Original Contribution

Circulating 25-Hydroxyvitamin D and Risk of Kidney Cancer

Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

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Although the kidney is a major organ for vitamin D metabolism, activity, and calcium-related homeostasis, little is known about whether this nutrient plays a role in the development or the inhibition of kidney cancer. To address this gap in knowledge, the authors examined the association between circulating 25-hydroxyvitamin D (25(OH)D) and kidney cancer within a large, nested case-control study developed as part of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Concentrations of 25(OH)D were measured from 775 kidney cancer cases and 775 age-, sex-, race-, and season-matched controls from 8 prospective cohort studies. Overall, neither low nor high concentrations of circulating 25(OH)D were significantly associated with kidney cancer risk. Although the data showed a statistically significant decreased risk for females (odds ratio = 0.31, 95% confidence interval: 0.12, 0.85) with 25(OH)D concentrations of $\geq$75 nmol/L, the linear trend was not statistically significant and the number of cases in this category was small ($n = 14$). The findings from this consortium-based study do not support the hypothesis that vitamin D is inversely associated with the risk of kidney cancer overall or with renal cell carcinoma specifically.

case-control studies; cohort studies; kidney neoplasms; prospective studies; vitamin D

Abbreviations: CI, confidence interval; ICD-8 (9), *International Classification of Diseases*, Eighth (Ninth) Revision; ICD-10: *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision; ICD-O, *International Classification of Diseases for Oncology*; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; VDPP, Cohort Consortium Vitamin D Pooling Project of Rarer Cancers.

In the United States, kidney cancer incidence has been increasing at a rate of approximately 2% per year and accounts for 2.6% of all newly diagnosed cancer cases (1). Renal cell carcinoma is the most common type of kidney cancer, and incidence rates of this histologic type are twice as high among males compared with females (2). The established risk factors for renal cell carcinoma are cigarette smoking, hypertension, and obesity (3).

Recent widespread interest has focused on the health-promoting effects of vitamin D, the ''sunshine'' vitamin.

Vitamin D is well known for its role in promoting bone health through the regulation of bone growth and remodeling as well as calcium homeostasis (4). In addition, there is increasing laboratory evidence that vitamin D is an anticarcinogenic agent (4, 5). Vitamin D is obtained from exposure to ultraviolet light (sunlight) and certain foods such as oily fish and vitamin-D-fortified milk, orange juice, and cereal. It is metabolized to 25-hydroxyvitamin D (25(OH)D), the accepted biomarker of vitamin D status (6), which is activated to 1,25 dihydroxyvitamin D in the kidney. This

metabolite in turn regulates the expression of many proteins involved in cellular proliferation, differentiation, and apoptosis (7).

Studies indicate that vitamin D, measured as circulating 25(OH)D, may be associated with a reduced risk of several types of cancer, including colon, breast, and prostate (8–11). Although the kidney is a major organ for vitamin D metabolism and activity, and related calcium homeostasis, little is known about the association between vitamin D and cancer in this organ. Ecologic studies conducted in the United States and globally have shown an inverse association between levels of solar ultraviolet irradiance and kidney cancer incidence (12, 13). In contrast, 2 prospective cohort and 2 case-control studies focusing on dietary vitamin D reported no statistically significant association with the development of kidney cancer (14–17). However, the relevance of these studies is limited by study design issues (14, 16), a small number of cases (15), and the absence of data on vitamin D from ultraviolet light exposure (14–17), the principal source of circulating vitamin D.

In this study, the association between circulating 25(OH)D and kidney cancer was examined within a large, nested case-control study developed as part of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP). For this investigation, prediagnostic 25(OH)D concentrations were measured and data were analyzed from 775 kidney cancer cases and 775 controls participating in 8 prospective cohorts.

MATERIALS AND METHODS

A detailed description of cohorts participating in VDPP and the general methods for the project are provided in a separate paper (18). Of the 10 cohorts in VDPP, the following 8 contributed cases of kidney cancer: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC); the Cancer Prevention Study II Nutrition Cohort (CPS-II); CLUE; the Multiethnic Cohort Study (MEC); the New York University Women's Health Study (NYU-WHS); the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO); the Shanghai Men's Health Study (SMHS); and the Shanghai Women's Health Study (SWHS).

From these 8 cohorts, plasma/serum samples from 783 kidney cancer cases and 783 controls, alive and not diagnosed with cancer at the time of case diagnosis, and matched on age at blood collection (±1 year), sex, race (white/black/Asian/other), and date of blood draw (±30 days), were sent to the laboratory for measurement of circulating 25(OH)D. Five cases were excluded after 25(OH)D measurement because they were found to have cancer of the ureter (*International Classification of Diseases*, Eighth Revision (ICD-8)/*International Classification of Diseases*, Ninth Revision (ICD-9) code 189.2 or *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) code C66 or *International Classification of Diseases for Oncology* (ICD-O) code C66.9) or cancer of a urinary organ, site unspecified (ICD-8/ICD-9 code 189.9 or ICD-10 code C68 or ICD-O code C68–C68.9). Furthermore, 2 cases were excluded after 25(OH)D measurement because their date of diagnosis was prior to their date of

blood draw, and 1 control was excluded because no 25(OH)D data were returned from the laboratory. The remaining 776 cases and 782 controls were eligible to be included in the analytic data set. Because only matched pairs were analyzed, the final analytic data set consisted of 775 matched case-control pairs. Cases included 708 with renal cell carcinoma (ICD-8/ICD-9 code 189.0 or ICD-10 code C64 or ICD-O code 64.9) and 67 with carcinoma of the renal pelvis (ICD-8/ICD-9 code 189.1 or ICD-9/ICD-10 code C65 or ICD-O code 65.9).

All serum/plasma samples were measured for 25(OH)D at Heartland Assays, Inc., as described in Gallicchio et al. (18). The quality control measures included use of samples of the vitamin D standard from the National Institute of Standards and Technology (NIST) at both a "normal" (~65 nmol/L) and a "low" (~35 nmol/L) level. As reported in Gallicchio et al. (18) for the VDPP, interbatch and intrabatch coefficients of variation for low-level samples were 12.7% and 9.3%, respectively; interbatch and intrabatch coefficients of variation for normal-level samples were 13.6% and 11.0%, respectively. The median interbatch coefficient of variation for the cohort quality control samples was 13.2% (range: 4.8%–17.0%); the median intrabatch coefficient of variation for the cohort quality control samples was 9.9% (range: 3.8%–16.4%).

The main analyses described in this paper were conducted by using clinically defined cutpoints (4, 19, 20): <25 nmol/L, 25–<37.5 nmol/L, 37.5–<50 nmol/L, 50–<75 nmol/L, 75–<100 nmol/L, and ≥100 nmol/L. The referent category chosen was 50–<75 nmol/L because this range includes the mean level of the US population (62.91 nmol/L, standard error of the mean, 0.81 for males; 61.54 nmol/L, standard error of the mean, 0.85 for females) according to 2000–2004 National Health and Nutrition Examination Survey data (21).

In addition to the core VDPP variables, the following additional variables were requested for inclusion in the kidney cancer analyses: family history of renal cancer, history of high blood pressure at blood draw, and history of diabetes at blood draw. The Wald statistic, generated by using conditional logistic regression, was used to test the significance of differences between the kidney cancer cases and controls for selected variables, including median 25(OH)D concentrations. Variables in the VDPP data set that were 1) associated with both 25(OH)D and kidney cancer or 2) identified based on the literature as risk factors for kidney cancer, or both, were included in the fully adjusted models; these variables were education, body mass index, height, smoking status, current alcohol drinking, history of high blood pressure; and history of diabetes. All of these variables were treated as categorical in the model with the exception of height, which was treated as a continuous variable. Data on physical activity were also obtained because this variable has been shown to be associated with both kidney cancer and circulating 25(OH)D (22, 23); however, this variable may be in the causal pathway and not a confounder. For this reason, physical activity was not included in the fully adjusted model.

Conditional logistic regression models adjusting for the variables listed above were constructed to estimate the

Table 1. Characteristics of Participants, by Cohort, in the Investigation of Kidney Cancer Within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

Cohort	No. of Cases	No. of Controls	Median Years From Blood Collection to Cancer Diagnosis (Interquartile Range)	Median Circulating 25(OH)D, nmol/L (Interquartile Range)	
				Cases	Controls
ATBC	286	286	8.5 (4.6–12.4)	33.8 (22.7–47.5)	31.6 (21.5–47.5)
CLUE	102	102	10.9 (5.1–15.9)	62.8 (46.7–80.4)	63.7 (49.7–81.3)
CPS-II	58	58	2.4 (1.1–3.7)	65.5 (45.2–74.8)	59.0 (43.5–83.7)
MEC	64	64	2.2 (1.1–3.4)	48.9 (35.5–78.4)	53.3 (39.3–73.0)
NYU-WHS	35	35	10.8 (5.2–15.4)	37.8 (22.7–50.0)	39.7 (30.4–56.1)
PLCO	161	161	5.1 (2.4–6.8)	53.0 (40.4–64.5)	55.0 (43.0–68.5)
SMHS	32	32	2.2 (0.8–3.1)	39.5 (32.6–51.9)	38.5 (28.0–52.9)
SWHS	37	37	4.7 (3.1–7.3)	37.6 (28.4–42.0)	30.9 (23.5–41.9)
Total	775	775	5.5 (2.7–9.9)	44.4 (30.7–62.9)	45.4 (30.2–62.5)

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CPS-II, Cancer Prevention Study II Nutrition Cohort; MEC, Multiethnic Cohort Study; NYU-WHS, New York University Women's Health Study; 25(OH)D, 25-hydroxyvitamin D; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

overall odds ratios and 95% confidence intervals for kidney cancer by 25(OH)D concentration, examined by using the 6-category clinically defined cutpoint variable. Trend tests were conducted by assigning values of 1–6 to the respective 25(OH)D categories and treating the new variable as continuous in the model. Unconditional logistic regression analyses using a 5-category 25(OH)D variable with the categories of 75–<100 nmol/L and ≥100 nmol/L combined adjusting for the matching factors and the other potential confounders listed above were also conducted to examine the associations between 25(OH)D and kidney cancer in strata based on predefined categories of sex, season (winter/summer), age at blood collection, race, latitude, length of follow-up, calcium intake/supplementation, body mass index, cigarette smoking, history of high blood pressure, and history of diabetes. No differences in the investigated association were observed in these stratified analyses; thus, with the exception of the sex- and season-specific analyses, the results of the stratified analyses are not presented here.

Additionally, pooled analyses using cohort-, sex-, and season-specific quartile cutpoints (using the 2-season variable), based on the distribution of circulating 25(OH)D among all controls from all VDPP cancer sites combined, were also conducted. Both conditional and unconditional models were run with the lowest fourth as the referent category; the results were similar. Analyses to adjust for season using the residual method were also conducted, as described in Gallicchio et al. (18). Residual adjustment for season takes into account the gradual nature of changes in concentrations of 25(OH)D over the year, which may be better than adjusting for season. For the residual analyses, conditional logistic regression models were run with the lowest fourth as the referent category.

All analyses described above were conducted for all kidney cancer cases (and matched controls) and then for renal cell carcinoma cases (and matched controls) only. Analyses were also conducted by excluding cases (and matched controls) diagnosed within 2 years of blood draw. Because the resulting estimates from these analyses were similar, only the stratified results based on all cases (and matched controls) are presented.

Finally, meta-analyses were conducted to examine the overall and sex-specific associations of both low (<25 nmol/L) and high (≥75 nmol/L) concentrations of circulating 25(OH)D compared with the referent category of 50–<75 nmol/L with kidney cancer for all of the contributing study cohorts. Pooled multivariate log odds ratio estimates adjusted for the covariates in the models described above (e.g., education, body mass index, high blood pressure) were obtained by using inverse-variance weights in random-effects models. Statistical heterogeneity was assessed by using the DerSimonian and Laird Q statistic (24). Because of small numbers of cases and controls in the Shanghai Women's Health Study and the Shanghai Men's Health Study, data from these cohorts were combined for the overall meta-analyses. In addition, because of small numbers (≤1 case in the high or low 25(OH)D category), not all cohorts contributed to all of the meta-analyses. Specifically, the New York University Women's Health Study dropped out of the overall and female-specific high versus referent 25(OH)D concentration meta-analyses; CLUE, the Cancer Prevention Study II Nutrition Cohort, and the Multiethnic Cohort Study dropped out of the female-specific low versus referent 25(OH)D concentration meta-analyses; and the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort Study, and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial dropped out of the female-specific high versus referent 25(OH)D concentration meta-analyses. To explore the influence of each cohort on the results, the meta-analyses described above were repeated by excluding one cohort at a time.

Table 2. Selected Characteristics of Cases and Controls in the Investigation of Kidney Cancer Within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

Characteristic	Cases (N = 775)			Controls (N = 775)			P Value[a]
	No.	%	Median (Interquartile Range)	No.	%	Median (Interquartile Range)	
Age at blood collection, years			60 (54–66)			60 (54–66)	Matched
Sex							Matched
Male	577	74.5		577	74.5		
Female	198	25.5		198	25.5		
Race							Matched
White	623	80.4		621	80.1		
Black	26	3.4		29	3.7		
Asian	83	10.7		83	10.7		
Other	40	5.2		39	5.0		
Missing	3	0.4		3	0.4		
Education							0.39
Less than high school	179	23.1		202	26.1		
Completed high school	153	19.7		129	16.6		
Vocational school	148	19.1		134	17.3		
Some college	160	20.6		165	21.3		
College graduate	75	9.7		72	9.3		
Graduate studies	54	7.0		65	8.4		
Missing	6	0.8		8	1.0		
Latitude, °							0.31
<35	154	19.9		148	19.1		
35–42	239	30.8		252	32.5		
>42	382	49.3		375	48.4		
Family history of any cancer							0.18
Yes	270	34.8		278	35.9		
No	277	35.7		310	40.0		
Missing	228	29.4		187	24.1		
Height, cm			172.7 (166.0–178.0)			172.0 (165.1–177.0)	<0.01
Body mass index, kg/m²							0.01
<25.0	251	32.4		296	38.2		
25.0–29.9	316	40.8		299	38.6		
≥30.0	156	20.1		126	16.3		
Missing	52	6.7		54	7.0		
Cigarette smoking							<0.01
Never	208	26.8		250	32.3		
Former	193	24.9		173	22.3		
Current	366	47.2		345	44.5		
Missing	8	1.0		7	0.9		

Table continues

Statistical analyses were performed by using SAS software, versions 9.1.3 and 9.2 (SAS Institute, Inc., Cary, North Carolina). All meta-analyses were conducted by using the R function MiMa (25) in R version 2.8.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall, the median follow-up time for cases (time from blood draw to case diagnosis) was 5.5 years (interquartile range: 2.7–9.9) (Table 1). Median circulating 25(OH)D for the kidney cancer cases and controls was 44.4 nmol/L

Table 2. Continued

Characteristic	Cases (N = 775)			Controls (N = 775)			P Value[a]
	No.	%	Median (Interquartile Range)	No.	%	Median (Interquartile Range)	
Current alcohol drinker							0.42
Yes	440	56.8		460	59.4		
No	230	29.7		221	28.5		
Missing	105	13.5		94	12.1		
Physical activity, intensity							0.04
Low/none	255	32.9		244	31.5		
Light	247	31.9		234	30.2		
Moderate	85	11.0		96	12.4		
Vigorous	90	11.6		121	15.6		
Missing	98	12.6		80	10.3		
History of high blood pressure							<0.01
Yes	267	34.5		206	26.6		
No	495	63.9		566	73.0		
Missing	13	1.7		3	0.4		
History of diabetes							0.68
Yes	52	6.7		50	6.5		
No	701	90.5		715	92.3		
Missing	22	2.8		10	1.3		
Supplement use characteristics							
Current supplement, any							0.88
Yes	171	22.1		171	22.1		
No	438	56.5		442	57.0		
Missing	166	21.4		162	20.9		
Current vitamin D supplement							0.32
Yes	37	4.8		44	5.7		
No	471	60.8		459	59.2		
Missing	267	34.5		272	35.1		
Current calcium supplement							0.79
Yes	98	12.6		105	13.5		
No	585	75.5		577	74.5		
Missing	92	11.9		93	12.0		
Dietary intake/day							
Energy, kcal			2,137.2 (1,647.8–2,712.3)			2,161.5 (1,653.7–2,799.1)	0.32
Vitamin D, IU			169.6 (115.6–248.5)			169.9 (112.2–241.4)	0.48
Calcium, mg			912.3 (622.0–1,385.4)			1,003.9 (610.6–1,383.5)	0.35
Fish, g			25.4 (13.8–43.0)			24.2 (12.6–42.9)	0.09
Dairy, g			251.8 (66.8– 718.9)			262.8 (70.6–698.1)	0.93

[a] Wald test from conditional logistic regression, excluding subjects with missing data.

(interquartile range: 30.7–62.9) and 45.4 nmol/L (interquartile range: 30.2–62.5), respectively (P = 0.71).

The distribution of selected characteristics of the cases and controls is shown in Table 2. Approximately 75% of the participants were male, the majority were white (80.4% of cases and 80.1% of controls), and the median age at blood collection of both cases and controls, overall, was 60 years. For both males and females, cases were more likely than

Table 3. Odds Ratios and 95% Confidence Intervals for the Association Between Circulating 25(OH)D and Risk of Kidney Cancer Within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers, Overall and for Renal Cell Carcinoma Subtype and Cases Diagnosed More Than 2 Years After Blood Draw

| | Circulating 25(OH)D, nmol/L | | | | | | | | | | | | P Value |
| | <25 | | 25–<37.5 | | 37.5–<50 | | 50–<75 | | 75–<100 | | ≥100 | | |
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
All kidney cancers													
No. of cases		119		164		173		219		80		20	
No. of controls		136		152		144		240		75		28	
Crude	0.97	0.68, 1.37	1.16	0.85, 1.58	1.30	0.97, 1.74	1.0	Referent	1.14	0.78, 1.67	0.77	0.40, 1.45	0.76
Multivariate adjusted[a]	0.94	0.64, 1.37	1.18	0.84, 1.67	1.18	0.85, 1.62	1.0	Referent	1.19	0.78, 1.83	0.92	0.44, 1.92	0.86
Renal cell carcinomas													
No. of cases		111		145		155		202		77		18	
No. of controls		123		138		132		220		70		25	
Crude	0.99	0.69, 1.42	1.12	0.81, 1.56	1.27	0.94, 1.73	1.0	Referent	1.18	0.80, 1.75	0.76	0.39, 1.51	0.84
Multivariate adjusted[a]	0.94	0.63, 1.39	1.13	0.78, 1.63	1.12	0.80, 1.58	1.0	Referent	1.24	0.79, 1.93	0.96	0.43, 2.14	0.67
All kidney cancers diagnosed >2 years after blood draw													
No. of cases		106		129		146		185		51		16	
No. of controls		119		124		118		194		56		22	
Crude	0.95	0.65, 1.39	1.09	0.77, 1.54	1.30	0.94, 1.79	1.0	Referent	0.92	0.58, 1.44	0.71	0.34, 1.47	0.67
Multivariate adjusted[a]	0.91	0.61, 1.38	1.10	0.75, 1.63	1.15	0.80, 1.66	1.0	Referent	0.91	0.54, 1.52	0.79	0.33, 1.88	0.95

Abbreviations: CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

[a] Conditional models were adjusted for education, body mass index, height, smoking status, history of high blood pressure, history of diabetes, and alcohol drinking.

controls to report a history of high blood pressure. Among males, but not females, cases were taller, had a higher mean body mass index, were more likely to be categorized as overweight or obese, and were more likely to report being a current smoker compared with controls (data not shown). There were no statistically significant differences among cases and controls with respect to dietary intake or supplement use variables.

As shown in Table 3, 25(OH)D concentrations were not significantly associated with the risk of developing kidney cancer for males and females combined (P-trend = 0.76). Adjustment for covariates that have been shown in previous studies to be associated with kidney cancer, including body mass index, height, smoking status, history of high blood pressure, current alcohol drinking, and education, did not significantly change the results (P-trend = 0.86). Similar results for the unadjusted and adjusted conditional logistic regression modeling were obtained when examining renal cell carcinomas only (P-trend = 0.67 for the multivariate-adjusted model) and when limiting the sample to cases diagnosed more than 2 years after blood draw and their matched controls (P-trend = 0.95 for the multivariate-adjusted model). After excluding subjects from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, who constituted 36.9% of the sample, the multivariate-adjusted

odds ratios for the highest and lowest categories of 25(OH)D tended to be more inverse at both the high and low extremes compared with the analysis including all cohorts (<25 nmol/L odds ratio (OR) = 0.75, 95% confidence interval (CI): 0.40, 1.41; ≥100 nmol/L OR = 0.57, 95% CI: 0.27, 1.17; P-trend = 0.32). Analyses using the pooled cohort-, sex-, and season-specific quartile cutpoints, as well as those using residual adjustment for season, showed no increase or decrease in risk of kidney cancer or renal cell carcinoma in the highest quartile compared with the lowest quartile of circulating 25(OH)D (data not shown).

In the analyses stratified by sex (Table 4), low concentrations of circulating 25(OH)D were not associated with kidney cancer risk for either males (OR = 1.04, 95% CI: 0.68, 1.58) or females (OR = 0.66, 95% CI: 0.24, 1.77). High 25(OH)D concentrations (≥75 nmol/L) were associated with a nonstatistically significant increased risk of kidney cancer for males (OR = 1.52, 95% CI: 0.95, 2.41), even after excluding cohort subjects from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (OR = 1.52, 95% CI: 0.89, 2.59). In contrast, among females, high concentrations of 25(OH)D were associated with a statistically significant decreased risk of kidney cancer (OR = 0.31, 95% CI: 0.12, 0.85). Overall, there was no statistical evidence of a sex–25(OH)D interaction (P = 0.42). No differences in

Table 4. Odds Ratios and 95% Confidence Intervals for the Association Between Circulating 25(OH)D and Risk of Kidney Cancer Within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers, by Sex and Season

| Strata | Circulating 25(OH)D, nmol/L | | | | | | | | | | P Trend |
| | <25 | | 25–<37.5 | | 37.5–<50 | | 50–<75 | | ≥75 | | |
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Males											
No. of cases		98		117		123		153		86	
No. of controls		113		108		102		179		75	
Multivariate adjusted[a]	1.04	0.68, 1.58	1.33	0.88, 2.01	1.36	0.94, 1.99	1.0	Referent	1.52	0.95, 2.41	0.67
Females											
No. of cases		21		47		50		66		14	
No. of controls		23		44		42		61		29	
Multivariate adjusted[a]	0.66	0.24, 1.77	0.84	0.41, 1.71	0.79	0.39, 1.60	1.0	Referent	0.31	0.12, 0.85	0.65
Winter[b]											
No. of cases		97		101		90		83		27	
No. of controls		98		93		84		89		29	
Multivariate adjusted[c]	1.14	0.71, 1.84	1.25	0.79, 1.96	1.18	0.75, 1.85	1.0	Referent	0.99	0.52, 1.90	0.49
Summer[b]											
No. of cases		22		63		83		136		73	
No. of controls		38		59		60		151		74	
Multivariate adjusted[c]	0.68	0.35, 1.31	1.09	0.66, 1.79	1.40	0.88, 2.21	1.0	Referent	1.26	0.78, 2.03	0.38

Abbreviations: CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

[a] Conditional models were adjusted for education, body mass index, height, smoking status, history of high blood pressure, history of diabetes, and alcohol drinking.

[b] Winter was defined as December–May and summer as June–November.

[c] Unconditional models were adjusted for date of blood draw, age at blood collection, race, sex, education, body mass index, height, smoking status, history of high blood pressure, history of diabetes, and alcohol drinking.

the associations between circulating 25(OH)D and kidney cancer were observed for individuals who had their blood drawn in the winter season compared with individuals who had their blood drawn in the summer season.

The associations with kidney cancer for both low (<37.5 nmol/L) and high (≥75 nmol/L) concentrations of circulating 25(OH)D compared with the referent category of 50–<75 nmol/L in each of the contributing study populations are shown on Figure 1. Overall, the pooled odds ratios for the high and low categories of 25(OH)D versus the referent category were 1.01 (95% CI: 0.65, 1.58) and 1.12 (95% CI: 0.79, 1.59), respectively. The pooled odds ratios for males and females for the high category of 25(OH)D versus the referent category were 1.33 (95% CI: 0.80, 2.24) and 0.52 (95% CI: 0.06, 4.89), respectively. The pooled odds ratios for males and females for the lowest category of 25(OH)D versus the referent category were 1.07 (95% CI: 0.71, 1.61) and 0.73 (95% CI: 0.17, 3.22), respectively. There was no evidence of statistical heterogeneity across studies in any of the meta-analyses (data not shown). Results from analyses that excluded cohorts one at a time showed no substantial changes in the pooled odds ratios.

DISCUSSION

The findings from this large consortium-based prospective study do not support the hypothesis that circulating 25(OH)D concentrations are associated with the risk of kidney cancer overall or the renal cell carcinoma subtype. Although our data suggest a possible decrease in risk for females associated with high 25(OH)D concentrations (≥75 nmol/L), the linear trend was not statistically significant and the number of cases in this category was small (n = 14). The overall null results we report for kidney cancer are similar to the results examining circulating 25(OH)D in relation to the other VDPP rarer cancer outcomes, including endometrial cancer (26), ovarian cancer (27), upper gastrointestinal cancer (28), and non-Hodgkin lymphoma (29). In contrast, the data from VDPP indicate an increased risk of pancreatic cancer associated with 25(OH)D concentrations of 100 nmol/L or more (30).

Despite the fact that the kidney is a major organ for vitamin D metabolism and activity, few studies have been conducted on vitamin D and kidney cancer. To our knowledge, there are no prospective serum-based investigations, and all published studies examined dietary intake of vitamin D as a measure of vitamin D status. All but one of these
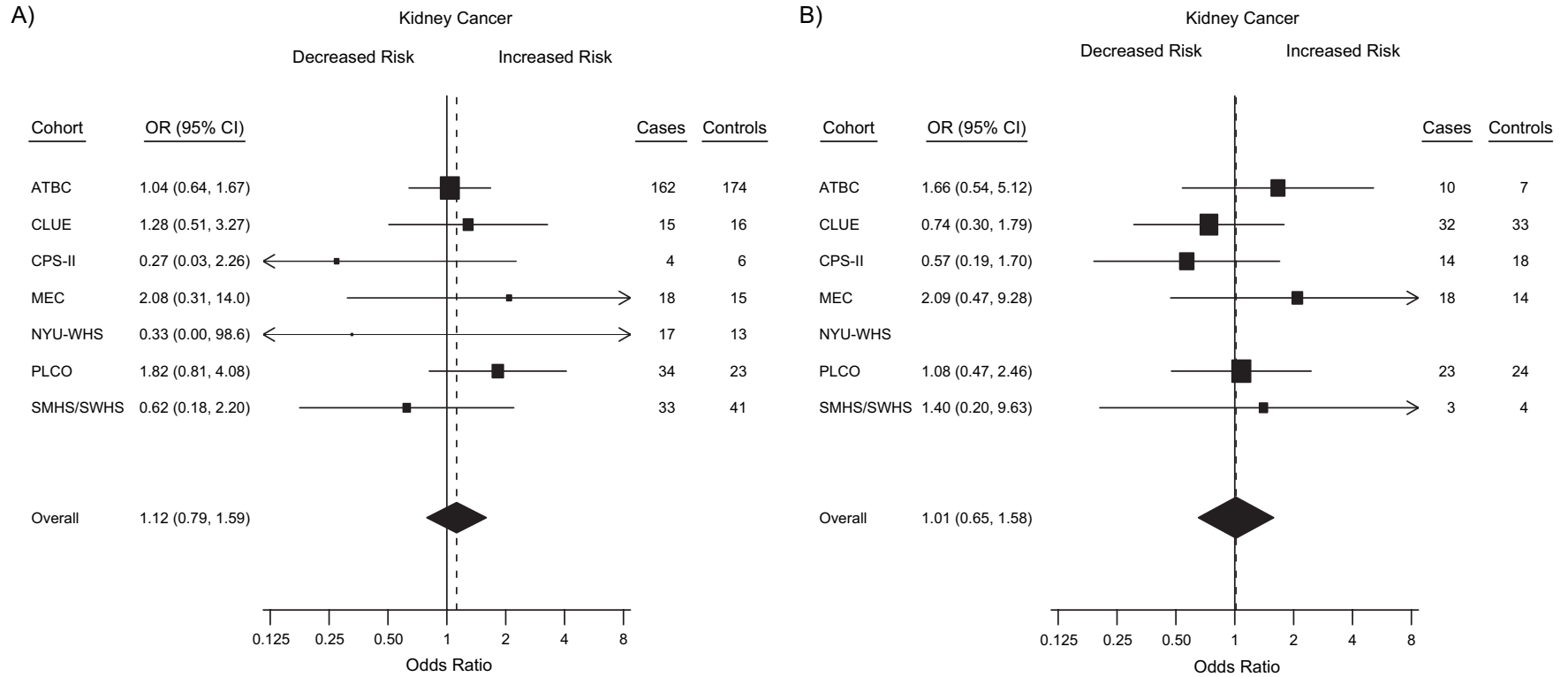
Figure 1. Forest plots for the meta-analysis of the association between circulating 25-hydroxyvitamin D (25(OH)D) and the risk of kidney cancer within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Risk estimates, by cohort, for subjects with circulating 25(OH)D concentrations of A) <37.5 nmol/L and B) ≥75 nmol/L compared with the referent group (50–<75 nmol/L). Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from conditional logistic regression models adjusted for education, body mass index, height, smoking status, history of high blood pressure, history of diabetes, and alcohol drinking. The boxes show the odds ratios, the bars show the 95% confidence intervals, and the size of each box is inversely proportional to the variance of the log odds ratio estimate in each cohort. The overall estimates (diamonds) were derived from a meta-analysis using random-effects modeling. NYU-WHS data are not included in the highest versus reference category forest plot (B) because there were zero cases of kidney cancer among cases in the highest category. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CPS-II, Cancer Prevention Study II Nutrition Cohort; MEC, Multiethnic Cohort Study; NYU-WHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SMHS/SWHS, Shanghai Men's Health Study/Shanghai Women's Health Study.

studies, however, reported findings consistent with our overall null result. For example, prospective cohort studies of male smokers in Finland (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) and women in Iowa (the Iowa Women's Health Study) showed no statistically significant association between vitamin D intake and renal cell carcinoma after adjustment for age (15) and other potential confounders such as high blood pressure (17). Furthermore, a case-control study conducted in Denmark showed no association between the intake of individual foods rich in vitamin D (i.e., fish and eggs) and renal cell carcinoma risk (16), and a large case-control study conducted in central and eastern Europe observed no statistically significant increase or decrease in renal cell carcinoma risk with total vitamin D intake (31). In contrast, one Italian case-control study of 767 cases and 1,532 controls reported a statistically significant inverse association between dietary vitamin D intake, based on a 78-item food frequency questionnaire, and the risk of renal cell carcinoma; however, this finding was observed among only females (OR = 0.60), participants with a high body mass index (≥ 25 kg/m^2) (OR = 0.65), and never smokers (OR = 0.61).

In general, studies, primarily ecologic, investigating the association between cancer risk and sun exposure have reported an inverse relation between kidney cancer incidence and mortality with ultraviolet B light exposure (12, 13, 32–34). For example, Mohr et al. (12) examined the association between ultraviolet B exposure and renal cancer risk in 175 countries using latitude and solar ultraviolet B irradiance. For both males and females, the highest renal carcinoma risk rates were found in countries situated at the highest latitudes. Furthermore, an occupational cohort study exploring the relation between ultraviolet exposure and cancer risk among Swedish male construction workers found that participants exposed to the highest level of occupational sunlight had a reduced kidney cancer risk (35). Additionally, a recent central and eastern European case-control study reported inverse associations between occupational ultraviolet exposure and renal cell carcinoma risk that, after stratification, were limited to males residing in the highest latitudes (36). Similar inverse associations in case-control studies have been reported between occupational sunlight exposures and other cancers such as diffuse large B-cell lymphoma, follicular lymphoma, and rectal and prostate cancer (refer, for example, to Boffetta et al. (37), Slattery et al. (38), and John et al. (39)).

A major strength of the present investigation is the inclusion of a large number of kidney cancer cases from multiple cohort studies that incorporated a wide range of vitamin D concentrations and latitudes. Furthermore, since the study is prospective, with vitamin D status assessed from blood samples collected before cancer diagnosis, the influence of reverse causality was minimized. Moreover, circulating 25(OH)D concentrations were assayed by a single laboratory to reduce interlaboratory variation. Additionally, this measure of vitamin D exposure represents an internal dose that includes the 2 major sources of vitamin D: sun exposure and intake. Finally, this study collected data on a number of potential confounders

such as high blood pressure and body mass index that were used in the analysis to allow for a more accurate estimation of the association between 25(OH)D and kidney cancer risk.

Limitations of our study include measurement of only a single blood sample; 25(OH)D measurements from multiple time points would have resulted in more precise estimates of exposure. However, it should be noted that data from several studies suggest that 25(OH)D concentrations are relatively stable when samples are collected during the same season in different years. For example, a study conducted in the New York University Women's Health Study found an intraclass correlation coefficient for circulating 25(OH)D of 0.78 (95% CI: 0.64, 0.88) in 30 healthy women who contributed 3 samples each at yearly intervals (Anne Zeleniuch-Jacquotte, New York University School of Medicine, personal communication, 2009). Other limitations include the possibility that the etiologically relevant time period of exposure was missed with the single blood sample and limited power to examine associations among subgroups with a small number of cases.

In summary, the combined data from 8 prospective cohort studies do not support the hypothesis that higher circulating 25(OH)D measured in prediagnostic blood specimens is associated with a decreased risk of kidney cancer overall or with renal cell carcinoma specifically.

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