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Vitamin D binding protein and risk of renal cell carcinoma in the prostate, lung, colorectal and ovarian cancer screening trial

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Our group has conducted two previous studies on the association between vitamin D binding protein (DBP) and renal cell carcinoma (RCC), the most common form of kidney cancer, finding strong inverse associations. We undertook the current analysis to replicate our findings in a different study population that included women and nonsmokers. We conducted a nested case–control study in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). Cases (n = 323) were matched 1:1 to controls on age (±1 year), race/ethnicity, date of blood collection (±30 days) and sex. We performed conditional logistic regression to estimate the odds ratios and 95% confidence intervals for the association between quartiles of circulating DBP and risk of RCC. We observed a statistically significant positive association between DBP and RCC that persisted after adjustment for history of diabetes, history of hypertension, family history of renal cancer, body mass index and smoking status (mv-adj Q4 *vs.* Q1 OR = 4.1, 95% CI = 2.2–7.8; p-trend <0.0001). These findings were similar when we restricted to cases with at least 2 years of follow-up and no major weight loss, suggesting that our findings are not due to reverse causality. In the present study, those with higher serum concentrations of DBP were at increased risk of RCC, in contrast to previously published findings. Further research is necessary to determine the true association between DBP and risk of RCC, and whether different DBP phenotypes may have different associations with risk of RCC.

Introduction

Kidney cancer is estimated to be the sixth most common cancer in men in 2018 (42,680 cases), and the 10th most common cancer among women (22,660 cases) in the United States. About 14,970 (10,010 men and 4,960 women) people are predicted to die from kidney cancer in 2018.[1] The most common histological subtype is renal cell carcinoma (RCC). Established risk factors for this cancer include smoking, obesity and hypertension, all of which are positively associated with risk of RCC.[2] In the United States, an estimated 40% of RCC cases are attributable to obesity.[2] Other suggested associations include a positive association with acetaminophen use, and a positive association with weight gain independent of obesity.[3–5] While most RCC is sporadic, approximately 2–4% of kidney cancers can be attributed to hereditary factors such as VHL syndrome, and some studies suggest an increased risk for individuals with a first degree family history RCC.[2] Evidence has shown that higher vitamin D status may be protective for some cancers, primarily colorectal.[6] However, for cancer at other sites including the kidney, studies have demonstrated no association between vitamin D and risk,[6–8] with the exception of prostate cancer which is positively associated.[9] The association between circulating 25-hydroxyvitamin D (25(OH)D) and risk of kidney cancer has previously been examined in a pooled analysis of data from seven cohorts including the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). This study found no association between 25(OH)D and kidney cancer.[7]

The majority of circulating vitamin D is bound to vitamin D binding protein (DBP). In addition to its role in vitamin D transport, DBP has several other biologic mechanisms that may be relevant to cancer risk. For example, when deglycoslyated by T and B-cell glycosidases, DBP is involved in macrophage activation in the form of DBP-macrophage activating factor (DBP-MAF).[10] DBP is also involved in apoptosis and angiogenesis.[10] All of these are related to tumor growth and inhibition, and

Additional Supporting Information may be found in the online version of this article.

Key words: cancer, vitamin D, renal cancer, PLCO, DBP

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; ATBC: alpha-tocopherol, beta-carotene cancer prevention; BMI: body mass index; CI: confidence intervals; CPS-II: American Cancer Society Cancer Prevention Study-II; DBP: vitamin D binding protein; DBP-MAF: DBP-macrophage activating factor; OR: odds ratios; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RCC: renal cell carcinoma

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What's new?

Vitamin D binding protein (DBP) plays several biological functions of potential relevance to cancer risk. However, its role in renal cell carcinoma (RCC) remains unclear. This prospective, relatively large nested case–control study revealed a statistically significant positive association between DBP and RCC that persisted after adjustment for diabetes, hypertension, renal cancer family history, body mass index, and smoking status. This is a novel finding that runs in opposition to previous cohort studies investigating the association between DBP and risk of RCC, calling for further research on the true association between DBP and RCC and the potential roles of different DBP phenotypes.

thus could reasonably be related to the association between DBP and RCC. Previous studies of the association between DBP and RCC have been conducted in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study[11] and the American Cancer Society Cancer Prevention Study-II (CPS-II) Cohort,[12] and both found strong inverse relationships between serum DBP and risk of RCC, despite there being no association between 25(OH)D and RCC. CPS-II was a relatively small study (n = 87 cases) and the ATBC Study (n = 262) was conducted only among male smokers in Finland. Thus, the findings require replication in larger studies that include women and non-smokers. The present analysis was conducted in 323 cases and 323 controls from the PLCO.

Methods

Study population

The PLCO Trial is a large-scale prospective study with the primary goal of determining the efficacy of cancer screening on preventing cancer deaths among the named cancers. Details of the study have been published previously.[13] Briefly, participants aged 55–74 were enrolled from 10 centers in the United States between 1993 and 2001 and were randomized to either an intervention or control arm. There were a total of 76,685 men and 78,216 women in the trial, with 38,340 and 39,105, respectively, in the screening arm and the rest in the control (nonscreening) arm. The trial period ended in 2006, but active follow up will continue through 2020. All participants completed a detailed questionnaire at enrollment including information on demographics, diet, cancer risk factors, family history and personal cancer history. Participants randomized to the screening arm of the trial provided a nonfasting blood sample at baseline and in subsequent screening exams. All samples were shipped overnight to a central repository and stored at −70°C. The PLCO trial was approved by the Institutional Review Board of the US National Cancer Institute and written informed consent was obtained from all participants.

We conducted a case–control study nested within the PLCO Trial. All incident cases of RCC (ICD code: C64.9) who were diagnosed before February of 2011 and who provided a blood sample prior to diagnosis were included. Eligible cases were matched to controls 1:1 using incidence density sampling on age (±1 year), race/ethnicity, date of blood collection (±30 days) and sex. Our final sample included 323 cases and 323 controls.

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 at least two blinded quality control duplicates from two individuals, one White and one Black. The interbatch and intrabatch coefficients of variation ranged from 7.0 to 11.9% and 0.0 to 16.0%, respectively.

Statistical analysis

Means and percentages of baseline characteristics by case status and DBP concentration were calculated. p values for the

Table 1. Selected baseline characteristics (Mean [SD] or percent) for renal cell carcinoma case and control subjects in the PLCO Study

Characteristic	Controls (n = 323)	Cases (n = 323)	p-value[1]
Age (years)	63 (5)	63 (5)	Matched
Male	68	68	Matched
Race/Ethnicity			Matched
White, non-Hispanic	89.2	89.2	
Black, non-Hispanic	6.2	6.2	
Hispanic	1.6	1.6	
Other	3.1	3.1	
BMI (kg/m^2)			<0.0001
<25	34.6	22.4	
25 to <30	49.1	41.9	
≥30	16.4	35.7	
Aspirin use	50.7	51.4	0.88
Ibuprofen use	26.6	28.6	0.55
Smoking status			<0.0001
Never	48.3	43.7	
Current/quit <15 years	9.6	10.2	
Former quit ≥15 years	42.1	46.1	
History of diabetes	4.6	10.5	0.004
History of hypertension	28.5	45.3	<0.0001
Completed college	38.1	30.0	0.03
Family history of any cancer	54.3	51.6	0.47
Family history of kidney cancer	34.5	43.2	0.86

[1]Chi square test for categorical variables, Wilcoxon test for continuous variables, McNemar test for binary variables.

Table 2. Selected baseline characteristics (Mean [SD] or percent) by quartile of vitamin D binding protein in the PLCO Study

	Quartile of vitamin D binding protein (μg/ml)				
Characteristic	**Q1 (<207)**	**Q2 (207 to <257)**	**Q3 (257 to <316)**	**Q4 (≥316)**	***p*-value[1]**
Age	63.1 (6)	62.8 (5)	63.4 (5)	62.9 (5)	0.52
Male	72.3	75.7	75.2	50.0	<0.0001
Race/ethnicity					0.28
White, non-Hispanic	91.1	93.6	85.5	88.9	
Black, non-Hispanic	4.5	2.1	8.9	7.2	
Hispanic	2.7	1.4	1.9	0.6	
Other	1.8	2.9	3.7	3.3	
BMI (kg/m^2)					0.62
<25	23.4	25.7	30.7	31.1	
25 to <30	51.4	49.3	42.9	41.8	
≥30	25.2	25.0	26.4	27.1	
Aspirin use	52.7	51.4	49.1	52.2	0.91
Ibuprofen use	31.3	28.6	27.2	25.0	0.70
Smoking status					0.07
Never smoker	43.8	50.0	43.0	47.8	
Current/quit <15 years	3.6	7.9	12.2	12.8	
Former quit ≥15 years	52.7	42.1	44.8	39.4	
History of diabetes	12.5	6.4	8.9	3.9	0.04
History of hypertension	33.0	32.9	39.4	39.4	0.43
Completed college	37.5	40.0	31.8	30.0	0.20
Family history of any cancer	52.7	55.7	48.6	56.2	0.42
Family history of kidney cancer	67.0	39.3	38.8	20.8	0.08

[1]chi-square or Fisher's exact (<5 expected cell count) for categorical variables and Wilcoxon test for continuous and dichotomous variables.

differences between groups were determined using the chi-square test for categorical and dichotomous variables or the Wilcoxon test for continuous variables. We used conditional logistic regression to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the association between DBP concentration and RCC. Quartile cut points for DBP concentration were determined based on the distribution in the controls and were included in the model as indicator variables with the first quartile as the reference category (Quartiles in μg/ml: <207, 207 to <257, 257 to <316, ≥316). In sensitivity analyses, we also created categories using quartile cut points from previously published studies to facilitate comparison across studies with different distributions of DBP concentration (Quartiles in μg/ml; CPS-II: <272, 272 to <294, 294 to <334, ≥334[11] ATBC: <255, 255 to ≤323, 323 to <406, ≥406[12]).

Factors known or hypothesized to be associated with either DBP or RCC were evaluated as possible confounders. Factors included in the final model were: history of diabetes (yes, no), history of hypertension (yes, no), family history of renal cancer (yes, no), body mass index (BMI; <25, 25 to <30, ≥30 kg/m^2), and smoking status (never, current smokers/recent quitter [quit <15 years ago], former smokers [quit 15+ years ago]). All covariate information was reported by participants on the baseline questionnaire. Stratified analyses were conducted using unconditional logistic regression adjusting for the matching factors. The main model results were unchanged when this approach was used instead of conditional logistic regression, making biased estimates unlikely. Analyses were performed stratifying by sex (male, female), smoking status (ever smoked, never smoked), number of pack-years (above median, below median; for smokers only) and weight change since age 50 (gained, lost, or maintained within 5 lbs.). We were unable to stratify by race/ethnicity due to a low number of nonwhites (n = 70) in the dataset. However, sensitivity analyses were performed restricting to non-Hispanic Whites. We also conducted sensitivity analyses excluding cases that occurred within 2 years of blood collection as well as those with a large recent weight loss (>40 lbs since age 50) to address the possibility of reverse causation. Analyses were conducted stratifying by stage among the cases with available stage data (n = 116).

Data availability. The data that support the findings of our study are available from the corresponding author upon reasonable request.

Results

Distributions of population characteristics by case status and DBP quartile are shown in Tables 1 and 2, respectively. Cases were more likely to have a higher BMI, to have smoked, and to have a history of diabetes and history of hypertension but were less likely to have a college degree (Table 1). Men had lower DBP concentrations than women. Current smokers

Table 3. Association between circulating vitamin D binding protein concentration and risk of renal cell carcinoma in the PLCO Study

	Quartile of vitamin D binding protein (μg/ml)				
	Q1 (<207)	Q2 (207–257)	Q3 (257–316)	Q4 (>316)	*p*-trend
Cases/Controls	32/80	58/82	132/82	101/79	
OR (95% CI)[1]	1.0 (ref)	1.9 (1.1–3.3)	4.4 (2.6–7.7)	3.9 (2.6–7.7)	<0.0001
OR (95% CI)[2]	1.0 (ref)	2.2 (1.2–4.0)	4.8 (2.6–8.7)	4.1 (2.2–7.8)	<0.0001

[1]Conditioned on matching factors.
[2]Conditioned on matching factors. Additionally, adjusted for history of diabetes, history of hypertension, family history of renal cancer, BMI and smoking status.

were more likely to have higher DBP concentrations, while former smokers were more likely to have lower DBP. Those with a history of diabetes were more likely to be in Q1 than higher quartiles (Table 2).

The association between quartile of DBP and RCC is shown in Table 3. In models conditioned on the matching factors, we observed a positive association between DBP and RCC (Q4 *vs.* Q1 OR = 3.9, 95% CI = 2.6–7.7; *p*-trend = <0.0001, Table 3).

Table 4. Association between circulating vitamin D binding protein concentration and risk of renal cell carcinoma in the PLCO Study, stratified by selected variables

		Quartile of vitamin D binding protein (μg/ml)				
Characteristic		Q1 (<207)	Q2 (207–257)	Q3 (257–316)	Q4 (>316)	*p*-interaction
Sex						
Male	Cases/controls OR (95% CI)	22/59 1.0 (ref)	45/61 2.5 (1.3,4.9)	102/59 5.9 (3.2,11.1)	50/40 4.3 (2.2,8.6)	0.80
Female	Cases/controls OR (95% CI)	13/29 1.0 (ref)	17/22 1.1 (0.4,3.1)	28/19 2.7 (1.0,7.3)	46/34 2.8 (1.1,7.1)	
BMI (kg/m^2)						
<30	Cases/controls OR (95% CI)	18/65 1.0 (ref)	39/66 2.2 (1.1,4.3)	87/69 4.6 (2.4,8.5)	63/66 3.7 (2.0,7.1)	0.56
≥30	Cases/controls	14/14	19/16	45/11	37/11	
	OR(95% CI)	1.0 (ref)	1.4 (0.5,4.0	4.7 (1.7,13.1)	4.2 (1.5,11.9)	
Weight change since age 50						
Gained >5 lbs	Cases/Controls	16/41	29/44	79/34	65/42	0.17
	OR(95% CI)	1.0 (ref)	2.0 (0.9,4.4)	4.7 (2.3,9.8)	1.4 (0.5,3.6)	
Lost >5 lbs	Cases/Controls	6/10	9/16	17/12	9/9	
	OR(95% CI)	1.0 (ref)	1.4 (0.5,3.6)	5.7 (2.2,14.7)	4.2 (1.3,13.6)	
Maintained	Cases/Controls	10/29	20/22	36/36	27/28	
	OR(95% CI)	1.0 (ref)	2.7 (1.1,6.9)	2.6 (1.1,6.0)	3.1 (1.3,7.5)	
Smoking status						
Never smoked	Cases/controls	12/37	30/40	51/41	48/38	0.87
	OR(95% CI)	1.0 (ref)	2.5 (1.1,5.8)	4.7 (2.1,10.7)	4.6 (2.0,10.7)	
Ever smoked	Cases/controls	20/43	28/42	81/41	53/41	
	OR(95% CI)	1.0 (ref)	1.7 (0.8,3.5)	4.9 (2.5,9.7)	3.5 (1.7,7.1)	
Pack Years						
<30	Cases/Controls	12/23	13/21	38/24	22/26	0.09
	OR(95% CI)	1.0 (ref)	1.4 (0.5,3.9)	3.6 (1.4, 8.9)	2.0 (0.8,5.3)	
≥30	Cases/Controls	8/20	15/21	43/17	31/15	
	OR(95% CI)	1.0 (ref)	1.9 (0.6,5.7)	6.7 (2.4,19.0)	6.4 (2.2,19.0)	
Tumor T-stage						
1 or 2	Cases/Controls	7/12	12/17	29/17	20/22	0.93
	OR(95% CI)	1.0(ref)	1.7 (0.5,6.3)	4.0 (1.1,14.1)	2.9 (0.8,10.5)	
3 or 4	Cases/Controls	5/13	7/12	18/10	18/13	
	OR(95% CI)	1.0(ref)	1.7 (0.4,7.6)	4.3 (1.1,17.1)	2.8 (0.8,13.3)	

All models adjusted for age, sex, race/ethnicity, history of hypertension, history of diabetes, BMI and smoking status.

This association was unchanged after multivariable adjustment (Q4 *vs*. Q1 OR = 4.1, 95% CI = 2.2–7.8; *p*-trend = <0.0001, Table 3). Sensitivity analyses were performed removing matched pairs where the case was diagnosed within 2 years of blood collection or experienced a large weight loss (>40 lbs), with no effect on the overall trend (mv-adj Q4 *vs*. Q1 OR = 4.6 CI = 2.3–9.1 *p*-trend = <0.0001, Supporting Information Table S1). Using DBP cut points from previous studies in the CPS-II[12] and ATBC[11] cohorts yielded similar results in the PLCO cohort (ATBC cutpoints Q4 *vs*. Q1 OR = 3.7 95% CI = 1.6–8.7; CPS-II cutpoints Q4 *vs*. Q1 OR = 2.1 95% CI = 1.3–3.5; Supporting Information Table S2).

There was a suggestion that the association between DBP and RCC was stronger among those with a greater pack-year smoking history (above median of 30: Q4 *vs*. Q1 OR = 6.4 95% CI = 2.2–19.0; below median: Q4 *vs*. Q1 OR = 2.0 95% CI = 0.8–5.3; *p*-interaction = 0.09 Table 4). We observed no DBP interaction with sex, BMI, weight change, smoking status or tumor stage at diagnosis (Table 4). Our results were very similar when restricting the analysis to only Whites (Q4 *vs*. Q1 OR = 4.6 95% CI = 2.3–9.1; *p*-trend = <0.0001). Results were also consistent when restricting to only males who had ever smoked in the dataset (Q4 *vs*. Q1 OR = 3.4 95% CI = 1.5–7.9; *p*-trend = 0.0004; Supporting Information Table S3). Although the sample size was small, restricting to male current smokers yielded point estimates similar to those observed overall (Q4 *vs*. Q1 OR = 3.0 95% CI = 0.2–52.3; *p*-trend = 0.73, Supporting Information Table S3).

Discussion

In this prospective study, we found a strong, statistically significant positive association between DBP quartile and RCC that persisted after adjustment for multiple potential confounding factors. Our findings were similar when we restricted to cases with at least 2 years of follow up and no major weight loss, suggesting that our findings are not due to reverse causality.

Our findings differ from those reported in the two previous studies on this topic.[11,12] Both previous studies found strong inverse associations between DBP and RCC. Consistency in our findings when using the quartile cut points from these two studies suggest that the difference cannot be attributed to different distributions of DBP concentrations across the three study populations. If differences in the demographic characteristics of the cohorts were to explain our findings, we would expect the ATBC Study to differ from the other two cohorts, as the ATBC cohort was recruited in Finland and comprised only male smokers whereas the CPS-II and PLCO cohorts were both recruited from multiple sites in the United States during overlapping calendar periods (CPS-II in 1992–1993, and PLCO in 1993–2001). It should be noted that restricting our analysis to male smokers did not alter the findings, further suggesting that differences in characteristics of the study participants cannot explain these discrepant findings. Additionally, CPS-II and PLCO laboratory measurements were performed at the same time at the Clinical Support Laboratory, SAIC-Frederick, Frederick National Laboratory for Cancer Research (Frederick, MD) using the DBP polyclonal assay from ALPO Diagnostics (Salem, NH). Therefore, laboratory error or differences in assay do not explain the different findings in PLCO compared to the other two populations.

One possible explanation for the different associations across studies is genetics. DBP is encoded by the *GC* gene, which is located on the long arm of chromosome 4. Two SNPs, rs7041 and rs4588, encode three different variants of the DBP protein, Gc1s, Gc1f and Gc2 which result in six different phenotypes. Although little work has been done examining the role of DBP isoform on cancer risk, one recent study reported that the Gc1f/Gc1f phenotype was associated with a reduced risk of cancer at all sites compared to other phenotypes.[14] Importantly, this phenotype has also been shown to have the highest Gc-MAF activity.[15] If the DBP phenotypes have different associations with cancer risk, and if the predominant DBP phenotype differed across these three studies, this could explain the different results across these three studies. However, it should be noted that the Gc1f/Gc1f phenotype is the least common in populations of European descent, which may argue against it driving the inverse findings in the ATBC and CPS-II Study populations, which were largely White. Alternatively, these findings could be due to chance. Additional studies are required to elucidate the true association between DBP and RCC, and future studies should examine whether DBP phenotype may influence RCC risk.

Our study's strengths are its relatively large size, the prospective nature of the cohort, excellent laboratory reproducibility and the inclusion of women and nonsmokers in the study population. Furthermore, we had detailed information on many potential confounding factors for which we could adjust in multivariable models. Unfortunately, our study population was largely White, possibly limiting our ability to generalize our findings to other racial or ethnic groups, particularly as DBP phenotypes are known to differ meaningfully across ethnic groups.[16] We also lacked information on genotype, preventing us from examining the role of DBP phenotype in the DBP-RCC association.

In the present study, those with higher serum concentrations of DBP were at substantially increased risk of RCC. Further research is necessary to determine the true association between DBP and risk of RCC, and whether different DBP phenotypes may have different associations with risk of RCC.

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