WCRF-AICR Continuous Update Project: Systematic Literature Review of Prospective Studies on Circulating 25-hydroxyvitamin D and Kidney Cancer Risk

The Journal of Steroid Biochemistry and Molecular Biology

Andrea L. Darling, Leila Abar and Teresa Norat

Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College, St Mary's Campus, Norfolk Place, London W2 1PG, UK

andrea.darling@imperial.ac.uk / a.l.darling@surrey.ac.uk[1]

l.abar@imperial.ac.uk

t.norat@imperial.ac.uk

Corresponding Author: Dr Andrea L. Darling[1]

[1]Present address: Dr Andrea L. Darling: Postdoctoral Research Fellow, Department of Nutritional Sciences, School of Biosciences and Medicine, Dorothy Hodgkin Building, University of Surrey, Guildford, GU2 7XH. +0044 (0)1483 689222. a.l.darling@surrey.ac.uk

Running Title: Circulating 25-hydroxyvitamin D and Kidney Cancer Risk

Financial Support

This work was funded as part of the World Cancer Research Fund International/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project (Grant Number 2007/SP01) (TN and LA). ALD was funded by the Imperial College National Institute of Health Research (NIHR) Biomedical Research Centre (BRC).

The views expressed in this review are the opinions of the authors. The views may not represent the views of World Cancer Research Fund International/American Institute for Cancer Research (WCRF/AICR) and may differ from those in future updates of the evidence related to food, nutrition, physical activity, and cancer risk. The sponsor of this study had no role in the decisions about the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflict of Interest:

None of the authors reported a conflict of interest related to the study

Manuscript notes:

Word count=2139 (excluding references); 2 figures and 1 table

Author declaration:

ALD, LA and TN all contributed to the revision of and approval of the manuscript and had full access to all study data. Specifically, the literature search and data extraction was undertaken by LA, with data extraction checked in duplicate by ALD. The systematic review analysis was conducted by ALD and interpreted by ALD and TN. The first version of the manuscript was written by ALD and co-authors contributed to the final version. ALD holds responsibility for the integrity and accuracy of the data analysis and the final results. TN is the Continuous Update Project primary investigator and supervised the systematic review process.

Abstract

As part of the World Cancer Research Fund/ American Institute for Cancer Research (WCRF-AICR) Continuous Update project we performed a systematic review of prospective studies with data for both measured or predicted 25(OH)D concentration and kidney cancer risk. PubMed was searched from inception until 1st December 2014 using WCRF/AICR search criteria.

The search identified 4 papers suitable for inclusion, reporting data from three prospective cohort studies, one nested case-control study and the Vitamin D Pooling Project of Rarer Cancers (8 nested case-control studies). Summary effect sizes could not be computed due to incompatibility between studies. All studies except the Pooling Project suggested a reduced risk of kidney cancer by 19-40% with higher or adequate vitamin D status, . However, these estimates only reached statistical significance in one cohort (Copenhagen City Heart Study; CCHS, HR=0.75 (0.58 to 0.96)). In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a significant reduction in risk by 18% was seen when using combined matched and non-matched controls OR=0.82 (0.68, 0.99), but not when using only matched controls (OR=0.81 (0.65, 1.00). Pooled (but not single cohort) data for predicted 25(OH)D from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) showed a statistically significant reduction in risk by 37% (HR=0.63 (0.44, 0.91)).

There is no clear explanation for the inconsistency of results between studies, but reasons may include prevalence of smoking or other study population characteristics. Methods for assessing circulating 25(OH)D levels and control for confounders including seasonality or hypertension do not seem explanatory.

Keywords: Kidney Cancer, 25-hydroxyvitamin D, Systematic Review, Vitamin D, Nutrition

Highlights

- A systematic review of studies assessing 25(OH)D status and kidney cancer risk.
- Four cohort or nested case-control studies and one Pooling Project were included.
- Subject populations and smoking prevalence may explain between cohort differences.
- An association between low 25(OH)D and kidney cancer risk could not be ruled out.

1.0. Introduction

Kidney cancer is the 14th most frequent cancer worldwide[1] with renal cell carcinoma the most common type. Incidence rates increased until the middle of the 1990s and then stabilized, but recent estimates suggest that in some countries incidence rates are still increasing[2]. These trends might have been influenced by the use of new imaging tests and the changing prevalence of known risk factors including smoking and obesity[3].

The kidneys are the main tissue in the body responsible for hydroxylation of the circulating metabolite 25(OH)D to the active hormone 1,25-dihydroxyvitaminD ($1,25(OH)_2D$). Most kidney cancers are of epithelial cell origin, and vitamin D has known beneficial anti-neoplastic properties in human epithelium[4]. An inverse relationship has been found between occupational UVB exposure and renal cell carcinoma risk in men, which could be partly attributable to vitamin D status[5]. In this systematic review we assessed the evidence from prospective studies on vitamin D status and kidney cancer risk, examining potential sources of heterogeneity between studies.

2.0 Materials and Methods

2.1. Search Strategy and Study Selection

The search criteria and data extraction protocol used were those used in the WCRF/AICR Continuous Update Project (full protocol available at http://wcrf.org/sites/default/files/protocol_kidney_cancer.pdf). Two reviewers independently selected the articles and extracted the data for the most highly adjusted model reported in each paper for renal cell carcinoma or kidney cancer. Figure 1 illustrates the flow of articles through the selection process. Four articles were relevant for inclusion containing data on three cohort studies (Copenhagen City Heart Study (CCHS)[6], Nurses' Health Study (NHS), Health Professionals Follow-Up Study (HPFS)[7], a nested case-control study (European Prospective Investigation into Cancer and Nutrition (EPIC) [8] and the Pooling Project of Rarer Cancers[9], which included 8 nested case control studies (see Table 1 for details). A report from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC)[10] was excluded as this cohort was already included in the Pooling Project[9]. Circulating 25(OH)D was assessed from serum or plasma samples in all studies except the NHS and HPFS[7] whereby 25(OH)D was predicted using validated regression models that included major determinants of vitamin D status.

FIGURE 1 ABOUT HERE

2.2. Data analysis

Study results were tabulated and shown in a forest plot. Summary estimates were not calculated due to the differences in the increment units and contrasts used in the studies. Contrasts chosen for inclusion in the forest plot were those closest to the well-established 25(OH)D cut off points of >75nmol/L[11] for optimal vitamin D status, compared to <25nmol/L

(referent) for vitamin D deficiency. It must be borne in mind that these cut-off points have much debated in vitamin D literature. For the Pooling Project[9] (combined male and female estimate) the reference category was changed to <25nmol/L and the top two categories combined to produce a cut-off point of ≥75nmol/L, using the method described by Hamling et al. (2008)[12]. Two studies (CCHS, EPIC) presented the data for continuous increments of 25(OH)D and are also shown in the same forest plot. To increase the comparability across study results, the HR of the CCHS data[6] was recalculated to increments of doubling of 25(OH)D levels (originally expressed for reduction).

3.0. Results

Study characteristics are shown in Table 1. Overall, the studies on measured 25(OH)D concentration included 1390 kidney cancer or renal cell carcinoma cases. From these, 775 kidney cancer cases are from the Vitamin D Pooling Project of Rarer Cancers, 55 cases are from the CCHS and 560 renal cell carcinoma cases are from EPIC. In the Vitamin D Pooling Project, the results for kidney cancer and renal cell carcinomas were similar. In all studies, 25(OH)D was measured in only a single blood sample. The NHS and HPFS cohorts [7] used predicted plasma 25(OH)D and included 408 cancer cases.

TABLE 1 ABOUT HERE

Figure 2 illustrates the forest plot of predicted or actual plasma vitamin D and kidney cancer. The Pooling Project [9] did not support an association of circulating 25(OH)D concentration with the risk of RCC, with an odds ratio of 1.18 (95% CI 0.63, 2.22) for the ≥75nmol/L as compared with <25 nmol/L(referent), and an odds ratio of 1.12 (0.79,1.59) for 25(OH)D concentration <37.5 nmol/L, as compared with 50-75 nmol/L (referent)(data not shown in the Figure). For continuous data, in the CCHS[6] lower plasma 25(OH)D was significantly related with a higher risk of kidney cancer[6]. The Hazard ratio for a 50% reduction in plasma 25(OH)D was 1.34 (1.04,1.73). Equivalent data for a 50% increase in plasma 25(OH)D was estimated as 0.75 (0.58, 0.96). In the EPIC study[8] a doubling of 25(OH)D concentration was associated with a reduced odds of developing RCC of 0.82 (0.68, 0.99) in the combined control model (data not shown in the Figure 2), and 0.81 (0.65, 1.00) for the matched control model [8].

For the studies on predicted vitamin D score, there was a non-statistically significant trend for a reduced risk of RCC by 40% in the NHS (women; HR=0.60 (0.35, 1.02) and by 34% in the HPFS (men; HR=0.66 (0.40, 1.09) for the top quintile of predicted 25(OH)D versus the lowest quintile (referent)[7]. Pooled results from the NHS and HPFS showed a statistically significant reduction in risk of RCC by 37% (HR=0.63 (0.44, 0.91) for equivalent quintiles [7](data not

shown). In continuous analyses, the HR per 10 ng/mL (25nmol/L) of predicted 25 (OH)D were 0.61 (0.35, 1.04) in the HPFS cohort, 0.70(0.45, 1.07) in the NHS cohort[7] and 0.66 (0.47 to 0.92) (ptrend=0.009) for both combined.

FIGURE 2 ABOUT HERE

Sub-analyses undertaken in the Pooling Project showed that women with the highest 25(OH)D (i.e. 75nmol/L or over) have a significantly reduced risk of all kidney cancer than women with 25(OH)D of 50-74nmol/L[9]. However, this effect was not statistically significant when <25nmol/L (referent) was compared with ≥75nmol/L (Table 1). However, there was no effect modification by sex in the EPIC study[8], and in the cohorts with predicted circulating 25(OH)D scores (NHS and HPFS), similar inverse associations were observed in men and women.

4.0. Discussion

This systematic review showed inconsistent evidence as to whether kidney cancer risk is related to vitamin D status. No association was observed in the Pooling Project of Rarer Cancers[9]. A significant inverse association with kidney cancer was observed in the CCHS [6] (only 55 kidney cancer cases) and in EPIC, lower risk of renal cell carcinoma was observed with a doubling of circulating 25(OH)D concentration, but only when combined controls rather than matched controls were used. Also, when combined, the two studies using predicted 25(OH)D scores (NHS and HPFS) showed significant inverse association with kidney cancer risk. However, results were not statistically significant for the two cohorts separately.

The reasons for the different results between cohorts are unclear. In EPIC [8] $25(OH)D_3$ was determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS). Both the Pooling Project[13] and the CCHS[6] used DiaSorin Liaison TOTAL 25(OH)D chemiluminescent immunoassay for measuring both 25(OH)D2 and 25(OH)D3. It is known that radioimmunoassay (RIA) and chemiluminescent immunoassay (CLIA) measurements of 25(OH)D (e.g.) differ from chemical based measurements (e.g. High Performance Liquid Chromatography (HPLC) or LC-MS) of 25(OH)D by up to 18%[14]. Two study results (CCHS [6] and the Pooling Project[9]) which used the same measurement technique (DiaSorin Liaison 25(OH)D TOTAL) gave different results, which measures both 25-hydroxyvitamin D3 ($25(OH)D_3$) and 25-hydroxyvitamin D2 ($25(OH)D_2$). The EPIC study[8] was the only study to use LC-MS to assess vitamin D status, using only the $25(OH)D_3$ measurement in the analysis as $25(OH)D_2$ was not detectable in most samples. It is unlikely that the inclusion of $25(OH)D_2$ in some of the analyses, but not others explains any difference in results between-studies as $25(OH)D_2$ is usually present in much lower concentrations than $25(OH)D_3$ in human blood, and most likely has lower biological efficacy[15]. Some differences between study results may be due to differences in study follow up times. For instance, the CCHS cohort had a relatively long follow-up (28 years) and showed a statistically significant result, as did HPFS and NHS studies (22 years), which showed a significant reduction in risk with increasing 25(OH)D

concentration (pooled data for both cohorts only). A longer follow up time may render the baseline 25(OH)D measurement less representative of the persons vitamin D status closer to the time of diagnosis. This must be borne in mind when interpreting the results for the studies with longer follow-up times.

All studies controlled for season of blood collection using either residual adjustment[6, 9] or trigonometric functions[8] in the models, and also all studies controlled for main potential confounders including BMI and smoking. The Pooling project[9] adjusted for hypertension and in a sub analysis in EPIC[8], adjustment for hypertension did not modify the results. The CCHS[6], with a small number of cases, did not adjust for hypertension.

The proportion of current and former smokers was highest in the Pooling Project, with 37% of kidney cancer cases coming from participants in the ATBC cohort[9]. Smokers may have an increased risk of kidney cancer but also have a lower level of circulating 25(OH)D[16]. In the ATBC cohort, median circulating 25(OH) levels (31.6nmol/L in the controls) were lower than the average in the overall study populations. After exclusion of the ATBC participants from the Vitamin D Pooling project analyses, a U shape relationship was suggested with odds ratios of 0.75 (95% CI: 0.40-1.41) for <25 nmol/L and 0.57 (95% CI:0.27, 1.17) for ≥100 nmol/L compared to 50-75 nmol/L. In the Pooling Project, high 25(OH)D concentrations (≥75 nmol/L) were associated with a non-statistically significant increased risk of kidney cancer for males (OR : 1.52, 95% CI: 0.95, 2.41) compared with 50-<75nmol/L (referent). These results remained similar when the cohort subjects from the ATBC were excluded. 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) compared with 50-<75mol/L, although, there was no statistical evidence of a sex–25(OH)D interaction (P : 0.42). Of note, in the EPIC study the stratified odds ratios for a doubling in circulating 25(OH)D values were 0.79 (95% CI: 0.60-1.05) in never smokers, 0.70 (95% CI: 0.50-0.98) in former smokers but 0.93 (0.69-1.26) in current smokers, suggesting a weaker association in current smokers. In other stratified analyses within the EPIC study, strongest inverse associations with circulating

25(OH)D levels were observed among the obese participants but there was no significant interaction with BMI, smoking, sex or other factors investigated.

5.0. Conclusion

There is no clear explanation for the inconsistent results seen in this review, but differences in study populations and specifically the prevalence of smoking might partially explain it. For instance, EPIC and the CCHS were in European populations, whereas the Pooling Project included populations from Asia, Europe and USA. This review is limited by the small number of studies in the review and the possibility of publication bias. Overall, the existing evidence does not rule out a possible beneficial effect of adequate vitamin D status against kidney cancer development.

References

1. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [INTERNET] 2013 [cited Accessed 20/02/2015]; Available from: http://globocan.iarc.fr

2. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. European urology. 2015; 67(3): 519-30.

3. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nature reviews Urology. 2010; 7(5): 245-57.

4. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nature reviews Cancer. 2014; 14(5): 342-57.

5. Karami S, Boffetta P, Stewart P, Rothman N, Hunting KL, Dosemeci M, et al. Occupational sunlight exposure and risk of renal cell carcinoma. Cancer. 2010; 116(8): 2001-10.

6. Afzal S, Bojesen SE, Nordestgaard BG. Low plasma 25-hydroxyvitamin D and risk of tobacco-related cancer. Clinical chemistry. 2013; 59(5): 771-80.

7. Joh HK, Giovannucci EL, Bertrand KA, Lim S, Cho E. Predicted plasma 25-hydroxyvitamin D and risk of renal cell cancer. Journal of the National Cancer Institute. 2013; 105(10): 726-32.

8. Muller DC, Fanidi A, Midttun O, Steffen A, Dossus L, Boutron-Ruault MC, et al. Circulating 25-hydroxyvitamin D3 in relation to renal cell carcinoma incidence and survival in the EPIC cohort. American journal of epidemiology. 2014; 180(8): 810-20.

9. Gallicchio L, Moore LE, Stevens VL, Ahn J, Albanes D, Hartmuller V, et al. Circulating 25-hydroxyvitamin D and risk of kidney cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American journal of epidemiology. 2010; 172(1): 47-57.

10. Mondul AM, Weinstein SJ, Moy KA, Mannisto S, Albanes D. Vitamin D-binding protein, circulating vitamin D and risk of renal cell carcinoma. International journal of cancer Journal international du cancer. 2014; 134(11): 2699-706.

11. Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. Advances in experimental medicine and biology. 2014; 810: 500-25.

12. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Statistics in medicine. 2008; 27(7): 954-70.

13. Gallicchio L, Helzlsouer KJ, Chow WH, Freedman DM, Hankinson SE, Hartge P, et al. Circulating 25-hydroxyvitamin D and the risk of rarer cancers: Design and methods of the

Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American journal of epidemiology. 2010; 172(1): 10-20.

14. Carter GD, Berry JL, Gunter E, Jones G, Jones JC, Makin HL, et al. Proficiency testing of 25-hydroxyvitamin D (25-OHD) assays. The Journal of steroid biochemistry and molecular biology. 2010; 121(1-2): 176-9.

15. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. The American journal of clinical nutrition. 2012; 95(6): 1357-64.

16. Cutillas-Marco E, Fuertes-Prosper A, Grant WB, Morales-Suarez-Varela M. Vitamin D deficiency in South Europe: effect of smoking and aging. Photodermatology, photoimmunology & photomedicine. 2012; 28(3): 159-61.

Legends for Tables and Figures

Table 1: Studies on circulating 25(OH)D concentration and kidney cancer incidence identified in systematic review

Figure 1: Flow chart of the search for articles on vitamin D status and kidney cancer- PubMed inception to 1st December 2014

Figure 2: Association between circulating 25(OH)D and kidney cancer.

Note for figure 2: *Reference category changed so risk is for a 50% increase in 25(OH)D rather than a 50% decrease **Reference category was changed to <25nmol/L and the top two categories pooled to produce a cut-off point of =>75nmol/L ***ATBC; CLUE; CPS-II; MEC; NYU-WHS; PLCO; SMHS/SWHS **** Matched control data displayed here; combined control data gave a statistically significant effect (OR=0.82 (0.68, 0.99)).

Table 1

Author, year	Country, design	Study name	25(OH)D Measure, ratio±	Method 25(OH)D	Form of 25(OH)D	Cases	Years follow up	Type	Sex	Ratio	LCI	UCI	Contrast (High vs. Low)	Controls matched to cases by:	Data adjustments
Afzal et al. 2013[6]	Denmark, Prospective cohort	CCHS	Plasma 25(OH)D, HR	DiaSorin Liaison TOTAL CLIA	D2/D3	55	28	KC	M/ W	0.75	0.58	0.96	50% reduction in 25(OH)D no vs. yes (referent)	-	Age, sex, smoking, BMI, alcohol, leisure time and work-related physical activity, education.
Gallicchio et al. 2014[9]	Various, Nested Case control	Pooling Project of Rarer Cancers [d]	Serum and Plasma 25(OH)D, OR	DiaSorin Liaison TOTAL CLIA	D2/D3	775	2.2-10.9	RCC	M/ W	1.18	0.63	2.22	≥75 nmol/L vs. <25nmol/L (referent)	Age, sex, race, and season	Education, BMI, smoking status, hypertension, diabetes, height, alcohol
								KC	M	1.46	0.78	2.72			
									W	0.47	0.12	1.90			
Joh et al. 2013[7]	USA, Prospective cohort	NHS	Predicted 25(OH)D [e] HR	Predicted	-	201	22	RCC	W	0.60	0.35	1.02	80 nmol/L vs.56 nmol/L (referent)	-	Age, BMI, smoking status, history of hypertension and diabetes, and parity (F)
										0.70	0.45	1.07	Per 10ng/mL* increment		
		HPFS	Predicted 25(OH)D [e] HR	Predicted	-	207	22	RCC	M	0.66	0.40	1.09	70 nmol/L vs. 50 nmol/L (referent)		
										0.61	0.35	1.04	Per 10ng/mL[b] increment		
Muller et al. 2014[8]	Europe, Nested Case Control	EPIC	Plasma 25(OH)D, OR	LC-MS	D3 *(D2 undetectable)*	560	6.7	RCC	M/ W	0.81	0.65	1.00	Doubling in 25(OH)D yes vs. no (referent)	Country, sex, date of blood collection, birth date	Alcohol intake, BMI, smoking

[a]: quartile dose average of summer and winter quartile values, [b]: 10ng/mL=25nmol/L, [c]: Trial included male smokers only who smoked 5+ cigarettes per day, [d]: Pooling Project: 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); Shanghai Women's Health Study (SWHS), e: Predicted 25(OH)D based on race, UVB radiation at place of residence, leisure physical activity, BMI, dietary vitamin D, supplemental vitamin D, alcohol intake and use of postmenopausal hormone treatments (NHS only).

Note: ±OR=odds ratio, HR=hazard ratio LCI=lower confidence interval (95%), UCI=upper confidence interval (95%) EPIC=European Prospective Investigation into Cancer; NHS=Nurses Health Study, HPFS= Health Professionals Follow-up Study, CCHS=Copenhagen City Heart Study. KC=mixed kidney cancer type, RCC=renal cell carcinoma

Figure 1

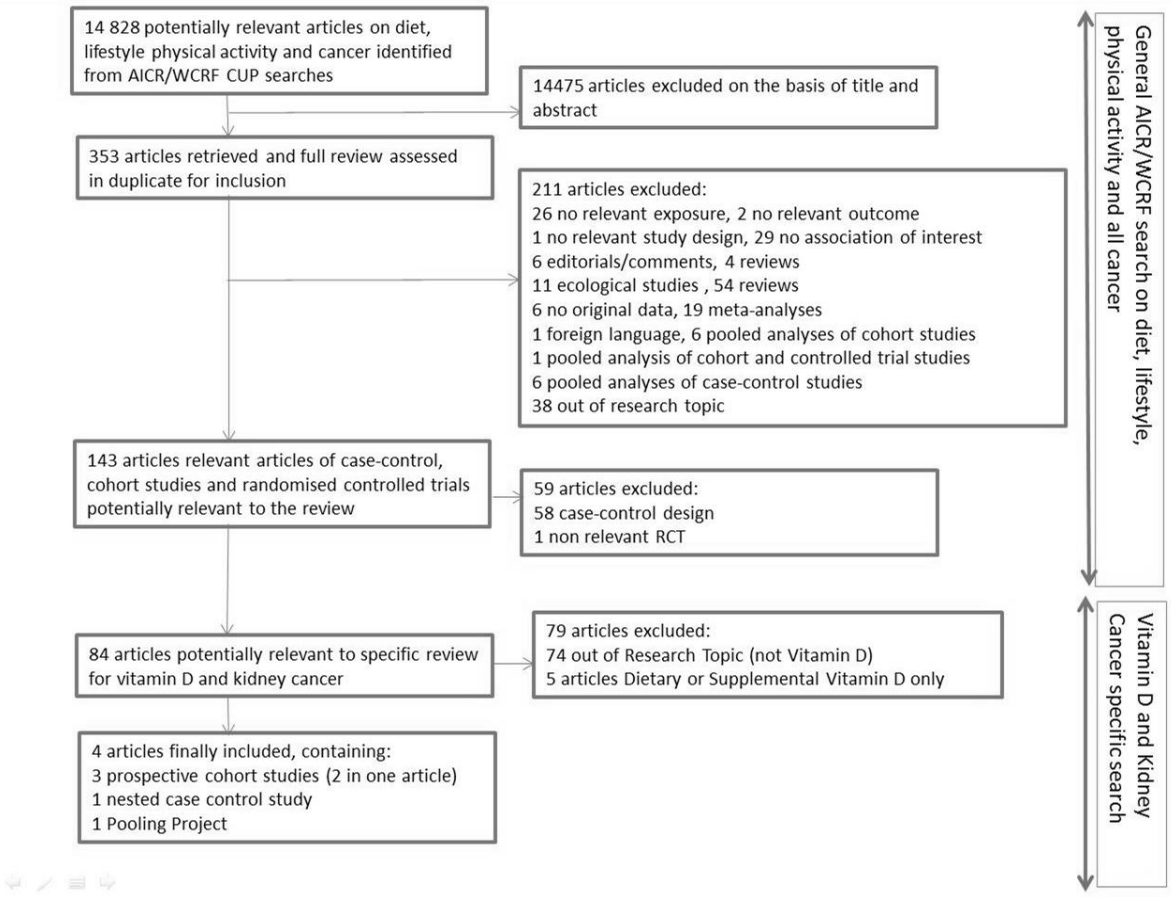
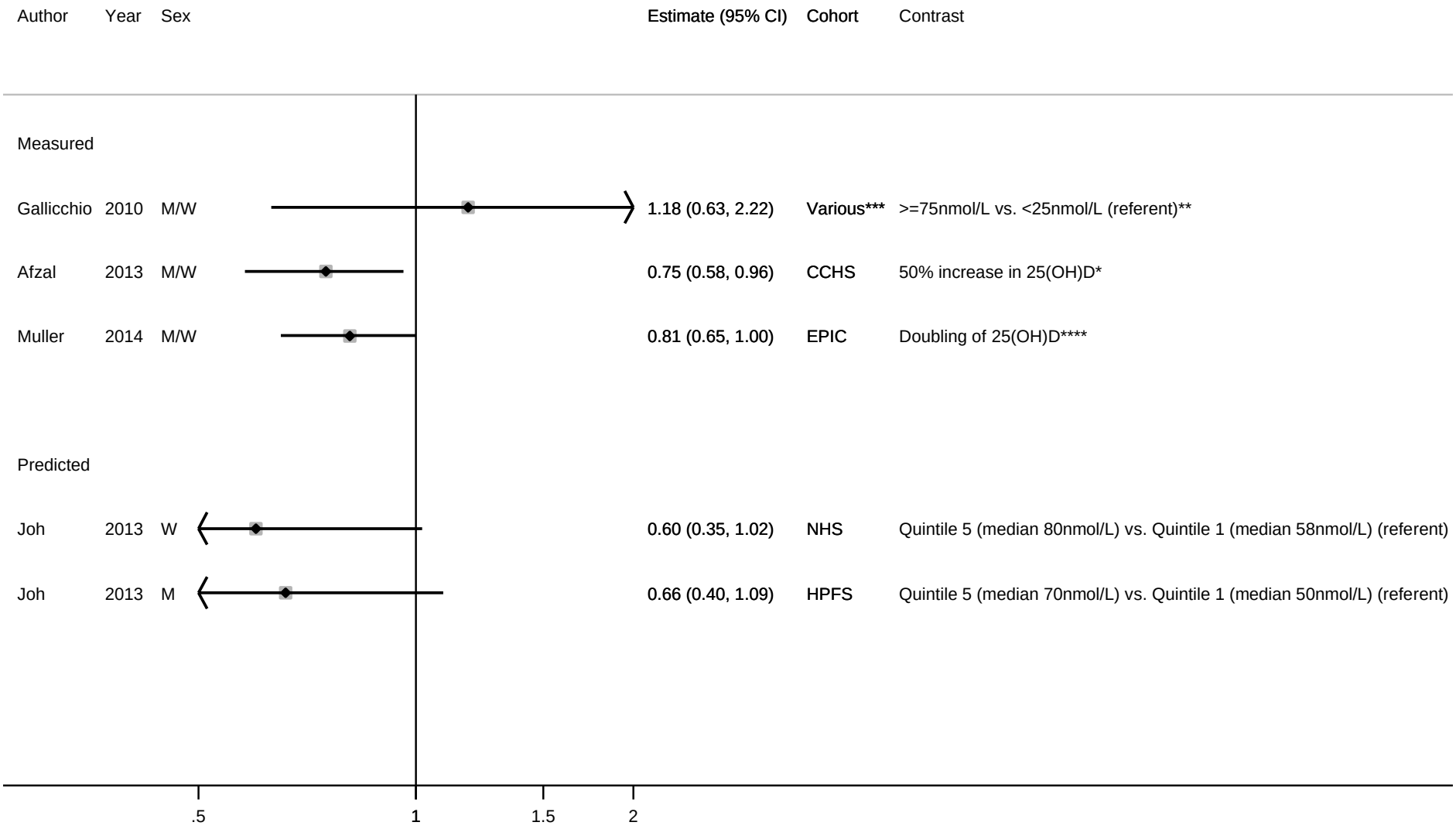

14 828 potentially relevant articles on diet, lifestyle physical activity and cancer identified from AICR/WCRF CUP searches
14475 articles excluded on the basis of title and abstract
353 articles retrieved and full review assessed in duplicate for inclusion
211 articles excluded:
26 no relevant exposure, 2 no relevant outcome
1 no relevant study design, 29 no association of interest
6 editorials/comments, 4 reviews
11 ecological studies , 54 reviews
6 no original data, 19 meta-analyses
1 foreign language, 6 pooled analyses of cohort studies
1 pooled analysis of cohort and controlled trial studies
6 pooled analyses of case-control studies
38 out of research topic
143 articles relevant articles of case-control, cohort studies and randomised controlled trials potentially relevant to the review
59 articles excluded:
58 case-control design
1 non relevant RCT
84 articles potentially relevant to specific review for vitamin D and kidney cancer
79 articles excluded:
74 out of Research Topic (not Vitamin D)
5 articles Dietary or Supplemental Vitamin D only
4 articles finally included, containing:
3 prospective cohort studies (2 in one article)
1 nested case control study
1 Pooling Project
General AICR/WCRF search on diet, lifestyle, physical activity and all cancer
Vitamin D and Kidney Cancer specific search

Figure 2


Author
Year
Sex
Estimate (95% CI)
Cohort
Contrast
Measured
Gallicchio 2010 M/W
1.18 (0.63, 2.22)
Various***
>=75nmol/L vs. <25nmol/L (referent)**
Afzal 2013 M/W
0.75 (0.58, 0.96)
CCHS
50% increase in 25(OH)D*
Muller 2014 M/W
0.81 (0.65, 1.00)
EPIC
Doubling of 25(OH)D****
Predicted
Joh 2013 W
0.60 (0.35, 1.02)
NHS
Quintile 5 (median 80nmol/L) vs. Quintile 1 (median 58nmol/L) (referent)
Joh 2013 M
0.66 (0.40, 1.09)
HPFS
Quintile 5 (median 70nmol/L) vs. Quintile 1 (median 50nmol/L) (referent)
.5
1
1.5
2