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Vitamin D binding protein and risk of renal cell carcinoma in the Cancer Prevention Study-II Cohort

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Abstract

Background—Kidney cancer has several well-established risk factors including smoking, obesity, and hypertension. These factors do not, however, completely account for its etiology. One previous study of vitamin D binding protein (DBP) and risk of renal cell carcinoma found a striking inverse association that warranted replication.

Methods—We conducted a nested case-control study in the American Cancer Society Cancer Prevention Study-II (CPS-II) Nutrition Cohort to prospectively examine circulating DBP concentration and renal cell carcinoma risk. Cases (n=87) were matched 1:1 to controls on gender, race, age (+/− 5 years), and date of blood collection (+/− 30 days). Odds ratios and 95% confidence intervals were estimated for quartiles of DBP using conditional logistic regression.

Results—There was a statistically significant inverse trend across quartiles of DBP (p-trend = 0.03) such that participants with higher DBP had a markedly decreased risk of renal cell carcinoma (vs. Q1: Q2 OR=0.93, 95% CI=0.41 – 2.11; Q3 OR=0.42, 95% CI=0.15 – 1.15; Q4 OR=0.33, 95% CI=0.10 – 1.06; p-trend=0.03).

Conclusions—Our findings demonstrate a strong inverse association between circulating DBP and risk of renal cell carcinoma, supporting the findings from previous research.

Impact—This is only the second study to examine vitamin D binding protein (DBP) and risk of kidney cancer, and one of only a handful of studies to examine circulating DBP and risk of cancer at any site. Our findings support emerging evidence for an etiologic role of DBP in cancer and may provide insights into the etiology of kidney and other cancers.

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Additional Information:

Ethics approval: The Emory University Institutional Review Board approves all aspects of the CPS-II Cohort. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Introduction

Kidney cancer is the 6th and 10th most commonly diagnosed cancer among men and women, respectively, in the US with an estimated 63 990 new cases diagnosed in 2017 and 14 400 deaths due to the disease (1). The most common histologic subtype is renal cell carcinoma, which has several well-established risk factors including smoking, obesity, and hypertension (2). However, these risk factors do not completely explain the etiology of this malignancy.

Vitamin D in circulation is primarily bound to vitamin D binding protein (DBP), which, in addition to its transport role, has been hypothesized to influence cancer risk through its non-vitamin D related biological functions, including being a member of the extracellular actin scavenger system, as well as playing a role in chemotaxis, macrophage activation, apoptosis, and angiogenesis (3, 4). The association between DBP and cancer is understudied, but a recent meta-analysis concluded that higher DBP concentrations were associated with a lower risk of cancer overall based on eight studies of six different cancers (5).

Because the kidney is the major organ site for vitamin D metabolism and resorption, several studies have examined whether higher vitamin D status may protect against risk of kidney cancer (6). Prospective studies examining 25-hydroxy-vitamin D (25(OH)D) in relation to kidney cancer risk do not support a strong association (6). By contrast, to our knowledge, only one investigation has examined circulating DBP in relation to risk of renal cell carcinoma, showing a striking inverse association with DBP status (7). This study was a nested case-control study conducted within the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study cohort, which was a study population of male smokers from southwestern Finland (7). Although the findings of this previously-conducted study were promising, they warranted replication, particularly in broader populations that included women and non-smokers. We therefore conducted a nested case-control study in the American Cancer Society Cancer Prevention Study-II (CPS-II) Nutrition Cohort to examine whether circulating DBP concentration was prospectively associated with risk of renal cell carcinoma.

Methods

Study Population

The CPS-II Nutrition Cohort is a prospective study of cancer incidence that began in 1992. Details of the study have been described previously (8). Briefly, participants from 21 states in the US provided detailed information on demographic, dietary, and lifestyle factors at baseline. Beginning in 1997, updated exposure and outcome information was collected from participants every two years, and between 1998 and 2001, a subset of the cohort provided a blood sample. The present analysis is a case-control study nested within the subset of CPS-II Nutrition who provided a blood sample and who were free of cancer at the time of blood collection (n=39,371). All cases of renal cell carcinoma that were diagnosed as the first primary cancer after blood collection through June 30, 2009 were included (n=87). Cases were identified one of two ways: 1) through self-report on the biennial questionnaires and were subsequently verified through linkage with medical records or state cancer registries or

2) through linkage with National Death Index. Cases were matched 1:1 with controls on age (+/− 1 year), date of blood collection (+/− 30 days), race, and gender.

Laboratory Measures

Serum DBP concentration was measured by the Clinical Support Laboratory, SAIC-Frederick, Frederick National Laboratory for Cancer Research (Frederick, MD) using the DBP polyclonal assay from ALPO Diagnostics (Salem, NH). Each batch contained blinded quality control samples from two individuals comprising approximately 10% of the total samples. The inter- and intra-batch coefficients of variation ranged from 5.7–8.7% and from 8.3–8.5%, respectively.

Statistical Analysis

Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs) for risk of renal cell carcinoma by quartiles of DBP. Factors that are known or hypothesized to be associated with either DBP or renal cell carcinoma were evaluated as potential confounding factors including the following: body mass index (BMI); smoking status; history of diabetes or kidney failure; physical activity; education level; dietary intakes of vitamin D, calcium, alcohol, and total energy; use of supplemental vitamin D or calcium; and family history of kidney or other cancers. Only BMI was associated with both renal cell carcinoma and DBP in our data. Thus, in addition to being conditioned on the matching factors (i.e., age, date of blood collection, race, and gender), models are presented further adjusted for BMI. We also present models additionally adjusted for supplemental vitamin D use, family history of cancer, and smoking status, as these variables were associated with either the exposure or outcome in our data. The significance of the trend across quartiles was assessed by creating a variable assigning the median DBP value to each quartile and modeling that as a continuous variable. Statistical significance was assessed using the Wald test. Exploratory analyses were conducted stratifying by sex, smoking status (never/ever), vitamin D supplement use (no, yes), BMI (<25, ≥25 kg/m^2), and family history of cancer (no, yes). Sensitivity analyses were conducted excluding cases diagnosed within one year of blood collection to address the possibility of reverse causation. Stratified and sensitivity analyses using unconditional logistic regression adjusted for the matching factors were conducted examining DBP dichotomized at the median. Statistical interaction was assessed using the likelihood ratio test.

Results

Characteristics of the study sample by case status and by DBP quartile are shown in Tables 1 and 2, respectively. Few differences were observed between cases and controls, with the exception of a slightly higher BMI among cases and greater vitamin D supplement use among controls (Table 1). Those in the highest quartile of DBP were younger, more likely to be female, had a lower BMI, and were more likely to have never smoked. There were also suggestions that those with the highest DBP were less likely to have a history of diabetes, were less likely to be a college graduate, ate fewer calories, drank less alcohol, were more likely to use vitamin D supplements, and were more likely to have a family history of cancer, although these associations were not statistically significant (Table 2).

We observed a strong inverse association between DBP and risk of renal cell carcinoma (OR=0.29, 95% CI=0.09 – 0.91, p-trend = 0.02, Table 3). This finding was slightly attenuated with further adjustment for BMI (OR=0.33, 95% CI=0.10 – 1.06, p-trend=0.03, Table 3). Further adjustment for supplemental vitamin D use, family history of cancer, and smoking status did not change the association (Table 3). We observed no statistically significant interaction between DBP and any of the factors examined including sex, smoking, supplemental vitamin D use, family history of any cancer, and BMI (all p>0.10). When cases diagnosed within one year of blood collection were excluded (n=18), results were very similar (≥ median DBP vs < median; OR=0.22, 95% CI=0.07 – 0.75).

Discussion

In this prospective investigation, we found that higher serum DBP concentration was strongly inversely associated with risk of renal cell carcinoma. This finding is consistent with the only previously published analysis on this topic which was conducted in the ATBC Study (7) among male smokers in southwestern Finland. Therefore, there was the possibility that the findings would not be generalizable to US populations, or to women or non-smokers. However, results from the current analysis, which was conducted in a mostly white US population including women and non-smokers, suggest that the inverse association between DBP and kidney cancer is generalizable to these populations.

The kidney is the key organ for vitamin D metabolism. DBP-bound 25(OH)D in the glomerular filtrate is absorbed by the proximal tubule epithelium through endocytic ligand binding and uptake by the plasma membrane megalin-cubilin receptor complex. Subsequently, 25(OH)D is converted to the active hormonal form, 1–25-dihydroxyvitamin D ($1,25(OH)_2D$) in parenchymal mitochondria and DBP undergoes lysosomal proteolysis (9, 10). Previous studies have examined circulating 25(OH)D in relation to risk of kidney cancer and found no strong associations (6). Further, in the previous analysis of DBP and kidney cancer, DBP did not appear to modify the risk association with circulating 25(OH)D (and vice versa). Taken together, the findings suggest that the biologic mechanism through which DBP influences risk of kidney cancer may be unrelated to its canonical role in vitamin D status and transport. DBP has other biologic actions that may play an important role in carcinogenesis and cancer progression, such as it being the parent molecule for DBP-macrophage activating factor (MAF) which has been shown to induce apoptosis as well as reduce proliferation and migration of cancer cells *in vitro*, and inhibit cancer in animal models (11–17).

Another possible explanation for our findings is reverse causality. That is, undiagnosed renal malignancies with disrupted physiology would incompletely resorb DBP and lead to decreased concentrations in circulation. However, our results were essentially identical when cases diagnosed within one year of blood collection were excluded from the analysis, arguing against reverse causality as the basis for our findings.

Our study has many strengths including the prospective design, reliable laboratory measurement of DBP, and detailed information on many potential confounding factors and effect modifiers. Although we used all available cases of renal cell carcinoma in the large

CPS-II cohort, our sample size was still somewhat small, as this is a relatively rare cancer. Thus, although we conducted exploratory analyses of effect modification, we had very limited statistical power to detect meaningful interactions with lifestyle factors, and these will require further investigation in larger study samples. Another possible limitation is that 98% of our study population was of European ancestry. There are several common isoforms of DBP that have different binding affinities for vitamin D compounds, and the prevalence of these isoforms differs markedly by race, particularly between white and black populations (18, 19). However, the impact of the different isoforms on non-vitamin D-related biological activities of DBP is less clear (19), although one study did find different inflammation-mediated MAF activity by isoform (20). In addition, there is evidence from other cancer sites that the DBP-cancer association may differ by race (21). The potential associations of DBP isoforms with risk of renal cell carcinoma requires further study. Given that there is an existing racial disparity in kidney cancer incidence in the US with higher rates among black men compared to white men, further study in non-white populations is warranted (2).

Our findings demonstrate a strong inverse association between circulating DBP and risk of renal cell carcinoma, supporting the findings from the one previously published study on this topic. Further study is required to determine if this association is causal and, if so, through what biological mechanisms. Understanding the latter, and examining the association in diverse populations, could provide new insights into the etiology of kidney and other cancers.

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Table 1

Selected characteristics [medians (interquartile range) or percent] for renal cell carcinoma case and control subjects in the CPS-II cohort

Characteristic	Controls (n=87)	Cases (n=87)	*p-value*[*]
Age (years)	70.4 (65.7 – 75.4)	70.8 (66.5 – 75.4)	*matched*
Male (%)	64.4	64.4	*matched*
Race			
White	97.7	97.7	*matched*
BMI[‡] (kg/m^2)	25.1 (22.9 – 28.1)	26.5 (24.0 – 28.7)	*0.10*
Smoking Status[‡]			
Never	47.5	35.8	*0.31*
Former	50.0	61.7	
Current	2.5	2.5	
History of diabetes[‡] (%)	10.3	17.2	*0.19*
History of kidney failure[†] (%)	0.0	1.2	*1.00*
Physically active[‡] (MET-hrs/week)	14.0 (7.0 – 24.5)	14.0 (7.0 – 24.9)	*0.89*
College graduate[†] (%)	47.7	52.9	*0.17*
Intake/day[‡]			
Total energy (kcal)	1 788 (1 488 – 2 147)	1 778 (1 437 – 2 082)	*0.88*
Dietary vitamin D (IU)	188 (148 – 283)	179 (128 – 292)	*0.87*
Dietary calcium (mg)	730 (583 – 1,112)	744 (563 – 1,071)	*0.94*
Alcohol (drinks)	0.10 (0 – 0.72)	0.10 (0 – 0.75)	*0.98*
Use of dietary supplements[‡] (%)			
Vitamin D	17.7	6.9	*0.09*
Calcium	38.2	36.1	*0.80*
Family history of kidney cancer[†]	2.3	0.0	*0.50*
Family history of any other cancer[‡]	65.5	58.6	*0.35*

[*] Chi square test or Fisher's exact test (when cells have expected counts <5) for categorical variables and Wilcoxon test for continuous variables

[†] Assessed at baseline in 1982

[‡] Assessed at the time closest to blood collection

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Table 2

Selected characteristics [medians (interquartile range) or percent] by quartile of circulating vitamin D binding protein concentration in the CPS-II cohort

Characteristic	Q1 (<272 μg/mL)	Q2 (272 – <294 μg/mL)	Q3 (294 – <334 μg/mL)	Q4 (≥ 334 μg/mL)	*p-value*[*]
Age (years)	71.6 (66.1 – 75.9)	72.5 (68.3 – 76.0)	70.1 (65.4 – 74.9)	67.8 (64.0 – 73.8)	*0.06*
Male (%)	74.0	72.6	64.1	38.2	*0.003*
Race (%)					
White	96.0	98.0	97.4	100.0	*0.69*
BMI[≠] (kg/m^2)	27.3 (23.6 – 29.6)	24.8 (23.0 – 27.4)	25.1 (22.1 – 27.5)	25.4 (23.2 – 28.2)	*0.09*
Smoking Status[≠] (%)					
Never	37.0	42.2	36.8	53.1	*0.52*
Former	63.0	55.6	57.9	43.8	
Current	0.0	2.2	5.3	3.1	
History of diabetes[≠] (%)	22.0	13.7	12.8	2.9	*0.10*
History of kidney failure[†] (%)	0	0	0	2.9	*0.25*
Physically active[≠] (MET-hrs/week)	14.0 (7.0 – 26.5)	14.0 (7.0 – 24.5)	14.0 (7.0 – 24.0)	13.9 (7.0 – 29.0)	*0.89*
College graduate[†] (%)	62.0	51.0	38.5	45.5	*0.77*
Intake/day[≠]					
Total energy (kcal)	1 881 (1 445 – 2 254)	1 842 (1 538 – 2 159)	1 719 (1 378 – 2 082)	1 628 (1 495 – 2 137)	*0.56*
Dietary vitamin D (IU)	178 (141 – 283)	183 (114 – 303)	167 (125 – 283)	188 (160 – 220)	*0.85*
Dietary calcium (mg)	738 (630 – 945)	786 (539 – 1 144)	671 (500 – 1 133)	742 (633 – 1 115)	*0.81*
Alcohol (drinks)	0.17 (0 – 0.87)	0.20 (0 – 1.13)	0.07 (0 – 0.37)	0.07 (0 – 0.60)	*0.38*
Use of dietary supplements[≠] (%)					
Vitamin D	11.9	9.8	6.5	22.3	*0.29*
Calcium	36.6	25.6	42.9	48.3	*0.21*
Family history of kidney cancer[†] (%)	0	0	2.6	2.9	*0.42*
Family history of any other cancer[≠] (%)	60.0	51.0	64.1	79.4	*0.07*

[*] Chi square test or Fisher's exact test (when cells have expected counts <5) for categorical variables and Wilcoxon test for continuous variables

[†] Assessed at baseline in 1982

[≠] Assessed at the time closest to blood collection

Table 3

Association between circulating vitamin D binding protein concentration and risk of renal cell carcinoma in the CPS-II cohort

	Q1 (<272 μg/mL)	Q2 (272 – <294 μg/mL)	Q3 (294 – <334 μg/mL)	Q4 (≥ 334 μg/mL)	p-trend
#cases / # controls	28 / 22	29 / 22	17 / 22	13 / 21	
OR (95% CI) *	1.0 (ref)	0.86 (0.40 – 1.88)	0.42 (0.16 – 1.12)	0.29 (0.09 – 0.91)	0.02
OR (95% CI) †	1.0 (ref)	0.93 (0.41 – 2.11)	0.42 (0.15 – 1.15)	0.33 (0.10 – 1.06)	0.03
OR (95% CI) ‡	1.0 (ref)	0.98 (0.42 – 2.31)	0.39 (0.14 – 1.08)	0.36 (0.11 – 1.22)	0.048
OR (95% CI) §	1.0 (ref)	1.00 (0.42 – 2.38)	0.36 (0.13 – 1.05)	0.33 (0.09 – 1.16)	0.041

*Conditioned on matching factors (age, sex, race, date of blood collection)

†Conditioned on matching factors (age, sex, race, date of blood collection); additionally adjusted for BMI

‡Conditioned on matching factors (age, sex, race, date of blood collection); additionally adjusted for BMI, supplemental vitamin D use, and family history of any cancer

§Conditioned on matching factors (age, sex, race, date of blood collection); additionally adjusted for BMI, supplemental vitamin D use, family history of any cancer, and smoking status

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