Taken together, it is therefore conceivable that differing results of the LURIC study and the NHANES-III are partly due to effects caused by variations in UV-B exposure, racial differences, and the way vitamin D levels were handled in the analyses as well as due to the lower serum 25(OH)D concentrations in the LURIC study, in which 66% of the study participants had 25(OH)D levels below 50 nmol/L compared with 34% of the study population of the NHANES-III.

Our finding that 1,25(OH)2D was not associated with increased risk of fatal cancer does not argue against a crucial role of 1,25(OH)D in the prevention of cancer because intracellular 1,25(OH)2D levels can best be estimated by serum 25(OH)D concentrations, which are rate limiting for the conversion of 25(OH)D to 1,25(OH)2D. Several different cell types, including cancer cells, have been shown to express 1α-hydroxylase and are therefore able to produce and regulate 1,25(OH)2D concentrations at the level of the individual tissue/cell (1, 21, 22). Furthermore, serum 1,25(OH)2D concentrations are tightly regulated by the kidney, decrease with

high calcium intake, and are not significantly influenced by geographic latitude and race, indicating that serum 1,25(OH)2D levels are not an adequate measure of whole-body vitamin D status (23-26).

Two interventional trials have already examined the effect of vitamin D supplementation on total cancer incidence/mortality (27, 28). In the Women's Health Initiative, a daily intake of 400 IU vitamin D_3 and 1,000 mg calcium carbonate was tested against placebo (27). In women assigned to calcium plus vitamin D supplementation, the HRs (95% CIs) for colorectal cancer mortality and total cancer mortality were 0.82 (0.52-1.29) and 0.89 (0.77-1.03), respectively, when compared with the placebo group. Taking into account that the vitamin D supplementation in the Women's Health Initiative study resulted in an estimated modest increase of 11.8 nmol/L in serum 25(OH)D levels, Giovannucci et al. calculated that the risk of total cancer mortality in the Health Professionals' Follow-up Study was 0.85 per increment of 11.8 nmol/L (10), a number that is close to the HR of 0.89 in the Women's Health Initiative (27) and to the HR of 0.82 (95% CI, 0.71-0.95) that was calculated for the fully adjusted model in our study. The anticarcinogenic effects of vitamin D are further supported by data from Lappe et al. (28), who recently showed that cancer incidence was significantly reduced in women randomly assigned to receive 1,100 IU vitamin D_3 plus calcium (HR, 0.49; 95% CI, 0.20-0.82 in the treatment compared with the placebo group). These data are in favor of a protective role of vitamin D against cancer development and/or progression and fit well to several effects of 1,25(OH)2D on the regulation of the cell cycle, the cellular differentiation, and the DNA repair (1-4).

In addition to its proposed role in the pathogenesis of cancer, hypovitaminosis D is also associated with an increased risk of fractures, falls, cardiovascular and thrombotic events, and infections, which may also contribute to increased mortality (8, 9, 29-31). This is supported by our previous results of the LURIC study that show an inverse association between serum 25(OH)D levels and all-cause mortality of the entire study cohort (32). Accordingly, the predictive value of vitamin D deficiency might be stronger for fatal cancer than for cancer incidence, a hypothesis that is supported by the results of the Health Professionals' Follow-up Study (10). Cancer mortality or all-cause mortality among patients with cancer might therefore be a better study endpoint to evaluate overall health benefits of a sufficient vitamin D status than detection of cancer cases alone. However, from our findings of an association between vitamin D deficiency and risk of fatal cancer, we cannot draw any further conclusions whether a sufficient vitamin D status is associated with fewer deaths due to cancer because it reduces cancer incidence, which would be in line with the data by Lappe et al. (28), or reduces aggressive cancer at presentation or improves survival after cancer diagnosis, as it has already been shown for early-stage non-small cell lung cancer patients (33, 34). These research questions could not be addressed by the available data from our study and therefore warrant further investigations to confirm and extend our findings.

Our results are limited because each participant of the LURIC study had only a single blood draw and no serial measurements of 25(OH)D that would provide a more accurate assessment of an individual's long-term vitamin D status. However, it has been implicated previously that 25(OH)D levels show a circannual variation but are not significantly different when measured 12 months apart (19), suggesting that the long-term vitamin D status of an individual could well be estimated by a single measurements of 25(OH)D when controlling for the season (month) of blood draw is done, as it was done in our study. Furthermore, in the LURIC study, which was not initially designed to evaluate the association between 25(OH)D and fatal cancer, we examined a specific study cohort, that is, patients referred to coronary angiography, and our results may therefore not apply for the general population. Despite adjustments for various possible confounders, we cannot rule out the existence of other unconsidered or unmeasured factors that may explain that vitamin D deficiency is only a nonspecific indicator of chronic illness and is not causally related to fatal cancer. Strengths of the LURIC study, however, include the validation of the 25(OH)D assay, the setting in a single geographic area, and the possibility to study the association between fatal cancer and mortality at lower 25(OH)D levels than in the NHANES-III.

In conclusion, our results show that low levels of 25(OH)D are associated with increased risk of fatal cancer in patients referred to coronary angiography. These data support other studies suggesting that vitamin D supplementation might be promising for the treatment and/or prevention of cancer and are in line with the national recommendation of the Canadian Cancer Society for the supplementation of 1,000 IU/d vitamin D for all adults during winter and for persons at high risk for vitamin D deficiency all year-round (35).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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