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Meta-analysis of longitudinal studies: Serum vitamin D and prostate cancer risk☆

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ABSTRACT

Aim: To review and summarize evidence from longitudinal studies on the association between serum 25-hydroxyvitamin D (25(OH)D) and the risk of prostate cancer (PC). *Methods*: Relevant prospective cohort studies and nested case-control studies published until July 2009 were identified by systematically searching Ovid Medline, EMBASE, and ISI Web of Knowledge databases and by cross-referencing. The following data were extracted in a standardized manner from eligible studies: first author, publication year, country, study design, characteristics of the study population, duration of follow-up, PC incidence/PC mortality according to serum vitamin D status and the respective risk ratios, and covariates adjusted for in the analysis. Due to the heterogeneity of studies in categorizing serum vitamin D levels, all results were recalculated for an increase in serum 25(OH)D by 10 ng/ml. Summary odds ratios (ORs) were calculated using meta-analysis methods. *Results*: Overall, eleven original articles were included, ten of which reported on the association between serum vitamin D levels and PC incidence and one article reported on the association with PC mortality. Meta-analysis of studies on PC incidence resulted in a summary OR (95% confidence interval, CI) of 1.03 (0.96–1.11) associated with an increase of 25(OH)D by 10 ng/ml ($P = 0.362$). No indication for heterogeneity and publication bias was found. *Conclusions*: According to available evidence from longitudinal studies, serum 25(OH)D is not associated with PC incidence.

1. Introduction

Although vitamin D is obtained from diet and dietary supplements, the main source for vitamin D is its production in the skin under the influence of solar ultraviolet B (UV-B) radiation. In 1980, Garland and Garland [1] hypothesized that lower levels of vitamin D resulting from much weaker UV-B radiation at higher latitudes may account for the striking geographical pattern of cancer mortality. Partly stimulated by this article, further research in this area has been conducted in observational studies over the past 20 years [2–4]. In 1990, Schwartz and Hulka [5] were the first to hypothesize that vitamin D deficiency may be a risk factor for prostate cancer (PC). Ecological studies consistently found an association between increasing latitude and increasing risk of PC [6–12], except for a study performed in Spain [13]. However, vitamin D intake was found to be unrelated to PC risk [14–16]. In recent years, several studies have addressed the association of PC risk and serum 25(OH)D levels, representing an integrated measure for vitamin D from diet, dietary supplements, and skin production [17]. The aim of this study was to provide a review and meta-analysis of longitudinal epidemiological studies evaluating the association between serum 25(OH)D levels and PC risk using methods for comprehensive trend estimation from summarized dose-response data [18].

2. Materials and methods

2.1. Identification of studies and study selection

A literature search was conducted to identify prospective cohort studies and nested case-control studies assessing the association between serum levels of 25(OH)D and PC incidence or mortality. We searched Ovid (Ovid Technologies, Inc., New York, 1950–June 28, 2009), EMBASE (Elsevier, Amsterdam, the Netherlands, 1980–July 2, 2009), and ISI Web of Knowledge (Thomson Scientific Technical Support, New York, 1945–July 4, 2009) databases for relevant articles by a search strategy using the following combinational terms (25-OH-D or cholecalciferol or calcidiol or calcitriol or 25-hydroxyvitamin D or hydroxycholecalciferols, 25-hydroxyvitamin D3 1-alpha-Hydroxylase or 1,25-dihydroxyvitamin D or vitamin D) AND (prostate) AND (cancer or tumor or neoplasm). No language restrictions were employed. Duplicate publications were deleted. Each title and abstract was checked for relevance. The full text was reviewed if the abstract indicated that the article reported associations between serum vitamin D and PC risk. Only original studies conducted among humans were considered for the review. Cross-referencing was employed to complement the study identification process.

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2.2. Data extraction

From eligible studies, the first author (Yin L) and the second author (Raum E) extracted the following data independently from each study in a standardized manner: author(s), publication year, country, study design, characteristics of the study population, duration of follow-up, PC incidence or mortality according to serum vitamin D status and the respective measures of relative risk (see below), as well as covariates adjusted for in the analysis. Any disagreement was resolved by consensus.

2.3. Statistical methods

Main outcome variables were measures of relative risks for the association between serum 25(OH)D levels and PC. When such data were not explicitly reported, they were derived from data provided in the articles or requested from the authors through personal contacts, wherever possible. For consistency, serum concentrations of 25(OH)D given in nmol/l were converted to ng/ml, using the pertinent conversion factor (1 ng/ml = 2.5 nmol/l). In most studies, PC incidence or mortality was reported stratified by various categories of 25(OH)D. Depending on available information, median, midpoints or means of the categories were used for meta-analysis. Due to the different categorization of 25(OH)D levels across studies, all results were recalculated for an increase in serum 25(OH)D by 10 ng/ml, both within studies (taking possible correlations resulting from a common reference category into account [18]), as well as across studies. Summary ORs from fixed and random effects models were calculated using standard meta-analysis methods [19].

In a conservative approach, the random effects' estimates, which allow for variation of true effects across studies, were taken as "main results" [20]. Random effects' estimates were derived using the DerSimonian–Laird method [21,22]. Heterogeneity was additionally assessed by the I^2 statistic. The funnel plot, Begg and Mazumdar rank correlation test and Egger's test of the intercept were employed to assess indications of publication bias [23]. Meta-regression and subgroup analyses were used to examine the relationship between regions (Europe vs. USA), 25(OH)D analysis methods (radioimmunoassay (RIA) vs. enzyme immunoassay (EIA); RIA vs. protein-binding assay (PBA)), according to control for seasonal variation of 25(OH)D and the sizes of effect observed in the studies. The R/S plus software, version 2.8.1, and the statistics software SAS©, version 9.1 (SAS Institute Inc., Cary, N.C., USA), were used for the analysis.

3. Results

3.1. Identification of studies and study quality

A flow diagram of the search process is given in Fig. 1. Total searches yielded 3481 entries. Following removal of 1115

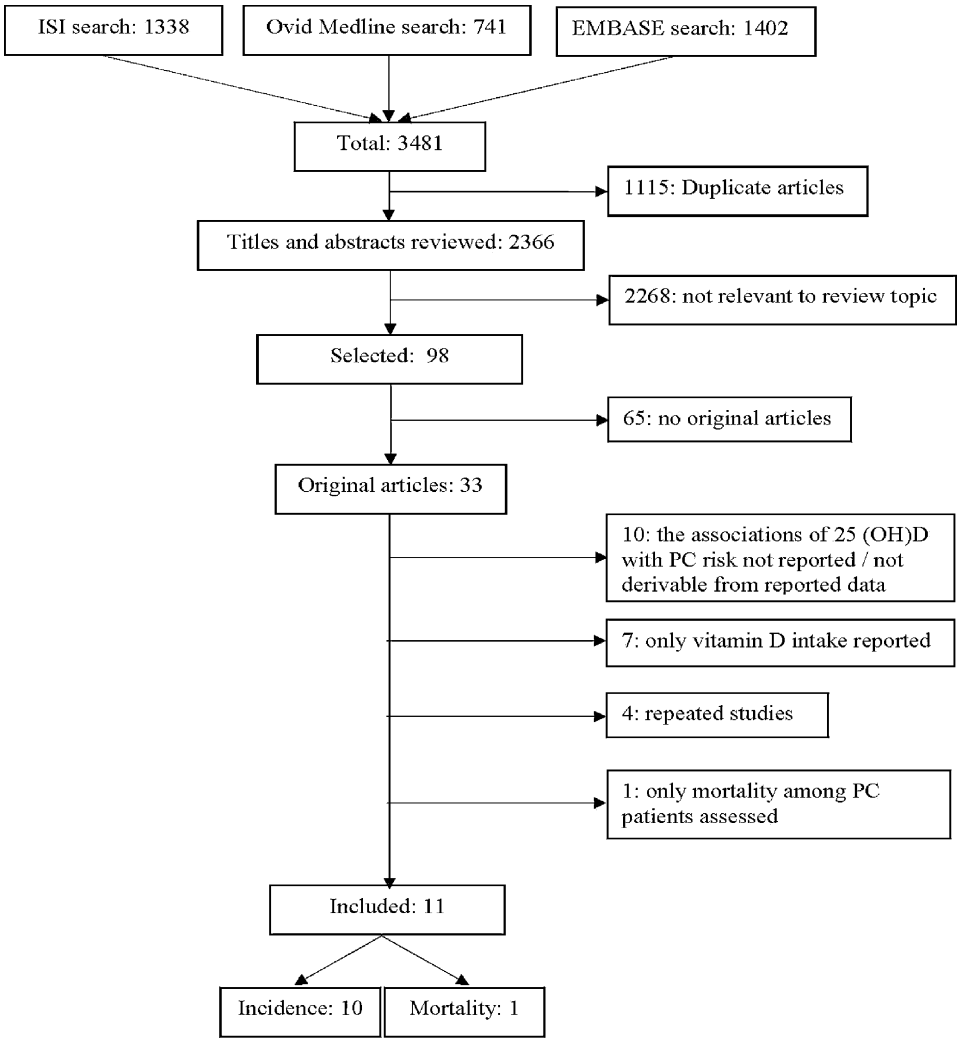

Fig. 1. Flow diagram of the literature search process.

duplicates, 2366 titles and abstracts were assessed and 98 articles appeared to be potentially relevant for inclusion into the review. 87 articles were excluded for the following reasons: no original articles but editorials, comments, reviews ($N = 65$), the associations of 25 (OH)D with PC risk not reported/not derivable from reported data ($N = 10$), only vitamin D intake reported ($N = 7$), repeated studies from the same study population ($N = 4$), only mortality among PC patients assessed ($N = 1$). The references of excluded studies are provided in Appendix A.

Articles from Gann et al. [24], Li et al. [25], Platz et al. [26], and Mikhak et al. [27], were all originating from the Health Professionals Follow-up study, three of which did not report the required data for calculating and transforming measures of association. After contacting the corresponding authors in a standardized manner, only Platz et al. [26] reported enough data for calculating and transforming measures of association as needed. Therefore, this study [26] was chosen to represent data from the Health Professionals Follow-up study even though two of the other studies were based on slightly longer follow-up and slightly larger case numbers [25,27]. The three other studies [24,25,27] were excluded. Tuohimaa et al. [28] reported results from a collaborative study in the Nordic European countries (Norway, Sweden, and Finland) in 2004. Because updated results from the Finnish cohort were reported in 2007 [29], the Finnish data from the 2004 publication [28] and an earlier publication from the same Finnish cohort (Helsinki Heart Study) (Ahonen et al. [30]) were excluded from the meta-analysis.

In total, 11 studies were included in our review [26,28,29,31–38]. One prospective cohort study reported on the association of serum 25(OH)D with PC mortality [36], whereas all other studies reported on the association with PC incidence, including nine nested case-control studies [26,28,29,31–33,35,37,38] and one prospective cohort study [34]. Details on the respective study design, the study populations, the study results, and covariates adjusted for are shown in Tables 1 and 2, and summarized below and in Fig. 2.

Table 1
Studies reporting on the association of serum 25(OH)D concentration with incidence of PC.

Ref.	Author (s), year	Study design[c]	Study population					RR (95% CI) of PC incidence according to 25 (OH) D (range or median) (ng/ml)[a,b]	Adjustment factors/ matching factors
			Country (baseline; follow-up)	No. partici pants		Age range (mean)	Setting		
				Cases	Controls				
[31]	Braun et al., 1995	NCCS	USA (1974; 1975–1992)	61	122	≥18 (57)	Population based	10–24.1: 1.0 24.1–29.5: 2.3 (0.7, 7.8) 29.6–35.4: 2.3 (0.7, 7.7) 35.5–41.3: 0.6 (0.1, 2.5) 41.3–70: 2.4 (0.8, 8.2)	No
[32]	Nomura et al., 1998	NCCS	USA (1965–1968; 1966–1993)	136	136	49–70 (58)	Japanese-American population	21–33: 1.0 34–40: 0.8 (0.4, 1.8) 41–47: 0.8 (0.4, 1.7) 48–92: 0.8 (0.4, 1.8)	Matched for: age, month and year of examination
[28]	Tuohimaa et al., 2004	NCCS	Norway (1973; 1974–1997) Sweden (1985,1986, 1990,1994; 1986–1997)	404 86	673 322	<40–60 40–>60	Population based	Norway: <8: 0.9 (0.3, 2.8) 8–15: 1.2 (0.9, 1.7) 16–23: 1.0 24–31: 1.2 (0.8, 1.7) ≥32: 1.8 (1.1, 2.8) Sweden: <8: 1.3 (0.1, 12.5) 8–15: 0.7 (0.3, 1.4) 16–23: 1.0 24–31: 1.0 (0.5, 1.8) ≥32: 1.5 (0.5, 4.4)	Matched for: age, date of the blood collection, country, and region within the country
[26]	Platz et al., 2004	NCCS	USA (1986–1995; 1993–1998)	460	460	40–75 (66)	Population based	Summer/fall/spring/winter 20.1/14.9/12.0/9.3: 1.00 24.1/22.4/16.6/15.8: 1.00 (0.67, 1.49) 27.6/25.4/20.9/19.9: 0.77 (0.51, 1.15) 32.9/31.1/24.5/24.6: 1.19 (0.79, 1.79)	Adjusted for: vigorous physical activity, family history, height, diabetes mellitus, vasectomy, cigarette smoking in the past 10 years, intake of energy, red meat, fish, lycopene, fructose, and α-linolenic acid, use of vitamin E, and selenium supplements. Matched for: year of birth, PSA[f] test prior to blood collection, and timing of blood collection-time of day, season, and year.
[33]	Jacobs et al., 2004	NCCS	USA (1983,1996; 1984–2002)	83	166	18–80 (67)	Population based	8.1-25.3: 1.00 25.4–32.7: 1.71 (0.68, 4.34) 32.8–59.7: 0.75 (0.29, 1.91)	Adjusted for: age at blood collection, clinic site, BMI[f] and cigarette smoking.
[34]	Baron et al., 2005	PCS	USA (1988–1992; 1992–2003)	65[d]	517[d]	N/A[h] (61)	Population based	<25.2: 1.00 25.2–34.0: 1.22 (0.66, 2.26) >34.0: 1.32 (0.72, 2.43)	Adjusted for: age, calcium treatment and log-calories.

Table 1 (*Continued*)

Ref.	Author (s), year	Study design[c]	Study population					RR (95% CI) of PC incidence according to 25 (OH) D (range or median) (ng/ml)[a,b]	Adjustment factors/ matching factors
			Country (baseline; follow-up)	No. participants		Age range (mean)	Setting		
				Cases	Controls				
[29]	Tuohimaa et al., 2007	NCCS	Finland (1981–1982; 1981–1997)	132	456	40–58 (51)	Middle-aged employees[e]	<16: 1.88 (1.15, 3.08) 16–23.6: 1.00 ≥23.7: 1.25 (0.64, 2.43)	Adjusted for: BMI, SBP, HDL-C[f] Matched for: age and season of the blood collection, region, accidental thawing, and treatment with gemfibrozil, the drug used in this trial population.
[35]	Faupel-Badger et al., 2007	NCCS	Finland (1985–1988; 1985–2007)	296	297	50–69 (N/A)[h]	Current smokers	≤14.79: 1.00 14.80–18.82: 0.88 (0.48, 1.61) 18.83–23.98: 0.59 (0.31, 1.11) >23.98: 0.89 (0.49, 1.62)	Adjusted for: age at randomization, BMI[f], and pack-years of smoking. Matched for: age, study clinic, treatment group and date of blood collection.
[37]	Ahn et al., 2008	NCCS	USA (1993–2001; 1993–2003)	749	781	55–74 (67)	Population based	5.1–17.0: 1.00 17.1–20.5: 1.10 (0.78, 1.56) 20.6–24.2: 1.53 (1.10, 2.13) 24.3–28.7: 1.33 (0.95, 1.86) 28.8–51.8: 1.18 (0.83, 1.68)	Adjusted for: study center, history of diabetes, BMI[f], physical activity, and total calcium intake. Matched for: age at cohort entry, time since initial screening, and calendar year of cohort entry
[38]	Travis et al., 2009	NCCS	Europe[g] (1992–2000; 1994–2000)	652	752	35–70 (61)	Population based	1–16.1: 1.00 16.2–20.1: 1.27 (0.89, 1.81) 20.2–23.6: 1.23 (0.85, 1.76) 23.7–28.3: 1.06 (0.73, 1.55) 28.4–65.5: 1.28 (0.88, 1.88)	Adjusted for: BMI,[f] smoking, alcohol intake, education, marital status, and physical activity. Matched for: study center, age at enrollment, time of day of blood collection, and time between blood draw and last consumption of food or drink.

[a] For consistency, serum concentrations of 25 (OH) D in nmol/l were converted to ng/ml using the conversion factor, 1 ng/ml = 2.5 nmol/l.
[b] RR: risk ratio; CI: confidence interval.
[c] Study design included: PCS: prospective cohort study; NCCS: nested case-control study.
[d] Data were given by personal contact.
[e] Employees were recruited from two governmental agencies and five industrial companies.
[f] PSA: prostate-specific antigen; BMI: body mass index; SBP: systolic blood pressure; HDL-C: high-density lipoprotein cholesterol.
[g] 7 European countries included: Germany, Greece, Italy, the Netherlands, Spain, Sweden, and United Kingdom.
[h] N/A: not available.

3.2. Characteristics of the study population

3.2.1. Studies on association with incidence of PC

Study 1. The first nested case-control study was reported by Braun et al. [31] based on a prospective cohort study of 20,305 county residents of Washington County, MD, USA, who were recruited during a blood collection campaign undertaken from August to November 1974. Sixty-one cases of PC were ascertained during the follow-up period from 1980 until 1992. Each PC case was matched to two controls for age (±1 year) and race in the same blood collection campaign. No statistically significant trends or differences

Table 2
Study reporting on the association of serum 25(OH)D concentration with mortality of PC.

Ref.	Author (s), year	Study design[c]	Study population					RR (95% CI) of PC mortality according to 25 (OH) D (range or median) (ng/ml)[a,b]	Adjustment factors/ Matching factors
			Country (baseline; follow-up)	No. participants		Age range (mean)	Setting		
				Deaths	Total				
[36]	Freedman et al., 2007	PCS	USA (1988–1994, 1988–2000)	47	7493	≥17 (44)	Population based	15.3: 1.00 31.9: 0.91 (0.39, 2.14)	Adjusted for: age, gender, race/ethnicity, and smoking history (pack-years)

[a] For consistency, serum concentrations of 25 (OH) D in nmol/l were converted to ng/ml using the conversion factor, 1 ng/ml = 2.5 nmol/l.
[b] RR: risk ratio; CI: confidence interval.
[c] Study design included: PCS: prospective cohort study.

between cases and controls were found in an analysis by quintiles of serum 25(OH)D levels (Fig. 2-1).

Study 2. A nested case-control study of serum 25(OH)D was performed by Nomura et al. [32], including 136 cases of PC and 136 matched controls in a cohort of 3737 Japanese-American men examined by the Honolulu Heart Program in Hawaii of USA after a surveillance period of 23 years (1967–1993). The controls were matched to PC cases for age (±1 year), month and year of examination (±1 month). Compared to the reference category with lowest 25(OH)D levels, PC risk was not significantly reduced in the other categories (P_{trend} = 0.68) (Fig. 2-2).

Study 3. A nested case-control study on Nordic men (Norway, Finland and Sweden) was performed by Tuohimaa et al. [28], based on 622 cases of PC and 1451 matched controls from the Janus Project in Norway (1973–1997), the Helsinki Heart study in Finland (1981–1997), and the Northern Sweden Health and Disease Cohort in Sweden (1985–1997), respectively. The controls were matched to the cases for age (±2 years) and date (±2 months,

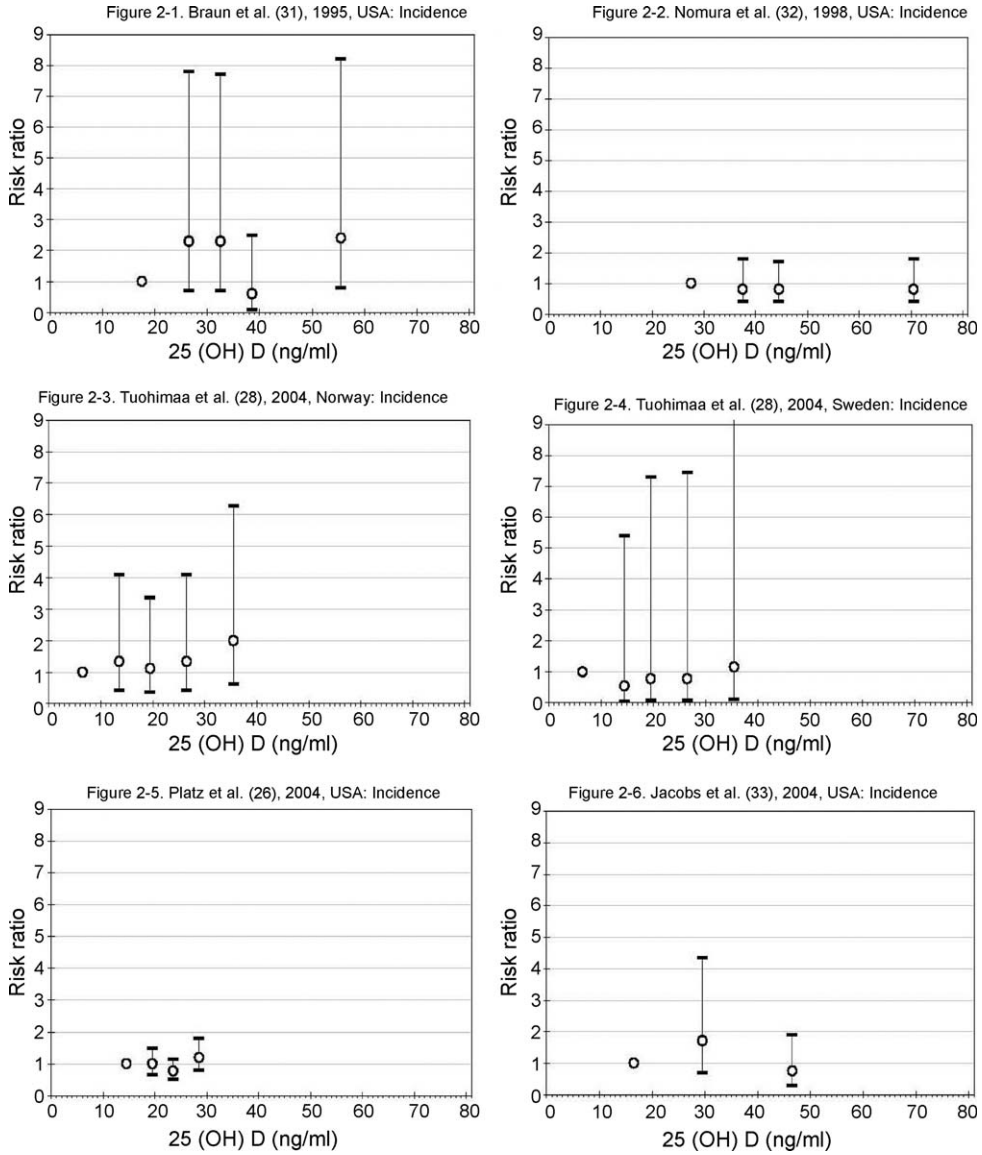

Fig. 2. Risk ratios and 95% confidence intervals of prostate cancer risk according to study specific serum 25(OH)D levels°.
°: Depending on available information, median, midpoints or means of the categories were used for definition of study specific levels of serum 25(OH)D categories.
Fig. 2-1. Braun et al. [31], 1995, USA: incidence.
Fig. 2-2. Normura et al. [32], 1998, USA: incidence.
Fig. 2-3. Tuohima et al. [28], 2004, Norway: incidence.
Fig. 2-4. Tuohima et al. [28], 2004, Sweden: incidence.
Fig. 2-5. Platz et al. [26], 2004, USA: incidence.
Fig. 2-6. Jacobs et al. [33], 2004, USA: incidence.
Fig. 2-7. Baron et al. [34], 2005, USA: incidence.
Fig. 2-8. Tuohimaa et al. [29], 2006, Finland: incidence.
Fig. 2-9. Faupel-Badger et al. [35], 2007, Finland: Incidence.
Fig. 2-10. Ahn et al. [37], 2008, USA: incidence.
Fig. 2-11. Travis et al. [38], 2009, Europe: incidence.
Fig. 2-12. Freedman et al. [36]. 2007, USA: mortality.

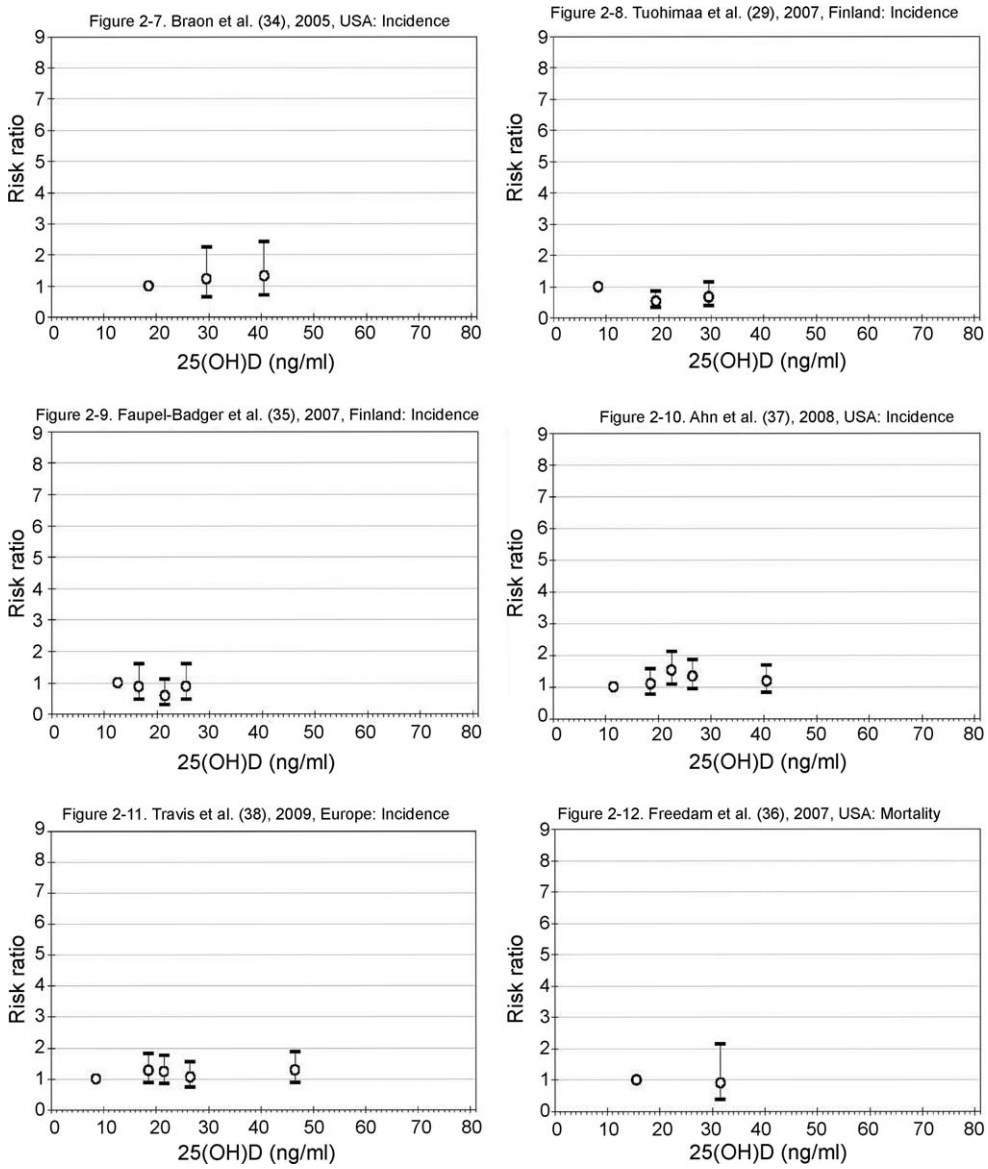

Fig. 2. (*Continued*).

in Norway ±6 months) of the blood sampling, country and the region inside the country. In the Norwegian study group, a significantly increased risk was seen at the highest vitamin D serum levels (OR = 1.8; 95% CI, 1.1–2.8), compared to third quintile (16–23 ng/ml). In the Swedish study group, no statistically significant differences were observed (Figs. 2-3, 2-4). Because Tuohimaa et al. [29] updated results for Finland, the Finnish data from this article were excluded.

Study 4. Platz et al. [26] conducted a nested case-control study of serum 25(OH)D based on 460 incident cases of PC that occurred in a cohort of 51,529 US men in the Health Professionals Follow-up Study aged 40–75 years. Controls were matched to cases for year of birth (±1 year), PSA test prior to blood collection, and the time of day of blood collection, season, and year. Participants were followed through 1998 after providing a blood sample in 1993/1995. No association between serum concentrations of 25(OH)D and incidence of PC was observed (P_{trend} = 0.59) (Fig. 2-5).

Study 5. The nested case-control study by Jacobs et al. [33] included 83 cases of PC and 166 controls, matched for age (within 5 years), treatment group (selenium or placebo), and clinic site. Cases and controls participated in the Nutritional Prevention of Cancer (NPC) trial, a randomized, double-blind, placebo-controlled trial conducted among 1312 participants to examine the effects of 200 μg per day of selenium on the recurrence of non-melanoma skin cancer (NMSC) during the period of 1983–2002. No significant association of serum 25(OH)D with risk of PC was observed (P_{trend} = 0.51) (Fig. 2-6).

Study 6. Baron et al. [34] conducted a prospective cohort study on the association between prediagnostic serum 25(OH)D levels and incidence of PC in a colorectal adenoma chemoprevention trial with application of either 3 g of calcium carbonate (1200 mg of calcium) or placebo, daily for four years. After a mean follow-up of 10.3 years, there were 70 incident PC cases. Baseline 25(OH)D levels were not associated with PC risk (P_{trend} = 0.70) (Fig. 2-7).

Study 7. A nested case-control study was performed in Finland by Tuohimaa et al. [29], including 132 PC cases identified from 19,000 middle-aged (40–58 years at the baseline) employees of two government agencies and five industrial companies within the

Helsinki Heart study during the period of 1981–1997. Four controls ($N = 456$) were matched per case by age (±2 years) and date (±2 months) of the blood sampling and the region inside the country. A U-shaped association of serum 25(OH)D with PC incidence was observed (Fig. 2-8).

Study 8. Another nested case-control study was conducted in Finland by Faupel-Badger et al. [35] among current smokers (at least five cigarettes per day) at entry, aged 50–69 years, in a large intervention trial, the α-Tocopherol, β-Carotene Prevention Study, which was a randomized, placebo-controlled, double-blind trial that examined the effect of daily supplementation of either α-tocopherol (5 mg), β-carotene (20 mg), both, or placebo for 5–8 years on incidence of lung and other cancers. Of the cases diagnosed during the intervention or follow-up period, 296 were randomly selected using incidence density sampling, matched 1:1 to controls on controls for age (±1 year), study clinic, treatment group, and date of blood draw (±28 days). No association between serum 25(OH)D and PC incidence was found ($P_{trend} = 0.97$) (Fig. 2-9).

Study 9. Ahn et al. [37] conducted a nested case-control study including 749 PC cases and 781 controls from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial during the period of 1993–2001, a large randomized controlled multicenter trial in the United States of approximately 155,000 men and women. One control was matched per case by age at cohort entry (5-year intervals), time since initial screening (1-year time window), and calendar year of cohort entry. No statistically significant trends in overall PC incidence were observed, but higher vitamin D levels were associated with an increased risk for aggressive disease (Gleason score ≥ 7 or clinical stage III or IV).

Study 10. A case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) was recently reported by Travis et al. [38]. The study included data from 7 of the 10 participating countries: Germany, Greece, Italy, the Netherlands, Spain, Sweden, and the United Kingdom during the period of 1994–2000. Serum concentrations of 25-hydroxyvitamin D were measured in 652 PC cases matched to 752 controls. Matching criteria were study center, age at enrollment (±6 months), time of day of blood collection (±1 h), and time between blood draw and last consumption of food or drink (<3, 3–6, >6 h; for Umeå < 4, 4–8, >8 h). No significant association was found between 25(OH)D and PC incidence ($P_{trend} = 0.188$).

3.2.2. Study on the association with mortality of PC

Study 11. A prospective study was performed by Freedman et al. [36] on the association between baseline serum vitamin D and deaths from PC in a cohort of 16,818 men and women aged 17 years or older, who participated in the Third National Health and Nutrition Examination Survey (NHANES III) in the United States. Overall, 47 deaths from PC occurred between 1988 and 2000. PC mortality was not related to serum 25(OH)D level ($P = 0.95$).

3.2.3. Results of meta-analyses

The results of meta-analyses on the association between serum 25(OH)D levels and PC incidence are shown in Fig. 3. All ORs refer to an increase of 25(OH)D by 10 ng/ml. ORs were essentially evenly distributed around 1, ranging from 0.76 to 1.91, and summary ORs very close to 1 were obtained in meta-analysis: fixed effects model: OR, 1.04; 95% CI, 0.98–1.10; $P = 0.191$; random effects model: OR, 1.03; 95% CI, 0.96–1.11; $P = 0.362$. No statistical heterogeneity was observed ($I^2 = 23.0\%$; $P = 0.22$). The funnel plot did not show

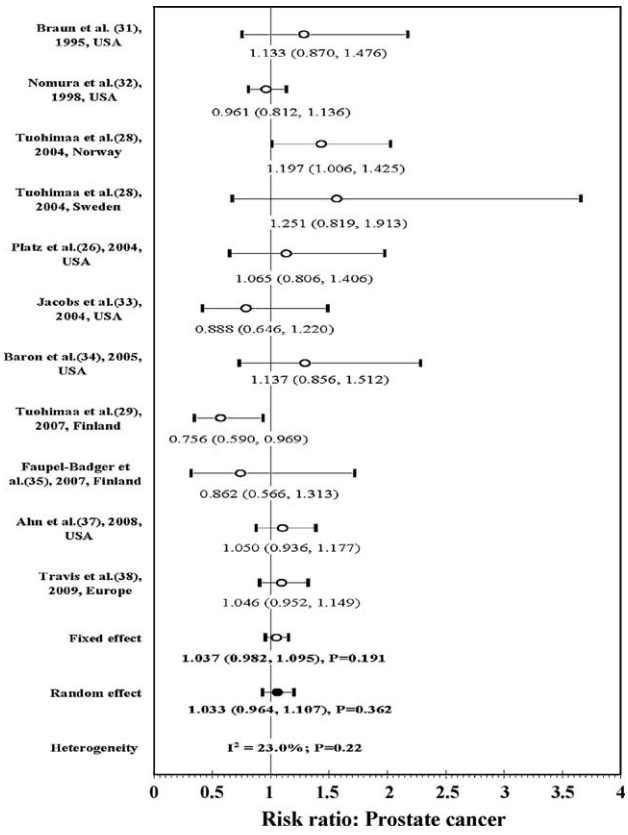

Fig. 3. Meta-analyses: risk ratios of prostate cancer incidence per 10 ng/ml increase in serum 25(OH)D.

evidence of publication bias (Kendall's tau = 0.02; $P = 1.00$; Egger's t value = −0.46, $P = 0.65$).

We investigated three factors as moderators in meta-regression, which could potentially influence the summary relative risk for PC, but no significant variation was found between regions (Europe vs. USA: $P = 0.943$), 25(OH)D analysis methods (radioimmunoassay (RIA) vs. enzyme immunoassay (EIA): $P = 0.829$; RIA vs. protein-binding assay (PBA): $P = 0.888$), or according to control for seasonal variation of 25(OH)D (yes vs. no: $P = 0.750$).

4. Discussion

To our knowledge, our review and meta-analysis is the first to summarize the results of studies on the association between serum 25(OH)D and PC incidence, which comprised a total of 7806 subjects including 3124 PC cases. We found no evidence that lower serum 25(OH)D levels are associated with increased PC risk. A possibly U-shaped relationship was suggested by some studies [26,28,29,35], but, overall, no consistent pattern emerged. Meta-regression did not reveal variation of study results according to geographical location, method of analyzing 25(OH)D concentration or control for seasonal variation.

The absence of an association of serum 25(OH)D with PC risk found in our meta-analysis is consistent with results from two meta-analyses reviewing the influence of vitamin D receptor gene polymorphisms on prostate cancer risk, which did not find a clear association either [39,40]. In general, prostate carcinogenesis takes a very long time. There is evidence that the vitamin D level might play a more important role during very early stages of carcinogenesis, since prostate cancer cells appear to lose 1-α-hydroxylase activity very early and therefore are resistant to the tumor suppressor activity of circulating 25(OH)D. 1-α-hydroxylase is important for converting the serum 25(OH)D to the active l-α-25-

dihydroxyvitamin-D3 ($1,25(OH)_2D_3$), and is present in normal prostatic epithelium [41,42].

Although $1,25(OH)_2D_3$ represents the biologically active form of vitamin D, which has been shown in experimental studies to reduce the degree of cell proliferation in the prostate, we chose to concentrate our analysis on the association between risk of PC and serum 25(OH)D rather than $1,25(OH)_2D_3$ for several reasons. 25(OH)D has a relatively long half-life in the circulatory system of about 2–3 weeks, compared to only about 4 h for $1,25(OH)_2D_3$. Furthermore, 25(OH)D represents an integrated measure for vitamin D from diet, dietary supplements, and skin production [17], and is a better marker of an individual's vitamin D exposure than serum $1,25(OH)_2D_3$. It is therefore not surprising that the association of PC with 1,25(OH)2D3 was less commonly assessed in previous epidemiological studies. However, five of the studies identified in our literature search have also evaluated the association between $1,25(OH)D_2D$ and PC incidence [26,31–34]. When we applied the same method for comprehensive trend estimation from summarized dose-response data in additional analyses, a summary OR (95% CI) of 1.04 (0.94–1.16) associated with an increase of $1,25(OH)D_2D$ by 10 pg/ml ($P = 0.403$) was obtained in both fixed and random effects models.

Our analysis has specific strengths and limitations. Strengths include comprehensive trend estimation and meta-analyses from summarized dose-response data over the entire range of serum 25(OH)D values using sophisticated statistical technique [18]. On the other hand, our analyses are limited by the data provided by the individual studies. Depending on the results reported, median, midpoints and mean 25(OH)D levels of the group had to be used for pooling. As a result, estimates of risk may be less accurate than if individual-level data had been available. Also, some earlier studies included in our meta-analysis did not provide risk estimates adjusted for potentially influential confounders, such as physical activity and smoking. In particular, potential confounding by physical activity was controlled for in only 2 studies [26,37]. It would have been interesting to stratify associations according to stage of this disease. However, stage-specific results were reported by three studies only using inconsistent classification schemes and not showing any systematic variation of associations by stage. Likewise, it would have been interesting to see whether results varied between cancers detected by screening or by symptoms. However, while this information was mostly unavailable, no major variation of results was observed between studies conducted in the "pre prostate-specific antigen (PSA) era" and more recent studies. Furthermore, despite the lack of indication of major publication bias in the formal evaluations employed, potential publication bias is impossible to be excluded completely, especially in the light of the low number of studies. Finally, although our review searched three databases, i.e., Ovid Medline, EMBASE, and ISI Web of Knowledge, and extensive checks for completeness by cross-referencing was employed, we cannot exclude having missed a relevant study.

5. Conclusions

Our review and meta-analysis does not support previous suggestions that serum 25(OH)D levels are inversely related to PC risk. However, available data are still sparse and in-depth analyses of the assessed associations in the context of additional longitudinal studies are highly desirable to enable more precise estimates and a better understanding of the role of vitamin D in PC carcinogenesis. Furthermore, future studies should aim to clarify a potential role of vitamin D in prognosis of patients with PC which are suggested by recent reports [43,44].

Conflict of interest

None.

Appendix A

Studies exclude from this review because of:

A.1. No original articles but editorials, comments, reviews

(1) Schwartz GG, Hulka BS. Is Vitamin D deficiency a risk factor for prostate-cancer—(hypothesis). *Anticancer Res* 1990; 10:1307–1311.
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A.5. Only mortality among PC patients assessed

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