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Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Circulating 25-Hydroxyvitamin D_3 and Survival after Diagnosis with Kidney Cancer

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Abstract

Prospective cohort studies have provided some evidence that circulating vitamin D is associated with risk of, and survival from, renal cell carcinoma (RCC), but it is unclear whether concentrations of vitamin D at the time of diagnosis of RCC are associated with prognosis. We conducted a case–cohort study of 630 RCC cases, including 203 deaths, from a multicenter case–control study in Eastern Europe. Vitamin D was assessed as 25-hydroxyvitamin D_3 [25(OH)D_3], and we used weighted Cox models to estimate hazard ratios (HR) and 95% confidence intervals (CI) by categories of season-adjusted 25(OH)D_3. Higher concentrations of 25(OH)D_3 were associated with lower risk of death after adjusting for stage, age, sex, and country (HR highest vs. lowest category 0.57; 95% CI, 0.34–0.97). The inverse associations of 25(OH)D_3 with death were most notable among those who died from non-RCC causes and those diagnosed with early-stage disease. In summary, 25(OH)D_3 concentration at diagnosis of RCC was inversely associated with all-cause mortality rates, but not specifically with RCC outcome. *Cancer Epidemiol Biomarkers Prev; 24(8); 1277–81. ©2015 AACR.*

Introduction

Each year, more than 300,000 new cases of kidney cancer are diagnosed worldwide, leading to approximately 130,000 deaths (1). The prognosis is strongly dependent on stage at diagnosis, with around 90% of stage I patients alive 5 years after diagnosis, compared with only 10% of stage IV patients (2).

Little is known about factors influencing survival after diagnosis of kidney cancer, apart from tumor stage and grade. We recently investigated circulating vitamin D and kidney cancer onset and survival in a prospective epidemiological cohort where blood samples were collected at entry to the cohort, an average of 7 years before diagnosis (3). In contrast to the Vitamin D Pooling Project, which found no evidence of an association (4), we reported an inverse association between vitamin D concentrations and risk of subsequent kidney cancer. This observation was consistent with another recent study in which investigators had estimated vitamin D levels (5). Further, we observed an increased rate of death after kidney cancer diagnosis for both low and high concentrations of vitamin D. Available data did not allow thorough analysis of cause-specific mortality, nor were we able to adjust for stage. This observation prompted us to investigate whether vitamin D concentrations in blood at kidney cancer diagnosis are associated with subsequent survival, and if such an association is independent of stage or other prognostic factors.

Materials and Methods

The K2 study

Participants included patients who were above 18 years of age and diagnosed with kidney cancer in one of four participating centers in Czech Republic, 1 center in Romania, and 1 center in Russia. We gave participants a standardized face-to-face short lifestyle questionnaire covering sociodemographic characteristics, anthropometric measures, medical history, family history, and tobacco and alcohol use. Clinical and pathologic data were abstracted from medical charts and pathologic reports. A majority of participants underwent nephrectomy, and the tumor was histologically confirmed. Follow-up for outcome (relapse, vital status, and cause of death where relevant) was performed every 6 to 12 months after diagnosis, using passive follow-up methods where possible (with confirmation of vital status through active follow-up methods in case of uncertainties), and active follow-up methods when no linkage to databases was possible. The study protocol was approved by the institutional review boards of the International Agency for Research on Cancer (IARC) and all collaborating institutions, and we obtained written informed consent from all participants.

Case–cohort sampling

Among 2,330 participants with questionnaire data available and a diagnosis of renal cell carcinoma (RCC), 1,005 participants

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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with no follow-up data at the time of this project were excluded. The majority of the cases with no follow-up for vital status were diagnosed at the end of the study period, and thus were not included in the active follow-up to ascertain vital status. In addition, patients diagnosed in Moscow hospitals who are not resident in the Moscow area were not followed-up, nor were patients diagnosed in Serbia. We additionally excluded 125 participants with no plasma sample available, 5 participants with inconsistencies in reference dates, and 7 participants with no information on stage. From the 1,188 remaining, we randomly selected 500 participants at baseline (the subcohort). We also included all participants who died during follow-up that were not randomly selected into the subcohort ($N = 93$), as well as 37 stage IV patients that had survived and were not randomly selected. Hence, a total of 630 participants diagnosed with kidney cancer were included in the study. The median follow-up of the randomly selected subcohort was 2.5 years. The demographic and clinical characteristics of the cohort did not differ substantially between those included in or excluded from the case–cohort sample (Supplementary Table S1).

Biosample processing and biochemical analysis

Venous blood was obtained before or at the time of the nephrectomy, prior to any treatment. Blood was collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA) and processed as rapidly as possible (usually within 2 hours). Plasma samples were stored at −80°C, except in Ceske Budejovice, Czech Republic, where samples were stored at −20°C. All samples were transported at −80°C to IARC for long-term storage at −150°C. Samples underwent a single thawing cycle for aliquoting of 400 μL for shipment to the Bevital Laboratory in Bergen, Norway (www.bevital.no), for analysis. Liquid chromatography coupled to tandem mass spectrometry was used to analyze vitamin D as $25(OH)D_2$ and $25(OH)D_3$ (6). $25(OH)D_2$ was undetectable in the majority of samples, so our analyses focus on $25(OH)D_3$. The laboratory is Vitamin D External Quality Assessment Scheme certified (DEQAS; www.deqas.org).

Statistical analysis

To adjust for seasonal variation, we modeled the expected $\log_2$ $25(OH)D_3$ concentration as a periodic function of day of blood draw using a pair of sine and cosine functions. To create season-adjusted categories, we grouped the residuals from this model at quartiles of their distribution among the randomly selected subcohort. We used Cox proportional hazards models with time since diagnosis (recruitment) as the time scale to estimate hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality by the season-adjusted categories of $25(OH)D_3$. We also modeled $25(OH)D_3$ continuously using restricted cubic splines with knots at its 10th, 33rd, 67th, and 90th percentiles, explicitly adjusting for seasonality by including the pair of sine and cosine functions. HRs for cause-specific mortality were calculated in a competing risks model using the data augmentation method (7). To account for the case–cohort design (8), we used the Barlow method to weight the likelihood and computed robust variance estimates (9, 10), slightly adjusted to account for the fact that we included all cases with stage IV disease (i.e., all stage IV cases received a weight of 1). We investigated potential effect modification by fitting interactions between season-adjusted $\log_2$ $25(OH)D_3$ and various factors. All models included stage, age at recruitment, and sex as covariates, with the baseline hazard stratified by country of recruitment. We additionally adjusted for body mass index (BMI, kg/m^2), smoking status (never, former, and current), and alcohol drinking status (never, former, and current). All P values are two-sided, and were calculated using the Wald test. Statistical analyses were performed using Stata 12.1 for Linux (Stata Corporation) and R version 3.1.1 (11).

Results

Demographic and clinical characteristics of the study sample by vital status at the end of follow-up are presented in Table 1. The

Table 1. Demographic and clinical characteristics of the participants by vital status at the end of follow-up

	Vital status		
	Alive *n* (%)	Dead *n* (%)	Total
Total	427 (100)	203 (100)	630
Sex			
Male	266 (62)	131 (65)	397
Female	161 (38)	72 (35)	233
Age at recruitment, y			
[26.7, 55)	118 (28)	37 (18)	155
[55, 65)	161 (38)	88 (43)	249
[65, 86.8]	148 (35)	78 (38)	226
Country			
Czech Republic	230 (54)	95 (47)	325
Russia	167 (39)	105 (52)	272
Romania	30 (7)	3 (1)	33
BMI (kg/m^2)			
[17.2, 25)	97 (23)	71 (35)	168
[25, 30)	184 (43)	82 (40)	266
[30, 58.5]	143 (33)	50 (25)	193
Missing	3 (1)	0 (0)	3
Smoking			
Never smoker	213 (50)	92 (45)	305
Former smoker	108 (25)	54 (27)	162
Current smoker	106 (25)	57 (28)	163
Diabetes			
Yes	65 (15)	39 (19)	104
No	362 (85)	164 (81)	526
Hypertension			
Yes	233 (55)	103 (51)	336
No	193 (45)	100 (49)	293
Missing	1 (0)	0 (0)	1
Stage			
I	269 (63)	38 (19)	307
II	38 (9)	10 (5)	48
III	56 (13)	54 (27)	110
IV	63 (15)	101 (50)	164
Missing	1 (0)	0 (0)	1
Grade			
1	73 (17)	7 (3)	80
2	173 (41)	53 (26)	226
3	67 (16)	50 (25)	117
4	15 (4)	18 (9)	33
Missing	99 (23)	75 (37)	174
Histology			
Conventional RCC	357 (84)	161 (79)	518
Papillary RCC	41 (10)	10 (5)	51
Chromophobe RCC	11 (3)	5 (2)	16
Other	14 (3)	4 (2)	18
Unknown	4 (1)	23 (11)	27
Season-adjusted circulating $25(OH)D_3$ category			
1 (lowest)	93 (22)	63 (31)	156
2	107 (25)	56 (28)	163
3	106 (25)	46 (23)	152
4 (highest)	121 (28)	38 (19)	159

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Table 2. HRs (95% CIs) for risk of all-cause and cause-specific mortality by season-adjusted categories of 25(OH)D_3 concentration

		Minimally adjusted[a]		Adjusted[b]	
D_3 category	N_{deaths}	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause					
1	63	1.00	0.015[c]	1.00	0.03[c]
2	56	1.14 (0.69–1.90)		1.12 (0.67–1.87)	
3	46	0.81 (0.48–1.37)		0.86 (0.51–1.44)	
4	38	0.57 (0.34–0.97)		0.59 (0.35–1.00)	
RCC					
1	42	1.00	0.56[d]	1.00	0.53[d]
2	43	1.32 (0.76–2.31)		1.30 (0.74–2.27)	
3	36	0.96 (0.54–1.70)		1.01 (0.57–1.79)	
4	31	0.68 (0.38–1.20)		0.70 (0.39–1.24)	
Non-RCC					
1	21	1.00		1.00	
2	13	0.79 (0.36–1.75)		0.76 (0.34–1.70)	
3	10	0.52 (0.21–1.28)		0.55 (0.23–1.35)	
4	7	0.36 (0.14–0.92)		0.36 (0.14–0.91)	

[a]Stratified by country, and adjusted for stage, age at recruitment, and sex.
[b]Adjusted for BMI (kg/m^2), smoking status, cigarettes per day, alcohol drinking status, and alcohol intake per day (mL).
[c]*P* values for the all-cause models are from tests against the null hypothesis that the 25(OH)D_3 coefficients are identically 0.
[d]*P* values for the competing risks model are from tests against the null hypothesis of no heterogeneity of the coefficients by cause of death (RCC vs. non-RCC).

sample included a higher proportion of men (63%) than women, and was predominantly recruited from the Czech Republic (52%) and Russia (43%), with only 5% of participants recruited in Romania. Those participants who survived to the end of follow-up had a similar age distribution to those who died during follow-up. Five hundred and eighteen of the 630 cases (82%) were conventional RCC. Fifty percent of the 203 deaths occurred among participants with a stage IV tumor, and 15% of those surviving to the end of follow-up had stage IV diagnoses. In contrast, 72% of those surviving to the end of follow-up were diagnosed with stage I–II disease. Measured 25(OH)D_3 concentrations ranged between 7 and 134 nmol/L, with a median of 43 nmol/L.

Hazard of death from any cause was inversely associated with circulating concentrations of 25(OH)D_3 (Table 2). After adjusting for stage, age, and sex, the hazard was 43% lower among those in the highest compared with the lowest group of seasonally adjusted concentration ($HR_{4\ vs.\ 1}$ 0.57; 95% CI, 0.34–0.97). Although no statistical evidence for heterogeneity by cause of death was noted ($P_{heterogeneity} = 0.53$), we estimated $HR_{4\ vs.\ 1}$ of 0.70 (95% CI, 0.39–1.24) for RCC-specific death, and 0.36 (95% CI, 0.14–0.91) for non-RCC causes of death, suggesting that this association was not specific to RCC death (Table 2). The HR for continuously varying 25(OH)D_3 (relative to a concentration of 50 nmol/L) is presented in Fig. 1. These estimates corroborate those in Table 2, suggesting a monotonic inverse association between 25(OH)D_3 and hazard of death.

Supplementary Fig. S1 presents HRs for a doubling in seasonally adjusted 25(OH)D_3 concentration separately by categories of several potential effect modifiers. The estimated magnitude of the association was consistent by sex, stage, histology, history of diabetes, smoking status, and alcohol intake status. There was some indication that the association might be stronger among those diagnosed at age 65 years or older, those with a history of hypertension, those with higher BMI, and those diagnosed with stage I or II RCC, but there was little statistical evidence of interaction with any of these factors.

Discussion

We investigated whether differences in circulating concentrations of 25(OH)D_3 at the time of diagnosis of RCC were associated with all-cause and RCC-specific survival. We observed that higher concentrations of 25(OH)D_3 were associated with a lower rate of death, but that this association was not restricted to RCC-specific death. We also observed an indication that this association might be somewhat stronger for those with a history of hypertension, advanced age at diagnosis, or early-stage disease.

We recently studied circulating 25(OH)D_3 and risk of RCC in a prospective case–control study nested within the EPIC cohort (3). This analysis indicated an inverse association between 25(OH)D_3 and risk of RCC as well as a nonlinear U-shaped association between prediagnostic 25(OH)D_3 and all-cause mortality after diagnosis of RCC. This observation prompted us to conduct the current analysis in newly diagnosed RCC cases with complete information on disease stage and cause of death. Results from the present study are not completely consistent with these initial findings from EPIC. In particular, we found no evidence of increased rate of death among patients with high 25(OH)D_3 at diagnosis, but rather an inverse association between 25(OH)D_3 and all-cause mortality across the range of observed concentrations.

Many studies have investigated circulating vitamin D and all-cause mortality in general populations. Consistent with our observation, many of these have reported high risk of death for

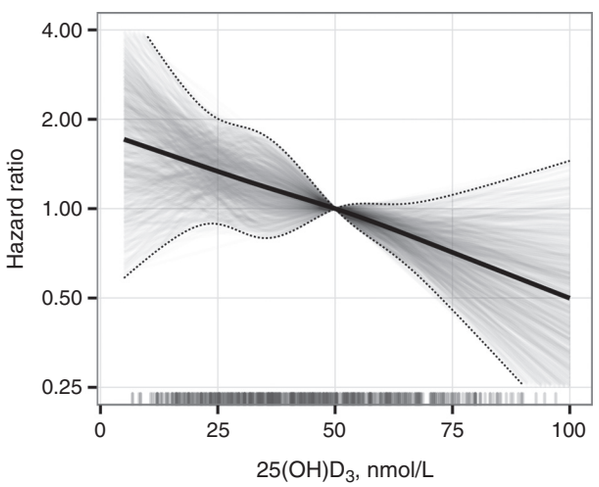

Figure 1.
Hazard ratio for all-cause mortality among RCC cases as a function of circulating concentration of 25(OH)D_3 at diagnosis, relative to a concentration of 50 nmol/L. 25(OH)D_3 was modeled using restricted cubic splines with knots at the 10th, 33rd, 67th, and 90th percentiles of its distribution. Estimates were derived from a Cox model stratified by country of recruitment, and adjusted for stage, age at recruitment, sex, and seasonality (sine and cosine functions of day of blood draw). Solid and dashed lines represent the maximum pseudolikelihood estimates and 95% CIs, respectively. The translucent lines are 1,000 draws from the multivariate normal distribution defined by the maximum pseudolikelihood estimates and their variance covariance matrix, and thus give an indication of the posterior density for the hazard ratio under a uniform prior on the regression coefficients. The "rug plot" shows the observed distribution of 25(OH)D_3.

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people with low concentrations (12–19), suggesting that the association observed in our study might reflect a general phenomenon rather than something specific to RCC prognosis. This would be consistent with our observation that any association might be stronger among those patients diagnosed with early- rather than advanced-stage tumors. The lack of heterogeneity by cause of death provides additional indirect evidence that the association between vitamin D and mortality is unlikely to exist exclusively among RCC patients.

Circulating vitamin D (measured as $25(OH)D_3$ in the current study) is converted to its active hydroxilated form calcitriol ($1,25(OH)D_3$) in the kidneys. Calcitriol is a potent steroid hormone that has been implicated by *in vitro* and *in vivo* models as having anticancer influence in a wide range of cancers by affecting multiple cancer hallmarks, including reducing angiogenesis, metastasis, cell invasion, inflammation, and proliferation, as well as stimulating apoptosis (20), and through these mechanisms, higher concentrations of circulating vitamin D may inhibit tumor progression, leading to improved survival. In addition, it is possible that kidney function is affected by the presence of the tumor, which may lead to disregulation of the conversion of circulating vitamin D to calcitriol. The effects of such disregulation on any causal association between vitamin D and RCC prognosis are difficult to predict. Given that we observe no evidence of heterogeneity by cause of death, we tentatively infer that circulating vitamin D is not causally associated with RCC tumor progression and prognosis, but is rather an indicator of general health status.

One limitation of our study is that we were unable to adjust for grade, which was unavailable for a substantial proportion (28%) of participants. Nevertheless, given that our results do not differ by cause of death, we consider it unlikely that tumor grade is an important confounder or effect modifier. Another limitation of our study is that we did not have information regarding the use of vitamin D supplements, although it is unlikely that supplement use was highly prevalent given that $25(OH)D_2$ concentrations were undetectable for the majority of participants. It is also possible that these results may not generalize beyond Central and Eastern European populations, but the remarkable consistency with results observed in nonclinical cohort studies suggests that that our results will generalize well, at least to a broader population of European origin.

In summary, we found that high $25(OH)D_3$ at diagnosis of RCC was associated with lower risk of death. This association was not restricted to RCC cause-specific death and appeared stronger for early-stage disease, supporting the notion of $25(OH)D_3$ being associated with lower overall death rates in general, rather than RCC prognosis specifically.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funding organization had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

Authors' Contributions

Conception and design: D.C. Muller, G. Scelo, D. Zaridze, P. Brennan, M. Johansson

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.C. Muller, G. Scelo, Ø. Midttun, P. Brennan, M. Johansson

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. Scelo, V. Janout, M. Johansson

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