Cancer Causes Control (2011) 22:319–340
DOI 10.1007/s10552-010-9706-3

REVIEW ARTICLE

Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose–response meta-analysis

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Received: 20 April 2010 / Accepted: 30 November 2010 / Published online: 4 January 2011

Abstract
Objective We systematically reviewed and meta-analyzed literature examining associations of vitamin D (dietary intake, circulating 25-hydroxy-vitamin-D (25(OH)D), and 1,25-dihydroxy-vitamin-D ($1,25(OH)_2D$) concentrations) with prostate cancer.
Methods We searched over 24,000 papers from seven electronic databases (to October 2010) for exposures related to vitamin D. We conducted dose–response random-effects meta-analyses pooling the log odds ratio (OR) and 95% confidence intervals (CI) per change in natural units of each exposure. The I^2 statistic quantified between-study variation due to heterogeneity.
Results Twenty-five papers were included. In prospective studies, the OR per 1,000 IU increase in dietary intake was 1.14 (6 studies; CI: 0.99, 1.31; $I^2 = 0\%$) for total prostate cancer and 0.93 (3 studies; 0.63, 1.39; $I^2 = 25\%$) for aggressive prostate cancer. Five case–control studies examined dietary intake, but there was a high degree of inconsistency between studies ($I^2 = 49\%$). The OR per 10 ng/mL increase in 25(OH)D was 1.04 (14 studies; 0.99, 1.10; $I^2 = 0\%$) for total prostate cancer and 0.98 (6 studies; 0.84, 1.15; $I^2 = 32\%$) for aggressive prostate cancer. The OR per 10 pg/mL increase in $1,25(OH)_2D$ was 1.00 (7 studies; 0.87, 1.14; $I^2 = 41\%$) for total prostate cancer and 0.86 (2 studies; 0.72, 1.02; $I^2 = 0\%$) for aggressive prostate cancer.
Conclusion Published literature provides little evidence to support a major role of vitamin D in preventing prostate cancer or its progression.

Keywords Vitamin D · Prostatic neoplasms · Review · Meta-analysis · Epidemiology

Electronic supplementary material The online version of this article (doi:10.1007/s10552-010-9706-3) contains supplementary material, which is available to authorized users.

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Introduction

In men, prostate cancer is the most common cancer in the UK and USA, and the fifth most commonly diagnosed cancer worldwide. There were 221,000 prostate cancer deaths worldwide in 2002, and it was the second most common cause of cancer death in UK men [1–3]. Older age, family history of prostate cancer and ethnicity are the only established risk factors and are not modifiable. There is interest in identifying modifiable risk factors, and in this regard, vitamin D has received considerable attention due to its role, observed in vitro, in reducing cell proliferation and promoting differentiation and apoptosis [4, 5]. Some

research, however, has suggested that increased vitamin D exposure may be associated with an increased risk of advanced prostate cancer [6, 7]. It is therefore important to stratify analyses by measures of cancer stage and grade in order to maximize insights from observational epidemiological research.

The main source of vitamin D is via the reaction of the skin to ultra-violet light from the sun [8] with a smaller contribution via the diet. Vitamin D is metabolized by the body to form two circulating vitamin D metabolites: 25(OH)D and $1,25(OH)_2D$. Of the two metabolites, $1,25(OH)_2D$ is several hundred-fold more biologically active than 25(OH)D, but the concentration of 25(OH)D is one hundred to one thousand fold higher [9]. It is thought that there are two different pathways by which vitamin D may be involved in prostate cancer etiology. One pathway is via the two circulating metabolites. The second pathway may be via local action within the prostate. Biological evidence indicates that the prostate produces its own $1,25(OH)_2D$ [10, 11]. Thus, it may be locally produced, not circulating vitamin D that is important. However, since prostate cancers have reduced 1-alphα-hydroxylase activity [12], and therefore reduced ability to locally convert 25(OH)D to $1,25(OH)_2D$, the main source of $1,25(OH)_2D$ to the prostate may be from the circulation [13]. Since serum $1,25(OH)_2D$ concentrations are tightly regulated, even moderate differences in circulating $1,25(OH)_2D$ levels may have an important physiological influence on prostate tissue [13]. In support of this idea, a randomized trial demonstrated a 22% increase in serum $1,25(OH)_2D$ (from 43.3 to 52.9 ng/mL), following $1,25(OH)_2D$ treatment, slowed biochemical progression in recurrent prostate cancer [14]. Both metabolites therefore have chemopreventative potential [4, 5] and both warrant investigation.

The World Cancer Research Fund (WCRF) Expert Report [15] presented a systematic review and meta-analyses of food, nutrition and physical activity in relation to cancer, including prostate cancer. The WCRF review searched the literature up to and including December 2005 and could not draw conclusions from the limited evidence on the effects of vitamin D on prostate cancer. A recent systematic review and meta-analysis [16] concluded that circulating concentrations of 25(OH)D and $1,25(OH)_2D$ were not associated with incident prostate cancer, but dietary intake of vitamin D was not assessed.

We updated the WCRF review, up to October 2010, using the same methodology, an inclusive search strategy and a wide range of search terms. We present a systematic review and meta-analysis of all the published literature investigating associations of vitamin D (dietary intake and circulating concentrations of 25-hydroxy-vitamin-D and 1,25-dihydroxy-vitamin-D) with risk of all prostate cancers and of aggressive prostate cancers. Compared with the most recent previously published review [16], our current review includes 14 studies assessing dietary intake, five additional studies assessing 25(OH)D and two additional studies assessing $1,25(OH)_2D$.

Materials and methods

Literature search

A systematic review of all published literature, including papers, letters, abstracts, reviews, and news articles was carried out up to December 2005 as part of a larger review for WCRF of the associations of food, nutrition, and physical activity with prostate cancer [15]. We updated this review up to June 2009 specifically for exposures related to vitamin D, using identical methodology. The following electronic databases were searched by a dedicated information specialist: Medline, Embase, BIOSIS, ISI, Cochrane Central, LILACS, and DARE. The search used a comprehensive number of terms related to prostate cancer and dietary intake, supplemental intake or circulating levels of all foods and nutrients to ensure high sensitivity (see Supplemental Information for search terms). The searches prior to 2009 also included search terms related to physical activity and anthropometry, but since these were not relevant to vitamin D, they were excluded from the update presented here. A weekly automated Medline alert (search terms: Vitamins, Vitamin D, Dietary Supplements, prostate cancer, prostatic neoplasms) was set up between June 2009 and October 2010 to identify any newly published studies after the main search was completed.

Inclusion and exclusion criteria

Pre-specified inclusion and exclusion criteria were used to determine whether to include papers. Only papers that had been peer-reviewed were included, not abstracts or letters. Papers were included if they presented primary epidemiological data reporting prostate cancer incidence and either: (a) circulating blood plasma or serum concentrations of either of the two main vitamin D metabolites: 25-hydroxy-vitamin-D (25(OH)D) or 1,25-dihydroxy-vitamin-D ($1,25(OH)_2D$) or (b) dietary and/or supplementary intake of vitamin D. Participants must have had the circulating blood vitamin D measurement taken prior to the cancer diagnosis. We excluded any paper that did not present primary data or that were animal or case studies. Papers reporting benign prostatic hyperplasia as the only outcome were excluded. Studies that reported on vitamin D being given in conjunction with chemotherapy were excluded, as the men would have pre-existing prostate cancer, whereas our interest was in the etiological role of vitamin D in carcinogenesis. Similarly,

studies that assessed the effect of vitamin D on prostate cancer survival were excluded. There was no language restriction.

In the first instance, titles and abstracts were assessed for relevance based on the above criteria. Only papers that were clearly ineligible were excluded at this stage. All potentially relevant papers were retrieved in full. All papers that mentioned general diet, vitamins or nutrients in the abstract, not necessarily vitamin D, were retrieved to ensure we did not miss studies that reported a vitamin D result in the paper but not in the abstract. Studies were included if they met the inclusion criteria listed earlier, and presented original data in a format that allowed calculation of the dose–response odds ratio for meta-analysis. Where papers did not present the necessary data for inclusion, authors were contacted requesting further information that would enable us to include their data in our meta-analysis.

Data extraction

Data were extracted using standardized forms by one reviewer and then double-checked by another. Information was extracted on outcome, exposure, and study design. Where data from one study were used in multiple papers, the analysis most relevant to our research question or based on the largest number of cases was used. Where results from a number of multivariable models were presented, the result adjusted for the greater number of potential confounders, but not over-adjusted for other variables potentially downstream of vitamin D exposure on the causal pathway, was selected.

Statistical analysis

In order to combine the estimates from each study in the systematic review, we carried out a dose–response meta-analysis that pools the log odds ratio per change in natural units of each exposure across the studies. Since the outcome (prostate cancer) is relatively rare, log odds, log risk, and log rate will be approximately equal, and effect-estimates are referred to as log odds from here on. This analysis assumes a linear relationship between the exposure and the log odds of the disease. The limited evidence-base (the maximum number of studies that could be included in any one meta-analysis was 14) meant that we were unable to extend our approach to the assessment of nonlinear relationships.

Our exposures were grouped into three categories: dietary intake, blood 25(OH)D, and blood $1,25(OH)_2D$. Units were standardized across studies using the following conversions: a) dietary intake was measured in International Units (IU/day), where 1 IU = 0.025mcg (mcg: micrograms); b) 25(OH)D was measured in nanograms per milliliter (ng/mL), where 1 ng/mL = 2.5 nmol/L (nmol/L: nanomoles per liter); and c) $1,25(OH)_2D$ was measured in picograms per milliliter (pg/mL), where 1 pg/mL = 0.001 ng/mL (1 pg/mL = 0.0024 nmol/L). We examined a dose–response per 1,000 IU increase in dietary intake and per 10 ng/mL or 10 pg/mL for circulating vitamin D.

Since the main source of circulating vitamin D is via sun exposure, vitamin D concentrations will be affected by season of blood draw. Therefore, a record was made of how season of blood draw was accommodated in each study. Where papers used different quantile cut-off points for 25(OH)D depending on season, the cut-offs for spring or winter/spring are presented here. It was expected that the range of exposure was likely to be wider in the summer but potentially inflated compared to differences across the year and narrower in the winter so less precise; thus, spring may act as a compromise. In a sensitivity analysis, we investigated whether effect-estimates were altered when summer or summer/autumn rather than spring or winter/spring quantile cut-offs were used, since this impacts on the calculation of the effect per one unit difference. For $1,25(OH)_2D$, the set of cut-offs that best reflected the median split were presented, as $1,25(OH)_2D$ is less variable by season.

Studies presented their results in different ways. For studies that presented the difference in means between men with and without prostate cancer, the log odds ratio per unit change was calculated using the Chene and Thompson method, which assumes an approximately normal distribution [17]. Where studies presented results as a set of odds ratios for ordinal exposure groups, the Greenland and Longnecker method [18] was used to derive an overall dose–response odds ratio. A detailed description of the application of these methods is given in Rowlands et al. [19].

We used Stata statistical software (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP) and in particular the metan command [20] to carry out fixed- and random-effects meta-analysis. As well as pooling all studies regardless of study design, we separately analyzed results from cohort/nested case–control studies, as cohort/nested studies are less prone to selection bias or reverse causality so are regarded as stronger sources of evidence than case–control studies. We calculated the I^2 value as the percentage of between-study variation due to heterogeneity [21], where 0% indicates no heterogeneity, and larger percentages indicate increasing heterogeneity. We investigated the contribution of study type (cohort/nested case–control versus case–control) to any heterogeneity. We tested the null hypothesis of no heterogeneity using a chi-squared p-value based on the Q-statistic. We have included estimates of the median vitamin D level from each study for comparison. Where we could not

estimate the median, we present the mean level. We assessed small study effects by inspecting funnel plots.

Separate meta-analyses were carried out for total prostate cancer and aggressive prostate cancer, with 'aggressive' prostate cancer defined as advanced stage and/or high grade (as defined in individual papers). If both stage and grade were presented in a paper, we prioritized stage when identifying aggressive cancer. A sensitivity analysis was carried out prioritizing grade instead of stage.

Results

Results of search strategy

The original literature search of all dietary exposures in 2005 identified 15,162 studies. After reviewing the titles and abstracts, 1,038 papers were initially classified as potentially relevant and the full papers retrieved, of which 557 papers were included in the meta-analysis of all exposures and 14 contained information on vitamin D. The update in June 2009 identified a further 9,236 papers, of which 70 were retrieved for further assessment and five contained information on vitamin D. A further two papers were included after contacting the authors for extra information that enabled them to be included in meta-analyses. Four further studies were identified via weekly automated Medline alerts between June 2009 and October 2010. This resulted in 25 studies overall for inclusion in the current meta-analysis (Fig. 1).

Of the 25 included papers, 13 presented data on dietary intake of vitamin D, 14 on 25(OH)D, and 7 on 1,25$(OH)_2$D. The characteristics of these studies are summarized in Table 1. They range in publication date from 1993 to 2010, and the earliest follow-up began in 1964. Seventeen were based in USA. Nine were prospective cohort studies, ten were case–control studies nested within prospective cohort studies, and six were case–control studies. Four studies were limited to white men, the rest were multi-ethnic or did not state a particular ethnicity. Fifteen studies recorded histologically confirmed prostate cancer. Only two studies presented data on both dietary intake and circulating vitamin D concentrations. The key results included in the meta-analyses, as published, are shown in Table 2 arranged by study type and year of publication.

Meta-analysis of dietary intake

There were eleven (six cohort/nested case–control) studies that examined the association of dietary intake of vitamin D (food and/or supplements) with total prostate cancer risk [22–32] and three with aggressive prostate cancer [30, 33, 34]. This gave a total of 8,722 total prostate cancer cases and 3,046 aggressive prostate cancer cases.

Based on cohort/nested case–control studies, the pooled random-effects odds ratio (OR) estimate per 1,000 IU increase in vitamin D intake (95% confidence interval) was 1.14 (0.99, 1.31; $p = 0.08$); whereas for case–control studies, the OR was 0.83 (0.28, 2.43; $p = 0.73$) (Fig. 2). Pooling across all studies gave an OR of 1.07 (0.87, 1.32; $p = 0.51$). There was evidence of between-study heterogeneity for the case–control studies ($I^2 = 49\%$, p for heterogeneity = 0.10) but not for the cohort/nested case–control studies ($I^2 = 0\%$, $p = 0.57$). There were only three studies that investigated aggressive prostate cancer as defined in our methods section [30, 33, 34]. Comparing the highest versus lowest intake group in Park [30] gave an OR of 0.90 (0.69, 1.18), for Kristal [33] gave an OR of 1.13 (0.59, 2.15) and for Kristal [34] gave an OR of 0.82 (0.48, 1.41). Pooling these three studies gave an OR per 1,000 IU increase in vitamin D intake of 0.93 (0.63, 1.39; $p = 0.73$) ($I^2 = 25\%$, $p = 0.27$).

Meta-analysis of circulating 25(OH)D

There were 14 cohort/nested case–control studies that investigated 25(OH) D and total prostate cancer [7, 27, 31, 35–45].This gave a total of 4,353 prostate cancer cases. There were 6 studies [27, 31, 40, 43–45] that included 871 aggressive prostate cancer cases. Overall, the pooled random-effects OR estimate per 10 ng/mL increase in 25(OH)D was 1.04 (0.99, 1.10; $p = 0.12$) (Fig. 3). There was no evidence of heterogeneity across studies ($I^2 = 0\%$, $p = 0.95$). For aggressive prostate cancer, the pooled random-effects OR per 10 ng/mL increase in 25(OH)D was 0.98 (0.84, 1.15; $p = 0.78$), but there was evidence of moderate heterogeneity ($I^2 = 32\%$, $p = 0.19$) (see Supplemental Figure 1).

Meta-analysis of circulating 1,25-dihydroxy-vitamin-D

There were 7 cohort/nested case–control studies that investigated associations of 1,25$(OH)_2$ D [27, 35–40] with total prostate cancer and two with aggressive prostate cancer [27, 40]. This gave a total of 1,361 prostate cancer cases and 696 aggressive prostate cancer cases. Overall, the pooled random-effects OR estimate per 10 pg/mL increase in 1,25$(OH)_2$D was 1.00 (0.87, 1.14; $p = 0.96$) (Fig. 4). There was some evidence of moderate heterogeneity ($I^2 = 41\%$, $p = 0.12$). The study by Corder [35] (the first study published on the associations of 1,25$(OH)_2$ D with prostate cancer) accounts for all of the heterogeneity, and removing this study from the analysis gives an OR of 1.02 (0.93, 1.12; $p = 0.67$). There were only two studies that investigated aggressive prostate cancer [27, 40]. Comparing

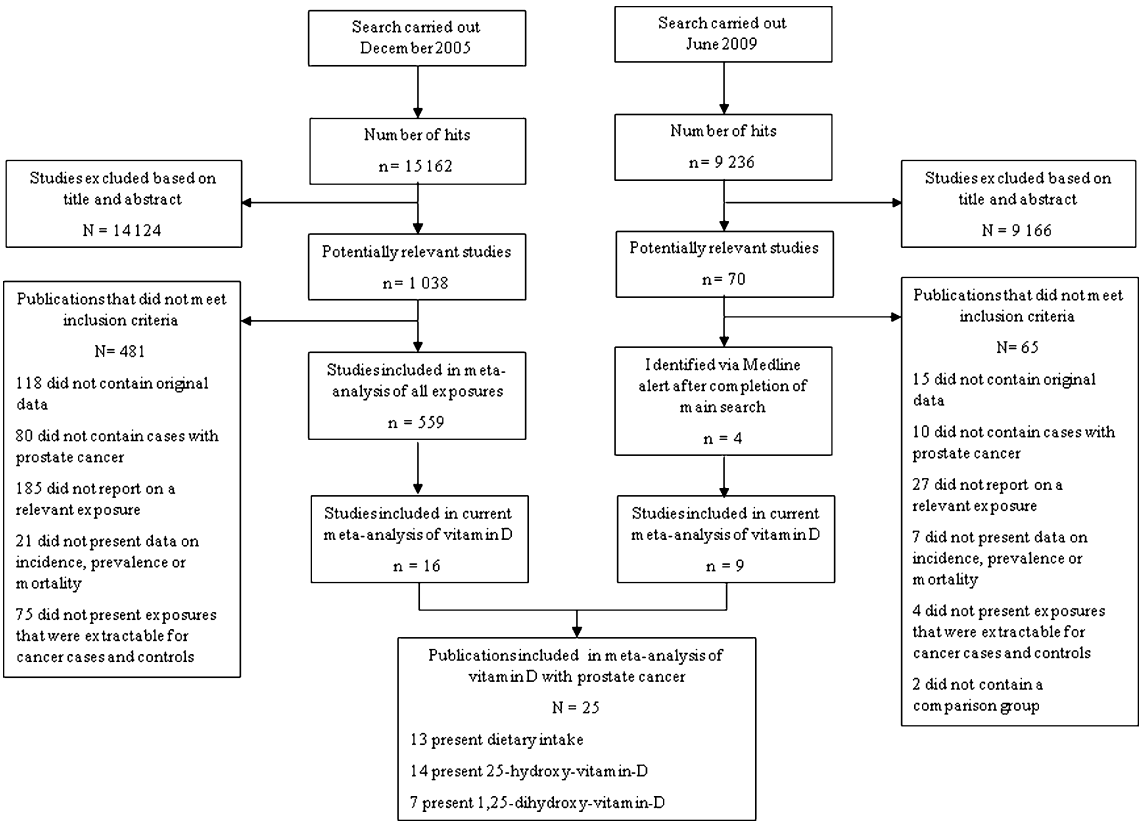

Fig. 1 Flow diagram showing the number of studies included and excluded

the highest versus the lowest level for Platz [27] gave an OR of 0.80 (0.36, 1.82) and for Li [40] gave an OR of 0.73 (0.43, 1.23). The pooled random-effects OR per 10 pg/mL increase in $1,25(OH)_2D$ for these two studies was 0.86 (0.72, 1.02; $p = 0.09$) ($I^2 = 0\%$, $p = 0.77$).

The funnel plots (see Supplemental Figure 2) provide little evidence of small study effects for dietary intake of vitamin D, circulating 25(OH)D, and $1,25(OH)_2$ D. The power to detect effects, however, is limited due to the small number of studies. A sensitivity analysis using summer or summer/autumn rather than spring or winter/spring quantile cut-offs gave the same effect-estimates. A sensitivity analyses using grade instead of stage gave similar pooled ORs.

Discussion

Summary

Our systematic review of more than 24,000 publications identified 25 studies examining the association of prostate cancer incidence with at least one of three indicators of vitamin D: dietary intake and circulating 25(OH)D and $1,25(OH)_2D$. These studies involved 14,174 men with prostate cancer for inclusion in our meta-analyses. There was no evidence of an association between dietary intake of vitamin D and aggressive prostate cancer risk. There was weak statistical evidence of a positive association with total prostate cancer risk if the meta-analysis was restricted to cohort/nested case–control studies (OR per 1,000 IU increase in vitamin D intake = 1.14; 95% CI: 0.99, 1.31; $p = 0.08$). There was no evidence of an association between 25(OH)D and total or aggressive prostate cancer risk. The UK National Diet and Nutrition Survey found that the median daily intake of vitamin D from food sources in men aged 19–64 years was 112 IU (SD = 72; $n = 181$) [46] and that the median concentration of plasma 25(OH)D in men aged 50–64 years was 20.3 ng/mL (SD = 8.5; $n = 190$) [47]. The median vitamin D levels are similar for most studies, apart from for diet (Fig. 2), and there is no discernable relationship between median vitamin D levels and effect sizes (there are too few studies to formally assess this).

There was no evidence of an association of $1,25(OH)_2D$ with total prostate cancer ($p = 0.6$). There was weak evidence of a possible small decreased risk of aggressive prostate cancer with increasing $1,25(OH)_2D$ ($p = 0.09$). This result was based on only two studies, so confidence intervals were wide (0.72, 1.02), but a potentially important protective effect of $1,25(OH)_2D$ cannot be excluded. Genes related to the vitamin D pathway suggest a link with

Table 1 Study characteristics

Author	Study name and location	Outcome and source	Follow-up (cohorts only)	Histologically confirmed	Age range (mean)	Ethnicity
Dietary intake						
Prospective cohort/nested case–control						
Chan [16]	Alpha Tocopherol Beta Carotene Cancer Prevention, South West Finland. Characteristics: Smokers	Incidence of prostate cancer. Source: population-based study Prospective cohort	1985–1988 to 1993	Yes	50–69	N/S
Berndt [15]	Baltimore Longitudinal Study of Aging, Baltimore and Washington DC regions, USA	Incidence and prevalence of prostate cancer. Source: population-based study Prospective cohort	1994–2002. Mean follow-up incident cases 1.1 year, prevalent cases 3.5 years	Yes	46–92 (68)	Mixed
Platz [21]	Health Professionals Follow-up study, USA	Death and incidence of prostate cancer. Source: population-based study Nested case–control	1993–1995 to 1998	No	40–75 (cases 66.5 controls 66.4)	White
Tseng [17]	NHANES I, USA	Incidence of prostate cancer. Source: population-based study Prospective cohort	1982–1984 to 1992	Yes	25–74 (58)	Mixed
Park [18]	Multethnic Cohort Study, California and Hawaii, USA	Incidence of prostate cancer. Source: cancer registry, mortality register, death certificates Prospective cohort	1993–1996 to 2002, average 8 years follow-up	N/S	45–75	Mixed
Ahn [30]	PLCO Cancer Screening Trial, Multicentre, USA	Incidence of prostate cancer. Source: population-based study Nested case–control	1993–July 2001 to October 2001	Yes	Cases 67.8 controls 67.6	Non-hispanic
Kristal [34]	Prostate Cancer Prevention Trial, USA and Canada	Incidence of prostate cancer. Source: population-based study Nested case–control	1994–2003	Yes	≥55 (cases 63.6 controls 62.6)	Mixed
Case–control						
Vlajinac [20]	Central Serbia	Incidence of prostate cancer. Source: incoming patients		Yes	(Cases 70.5 controls 71.5)	N/S
Key [22]	Oxfordshire, West Berkshire and Leeds, UK	Risk of prostate cancer. Source: histopathology records		Yes	Cases 68.1 controls 68.1	White
Deneo-Pellegrini [19]	Montevideo, Uruguay	Incident prostatic adenocarcinomas Source: incoming hospital patients		Yes	40–84 (cases 71.7 controls 69.6)	N/S
Kristal [24]	Washington State, USA	Incidence of prostate cancer. Source: cancer registry		Yes	40–64 (57) (cases 57.35)	Mixed
Tavani [22]	Greater Milan; Pordenone, Gorizia and Latina provinces; urban Naples, Italy	Incidence of prostate cancer. Source: incoming hospital patients		Yes	46–74 (cases 66 controls 63)	N/S
Holt [23]	NCI SEER, USA	Incidence of prostate cancer. Source: cancer registry		Yes	35–74 (cases 61.7 controls 61.1)	Mixed

Table 1 continued

Author	Study name and location	Outcome and source	Follow-up (cohorts only)	Histologically confirmed	Age range (mean)	Ethnicity
Circulating 25 hydroxy vitamin D and/or 1,25 dihydroxyvitamin D[a]						
Prospective cohort/nested case–control						
Corder [32]	Kaiser Permanente Medical Care Program of Northern Carolina, USA	Incidence of prostate cancer. Source: medical care screening plan	1964–1971 to Dec 1987	Yes	White cases 61 Black cases 53	White and black
		Nested case–control				
Braun [26]	Washington County, Maryland, USA	Incidence of prostate cancer. Source: population-based study	1974–1992	No	Cases 58.7 controls 58.7	White
		Prospective cohort				
Nomura [33]	Honolulu Heart Program, Oahu, Hawaii	Incidence of prostate cancer. Source: population-based study	1965–1968 to 1993	Yes	45–68	Japanese-American
		Nested case–control				
Jacobs [27]	Nutritional Prevention Cancer Trial, Eastern USA	Incidence of prostate cancer. Source: clinical trial	1983 and 1989 to 2002	N/S	Cases 68(6.1) controls 67.6 (7.4) at blood draw	White
		Nested case–control				
Platz [21]	Health Professionals Follow-up study, USA	Death and incidence of prostate cancer. Source: population-based study	1993–1995 to 1998	No	40–75 (cases 66.5 controls 66.4)	White
		Nested case–control				
Tuohimaa [7]	Helsinki Heart Study, Janus Project, VIP or MONICA projects, Finland, Norway, Sweden	Death and incidence of prostate cancer. Source: population-based study	1981–1982 and 1973 and 1986, 1990, 1994 to 1997	N/S	Cases 48.4	N/S
		Nested case–control				
Baron [25]	Calcium Trial, USA	Incidence of prostate cancer. Source: clinical trial	1988–1992 to Jan 2003	Yes	<80 (62)	Mixed
		Prospective cohort				
Faupel-Badger [29]	Alpha-tocopherol, Beta-Carotene Prevention Study, South west Finland, smokers	Incidence of prostate cancer. Source: population-based study	1985–1988 for 5–8 years	Yes	50–69	N/S
		Nested case–control				
Freedman [42]	NHANES III, USA	Prostate cancer mortality. Source: population-based study	1988–1994 to 2000	No	>17 (44)	Mixed
		Prospective cohort				
Li [28]	Physicians Health Study, USA. Male physicians	Incidence of prostate cancer. Source: population-based study	1982–2000. Mean length to follow-up 18 years	No	40–84	Mixed
		Nested case–control				
Ahn [30]	PLCO Cancer Screening Trial, Multicentre, USA	Incidence of prostate cancer. Source: population-based study	1993–July 2001 to October 2001	Yes	Cases 67.8 controls 67.6	Non-hispanic
		Nested case–control				
Travis [31]	EPIC. Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	Incidence of prostate cancer. Source: population-based study	1994–2000	No	Cases 61.0 controls 60.5	N/S
		Nested case–control				

Table 1 continued

Author	Study name and location	Outcome and source	Follow-up (cohorts only)	Histologically confirmed	Age range (mean)	Ethnicity
Barnett [44]	Osteoporotic Fractures in Men (MrOS) study, USA	Incident of prostate cancer. Source: population-based study Prospective cohort	2000–2002. Mean follow-up 5.3 years	No	Cases 72.5 controls 73.6	Mixed
Park [45]	Multethnic Cohort Study, California and Hawaii, USA	Incidence of prostate cancer. Source: cancer registry, mortality register, death certificates Prospective cohort	1993–1996 to 2002, average 8 years follow-up	N/S	45–75 (cases 68.9 controls 68.7)	Mixed

Studies ordered by year published

N/S not stated

[a] There were no case–control studies for circulating vitamin D

advanced disease in particular. The actions of $1,25(OH)_2D$ are mediated via the vitamin D receptor gene (VDR) [10], which is usually expressed in cells involved in calcium homeostasis, but it is also expressed in other cells, including the prostate [10]. A recent genetic association study and meta-analysis of 13 studies found an association between three VDR polymorphisms (*Bsm*I, *Apa*I, and *Taq*I) and prostate cancer grade [48]: *Apa*I-*a* and *Bsm*I-*b* increased the risk of a high grade, *Taq*I-*t* was protective. These polymorphisms modulate the activity of the VDR and therefore may modulate a protective effect of $1,25(OH)_2D$ with aggressive prostate cancers. Further large studies with aggressive prostate cancer as an outcome are required to obtain more precise estimates of effect and to mitigate against possible publication bias.

Strengths and limitations

Our systematic review and meta-analysis is the largest and most up-to-date investigation of the worldwide evidence on the association between vitamin D and prostate cancer, updating the WCRF Expert Report [15] which included dietary intake of vitamin D and blood 25(OH)D among the nutritional exposures that were investigated. A dedicated information specialist searched seven databases to ensure a comprehensive search, we used specialist statistical methods to meta-analyze as many observational studies as possible, not just those that reported results in a specific way, and we contacted authors for additional data to increase the number of included studies. These efforts should have considerably reduced the potential for search and inclusion bias in our meta-analysis.

Meta-analyses of observational studies must be interpreted carefully [49]. Results from individual studies that show evidence of an association are more likely to be reported in detail than results that find no evidence [50]. We attempted to minimize this problem by our comprehensive and highly sensitive search strategy and by deriving or estimating missing data from alternative presentations wherever possible to maximize the number of studies that were included. Five studies were excluded due to unusable data. Two presented high versus low categories only [51, 52], two presented *p*-values only [53, 54], and one presented no quantifiable results [55]). Two of the excluded studies present data from studies that were already included in our meta-analysis, albeit on a smaller sample (i.e., Ahn [31, 51] present data from the PLCO Cancer Screening Trial; Platz [27] and Giovannucci [52] present data from the Health Professionals Follow-up study). The three studies that are not represented in our meta-analysis included 4,373 men. Of these five excluded studies, the majority found no evidence of an association between vitamin D and prostate cancer. One excluded

Table 2 Key results

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
Dietary intake						
Prospective studies/nested case–control studies						
Chan [16]	184/27062	FFQ (IU/day[a])	High vs low:		RR:	Age, educational level, BMI, supplement group, smoking habits, energy intake. All smokers
			Q1*: mean 96	NS	1	
			Q2: 148		0.8 (0.5, 1.3)	
			Q3: 196		0.7 (0.5, 1.2)	
			Q4: 252		0.9 (0.6, 1.4)	
			Q5: 368		0.8 (0.5, 1.3)	
Berndt [15]	69/454	FFQ (IU/day[a])	High vs low:		OR:	Age, energy intake
			Q1*: mean 148	21/131	1	
			Q2: mean 248	18/134	0.73 (0.37, 1.47)	
			Q3: mean 376	30/120	1.21 (0.64, 2.3)	
Platz [21]	460/460	FFQ (IU/day)	Mean (SD):		*p*-value 0.31	Energy intake
			Cases 459 (268)			
			Controls 436 (271)			
Tseng [17]	131/3612 (27814 pyrs)	FFQ (IU/day)	High vs low:		RR:	Age, ethnicity, energy intake, area of residence, educational level, sun exposure, physical activity, smoking habits, alcohol consumption
			Q1*: mean 88	34/9391	1	
			Q2: 149	41/9205	0.9 (0.6, 1.3)	
			Q3: 239	56/9218	1.3 (0.8, 2.1)	
Park [18]	4404/82483	FFQ (IU)	High vs low:		RR:	Time since cohort entry, ethnicity, family history, education, BMI, smoking, energy intake
			Q1*: <66	639/NS	1	
			Q2: 66–136	938/NS	1.15 (1.03, 1.28)	
			Q3: 136–256	910/NS	1.06 (0.95, 1.19)	
			Q4: 256–521	940/NS	1.11 (1, 1.24)	
			Q5: >521	977/NS	1.09 (0.98, 1.22)	
Ahn, 2008 [30]	749/781	FFQ (IU)	Mean (SD):		*p*-value 0.67	Total energy intake
			Cases 416 (300)			
			Controls 418 (315)			
Case–control studies						
Vlajinac [20]	101/202	FFQ	High vs low:		OR:	Age, area of residence, hospital admittance, CHO, sugar, retinol, alpha-tocopherol, folic acid, vitamin B12, sodium, potassium, calcium, phosphorous, iron
			Q1*:	32/NS	1	
			Q2:	29/NS	0.81 (0.36, 1.81)	
			Q3: (not stated)	40/NS	0.7 (0.39, 1.24)	

Table 2 continued

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
Key (2293)[c]	328/328	FFQ (IU/day)	High vs low[a]:		OR:	Social class
			Q1*: mean 92	89/82	1	
			Q2: 152	80/82	0.9 (0.58, 1.4)	
			Q3: 208	79/82	0.89 (0.56, 1.4)	
			Q4: 316	80/82	0.89 (0.57, 1.38)	
Deneo-Pellegrini [19]	175/233	FFQ (IU/day)	High vs low:		OR:	Hospital, age, area of residence, urban/rural status, educational level, family history, BMI, energy intake
			Q1*: <75.2	44/58	1	
			Q2: 75.3–148.4	52/49	1.3 (0.7, 2.5)	
			Q3: 148.5–189.7	46/57	0.9 (0.5, 1.8)	
			Q4: >189.8	33/69	0.7 (0.4, 1.2)	
Tavani [22]	1294/1451	FFQ (IU/day[a])	High vs low:		OR:	Age, year of interview, study center, educational level, BMI, smoking habits, physical activity, energy intake, family history
			Q1*: <79.2	199/290	1	
			Q2: 79.2–105.2	260/290	1.22 (0.94, 1.59)	
			Q3: 105.3–127.2	234/291	1.05 (0.8, 1.38)	
			Q4: 127.3–162	293/290	1.27 (0.97, 1.66)	
			Q5: >162	308/90	1.32 (1.01, 1.75)	
Holt [23]	827/787	FFQ and supplements (IU/day[a])	High vs low:		OR:	Age
			Q1*: ≤276	188/190	1	
			Q2: 276.1–516	220/189	1.18 (0.89, 1.57)	
			Q3: 516.1–696	211/189	1.12 (0.85, 1.49)	
			Q4: ≥696.1	180/190	0.95 (0.72, 1.27)	
Dietary intake (advanced/high stage)						
Park [18]	738/82483	Diet and supplements (IU)	High vs low:		RR:	Time since cohort entry, ethnicity, family history, education, BMI, smoking, energy intake
			Q1*: <66	123/NS	1	
			Q2: 66–136	179/NS	1.18 (0.92, 1.51)	
			Q3: 136–256	142/NS	0.88 (0.68, 1.15)	
			Q4: 256–521	150/NS	0.95 (0.73, 1.23)	
			Q5: >521	144/NS	0.9 (0.69, 1.18)	
Kristal [24]	605/592	FFQ (IU/day[a])	High vs low:		OR:	Age, ethnicity, family history, educational level, BMI, number of PSA tests, vegetable intake, supplemental vitamins E, C and zinc, energy intake
			Q1*: <156	NS	1	
			Q2: 156–236		0.71 (0.37, 1.38)	
			Q3: 236–388		0.98 (0.53, 1.83)	
			Q4: 388–568		1.52 (0.84, 2.75)	
			Q5: > 568		1.13 (0.59, 2.15)	

Table 2 continued

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
Dietary intake (high grade)						
Park [18]	823/82483	Diet and supplements (IU)	High vs low:		RR:	Time since cohort entry, ethnicity, family history, education, BMI, smoking, energy intake.
			Q1*: <66	126/NS	1	
			Q2: 66–136	183/NS	1.13 (0.89, 1.44)	
			Q3: 136–256	155/NS	0.89 (0.69, 1.15)	
			Q4: 256–521	175/NS	1.04 (0.81, 1.33)	
			Q5: >521	184/NS	1.04 (0.81, 1.35)	
Kristal [34]	1703/9559	FFQ and supplements (IU/day[a])	High vs low:		OR:	Age, race, treatment arm, BMI
			Q1*: <168	37/1991	1	
			Q2: 168–324	28/2032	0.83 (1.49, 1.39)	
			Q3: 324–584	36/2017	1.06 (0.66, 1.72)	
			Q4: >584	26/1943	0.82 (0.48, 1.41)	
25 Hydroxy vitamin D						
Prospective cohort studies/nested case–control studies						
Corder [32]	59/59	Serum (ng/mL) RIA	Mean difference 1.12	59/59	*p*-value 0.41	Age, race, screened on or near same day of the year
Braun [26]	61/122	Serum (ng/mL) RIA	High vs low:		OR:	Age, ethnicity
			Q1*: <24.1	7/24	1	
			Q2: 24.1–29.5	17/25	2.3 (0.7, 7.8)	
			Q3: 29.6–35.4	16/24	2.3 (0.7, 7.7)	
			Q4: 35.5–41.3	4/25	0.6 (0.1, 2.5)	
			Q5: >41.3	17/24	2.4 (0.8, 8.2)	
Nomura [33]	136/136	Serum (ng/mL) RIA	High vs low:		OR:	Age, month and year of examination
			Q1*: <34	38/34	1	
			Q2: 34–40	35/36	0.8 (0.4, 1.8)	
			Q3: 41–47	30/32	0.8 (0.4, 1.7)	
			Q4: >47	33/34	0.8 (0.4, 1.8)	
Jacobs [27]	83/166	Plasma (ng/mL) RIA	High vs low:		OR:	Age, treatment group, clinic site, BMI, smoking habits
			Q1*: 8.1–25.3	26/58	1	
			Q2: 25.4–32.7	33/49	1.71 (0.68, 4.34)	
			Q3: 32.8–59.7	24/59	0.75 (0.29, 1.91)	

Table 2 continued

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
Platz [21]	460/460	Plasma (ng/mL) RIA	High vs low[b]:		OR:	Age, PSA test prior to blood draw, timing of blood draw, year of test, 1,25(OH)2D, family history, height, physical activity, diabetes, vasectomy, smoking habits, energy intake, red meat, fructose, linolenic acid, vitamin E supplements, selenium supplements, fish, lycopene
			Q1*: mean 13.9	109/114	1	
			Q2: 19.7	115/113	1 (0.67, 1.49)	
			Q3: 24	94/120	0.77 (0.51, 1.15)	
			Q4: 29.9	142/113	1.19 (0.79, 1.79)	
Tuohimaa [7]	622/1451	Serum (ng/mL[a]) RIA	High or low vs middle:		OR:	Age, date, area of residence (country and region), season
			Q1: <7.6	19/NS	1.5 (0.8, 2.7)	
			Q2: 7.6–15.6	169/NS	1.3 (0.98, 1.6)	
			Q3*: 15.6–23.6	229/NS	1	
			Q4: 23.6–31.6	138/NS	1.2 (0.9, 1.5)	
			Q5: >31.6	67/NS	1.7 (1.1, 2.4)	
Baron [25]	70/672	Serum (ng/mL) RIA	High vs low:		OR:	Age, treatment group
			Q1*: <25.2	NS	1	
			Q2: 25.2–34		1.22 (0.66, 2.26)	
			Q3: >34		1.32 (0.72, 2.43)	
Faupel-Badger [29]	296/297	Serum (ng/mL) EIA	High vs low:		OR:	Age, BMI, pack-yrs smoking
			Q1*: <14.79	83/75	1	
			Q2: 14.8–18.82	69/73	0.88 (0.48, 1.61)	
			Q3: 18.83–23.98	57/74	0.59 (0.31, 1.11)	
			Q4: >23.98	87/75	0.89 (0.49, 1.62)	
Freedman [42][c]	47/146578 pyrs	Serum (ng/mL) RIA	High vs low[b]:		RR:	Age, ethnicity, smoking history
			Q1*: mean 19.12	22/NS	1	
			Q2: 36.72	25/NS	0.91 (0.39, 2.14)	
Li [28]	492/664	Plasma (ng/mL) RIA	Low vs high[b]:		OR:	Age, smoking status, race, exercise, mutually adjusted for levels of 25(OH)D and 1,25(OH)2D
			Q1: <18.3	NS	1.01 (0.71, 1.44)	
			Q2: 18.3–24.4		1.26 (0.89, 1.8)	
			Q3: 24.4–31.1		1 (0.71, 1.41)	
			Q4*: >31.1		1	
Ahn [30]	749/781	Serum (ng/mL[a]) RIA	High vs low[b]:		OR:	Age, time since initial screening, year of entry, calendar year of cohort entry, study center, history of diabetes
			Q1*: 3.2–15.4	131/161	1	
			Q2: 15.4–18.8	118/158	0.92 (0.66, 1.30)	
			Q3: 18.8–22.1	175/154	1.39 (1.00, 1.92)	
			Q4: 22.1–26.6	178/154	1.41 (1.02, 1.94)	
			Q5: 26.6–55.2	147/154	1.14 (0.81, 1.60)	

Table 2 continued

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
Travis [31]	652/752	Serum (ng/mL[a]) EIA	High vs low:		OR:	Age, study center, time of day of blood collection, time between collection and last consumption of food and drink, BMI, smoking, alcohol intake, education, marital status, physical activity
			Q1*: 1–16.2	125/151	1	
			Q2: 16.2–20.2	143/150	1.27 (0.89, 1.81)	
			Q3: 20.2–23.6	128/151	1.23 (0.85, 1.76)	
			Q4: 23.6–28.3	114/150	1.06 (0.73, 1.55)	
			Q5: 28.3–65.5	142/150	1.28 (0.88, 1.88)	
Barnett [44]	297/1648	Mass spectrometry	High vs low:		HR:	Age, site, PASE score, family history, statin use, NSAID use
			Q1*: 3.1–19.9	68/411	1	
			Q2: 20–24.9	91/415	1.35 (0.91, 2.01)	
			Q3: 25–29.9	53/406	0.64 (0.41, 1.00)	
			Q4: 30–75.6	85/416	1.20 (0.81, 1.78)	
Park [45]	329/656	Plasma (ng/mL) RIA			OR:	Age at blood draw, fasting hours prior to blood draw, season, family history, BMI, education, physical activity, location, race, birth year, date of blood draw, time
			Q1: <20	53/106	1.10 (0.68, 1.78)	
			Q2: 20–30	98/204	1.04 (0.73, 1.48)	
			Q3*: 30–50	137/287	1	
			Q4: >50	41/59	1.52 (0.92, 2.51)	
25 Hydroxy vitamin D (advanced/high stage)						
Platz [21]	163/163	Plasma (ng/mL) RIA	High vs low[b]:		OR:	Age, PSA test prior to blood draw, timing of blood draw, year of test, 1,25(OH)2D, family history, height, physical activity, diabetes, vasectomy, smoking habits, energy intake, red meat, fructose, linolenic acid, vitamin E supplements, selenium supplements, fish, lycopene
			Q1*: mean 13.9	42/40	1	
			Q2: 19.7	46/37	1.14 (0.54, 2.41)	
			Q3: 24	31/44	0.55 (0.28, 1.12)	
			Q4: 29.9	44/42	0.78 (0.35, 1.73)	
Li [28]	236/332	Plasma (ng/mL) RIA	Low vs high[b]:		OR:	Age, smoking status, race, exercise, mutually adjusted for levels of 25(OH)D and 1,25(OH)2D
			Q1: <18.3	NS	1.27 (0.76, 2.13)	
			Q2: 18.3–24.4		1.33 (0.8, 2.2)	
			Q3: 24.4–31.1		0.97 (0.58, 1.6)	
			Q4*: >31.1		1	
Ahn [30]	137/781	Serum (ng/mL[a]) RIA	High vs low:		OR:	Age, time since initial screening, year of entry, study center, history of diabetes, BMI, physical activity, total calcium intake
			Q1*: 5.12–17	17/157	1	
			Q2: 17–20.5	18/156	1.16 (0.57, 2.35)	
			Q3: 20.5–24.2	37/157	2.09 (1.11, 3.93)	
			Q4: 24.2–28.7	34/156	1.98 (1.05, 3.74)	
			Q5: 28.7–51.8	31/155	1.83 (0.95, 3.5)	

Table 2 continued

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
Travis [31]	122/752	Serum (ng/mL[a]) EIA	High vs low:		OR:	Age, study center, time of day of blood collection, time between collection and last consumption of food and drink, BMI, smoking, alcohol intake, education, marital status, physical activity
			Q1*: 1–16.2	NS/151	1	
			Q2: 16.2–20.2	NS/150	1.61 (0.71, 3.65)	
			Q3: 20.2–23.6	NS/151	1.1 (0.4, 2.99)	
			Q4: 23.6–28.3	NS/150	0.83 (0.32, 2.12)	
			Q5: 28.3–65.5	NS/150	1.13 (0.37, 3.43)	
Park [45][c]	62/123	Plasma (ng/mL) RIA			OR:	Age at blood draw, fasting hours prior to blood draw, season, family history, BMI, education, physical activity, location, race, birth year, date of blood draw, time
			Q1*: <20	12/29	1	
			Q2: 20–30	23/37	1.93 (0.62, 6.04)	
			Q3:30–50	23/48	1.28 (0.41, 3.98)	
			Q4: >50	4/9	1.02 (0.19, 5.61)	
25 Hydroxy vitamin D (high grade)						
Ahn [30]	419/781	Serum (ng/m[a]) RIA	High vs low:		OR:	Age at cohort entry, time since initial screening, year of entry, calendar year of cohort entry, study center, history of diabetes, BMI, physical activity, total calcium intake
			Q1*: 5.12–17	63/157	1	
			Q2: 17–20.5	67/156	1.22 (0.79, 1.86)	
			Q3: 20.5–24.2	117/157	1.92 (1.30, 2.85)	
			Q4: 24.2–28.7	91/156	1.51 (1.00, 2.26)	
			Q5: 28.7–51.8	81/155	1.33 (0.88, 2.01)	
Travis [31]	170/752	Serum (ng/mL[a]) EIA	High vs low:		OR:	Age, study center, time of day of blood collection, time between collection and last consumption of food and drink, BMI, smoking, alcohol intake, education, marital status, physical activity
			Q1*: 1–16.2	NS/151	1	
			Q2: 16.2–20.2	NS/150	0.94 (0.42, 2.10)	
			Q3: 20.2–23.6	NS/151	0.63 (0.26, 1.49)	
			Q4: 23.6–28.3	NS/150	0.86 (0.36, 2.05)	
			Q5: 28.3–65.5	NS/150	0.83 (0.34, 2.07)	
Barnett [44]	151/1502	Serum (ng/mL) mass spectrometry	High vs low:		HR:	Age, site, PASE score, family history, statin use, NSAID use
			Q1*: 3.1–19.9	34/377	1	
			Q2: 20–24.9	48/372	1.42 (0.82, 2.45)	
			Q3: 25–29.9	28/381	0.75 (0.41, 1.39)	
			Q4: 30–75.6	41/372	1.11 (0.64, 1.91)	

Table 2 continued

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
1,25 Dihydroxy vitamin D						
Prospective cohort studies/nested case–control studies						
Braun [26]	61/122	Serum (pg/mL) RIA	High vs low:		OR:	Age, ethnicity
			Q1: < 30.7	10/24	1	
			Q2: 30.7–36.6	11/25	1.1 (0.4, 3.5)	
			Q3: 36.7–42.5	17/24	1.7 (0.6, 5.0)	
			Q4: 42.6–49.8	7/25	0.7 (0.2, 2.4)	
			Q5: >49.8	16/24	1.5 (0.5, 4.5)	
Corder [32]	59/59	Serum (pg/mL) RIA	Mean difference −2.76	59/59	*p*-value 0.004	Age, race, screened on or near same day of the year
Nomura [33]	136/136	Serum (pg/mL) RIA	High vs low:		OR:	Age, month and year of examination
			Q1*: <33	42/40	1	
			Q2: 33–39	32/30	1.0 (0.5, 2.1)	
			Q3: 40–48	28/34	0.7 (0.3, 1.6)	
			Q4: >49	34/32	1.0 (0.5, 2.1)	
Jacobs [27]	83/166	Plasma (pg/mL) RIA	High vs low:		OR:	Age, treatment group, clinic site, BMI, smoking habits
			Q1*: 13.7–27.5	27/56	1	
			Q2: 27.6–32.9	29/54	1.44 (0.59, 3.52)	
			Q3: 33–64.4	27/56	1.06 (0.42, 2.66)	
Platz [21]	460/460	Plasma (pg/mL) RIA	High vs low[b]:			Age, PSA test prior to blood draw, timing of blood draw, year of test, 25(OH)D, family history, height, physical activity, diabetes, vasectomy, smoking habits, energy intake, red meat, fructose, linolenic acid, vitamin E supplements, selenium supplements, fish, lycopene
			Q1*: mean 25.0	102/110	1	
			Q2: 30.0	103/115	0.93 (0.62, 1.39)	
			Q3: 34.3	120/122	1.04 (0.69, 1.56)	
			Q4: 38.8	135/113	1.25 (0.82, 1.9)	
Li [28]	492/664	Plasma (pg/mL) RIA	Low vs high[b]:		OR:	Age, smoking status, race, exercise, mutually adjusted for levels of 25(OH)D and 1,25(OH)2D
			Q1: <24.4	NS	0.91 (0.63, 1.33)	
			Q2: 24.4–32.0		1.35 (0.95, 1.92)	
			Q3: 32.0–39.5		0.94 (0.66, 1.36)	
			Q4*: >39.5		1	

Table 2 continued

Author	Total N cases/ controls or denominator	Measure (units)	Categories (mean or range exposure values)	Number of cases/ controls by exposure category	Key results	Adjustments (including matching variables)
1,25 Dihydroxy vitamin D (advanced/high stage)						
Platz [21]	460/460	Plasma (pg/mL) RIA	High vs low[b]:		OR:	Age, PSA test prior to blood draw, timing of blood draw, year of test, 25(OH)D, family history, height, physical activity, diabetes, vasectomy, smoking habits, energy intake, red meat, fructose, linolenic acid, vitamin E supplements, selenium supplements, fish, lycopene
			Q1*: mean 25.0	35/38	1	
			Q2: 30.0	40/29	1.24 (0.57, 2.73)	
			Q3: 34.3	40/49	0.77 (0.33, 1.76)	
			Q4: 38.8	48/47	0.8 (0.36, 1.82)	
Li [28]	236/332	Plasma (pg/mL) RIA	Low vs high[b]:		OR:	Age, smoking status, race, exercise, mutually adjusted for levels of 25(OH)D and 1,25(OH)2D
			Q1: < 24.4	NS	1.37 (0.81, 2.33)	
			Q2: 24.4–32.0		1.9 (1.14, 3.16)	
			Q3: 32.0–39.5		1.19 (0.69, 2.05)	
			Q4*: > 39.5		1	

NS not stated, *OR* odds ratio, *RR* rate ratio, *FFQ* food frequency questionnaire, *RIA* radioimmunoassay, *EIA* enzyme-linked immunoassay

*Reference category

[a] Units have been standardized. Original units were diet: mcg/day; 25(OH)D: nmol/L

[b] Cutoffs differ by season. Spring is presented here

[c] Author provided extra information not described in publication

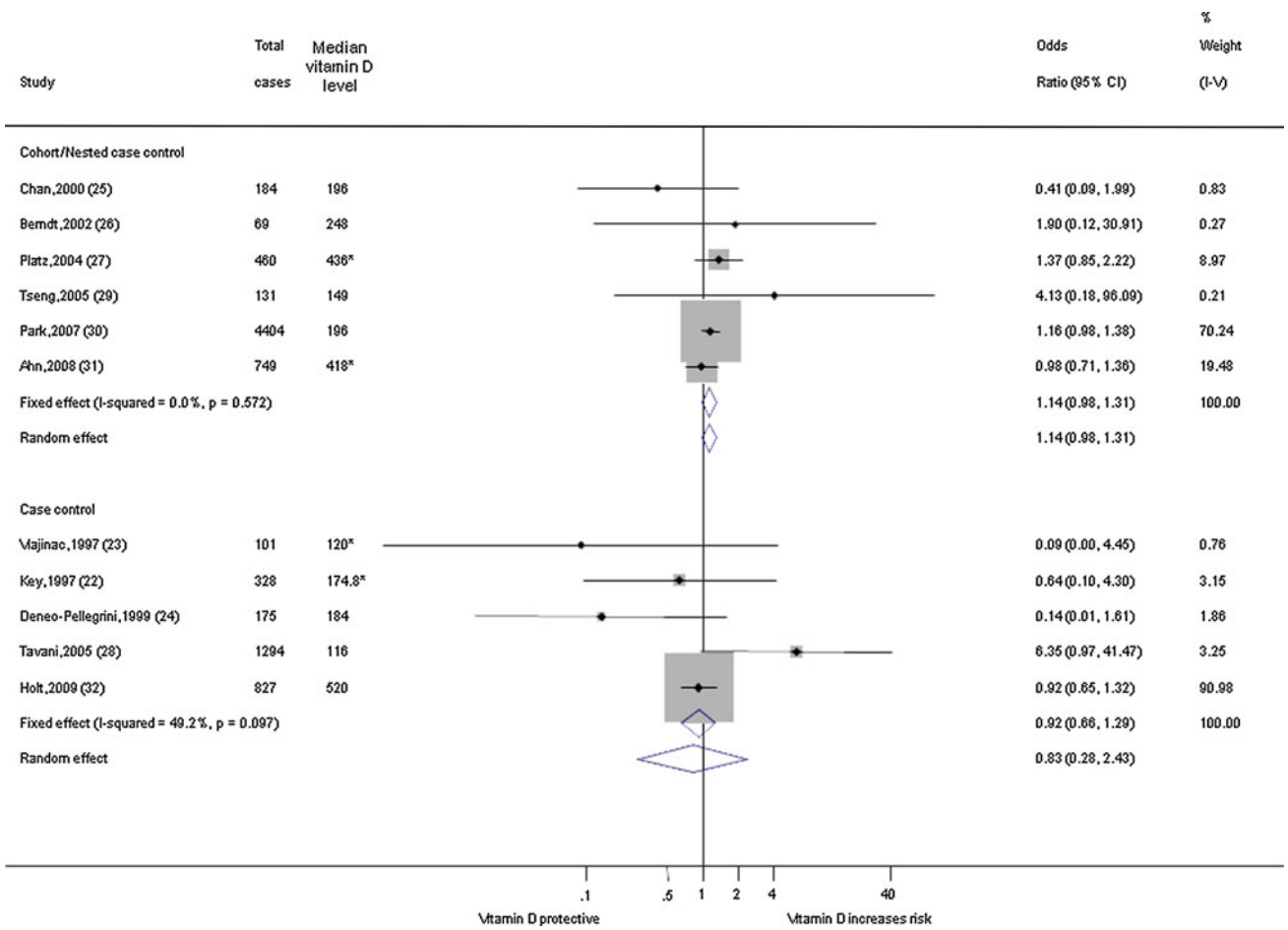

Fig. 2 Forest plot showing the association of dietary intake of vitamin D with total prostate cancer (OR per 100 IU increase). Studies ordered by study design and year of publication. Median vitamin D level is estimated, for the control group only where possible, from the available data. If median could not be estimated, the mean in the control group is given (*). P is *p*-value for heterogeneity. *IV* inverse variance, *CI* confidence interval

study found a 40% reduction in risk of prostate cancer (RR = 0.61; 95% CI: 0.41–0.89; p for trend = 0.05) in men who took >600 IU of supplemental vitamin D compared with men who did not take supplemental vitamin D [51]. Another found that cases had lower mean 25(OH)D than controls ($p = 0.008$), but there was no association with $1,25(OH)_2D$ [53]. Four studies were excluded as they presented data that were used in multiple papers and were therefore already included in our meta-analysis [56–59].

There was evidence of heterogeneity for certain outcomes, but we did not have enough studies to fully investigate the sources of this (apart from stratifying by study design), and therefore, we did not attempt meta-regressions or a priori defined subgroup analyses. There were too few studies to formally assess heterogeneity by factors such as country, age, ethnicity, or dietary intake stratified into diet alone versus diet plus supplements. There were not enough studies to fully investigate associations of vitamin D with aggressive prostate cancer.

Case–control studies investigating dietary intake with total prostate cancer gave variable results ($I^2 = 49\%$), but the cohort studies gave similar results ($I^2 = 0\%$). All of the studies investigating 25(OH)D and $1,25(OH)_2D$ were either cohort studies or prospective case–control studies nested within cohort studies. There was no evidence of heterogeneity within cohort/nested case–control studies investigating 25(OH)D with total prostate cancer or $1,25(OH)_2D$ and aggressive prostate cancer. There was evidence of heterogeneity between studies investigating 25(OH)D and aggressive prostate cancer ($I^2 = 32\%$) and within studies investigating $1,25(OH)_2D$ with total prostate cancer ($I^2 = 41\%$). The latter was explained by one study, Corder [35], which was the only study that presented a mean difference and p-value rather than results by quantiles.

There are several limitations in the analysis of the individual studies that could have influenced our pooled estimates. There may have been too little variation in vitamin D levels [8, 37, 60] to have generated an

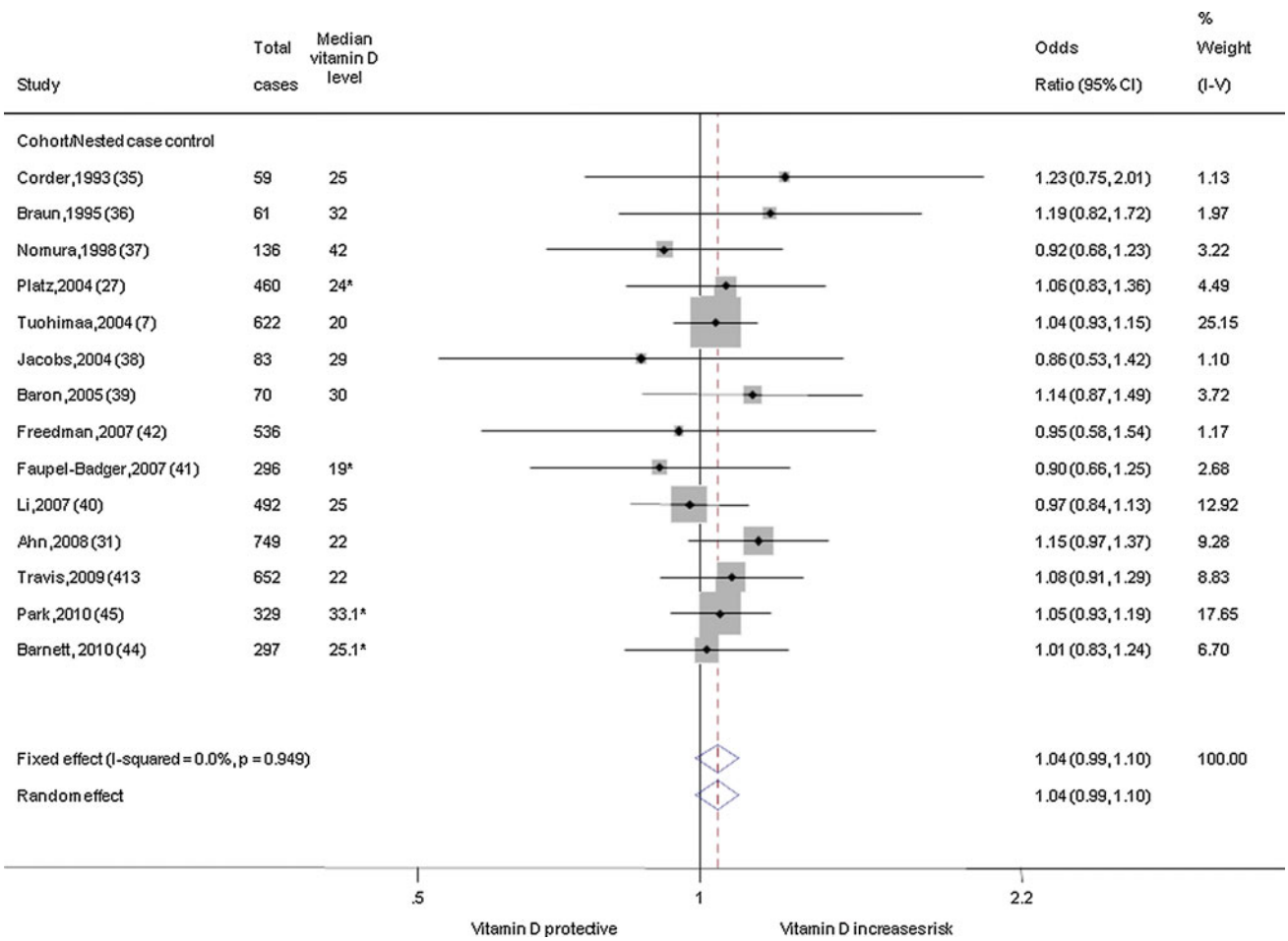

Fig. 3 Forest plot showing the association of circulating 25-hydroxy-vitamin-D with total prostate cancer (OR per 10 ng/mL increase). Studies ordered by study design and year of publication. Median vitamin D level is estimated, for the control group only where possible, from the available data. If median could not be estimated, the mean in the control group is given (*). P is *p*-value for heterogeneity. *IV* inverse variance, *CI* confidence interval

observable association with prostate cancer. Only three studies included only men with a dietary intake greater than the recommended daily allowance of 400 IU in their highest exposure group. If only extremely high or low levels have an effect on prostate carcinogenesis, then vitamin D is unlikely to be an important mechanism in the population. A low intake of vitamin D from food may be compensated for by a high circulating level due to sun exposure. Only one of the included studies adjusted for sun exposure [29], although this made no difference to effect-estimates. Park et al. [30] stratified their analysis by ethnicity, but still found no evidence of association in any ethnic group. Dairy intake may increase the risk of prostate cancer via several mechanisms, including the effects of calcium suppressing production of $1,25(OH)_2D$ [13, 61]. Dairy foods, including milk and margarine, are fortified with vitamin D in the USA and UK but not in the rest of Europe [62]. Dairy intake may therefore be a confounder, although few studies adjust for it. Alternatively, dairy intake may modify the protective effects of vitamin D on prostate cancer by suppressing $1,25(OH)_2D$ synthesis. Other metabolites may interact with the effects of vitamin D on prostate cancer risk. For example, high circulating concentrations of retinol (vitamin A) may increase prostate cancer risk since retinol dominates the proteins required by vitamin D to be active, thus, potentially interfering with any anti-cancer properties of vitamin D [13, 63]. Margarine is fortified with vitamins A and D in the USA and UK. The evidence regarding the association between retinol and prostate cancer is limited [15], but further research may reveal retinol to confound or modify the association of vitamin D and prostate cancer. Only one study adjusted for retinol [23], but we found no studies that investigated an interaction between retinol and vitamin D concentrations.

One of the studies included in the current meta-analysis [7] found a positive association of prostate cancer with both lowest intake of 25(OH)D (OR = 1.5; 95% CI: 0.8–2.7) and highest intake of 25(OH)D (OR = 1.7, 95% CI: 1.1–2.4). Such a nonlinear relationship would be missed in a dose–response meta-analysis, which assumes a

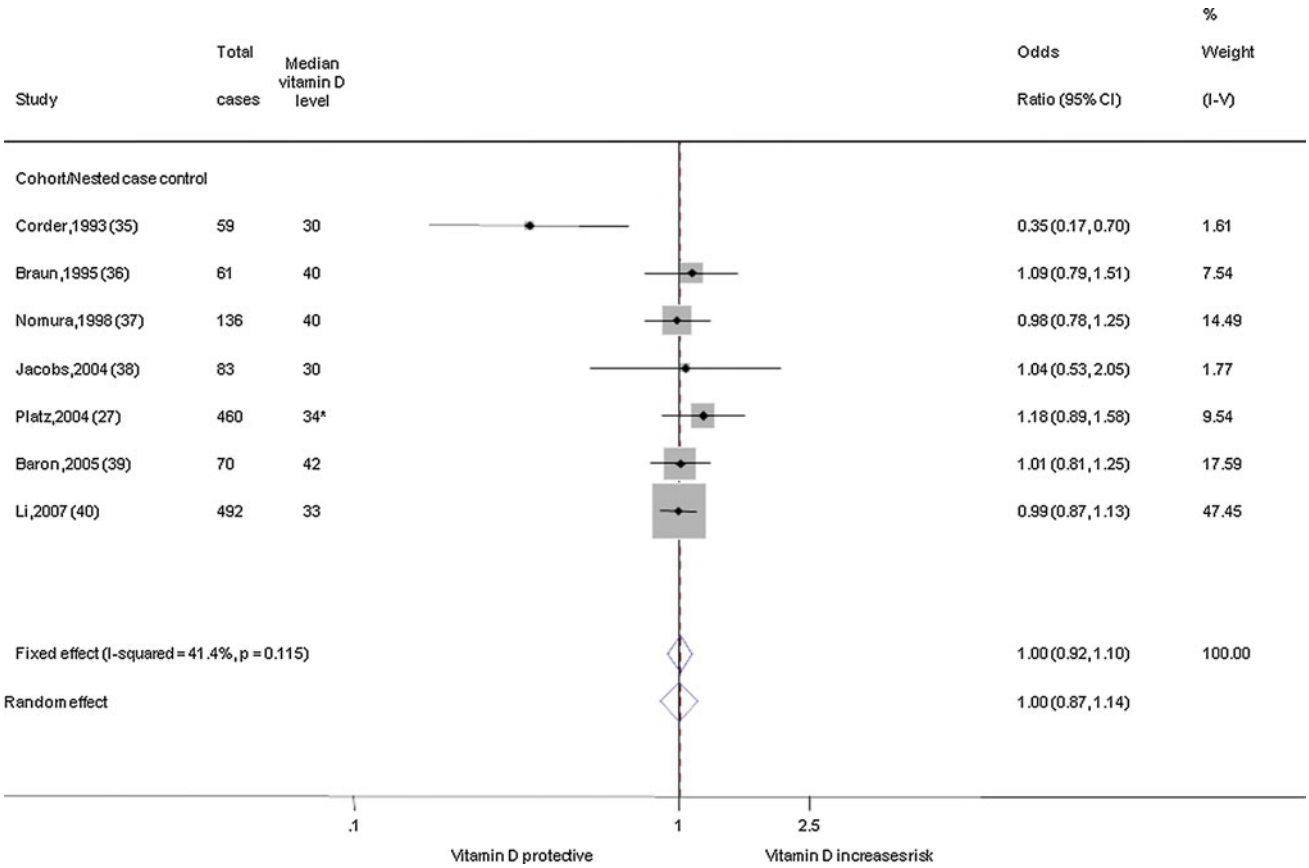

Fig. 4 Forest plot showing the association of circulating 1,25-dihydroxy-vitamin-D with total prostate cancer (OR per 10 pg/mL increase). Studies ordered by study design and year of publication. Median vitamin D level is estimated, for the control group only where possible, from the available data. If median could not be estimated, the mean in the control group is given (*). P is *p*-value for heterogeneity. *IV* inverse variance, *CI* confidence interval

linear relationship. As described in the methods, there were too few studies to examine whether there was a nonlinear relationship. A review by Yin et al. [16] concluded that four of ten included studies showed a possible U-shaped association [7, 27, 41, 59] but that overall there was no consistent pattern.

Studies uniformly used only a single sample of vitamin D assessed in adulthood. Platz et al. [27] reported an intraclass correlation of 0.70 for measurements of 25(OH)D taken approximately 3 years apart, indicating that a single measure has good validity for adulthood exposure. However, it may be childhood or lifetime exposure that is important. This is a limitation of both individual study design and the attempt to investigate vitamin D concentrations with prostate cancer at all. Serum stored for over 40 years was found to have the same predictive power as serum stored for up to 2 years, indicating that studies could explore associations of circulating vitamin D with adult disease risk using stored childhood serum [64]. Vitamin D was measured using radioimmunoassay in all but two studies that used enzyme-linked immunoassays [41, 43], so we could not investigate whether assay type was a source of heterogeneity across studies. Radioimmunoassay methods have differing sensitivities and specificities, which may render results incomparable. Most studies were conducted in the PSA-testing era, during which increasingly low volume, low-grade cancers are being detected. The observed weak positive associations with vitamin D intake or circulating concentrations may therefore reflect the fact that more affluent men tend to have PSA tests and be diagnosed with prostate cancer, and such men may have higher vitamin D exposure [65]. Thus, a true protective effect of vitamin D on prostate cancer could be masked by PSA detection bias related to socio-economic differentials on PSA screening. More affluent men may also be more healthy in general. Studies have suggested an inverse association between vitamin D and PSA level [66, 67], so studies based on cases detected by PSA testing may also generate biased results because of PSA-based misclassification of prostate cancer status that is related to the

degree of exposure. Alternatively, associations may differ for clinically relevant compared with screen-detected cancers.

Previous reviews

Huncharek et al. [68] published a systematic review and meta-analysis of 6 studies investigating dietary intake of vitamin D which found that the pooled relative risk was 1.16 (0.98, 1.38; $p = 0.37$) when comparing the highest intake category versus the lowest intake category. Of these 6 studies, 4 were included in our analysis of total prostate cancer [23, 24, 28, 29]. One study [33] was included in our analysis of aggressive prostate cancer only. One study included in Huncharek et al. did not define the range of exposure clearly so was not included in our meta-analysis [54]. We additionally included seven studies [22, 25, 27, 30–32, 34]. For one remaining study [26], it is unclear whether the study was included in Huncharek's meta-analysis, although it was discussed in the paper. In line with our previous publication [6] and the upper confidence limit from our meta-analysis, the Huncharek review cannot exclude the possibility that high intake of vitamin D increases prostate cancer risk. The Huncharek review did not investigate circulating concentrations of vitamin D.

Gupta et al. [69] published a review, without a formal meta-analysis, of the epidemiological literature investigating vitamin D and prostate cancer risk. They concluded that dietary intake of vitamin D did not appear to be protective, suggesting this null finding was due to intake not being high enough and reported that studies investigating 25(OH)D and prostate cancer risk gave conflicting results. These results are in line with our current study.

Yin et al. [16] published a systematic review and dose–response meta-analysis of ten studies investigating associations of 25(OH)D and $1,25(OH)_2D$ concentrations with incidence of prostate cancer, finding a pooled OR per 10 ng/mL of 1.03 (0.96, 1.11; $p = 0.36$) for 25(OH)D and a pooled OR per 10 pg/mL increase in circulating $1,25(OH)_2D$ of 1.04 (0.94–1.16). These results are in line with the current review and used similar methods. We included five extra studies assessing 25(OH)D [35, 40, 42, 44, 45], two extra studies assessing $1,25(OH)_2D$ [35, 40], and excluded one study [59] as we used a result from another paper that included the same cohort of men but presented the results in greater detail [7]. The Yin review did not investigate dietary intake, nor did they investigate associations of vitamin D with aggressive prostate cancer.

A recent dose–response meta-analysis by Gandini et al. [70] included only one extra study compared with the Yin review [40]. The Gandini review did not investigate dietary intake or circulating concentrations of $1,25(OH)_2D$, nor did they investigate associations of vitamin D with aggressive prostate cancer.

Conclusions

There is little evidence from the current epidemiological literature that increased dietary vitamin D or circulating concentrations of 25(OH)D were importantly associated with risk of prostate cancer. There was only weak evidence that increased circulating concentrations of $1,25(OH)_2D$ were associated with a decreased risk of aggressive prostate cancer, based on two studies only and with wide confidence intervals in the pooled estimate. More high-quality large-scale prospective observational studies are required, particularly including more aggressive prostate cancers. We suggest that future studies should analyze repeat measurements of vitamin D (to reduce exposure measurement error), possibly from cohort studies with long-term stored sera/plasma and ideally assess both dietary intake and circulating concentrations. Analyses need to account for sun exposure and dairy intake. Possible effect modifiers, such as vitamin D pathway genetic polymorphisms and retinol concentrations, should also be investigated.

Acknowledgments We would like to thank Margaret Burke, dedicated information specialist, for carrying out the systematic literature review in the electronic databases. This work was supported by Cancer Research UK (C31211/A10095 to RG, RMM, CM, WDF) and the World Cancer Research Fund (2006/15 to RMM, CM and WDF). The original Expert Report was funded by the World Cancer Research Fund (Davey Smith, G., Sterne, J.A.C., Bain, C. Burke, M., Donovan, J., Ebrahim, S., Egger, M., Emmett, P., Gunnell, D., Hooper, L., Ness, A. and Oliver, S. Systematic review of associations between diet, nutrition, physical activity and bladder, prostate and kidney cancer. World Cancer Research Fund. 1 September 2003–30 June 2006.).

References

1. Cancer Research UK (2008) Commonly diagnosed cancers worldwide
2. Cancer Research UK (2008) CancerStats report Prostate Cancer—UK, Cancer Research UK
3. Office for National Statistics (2007) Cancer incidence and mortality in the United Kingdom 2002–2004. Office for National Statistics
4. Jones G, Strugnell SA, DeLuca HF (1998) Current understanding of the molecular actions of vitamin D. Physiol Rev 78(4): 1193–1231
5. Chen TC, Holick MF (2003) Vitamin D and prostate cancer prevention and treatment. Trends Endocrinol Metabol 14(9): 423–430
6. Gilbert R, Metcalfe C, Oliver SE et al (2009) Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis. Int J Cancer 125(6): 1414–1423

7. Tuohimaa P, Tenkanen L, Ahonen M et al (2004) Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer 108:104–108
8. Schwartz GG (2005) Vitamin D and the epidemiology of prostate cancer. Semin Dial 18(4):276–289
9. Ali MM, Vaidya V (2007) Vitamin D and cancer. J Cancer Res Ther 3(4):225–230
10. Peehl DM, Feldman D (2003) The role of vitamin D and retinoids in controlling prostate cancer progression. Endocr Relat Cancer 10(2):131–140
11. Young MV, Schwartz GG, Wang L et al (2004) The prostate 25-hydroxyvitamin D-1{alpha}-hydroxylase is not influenced by parathyroid hormone and calcium: implications for prostate cancer chemoprevention by vitamin D. Carcinogenesis 25(6): 967–971
12. Chen TC, Wang L, Whitlatch LW, Flanagan JN, Holick MF (2003) Prostatic 25-hydroxyvitamin D-1alpha-hydroxylase and its implication in prostate cancer. J Cell Biochem 88(2):315–322
13. Giovannucci E (2005) The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control 16(2):83–95
14. Gross MD (2005) Vitamin D and calcium in the prevention of prostate and colon cancer: new approaches for the identification of needs. J Nutr 135(2):326–331
15. World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington, DC
16. Yin L, Raum E, Haug U, Arndt V, Brenner H (2009) Meta-analysis of longitudinal studies: serum vitamin D and prostate cancer risk. Cancer Epidemiol 33:435–445
17. Chene G, Thompson SG (1996) Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. Am J Epidemiol 144(6):610–621
18. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135(11):1301–1309
19. Rowlands MA, Gunnell D, Harris R, Vatten LJ, Holly JM, Martin RM (2009) Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. Int J Cancer 124(10):2416–2429
20. Harris RJ, Deeks JJ, Altman DG, Bradburn MJ, Harbord R, Sterne JAC (2008) Metan: fixed- and random-effects meta-analysis. Stata J 8(1):3–28
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
22. Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT (1997) A case-control study of diet and prostate cancer. Br J Cancer 76(5):678–687
23. Vlajinac HD, Marinkovic JM, Ilic MD, Kocev NI (1997) Diet and prostate cancer: a case-control study. Eur J Cancer 33(1):101–107
24. Deneo-Pellegrini H, De Stefani E, Ronco A, Mendilaharsu M (1999) Foods, nutrients and prostate cancer: a case-control study in Uruguay. Br J Cancer 80(3–4):591–597
25. Chan JM, Pietinen P, Virtanen M et al (2000) Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus (Finland). Cancer Causes Control 11(9): 859–867
26. Berndt SI, Carter HB, Landis PK et al (2002) Calcium intake and prostate cancer risk in a long-term aging study: the baltimore longitudinal study of aging. Urology 60(6):1118–1123
27. Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci E (2004) Plasma 1, 25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. Cancer Causes Control 15(3):255–265
28. Tavani A, Bertuccio P, Bosetti C et al (2005) Dietary intake of calcium, vitamin D, phosphorus and the risk of prostate cancer. Eur Urol 48(1):27–33
29. Tseng M, Breslow RA, Graubard BI, Ziegler RG (2005) Dairy, calcium, and vitamin D intakes and prostate cancer risk in the national health and nutrition examination epidemiologic follow-up study cohort. Am J Clin Nutr 81(5):1147–1154
30. Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN (2007) Calcium, vitamin D, and dairy product intake and prostate cancer risk: the Multiethnic Cohort Study. Am J Epidemiol 166(11):1259–1269
31. Ahn J, Peters U, Albanes D et al (2008) Serum vitamin D concentration and prostate cancer risk: a nested case-control study. J Natl Cancer Inst 100(11):796–804
32. Holt SK, Kwon EM, Peters U, Ostrander EA, Stanford JL (2009) Vitamin D pathway gene variants and prostate cancer risk. Cancer Epidemiol Biomark Prev 18(6):1929–1933
33. Kristal AR, Cohen JH, Qu P, Stanford JL (2002) Associations of energy, fat, calcium, and vitamin D with prostate cancer risk. Cancer Epidemiol Biomark Prev 11(8):719–725
34. Kristal AR, Arnold KB, Neuhouser ML et al (2010) Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol 172(5):566–577
35. Corder EH, Guess HA, Hulka BS et al (1993) Vitamin D and prostate cancer: a prediagnostic study with stored sera. Cancer Epidemiol Biomark Prev 2(5):467–472
36. Braun MM, Helzlsouer KJ, Hollis BW, Comstock GW (1995) Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). Cancer Causes Control 6(3):235–239
37. Nomura AM, Stemmermann GN, Lee J et al (1998) Serum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States). Cancer Causes Control 9(4):425–432
38. Jacobs ET, Giuliano AR, Martinez ME, Hollis BW, Reid ME, Marshall JR (2004) Plasma levels of 25-hydroxyvitamin D, 1, 25-dihydroxyvitamin D and the risk of prostate cancer. J Steroid Biochem Mol Biol 89–90(1–5):533–537
39. Baron JA, Beach M, Wallace K et al (2005) Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiol Biomark Prev 14(3):586–589
40. Li H, Stampfer MJ, Hollis JB et al (2007) A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. PLoS Med Public Libr Sci 4(3):e103
41. Faupel-Badger JM, Diaw L, Albanes D, Virtamo J, Woodson K, Tangrea JA (2007) Lack of association between serum levels of 25-Hydroxyvitamin D and the subsequent risk of prostate cancer in finnish men. Cancer Epidemiol Biomark Prev 16(12): 2784–2786
42. Freedman DM, Looker AC, Chang SC, Graubard BI (2007) Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 99(21):1594–1602
43. Travis RC, Crowe FL, Allen NE et al (2009) Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European prospective investigation into cancer and nutrition (EPIC). Am J Epidemiol 169(10):1223–1232
44. Barnett CM, Nielson CM, Shannon J et al. (2010) Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men. Cancer Causes and Control online
45. Park SY, Cooney RV, Wilkens LR, Murphy SP, Henderson BE, Kolonel LN (2010) Plasma 25-hydroxyvitamin D and prostate cancer risk: the multiethnic cohort. Eur J Cancer 46(5):932–936
46. Bates B, Lennox A, Swan G (2010) National diet and nutrition survey: headline results from year 1 of the rolling programme

(2008/2009). Food Standards Agency, Department of Health, London
47. Ruston D, Henderson L, Gregory J et al. (2004) The national diet and nutrition survey: adults aged 19–64 years. Volume 4: nutritional status (anthropometry and blood analytes), blood pressure and physical activity. TSO, London
48. Chen L, Davey SG, Evans DM et al (2009) Genetic variants in the vitamin d receptor are associated with advanced prostate cancer at diagnosis: findings from the prostate testing for cancer and treatment study and a systematic review. Cancer Epidemiol Biomark Prev 18(11):2874–2881
49. Egger M, Schneider M, Davey SG (1998) Spurious precision? Meta-analysis of observational studies. BMJ 316(7125):140–144
50. Bekkering GE, Harris RJ, Thomas S et al (2008) How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol 167(9):1017–1026
51. Ahn J, Albanes D, Peters U et al (2007) Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomark Prev 16(12):2623–2630
52. Giovannucci E, Rimm EB, Wolk A et al (1998) Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 58(3):442–447
53. Galic J, Simunovic D (2008) Prostate disease prevalence with epidemiological and hormonal analysis in randomly selected male population in Croatia. Coll Antropol 32(4):1195–1202
54. Chan JM, Giovannucci E, Andersson SO, Yuen J, Adami HO, Wolk A (1998) Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). Cancer Causes Control 9(6):559–566
55. Rodriguez C, McCullough ML, Mondul AM et al (2003) Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. Cancer Epidemiol Biomark Prev 12(7):597–603
56. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P (2000) Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control 11(9): 847–852
57. Gann PH, Ma J, Hennekens CH, Hollis BW, Haddad JG, Stampfer MJ (1996) Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. Cancer Epidemiol Biomark Prev 5(2):121–126
58. Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Hollis BW, Giovannucci E (2007) Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D, and prostate cancer risk. Prostate 67(9):911–923
59. Tuohimaa P, Tenkanen L, Syvala H et al (2007) Interaction of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. Cancer Epidemiol Biomark Prev 16(2): 302–307
60. Polek TC, Weigel NL (2002) Vitamin D and prostate cancer. J Androl 23(1):9–17
61. Gao X, LaValley MP, Tucker KL (2005) Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. J Natl Cancer Inst 97(23):1768–1777
62. Calvo MS, Whiting SJ, Barton CN (2005) Vitamin D intake: a global perspective of current status. J Nutr 135(2):310–316
63. Rohde CM, Manatt M, Clagett-Dame M, DeLuca HF (1999) Vitamin A antagonizes the action of vitamin D in rats. J Nutr 129(12):2246–2250
64. Bodnar LM, Catov JM, Wisner KL, Klebanoff MA (2009) Racial and seasonal differences in 25-hydroxyvitamin D detected in maternal sera frozen for over 40 years. Br J Nutr 101:278–284
65. Ross LE, Coates RJ, Breen N, Uhler RJ, Potosky AL, Blackman D (2004) Prostate-specific antigen test use reported in the 2000 national health interview survey. Prev Med 38(6):732–744
66. Weinrich S, Ellison G, Weinrich M, Ross KS, Reis-Starr C (2002) Low sun exposure and elevated serum prostate specific antigen in African American and Caucasian men. Am J Health Stud 17:148–150
67. Gross C, Stamey T, Hancock S, Feldman D (1998) Treatment of early recurrent prostate cancer with 1, 25-dihydroxyvitamin D3 (calcitriol). J Urol 159(6):2035–2039
68. Huncharek M, Muscat J, Kupelnick B (2008) Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26, 769 cases from 45 observational studies. Nutr Cancer 60(4):421–441
69. Gupta D, Lammersfeld CA, Trukova K, Lis CG (2009) Vitamin D and prostate cancer risk: a review of the epidemiological literature. Prostate Cancer Prostatic Dis 12(3):215–226
70. Gandini S, Boniol M, Haukka J et al. (2010) Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer. doi:10.1002/ijc.25439