Nutrition Research Reviews (2009), **22**, 188–203
doi:10.1017/S0954422409990151
© The Author 2009

Epidemiology of vitamin D in health and disease

Sihe Wang

Department of Clinical Pathology, Cleveland Clinic, Cleveland, OH, USA

Results from ecological, case–control and cohort studies have shown that vitamin D reduces the risk of bone fracture, falls, autoimmune diseases, type 2 diabetes, CVD and cancer. However, there is still epidemic vitamin D insufficiency especially among individuals living at high latitudes or with dark skin. Serum levels of 25-hydroxyvitamin D (25(OH)D) are considered the best biomarker of vitamin D nutritional status. Appropriate sunshine exposure or oral supplementation is necessary to maintain sufficient vitamin D status, which is generally accepted as serum 25(OH)D $>$ 75 nmol/l. Immunoassays, especially RIA, have been primarily used to measure serum 25(OH)D while liquid chromatography–MS (LC–MS) is considered the 'gold standard'. There is significant disparity among the immunoassays, and all immunoassays have considerable bias compared with LC–MS methods. Because of the variations among the results from these different assays, it is necessary that assay-specific reference ranges be established or standardisation of the assays take place. The present review focuses on ecological, case–control, and cohort studies that investigated the role of vitamin D in health and disease. In addition, analytical techniques used in laboratory evaluation of vitamin D nutritional status are also critically reviewed. The majority of the literature included in the present review is selected from that searchable in PubMed up to the end of September 2008.

Vitamin D: 25-Hydroxyvitamin D: Cancer: CVD: Autoimmune disease

Introduction

Even though the importance of vitamin D is gaining more public attention, rickets still exists in the USA in dark-skinned infants who are exclusively fed on breast milk[1]. Rickets was first described in the literature in the mid-1600s, and cod-liver oil and sunshine exposure were recognised as the cures for rickets in the late 19th century. Vitamin D was then discovered in the early 20th century[1]. There are two types of physiologically important vitamin D: cholecalciferol (D_3) and ergocalciferol (D_2). D_3 is synthesised in the skin from 7-dehydrocholesterol in cell membranes upon exposure to UVB (290–320 nm), while D_2 is plant and yeast derived and produced exogenously by UV irradiation of ergosterol[2,3]. Vitamin D in the circulation is metabolised to 25-hydroxyvitamin D (25(OH)D) in the liver and further metabolised to the active metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), in the kidney. The concentration of $1,25(OH)_2D$ is highly regulated by a variety of factors including serum parathyroid hormone and P[2,4].

The majority of circulating 25(OH)D and $1,25(OH)_2D$ is bound to vitamin D binding protein (DBP) (80–90 %) and albumin (10–20 %), while a small fraction of both 25(OH)D (0·02–0·05 %) and $1,25(OH)_2D$ (0·2–0·6 %) is free[5]. The vitamin D–DBP complex has been shown to be taken up by proximal tubules through the endocytic receptor megalin, after which DBP is proteolytically degraded, leaving the vitamin D metabolites for physiological action or metabolism[5,6]. Thus, measuring free vitamin D metabolites is not clinically indicated despite some efforts having been made to calculate the free plasma vitamin D metabolites based on measured total concentrations, DBP, and albumin concentrations[7]. The half-lives of vitamin D, 25(OH)D and $1,25(OH)_2D$ are approximately 24 h, 3 weeks and 4 h respectively[5]. In addition, liver production of 25(OH)D is not significantly regulated and is primarily dependent on the availability of vitamin D[5]. Therefore measuring the total levels of serum 25(OH)D is considered the best estimate of vitamin D nutritional status.

Vitamin D nutritional status has been linked to many pathophysiological conditions. The present review will focus on ecological, case–control and cohort studies exploring the role of vitamin D in health and disease. Serum levels of 25(OH)D and the means of obtaining vitamin D will also be discussed. In addition, analytical

Abbreviations: DBP, vitamin D binding protein; LC–MS, liquid chromatography–MS; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; RR, relative risk.

Corresponding author: Dr Sihe Wang, fax +1 216 444 4414, email wangs2@ccf.org

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

techniques used in laboratory evaluation of vitamin D nutritional status will be critically reviewed.

Measuring vitamin D metabolites

There are a few commercial immunoassays available for measuring serum 25(OH)D, and liquid chromatography–MS (LC–MS) is considered the 'gold standard'[5]. However, reporting both $25(OH)D_2$ and $25(OH)D_3$ may be confusing to clinicians without appropriate guidance[8]. Both 25(OH)D and $1,25(OH)_2D$ were found to be stable at room temperature for at least 72 h in either whole blood or serum[9]. Exposure to UV light or freeze–thaw cycles (up to eleven times) of serum did not change the concentrations[9]. The stability of serum 25(OH)D was confirmed by DiaSorin RIA for up to four freeze–thaw cycles[10].

The international Vitamin D Quality Assessment Scheme demonstrated that most commercial 25(OH)D methods were capable of producing reliable results for those samples containing only $25(OH)D_3$. However, the results were operator-dependent and most methods had significant bias compared with HPLC methods for samples with a substantial proportion of $25(OH)D_2$[11]. Evaluation of current RIA and chemiluminescent methods for serum 25(OH)D using patient samples showed substantial variability among the six methods (RIA including DiaSorin assays and chemiluminescent immunoassays) and the same methods used in the different laboratories, which may confound the diagnosis of hypovitaminosis D[12]. Comparing to an HPLC method for serum 25(OH)D measurement, significant positive proportional bias was observed for DiaSorin and IDS RIA as well as the discontinued Nichols Advantage protein-binding assay in the range of 20–50 nmol/l in serum samples before D_2 treatment[13]. All the immunoassays evaluated also underestimated serum $25(OH)D_2$ concentrations in samples after D_2 treatment[13]. Using LC–MS as the standard, DiaSorin Liaison showed different but not clinically significant results (however, there were only eight patient samples treated with vitamin D_2 included in the analysis) while the discontinued Nichols Advantage method showed significant difference[14]. A comprehensive evaluation of seven methods using 291 EDTA plasma samples (277 had no detectable $25(OH)D_2$ and fourteen had $25(OH)D_2$ between 5 and 8 nmol/l) showed that all methods except HPLC demonstrated considerable negative bias compared with LC–MS[15]. The deviation was more significant at levels of 25(OH)D $>$ 75 nmol/l than those $<$ 75 nmol/l for most immunoassays. The methods evaluated were HPLC, IDS RIA, IDS enzyme immunoassay (competitive immunoassay), Advantage (protein-binding assay), Liaison 1 and 2 (competitive immunoassay) and Elecsys (competitive electrochemiluminescent assay)[15].

Most HPLC methods require lengthy sample preparation including solid-phase extraction[16] and liquid–liquid extraction[17–19], followed by a lengthy HPLC ranging from 10 to 30 min. It should be noted that potential late elution peaks may interfere with the analysis of the succeeding samples[16]. In addition, the C-3 epimer of 25(OH)D could be a significant interferant in infants $<$ 1 year old, in which the epimer can be 8·7–61·1 % of the total 25(OH)D[16,20].

The LC–MS is considered the 'gold standard' technology for 25(OH)D quantification[5]. Most LC–MS methods employ ^2H-labelled $25(OH)D_3$ as the internal standard. $^2H_6$-labelled $25(OH)D_2$, while recently available, has a molecular weight of 418·2. With the loss of a water molecule, a fragment of 401·2 *m/z* is formed, interfering with $25(OH)D_3$ quantification. To improve ionisation efficiency, some methods employ a derivatisation strategy using a Cookson-type reagent[21,22] or the Diels–Alder derivatisation[23]. For direct measurement without derivatisation, sample preparation can be cumbersome. In general, sample preparation includes protein precipitation followed by solid-phase extraction[24–26] or liquid–liquid extraction[27–29]. Turbulent flow technology is a robust and rapid online purification tool for high efficiency extraction[30,31], and has been used for online sample cleaning in serum 25(OH)D quantification[20]. This technology is efficient to reduce labour-intensive sample preparation and to improve reproducibility.

Serum levels of 25-hydroxyvitamin D

Vitamin D 'deficiency' refers to serum levels of 25(OH)D resulting in histologically evident bone diseases such as osteomalacia and rickets, while vitamin D 'insufficiency' refers to alterations in the parathyroid hormone concentration which if such persists over time may contribute to bone loss and fracture[2]. In general, rickets can occur for children with serum 25(OH)D less than 25 nmol/l (10 ng/ml) and osteoporosis is possible for adults with a serum 25(OH)D level at 80 nmol/l (32 ng/ml) or less[32,33]. Therefore, it is generally accepted that serum 25(OH)D levels of 25 and 75 nmol/l (30 ng/ml) are the cut-off values for deficiency and insufficiency, respectively[34,35]. Vitamin D insufficiency is recognised as an epidemic issue, especially in areas of higher latitudes or low sunlight and for individuals with darker skin[4]. It has been estimated that 40–90 % of the elderly worldwide have vitamin D insufficiency[34]. Even in southern parts of the USA, 45 % of black individuals and 11 % of white individuals aged 40–79 years had 25(OH)D $\leq$ 37·5 nmol/l[36]. In Canada, the majority (93 %) of children at ages 9, 13 and 16 years had insufficient vitamin D levels ($\leq$ 75 nmol/l) and a significant fraction in each group had 25(OH)D $\leq$ 25 nmol/l, with higher percentages in the older groups[37]. The prevalence of vitamin D insufficiency (25(OH)D $<$ 75 nmol/l) in adults with cystic fibrosis was 76 % in a retrospective study spanning 2 years at a cystic fibrosis centre in Atlanta (GA, USA)[38]. A 32 % higher risk for vitamin D insufficiency (25(OH)D $<$ 75 nmol/l) was found for patients with chronic kidney disease in the Third National Health and Nutrition Examination Survey[39].

Currently the most commonly agreed cut-off for vitamin D insufficiency is 25(OH)D $<$ 75 nmol/l. This cut-off value was derived from studies using immunoassays or protein-binding assays which are significantly different from LC-based assays and vary significantly among these assays. Therefore, defining method-specific reference ranges or standardisation of 25(OH)D assays is important in

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

evaluation of vitamin D nutritional status and patient management.

Effectiveness and safety of supplementation

Both dietary supplementation and sunshine exposure are effective in preventing vitamin D deficiency, though there is concern of skin cancer due to prolonged solar UV radiation exposure[2,40]. There is clear evidence that UV light exposure, consuming vitamin D-fortified food and/or vitamin D supplementation has a positive impact on serum 25(OH)D. Individuals can tolerate vitamin D at doses above the current dietary reference intake levels which are 200 IU (1 μg = 40 IU) for children and adults up to 50 years of age, 400 IU for 51–70 years of age, and 600 IU for adults aged 71 years or older[3,41–43]. Short-term (8 weeks) and long-term (1 year) efficacy and safety for 14 000 IU/week supplementation of D_3 were evaluated in children and no study subject developed vitamin D intoxication while mean serum 25(OH)D increased from 110 to 135 nmol/l and from 38 to 90 nmol/l, respectively[44]. At physiological inputs of both oral and cutaneous forms, there is a rapid conversion of vitamin D_3 to 25(OH)D_3 at low vitamin D_3 concentrations and a much slower conversion rate at higher D_3 concentrations[45]. Therefore, the increase of serum levels of 25(OH)D depends upon the serum vitamin D_3 levels[45]. However, individual response to the same therapy (Calcichew D_3 Forte containing 1250 mg calcium carbonate and 400 IU D_3 per tablet[46]) was different; therefore, no single dose of vitamin D is appropriate for all[47]. In a 6-week randomised controlled study, supplementation with vitamin D_2 2000 IU daily, vitamin D_2 50 000 IU weekly, or vitamin D_3 2000 IU daily yielded equivalent outcomes (median increased from 42·5 to 90 nmol/l) in the treatment of hypovitaminosis D (25(OH)D < 50 nmol/l) among young children[48]. From a 6-month, prospective, randomised, double-blinded, double-dummy, placebo-controlled study of vitamin D_3 supplementation, an optimal dose of 4600 IU daily is predicted to achieve serum 25(OH)D levels of 75–220 nmol/l[49]. In a different study involving sixty-seven men in Omaha (41·2°N latitude), to sustain the serum 25(OH)D levels obtained through summer, approximately 3800 IU vitamin D_3 per d was needed[50]. It is generally accepted that serum levels of 25(OH)D < 250 nmol/l are safe and still significantly below the toxicity level[51]. Vitamin D intoxication is observed when serum 25(OH)D is higher than 374 nmol/l[3].

Vitamin D_2 and D_3

Though both vitamin D_2 and D_3 have been used as supplementation, vitamin D_2 was less efficient than vitamin D_3 for increasing serum 25(OH)D with either a single dose (50 000 IU) followed for 1 month, a single high dose (300 000 IU) followed for 24 weeks, or a daily dose (about 4000 IU) for 14 d[52–55]. Several mechanisms could contribute to this observation: 25(OH)D_2 has a lower affinity for DBP which results in a shorter half-life than 25(OH)D_3; also human liver enzymes may convert vitamin D_3 to 25(OH)D at a more rapid rate than vitamin D_2[54]. However, a recent randomised, placebo-controlled, double-blinded study of healthy adults showed that 1000 IU vitamin D_2 and D_3 daily for 11 weeks had the same effectiveness in maintaining serum 25(OH)D[56].

Vitamin D and all-cause death

There is reasonable evidence from epidemiological and case–control studies that maintaining sufficient vitamin D is important for bone health, muscle strength, cancer, autoimmunity and CVD[2,4,32]. In a large prospective study involving 13 331 participants followed for a median of 8·7 years in the Third National Health and Nutrition Examination Survey (which is a nationwide probability sample of non-institutionalised civilian persons), the lowest quartile of the baseline 25(OH)D (< 44·5 nmol/l) was associated with a 26 % increased rate of all-cause mortality compared with the highest quartile (> 80 nmol/l)[57]. The concentration range for reduced risk of mortality was 50–122·5 nmol/l, especially in women[57]. CVD and cancer mortalities were higher but not statistically significant in the lowest quartile of baseline 25(OH)D levels[57]. All-cause mortality but not CVD-cause mortality was higher in patients with 1,25$(OH)_2$D less than 52 pmol/l in 226 patients with chronic kidney disease stages 3 and 4[58]. Treatment with oral calcitriol was inversely associated with risk for mortality and combined death and dialysis initiation in pre-dialysis patients with chronic kidney disease for a median duration of 2·1 years of 258 subjects receiving calcitriol and 262 subjects without calcitriol[59]. Though the study limitations included non-randomisation, observational design, lack of information on cause of death, the exclusive enrolment of men, and the small sample size, it emphasised the importance of vitamin D in the healthcare of this patient population and the immediate need for randomised prospective clinical trials[60].

Vitamin D and bones

Vitamin D status plays a very important role in bone health. Rickets may present in children with serum levels of 25(OH)D < 25 nmol/l and osteoporosis is possible in adults with serum 25(OH)D levels < 80 nmol/l[32]. From a meta-analysis of double-blind randomised controlled trials of oral vitamin D supplementation (all used vitamin D_3) in older individuals (≥ 60 years) for either hip fracture (*n* 9294 subjects in five trials) or non-vertebral fracture (9820 subjects in seven trials), a vitamin D dose of 700–800 IU/d reduced risk of hip fracture by 26 % and non-vertebral fracture by 23 %, while no significant benefit was observed for 400 IU/d[61]. In a randomised double-blind controlled trial involving 2686 individuals, supplementation of 100 000 IU vitamin D_3 once every 4 months resulted in significantly reduced fractures and mortality compared with the matching placebo-treated group[62]. The average serum 25(OH)D concentration in the supplementation group was 74·3 nmol/l *v.* 53·4 nmol/l in the placebo group[62]. Serum 25(OH)D was positively associated with bone mineral density at the hip and spine in 414 older men (mean age 74 years) at a clinic visit[63]. However, a prospective study involving 60 689 women aged 40–74 years in central Sweden found no association between either baseline

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

dietary Ca or vitamin D and fracture risk with an average follow-up of 11·1 years[64]. In a case–control observational study within the European Prospective Investigation into Cancer and Nutrition-Oxford cohort, baseline plasma 25(OH)D levels (mean 80·4–83·7 nmol/l across the control and case groups) were not associated with fracture risk in 730 incident fracture cases and 1445 matched controls in 5 years after blood sample collection[65]. In a 1-year randomised, double-blind, placebo-controlled trial involving 320 elderly women (age 77·2 (SD 4·6) years) whose serum 25(OH)D levels were less than 60 nmol/l, supplementation with 1000 IU vitamin D_2 did not have additional benefits on bone structure, bone formation markers, or intestinal Ca absorption over an additional 1000 mg Ca per d, though the serum 25(OH)D was raised from 44·3 (SD 12·9) nmol/l to 59·8 (SD 13·8) nmol/l[66]. In conclusion, it is important to have adequate vitamin D for bone health and the doses higher than the current recommendation of dietary vitamin D are needed.

Vitamin D and muscles

Serum vitamin D levels are related to muscle strength, size and non-specific musculoskeletal muscle pain[32]. In a meta-analysis of five double-blind randomised controlled trials involving 1237 participants (mean age, 60 years), vitamin D supplementation reduced the corrected OR of falling by 22 % compared with those on Ca or placebo[67]. In a retrospective cross-sectional study of haemodialysis patients receiving active vitamin D analogues for control of secondary hyperparathyroidism (n 49) *v.* those who were not (n 30), patients in the vitamin D group had a larger thigh-muscle cross-sectional area and were stronger across strength measures after controlling for age and sex[68]. A low 25(OH)D level was associated with a high prevalence of falls in the previous year of blood draws in Japanese elderly women in a cross-sectional community-based survey involving 2957 subjects (950 men and 2007 women aged 65–92 years)[69]. In a retrospective study of 110 community-dwelling women with hip fractures, 96 % had 25(OH)D $<$ 80 nmol/l and 38 % had $\leq$ 22·5 nmol/l[70]. Those with 25(OH)D $\leq$ 22·5 nmol/l had poorer lower extremity function and higher falling rates compared with those with 25(OH)D $>$ 22·5 nmol/l[70]. Interestingly, higher testosterone levels had a decreased OR of falling and the fall reduction was further enhanced by vitamin D and Ca supplementation in 199 men and 246 women aged 65 + years living at home and followed for 3 years[71].

Vitamin D and autoimmune diseases

$1,25(OH)_2D_3$ regulates the growth and differentiation of multiple cell types displaying immunoregulatory and anti-inflammatory properties[72]. Cells involved in innate and adaptive immune responses including macrophages, dendritic cells, T and B cells can produce and respond to $1,25(OH)_2D_3$, leading to an enhancement of innate immunity and multifaceted regulation of adaptive immunity[72]. Plenty of published ecological, case–control and cohort studies show the importance of vitamin D in a variety of autoimmune diseases[72,73].

In a prospective, nested case–control study among more than 7 million US military personnel, the risk of multiple sclerosis significantly decreased (OR 0·59) with every 50 nmol/l increase of serum 25(OH)D[74]. A large case–control study based on death certificates by the National Cancer Institute found that the OR was 0·24 for the combined effect of the highest levels of residential and occupational sunlight exposure for multiple sclerosis while the OR was 1·38 for skin cancer[75]. Vitamin D was also suggested for treatment and prevention of multiple sclerosis[76].

Vitamin D is also important in reducing type 1 diabetes. In a birth-cohort study with 10 366 children born in 1966 in Finland, vitamin D supplementation was associated with an 88 % reduction in type 1 diabetes incidence in 30 years of life[77]. From a large multicentre trial covering many different European settings, vitamin D supplementation in infancy showed a protective effect for type 1 diabetes onset before the age of 15 years[78]. Recently, age-standardised incidence rates of type 1 diabetes in fifty-one world regions in 1990–4 were shown to be significantly inversely associated with UVB irradiance adjusted for cloud cover[79].

Some epidemiological evidence shows that vitamin D status is associated with systemic lupus erythematosus, rheumatoid arthritis and other autoimmune diseases[72,80,81]. However, more prospective controlled clinical research is needed in these areas.

Vitamin D and type 2 diabetes

Vitamin D deficiency impairs insulin secretion of pancreatic β-cells and increases insulin resistance in target tissues, both of which play critical roles in type 2 diabetes development[82]. In the Nurses' Health Study, 83 779 women with no history of diabetes, CVD or cancer were followed for 20 years[83]. Risk of type 2 diabetes was reduced by total Ca intake or supplemental vitamin D, while a combined daily dose of $>$ 1200 mg Ca and $>$ 800 IU vitamin D was associated with a 33 % risk reduction of type 2 diabetes compared with those with Ca $<$ 600 mg and $<$ 400 IU vitamin D[83]. Baseline serum 25(OH)D levels were inversely associated with the risk of type 2 diabetes in the Min-Finland Health Survey of 4097 eligible participants followed for 17 years[84]. The relative risk (RR) of the highest (mean 70·9 nmol/l) to the lowest (mean 22·4 nmol/l) serum 25(OH)D quartiles was 0·60[84]. In a combined analysis of two nested case–control studies with 412 cases and 986 controls in the Finnish Mobile Clinic Health Examination Survey (19 518 men and women aged $\geq$ 20 years) and the Mini-Finland Health Survey (8000 individuals aged $\geq$ 30 years) followed for 22 and 17 years, respectively, the relative odds of the highest (mean about 75 nmol/l) relative to the lowest (mean about 24 nmol/l) quartiles of baseline serum 25(OH)D was 0·28 for type 2 diabetes in men but not significant in women who had lower serum 25(OH)D (highest quartile mean about 63 nmol/l)[82].

Vitamin D and cardiovascular diseases

The mechanisms of the protective role of vitamin D in CVD are proposed to be inhibition of vascular smooth muscle

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

proliferation, suppression of vascular calcification, down-regulation of pro-inflammatory cytokines, up-regulation of anti-inflammatory cytokines, and the action of vitamin D as a negative endocrine regulator of the renin–angiotensin system[85].

Baseline dietary vitamin D intake was found to be inversely associated with the risk of hypertension in 28 886 US women aged ≥ 45 years followed for 10 years in the Women's Health Study[86]. In two prospective cohort studies including 613 men from the Health Professionals Follow-up Study and 1198 women from the Nurses' Health Study followed for 4–8 years, the RR of incident hypertension among men whose plasma 25(OH)D levels were < 37·5 nmol/l was 6·13 compared with those whose levels were ≥ 75 nmol/l, while in women the RR was 2·67[87]. A prospective nested case–control study of 18 225 men in the Health Professionals Follow-up study followed for 10 years showed that men with 25(OH)D ≤ 37·5 nmol/l had a RR of 2·42 for myocardial infarction compared with those with 25(OH)D ≥ 75 nmol/l[88]. Among 4839 participants of the National Health and Nutrition Examination Survey 2001–2004, the prevalence ratio of peripheral arterial disease after multivariable adjustment was 1·35 for each 25 nmol/l lower baseline serum 25(OH)D[89]. In a prospective cohort study of 3258 consecutive patients (mean age 62 years) scheduled for coronary angiography followed for a median of 7·7 years, the multivariate-adjusted hazard ratios for patients in the lower two serum 25(OH)D quartiles were 2·08 and 1·53 for all-cause death and 2·22 and 1·82 for cardiovascular mortality, respectively, compared with the highest quartile[90]. Similar but less significant relationships were also found for serum $1,25(OH)_2D$[90].

CVD is the leading cause of death (>70 %) in dialysis patients and some form of vitamin D intake is recommended in those patients[91]. Vitamin D deficiency has been known to affect cardiac contractility, vascular tone, cardiac collagen content and tissue maturation, while treatment with vitamin D improves survival rates in the patients with end-stage renal disease[92]. In a prospective cohort study (follow for 61 (SD 23) months) comparing the risk of death between users (*n* 162) and non-users (*n* 80) of oral $1,25(OH)_2D_3$ in a cohort of end-stage renal disease undergoing haemodialysis, the vitamin D users showed a hazard ratio of 0·287 compared with non-users for death from CVD[93]. Baseline serum 25(OH)D was significantly associated with a reduction of fatal or non-fatal cardiovascular events in 230 peritoneal dialysis patients followed for 3 years or until death with every 1-unit increase in log-transformed serum 25(OH)D associated with a 44 % reduction[94]. Low serum levels of 25(OH)D and $1,25(OH)_2D$ were independent risk factors for fatal strokes during a median follow-up of 7·75 years in the Ludwigshafen Risk and Cardiovascular Health study with 3316 patients who were referred to coronary angiography[95].

However, highly elevated serum 25(OH)D levels (≥ 222·5 nmol/l) had an adjusted OR of 3·18 for IHD in a cross-sectional case–control study with 143 patients with either angiographic evidence of coronary artery disease or acute myocardial infarction and seventy controls[96]. In a randomised prospective study involving 36 282 postmenopausal women (aged 50–79 years) in the Women's Health Initiative study, supplementation of 500 mg calcium carbonate with 200 IU vitamin D_3 twice daily neither increased nor decreased coronary or cerebrovascular risk in 7 years of follow-up[97], probably due to the inadequate intervention vitamin D dose or concurrent use of vitamin D and/or Ca in the controls[98].

Overall, there is strong evidence that maintaining sufficient vitamin D nutritional status has a significantly favourable impact on cardiovascular and cerebrovascular diseases.

Vitamin D and cancer

$1,25(OH)_2D$-mediated repression or activation of proto-oncogenes or tumour-suppression genes that are related to cell proliferation and differentiation has been observed in a variety of normal and tumour tissues, including the small and large intestines[99]. This genetic mechanism seems responsible for the anti-cancer properties observed for vitamin D.

From ecological, case–control and cohort studies, sunlight was shown to be inversely associated with mortality or incidence of prostate, breast, ovary and colon cancer[100–102]. Serum levels and dietary vitamin D are associated with reduced risks of colorectal cancer and, less certainly, prostate cancer[101]. Solar UVB radiation was found to be associated with reduced risks of breast, colon, ovary, prostate and non-lymphoma cancer while an inverse correlation between mortality rates and UVB radiation was found for bladder, oesophageal, kidney, lung, pancreatic, rectal, stomach and corpus uteri cancer in a ecological study covering the entire USA with only a few states excluded[103]. In a large cohort consisted of 416 134 skin cancer and 3 776 501 non-skin cancer as the first cancer extracted from thirteen cancer registries, risk for all second solid primary cancers except skin and lip cancers after skin melanoma were significantly lower for the sunny countries[104]. This relationship is more pronounced after non-melanoma skin cancer as the first cancer[104]. From a prospective cohort study (Health Professionals Follow-Up Study) followed for up to 14 years, serum 25(OH)D levels were predicted for 47 800 men via a multiple linear regression model including variables of dietary and supplementation vitamin D, skin pigmentation, adiposity, geographic residency and leisure-time physical activity[105]. From multivariable models, an increase in predicted serum 25(OH)D of 25 nmol/l was associated with a 17 % reduction in cancer incidence and a 29 % reduction in total cancer mortality[105]. In another prospective cohort study involving 363 renal transplant recipients followed for at least 3 years, pre-transplant serum $25(OH)D_3$ levels were inversely associated with cancer incidence after the transplantation[106].

Colorectal cancer

There are many trials reporting an inverse relationship between vitamin D and colorectal or colon cancer. In 12 823 men and 14 922 women with diagnosis of colon cancer, the survival rate 18 months after diagnosis was dependent on the season of diagnosis, with higher calculated serum

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

$25(OH)D_3$ levels at diagnosis offering better survival rates[107]. In a large cohort study of 34 702 postmenopausal women followed for 9 years, both Ca and vitamin D intakes were inversely associated with rectal cancer risk, though the trend for vitamin D was not significant[108]. It is worth mentioning that Ca and vitamin D intakes had additive protective effects for rectal cancer risk in the population[108]. In a population-based, case–control study of colorectal cancer in Wisconsin women (678 controls, 348 colon and 164 rectal cancers), high Ca intake was associated with reduced colon and rectal cancer risk[109]. Similar relationships were found with vitamin D intake but were less significant[109]. In a population-based case–control study of 352 colon and 217 rectal cancers with 512 controls, dietary vitamin D was inversely associated with colorectal cancer risk, while dietary Ca was not[110]. One shortcoming of the study is that the supplementation of vitamin D and Ca was not ascertained[110]. In a prospective study of 60 866 men and 66 883 women followed for up to 5 years, both Ca and vitamin D intakes were inversely associated with colorectal cancer risk[111]. From a large population-based study with 48 115 US women followed for 22 years, both Ca and vitamin D intakes were weakly inversely associated with distal colorectal adenoma risk, while vitamin D intake was strongly associated with reduced risk of distal colon adenoma[112]. In a multicentre randomised clinical trial of 1905 participants designed for dietary effects on recurrence of colorectal adenoma, dietary and supplement data were collected in each of the 4 years[113]. Total vitamin D intake was weakly inversely associated with adenoma recurrence, while Ca was not[113]. Ca supplementation was found to reduce colorectal adenoma recurrence only when the serum 25(OH)D was $> 72{\cdot}8$ nmol/l (median level) and serum 25(OH)D levels were inversely associated with the risk only among the subjects having the Ca supplement in a multicentre, placebo-controlled randomised trial of Ca supplementation for the prevention of colorectal adenoma recurrence involving 803 patients[114].

However, there are many trials reporting non-significant relationship between vitamin D and colorectal or colon cancer. Both vitamin D and Ca intakes were found inversely associated with colon cancer risk in a prospective study of 47 935 US male health professionals followed for 6 years, but the associations were not significant after adjusted for confounding variables[115]. From a multi-state cohort study of 1993 colon cancer cases and 2410 population-based controls in the USA, dietary Ca but not dietary vitamin D was inversely associated with colon cancer, while vitamin D supplementation was inversely associated with colon cancer risk[116]. Similarly, from a population-based study involving 61 463 women in Sweden followed for an average of 11·3 years, dietary Ca, not vitamin D, was inversely associated with colorectal cancer risk[117]. Intakes of Ca and vitamin D were not associated with the risk of colorectal cancer in a large, prospective, female cohort from the US Women's Health Study with 39 876 women aged > 45 years followed for an average of 10 years[118]. Ca, but not vitamin D intake, was inversely associated with the risk of both colorectal adenoma and cancer in another large prospective cohort study of 73 034 French women followed for up to 7 years[119]. Daily supplementation of Ca with vitamin D for 7 years had no effect on the incidence of colorectal cancer among postmenopausal women in a randomised, double-blind, placebo-controlled trial involving 36 282 postmenopausal women from forty Women's Health Initiative centres[120].

To understand the conflicting results from these studies, a few factors should be considered: (1) subjects' baseline intake of Ca and vitamin D; (2) duration of the studies, considering the long latency (10–20 years) of colon cancer; (3) insufficient vitamin D intake in the intervention studies, considering that serum 25(OH)D > 80 nmol/l is considered sufficient and most dietary studies had intake of only 400–500 IU/d[32,121]. There are many confounders associated with dietary vitamin D studies including *in vivo* vitamin D synthesis upon exposure to UVB. Therefore, measuring serum levels of 25(OH)D is a more accurate way of assessing vitamin D status in a clinical study exploring the association of vitamin D with diseases.

In a case–control study with 473 primary distal colorectal adenoma cases and 507 controls, plasma 25(OH)D showed a linear trend (not statistically significant) toward decreasing risk of the adenoma[122]. A nested case–control study within a Finnish clinical trial cohort involving 146 cases (ninety-one colon, fifty-five rectal cancer) and 290 controls showed that baseline serum 25(OH)D, not $1,25(OH)_2D$, in cases was significantly lower by 11·6 % with an average of 3·5 years between sample collection and case diagnosis[123]. Another case–control study involving 239 colorectal adenoma and 228 controls showed an inverse association between serum 25(OH)D and colorectal adenoma risk; the relationship was strengthened by Ca intake above the median[124]. A subset (179 colorectal cancer cases and 356 controls) of the Health Professionals Follow-up Study was followed for 8 years, and higher plasma 25(OH)D levels were significantly associated with decreased risk of colon cancer[125]. When pooled with the Nurses' Health Study, higher plasma 25(OH)D levels were significantly inversely associated with both colorectal and colon cancers[125]. A more recent case–control study in Japan involving 375 colorectal cancers with two controls for each case showed that the lowest quartile of plasma 25(OH)D was associated with an increased risk of rectal cancer in both men and women, though no significant correlation was observed between plasma 25(OH)D and colorectal cancer in the 11·5-year follow-up after blood collection[126]. An analysis of eighteen prospective cohort or retrospective case–control studies showed that individuals with intake of ≥ 1000 IU/d or serum 25(OH)D $\geq 82{\cdot}5$ nmol/l had a 50 % lower incidence of colorectal cancer compared with reference values (100 IU/d or $< 32{\cdot}5$ nmol/l)[127]. A meta-analysis of five nested case–control studies of serum 25(OH)D in association with colorectal cancer risk showed that a 50 % lower risk of colorectal cancer was associated with serum 25(OH)D $\geq 82{\cdot}5$ nmol/l compared with serum 25(OH)D ≤ 30 nmol/l[128].

Breast cancer

Breast cancer is the most commonly diagnosed cancer in US women[129]. The vitamin D receptor is present in breast tissue and $1,25(OH)_2D$ has anti-proliferative and pro-differentiation effects on breast cancer cells[130]. Vitamin D

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

and Ca are metabolically interrelated and are suggested in playing a role in the development of breast cancer by some epidemiological studies[129]. In an analysis of the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, among a cohort of 5009 white women followed for an average of 17·3 years, several measures of sunlight exposure and dietary vitamin D intake were associated with a reduced risk of breast cancer[131]. The highest risk reduction was observed for women who lived in US regions of high solar radiation while no risk reduction was observed for the women who lived in regions of low solar radiation[131]. In a population-based case–control study in Germany involving 278 premenopausal cases and 666 age-matched controls, vitamin D intake was significantly inversely associated with breast cancer risk[132]. During 16 years of follow-up of 88 691 women in the Nurses' Health Study, both dairy Ca (RR 0·69; >800 *vs.* ≤200 mg/d) and total vitamin D intake (RR 0·72; >500 *vs.* ≤150 IU/d) had inverse associations with breast cancer risk in premenopausal but not postmenopausal women[133]. From a large prospective cohort study of 34 321 postmenopausal women followed for 18 years in the Iowa Women's Health Study, women with vitamin D intake >800 IU/d had an adjusted risk for breast cancer of 0·89 (weak association) compared with those with vitamin D intake <400 IU/d[134]. From a population-based case–control study in Canada involving 972 newly diagnosed invasive breast cancer and 1135 controls, reduced breast cancer risk was associated with increased sunlight exposure from age 10 to 19 years[135]. In addition, cod liver oil use and increased milk consumption were also associated with a reduced risk of breast cancer[135]. The associations were weaker for women aged 20–29 years and null for women aged 45–54 years[135]. The importance of adolescent exposure to vitamin D on breast cancer risk reduction in adulthood was not observed in either the Nurses' Health Study or the Nurses' Health Study II in which diet during high school was assessed by dietary questionnaire at adulthood[136,137]. However, dietary Ca but not vitamin D was found to be inversely associated with breast cancer risk in the Cancer Prevention Study II Nutrition Cohort of 68 567 postmenopausal women followed up to 9 years[138]. Though these studies are important at initial identification of a vitamin D and breast cancer relationship, dietary vitamin D intake cannot be considered a complete assessment of vitamin D nutritional status[129].

Among 790 breast cancer survivors in the Health, Eating, Activity, and Lifestyle Study, forty-nine (6·2 %) had serum 25(OH)D <25 nmol/l and 548 (69·4 %) had serum 25(OH)D between 25 and 80 nmol/l[139]. The overall mean serum 25(OH)D was 62 (SD 26) nmol/l, while African American survivors had 45·3 (SD 21·8) nmol/l and Hispanic survivors had 55·3 (SD 23) nmol/l[139]. In a case–control study followed for about 6 years nested within the Nurses' Health Study involving 701 cases and 724 controls, cases had a significantly lower plasma 25(OH)D than controls, while mean $1,25(OH)_2D$ levels were similar in the two cohorts[140]. Serum 25(OH)D was significantly inversely associated with postmenopausal breast cancer risk in a population-based case–control study in Germany with 1394 cases and 1365 controls[141]. Compared with the lowest category (<30 nmol/l serum 25(OH)D), OR in other categories for breast cancer were 0·57 (30–45 nmol/l), 0·49 (45–60 nmol/l), 0·43 (60–75 nmol/l) and 0·31 (≥75 nmol/l)[141]. In a short-term (mean 3·9 years between blood draw and cancer diagnosis) prospective cohort case–control study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, neither serum 25(OH)D nor $1,25(OH)_2D$ was associated with breast cancer risk in the postmenopausal women[142]. This negative finding may be due to the very short period of follow-up.

In conclusion, epidemiological evidence of protective effects of vitamin D on breast cancer risk is strong, though some conflicting data have been reported.

Lymphoma

Strong evidence from case–control studies exists for protection against non-Hodgkin lymphoma by sun exposure and vitamin D intake. In a case–control study involving 704 adults with non-Hodgkin lymphoma and 694 controls in Australia, sun exposure was inversely associated with the risk of non-Hodgkin lymphoma, especially in women and in childhood[143]. Sunbathing and sunburns at age 20 years, 5–10 years before the interview, and sun exposure during vacations abroad were inversely associated with the risks of non-Hodgkin lymphoma as well as Hodgkin lymphoma, though the association was weaker for Hodgkin lymphoma in a population-based case–control study with 3740 patients and 3187 controls in Denmark and Sweden[144]. UV radiation exposure but not dietary vitamin D was associated with a reduced risk of non-Hodgkin lymphoma in a case–control study with 551 cases and 462 controls in the USA[145]. UV radiation exposure was also found to reduce overall lymphoma risk in a population-based case–control study with 710 paired malignant lymphoma cases and controls in Germany[146]. Total sun exposure was found inversely related to the risk of non-Hodgkin lymphoma in a population-based case–control study in the USA with 387 cases and 535 controls[147]. In a pooled analysis including ten case–control studies covering 8243 cases and 9697 controls in the USA, Europe and Australia, the risk of non-Hodgkin lymphoma fell significantly with the composite measure of increasing recreational sun exposure (OR 0·76 for the highest category)[148]. In a hospital-based case–control study with 190 cases and 484 controls, the risk of non-Hodgkin lymphoma was reduced by the intake of vitamin D, PUFA and linoleic acid[149].

Prostate cancer

There are perplexing data on the relationship between vitamin D and prostate cancer risk[32]. Analysis of a cohort of 3414 white men, among whom 153 developed prostate cancer after up to 21 years of follow-up in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, residential sunlight exposure was associated with significant and substantial reductions in prostate cancer risk[150]. An inverse correlation between the UVB levels and prostate cancer incidence and mortality rates were observed for white men, while for black men only prostate cancer incidence was significantly inversely

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

associated with UVB radiation in the continental USA[151]. However, both higher latitude and July UVB radiation were associated with a higher risk of prostate cancer mortality rates in the USA in the periods of 1970–94 and 1950–69, indicating that both high and low levels of vitamin D impose risk for prostate cancer mortality[152].

Effects of dietary vitamin D on prostate cancer can be confounded by other ingredients in the food that can be either risk enhancers or reducers for prostate cancer[152]. In a population-based case–control study in Sweden with 526 cases and 536 controls, dietary vitamin D intake was not associated with prostate risk while Ca intake was positively associated with prostate cancer risk[153]. Dietary vitamin D intake was shown not to be associated with prostate cancer risk in another population-based, case–control study involving 605 incident cases and 592 controls in the USA[154]. Dietary vitamin D was not significantly associated with prostate cancer risk, while Ca intake was a positive risk in a prospective study of 3612 men followed for up to 10 years in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study[155]. Comparing 1294 men with incident prostate cancer with 1451 men admitted to hospital for acute non-neoplastic diseases in Italy, no material association of dietary Ca or vitamin D with prostate cancer risk was found[156]. No association of either dietary vitamin D or Ca intake with prostate cancer risk was found for 82 483 men followed for a mean of 8 years in the Multiethnic Cohort Study[157]. In a meta-analysis of 26 769 cases from forty-five observational studies, neither dietary vitamin D nor Ca demonstrated a significant association with prostate cancer risk[158]. Most of the study subjects had very low vitamin D intake and therefore the true effects of vitamin D on prostate cancer might not be determined by these data.

Using serum or plasma levels of vitamin D metabolites as indicators of vitamin D nutritional status, many case–control studies showed no significant relationship between vitamin D and prostate cancer. In a nested case–control study including 232 cases and 414 age-matched controls in the 14 916 participants of the Physicians' Health Study followed for 10 years, no significant association between either 25(OH)D or $1,25(OH)_2D$ and prostate cancer risk was observed[159]. No significant association was found between prostate cancer risk and either 25(OH)D or $1,25(OH)_2D$ in a nested case–control study in a cohort of 3737 Japanese American men followed for over 23 years[160]. In a prospective case–control study involving 460 men who developed prostate cancer and an equal number of controls in the Health Professionals Follow-up study followed for up to 5 years, there was no inverse association between plasma 25(OH)D or $1,25(OH)_2D$ and incident prostate cancer risk[161]. No significant inverse correlation between 25(OH)D or $1,25(OH)_2D$ with prostate cancer risk was observed in a nested case–control study involving eighty-three cases and 166 controls within the Nutrition Prevention of Cancer trial followed for up to 19 years[162]. No statistically significant trend was observed for overall prostate cancer risk with increasing season-standardised serum 25(OH)D in a nested case–control study with 749 cases and 781 controls within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial followed for up to 10 years[163]. However, serum 25(OH)D levels greater than the lowest quintile were associated with an increased risk of aggressive disease[163].

Contrarily, there are studies showing a significant relationship between serum or plasma vitamin D status and prostate cancer risk. In a nested case–control study involving 149 prostate cancer cases and four controls for each case based on a 13-year follow-up of about 19 000 middle-aged men within the Helsinki Heart Study, prostate cancer risk was inversely associated with baseline serum 25(OH)D, with an OR of 1·7 for serum 25(OH)D levels below the median compared with those above the median[164]. This relationship was more pronounced among the young men (aged < 52 years), with an OR of 3·5[164]. In a longitudinal nested case–control study with 622 prostate cancer cases and 1451 controls on Nordic men using serum banks of about 200 000 samples followed for up to 24 years, both low (≤ 19 nmol/l) and high (≥ 80 nmol/l) serum 25(OH)D had association with higher prostate cancer risk[165]. The optimal concentration of serum 25(OH)D was 40–60 nmol/l[165]. Low serum 25(OH)D (≤ 40 nmol/l) significantly strengthened the relationship between the risk of prostate cancer and factors related to the metabolic syndrome while serum 25(OH)D was not significantly associated with prostate cancer risk in a longitudinal nested case–control study with 132 prostate cancer cases and 456 controls within a cohort of 18 939 Finnish middle-aged men followed for about 16 years in the Helsinki Heart Study[166]. In a prospective case–control study with 1066 men with incident prostate cancer and 1618 controls among 14 916 men followed for 18 years within the Physicians' Health Study, men with serum levels of both 25(OH)D and $1,25(OH)_2D$ below the medians had a significantly increased risk of aggressive prostate cancer[167]. There was also significant interaction between circulating 25(OH)D and vitamin D receptor genotype for prostate cancer risk[167].

Overall, the relationship between prostate cancer risk and vitamin D nutritional status is conflicting and not conclusive. Genetic polymorphisms seem to play an important role. Further long-term comprehensive studies evaluating the effects of both serum levels of 25(OH)D and genetic variations in vitamin D receptor on prostate cancer risk are needed.

Ovarian cancers

The evidence on the relationship between vitamin D and ovarian cancer is contradictory and no definitive conclusion can be drawn from the data currently available.

Residential exposure to sunlight was significantly inversely correlated with mortality of ovarian cancer from data collected from 1984 to 1995 in twenty-four US states[102]. In an analysis of UVB data for July 1992 and cancer mortality rates in the USA for 1970–94, solar UVB radiation was associated with a reduced risk of ovarian cancer[103]. Fatal ovarian cancer in the 100 largest US cities in 1979–88 was inversely associated with mean annual intensity of local sunlight[168]. UVB irradiance was also inversely associated with ovarian cancer risk based on age-adjusted incidence rates for 175 countries using the

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

Table 1. Selected studies on relationship between blood 25-hydroxyvitamin D (25(OH)D) (nmol/l) and risk for various diseases

Reference	Study design	Duration (years)	Study population	Low 25(OH)D	High 25(OH)D	OR (high/low)	Disease
Melamed *et al.* (2008)[57]	Survey	Up to 12	Third National Health and Nutrition Examination Survey	<44·5	>80·3	0·79*	Overall mortality (for women 25(OH)D < 50 and >125 posed significant risk)
Trivedi *et al.* (2003)[62]	Randomised double-blind controlled trial: 100 000 IU D_3 or placebo	5	General community dwellers, 65–85 years of age	53·4 (SD 21·1), placebo group	74·3 (SD 20·7), D_3 group	0·78*	Fractures
Roddam *et al.* (2007)[65]	Nested case–control	5	European Retrospective Investigation into Cancer and Nutrition-Oxford cohort	<50	≥100	1·26 (men); 0·94 (women)	Fractures
Suzuki *et al.* (2008)[69]	Cross-sectional	1	Japanese community dwellers, 62–92 years of age	<50	≥50	1·71 (men); 0·66* (women)	Falls
LeBoff *et al.* (2008)[70]	Retrospective	1	Community-dwelling women with hip fractures	≤22·5	>22·5	0·58*	Falls
Munger *et al.* (2006)[74]	Nested case–control	<1–13	US military personnel	<63·3	>99·1	0·38*	Multiple sclerosis
Mattila *et al.* (2007)[84]	Prospective cohort	17	Mini-Finland Health Survey	<30	>55	0·60*	Type 2 diabetes
Knekt *et al.* (2008)[82]	Two nested case–control	17–22	Finish Mobile Mini-Finland	≤32	≥58	0·28* (men)	Type 2 diabetes
				≤26	≥49	1·14 (women)	
Forman *et al.* (2007)[87]	Prospective cohort	4–8	Health Professionals Follow-up Nurses' Health Study	<37·5	≥75	0·16* (men) 0·37* (women)	Hypertension
Giovannucci *et al.* (2008)[88]	Nested case–control	10	Health Professionals Follow-up	≤37·5	≥75	0·41*	Myocardial infarction
Melamed *et al.* (2008)[89]	Survey	NA	National Health and Nutrition Examination Survey 2001–2004	<44·5	≥73	0·56*	Peripheral arterial disease
Dobnig *et al.* (2008)[90]	Prospective cohort	Median 7·7	Patients scheduled for coronary angiography	≤25·3	≥59	0·45*	Cardiovascular mortality
						0·48*	All-cause mortality
Rajasree *et al.* (2001)[96]	Cross-sectional case–control	NA	IHD *v.* controls	<222·5	≥222·5	3·18*	IHD
Giovannucci *et al.* (2006)[105]	Prospective cohort	Up to 14	Health Professionals Follow-up	NA	Increase of 25·0	0·83*	Total cancer incidence
						0·71*	Total cancer mortality
Ducloux *et al.* (2008)[106]	Prospective cohort	5	Kidney transplant patients	<25	>80	0·27*	All cancer
Levine *et al.* (2001)[122]	Case–control	NA	Primary adenoma *v.* controls	≤38	≥85·8	0·74	Colorectal adenoma
Tangrea *et al.* (1997)[123]	Nested case–control	1–7	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	≤24·5	>48·3	0·6	Large bowel cancer
Peters *et al.* (2001)[124]	Case–control	NA	Colorectal adenoma *v.* controls	NA	Increase of 25·0	0·74*	Colorectal adenoma
Wu *et al.* (2007)[125]	Nested case–control	Up to 8	Health Professionals Follow-up	Median 48·3	Median 97·0	0·46*	Colon cancer
Otani *et al.* (2007)[126]	Nested case–control	11·5	Japan Public Health Center-based Prospective Study	<57·3	≥80·3	0·075 (men)	Colorectal cancer
				<46·8	≥67·5	0·33 (women)	
Gorham *et al.* (2005)[127]	Meta-analysis	2–8	General healthy population	<32·5	≥82·5	0·50*	Colorectal cancer
Gorham *et al.* (2007)[128]	Meta-analysis	2–25	General healthy population	≤30	≥82·5	0·50*	Colorectal cancer
Bertone-Johnson *et al.* (2005)[140]	Nested case–control	6–7	Nurses' Health Study Cohort	≤45	≥92·5	0·73	Breast cancer
Abbas *et al.* (2008)[141]	Case–control	NA	Postmenopausal residents	<30	≥75	0·31*	Breast cancer
Freedman *et al.* (2008)[142]	Prospective nested case–control	Mean 3·9	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	<45·8	≥84·3	1·04	Breast cancer
Gann *et al.* (1996)[159]	Nested case–control	10	Physicians' Health Study	≤53·3	≥93·8	0·92	Prostate cancer
Nomura *et al.* (1998)[160]	Nested case–control	23	Japanese-Americans in Hawaii	<85	>120	0·8	Prostate cancer
Jacobs *et al.* (2004)[162]	Nested case–control	19	Nutritional Prevention Cancer Trial	≤63·3	≥82	0·75	Prostate cancer
Ahn *et al.* (2008)[163]	Case–control	10	Prostate, Lung, Colorectal, and Ovarian Cancer Trial	≤42·5	≥71·8	1·25	Prostate cancer
						1·37*	Gleason sum ≥ 7 or stage III or IV prostate cancer
Ahonen *et al.* (2000)[164]	Nested case–control	13	Helsinki Heart Study	≤40	>40	0·59*	Prostate cancer
Tuohimaa *et al.* (2004)[165]	Nested case–control	Up to 24	Nordic men	≤19	40–59	0·67*	Prostate cancer
				40–59	≥80	1·7*	Prostate cancer

Tworoger *et al.* (2007)[175]	Nested case–control	Up to 15	Nurses' Health Study, Nurses' Health Study II, and Women's Health Study	<43·5	>69·3	0·83	Ovarian cancer
Stolzenberg-Solomon *et al.* (2006)[177]	Nested case–control	Up to 16	Male Finnish smokers	<32	>65·5	2·92*	Pancreatic cancer
Chen *et al.* (2007)[180]	Nested case–control	5·25	Men	<20·3	>51·6	1·77*	Oesophageal squamous cell carcinoma
			Women	<18·7	>45·9	1·06	

NA, not available.
*OR were statistically significant ($P < 0·05$).

International Agency for Research on Cancer GLOBOCAN database[169]. In a case–control study in Mexico City with eighty-four new cases of ovarian cancer and 629 controls, dietary vitamin D intake was significantly associated with reduced ovarian cancer risk[170]. However, other dietary studies yielded negative results. In a hospital-based case–control study with 1031 ovarian cancer patients and 2411 controls in Italy, dietary vitamin D was not significantly associated with epithelial ovarian cancer risk[171]. A case–control study in Hawaii and Los Angeles with 558 patients and 607 controls did not show a significantly inverse association between dietary vitamin D and the risk of ovarian cancer[172]. No significant relationship was found for dietary vitamin D and ovarian cancer risk in a prospective cohort study among 31 925 subjects followed for an average of 8·3 years[173]. No significant association between dietary vitamin D intake and ovarian cancer risk was found in a meta-analysis of twelve prospective cohort studies that consisted of 553 217 women, among whom 2132 had epithelial ovarian cancer[174]. In a nested case–control study with 224 cases and 603 controls within the Nurses' Health Study, Nurses' Health Study II, and Women's Health Study, neither plasma 25(OH)D nor $1,25(OH)_2D$ was significantly associated with ovarian cancer risk[175].

Other cancers

There are limited reports on the relationship between vitamin D nutrition status and the risk of other types of cancer. More prospective studies are needed.

In the Health Professionals Follow-up Study with 47 800 men followed for 14 years, an increment of plasma 25(OH)D of 25 nmol/l was associated with significant reduction of the following cancers: pancreatic cancer (RR 0·49); oesophageal cancer (RR 0·37); colorectal cancer (RR 0·63)[105]. In an analysis of two prospective cohort studies of 46 771 men in the Health Professionals Follow-up Study followed for 14 years and 75 427 women in the Nurses' Health Study followed for 16 years, higher vitamin D intake was associated with a lower risk of pancreatic cancer[176]. The association was stronger in men than in women[176]. Contrarily, higher serum 25(OH)D was associated with an increased risk for pancreatic cancer in a prospective nested case–control study with 200 cases and 400 controls within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort of male Finnish smokers[177]. However, caution should be taken in interpreting the results due to the special study population who smoked and obtained vitamin D primarily from fish, which may contain ingredients that increase the risk for pancreatic cancer[178]. Higher dietary vitamin D intake was associated with an increased risk for laryngeal cancer in a hospital-based case–control study with 527 cases and 1297 controls[179]. In a prospective case–control study with 979 cases and 1105 controls followed for 6 years in China, higher serum 25(OH)D was associated with a higher risk for oesophageal squamous cell carcinomas in men but not in women[180]. No association was found between serum 25(OH)D with either gastric cardia or non-cardia adenocarcinoma[180]. It is noticeable that the serum 25(OH)D

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

level was low in the study population, with the 75th percentile at 48·7 nmol/l[180]. Among 100 multiple myeloma cases, 40 % had serum 25(OH)D ≤ 36 nmol/l, 35 % had serum 25(OH)D 36–75 nmol/l, and only 25 % had ≥ 75 nmol/l[181]. Based on the age-adjusted incidence rates for 175 countries in a UN cancer database (GLOBOCAN), lower levels of UVB and higher intakes of energy from animal foods were independently associated with a higher risk for kidney cancer[182]. No significant relationship was found between endometrial cancer and dietary vitamin D in a pooled analysis of three case–control studies[183]. Intermittent sun exposure was significantly inversely associated with the risk of death in 260 melanoma patients within a population-based case–control study in Italy followed for up to 21 years[184].

Conclusions

There is strong evidence that maintaining sufficient vitamin D nutritional status is beneficial to bone health, muscle strength, cardiovascular and cerebrovascular diseases, autoimmune disease, type 2 diabetes and many types of cancer. The best biomarker for vitamin D nutritional status is serum level of total 25(OH)D. The epidemiological studies are heterogeneous in respect of study design, study population and technologies used for 25(OH)D quantification. Based on the data summarised in Table 1, serum 25(OH)D level of at least 50 nmol/l seems required for beneficial impact on general health, bone metabolism, muscle strength, autoimmune disease, type 2 diabetes, CVD and various cancers. The optimal serum 25(OH)D concentration may be over 75 or 80 nmol/l. However, 25(OH)D levels higher than 125 nmol/l or 222·5 nmol/l may present adverse impacts on general mortality and IHD, respectively. The best serum 25(OH)D level for prostate cancer prevention might be 40–60 nmol/l. Prospective intervention studies are needed to define the optimal levels of vitamin D nutritional status for a variety of diseases.

The sufficient level of vitamin D nutritional status is currently considered to be serum 25(OH)D > 75 nmol/l, which is derived from the clinical studies using immunoassays or protein-binding assays. These assays show significant disparities among themselves and significant bias compared with LC–MS, which is considered the 'gold standard'. Therefore, to better serve patients and advance the understanding of the relationship between vitamin D nutritional status and health and disease, assay-specific reference ranges should be established, or all assays should be standardised to LC–MS with an appropriate reference range established.

Acknowledgements

The present research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

The author declared no potential conflicts of interest.

References

1. Rajakumar K (2003) Vitamin D, cod-liver oil, sunlight, and rickets: a historical perspective. *Pediatrics* **112**, E132–E135.
2. Wolpowitz D & Gilchrest BA (2006) The vitamin D questions: how much do you need and how should you get it? *J Am Acad Dermatol* **54**, 301–317.
3. Holick MF (2007) Vitamin D deficiency. *N Engl J Med* **357**, 266–281.
4. Holick MF (2004) Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* **80**, 1678S–1688S.
5. Zerwekh JE (2008) Blood biomarkers of vitamin D status. *Am J Clin Nutr* **87**, 1087S–1091S.
6. Nykjaer A, Dragun D, Walther D, *et al*. (1999) An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D_3. *Cell* **96**, 507–515.
7. Al-oanzi ZH, Tuck SP, Raj N, *et al*. (2006) Assessment of vitamin D status in male osteoporosis. *Clin Chem* **52**, 248–254.
8. Binkley N, Drezner MK & Hollis BW (2006) Laboratory reporting of 25-hydroxyvitamin D results: potential for clinical misinterpretation. *Clin Chem* **52**, 2124–2125.
9. Lissner D, Mason RS & Posen S (1981) Stability of vitamin-D metabolites in human-blood serum and plasma. *Clin Chem* **27**, 773–774.
10. Antoniucci DM, Black DM & Sellmeyer DE (2005) Serum 25-hydroxyvitamin D is unaffected by multiple freeze–thaw cycles. *Clin Chem* **51**, 258–261.
11. Carter GD, Carter R, Jones J, *et al*. (2004) How accurate are assays for 25-hydroxyvitamin D? Data from the international vitamin D external quality assessment scheme. *Clin Chem* **50**, 2195–2197.
12. Binkley N, Krueger D, Cowgill CS, *et al*. (2004) Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. *J Clin Endocrinol Metab* **89**, 3152–3157.
13. Glendenning P, Taranto M, Noble JM, *et al*. (2006) Current assays overestimate 25-hydroxyvitamin D_3 and underestimate 25-hydroxyvitamin D_2 compared with HPLC: need for assay-specific decision limits and metabolite-specific assays. *Ann Clin Biochem* **43**, 23–30.
14. Terry AH, Sandrock T & Meikle AW (2005) Measurement of 25-hydroxyvitamin D by the Nichols ADVANTAGE, DiaSorin LIAISON, DiaSorin RIA, and liquid chromatography–tandem mass spectrometry. *Clin Chem* **51**, 1565–1566.
15. Roth HJ, Schmidt-Gayk H, Weber H, *et al*. (2008) Accuracy and clinical implications of seven 25-hydroxyvitamin D methods compared with liquid chromatography–tandem mass spectrometry as a reference. *Ann Clin Biochem* **45**, 153–159.
16. Lensmeyer GL, Wiebe DA, Binkley N, *et al*. (2006) HPLC method for 25-hydroxyvitamin D measurement: comparison with contemporary assays. *Clin Chem* **52**, 1120–1126.
17. Alvarez JC & De Mazancourt P (2001) Rapid and sensitive high-performance liquid chromatographic method for simultaneous determination of retinol, α-tocopherol, 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2 in human plasma with photodiode-array ultraviolet detection. *J Chromatogr B Biomed Sci App* **755**, 129–135.
18. Turpeinen U, Hohenthal U & Stenman UH (2003) Determination of 25-hydroxyvitamin D in serum by HPLC and immunoassay. *Clin Chem* **49**, 1521–1524.

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

19. Olkowski AA, Aranda-Osorio G & McKinnon J (2003) Rapid HPLC method for measurement of vitamin D_3 and 25(OH)D_3 in blood plasma. *Int J Vitam Nutr Res* **73**, 15–18.
20. Singh RJ, Taylor RL, Reddy GS, *et al*. (2006) C-3 epimers can account for a significant proportion of total circulating 25-hydroxyvitamin D in infants, complicating accurate measurement and interpretation of vitamin D status. *J Clin Endocrinol Metab* **91**, 3055–3061.
21. Higashi T, Awada D & Shimada K (2001) Simultaneous determination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 in human plasma by liquid chromatography–tandem mass spectrometry employing derivatization with a Cookson-type reagent. *Biol Pharm Bull* **24**, 738–743.
22. Higashi T, Shibayama Y, Fuji M, *et al*. (2008) Liquid chromatography–tandem mass spectrometric method for the determination of salivary 25-hydroxyvitamin D_3: a noninvasive tool for the assessment of vitamin D status. *Anal Bioanal Chem* **391**, 229–238.
23. Aronov PA, Hall LM, Dettmer K, *et al*. (2008) Metabolic profiling of major vitamin D metabolites using Diels–Alder derivatization and ultra-performance liquid chromatography–tandem mass spectrometry. *Anal Bioanal Chem* **391**, 1917–1930.
24. Vogeser M, Kyriatsoulis A, Huber E, *et al*. (2004) Candidate reference method for the quantification of circulating 25-hydroxyvitamin D_3 by liquid chromatography–tandem mass spectrometry. *Clin Chem* **50**, 1415–1417.
25. Tsugawa N, Suhara Y, Kamao M, *et al*. (2005) Determination of 25-hydroxyvitamin D in human plasma using high-performance liquid chromatography–tandem mass spectrometry. *Anal Chem* **77**, 3001–3007.
26. Chen HP, McCoy LF, Schleicher RL, *et al*. (2008) Measurement of 25-hydroxyvitamin D_3 ($25OHD_3$) and 25-hydroxyvitamin D_2 ($25OHD_2$) in human serum using liquid chromatography–tandem mass spectrometry and its comparison to a radioimmunoassay method. *Clin Chim Acta* **391**, 6–12.
27. Saenger AK, Laha TJ, Bremner DE, *et al*. (2006) Quantification of serum 25-hydroxyvitamin D_2 and D_3 using HPLC–tandem mass spectrometry and examination of reference intervals for diagnosis of vitamin D deficiency. *Am J Clin Pathol* **125**, 914–920.
28. Maunsell Z, Wright DJ & Rainbow SJ (2005) Routine isotope-dilution liquid chromatography–tandem mass spectrometry assay for simultaneous measurement of the 25-hydroxy metabolites of vitamins D_2 and D_3. *Clin Chem* **51**, 1683–1690.
29. Capote FP, Jimenez JR, Granados JMM, *et al*. (2007) Identification and determination of fat-soluble vitamins and metabolites in human serum by liquid chromatography/triple quadrupole mass spectrometry with multiple reaction monitoring. *Rapid Commun Mass Spectrom* **21**, 1745–1754.
30. Grant RP, Cameron C & Mackenzie-McMurter S (2002) Generic serial and parallel on-line direct-injection using turbulent flow liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom* **16**, 1785–1792.
31. Zimmer D, Pickard V, Czembor W, *et al*. (1999) Comparison of turbulent-flow chromatography with automated solid-phase extraction in 96-well plates and liquid–liquid extraction used as plasma sample preparation techniques for liquid chromatography–tandem mass spectrometry. *J Chromatogr A* **854**, 23–35.
32. Grant WB (2006) Epidemiology of disease risks in relation to vitamin D insufficiency. *Prog Biophys Mol Biol* **92**, 65–79.
33. Heaney RP (2004) Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr* **80**, 1706S–1709S.
34. Cherniack EP, Florez H, Roos BA, *et al*. (2008) Hypovitaminosis D in the elderly: from bone to brain. *J Nutr Health Aging* **12**, 366–373.
35. Dawson-Hughes B, Heaney RP, Holick MF, *et al*. (2005) Estimates of optimal vitamin D status. *Osteoporos Int* **16**, 713–716.
36. Egan KM, Signorello LB, Munro HM, *et al*. (2008) Vitamin D insufficiency among African-Americans in the southeastern United States: implications for cancer disparities (United States). *Cancer Causes Control* **19**, 527–535.
37. Mark S, Gray-Donald K, Delvin EE, *et al*. (2008) Low vitamin D status in a representative sample of youth from Quebec, Canada. *Clin Chem* **54**, 1283–1289.
38. Wolfenden LL, Judd SE, Shah R, *et al*. (2008) Vitamin D and bone health in adults with cystic fibrosis. *Clin Endocrinol (Oxf)* **69**, 374–381.
39. Mehrotra R, Kermah D, Budoff M, *et al*. (2008) Hypovitaminosis D in chronic kidney disease. *Clin J Am Soc Nephrol* **3**, 1144–1151.
40. Hedges T & Scriven A (2008) Sun safety: what are the health messages? *J R Soc Promot Health* **128**, 164–169.
41. Cranney A, Weiler HA, O'Donnell S, *et al*. (2008) Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. *Am J Clin Nutr* **88**, 513S–519S.
42. Vieth R (1999) Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* **69**, 842–856.
43. National Academy of Sciences, Institute of Medicine & Food and Nutrition Board (1997) Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=4&tax_subject=256&topic_id=1342&level3_id=5141&level4_id=10587 (accessed 19 August 2009).
44. Maalouf J, Nabulsi M, Vieth R, *et al*. (2008) Short- and long-term safety of weekly high-dose vitamin D-3 supplementation in school children. *J Clin Endocrinol Metab* **93**, 2693–2701.
45. Heaney RP, Armas LAG, Shary JR, *et al*. (2008) 25-Hydroxylation of vitamin D_3: relation to circulating vitamin D_3 under various input conditions. *Am J Clin Nutr* **87**, 1738–1742.
46. The Electronic Medicines Compendium (2007) Calcichew-D_3 Forte Chewable Tablets. http://emc.medicines.org.uk/document.aspx?documentId=1989 (accessed 19 August 2009).
47. Ryan PJ (2007) Vitamin D therapy in clinical practice. One dose does not fit all. *Int J Clin Pract* **61**, 1894–1899.
48. Gordon CM, Williams AL, Feldman HA, *et al*. (2008) Treatment of hypovitaminosis D in infants and toddlers. *J Clin Endocrinol Metab* **93**, 2716–2721.
49. Aloia JF, Patel M, DiMaano R, *et al*. (2008) Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr* **87**, 1952–1958.
50. Heaney RP, Davies KM, Chen TC, *et al*. (2003) Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* **77**, 204–210.
51. Jones G (2008) Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr* **88**, 582S–586S.
52. Armas LAG, Hollis BW & Heaney RP (2004) Vitamin D_2 is much less effective than vitamin D_3 in humans. *J Clin Endocrinol Metab* **89**, 5387–5391.
53. Trang HM, Cole DE, Rubin LA, *et al*. (1998) Evidence that vitamin D_3 increases serum 25-hydroxyvitamin D more

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

efficiently than does vitamin D_2. *Am J Clin Nutr* **68**, 854–858.
54. Houghton LA & Vieth R (2006) The case against ergocalciferol (vitamin D_2) as a vitamin supplement. *Am J Clin Nutr* **84**, 694–697.
55. Leventis P & Kiely PDW (2009) The tolerability and biochemical effects of high-dose bolus vitamin D_2 and D_3 supplementation in patients with vitamin D insufficiency. *Scand J Rheumatol* **38**, 149–153.
56. Holick MF, Biancuzzo RM, Chen TC, *et al*. (2008) Vitamin D_2 is as effective as vitamin D_3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* **93**, 677–681.
57. Melamed ML, Michos ED, Post W, *et al*. (2008) 25-Hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* **168**, 1629–1637.
58. Inaguma D, Nagaya H, Hara K, *et al*. (2008) Relationship between serum 1,25-dihydroxyvitamin D and mortality in patients with pre-dialysis chronic kidney disease. *Clin Exp Nephrol* **12**, 126–131.
59. Kovesdy CP, Ahmadzadeh S, Anderson JE, *et al*. (2008) Association of activated vitamin D treatment and mortality in chronic kidney disease. *Arch Intern Med* **168**, 397–403.
60. Patel TV & Singh AK (2008) Does treatment with calcitriol improve survival in predialysis patients with chronic kidney disease? *Nat Clin Pract Endocrinol Metab* **4**, 484–485.
61. Bischoff-Ferrari HA, Willett WC, Wong JB, *et al*. (2005) Fracture prevention with vitamin D supplementation – a meta-analysis of randomized controlled trials. *JAMA* **293**, 2257–2264.
62. Trivedi DP, Doll R & Khaw KT (2003) Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *Br Med J* **326**, 469–472.
63. Saquib N, von Muhlen D, Garland CF, *et al*. (2006) Serum 25-hydroxyvitamin D, parathyroid hormone, and bone mineral density in men: the Rancho Bernardo study. *Osteoporos Int* **17**, 1734–1741.
64. Michaelsson K, Melhus H, Bellocco R, *et al*. (2003) Dietary calcium and vitamin D intake in relation to osteoporotic fracture risk. *Bone* **32**, 694–703.
65. Roddam AW, Neale R, Appleby P, *et al*. (2007) Association between plasma 25-hydroxyvitamin D levels and fracture risk – The EPIC-Oxford study. *Am J Epidemiol* **166**, 1327–1336.
66. Zhu K, Bruce D, Austin N, *et al*. (2008) Randomized controlled trial of the effects of calcium with or without vitamin D on bone structure and bone-related chemistry in elderly women with vitamin D insufficiency. *J Bone Miner Res* **23**, 1343–1348.
67. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, *et al*. (2004) Effect of vitamin D on falls – a meta-analysis. *JAMA* **291**, 1999–2006.
68. Gordon PL, Sakkas GK, Doyle JW, *et al*. (2007) Relationship between vitamin D and muscle size and strength in patients on hemodialysis. *J Ren Nutr* **17**, 397–407.
69. Suzuki T, Kwon J, Kim H, *et al*. (2008) Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. *J Bone Miner Res* **23**, 1309–1317.
70. LeBoff MS, Hawkes WG, Glowacki J, *et al*. (2008) Vitamin D-deficiency and post-fracture changes in lower extremity function and falls in women with hip fractures. *Osteoporos Int* **19**, 1283–1290.
71. Bischoff-Ferrari HA, Orav EJ & Dawson-Hughes B (2008) Additive benefit of higher testosterone levels and vitamin D plus calcium supplementation in regard to fall risk reduction among older men and women. *Osteoporos Int* **19**, 1307–1314.
72. Adorini L & Penna G (2008) Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol* **4**, 404–412.
73. Ascherio A & Munger K (2008) Epidemiology of multiple sclerosis: from risk factors to prevention. *Semin Neurol* **28**, 17–28.
74. Munger KL, Levin LI, Hollis BW, *et al*. (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* **296**, 2832–2838.
75. Freedman DM, Dosemeci H & Alavanja MCR (2000) Mortality from multiple sclerosis and exposure to residential and occupational solar radiation: a case–control study based on death certificates. *Occup Environ Med* **57**, 418–421.
76. Brown SJ (2006) The role of vitamin D in multiple sclerosis. *Ann Pharmacother* **40**, 1158–1161.
77. Hypponen E, Laara E, Reunanen A, *et al*. (2001) Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* **358**, 1500–1503.
78. Dahlquist G, Patterson C, Soltesz G, *et al*. (1999) Vitamin D supplement in early childhood and risk for type I (insulin-dependent) diabetes mellitus. *Diabetologia* **42**, 51–54.
79. Mohr SB, Garland CF, Gorham ED, *et al*. (2008) The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. *Diabetologia* **51**, 1391–1398.
80. Merlino LA, Curtis J, Mikuls TR, *et al*. (2004) Vitamin D intake is inversely associated with rheumatoid arthritis – results from the Iowa Women's Health Study. *Arthritis Rheum* **50**, 72–77.
81. Kamen DL, Cooper GS, Bouali H, *et al*. (2006) Vitamin D deficiency in systemic lupus erythematosus. *Autoimmun Rev* **5**, 114–117.
82. Knekt P, Laaksonen M, Mattila C, *et al*. (2008) Serum vitamin D and subsequent occurrence of type 2 diabetes. *Epidemiology* **19**, 666–671.
83. Pittas AG, Dawson-Hughes B, Li T, *et al*. (2006) Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* **29**, 650–656.
84. Mattila C, Knekt P, Maennistoe S, *et al*. (2007) Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. *Diabetes Care* **30**, 2569–2570.
85. Zittermann A, Schleithoff SS & Koerfer R (2005) Putting cardiovascular disease and vitamin D insufficiency into perspective. *Br J Nutr* **94**, 483–492.
86. Wang L, Manson JE, Buring JE, *et al*. (2008) Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension* **51**, 1073–1079.
87. Forman JP, Giovannucci E, Holmes MD, *et al*. (2007) Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* **49**, 1063–1069.
88. Giovannucci E, Liu Y, Hollis BW, *et al*. (2008) 25-Hydroxyvitamin D and risk of myocardial infarction in men – a prospective study. *Arch Intern Med* **168**, 1174–1180.
89. Melamed ML, Muntner P, Michos ED, *et al*. (2008) Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease – results from NHANES 2001 to 2004. *Arterioscler Thromb Vasc Biol* **28**, 1179–1185.

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

90. Dobnig H, Pilz S, Scharnagl H, *et al*. (2008) Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* **168**, 1340–1349.
91. Moe SM (2007) Vitamin D cardiovascular disease, and survival in dialysis patients. *J Bone Miner Res* **22**, V95–V99.
92. Achinger SG & Ayus JC (2005) The role of vitamin D in left ventricular hypertrophy and cardiac function. *Kidney Int* **67**, S37–S42.
93. Shoji T, Shinohara K, Kimoto E, *et al*. (2004) Lower risk for cardiovascular mortality in oral 1α-hydroxy vitamin D_3 users in a haemodialysis population. *Nephrol Dial Transplant* **19**, 179–184.
94. Wang AYM, Lam CWK, Sanderson JE, *et al*. (2008) Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. *Am J Clin Nutr* **87**, 1631–1638.
95. Pilz S, Dobnig H, Fischer JE, *et al*. (2008) Low vitamin D levels predict stroke in patients referred to coronary angiography. *Stroke* **39**, 2611–2613.
96. Rajasree S, Rajpal K, Kartha CC, *et al*. (2001) Serum 25-hydroxyvitamin D_3 levels are elevated in South Indian patients with ischemic heart disease. *Eur J Epidemiol* **17**, 567–571.
97. Hsia J, Heiss G, Ren H, *et al*. (2007) Calcium/vitamin D supplementation and cardiovascular events. *Circulation* **115**, 846–854.
98. Michos ED & Blumenthal RS (2007) Vitamin D supplementation and cardiovascular disease risk. *Circulation* **115**, 827–828.
99. Lamprecht SA & Lipkin M (2003) Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer* **3**, 601–614.
100. van der Rhee HJ, de Vries E & Coebergh JWW (2006) Does sunlight prevent cancer? A systematic review. *Eur J Cancer* **42**, 2222–2232.
101. Kricker A & Armstrong B (2006) Does sunlight have a beneficial influence on certain cancers? *Prog Biophys Mol Biol* **92**, 132–139.
102. Freedman DM, Dosemeci M & McGlynn K (2002) Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case–control study. *Occup Environ Med* **59**, 257–262.
103. Grant WB (2002) An estimate of premature cancer mortality in the US due to inadequate doses of solar ultraviolet-B radiation. *Cancer* **94**, 1867–1875.
104. Tuohimaa P, Pukkala E, Scelo G, *et al*. (2007) Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: vitamin D as a possible explanation. *Eur J Cancer* **43**, 1701–1712.
105. Giovannucci E, Liu Y, Rimm EB, *et al*. (2006) Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* **98**, 451–459.
106. Ducloux D, Courivaud C, Bamoulid J, *et al*. (2008) Pretransplant serum vitamin D levels and risk of cancer after renal transplantation. *Transplantation* **85**, 1755–1759.
107. Moan J, Porojnicu AC, Robsahm TE, *et al*. (2005) Solar radiation, vitamin D and survival rate of colon cancer in Norway. *J Photochem Photobiol B Biol* **78**, 189–193.
108. Zheng W, Anderson KE, Kushi LH, *et al*. (1998) A prospective cohort study of intake of calcium, vitamin D, and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev* **7**, 221–225.
109. Marcus PM & Newcomb PA (1998) The association of calcium and vitamin D, and colon and rectal cancer in Wisconsin women. *Int J Epidemiol* **27**, 788–793.
110. Pritchard RS, Baron JA & deVerdier MG (1996) Dietary calcium, vitamin D, and the risk of colorectal cancer in Stockholm, Sweden. *Cancer Epidemiol Biomarkers Prev* **5**, 897–900.
111. McCullough ML, Robertson AS, Rodriguez C, *et al*. (2003) Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control* **14**, 1–12.
112. Oh K, Willett WC, Wu K, *et al*. (2007) Calcium and vitamin D intakes in relation to risk of distal colorectal adenoma in women. *Am J Epidemiol* **165**, 1178–1186.
113. Hartman TJ, Albert PS, Snyder K, *et al*. (2005) The association of calcium and vitamin D with risk of colorectal adenomas. *J Nutr* **135**, 252–259.
114. Grau MV, Baron JA, Sandler RS, *et al*. (2003) Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* **95**, 1765–1771.
115. Kearney J, Giovannucci E, Rimm EB, *et al*. (1996) Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am J Epidemiol* **143**, 907–917.
116. Kampman E, Slattery ML, Caan B, *et al*. (2000) Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). *Cancer Causes Control* **11**, 459–466.
117. Terry P, Baron JA, Bergkvist L, *et al*. (2002) Dietary calcium and vitamin D intake and risk of colorectal cancer: a prospective cohort study in women. *Nutr Cancer* **43**, 39–46.
118. Lin J, Zhang SM, Cook NR, *et al*. (2005) Intakes of calcium and vitamin D and risk of colorectal cancer in women. *Am J Epidemiol* **161**, 755–764.
119. Kesse E, Boutron-Ruault MC, Norat T, *et al*. (2005) Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer* **117**, 137–144.
120. Wactawski-Wende J, Kotchen JM, Anderson GL, *et al*. (2006) Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* **354**, 684–696.
121. Newmark HL & Heaney RP (2006) Calcium, vitamin D, and risk reduction of colorectal cancer. *Nutr Cancer* **56**, 1–2.
122. Levine AJ, Harper JM, Ervin CM, *et al*. (2001) Serum 25-hydroxyvitamin D, dietary calcium intake, and distal colorectal adenoma risk. *Nutr Cancer* **39**, 35–41.
123. Tangrea J, Helzlsouer K, Pietinen P, *et al*. (1997) Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control* **8**, 615–625.
124. Peters U, McGlynn KA, Chatterjee N, *et al*. (2001) Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* **10**, 1267–1274.
125. Wu K, Feskanich D, Fuchs CS, *et al*. (2007) A nested case–control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *J Natl Cancer Inst* **99**, 1120–1129.
126. Otani T, Iwasaki M, Sasazuki S, *et al*. (2007) Plasma vitamin D and risk of colorectal cancer: the Japan Public Health Center-Based Prospective Study. *Br J Cancer* **97**, 446–451.
127. Gorham ED, Garland CF, Garland FC, *et al*. (2005) Vitamin D and prevention of colorectal cancer. *J Steroid Biochem Mol Biol* **97**, 179–194.

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

128. Gorham ED, Garland CF, Garland FC, *et al*. (2007) Optimal vitamin D status for colorectal cancer prevention – a quantitative meta analysis. *Am J Prev Med* **32**, 210–216.
129. Cui Y & Rohan TE (2006) Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol Biomarkers Prev* **15**, 1427–1437.
130. Rohan T (2007) Epidemiological studies of vitamin D and breast cancer. *Nutr Rev* **65**, S80–S83.
131. John EM, Schwartz GG, Dreon DM, *et al*. (1999) Vitamin D and breast cancer risk: The NHANES I Epidemiologic Follow-up Study, 1971–1975 to 1992. *Cancer Epidemiol Biomarkers Prev* **8**, 399–406.
132. Abbas S, Linseisen J & Chang-Claude J (2007) Dietary vitamin D and calcium intake and premenopausal breast cancer risk in a German case–control study. *Nutr Cancer* **59**, 54–61.
133. Shin MH, Holmes MD, Hankinson SE, *et al*. (2002) Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst* **94**, 1301–1311.
134. Robien K, Cutler GJ & Lazovich D (2007) Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. *Cancer Causes Control* **18**, 775–782.
135. Knight JA, Lesosky M, Barnett H, *et al*. (2007) Vitamin D and reduced risk of breast cancer: a population-based case–control study. *Cancer Epidemiol Biomarkers Prev* **16**, 422–429.
136. Frazier AL, Li L, Cho EY, *et al*. (2004) Adolescent diet and risk of breast cancer. *Cancer Causes Control* **15**, 73–82.
137. Frazier AL, Ryan CT, Rockett H, *et al*. (2003) Adolescent diet and risk of breast cancer. *Breast Cancer Res* **5**, R59–R64.
138. McCullough ML, Rodriguez C, Diver WR, *et al*. (2005) Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II nutrition cohort. *Cancer Epidemiol Biomarkers Prev* **14**, 2898–2904.
139. Neuhouser ML, Sorensen B, Hollis BW, *et al*. (2008) Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. *Am J Clin Nutr* **88**, 133–139.
140. Bertone-Johnson ER, Chen WY, Holick MF, *et al*. (2005) Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* **14**, 1991–1997.
141. Abbas S, Linseisen J, Slanger T, *et al*. (2008) Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer – results of a large case–control study. *Carcinogenesis* **29**, 93–99.
142. Freedman DM, Chang SC, Falk RT, *et al*. (2008) Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* **17**, 889–894.
143. Hughes AM, Armstrong BK, Vajdic CM, *et al*. (2004) Sun exposure may protect against non-Hodgkin lymphoma: a case–control study. *Int J Cancer* **112**, 865–871.
144. Smedby KE, Hjalgrim H, Melbye M, *et al*. (2005) Ultraviolet radiation exposure and risk of malignant lymphomas. *J Natl Cancer Inst* **97**, 199–209.
145. Hartge P, Lim U, Freedman DM, *et al*. (2006) Ultraviolet radiation, dietary vitamin D, and risk of non-Hodgkin lymphoma (United States). *Cancer Causes Control* **17**, 1045–1052.
146. Weihkopf T, Becker N, Nieters A, *et al*. (2007) Sun exposure and malignant lymphoma: a population-based case–control study in Germany. *Int J Cancer* **120**, 2445–2451.
147. Soni LK, Hou LF, Gapstur SM, *et al*. (2007) Sun exposure and non-Hodgkin lymphoma: a population-based, case–control study. *Eur J Cancer* **43**, 2388–2395.
148. Kricker A, Armstrong BK, Hughes AM, *et al*. (2008) Personal sun exposure and risk of non Hodgkin lymphoma: a pooled analysis from the Interlymph Consortium. *Int J Cancer* **122**, 144–154.
149. Polesel J, Talamini R, Montella M, *et al*. (2006) Linoleic acid, vitamin D and other nutrient intakes in the risk of non-Hodgkin lymphoma: an Italian case–control study. *Ann Oncol* **17**, 713–718.
150. John EM, Dreon DM, Koo J, *et al*. (2004) Residential sunlight exposure is associated with a decreased risk of prostate cancer. *J Steroid Biochem Mol Biol* **89–90**, 549–552.
151. Colli JL & Grant WB (2008) Solar ultraviolet B radiation compared with prostate cancer incidence and mortality rates in United States. *Urology* **71**, 531–535.
152. Grant WB (2004) Geographic variation of prostate cancer mortality rates in the United States: implications for prostate cancer risk related to vitamin D. *Int J Cancer* **111**, 470–471.
153. Chan JM, Giovannucci E, Andersson SO, *et al*. (1998) Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). *Cancer Causes Control* **9**, 559–566.
154. Kristal AR, Cohen JH, Qu PP, *et al*. (2002) Associations of energy, fat, calcium, and vitamin D with prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* **11**, 719–725.
155. Tseng M, Breslow RA, Graubard BI, *et al*. (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**, 1147–1154.
156. 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**, 27–33.
157. Park SY, Murphy SP, Wilkens LR, *et al*. (2007) Calcium, vitamin D, and dairy product intake and prostate cancer risk – The Multiethnic Cohort Study. *Am J Epidemiol* **166**, 1259–1269.
158. 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**, 421–441.
159. Gann PH, Ma J, Hennekens CH, *et al*. (1996) Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. *Cancer Epidemiol Biomarkers Prev* **5**, 121–126.
160. Nomura AMY, 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**, 425–432.
161. Platz EA, Leitzmann MF, Hollis BW, *et al*. (2004) Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. *Cancer Causes Control* **15**, 255–265.
162. Jacobs ET, Giuliano AR, Martinez EM, *et al*. (2004) Plasma levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and the risk of prostate cancer. *J Steroid Biochem Mol Biol* **89–90**, 533–537.
163. 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**, 796–804.
164. Ahonen MH, Tenkanen L, Teppo L, *et al*. (2000) Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* **11**, 847–852.

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press

165. 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.
166. 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 Biomarkers Prev* **16**, 302–307.
167. Li HJ, Stampfer MJ, Hollis JBW, *et al*. (2007) A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. *PLoS Med* **4**, 562–571.
168. Lefkowitz ES & Garland CF (1994) Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int J Epidemiol* **23**, 1133–1136.
169. Garland CF, Mohr SB, Gorham ED, *et al*. (2006) Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. *Am J Prev Med* **31**, 512–514.
170. Salazar-Martinez E, Lazcano-Ponce EC, Lira-Lira GG, *et al*. (2002) Nutritional determinants of epithelial ovarian cancer risk: a case–control study in Mexico. *Oncology* **63**, 151–157.
171. Bidoli E, La Vecchia C, Talamini R, *et al*. (2001) Micronutrients and ovarian cancer: a case–control study in Italy. *Ann Oncol* **12**, 1589–1593.
172. Goodman MT, Wu AH, Tung KH, *et al*. (2002) Association of dairy products, lactose, and calcium with the risk of ovarian cancer. *Am J Epidemiol* **156**, 148–157.
173. Koralek DO, Bertone-Johnson ER, Leitzmann MF, *et al*. (2006) Relationship between calcium, lactose, vitamin D, and dairy products and ovarian cancer. *Nutr Cancer* **56**, 22–30.
174. Genkinger JM, Hunter DJ, Spiegelman D, *et al*. (2006) Dairy products and ovarian cancer: a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev* **15**, 364–372.
175. Tworoger SS, Lee IM, Buring JE, *et al*. (2007) Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer. *Cancer Epidemiol Biomarkers Prev* **16**, 783–788.
176. Skinner HG, Michaud DS, Giovannucci E, *et al*. (2006) Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epidemiol Biomarkers Prev* **15**, 1688–1695.
177. Stolzenberg-Solomon RZ, Vieth R, Azad A, *et al*. (2006) A prospective nested case–control study of vitamin D status and pancreatic cancer risk in male smokers. *Cancer Res* **66**, 10213–10219.
178. Michaud DS (2006) Vitamin D and pancreatic cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort. *Cancer Res* **66**, 9802–9803.
179. Bidoli E, Bosetti C, La Vecchia C, *et al*. (2003) Micronutrients and laryngeal cancer risk in Italy and Switzerland: a case–control study. *Cancer Causes Control* **14**, 477–484.
180. Chen W, Dawsey SM, Qiao YL, *et al*. (2007) Prospective study of serum 25(OH)-vitamin D concentration and risk of oesophageal and gastric cancers. *Br J Cancer* **97**, 123–128.
181. Badros A, Goloubeva O, Terpos E, *et al*. (2008) Prevalence and significance of vitamin D deficiency in multiple myeloma patients. *Br J Haematol* **142**, 492–494.
182. Mohr SB, Gorham ED, Garland CF, *et al*. (2006) Are low ultraviolet B and high animal protein intake associated with risk of renal cancer? *Int J Cancer* **119**, 2705–2709.
183. McCullough ML, Bandera EV, Moore DF, *et al*. (2008) Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature. *Prev Med* **46**, 298–302.
184. Rosso S, Sera F, Segnan N, *et al*. (2008) Sun exposure prior to diagnosis is associated with improved survival in melanoma patients: results from a long-term follow-up study of Italian patients. *Eur J Cancer* **44**, 1275–1281.

NS Nutrition Research Reviews

https://doi.org/10.1017/S0954422409990151 Published online by Cambridge University Press