WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

Vitamin D and Cancer

IARC 2008

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC

Working Group Reports

Volume 5

Vitamin D and Cancer

Published by the International Agency for Research on Cancer,
150 Cours Albert Thomas, 69372 Lyon Cedex 08, France

Distributed by
WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int)

IARC Library Cataloguing in Publication Data

IARC Working Group on Vitamin D

Vitamin D and cancer / a report of the IARC Working Group on Vitamin D

(IARC Working Group Reports ; 5)

1. Neoplasms – etiology 2. Neoplasms – prevention & control
3. Vitamin D – adverse effects 4. Vitamin D – therapeutic use 5. Risk Factors
I. Title II. Series

ISBN 978 92 832 2446 4 (NLM Classification: W1)

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Suggested citation:. IARC. Vitamin D and Cancer. IARC Working Group Reports Vol.5, International Agency for research on Cancer, Lyon, 25 November 2008.

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Terminology and abbreviations

The letter "D" attached to vitamin or 25-hydroxyvitamin or 1α,25-dihydroxivitamin will be written "D" if it refers to the D_2 or to the D_3 forms. "D_2" and "D_3" will be used if distinction between the two forms is of importance.

Vitamin D_2 = ergocalciferol (e.g., produced from yeasts and found present in many fortified food products).
Vitamin D_3 = cholecalciferol
25-hydroxyvitamin D_3 = calcidiol
1α,25-dihydroxyvitamin D_3 = calcitriol
7-dehydrocholestrol (7-DHC) = Provitamin D_3
Previtamin D_3 = isomeric form of 7-DHC under UVB irradiation
1µg vitamin D = 40 IU
For 25-hydroxyvitaminD 1 ng/mL = 2.4962 nmol/L, i.e., ~2.5 nmol/L or ~2.5 pmol/mL
For 1,25-dihydroxyvitamin D_3: 1 pg/ml = 0.00240 pmol/ml =

2.4 fmol/mL or 2.4 pmol/L

d stands for deci; m stands for milli; µ stands for micro; n stands for nano; p stands for pico; and f stands for femto

Abbreviations for measure of risk in epidemiological and clinical studies

OR:	Odds ratio, provides the point estimate of the risk to being exposed to a factor in subjects with a disease as compared to subjects without the disease. The OR is used in the context of case-control and nested case control studies.
RR	Relative risk, provides the point estimate of disease risk after exposure to a factor versus non exposure to it. It is used in cohort studies and randomised trials when cumulative risk is used as the endpoint
HR:	Hazard ratio, provides the point estimate of disease risk after exposure to a factor versus non exposure to it. It is used in cohort studies when disease occurrence timing is used as the endpoint.
SIR:	Standard incidence ratio, provides a point estimate of the ratio between two incidence rates that have been adjusted for the same factor(s) (mostly age).
95% CI:	Numerical interval that defines the lower and upper bounds outside of which the real point estimate has less than a 5% chance of being found.

Abbreviations commonly used in the report

BCC:	Basal cell carcinoma
BMI:	Body mass index, equivalent to the weight in kg divided by the square of the height in metres.
CC:	Case control study (data on exposure are collected retrospectively, after the disease has occurred)
CM:	Cutaneous melanoma
CMM:	Cutaneous malignant melanoma (equivalent to CM)
CVD:	Cardiovascular diseases
NCC:	Nested case-control study (case-control study within a prospective cohort and data on exposure are collected before disease occurrence)
NHANES:	National Health and Nutrition Examination Survey in the USA
NHS:	Nurse's Health Study in the USA
NMSC:	Non melanoma skin cancer (includes SCC and BCC)
PHC:	Professional Health Cohort study in the USA
PTH:	Parathyroid hormone
RCT:	Randomised controlled trial
SCC:	Squamous cell cancer
VDR:	Vitamin D receptor
WHI:	Women's Health Initiative
WHS:	Women's Health Study

Chapter 1 – Summary overview of the report

Ecological studies, mainly conducted in the USA, have shown an increasing risk of several cancers and other chronic conditions with increasing latitude of residence, suggesting that these diseases might be related to vitamin D status. This "vitamin D hypothesis" was first reinforced by evidence that vitamin D can inhibit cell proliferation and promote apoptosis *in vitro*, and secondly, by the discovery that several tissues could locally produce the physiologically active form of vitamin D, 1α,25-dihydroxyvitamin D, which has anti carcinogenic properties.

IARC has established a Working Group (WG) of international experts to investigate whether or not a causal relationship exists between vitamin D status and cancer risk. The WG has systematically reviewed the epidemiological literature on vitamin D and cancer and has performed a meta-analysis on observational studies of serum 25-hydroxyvitamin D levels (the best available biomarker of an individual's vitamin D status) and the risk of colorectal, breast and prostate cancers and of colorectal adenomas.

Much of the data suggesting a link between vitamin D status and cancer have been derived from ecological studies that assessed the correlation between latitude and cancer mortality. However, causal inference from ecological studies is notoriously perilous as, among other things, these studies cannot adequately control for confounding by exposure to various cancer risk factors which also vary with latitude (e.g. dietary habits or melatonin synthesis). Studies from the USA show a weak association between latitude and vitamin D status and that other factor such as outdoor activities and obesity are better predictive factors of vitamin D status. In Europe, the opposite has been found, with a south to north increase in serum 25-hydroxyvitamin D that parallels a similar gradient in the incidence of colorectal, breast and prostate cancers.

In people of the same age and skin complexion, there is considerable inter individual variation in serum 25-hydroxyviatmin D even with similar levels of sun exposure.

Many physiological mechanisms have evolved through history to avoid accumulation of vitamin D in the body. The higher existing serum 25-hydroxyvitamin D levels are, the less effective additional exposure to sources of UVB radiation and vitamin D supplements will be in raising them further.

This report outlines a meta-analysis on observational studies. The results show evidence for an increased risk of colorectal cancer and colorectal adenoma with low serum 25-hydroxyvitamin D levels. Overall, the evidence for breast cancer is limited, and there is no evidence for prostate cancer. Two double-blind placebo controlled randomised trials (the Women's Health Initiative trial (WHI) in the USA and one smaller trial in the UK) showed that supplementation with vitamin D (10 µg per day in the WHI trial, and 21 µg per day in the UK trial) had no effect on colorectal or breast cancer incidence. There are many reasons to explain the apparent contradiction between observational studies and randomised trials on colorectal cancer incidence, including the use of too low doses of vitamin D, or in the WHI trial, an interaction with hormone therapy. Some laboratory and epidemiological data suggest that vitamin D could be more influential on cancer progression and thus cancer mortality, rather than cancer incidence.

New observational studies are unlikely to disentangle the complex relationships between vitamin D and known cancer risk factors. Also, studies on vitamin D and cancer should not be isolated from associations with other health conditions, particularly cardiovascular disease. A published meta-analysis on randomised trials found that the intake of ordinary doses of vitamin D supplements (10 to 20 µg, i.e. 400 to 800 IU per day) reduces all cause mortality in subjects 50 years old and over, many of whom had low vitamin D status at the trials inception. Patients with chronic kidney disease who were treated with vitamin D supplements also have reduced mortality. A recent analysis of the Third National Health and Nutrition Examination Survey (NHANES III) cohort data from the USA showed increased mortality in subjects with low vitamin D status. None of these studies could identify a specific cause of death responsible for the differences in overall mortality.

Currently, the key question is to understand whether low vitamin D status causes an increased risk of cancer, other chronic health conditions and death, or is simply a consequence of poor health status. If the first hypothesis is true, then supplementation with vitamin D is likely to prevent some diseases and improve health status. If the second hypothesis is true, then supplementation is less likely to prevent diseases or improve health status. Failure of the two aforementioned randomised

trials to decrease cancer incidence (particularly colorectal cancer) favours the second hypothesis but these trials should by no means be considered as providing a definite answer.

The only way to further address the cause-effect issue is to organise new randomised trials to evaluate the impact of vitamin D on all-cause mortality and on the incidence and mortality from common conditions including cancer. These trials should make sure that key parameters of vitamin D status (e.g., serum 25-hydroxyvitamin D levels before and in trial) can be assessed.

Some groups advocate increasing vitamin D status (e.g., above 30 ng/mL of serum 25-hydroxyvitamin D) through more exposure to ultraviolet radiation or by taking high doses of vitamin D supplements (i.e., more than 50 µg per day). However, the health effects of long term exposure (i.e., for 1 year or more) to high levels of vitamin D are largely unknown. Past experience has shown that in well fed populations, an increased intake of some compounds such as anti oxidants (e.g., beta-carotenes, selenium, and vitamin E) or hormones may actually be detrimental for health and mortality. These findings conflicted with earlier laboratory and observational studies that were suggesting health benefits for these coumpounds. For example, many women were advised to use hormone replacement therapy (HRT) for prevention of several chronic conditions (e.g., osteoporosis, coronary heart diseases). In the recent past, large epidemiological and randomised studies have demonstrated an increased risk of breast cancer and cardiovascular disease associated with HRT used for more than one year.

If little is known about the possible adverse health events associated with long-term (i.e., one year or more) maintenance of high serum 25-hydroxyvitamin D, recent data from the NHANES III and the Framingham Heart Study in the USA suggest that mortality and cardiovascular events increase in line with increasing doses of serum 25-hydroxyvitamin D levels above 40 ng/mL.

Therefore, before changing existing recommendations on vitamin D requirements, we should wait for the results of new randomised trials, including an analysis of the health impact of vitamin D supplementation according to a baseline serum 25-hydroxyvitamin D level.

Chapter 2 – Objectives and format of the report

2.1 Background

In all vertebrates, the ionised calcium is implicated in mechanisms such as muscular contraction, cell adhesion, or bone formation. Calcium is an important cellular messenger and is involved in cellular growth and in cell cycle.

Since animals left calcium rich oceans some 350 millions year ago to evolve on earth's crust, vitamin D has always played a vital role for maintaining adequate calcium concentration in the blood and building and maintaining a robust skeleton through intestinal extraction of calcium from foodstuffs and bone metabolism.

Exposure of the skin to ultraviolet B radiation (UVB; 280-315 nm) induces not only the synthesis of vitamin D_3 from 7-dehydrocholesterol (7-DHC) but also formation of the physiologically active metabolites of vitamin D, the 1α,25-dihydroxyvitamin D which mainly acts through binding to the vitamin D receptor (VDR). Also, vitamin D a "secosteroid", i.e., a molecule that are very similar in structure to steroids by one of the four steroid rings is broken and B-ring carbons atoms are not joined. Thus vitamin D is more like a hormone and not strictly a vitamin according to the classical criteria that an essential nutrient is a substance the body cannot synthesise in sufficient quantities itself. Also, vitamins are usually involved in biochemical reactions, while 1α,25-dihydroxyvitamin D exerts its action via VDR.

As humans moved from UVB rich equatorial areas to more northern areas, natural selection favoured steadily lighter skins, so that less and less UVB was necessary to synthesise the vitamin D required for optimal skeleton robustness and muscle functioning (Loomis, 1967). Landmark works by Jablonski and Chaplin (2000) have shown that skin reflectance is strongly correlated with absolute latitude and UV radiation levels, suggesting that the main role of melanin pigmentation in humans is the regulation of the effects of UV radiation on the contents of blood vessels located in the dermis. This regulation is deemed to protect against the UV induced degradation of folic acid, a member of the vitamin B family that is essential for numerous vital metabolic and reproductive functions. Folic acid has, among other functions, involvement in the development of the neural tube[1], spermatogenesis, and DNA replication.

Evolutionary pressure led to the lightning of skin of Homo sapiens migrating further away from the equator that represents a compromise solution to the conflicting physiological requirements of photo protection for folic acid preservation and endogenous UVB induced vitamin D_3 synthesis. Female skin is generally lighter than that of the male, and this may be required to permit synthesis of the relatively higher amounts of vitamin D_3 necessary during pregnancy and lactation.

When rural populations of Europe and North America started to migrate to smog filled industrialised cities in the nineteenth century, the lack of sufficient sunlight and food rich in vitamin D precipitated a clinical expression of severe vitamin D deficiency which manifested as rickets in children and osteomalacia in women of childbearing age. A causal relationship exists between the physiologically active form of vitamin D and innate and adaptive immunity to infections: recurrent infections are commonly associated with rickets, and overall mortality is high in deprived children.

It was only at the beginning of the twentieth century that supplementation with cod liver oil (a rich dietary source of vitamin D_3) and later sun exposure were used to cure rickets and osteomalacia. Interested readers may consult excellent historical reviews of vitamin D deficiency diseases (Rajakumar *et al.,*2003, 2005, 2007).

In 1941, Apperley described for the first time an association between cancer mortality rates and latitudinal location of states in the USA and of provinces in Canada. Laboratory experiments have shown that in addition to its action on calcium and bone metabolism, the physiologically active form of vitamin D, the 1α,25-dihydroxyvitamin D, inhibits cellular proliferation, and promotes differentiation and apoptosis, all properties compatible with antineoplastic action. But the serum concentration of 1α,25-dihydroxyvitamin D is very stable and very similar between subjects, and thus, its involvement in cancerous processes was not seen as a valid hypothesis. This view changed with the discovery of extra-renal production of 1α,25-dihydroxyvitamin D coupled with existence of vitamin D receptors (VDR) in various organs. Local production of 1α,25-dihydroxyvitamin D is likely to depend more on

circulating 25-hydroxyvitamin D status, which is highly variable between subjects and is influenced by UVB exposure and dietary intakes of vitamin D. This discovery has led to the hypothesis that autocrine or paracrine production of 1α,25-dihydroxyvitamin D could prevent several cancers (e.g., prostate, colon, breast, pancreas, and ovary) and attenuate their progression. Altogether, these elements support the hypothesis that high serum 25-hydroxyvitamin D status could decrease the risk of cancer.

2.2 Objectives of the report

In the recent past, vitamin D has been the focus of keen interest and of much work on its potential to reduce the risk of cancer and of other chronic conditions.

In 2007, IARC convened a Working Group of international scientists with expertise in basic and clinical sciences, in epidemiology and biostatistics, and who all had worked in the field of cancer. Some of the scientists had particular expertise in vitamin D research. In addition, experts having participated in little or no research on vitamin D were invited because of their expertise in methodological issues.

The focus of the Working group was the current state of knowledge and level of evidence of a causal association between vitamin D status and cancer risk, i.e., do changes in vitamin D status cause changes in cancer risk, and if so which cancers?

To explore this question, the Working Group has as far as possible considered all aspects of scientific knowledge on vitamin D that could be relevant to cancer. Also, over five decades, vitamin D has been much studied in bone metabolism, especially for osteoporosis, fractures, and postural instability of elderly people, and this vast body of knowledge had to be taken into account when addressing cause-effect relationships.

The Working Group started its activities in June 2007 and the full Working Group met on two occasions (Lyon in December 2007, Paris in May 2008).

2.3 Format of the report

Chapters 2 to 8 summarise key information for appraising studies on vitamin D and cancer. In chapters 9 to 17, studies on vitamin D (or putative surrogates of vitamin D status) and cancer are detailed. Chapter 13 presents a genuine meta-analysis of observational studies of serum 25-hydroxyviatmin D levels and cancer which was done within the objectives of the Working Group. Chapters 18 to 21 are syntheses and discussion of selected issues, and a recommendation for the organization of new double-blind, placebo controlled randomised trials.

We have tried to avoid as much as possible the vast “grey literature” on vitamin D, that represents opinions rather than hard facts, but readers are redirected to reviews for topics beyond the scope of this Report.

Details regarding topics not related to cancer but otherwise of interest have been inserted as “Endnotes” at the end of each chapter.

The references were arranged in a single section.

2.4 Overview of the methodology used

Specific methods used for the different topics addressed in the report are described at the beginning of chapters or sections. In summary, a systematic review of the literature in MEDLINE and them references cited in articles is presented in Chapter 5, Chapters 9 to 15, and for the non-Hodgkin lymphoma section of Chapter 16, as these chapters address epidemiological, experimental, survival and toxicological data. The systematic search was particularly exhaustive in Chapters 12 and 13, due to the meta-analysis of observational studies on serum 25-hydroxyvitamin D levels and cancer risk.

For Chapters 6, 7, 17, and for the section on VDR variants in Chapter 16, a review of the most relevant literature was done.

Chapters 3, 4 and 8 summarises the current knowledge on ultraviolet radiation and skin cancer and the basic biology relevant to this report. Readers interested in more details are invited to consult the literature cited in these chapters.

Chapter 3 – Sunlight and skin cancer: recall of essential issues

3.1 The skin cancer burden

Increasing incidence of skin cancer starting around the 1950s have been described in all light-skinned populations, and to some extent, in several Asian and South American populations. These increases concerned all types of skin cancer, including squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and cutaneous melanoma. Most recent cancer registry data show that in and after 2004, skin cancer incidence is still rising in nearly all light-skinned populations.

In Denmark, Sweden, and Norway, the incidence of cutaneous melanoma per 100,000 persons (Age adjusted on World Standard population) rose from below 2 cases per year in the early 1950s to 13 to 15 cases per year in 2005 (Engholm *et al.,*2008)). In Queensland, Australia, this increase was from 46 cases in 1982-88 to 67 cases per 100,000 in 2005 (Queensland, 2008).

In many light-skinned populations BCC and SCC combined are the most frequent cancers. While treatment of BCC and SCC does not require radiotherapy or chemotherapy, surgical and dermatological management of these cancers in the United States entailed in 1995 an overall direct cost representing 4.5% of costs associated with management of all cancer sites (Housman *et al.,*2003).

In 1992, IARC reviewed the epidemiological evidence, evidence from studies with experimental animals and other relevant data including mechanistic studies and concluded that sun exposure is the main environmental cause of cutaneous melanoma and of non-melanocytic skin cancer: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (IARC, 1992).

3.2 Wavelengths of solar radiation relevant to skin cancer

Optical solar radiation includes UV radiation, visible light and infrared radiation. Wavelengths less than 290 nm are absorbed by the atmosphere and do not reach the earth's surface. The Commission Internationale de l'Eclairage (CIE) divides the UV region into UVC (100 – 280 nm), UVB (280-315 nm) and UVA (315-400 nm). UVB is stopped by glass and plastic films, and neither sunburn nor endogenous vitamin D synthesis can be caused by exposure to the sun through a window.

The variation in biological effects (e.g. skin carcinogenesis) by wavelength is referred to as the action spectrum. The action spectra for sunburn (erythema) (Parrish *et al.,*1982) and production of pyrimidine dimers (Freeman *et al.,*1989) have been determined for human skin. It is not possible from observational studies of humans exposed to sunlight to determine which wavelengths are primarily responsible for skin cancer because although the composition of solar radiation varies by latitude, season, time of day and atmospheric factors, and measuring the exposure to radiation of different wavelengths and separating their effects is too difficult. Instead, information on the action spectra for skin cancer has come from experimental studies of laboratory animals.

The albino hairless mouse is a suitable animal model for SCC. Experiments show that for these mice, the UVB component of sunlight is particularly important for the induction of SCC (de Gruijl *et al.,*1993) and that the action spectrum is similar to the action spectrum for erythema (sunburn) for humans (Parrish *et al.,*1982).

There are no data on UV action spectrum for BCC and there is no suitable animal model for melanoma. It was initially thought from a fish model and from a model using that a South American opossum (*Monodelphis domestica*), that the action spectrum for melanoma could extend into the UVA range (Setlow *et al.,*1993, Ley, 2001). But studies using a new mouse model (hepatocyte growth factor/scatter factor (HGF/SF) mouse) are consistent with UVB, not UVA, being responsible for induction of melanoma (De Fabo *et al.,*2004).

3.3 Action spectra for sunburn, skin cancer and vitamin D synthesis

The action spectrum of UVB for vitamin D synthesis in the skin is fairly similar to the UVB action spectrum for SCC and skin erythema, which implies that exposure to UVB will automatically increase both endogenous vitamin D synthesis, and risk of sunburn and of SCC, and of other UVB-induced skin damage (e.g., solar keratoses and local and systemic immune depression). The key difference however, is that vitamin D synthesis in unprotected skin fades away after 5 to 10 minutes of UVB exposure (see Chapter 4), depending on skin content of 7-dehydrocalciferol, pigmentation and amount of UVB in the solar spectrum, itself dependent on season, latitude, hour of the day, air pollution and cloud cover. In contrast, the longer unprotected skin is exposed to the sun, the greater the risk of skin cancer or of other UV-induced skin damage. Thus, duration of sun exposure beyond skin capacity to form vitamin D will not further increase vitamin D, but will increase skin cancer risk.

3.4 Malignant melanoma of the skin ("melanoma")

The continuation of this chapter is restricted to populations of European origin unless specified otherwise, because skin cancer is rare in people of non-European origin.

Several threads of evidence support the hypothesis that sun exposure causes melanoma. This hypothesis originally arose from an analysis of melanoma mortality by latitude in Australia, in which the mortality was generally highest for low latitudes, (Lancaster, 1956), and was subsequently supported by many further studies (IARC, 1992). Studies in migrants have shown that melanomas occur less frequently in people who have migrated from a place with low ambient sunlight to a place with high ambient sunlight than in life-long residents of the destination place and more frequently in migrants from a place with high ambient sunlight to a place with low ambient sunlight than in life-long residents of the destination place (Whiteman *et al.,*2001). For example, migrants from the United Kingdom (high latitude) to Australia (lower latitude) have lower incidence of melanoma than do life-long residents of Australia (Holman and Armstrong, 1984). Melanomas occur more frequently in people whose skin is susceptible to the effects of sunlight – for example, the incidence of melanoma for US whites is 18.9 per 100,000 person years and 1.0 for US blacks (U.S. Cancer Statistics Working Group, 2007), and within people of the same ethnic background, various measures of susceptibility such as skin colour, ability to tan and susceptibility to sunburn are all associated with risk of melanoma (Bliss *et al.,*1995). Melanomas occur more frequently on body sites that are exposed to sunlight than on body sites that are rarely if ever exposed (Green *et al.,*1993), although they are relatively common on intermittently exposed sites.

Case-control studies generally show that intermittent exposure to sunlight is positively associated with risk of melanoma, but that more continuous exposure (such as would occur for outdoor workers) is inversely associated with risk of melanoma. From the most recent meta-analysis, the pooled relative risks for the highest versus lowest category of exposure (however measured) were 1.34 (95% CI 1.02-1.77) for total exposure, 1.61 (1.31-1.99) for intermittent exposure, 0.95 (0.87-1.04) for chronic exposure and 2.03 (1.73-2.37) for history of sunburn (Gandini *et al.,*2005); however, for chronic exposure, the relative risk was stronger at higher latitudes (Gandini *et al.,*2005). Sun exposure early in life seems to play a greater role than exposure later in life, (Autier and Doré, 1998), however Whiteman *et al.,*(2001) found evidence for this from studies of residential exposure, but no consistent evidence from studies of personal exposure to sunlight.

Meta analyses of studies of sun exposure should be interpreted with caution. Sun exposure is ubiquitous and likely to be poorly recalled and subject to recall bias in case-control studies from which most of the evidence is derived. The various studies included in the meta-analyses have measured total, chronic and intermittent exposure in many ways that are usually not compatible with constructing exposure-response curves. Recall of sunburns is the most consistently measured aspect of sun exposure, and while this is taken to be indicative of an intermittent pattern of exposure, it provides no information about the amount of exposure.

The relationship between sunlight and risk of melanoma is further complicated by anatomic site-specific patterns of exposure that are associated with multiple pathways to melanoma. The anatomical distribution of melanoma varies with age: melanomas arising in patients aged 50 years and over being more frequently located at chronically exposed body sites, whereas melanomas arising in patients aged less than 50 years are more frequently located at intermittently exposed body sites (Elwood and Gallagher, 1998). Melanomas occurring on the trunk are associated with relatively

young age at onset, and the occurrence of naevi (Whiteman *et al.,*1998) and many have a mutation in the *BRAF* proto-oncogene (Maldonado *et al.,*2003). In contrast, melanomas occurring on usually sun exposed sites tend to occur in older age, have a weaker association with the presence of naevi and are less likely to have *BRAF* mutations.

Notwithstanding these limitations, the fraction of disease in the population (PAF) attributable to sun exposure has been estimated at 96% in males and 92% in females in the USA, by comparison of white and black populations (Armstrong and Kricker, 1993). Comparison of white populations in New South Wales, Australia, with ethnically similar populations in England and Wales gives a PAF of 89% (males) and 79% (females) (Armstrong and Kricker, 1993).

3.5 Squamous cell carcinoma (SCC)

The evidence that sun exposure causes SCC is strong. In Australia and the USA, the incidence of SCC increases with proximity to the equator (Scotto and Fears, 1983, Giles *et al.,*1988). In the USA, the relationship with ambient UV measurements is strongest for SCC and weakest for melanoma (Armstrong and Kricker, 2001). SCCs occur almost exclusively on parts of the body that are the most heavily exposed to sunlight (Armstrong *et al.,*1997). Migrants from the United Kingdom to Australia have a substantially lower risk than native-born Australians and the risk decreases with increasing age at migration (English *et al.,*1998). People whose skin is sensitive to sunlight are at increased risk (IARC, 1992).

Evidence from case-control studies of personal exposure generally shows that the risk increases directly with total exposure. Armstrong and Kricker (2001) performed a meta-analysis of existing case-control studies; the pooled relative risks comparing the highest versus lowest category of exposure were 1.53 (1.02–2.27) for total exposure, 1.64 (1.26–2.13) for occupational exposure, 0.91 (0.68–1.22) for intermittent exposure and 1.23 (0.90–1.69) for a history of sunburn. There is a paucity of well-conducted epidemiological studies from which a dose-response curve can be estimated with confidence.

A randomised controlled trial of sunscreen use in Queensland showed a reduced risk for SCC in the sunscreen group (relative risk = 0.61 (95% CI 0.46-0.81)) (Green *et al.,*1999). Other randomised trials have shown that their use can prevent the appearance of new solar keratoses (likely precursors to SCC) and cause regression in existing solar keratoses (Boyd *et al.,*1995, Thompson *et al.,*1993).

Most SCCs show mutations in the tumour suppressor gene *tp53* that are consistent with the effects of sunlight in producing pyrimidine dimers in DNA (Wikonkal and Brash, 1999), and rats and mice exposed to sunlight or to artificial sources of UV light develop high numbers of SCCs (IARC, 1992).

3.6 Basal cell carcinoma (BCC)

As for SCC, the incidence of BCC increases with proximity to the equator in Australia and the USA (Scotto and Fears, 1983, Giles *et al.,*1988). It is most common on anatomic sites usually exposed to sunlight, but is relatively more common than SCC on occasionally exposed sites (Armstrong *et al.,*1997). Migrants from the United Kingdom to Australia have substantially lower risk than native-born Australians and the risk decreases with increasing age at migration (Kricker *et al.,*1991). People whose skin is sensitive to sunlight are at increased risk (IARC, 1992).

Evidence from case-control studies of personal exposure suggests that intermittent exposure is more important than chronic exposure. Armstrong and Kricker (2001) reported pooled relative risks comparing the highest versus lowest category of exposure of 0.98 (0.68-1.41) for total exposure, 1.19 (1.07-1.32) for occupational exposure, 1.38 (1.24-1.54) for intermittent exposure and 1.40 (1.29-1.51) for a history of sunburn. The Queensland randomised trial of sunscreen showed no benefit for BCC (Green *et al.,*1999).

Similar mutations in the tumour suppressor gene *tp53* to those seen in SCC have been found in BCC (Ponten *et al.,*1997).

3.7 Exposure to artificial UV light and skin cancer

Sunbeds used for tanning purposes emit high intensity UVA and a small proportion (2 to 4%) of UVB. Over the past two decades, there has been an increase in the use of artificial sources of UV in indoor tanning facilities, mainly in countries with low all-year round ambient sunshine.

An IARC Working Group has performed a systematic review of the potential association between sunbed use and skin cancer (IARC, 2006, 2007). The Working Group undertook a meta-analysis of the 23 available published studies (22 case–control, 1 cohort) in fair-skinned populations, which investigated the association between indoor tanning and melanoma risk. The relative risk (RR) associated with use of indoor tanning facilities was 1.14 (95% CI: 1.00–1.31) compared to no use of indoor tanning facilities from 19 informative studies. When the analysis was restricted to the 9 population-based case–control studies and the cohort study, the relative risk of melanoma associated with indoor tanning was 1.17 (95% CI: 0.96–1.42). In addition, studies on exposure to indoor tanning appliances found some evidence for an increased risk of squamous cell carcinoma (3 studies, RR=2.25, 95% CI: 1.08-4.70) , but not for basal cell carcinoma (4 studies, RR=1.03, 95% CI: 0.56-1.90).

Seven epidemiological studies assessed the melanoma risk associated with sunbed use according to age. All these studies found relative risks of melanoma ranging from 1.4 to 3.8 with sunbed use starting during adolescence or during young adulthood (Figure 3.1). The meta-analysis of these 7 studies found a 75% overall increase in melanoma risk (summary relative risk: 1.75, 95% CI: 1.35-2.26) when sunbed use began before 35 years of age. In addition, the sunbed Working Group found some evidence for an increased risk of SCC, especially when age at first use was less than 20 years.

The anatomic distribution of melanoma and of BCC is changing, with more BCC diagnosed on the trunk of Dutch citizens, and incidence of melanoma on the trunk in Swedish females surpassing that on the lower limbs (de Vries *et al.,*2004; Dal *et al.,*2007). Sunbed use is widespread in the Netherlands and in Nordic countries, and the changes recently observed on the anatomical distribution of BCC and melanoma in these countries supports the hypothesis that sunbed use is implicated in the epidemic of skin cancer in these countries.

3.8 Conclusion

Skin cancer incidence is still rising in nearly all light-skinned populations.

Evidence published since the IARC monograph on solar and ultraviolet radiation supports the conclusion that exposure to sunlight causes melanoma, BCC and SCC. Key issues in determining the risk of melanoma due to sun exposure include obtaining better information on dose-response relationships, the role of the pattern of exposure for melanoma and BCC and the role of exposure at various times in life.

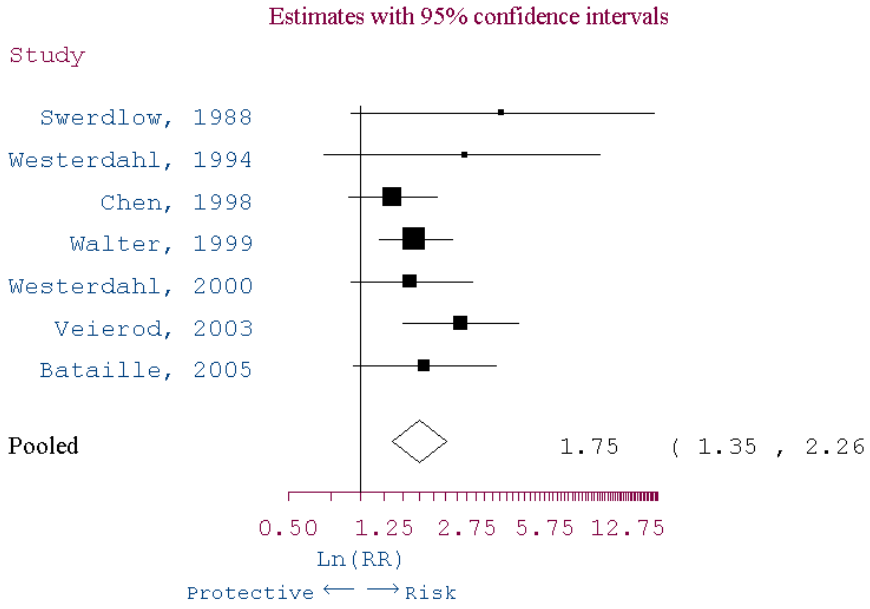
The data on ambient exposure indicate that early life exposure is important for melanoma, SCC and BCC, although the evidence from personal exposure is less consistent. Case-control studies of SCC are consistent with late effects of sunlight as is the data from randomised controlled trials of sunscreen use.

Exposure to artificial UV light from sunbeds increases the risk of melanoma and SCC, especially when the first exposure takes place before 35 years of age.

UVB appears to be largely responsible for the induction of SCC and its action spectrum is similar to that for the synthesis of vitamin D. However, there remains some uncertainty for melanoma, with the possibility that UVA may play a role and there is insufficient evidence to draw any conclusion for BCC.

Exposure to UVB increases endogenous vitamin D synthesis and risk of skin cancer. However, skin synthesis of vitamin D is self-limited and in light-skinned people, it fades away after 5 to 10 minutes. Longer durations of sun exposure will not further increase vitamin D, but will increase skin cancer risk.

Figure 3.1 - Relative risk for cutaneous melanoma associated with first use of indoor tanning facilities in youth: estimates of 7 studies and pooled estimate (From IARC, 2006).



Chapter 4 – Sources of vitamin D

4.1 Overview of vitamin D physiology

Endogenous synthesis of vitamin D_3 (cholecalciferol) takes place in the skin under the influence of UVB radiation. Exogenous vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) comes from dietary intake. The overall vitamin D intake is the sum of cutaneous vitamin D_3 and nutritional vitamin D_2 and D_3.

Vitamin D on its own has no physiological action. To be physiologically active, vitamin D must first be hydroxylated in the liver by the enzyme CYP27A1 (also called the 25-hydroxylase) in 25-hydroxyvitamin D_2 or 25-hydroxyvitamin D_3 (25-hydroxyvitamin D). The 25-hydroxyvitamin D is inactive, and an additional hydroxylation in the kidney by the enzyme CYP27B1 (also called 1α-hydroxylase) is necessary for production of the physiologically active vitamin D metabolite, the 1α,25-dihydroxyvitamin D_2 and the 1α,25-dihydroxyvitamin D_3 (calcitriol). When 1,25(OH)2D is sufficiently available, the enzyme CYP24A1 metabolises the 1α,25-dihydroxyvitamin D in 1α,24,25-dihydroxyvitamin D, which is further catabolised to calcitroic acid.

The best known function of 1α,25-dihydroxyvitamin D is the maintenance of calcium homeostasis primarily by promoting the intestinal absorption of calcium and phosphorus, decreasing the clearance of these minerals from the kidney, and promoting bone mineralisation.

Calcium is the most abundant mineral in the human body. The average adult body contains in total approximately 1 kg, 99% in the skeleton in the form of calcium phosphate salts. The free ion calcium is crucial for numerous vital functions including muscle functioning (including the cardiac muscle), conduction of electric impulses in nerves, cell adherence and so on. Serum levels of calcium are tightly regulated and total calcium ranges between 2.2-2.6 mmol/L (9-10.5 mg/dL) and 1.1-1.4 mmol/L (4.5-5.6 mg/dL) for ionised calcium. Slightly too low or too high calcium levels leads to acute muscular symptoms (tetany if hypocalcaemia) and cardiac arrhythmias, that can be lethal. If serum calcium tends to decrease (e.g., due to too low vitamin D status causing insufficient intestinal calcium absorption), then the parathyroid glands release the parathyroid hormone (PTH) into the blood stream. The PTH will (i) reabsorb calcium from bones and restore normal serum calcium levels, and (ii) stimulate kidney CYP27B1 activity that will boost the transformation of 25-hydroxyvitamin D into 1α,25-dihydroxyvitamin D and increase intestinal absorption of calcium. Increasing serum calcium concentrations decreases PTH release and a direct negative feedback from 1α,25-dihydroxyvitamin D on PTH release also exists.

The interplay of these enzymatic functions and feedbacks ensures stability of calcium serum levels (Adams *et al.,*1982). In subjects with normal vitamin D status or with low vitamin D status, exposure to a single UVB course will lead to transient increases in vitamin D that will last a few days (Figure 4.1). Serum 25-hydroxyviatmin D levels will not vary much in subjects with normal vitamin D status, while in subjects with low status these levels will increase and come closer to those of subjects with normal vitamin D status. Serum 1α,25-dihydroxyvitamin D levels will slightly increase in subjects with normal vitamin D status and will sharply increase in subjects with low vitamin D status. The latter increase results from the abundance of serum PTH present with low vitamin D status and thus low calcium absorption in the small intestine. Results from the study by Adams et al., (1982) also shows that the serum level of 25-hydroxyvitamin D is more stable than vitamin D that varies with exposure to UVB, and serum 1α,25-dihydroxyvitamin that depends on serum PTH concentration. Because of its relatively long half life ($\tau_{1/2}$ = 12.9 (SD: 3.6 d)) (Davie MW et al., 1982), the serum 25-hydroxyvitamin D level is considered as the best gauge of individual vitamin D status.

4.2 Endogenous skin synthesis of vitamin D_3

4.2.1 Summary of mechanisms

Endogenous synthesis of vitamin D_3 consists of a UVB-induced photochemical reaction resulting in the formation of previtamin D_3 from the provitamin D_3 7-dehydrocholesterol (7-DHC) in basal and suprabasal layers of the skin (Figure 4.2). 7-DHC is formed in the skin from cholesterol thanks to the Δ^7-reductase present in the epidermal keratinocytes (Bonjour *et al.,*1987). Approximately 65% of 7-DHC per unit area is found in the epidermis; the remaining 35% is in the dermis. The 5,7-diene of 7-

DHC absorbs UVB radiation causing it to isomerise, resulting in a bond cleavage between carbon 9 and 10 to form a 9,10-seco-sterol, the previtamin D_3. The action spectrum for previtamin D_3 production spans between 260 and 315 nm (CIE, 2006). Maximum spectral effectiveness ranges from 297 to 303 nm.

The effectiveness of UVB on the formation of previtamin D_3 in the skin is influenced by several factors including UVB absorbing molecules like melanin, DNA, RNA, proteins, and 7-DHC skin content.

Previtamin D_3 then undergoes nonenzymatic isomerisation to form vitamin D_3 and this process is temperature-dependent, i.e., the higher the temperature, the larger the amount of previtamin D_3 that isomerises into vitamin D_3. The vitamin D_3 formed in the skin is then swept out into the blood stream by the Vitamin D Binding protein (DBP), and α-globulin that has a high affinity to vitamin D and its metabolites. The constant extraction of vitamin D from the skin by DBP avoids the local accumulation of vitamin D_3 and allows perpetuation of the isomerisation of previtamin D_3 into vitamin D_3.

UVB-triggered conversion of 7-DHC to previtamin D_3 is a rapid reaction which needs only a few seconds. In contrast, the half life ($\tau_{1/2}$) of the isomerisation of previtamin D_3 to vitamin D_3 in human skin is approximately 2.5 hours (Tian *et al.,*1993). The circulating concentrations of vitamin D_3 are at their maximum levels within 12-24 hours after UVB exposure (Chen *et al.,*2007b; Adams *et al.,*1982).

The quantities of vitamin D_3 synthesised by the skin are very small compared with the concentration of the precursor 7-DHC (assumed ≈ 2,000 ng/cm^2). Human skin subjected to ultraviolet radiation *in vivo* produces about 25 ng vitamin D_3 per cm^2 according to a conversion rate of 7-DHC to vitamin D_3 of 1.3% (Davie and Lawson, 1980). The ultraviolet spectrum irradiating the skin modulates the respective proportions of previtamin D_3 photosynthesis and its photo-isomerisation in vitamin D_3, lumisterol, and tachysterol (MacLaughlin *et al.,*1982). In this respect, quantities of vitamin D3 synthesised in the skin may be different if say, artificial sources of UV are used instead of natural sunlight.

4.2.2 Constitutive limiting rate for endogenous vitamin D synthesis in the skin

Vitamin D is toxic at high doses. If sun worshippers or light-skinned people living in sunny areas do not suffer from vitamin D intoxication, it is due to photochemical and photodegradation mechanisms that prevent high production of vitamin D_3 in the skin.

Mechanism 1: photo-isomerisation to tachysterol and lumisterol

Initial exposure of bare skin to UVB will induce photo-isomerisation of 7-DHC into vitamin D_3. But, after 5 to 10 minutes, further UVB exposure causes previtamin D_3 to convert to inactive isomers such as lumisterol and tachysterol (Holick *et al.,*1981; MacLaughlin *et al.,*1982) (Figure 4.3). Lumisterol and tachysterol are in a quasi-stationary state with previtamin D_3, and as soon as previtamin D_3 stores are depleted, exposure of cutaneous lumisterol and tachysterol to UVB radiation may promote the photoisomerisation of these products back to previtamin D_3.

As a result, whatever the skin type, never more than 10 to 15% of the 7-DHC undergoing photo-isomerisation will end up as vitamin D3, and the rest will end up as little quantities of tachysterol and greater quantities of lumisterol. The difference between light and dark skin is that longer exposure to UVB is needed for darker skin to reach the ~15% photo-isomerisation of 7-DHC in vitamin D_3.

Mechanism 2: photodegradation of vitamin D3

Vitamin D3 proves to be exquisitely sensitive to sunlight once formed in the skin (Webb *et al.,*1989). High sunlight exposure results in its rapid photodegradation into a variety of photoproducts, including 5,6-transvitamin D, suprasterol I, and suprasterol II. Exposure for as little as 10 minutes in Boston in the summer resulted in the photodegradation of 30% of vitamin D_3. After 0.5, 1 and 3 hours greater than 50%, 75% and 95% were destroyed, respectively (Webb *et al.,*1989).

4.2.3 Clinical observations on expression of regulation of endogenous vitamin D synthesis

Individuals of the same skin phototype when exposed to UVB do not experience similar increases in serum levels of 25-hydroxyvitamin D. Regulation mechanisms prevent excessive

increases in serum levels. These mechanisms may involve the aforementioned mechanisms 1 and 2 but also other downstream mechanisms like the saturation of DBP for vitamin D transportation, liver transformation of 25-hydroxyvitamin D and other as yet unknown factors and processes.

Endogenous response to UVB of elderly people depends on their baseline serum 25-hydroxyvitamin D levels and subjects with the greatest degree of vitamin D depletion showed the greatest response in increasing serum 25-hydroxyvitamin D after UVB irradiation with sub-erythemal doses (Corless *et al.,*1978; Snell *et al.,*1978). Snell *et al.,*(1978) randomised 24 subjects aged 70 to 100 years to UVB irradiation on the back with a Wotum Sun Ultra Vitalux lamp (spectrum of 250-310 nm) versus no irradiation. The irradiation schedule was not reported. After four weeks, the mean serum 25-hydroxyvitamin D levels rose from 3.6 to 9.7 ng/mL (thus an average increase of 6.1 ng/mL) in the irradiation group while it stayed around 3.2 ng/mL in the control group. Of note, increases of serum 25-hydroxyvitamin D in irradiated subjects varied from 12 ng/mL in subjects with baseline levels less than 3 ng/mL to nearly zero in subjects with baseline levels above 20 ng/mL.

Vitamin D synthesis in skin is limited and confined to the initial exposures. By irradiating a limited area of the back with a mercury arc lamp whose spectrum is rich in UVB, Davie and Lawson (1980) showed that the increase in serum 25-hydroxyvitamin level maximised after the first 5 minutes of exposure, and then became progressively less efficient. A Danish group performed a randomised trial in Caucasian females aged 50 years and over, assigned to a control group (21 women), a group (n=20) with 4 UVA-tanning sessions on machines of 0.4% UVB spectrum, and a group (n=15) with 4 UVA-tanning sessions on machines of 1.4% UVB spectrum (Thieden *et al.,*2008). 37 to 64% of sunbed sessions had side effects such as erythema and polymorphic light eruption. The average baseline serum 25-hydroxyvitamin D level was 19 ng/mL. Levels did not change in the control group, but after 4 sunbed sessions, they significantly increased by an average of 5 ng/mL and by 11 ng/mL in the 0.4% and 1.4% UVB groups, respectively. After 4 more sessions, non significant increases of only 1.2 and 0.2 ng/mL, respectively, were noticed. Thus, a plateau in circulating 25-hydroxyvitamin D was rapidly reached after only a few sessions. Highest increases in serum 25-hydroxyvitamin D levels were observed in subjects with the lowest baseline levels (i.e., below 12 ng/mL).

4.2.4 UVB in vitamin D skin synthesis and in carcinogenic action

The paradoxical effects of sun exposure are erythema (reddening of the skin after sun exposure) and the positive impact on vitamin D_3 synthesis. The action spectra for previtamin D_3 formation, erythema, and formation of cyclobutane pyrimidine dimers (CPD's) from DNA all peak in the UVB range (Wolpowitz and Gilchrest, 2006). Figure 4.4 shows the similarity between the action spectra for vitamin D_3 production and erythema. Therefore, photosynthesis of vitamin D_3 cannot be dissociated from acute and chronic photodamage, including photocarcinogenesis (Wolpowitz & Gilchrest, 2006).

4.2.5 Conclusions for endogenous vitamin D synthesis

Endogenous synthesis of vitamin D is controlled by several sunlight-dependent mechanisms working at skin level that averts production of high quantities of vitamin D. So, if sunlight is crucial for the skin synthesis of vitamin D, it also regulates the amount of synthesis in the skin.

In fair-skinned individuals the maximum possible previtamin D_3 synthesis occurs rapidly, within a few minutes of summer sun exposure and equilibrium in the various products is reached shortly after UVB irradiation begins, indicating that prolonged exposure to UVB does not result in continuous increases in vitamin D_3 production (Holick, 2004a). Maximum vitamin D_3 synthesis in all individuals occurs at suberythemogenic UV doses (Holick, 1981), and longer exposures add nothing to the vitamin D pool despite linearly increasing DNA damage (Wolpowitz & Gilchrest, 2006).

Best estimates are that at around 40° of latitude during a sunny summer day, a fair-skinned person could achieve maximum pre–vitamin D_3 production by 5 to 10 minutes exposure, two or three times a week, of the face and forearms to midday sunlight (Holick, 2005, 2007; Wolpowitz & Gilchrest, 2006). The time may be 30 minutes for dark skinned subjects or if the weather is cloudy.

4.3. Exogenous sources of vitamin D

4.3.1 Dietary sources of vitamin D

There is good evidence from randomised trials that a dietary intake of vitamin D increases serum levels of 25-hydroxyvitamin D (Cranney *et al.,*2007). However, a few foods naturally contain appreciable amounts of vitamin D_3 to have an impact on dietary intake: fish liver, fish liver oils, fatty fish and egg yolks. It has been verified that oily fish such as salmon, mackerel and bluefish are excellent sources of vitamin D_3. Interestingly, novel investigations have shown that farmed salmon, the most widely consumed fish in the US, contained about one quarter of the vitamin D_3 found in wild Alaskan salmon (Lu *et al.,*2007; Chen *et al.,*2007b).

Some countries practice fortification of certain foods with vitamin D, most often milk, cereals, margarine and/or butter and infant formula with up to 25 µg vitamin D_3 per litre. In other countries pregnant women or newborn children are prescribed between 10 and 25 µg vitamin D daily. The mean intake of vitamin D in different studies varies by age group, food and supplementation habits and gender. Recent publications from various parts of Europe have shown that a substantial part of the population including pre-school children has a vitamin D intake below the recommended daily doses.

4.3.2 Vitamin D_2 and vitamin D_3

Exogenous vitamin D comprises of two closely related substances of nutritional importance: vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D_3 is formed from its precursor 7-DHC which is amply found in human and animal skin. Vitamin D_2 is formed by UV radiation from its precursor ergosterol and occurs in plants, especially yeasts and fungi. However, plants are a poor source of vitamin D_2. Synthetic vitamin D_2 is produced by UV irradiation of ergosterol to be added to food or given as supplements. The two vitamins only differ by the side chain to the sterol skeleton. The World Health Organization (WHO) has recommended as early as 1950 that 1 IU vitamin D be equivalent to 25 ng crystalline vitamin D_3, and no distinction was made between vitamin D_3 and vitamin D_2 (WHO, 1950). Both forms of vitamin D are biologically inactive and require further enzymatic activation in the organism.

The biological equivalence of the two vitamin D isoforms is at the centre of a controversy. A double-blind randomised trial showed that orally administered vitamin D_3 increases the serum vitamin D status (25-hydroxyvitamin D_3 plus 25-hydroxyvitamin D_2) more efficiently (factor = 1.7) than vitamin D_2 when given in equimolar amounts over 14 days to healthy volunteers (Trang *et al.,*1998). The assumption that vitamins D_2 and D_3 have equal nutritional value is probably wrong and should be reconsidered (Trang *et al.,*1998; Houghton and Vieth, 2006). Also, some studies suggest that vitamin D_2 supplementation can suppress endogenously formed 25-hydroxyvitamin D_3 and also 1α,25-dihydroxyvitamin D_3 (Tjellesen *et al.,*1986; Hartwell *et al.,*1989; Harris *et al.,*1999), but a study by Matsuoka *et al.,*(1992) showed no interference of intakes of 1,250 µg per day of vitamin D_2 and vitamin D_3 release from the skin after UVB exposure.

A recent randomised, placebo-controlled, double-blinded study of healthy adults aged 18-84 years demonstrated that a daily 25 µg dose of vitamin D_2 was as effective as 25 µg vitamin D_3 in maintaining serum 25-hydroxyvitamin D levels (Holick *et al.,*2008). Vitamin D_2 did not negatively influence serum 25-hydroxyvitamin D_3 levels.

Considered altogether, these data suggest that vitamin D_2 seems to be equally as effective as vitamin D_3 in maintaining 25-hydroxyvitamin D status.

4.3.3 Limiting rate for exogenous vitamin D pathway

Byrne *et al.,*(1995) meta-analysed dose-responses to vitamin D supplementation within recommended dose ranges and found an average increase of 0.88 ng/mL in 25-hydroxyvitamin D levels per µg per day of vitamin D (Byrne *et al.,*1995). Other studies found that the incremental consumption of 1 µg per day of vitamin D3 by healthy young adults raises serum 25-hydroxyvitamin D by 0.4 ng/mL (Vieth, 2006; Lappe *et al.,*2007). A large meta-analysis of 17 randomised trials (mainly

done in adults) found dose response rates of 1 µg per day vary from 0.16 to 0.32 ng/mL (Cranney *et al.,*2007).

These dose-response rate estimates for dietary vitamin D intakes are to be taken with caution, because firstly, there is substantial heterogeneity between studies that assessed changes in 25-hydroxyvitamin D level according to supplementation (Cranney *et al.,*2007). Furthermore, it is known for at least three decades that in elderly people, response to oral supplementation is substantially influenced by pre-existing serum 25-hydroxyvitamin D levels (MacLennan & Hamilton, 1977; Lovell *et al.,*1988; see also Lovell *et al.,*1988 for a review of older literature).

More recently, in the randomised trial that tested the biological equivalence of 100 µg per day of vitamin D_2 and D_3 in healthy volunteers 38±9 years old, Trang *et al.,*(1998) observed increases in 25-hydroxyvitamin D levels of 10 to 16 ng/mL when baseline levels were below 10 ng/mL, and linearly decreases to 4 to 8 ng/mL when baseline levels were 25 ng/mL or more (Figure 4.5).

In a large study of 7,564 postmenopausal women from 25 countries on 5 continents having osteoporosis, Lips *et al.,*(2001) showed that supplements of 10 to 15 µg per day led to increases of serum 25-hydroxyvitamin D levels of 23.2 (SD: 12.8) when baseline levels were < 10 ng/mL, 15.8 (SD: 10.2) when baseline levels were 10-20 ng/mL and 5.4 (SD: 11.8) when baseline levels were higher than 20 ng/mL.

A randomised trial of 25 subjects 18-35 years of age and 25 subjects 62-79 years of age with 20 µg vitamin D_3 per day over 8 weeks succeeded in increasing their serum 25-hydroxyvitamin D levels by 9 ng/mL in both the younger and older age groups (Harris *et al.,*2002). However, increases in serum levels was about 16 ng/mL when baseline levels were 12 ng/mL or less, while it was less than 5 ng/mL when baseline levels were higher than 30 ng/mL.

Vieth *et al.,*(2004) randomised 32 healthy subjects (80% women and mean age 54 (SD: 12)) to 15 µg per day or 100 µg per day of vitamin D. The baseline 25-hydroxyvitamin D level was 50 ng/mL in both groups. In the 15 µg group, levels increased to 70 ng/mL and to 110 ng/mL in the 100 µg group. Thus median increases in 25-hydroxyvitamin D per 1 µg per day of vitamin D were 0.88 ng/mL and 0.24 ng/mL, respectively.

A double-blind, placebo controlled trial in Finish women 65-85 years randomised to received placebo, 5, 10 or 20 µg per day of vitamin D for 12 weeks showed a dose-response rate inversely correlated with baseline serum 25-hydroxyvitamin D levels, i.e., the higher the serum 25-hydroxyvitamin D before randomisation, the lower the increase after intakes of vitamin D supplements (Viljakainen *et al.,*2006).

In Norway, high dose vitamin D supplements were used in a trial testing a compound for the treatment of depression, overweight and obesity (Jorde *et al.,*2008). High doses were used because overweight and obese subjects tend to sequestrate vitamin D in fat tissues. Age ranged from 23 to 70 years, and baseline BMI from 27 to 47. Mean 25-hydroxyvitamin D increased from 21 to 35 ng/mL in the group that received 71 µg vitamin D per day, and from 22 to 45 ng/mL in the group assigned to 143 µg vitamin D per day. Therefore, for each µg of daily supplement, the average increase in serum 25-hydroxyvitamin D was only of 0.16 to 0.20 ng/mL, i.e., figures quite close to those obtained by Vieth *et al.,*(2004) with 100 µg per day.

In the meta-analysis of randomised trials (Cranney *et al.,*2007), sub-group analysis of trials in institutionalised subjects with low vitamin D status showed increases of 0.8 ng/mL in mean 25-hydroxyvitamin D per µg of vitamin D, which is much more than the aforementioned overall 0.16 to 0.32 ng/mL found in all trials. Likewise, a randomised trial in France including women aged 65 years and older with serum 25-hydroxyvitamin D levels below 12 ng/mL tested daily 10 µg of vitamin D and 0.5 g elementary calcium against placebo (Brazier *et al.,*2005). After 12 months, an increase in serum levels of 17 ng/mL was observed in the intervention versus the placebo group, corresponding to a daily increase of 1.7 ng/mL per µg vitamin D. The latter figure is in line with prediction from the linear regression trend in Figure 4.5.

Healthy adults and elderly subjects without supplementation have slow and steady decreasing serum 25-hydroxyvitamin D levels as the seasons progress towards winter, yet response to supplementation is efficient and a new plateau of vitamin D status is reached (Heaney *et al.,*2003; Viljakainen *et al.,*2006). However, increases in serum 25-hydroxyvitamin D levels induced by

supplementation will be higher in subjects with low vitamin D status than in subjects with high vitamin D status before supplementation. Moreover, for the same baseline serum 25-hydroxyvitamin D, dose-response to supplementation decreases with increasing dose.

4.3.4 Conclusions on exogenous sources of vitamin D

Similarly to endogenous synthesis, regulation mechanisms seem to restrict increases in serum levels of 25-hydroxyvitamin D that would be expected with increasing vitamin D intakes, and restrictions are gradually more pronounced if serum levels prior to intake are high.

A consequence is that the same vitamin D dose will lead to substantial increases in 25-hydroxyvitamin D levels in subjects with low vitamin D status while it may have little influence on levels in subjects with high vitamin D status.

It is probable that several limiting mechanisms are common to endogenous and exogenous sources of vitamin D.

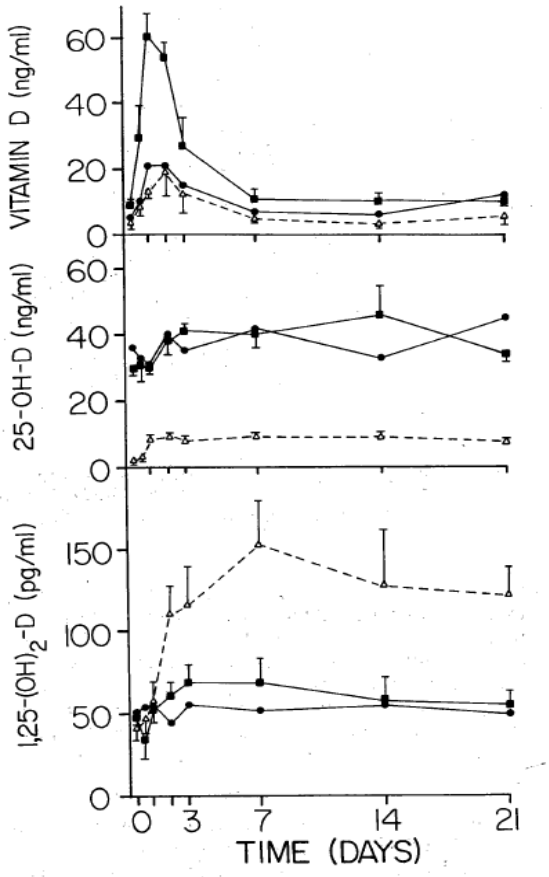


Figure 4.1 – *Original caption*: Changes in Serum Concentrations of Vitamin D and its Metabolites after Exposure to Ultraviolet Radiation. (Adams *et al*.Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects. NEJM. 1982;306(12):722-725. Copyright © 1982 Massachusetts Medical Society. All rights reserved.)

Concentrations of vitamin D, 25-OH-D, and 1 ,25-(OH)sD were measured in three normal subjects exposed to three minimal erythemal doses of ultraviolet radiation (UVR) (solid squares, solid lines), in a representative normal subject exposed to one minimal erythemal dose of UVR (solid circles, solid lines), and in three vitamin-D-deficient patients exposed to one minimal erythemal dose of UVR (open triangles, dashed lines). Bars denote S.E.M.

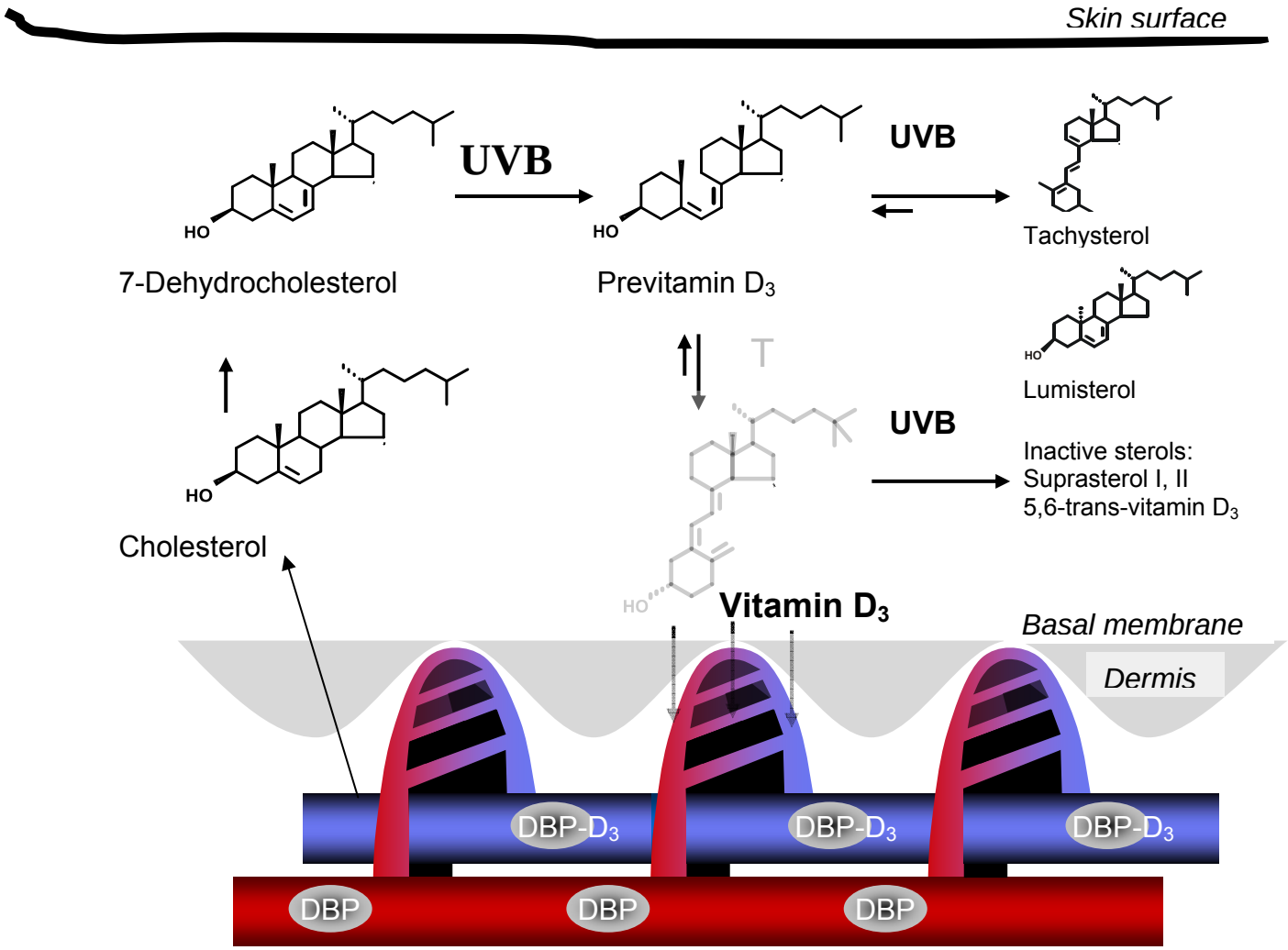


Figure 4.2 - Photochemical synthesis of vitamin D_3 in human skin (from Bodo Lehmann, personal collection). The provitamin D_3 7-dehydrocholesterol (7-DHC) is formed in the skin from circulating cholesterol. The 7-DHC absorbs UVB radiation causing it to isomerise, resulting in the previtamin D_3. Previtamin D_3 then undergoes nonenzymatic isomerisation to form vitamin D_3. The vitamin D_3 formed in the skin is then swept out into the blood stream by the Vitamin D Binding protein (DBP), and α-globulin that has a high affinity to vitamin D and its metabolites. The constant extraction of vitamin D from the skin by DBP avoids the local accumulation of vitamin D_3 and allows perpetuation of the isomerisation of previtamin D_3 into vitamin D_3. UVB-triggered conversion of 7-DHC to previtamin D_3 is a rapid reaction which needs only a few seconds. In contrast, the half life ($\tau_{1/2}$) of the isomerisation of previtamin D_3 to vitamin D_3 in human skin is approximately 2.5 hours. The circulating concentrations of vitamin D_3 are at their maximum levels within 12-24 hours after UVB exposure. A few minutes after start of UVB exposure, the previtamin D_3 also transforms in inter tachysterol and lumisterol, and the UVB further promotes degradation of vitamin D_3 in inactive suprasterol and other inert compounds.

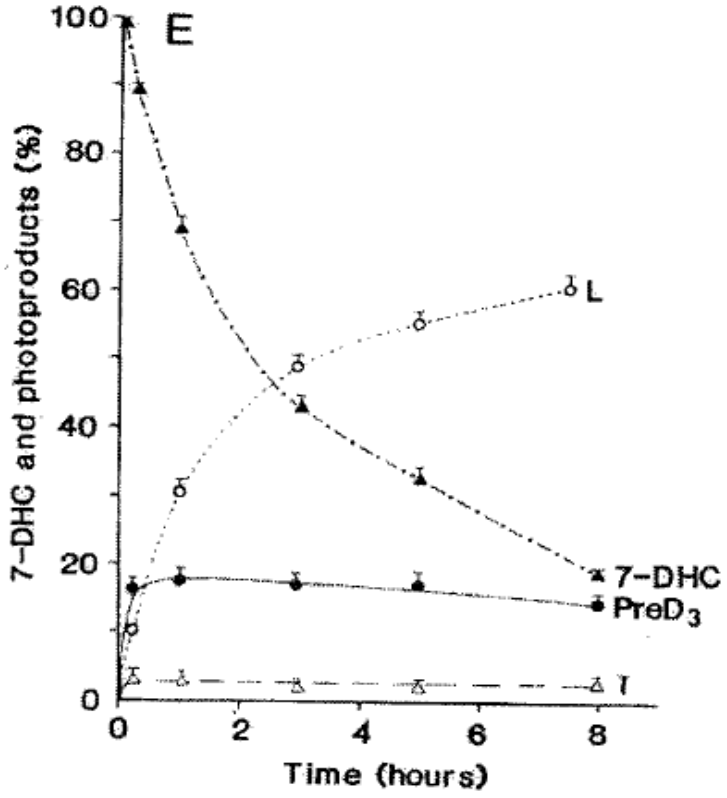


Figure 4.3 – *Original caption*: Exposure of provitamin D_3 to simulated equatorial sunlight, resulting in the photoproduction of precholecalcifenol (previtamin D_3) [from 7-dehydrocholesterol (7-DHC)] and its photoisomers lumisterol (Li) and tachysterol (T3). (From Holick, *et al*. Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator. Science. 1981 Feb 6;211(4482):590-3. Reprinted with permission from AAAS. "Readers may view, browse, and/or downlaod material for temporary copying purposes only, provided these are for noncommercial personal purposes. Except as provided by law, this material may not be further reproduced, distributed, transmitted, modified, adapted, perfomed, displayed, published, or sold in whoe or in part, without prior written permission from the publisher.").

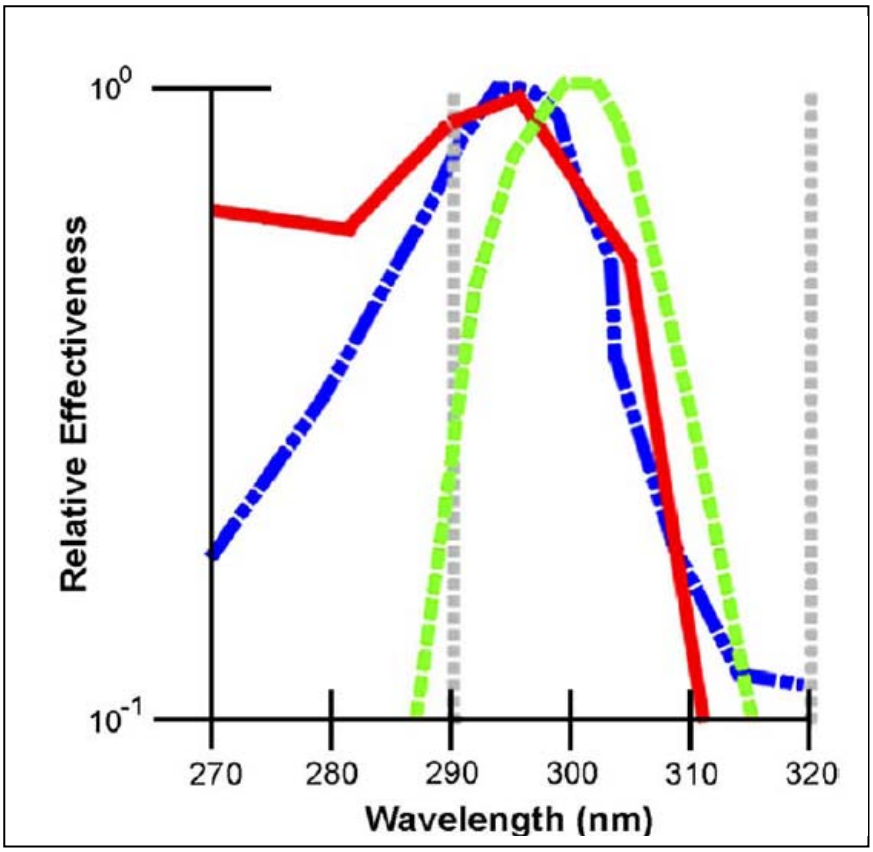


Figure 4.4 – *Caption of original article:* Cutaneous vitamin D synthesis cannot be dissociated from harmful effects of UV radiation. Dashed and dotted line (blue) shows spectrum of previtamin D_3 formation obtained from plotting reciprocal of photoenergy (1/w cm_2). Dashed line (green) represents both action spectrum of induction of squamous cell carcinoma in human beings mathematically derived from experimental data obtained from murine skin, and wavelength dependence of induction of DNA damage, in this case cyclobutane pyrimidine dimers, in human skin (adapted121). Solid line (red) shows erythema action spectrum from human skin (m2/J) (adapted 26). Note that peaks of these 3 curves all occur within UVB spectrum (290-320 nm) (dashed gray lines). (From Wolpowicz & Gilchrest, The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol. 2006 Feb;54(2):301-17. With permission).

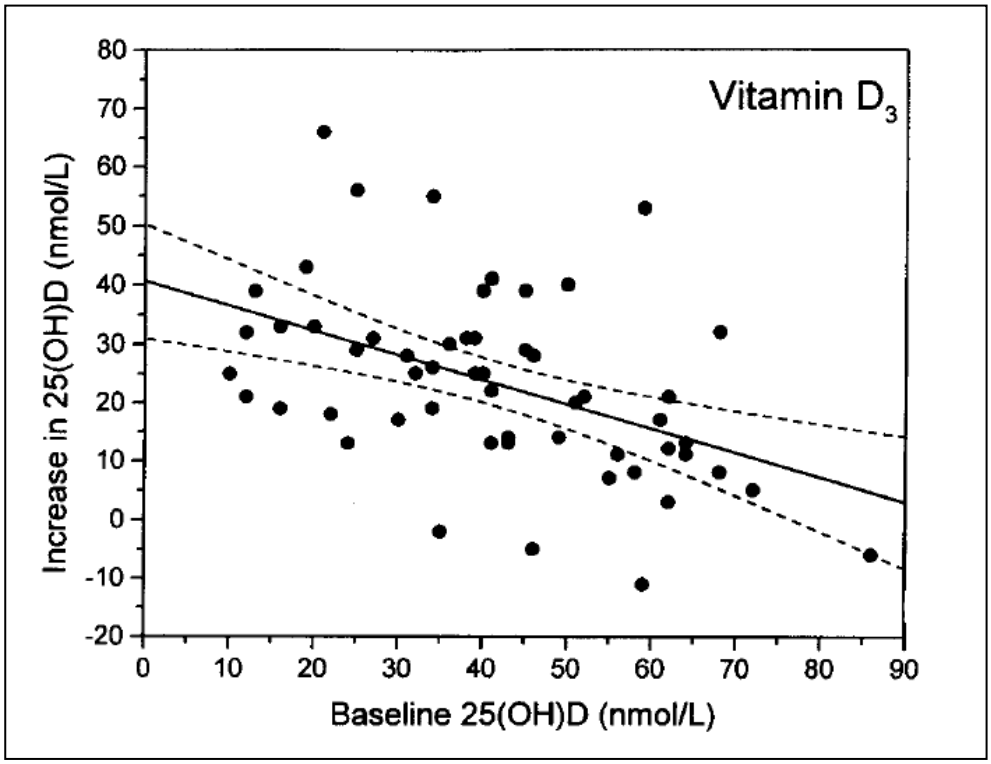


Figure 4.5 – *Original caption*: A plot of baseline 25-hydroxyvitamin D concentrations versus the increase in 25-hydroxyvitamin D concentrations after 100 µg per day vitamin D_3 supplementation in healthy volunteers. The data showed a significant inverse relation ($r = 0.472$, $P < 0.001$). Dotted lines indicate the 95% CI of the mean. For ng/mL, divide nmol/L by 2.5 (From Trang *et al.,* Am J Clin Nutr. 1998;68:854-8. American Society for Nutrition.).

Chapter 5 – Toxicity of vitamin D and long term health effects

The toxic effects of vitamin D are associated with the role of free serum 1α,25-dihydroxyvitamin D in the regulation of plasma calcium via increased intestinal absorption or increased mobilisation of bone calcium. Excessive serum concentration of 1α,25-dihydroxyvitamin D may be due to excess production (e.g., in certain diseases like sarcoïdosis) or by displacement from the Vitamin D Binding Protein (DBP) because of excess intakes of vitamin D.

Knowledge of non-bone, non-calcium adverse effects that could be associated with the maintenance of high vitamin D status is currently very limited and needs further investigation.

5.1 Acute toxicity of vitamin D

Since 1928, it has been known that excessive daily vitamin D ingestion (200,000 – 300,000 IU, i.e., 5,000 – 7,500 µg) produces toxic effects in humans (Hess, 1928). Anecdotal case reports on vitamin intoxication are generally associated with over-the counter-supplements (Koutkia, Chen *et al.,*2001; Propp and Scharfman, 1956; Hoff, 1980; Marriott, 1997) but also with drinking fortified milk (Jacobus *et al.,*1992) and dermatological preparations containing high amounts of vitamin D (Gottswinter *et al.,*1983).

Acute vitamin D intoxication with hypercalcemia may clinically evoke a myocardial infarction (Linden, 1974; Ashizawa *et al.,*2003). Hypercalcemia could also lead to an increased calcium excretion into urine. Prolonged hypercalcemia can cause kidney damage (kidney stones and renal dysfunction), calcification of soft tissues, including kidney, blood vessels, heart and lungs.

5.2 Long-term use of less than 25 µg vitamin D supplements per day

A review of nineteen earlier studies on continuous low dose supplementation (or higher doses given intermittently) concluded that hypercalcemia was a rare event and usually associated with a predisposing cause (Byrne *et al.,*1995).

The Cochrane review of vitamin D and calcium supplements for fracture prevention (Avenell *et al.,*2005) concluded that hypercalcemia risk was 2.4 times higher (95%CI 1.52 to 3.71) when vitamin D or its analogues were used compared to a placebo or calcium. The risk of hypercalcemia was particularly high for the use of 1α,25 dihydroxyvitamin D (RR 14.94, 95% CI 2.95 to 75.61). A review of the same topic done by the University of Ottawa (Canada) for the US Department of Health and Human Services (Cranney *et al.,*2007)[2] also concluded that there is little evidence from trials that long-term vitamin D supplementation of between 10 and 25 µg per day would be harmful.

A meta-analysis of randomised trials of vitamin D and calcium supplements found a 7% (-1%;13%) reduction in all-cause mortality (Autier and Gandini, 2007) in elderly people with low vitamin D status. This result indicates that fatal adverse events are not likely with long-term use of supplements containing 10 to 20 µg of vitamin D and 0.5 to 1.2 g of elementary calcium.

A randomised trial in France including 192 women aged 65 years and over with serum 25-hydroxyvitamin D levels less than 12 ng/mL tested daily with 10 µg of vitamin D and 0.5 g elementary calcium against a placebo (Brazier *et al.,*2005). This trial made a systematic assessment of a number of a-priori defined clinical and biological endpoints for all key body systems. After 12 months, no difference in adverse events was noticed between the intervention and the control groups, apart from greater uric acid concentrations in the intervention group.

5.3 Use of high doses of vitamin D supplements over several weeks or months

Studies on the safety intakes of high dose vitamin D (i.e., 100 µg up to 1,250 µg per day) were done over short periods, from a few weeks to 6 months, and rarely for one year or more (Vieth, 1999; SCF, 2002; Heaney *et al.,*2003; Kimball *et al.,*2007; Vieth *et al.,*2004). Hypercalcemia was not found in these studies despite 25-hydroxyvitamin D levels that could reach 155 ng/mL over 6 months (Kimball *et al.,*2007). Anecdotal reports on subjects taking very high doses (i.e., 100 to 200 µg per day) of vitamin D supplements during several years were not associated with hypercalcemia (Kimball and Vieth, 2008). These studies illustrate the tight regulation of calcium balance.

One trial randomised 208 postmenopausal African American women to placebo or to oral doses of vitamin D of 20 µg per day over 2 years followed by 50 µg per day over the third year. No serious adverse event was reported, but a few (3) women had hypercalciura (Talwar *et al.,*2007). This trial was too small to capture rare but serious adverse events. The reporting of adverse events was not clear and a comprehensive search of side effects (e.g., via analysis of key biochemical parameters in serum and urine) seems not to have been done.

A double-blind placebo controlled randomised trial in Norway of the impact of vitamin D supplements on symptoms of depression in obese and overweight subjects were given the equivalent of 143 µg per day of vitamin D over one year to 116 subjects (47 males and 69 females) aged 26 to 70 years (Jorde *et al.,*2008). Baseline serum 25-hydroxyvitamin D level was 12.3 ng/l, and at 12 months, it was 45.2 ng/l. No serious adverse event was attributed to the high dose vitamin D intervention group.

A 3-year placebo-controlled randomized trial in post menopausal women found increased serum LDL concentrations and decreased serum HDL concentrations in women taking 7.5 µg per day of vitamin D, thus possibly increasing their cardiovascular risk (Tuppurainen *et al.,* 1995; Heikkinen *et al.,* 1997). This trial also found positive long-term effect of hormone replacement therapy on serum lipid concentrations. Results from this trial must be taken with caution as the the Women's Health Initiative trial showed increased rate of cardiovascular events with HRT use (Rossouw *et al*., 2002) and the meta-analysis of randomized trial on vitamin supplements found a reduced risk of overall mortality (Autier & Gandini, 2007).

During one year, 30 morbidly obese patients were administered after bariatric surgery 180 µg per day of vitamin D in addition to supplemention with 20 µg (Carlin et al., 2008). This study was a randomized trial on vitamin D supplemention with a control group of 30 patients who received 20 µg per day of vitamin D supplements. No significant adverse effects with high dose vitamin D were encountered in this small trial.

5.4 Discussion of the safety of long-term use of high doses of vitamin D

Although studies on high doses of vitamin D did not report serious adverse health events associated with high intakes of vitamin D, the conclusions about the health consequences of high vitamin D intake over several years possible are quite limited because most studies:

- Did not exceed a few weeks or months.
- Typically included young, healthy subjects more likely to tolerate high doses of vitamin D.
- Typically excluded subjects more likely to develop adverse events such as chronic liver or kidney disease.
- Did not include enough subjects to be able to detect less frequent but serious adverse events.
- Monitored only a few pre-defined biochemical parameters, and clinical or biochemical endpoints other than those related to bone and calcium metabolism were not assessed (the aforementioned trial of Brazier *et al.,(*2005) is an exception).
- Did not report on any clinical or biochemical abnormality observed during the studies.
- Did not examine possible long term side effects in various age and ethnic groups.

Other information suggests a need for caution as to different adverse events possibly associated with the long term maintenance (i.e., 2-3 years and more) of high vitamin D status in healthy, well fed subjects.

First, experiences gathered from other vitamins and other micronutrients show that both too low and too high intakes are detrimental. Numerous laboratory data and observational studies have suggested that increasing body levels of anti-oxidants (beta-carotenes, vitamin A and retinoids, vitamin C, vitamin E, selenium) and folic acid could contribute to preventing cancer and other chronic conditions, mainly cardiovascular disease. Since 1990, cohort studies and randomised trials have revealed health hazards often associated with supplementation and maintenance of high physiological concentrations of these compounds over long periods in otherwise well-fed subjects [3].

Meta-analyses of randomised trials on supplementation with anti-oxidant supplements (alone or in combination) in well nourished populations found no impact on gastro-intestinal cancer risk, but found a significantly increased risk for all-cause mortality of 6% associated with the taking of these supplements, mainly for beta carotene (7% increase), vitamin A (16% increase), and vitamin E (4% increase) (Bjelakovic *et al.,*2004, 2007). As a result of these findings, current recommendations are very cautious or discourage well fed people from taking anti-oxidants and folic acid supplements, and some countries (e.g., the European Union) are implementing more stringent regulation on the commercialisation of these supplements.

Even the safety of calcium supplements has been recently questioned by a randomised trial in healthy postmenopausal women; the trial found that taking 1 g of elementary calcium per day conveyed a significantly increased risk of cardiovascular events (Bolland *et al.,*2008).

Second, recently published results from prospective cohort studies in the USA, one from the Third National Health and Nutrition Examination Survey (NHANES III), and one from the Framingham Offspring Study suggest that low as well as high 25-hydroxyvitamin D could be associated with increased all-cause mortality (Melamed *et al.,*2008) and incidence of cardiovascular diseases (Wang *et al.,*2008). Risks are more pronounced for low 25-hydroxyvitamin D, but figures 5.1, 5.2 and 12.2 suggest that individuals with high 25-hydroxyvitamin D levels over the long term could also be at higher risk of death, from cancer or from a cardiovascular event. In the NHANES III study (Figures 5.1 and 12.2) higher mortality risk was observed for subjects with unusually high 25-hydroxyvitamin D above 49 ng/mL (during the winter in northern areas, 100 to 125 µg per day of vitamin D supplement is required to maintain such a level – Heaney *et al.,*2003). The NHANES III study is however sometimes difficult to interpret because all the northern states had blood samples taken in the summer while in southern states, blood samples were taken in the winter (Looker *et al.,*2002; see Chapter 12). In the Framingham study, the lowest risks were found in subjects with baseline 25-hydroxyvitamin D levels of 20 to 25 ng/mL, and then increased for higher values (Figure 5.2).

Thirdly, an increased risk of cancer with higher levels of serum 25-hydroxyvitamin D have been found in some observational studies (see Chapter 11). The first prospective study on serum 25-hydroxyvitamin D and colorectal cancer reported a U-shaped relationship with minimal risk for serum levels between 20 and 41 ng/mL, which increased for levels below 20 ng/mL of above 41 ng/mL (Garland *et al.,*1989)(Figure 5.3).

A U-shaped relationship between serum 25-hydroxyvitamin D levels and prostate cancer was found by a large case-control study in Finland and Norway (Tuohimaa *et al.,*2004) (Figure 5.4). Subjects with serum 25-hydroxyvitamin D concentration levels 16-24 ng/mL had the lowest risk of prostate cancer, while increased risks were found for levels less than 7.6 ng/mL (non-significant increase) and higher than 32 ng/mL (significant increase).

Other observational studies yielded results in total contradiction to the expectation of a lower cancer risk associated with higher vitamin D status. In the α-Tocopherol, β-Carotene Cancer Prevention Trial (ATBC) in Finnish smokers, higher 25-hydroxyvitamin D concentrations were associated with a 3-fold increase in the risk of pancreatic cancer (highest versus lowest quintile, >27 versus <130 ng/mL) (Stolzenberg-Salomon *et al.,*2006). Increased risk of squamous dysplasia of the oesophagus and of oesophageal squamous cell carcinomas were significantly associated with high serum 25-hydroxyvitamin D concentrations in prospective studies in Chinese populations suffering from nutritional deficiencies (Chen *et al.,* 2007a; Abnet *et al.,*2007).

The “J” or “U-shaped” curve described between serum concentrations of several anti-oxidative substances and mortality or adverse events seems therefore to also to exist for vitamin D (see endnote 1, Bleys *et al.,*2008 for selenium, Miller *et al.,*2005 for vitamin E). If real, this type of dose-effect relationship would mean that increasing 25-hydroxyvitamin D could bring health benefits among subjects with low vitamin D status, while it could lead to increased risks in subjects who have a high or a very high vitamin D status before starting to take supplements. In this respect too, the higher the dose of supplements, the greater the number of subjects at increased risk of vitamin D-induced adverse events.

Lastly, several studies suggested adverse events that could be associated with long-term maintenance of high vitamin D status:

1/ 1α,25-dihydroxyvitamin D increases the intestinal absorption of calcium and phosphates, but also the absorption of other essential minerals (magnesium, iron, zinc, cupper, selenium, vanadium, cobalt). It also increases the absorption of toxic metal ions (lead, cadmium, aluminium) and several radioactive isotopes (Moon, 1994). Cadmium is a known carcinogen (IARC, 1993) and the accumulation of aluminium in the brain could be implicated in Alzheimer's disease (Moon *et al.,*1992; Schcherbatykh and Carpenter, 2007). Blood lead concentrations are higher in the summer than in winter (Baghurst *et al.,*1992; Ladlaw *et al.,*2005; Yiin *et al.,*2000), and higher summertime 25-hydroxyvitamin D in 4 to 8 year old children seems associated with a seasonal increase in blood lead (Kemp *et al.,*2007).

2/ The Women's Health Initiative trial reported a 17% (2%;34%) increase in the risk of kidney stones among postmenopausal women receiving 10 µg of vitamin D and 1000 mg of elemental calcium per day (Jackson *et al.,*2006), but this increase was probably due to calcium supplements, and not to vitamin D supplements. Other randomised trials testing vitamin D supplements did not report a higher incidence of kidney stones (Cranney *et al.,*2007).

5.5 Conclusions

Long-term use of low dose vitamin D supplements (less than 25 µg per day) is not associated with serious adverse events and it could reduce all-cause mortality in elderly subjects with low vitamin D status.

Few studies have examined health effects other than on bone and calcium metabolism of the long-term use of high doses (say, greater than 25 µg per day) of vitamin D. Most were short-term studies that looked at selected parameters related to calcium metabolism, and an assessment of key clinical or physiologic parameters was not performed. The few randomised trials that tested high vitamin D intakes were too small to capture rare but serious adverse events.

Health effects of long term maintenance of high levels of serum 25-hydroxyvitamin D (say above 30 ng/mL for several years) in well fed subjects have practically never been studied. Recent data suggests that similar to some anti-oxidants, the risk of negative health outcomes would be associated with low serum 25-hydroxyvitamin D levels and also probably with high serum 25-hydroxyvitamin D levels (although the risk would be lower than for low levels).

Thus at present, the consequences of long-term consumption (i.e., two years or more) of more than 25 µg per day of vitamin D supplements by adults and of long term maintenance of high serum 25-hydroxyvitamin D levels (i.e., say, 40 ng/mL and more) are largely unknown.

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[1] Deficiency in folic acid is deemed to be a major cause of spina bifida, a severe congenital malformation affecting the lower part of the backbone due to absence of full closing of the neural tube.

[2] Cranney A, Horsley T, O'Donnell S, Weiler HA, Puil L, Ooi DS, Atkinson SA, Ward LM, Moher D, Hanley DA, Fang M, Yazdi F, Garritty C, Sampson M, Barrowman N, Tsertsvadze A, Mamaladze V. Effectiveness and Safety of Vitamin D in Relation to Bone Health. Evidence Report/Technology Assessment No. 158. Prepared by the University of Ottawa Evidence-based Practice Centre (UO-EPC) under Contract No. 290-02-0021. AHRQ Publication No. 07-E013. Rockville, MD: Agency for Healthcare Research and Quality. August 2007

[3] **Additional information on studies and trials that tested the value of folic acid and anti-oxidants for the prevention of cancer and other chronic conditions**.

Beta-carotenes

Observational epidemiological studies have consistently suggested that beta-carotene is associated with decreased cancer risk, particularly of lung cancer. In contrast, randomised trials testing the effect of beta-carotene supplementation on cancer incidence and mortality generally have not been supportive (IARC, 1998a; Vaino *et al.,*1998; Cook *et al.,*2000). Two of these trials, the ATBC (ATBC, 1994) and the CARET (Omenn *et al.,*1996) yielded results showing serious harmful effects of beta carotene used as supplements: total mortality was significantly increased in intervention groups mainly because beta carotene was given to smokers or past asbestos workers and increased the lung cancer incidence by 18% and 28% respectively. A meta-analysis of randomised trials concluded that beta-carotene supplementation significantly increased (by 24%) the risk of lung cancer among current smokers (Tanvetyanon and Bepler, 2008).

Vitamins A and retinoids

These compounds were initially shown to modulate differentiation in many experimental systems (IARC, 1998b, 1999). No significant effects on mortality rates were observed for supplementation with a combination of retinol and zinc (Blot *et al.,*1993), or beta-carotene and vitamin A (Omenn *et al.,*1996). One large randomised trial of a vitamin A analogue, feretinide showed no impact on the occurrence of secondary breast cancer in breast cancer survivors (Veronesi *et al.,*1999). In 1998, systematic reviews by IARC Expert Groups concluded that there was evidence suggesting a lack of anti-cancer activity of preformed vitamin A compounds, and thus also of vitamin A (Table 1) (IARC, 1998b). Similar conclusions were reached with retinoids, a class of compounds structurally related to vitamin A (IARC 1999). Also, some of these retinoid compounds are teratogenic in humans or in animals (Table 1) (IARC, 1999).

Vitamin C

Vitamin C is deemed to be a free-radical scavenger, and high intakes of foodstuffs rich in vitamin C (e.g., citrus fruits) could play a role in decreasing gastric cancer incidence. Double-blind randomised trials of supplementation with ascorbic acid (1g twice per day) combined with other anti-oxidants (usually vitamin E, selenium, beta-carotene) in populations at high risk for gastric cancer in China and Venezuela did not result in higher rates of regression of dysplastic lesions in the stomach (You *et al.,*2006; Plummer *et al.,*2007).

Vitamin E

Vitamin E has anti-oxidant properties that were deemed to play a role in controlling cellular oxidative damage. In the ATBC study (ATBC, 1994) the group receiving a vitamin E supplement (50 IU per day) had no reduction in lung cancer incidence but a 34% reduction in prostate cancer incidence. However deaths from cerebrovascular accidents doubled. A randomised placebo-controlled trial within the Women's Health Initiative Study found no effect of 600 IU per day of vitamin E on cancer risk (Lee *et al.,*2005). A meta-analysis of vitamin E supplementation including 16 randomised trials suggests that high doses of vitamin E supplementation above 200 IU per day may increase all-cause mortality (Miller *et al.,*2005).

Selenium

Selenium is involved in defence mechanisms against oxidative stress through selenoproteins. Selenium at high doses is known to be toxic. Selenium supplementation with doses around 200µg per day was thought to prevent non-melanoma skin cancer, and colorectal and prostate cancer. Selenium has been part of several trials, but it was often mixed with vitamins and it is thus difficult to isolate an effect specific to this compound.

The Nutritional Prevention of Cancer (NPC) Trial (Clark *et al.,*1996) was a placebo-controlled randomised trial to test whether selenium supplements could reduce the incidence of non-melanoma skin cancer. The incidence of non-melanoma skin cancer remained the same in the intervention and in the placebo groups. However the group that received the supplement had statistically significant reductions of approximately 40% and 50% in overall cancer incidence and cancer mortality, respectively. Main reductions in incidence were observed for prostate, colorectal and lung cancer. Separate follow-up of lung cancer and prostate cancer showed a reduction of the incidence of these two cancers in subjects who had low serum selenium levels at baseline, and not in subjects with higher levels at baseline (Reid *et al.,*2002; Duffied-Lillico *et al.,*2002). A re-analysis of the trial data showed that all the protective effect was confined to males, and that selenium supplements decreased cancer risk in subjects with low serum selenium levels at baseline, whereas these supplements seemed to increase cancer risk in subjects with high selenium levels at baseline (Duffield-Lillico *et al.,*2002).

A randomised trial organised within the NPC Trial failed to show reduction of colonic polyps with selenium supplementation (Reid *et al.,*2006), but again, a significant decrease was noticeable among subjects with low serum selenium levels at baseline while in subjects with high serum selenium level at baseline, the frequency of polyps was greater, although statistically not significant.

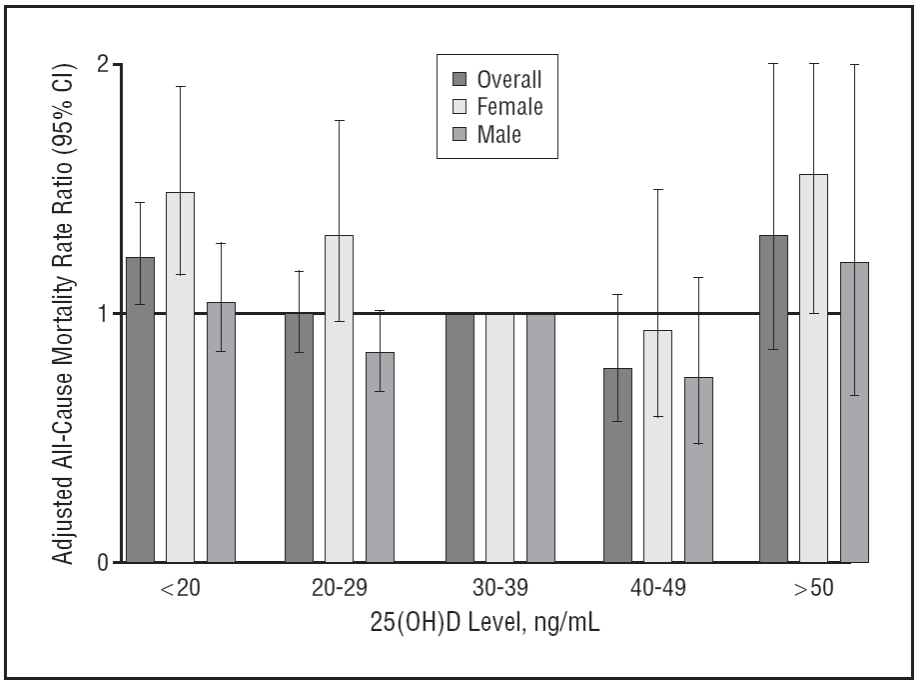
Recent results of the Third National Health and Nutrition Examination Survey (NHANES III) cohort study in the USA calls for caution with use of this compound, as the study suggests a U shaped curve in associated risk with serum selenium levels and all-cause and cancer mortality. Higher mortality was observed in subjects with low or with high serum levels of selenium, and lower mortality around some optimal serum levels (Bleys *et al.,*2008).

Therefore, supplementation with selenium has little influence on cancer risk, and instead can be detrimental for subjects who have high levels of serum selenium.

Folic acid

Folic acid plays an important role in DNA repair, synthesis and methylation reactions. Two randomised placebo-controlled trials indicate that folic acid supplements may in reality increase the risk of colorectal and prostate cancer, and of adenomatous polyps (Lonn *et al.,*2006; Cole *et al.,*2007).

Figure 5.1 –The figure caption in original article is below the figure (Melamed *et al.,*2008, with permission). The *referent category* are subjects with serum 25-hydroxyvitmain D (25(OH)D) levels between 30 and 39 ng/Ml (Melamed et al. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. Arch Int Med 2008;168(15):1629-1637. Copyright 2008 American Medical Association. All rights reserved.).



Associations between 25-hydroxyvitamin D (25[OH]D) levels and all-cause mortality in 13 331 participants of the Third National Health and Nutrition Examination Survey, overall and by sex. To convert 25(OH)D to nanomoles per liter, multiply by 2.496. CI indicates confidence interval.

Figure 5.2 Nonlinearity of multivariable-adjusted relation between baseline vitamin D status and incident cardiovascular events. Lowest risks of cardiovascular event were found in subjects with baseline 25-hydroxyvitamin D of 20 to 25 ng/mL. The risk increased for values below 20 ng/mL or above 25 ng/mL. (Wang et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation, 2008;117:503-511.)

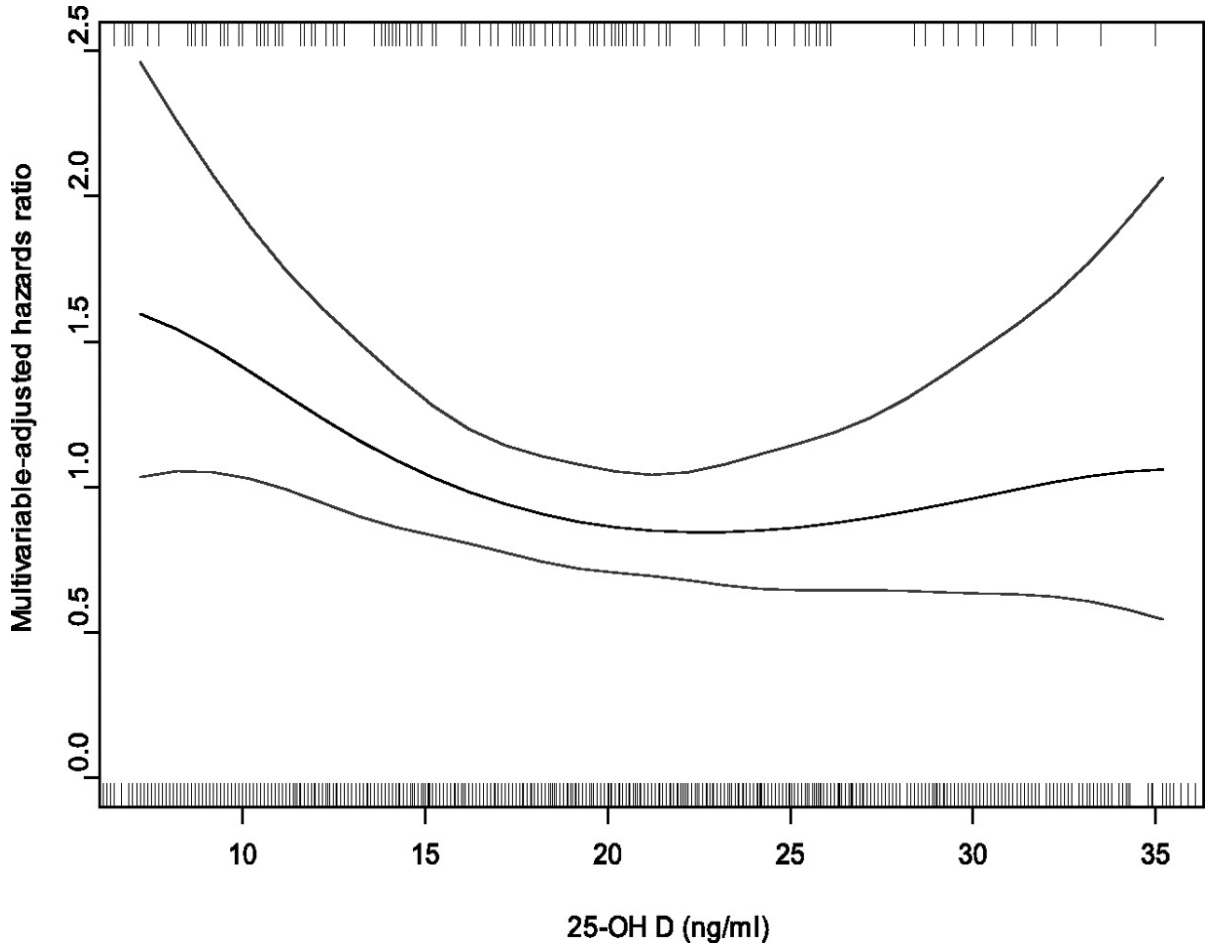


Figure 5.2 – *Caption of the original article:* Nonlinearity of multivariable-adjusted relation between baseline vitamin D status and incident cardiovascular events. Solid lines show estimated relation of adjusted hazard ratios (with 95% confidence limits) and 25-OH D levels when time to cardiovascular event is modelled as a function of penalised regression splines of 25-OH D levels with adjustment for all other covariates. Hatched lines on the horizontal axis represent cardiovascular events (top axis) and censored individuals (bottom axis).

Figure 5.3 – *Caption in original article*: Risk of colon cancer by quintile of serum 25-hydroxyvitamin D. Numbers in columns = no of cases/no of controls.*p≤005. (Reprinted from The Lancet, 2(8673), Garland et al. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study.1176-8. Copyright 1989, with permission from Elsevier.")

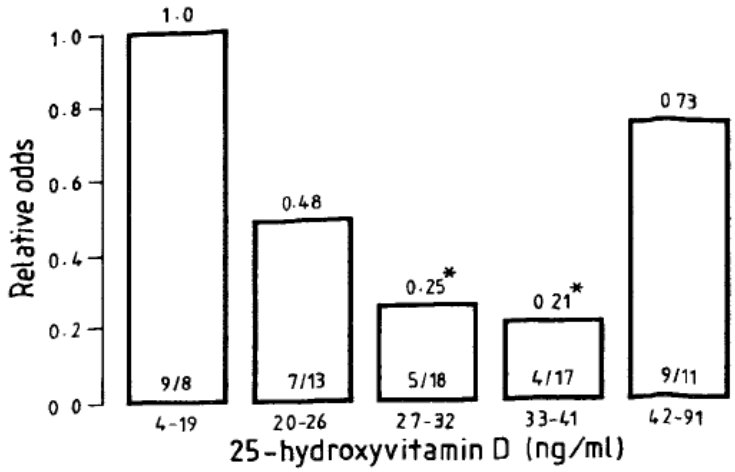
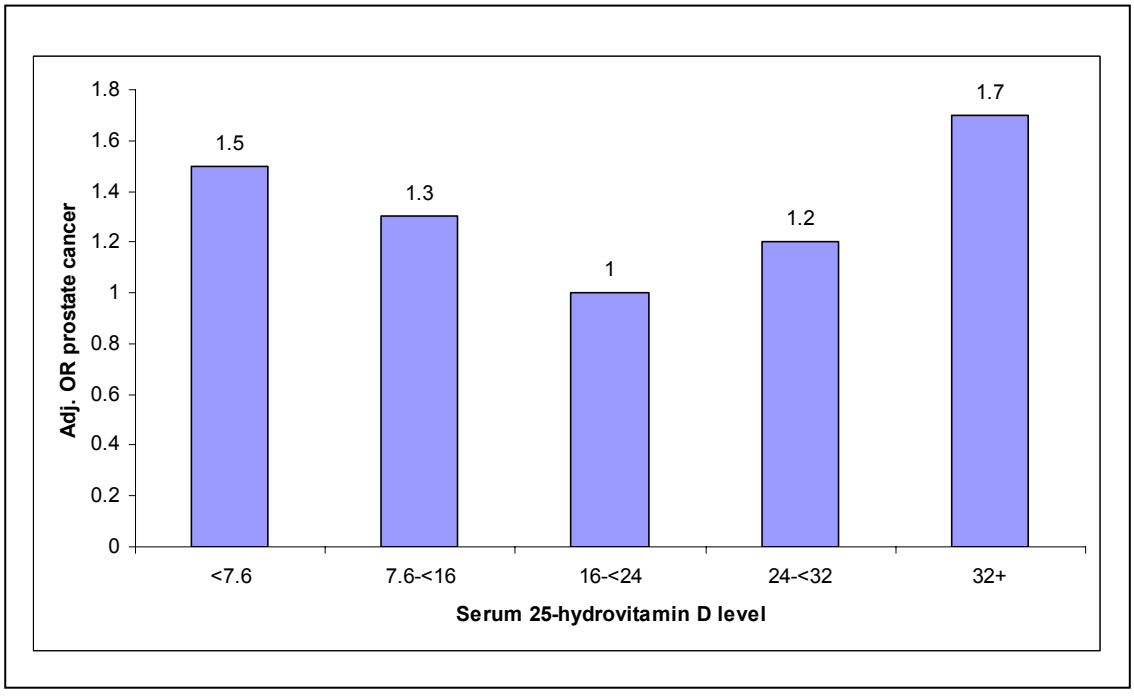


Figure 5.4 – Adjusted risk of prostate cancer in a cohort of men in Finland, Norway and Sweden according to serum 25-hydroxyvitamin D level at baseline (from Tuohimaa *et al.*, 2004, adapted). The risk was not statistically significant for serum levels below 7.6 ng/mL, and it was significant for levels ≥32 ng/mL.



Chapter 6 – Current recommendations for vitamin D intakes

Internationally, the recommendations for vitamin D intake have been based upon levels presumed necessary for the prevention of vitamin D deficiency diseases, mainly rickets and osteomalacia that affect children and women in childbearing age. The vitamin D requirements for healthy adults have never been precisely defined (SCF, 2002). In addition, the lack of a standard approach for deriving nutrient recommendations has resulted in wide between country heterogeneity in terms of recommended intake levels (Doets *et al.,*2008). The potential confusion is compounded by the use of different terminologies, such as estimated average requirement (EAR), recommended dietary allowance (RDA), adequate intake level (AI), and tolerable upper intake level (UL), with many local variants, which are used to express requirement levels. Below, vitamin D intake recommendations from major health agencies and different world regions are briefly reviewed.

6.1 WHO/FAO

A joint WHO/FAO report entitled Expert Consultation on Diet, Nutrition and Prevention of Chronic Diseases (2003) [4] makes recommendations based on the latest scientific evidence available at the time of publication pertaining to relevant interventions for chronic disease risk reduction and with the overall aim of implementing more effective and sustainable policies and strategies to deal with the increasing public health challenges related to diet and health. The report lists vitamin D as having "insufficient" evidence to merit a recommendation for cancer risk reduction. However, the report does recommend intakes of vitamin D and calcium for fracture risk reduction in osteoporosis.

Another joint report from the WHO/FAO expert consultation on Vitamin and Mineral Requirements in Human Nutrition (2004)[5] took one of the recommendation made by MF Holick (1994) saying that the most efficient and physiologically relevant way of acquiring vitamin D is via sun exposure for approximately 30 minutes per day on the hands and face. The report does not at all discuss issues related to skin complexion and variable ability to synthesise vitamin D. Following Holick (1994), in situations where the skin synthesis of vitamin D is negatively influenced (high latitude, winter season, dark skin pigmentation, older age, clothing, sunscreen use), the report provides recommendations for dietary intake ranging from 5 µg/day (infants, children, adolescents, adults up to 50 years old, pregnant women, lactating women) to 10 µg/day (adults 51-65years old) to 15 µg/day (adults >65years and over).

6.2 Europe

Most European countries provide recommendations for vitamin D intake specific to their own populations (Doets *et al.,*2008). In most countries, specific recommendations are provided for different age ranges and at-risk population groups (infants, pregnant and lactating women). Overall, the recommendations vary greatly from country to country. For adults aged 25 to 50 years old, the recommendations range from no supplementation in the United Kingdom, 2.5 µg/day in the Netherlands and Russian Federation to 10 µg/day in Albania and Iceland, with the majority of countries recommending an intake of 5 µg/day (Doets *et al.,*2008). In most countries, dietary vitamin D recommendations are higher for infants, children, adolescents, and adults aged 70 years or more with the maximum being 22.5 µg/day for infants in France. In the United Kingdom, a report of the Department of Health Committee on Medical Aspects of Food and Nutrition Policy has not established an RNI for children older than 3 years, or for adults younger than 65 years (Department of Health, 1998). For Finland, Germany, Switzerland and Austria the recommended daily intake of vitamin D is 5-10 µg/day for most of the population (National Nutrition Council, 1999; Deutsche Gesellschaft für Ernährung *et al.,*2000). In Norway, the National Council on Nutrition and Physical Activity has recommended daily consumption of cod-liver oil supplements, which contains other nutrients in addition to vitamin D (Brustad *et al.,*2004; Rimestad *et al.,*2001). The European Union's Scientific Committee on Food (SCF) has provided Population Reference Intakes (PRI) for vitamin D as follows: 6-11 month 10-25 µg; 1-3 years 10 µg; 4-10 years 0-10 µg; 11-17 years 0-15 µg; 18-64 years 0-10 µg; ≥ 65 years 10 µg; pregnancy 10 µg; lactation 10 µg (SCF, 1993). The European Union has supported a project towards a strategy for optimal vitamin D fortification named OPTIFORD (Andersen *et al.,*2001) as well as the EURRECA (EURopean micronutrient RECommendations Aligned) project aiming at identifying and addressing the problem of differences between countries in micronutrient

recommendations. A list of publications on vitamin D issues from the OPTIFORD project is appended at the end of the chapter. [6]

The EU Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Limit of Vitamin D (SCF, 2002) identifies age specific tolerable upper limit (UL) of intakes of 25µg/day (infants/children ages 0-10 yrs old) and 50µg/day (children/adults from 11+ yrs old, pregnant/lactating women) (Table 1). The committee selected the value of 100 µg/day of vitamin D based on the results of the clinical trial by Vieth *et al.,*(Vieth, 2001) as the No Observed Adverse Effect Level (NOAEL) and applied an uncertainty factor (UF) of 0.5 to arrive at the calculation of 50 µg/day UL in adults.

6.3 United States of America (USA) and Canada

In the USA, current recommendations for the Adequate Intake (AI) of vitamin D are established by the Institute of Medicine (IOM). The AI recommendations are 5 µg/day (200 IU) for newborns and children/adults from between 1 month to 50 years old; 10 µg/day for adults aged between 51 and 70 years and 15 µg/day for individuals >70 years (FNB, 1999). Canadian recommendations for vitamin D intake are also based on the nutrient reference values established by the IOM (15).[7] The IOM has established a safe Upper Intake Level (UL) of 25ug/day of vitamin D in infants (0-1 years old) and 50 µg/day in all others, including pregnant and lactating women (FNB, 1999). In addition, the 2005 Dietary Guide-Lines for Americans, published by the US Department of Health and Human Services and the US Department of Agriculture, recommends that older adults, as well as individuals with dark skin or those not exposed to sufficient sunlight consume additional vitamin D from vitamin D fortified foods and/or supplements.[8]

6.4 Australia, New Zealand

The current guidelines for recommended vitamin D intake (Adequate intake) for Australia and New Zealand differ by age group: 5 µg/day from birth to 50 years of age, including pregnant and lactating women, 10 µg/day for people aged 51-70 years, and 15 µg/day thereafter (Commonwealth Dept of Health and Ageing Australia *et al.,*2006). Safe UL have been established as 25 µg/day in infants and 80 µg/day for all others (Commonwealth Dept of Health and Ageing Australia *et al.,*2006).

6.5 Special groups

In many European countries, as well as in North America, Australia and New Zealand, a higher level of vitamin D intake is often recommended for special groups, namely, pregnant/lactating women, infants, and elderly people. Migrants from sunny areas with pigmented skin, little outdoor activities and strict dress codes leaving practically no skin directly sun exposed are at particularly high risk of vitamin D deficiency and deserve special attention (see Chapter 7).

6.5.1 Pregnant and lactating women

Some studies have shown that vitamin D metabolism is altered in pregnancy. Pregnancy is characterised by an increase in the maternal serum level of 1α,25-dihydroxyvitamin D_3 (Bouillon *et al.,*1981) due to a putative placental synthesis of this hormone (Delvin *et al.,*1985). The physiological role of the elevated circulating 1α,25-dihydroxyvitamin D_3 is not clear. It seems, however, that changes the vitamin D metabolism of pregnant woman do not influence maternal vitamin D requirements. Conversely, it is very clear that transfer of vitamin D from mother to fetus is important for the neonate's growth rate, bone development and probably for other biological processes.

In contrast to pregnancy, during lactation there is no indication of any change in serum vitamin D levels or metabolites (Sowers *et al.,*1998; Kovacs and Kronenberg, 1997). Vitamin D content of human milk is relatively low and amounts maximally 0.6-1 µg/L (Specker *et al.,*1985). Because human milk is a poor source of vitamin D rickets is still found in breast-fed infants deprived of sunlight exposure. (Pettifor and Daniels, 1997; Brunvand and Nordshus, 1996). There is little evidence that increasing vitamin D supplementation to lactating mothers results in an increased transfer of vitamin D to the infant in breast milk (Sowers *et al.,*1998).

6.5.2 Newborns

Infants have a relatively high need of vitamin D because of their high rate of skeletal growth. At birth, infants have acquired in uteri the vitamin D reserves that must carry them through the first months of the life. It has been found that 64% of French neonates have serum vitamin D levels below < 12 ng/mL which corresponds to a severe vitamin D deficiency (Zeghoud *et al.,*1997). Breast-fed infants are particularly at risk because of the low concentrations of vitamin D in human milk (Specker *et al.,*1985). Additionally, the situation worsens when there is a restriction in exposure to sunlight for seasonal, latitudinal, cultural or social reasons. Infants born in the autumn months at extreme latitudes are particularly at risk because they spend the first months of their life indoors and therefore have little opportunity to endogenously synthesise vitamin D during this period. Accordingly, sporadic cases of rickets are still being reported in many northern areas but almost always in infants fed with human milk (Pettifor and Daniels, 1997; Brunvand and Nordshus, 1996; Binet and Kooh, 1996; Gessner *et al.,*1997). Infant formula is supplemented with vitamin D at levels sufficient to prevent rickets.

6.5.3 Elderly people

Several studies have demonstrated an age-related decline in vitamin D metabolism (Holick, 1994), including the rate of skin synthesis, the rate of hydroxylation, and the response of target tissues (e. g. bone) (see Chapter 7). Various supplementation schemes (often also including calcium) using continuous daily oral taking of 10 to 20 µg of vitamin D, or intermittent intramuscular injection of depot vitamin D_2 (Burns and Paterson, 1985), or spending 30 minutes outdoor every day (Reid *et al.,*1986) have all shown ability to increase serum 25-hydroxyvitamin D levels in elderly subjects.

6.6 Conclusions

This chapter has highlighted the existence of a wide heterogeneity in terms of recommendations on levels of dietary vitamin D amongst countries, population groups and age-ranges. Differences in national recommendations may result in confusion for policy makers, health professionals and consumers.

There is growing awareness that vitamin D is required in sufficient amounts for adequate bone health. To date recommendations for vitamin D intakes are done in order to secure optimal bone health. No recommendations are in place from governments or health agencies for recommending increases in body vitamin D status that could eventually contribute to prevent cancer or other chronic diseases.

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[4] http://whqlibdoc.who.int/trs/WHO_TRS_916.pdf

[5] http://whqlibdoc.who.int/publications/2004/9241546123.pdf

[6] **OPTIFORD related publications**

Andersen R, Brot C, Ovesen L (2001) Towards a strategy for optimal vitamin D fortification (OPTIFORD). Nutr Metab Cardiovasc Dis, 11: Suppl. to No. 4, pp 74-77.

Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman KD, Chabros E, Charzewska J, Flynn A, Jakobsen J, Kärkkäinen M, Kiely M, Lambarg-Allardt C, Moreiras O, Natri AM, O'Brien M, Rogalska-Niedzwiedz M, Ovesen L (2005) Teenage girls and elderly women living in northern Europe have low winter vitamin D status. Eur J Clin Nutr, 59, 533-541.

Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman KD, Jakobsen J, Lamberg-Allardt C, Ovesen L (2007) Pakistani immigrant children and adults in Denmark have severely low vitamin D status. Eur J Clin Nutr, 62, 625-634.

Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman KD, JakobsenJ, Lamberg-Allardt C, Ovesen L (2008) Effect of vitamin D supplementation on bone and vitamin D status among Pakistani immigrants in Denmark: a randomised double-blinded placebo-controlled intervention study. Br J Nutr, 100, 197-207.

Viljakainen HT *et al.,*(2006) A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomised placebo-contraolled 1-year intervention. J Bone Miner Res, 21, 836-844

Viljakainen HT *et al.,*(2006) A seasonal variation of calcitropic hormones, bone turnover and bone mineral density in early and mid-puberty girls – a cross-sectional study. Br J Nutr, 96, 124-130

Viljakainen HT *et al.,*(2006) How much vitamin D3 do the elderly need? J Am Coll Nutr, 25, 429-435.

Natri AM *et al*,(2006) Bread fortified with cholecalciferol increases the serum 25-hydroxyvitamin D concentration in women as effectively as a cholecalciferol supplement. J Nutr,136, 123-7.

McCarthy D, Collins A, O'Brien M, Lamberg-Allardt C, Jakobsen J, Charzewska J, Kiely M, Flynn A, Cashman KD (2006) Vitamin D intake and status in Irish elderly women and adolescent girls.

Ir J Med Sci, 175, 14-20.

Cusack S, Mølgaard C, Michaelsen KF, Jakobsen J, Lamberg-Allardt CJ, Cashman KD (2006) Vitamin D and estrogen receptor-alpha genotype and indices of bone mass and bone turnover in Danish girls. J Bone Miner Metab, 24, 329-36.

[7] http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2007/2007_130-eng.php

[8] http://www.health.gov/dietaryguidelines/dga2005/document/pdf/DGA2005.pdf

Chapter 7 – Determinants of vitamin D status

7.1 Measurement of 25-hydroxyvitamin D level

Serum 25-hydroxyvitamin D level is considered to be the best biomarker for reflecting individual vitamin D status, mainly when measured in winter. Various methods are available for the assessment of serum 25-hydroxyvitamin D levels. Current methods are radio-immunoassay, high pressure liquid chromatography, chemiluminescence immunoassay and liquid chromatography-tandem mass spectrometry (Hollis and Horst, 2007). However, these methods have not been standardised, so between-study comparisons can be delicate (SACN, 2007; Lips *et al.,*1999). Lips *et al.,*1999 report in a cross-calibration study of the 25-hydroxyvitamin D assays of five laboratories differences of 38% between the highest and the lowest values. Hypponen *et al.,*2007 reported that the average 25-hydroxyvitamin D concentrations as measured by enzyme immunoassay were on average 6.28 ng/mL lower compared with Diasorin radio-immunoassay.

7.2 Skin synthesis

7.2.1 Exposure to solar ultraviolet B radiation (UVB)

For centuries, the ultraviolet B radiation contained in the sunlight has been the major sources of vitamin D for most human populations, and it is the only source if available food stuffs do not contain vitamin D. Endogenous synthesis of vitamin D will depend on amounts of UVB reaching earth surface, on skin surface exposed to UVB and on skin pigmentation.

Many factors influence the amount of UVB radiation reaching the earth surface. A quantitative review of these factors can be found in Engelsen (2005), Web (2006), and Kimlin (2008). In summary, these factors are:

- UVB is mainly present in sunlight between 10 am and 3 pm solar hour.
- The season: UVB is more abundant during the summer or the hot season.
- The thickness of the stratospheric ozone layer.
- Place of residence: in general, more UVB penetrates the atmosphere at low latitudes, i.e. the closer to the equator, the higher the amount of UVB that reaches earth's surface.
- The earth surface: the sand and the snow reflect the UVB, and the skin receives the reflected UVB added to the direct UVB from the sun.
- Meteorology: clouds may filter out much of the UVB, even at the equator.
- Air quality: micro particles hanging in the air may absorb UVB and thus reduce

The UVB-induced synthesis of vitamin D3 in human skin is additionally dependent on several factors, including:

- Time spent outdoor.
- Hours of the day of outdoor activities.
- Skin type, pigmentation.
- Age of subjects, as endogenous skin synthesis capacity decreases with age.
- Sun protection habits, mainly in populations where clothing (garments and veils) cover most of the skin surface.

7.2.2 Seasonal variations

Seasonal variation in serum 25-hydroxyvitamin D levels is long known for a long time (Stamp and Round, 1974), and the winter level of serum 25-hydroxyvitamin D is considered to provide the

best indication of individual vitamin D status. Peak serum 25-hydroxyvitamin D levels are found in late summer, beginning of autumn, and lowest levels are found at the end of the winter (Figure 7.1). [9] The traditional view is that to maintain vitamin D status during the winter, pools of vitamin D must be constituted during the preceding summer (e.g., Lawson *et al.,*1979).

Peak serum 25-hydroxyvitamin D levels of 80 ng/mL and higher have been described in healthy young adults with heavy summer sun exposure (Vieth, 1999; Barger-Lux and Heaney, 2002). Studies in 26 young healthy men having extended outdoor activity totalling 38 hours sun exposure per week on average displayed serum 25-hydroxyvitamin D levels ranging between 20 and 90 ng/mL in the late summer, and between 20 and 52 ng/mL at the end of the winter. Only two men had levels below 20 ng/mL at the end of the winter (Barger-Lux and Heaney, 2002).

The reason for seasonal variation is that the ambient ultraviolet B radiation necessary for skin synthesis of vitamin D from 7-dehydrocholesterol, is more abundant in summer than winter. The seasonal variation of ultraviolet B radiation will be more important in the higher latitudes than in the tropics, because of the steadily increasing variations in sun elevation angles with increasing latitude. Lower angles of incoming solar radiation means that ultraviolet radiation has to travel a greater distance through the atmosphere, which means that a lot of the radiation is absorbed before reaching earth surface. In addition, the skin synthesis of ultraviolet B radiation will be reduced in colder areas due to the greater cloud cover and as more clothing is worn leaving less skin exposed to sunlight. In the British cohort study, Hypponen and Power (2007) found a two-fold lower serum 25-hydroxyvitamin D level in February than in September. Seasonal variations tend to attenuate with ageing. The seasonal variation in young British adults had a magnitude of about three (Juttmann *et al.,*1981), while it was only 1.6 in community dwelling British 70 to 88 years old (Lester *et al.,*1977).

In some areas, like in most northern areas of the Nordic countries, seasonal variations in vitamin D status may be nonexistent or reduced due to high intakes of marine foods during the winter season (e.g., the Norwegian "Mølje" meals; Brustad *et al.,*2003, 2004a, 2004b, 2007). A study in northern Norway in a small sample of adults found a seasonal variation, but the lowest serum 25-hydroxyvitamin D level measured at the end of the winter was 20.2 ng/mL, a quite high figure (Vik *et al.,*1980).

Of note, seasonal variations would be a genuine feature of serum 25-hydroxyvitamin D level. According to a cross-sectional study in healthy adult volunteers, serum 1α,25-dihydroxyvitamin D level does not vary during the year, illustrating again the tight physiological control of this compound (Chesney *et al.,*1981). However, a study in the Netherlands on eight volunteers with monthly blood drawn showed a seasonal variation in serum 1α,25-dihydroxyvitamin D levels (Juttmann *et al.,*1981).

7.2.2 Latitudinal variations

The topic of latitude is addressed in more detail in chapter 9.

The UVB content of the solar spectrum increases sharply with decreasing latitude. Therefore, it has been proposed that the relation between latitude and plasmatic 25-hydroxyvitamin D levels was mediated by latitude being an indicator of ambient UVB irradiation. Webb *et al.,* (1988a) suggested that at latitudes of 42°N and beyond, vitamin D synthesis in the skin is almost impossible between November and February because no ultraviolet B radiation reaches the earth's surface. Another study using comparable model approach, concluded that during some (winter) months of the year, under clear sky conditions no cutaneous vitamin D production occurs at 51 degrees latitude and higher (Engelsen et al., 2005).

However, latitude by itself is not a good indicator for potential vitamin D production, and thus, latitude is of little use for estimating the vitamin D status of a population (Kimlin, 2008, see Chapter 9).

7.2.4 Sunscreen use

Constitutive (or permanent) melanin in the skin acts as a natural sunscreen, preventing UVB radiation from reaching skin cells[10]. Application of sunscreen onto the skin can potentially reduce pre-vitamin D formation in a similar way. In two small studies, circulating 25-hydroxyvitamin D concentrations have been shown to be lower after a single application of a sunscreen prior to exposure to a one minimal erythemal dose of ultraviolet radiation (Matsuoka *et al.,*1987) and in elderly people long-term habitual sunscreen users (Matsuoka *et al,* 1988).

Vitamin D and Cancer

A small Spanish case-control study in elderly subjects has shown that long term sunscreen use results only in a minor reduction of circulating 25-hydroxyvitamin D concentrations with no biochemical signs of low vitamin D status (Farrerons *et al.,*1998). A large, controlled Australian randomised trial found equal increases of circulating 25-hydroxyvitamin D concentrations in daily sunscreen users and placebo controls after one summer season, with no signs of low vitamin D status even in elderly subjects (Marks *et al.,*1995). Although more research is necessary to better elucidate any impact of chronic sunscreen use on vitamin D status, particularly in at risk populations, it is likely that incomplete application of sunscreen or passage of ultraviolet B radiation through the sunscreen may still allow endogenous vitamin D production.

Brisbane, Australia, is located in a tropical area and is populated with highly sun sensitive people. Serum 25-hydroxyvitamin D levels were found to be higher in subjects using high sun protection factor sunscreen, used to putting sunscreen on their face, and who wore a hat when in the sun (Kimlin *et al.,* 2007). These associations are the reverse of what would be expected, but correspond to the "hat paradox", i.e., subjects more likely to be in the sun and thus to have higher endogenous vitamin D production, are also more likely to use sun protection methods.

Theoretical impact of sunscreen use on endogenous vitamin D synthesis has also been modelled. For instance, Sayre and Dowdy (1997) concluded that the use of SPF-15 sunscreen blocked the pre-vitamin D_3 synthesis more effectively than erythemal reactions. However, conclusions from such modelling exercises were not supported by results in above mentioned studies on sunscreen use and vitamin D status in communities.

So, overall, relying on studies and randomized trials reflecting actual sun exposure habits, sunscreen use seems not to affect endogenous vitamin D production. However, there is a lack of studies on sunscreen use and vitamin D status in areas distant from the Equator, although sunscreen use is probably not common during outdoor activities taking place in latitudes greater than 45°.

7.2.5 Decreased sun exposure

Clothing

Decreased vitamin D status in spite of abundant sunlight may be associated with outdoor activities being rare, abundant garments concealing nearly all the skin surface, especially in women and in dark skinned populations (Okonofua *et al.,*1986; Meddeb *et al.,*2005; Dawodu *et al.,*1998; Feleke *et al.,*1999; Mishal *et al.,*2001; Islam *et al.,*2008; Woo *et al.,*2008). Veiling according to religious dress code is particularly associated with low vitamin D status in women. In the United Arab Emirates (UAE), a comparison between three samples of women 19-44 years showed mean serum 25-hydroxyvitamin D levels of 8.6 ng/mL in 33 UAE women, 12.6 ng/mL in 25 non-Gulf Arab women, and 64.3 ng/mL in European women residing in the UAE (Dawodu *et al.,*1998). Veiled Turkish adolescent women had mean serum 25-hydroxyvitamin D levels of 11.3 ng/mL, and women of the same age not veiled had levels at least twice as high (Hatun *et al.,*2005).

Of note, in addition to restricted sun exposure, Muslim women from Arab or African origin have lower food intakes of vitamin D (Glerup *et al.,*2000; Gannagé-Yared *et al.,*2005).

Medical conditions

Certain medical conditions (e.g. xeroderma pigmentosum, basal cell nevus syndrome, lupus erythematosus, organ transplant recipients, immunosuppressive therapy) necessitate decreased sun exposure, thus increasing the risk for low vitamin D status. A small study on renal transplant patients who were receiving immunosuppressive therapy and who had been advised to avoid sun exposure showed significantly lower blood 25-hydroxyvitamin D levels when compared to age/gender matched control subjects (Querings and Reichrath, 2004).

Xeroderma pigmentosum (XP) is a rare hereditary disease affecting DNA repair mechanisms. XP patients are extremely sensitive to the damaging effects of ultraviolet radiation and develop numerous skin cancers. Their level of photoprotection is thus very high. A small study in 3 XP patients study showed circulating 25-hydroxyvitamin D levels ranging from 7.8 to 14.1 ng/mL (Querings *et al.,*2006). A study on 8 XP patients with adequate dietary vitamin D intake had mean 25-hydroxyvitamin D serum levels of 17 (SD: 1.5) ng/mL (Sollitto *et al.,*1997). Therefore, critically low levels serum of 25-hydroxyvitamin D levels may exist in XP patients.

7.3 Individual characteristics and lifestyle

7.3.1 Gender

Several epidemiologic surveys in Europe and in the United States indicate lower plasma levels of 25-hydroxyvitamin D in women compared with men. In the Third National Health and Nutrition Examination Survey (NHANES III), Scragg *et al.,*2004 detected lower estimates for women compared with men, respectively 29.04 (SD: 0.32) ng/mL and 31.52 (SD: 0.36) ng/mL. A difference in serum 25-hydroxyvitamin D levels of the same magnitude was found in British adults (Hypponen and Power, 2007). In a Dutch population, women had a 2.4 (SD: 0.6) ng/mL ($p < 0.001$) lower 25-hydroxyvitamin D levels than men, but after adjustment for percentage body fat the difference was -0.08 (SD: 0.88) ng/mL ($p=0.16$) (van Dam *et al.,*2007). Thus sex differences in body fat can partly explain these sex differences in vitamin D status, as serum 25-hydroxyvitamin D levels are inversely correlated with body fat and women have in general higher body fat than men.

7.3.2 Age

Cross-sectional studies have documented an age-dependent decline in serum 25-hydroxyvitamin D and 1α,25-dihydroxyvitamin D, and this age-related decline steadily worsened with institutional placement, decreasing functioning and increasing frailty (Corless *et al.,*1975; Bouillon *et al.,*1987). Institutionalised elderly people with low and very low vitamin D status are commonly encountered in areas with high ambient sunshine, such as in Florida (Woods *et al.,*1989).

Cross-sectional studies in 223 English healthy subjects aged 20 to 96 years (Baker *et al.,*1980) and in 596 Danish healthy subjects aged 18 to 93 years (Lund and Soressen, 1979) showed a decline of serum 25-hydroxyvitamin D levels of 0.33-0.40 ng/mL per year on average. In a sample of 142 Dutch subjects aged 70–88 years, serum 25-hydroxyvitamin D concentrations fell with increasing age ($r = -0.27$, $p < 0.05$), by 0.6 ng/mL for each year of age (Baynes *et al.,*1997). The age decline is found in both summer and winter periods (Scharla, 1998).

The possible causes for this age-dependent increase in low vitamin D status are multiple. First, decreased daily intake of dietary vitamin D associated with a lower everyday exposure to sunlight is common with ageing (Holick, 1994).

Second, compared to young adults, elderly people have a decreased ability to synthesise vitamin D (Holick *et al.,*1989). Laboratory studies on human skin samples have shown an age-dependent decrease in pro-vitamin D_3 (the 7-dehydrocholesterol) in the epidermis where 80% of the vitamin D is synthesised in the skin (MacLaughlin and Holick, 1985). Compared to subjects aged less than 20 years old, the vitamin D production capacity of the skin of subjects 65 years old and older was decreased by a factor of 2 (MacLaughlin and Holick, 1985). The changing structure of the skin shows an age-dependent decrease in thickness paralleled by a decrease in concentration in the vitamin D precursor necessary for the synthesis of the active form 1α,25-dihydroxyvitamin D (Tan *et al.,*1982; Need *et al.,*1993; McCullough *et al.,*2003).

Third, an age-related decline in renal production of 1α,25-dihydroxyvitamin D has also been proposed as a mechanism for the lower production of vitamin D in elderly people (Slovik *et al.,*1981), and this decline in hydroxylation capacity could be due to the general age-related decline in renal function. Combined together, all these elements may be responsible for the lower levels of 25-hydroxyvitamin D and the associated higher plasma levels of PTH in elderly people (Shearer, 1997).

Randomised trials have shown that intestinal absorption of vitamin D may not decrease with age when daily doses do not exceed 20 µg per day, but absorption is lower in elderly subjects compared to younger subjects when daily doses are in the order of 45 µg per day (Harris *et al.,*1999, 2002). In addition, an age-related decrease in intestinal absorption of calcium exists, due to the decreased sensitivity of intestinal cells to the action of 1α,25-dihydroxyvitamin D that may contribute to the negative calcium balance, secondary hyperparathyroidism, and bone loss observed in elderly people.

7.3.3 Obesity

A considerable amount of data associates overweight and obesity with chronically low levels of 25-hydroxyvitamin D (Table 7.1). (Bell *et al.,*1985; Need *et al.,*1993; Reinehr *et al.,*2007; Martins *et al.,*2007; Scragg *et al.,*2004; Chiu *et al.,*2004; Snijder *et al.,*2005; Rockell *et al.,*2005; Rockell *et*

*al.,*2006; Arunabh *et al.,*2003; Wortsman *et al.,*2000; Yanoff *et al.,*2006; van Dam *et al.,*2007; Liel *et al.,*1988; Compston *et al.,*1981; Hey *et al.,*1982; Buffington *et al.,*1993; Parikh *et al.,*2004; Florez *et al.,*2007; Hypponen and Power,2006, 2007). This negative association is independent from other factors such as age, sex and race (Parikh *et al.,*2004), and also from the seasons. Nonetheless, the greatest difference between lean, overweight and obese subjects in serum 25-hydroxyvitamin D levels was observed for peak levels reached during the summer and the autumn (Bolland *et al.,*2007). At the end of winter, differences were less pronounced.

The negative association between 25-hydroxyvitamin D and overweight and obesity is less pronounced with body mass index (BMI = (weight in kg)/(height in cm)^2), than with the percentage body mass constituted in fat tissues. Wortsman *et al.,*2000 observed an increase in serum 25-hydroxyvitamin D levels in obese and non-obese subjects after exposure to UVB irradiation. The increase was less in obese subjects and the content of 7-dehydrocholesterol in the skin wasn't different between the obese and non-obese subjects. Obese people can have the same skin capacity to produce vitamin D, but the release of metabolites into the circulation is altered, possibly because of sequestration in the subcutaneous fat (Wortsman *et al.,*2000).

Arunabh *et al.,*2003 found in young healthy women a progressive decrease of serum 25-hydroxyvitamin D concentration with increasing percentage body fat content measured by dual energy x-ray absorptiometry. The inverse relation between serum 25-hydroxyvitamin D level and BMI was less pronounced. The same findings were done in 453 Dutch women aged 65 years old and over after adjustment for age, smoking and season (Snijder *et al.,*2005; van Dam *et al.,*2007) (Figure 7.2), as well as in 121 Spanish women of mean age 45 (Vilarrasa *et al.,*2007). So, using BMI as a proxy for body fat underestimates the inverse association between body fat composition and circulating vitamin D metabolites and the percentage of the body constituted of fat tissues.

The prevalence of low levels of serum 25-hydroxyvitamin D in obese individuals has been attributed different reasons. A decreased exposure to sunlight because of limited mobility has been postulated, but also a negative feedback from elevated circulating 1α,25-dihydroxyvitamin D and PTH levels on the hepatic synthesis of 25-hydroxyvitamin D and excessive storage of vitamin D metabolites in the adipose tissue (Liel et al.,1988; Compston et al.,1981; Worstman et al.,2000; Mawer et al.,1972; Bell et al.,1985). Recent studies have found high serum PTH levels to be associated with obesity, regardless of age, sex and race (Kamycheva et al.,2004; Parikh et al.,2004; Yanoff et al.,2006), especially with total amount of fat tissues (Snijder et al.,2005). This secondary hyperparathyroidism ceases after a return to normal weight.

7.3.4 Smoking

Smoking has been associated with changes in vitamin D metabolism and smokers have been shown to have lower vitamin D status in most (Brot *et al.,*1999; Hermann *et al.,*2000; Supervia *et al.,*2006) but not all (Kimlin *et al.,*2007) studies. It remains to be determined if and why smoking may affect vitamin D status and whether smoking cessation leads to a normalisation of circulating vitamin D levels. It has been speculated that such changes may relate to increased activity of some liver enzymes induced by smoking (Kimlin *et al.,*2007), but they could also be due to decreased sun exposure, reduced dermal production, increased vitamin D catabolism or other dietary and lifestyle differences between smokers and non-smokers. Serum PTH levels are also lower in smokers than in non–smokers (Jorde *et al.,*2005), the 1α,25-dihydroxyvitamin D-PTH axis seems blunted and intestinal calcium absorption is impaired (Need *et al.,*2002). Lower vitamin D status and impaired intestinal calcium absorption would explain the higher prevalence of osteoporosis among smokers (Brot *et al.,*1999).

7.3.5 Physical activity

Physical activity is associated with increased vitamin D status (Scragg *et al.,* 1995; Looker, 2007). The mechanism by which physical activity increases serum 25-hydroxyvitamin D levels remains speculative. Physical activity could also just be a surrogate measure for sun exposure, healthier lifestyle, a diet richer in vitamin D and calcium, less overweight, and so on.

7.3.6 Skin pigmentation and ethnicity

Endogenous vitamin D production varies with ethnicity. Table 7.2 summarises studies that looked at serum 25-hydroxyvitamin D levels according to ethnicity.

In Africa, serum 25-hydroxyvitamin D levels seem quite high in non-Muslim, non veiled populations (Okonofua *et al.,*1986; M'Buyamba-Kabangu *et al.,*1987; Cornish *et al.,*2000; Wejse *et al.,*2007). These levels decrease in populations where women are veiled or tend to have restricted outdoor activity, in spite of abundant sunlight (Okonofua *et al.,*1986; Meddeb *et al.,*2005; Feleke *et al.,*1999). Furthermore, even in a sunny climate, subjects with black skin have lower circulating 25-hydroxyvitamin D levels than subjects with light skin (M'Buyamba-Kabangu *et al.,*1987).

Differences in the skin's capacity to produce vitamin D are of particular consequence for darker skinned individuals living in more northern latitudes. North-Africans, black Africans and Asians with dark skin residing in Europe, North America or Australia have low vitamin D status, most probably lower than the status they had in their country of origin (Hunt *et al.,*1976; Munt *et al.,*1977; Meulmeester *et al.,*1990; Koch *et al.,*1993; Henriksen *et al.,*1995; Harris *et al.,*2000; Skull *et al.,*2003; Meyer *et al.,*2004; Ford *et al.,*2006; Erkal *et al.,*2006; Reed *et al.,*2007; McGillivray *et al.,*2007; Mytton *et al.,*2007; Holvik *et al.,*2007; van der Meer *et al.,*2008). As a consequence, in high latitude countries, cases of rickets, of osteomalacia and of chronic musculoskeletal pain are nowadays essentially found among children and women of childbearing age that migrated from sunny countries.

The NHANES III survey and other studies showed that for both sexes and at any age, African Americans tend to have lower levels of circulating 25-hydroxyvitamin D than white Americans, while levels in Hispanic Americans appear to be intermediate (Table 7.2). Lower serum 25-hydroxyvitamin D level between white and African Americans is observed across seasons and even when vitamin D intake of African Americans seemed adequate (Harris *et al.,*1998; Nesby-O'Dell *et al.,*2002; Arunabh *et al.,*2003). In Boston, a northern U.S. city, compared to white American women, African American women have significantly lower circulating 25-hyroxyvitamin D levels all year round and have smaller increases between winter and summer (Harris and Dawson-Hughes, 1998). Paradoxically, lower vitamin D status in African Americans than in white Americans is also found in US states like Arizona, where there is high ambient sunshine all the year round (Jacobs *et al.,*2008);

Canadian aboriginals have darker skin and lower vitamin D status than Canadian whites (Weiler *et al.,*2007). Interestingly, aboriginals living in rural areas have serum 25-hydroxyvitamin D levels higher than aboriginals living in cities, but still lower than urban whites. These differences probably reflect both differences in skin pigmentation (between whites and aboriginals) and in outdoor activities (between rural and urban aboriginals).

Although these ethnic differences in circulating 25-hydroxyvitamin D levels may in part be due to possible racial/ethnic differences in the intake of vitamin D rich foods (Calvo *et al.,*2005; Moore *et al.,*2005; Maxwell *et al.,*2006), the effect is more likely to be a direct result of melanin skin content. Melanin is a dark pigment that absorbs ultraviolet B radiation and thus prevents the entrance of photons into skin cells in deeper layers of the epidermis and dermis where most of pro-vitamin D_3 is formed.

In vitro studies show that lighter skin has a higher conversion rate of 7-dehydrocholesterol to pre-vitamin D compared to darker skin, which appears to have a higher threshold of ultraviolet B radiation exposure for pro-vitamin D_3 production (Chen *et al.,*2007b).

Results from small experimental studies in humans also show differences in circulating 25-hydroxyvitamin D levels based on the degree of skin pigmentation. A study of healthy adults with different skin types exposed to a 0.75 minimal erythemal dose of simulated sunlight 3 times a week for 12 weeks showed a much higher increase in circulating 25-hydroxyvitamin D compared to baseline levels in subjects with lighter versus darker skin (Chen *et al.,*2007b). Similar observations have been made after one-time exposure of subjects to one minimal erythemal dose of ultraviolet radiation (Clemens *et al.,*1982). Seventy-two subjects with different skin phototypes had 90% of their skin exposed to UVB 3 times a week for 4 weeks (Armas *et al.,*2008). This study calculated that to reach the same serum 25-hydroxyvitamin D level, compared to white Americans, African Americans needed UVB doses 40% higher, and sub-Saharan Africans needed UVB doses two times higher. These estimates must be taken with caution because the equations used to calculate the UVB dose needed did not consider serum 25-hydroxyvitamin D levels before exposure to the artificial UVB sources. The need of longer duration sun exposure to produce vitamin D in skin has also been shown in other ethnic groups, such as Pakistani and Indian persons living in Great Britain (Lo *et al.,*1986).

But relationships between vitamin D and ethnicity are complex and cannot be simply explained by lower capacity to synthesise vitamin D in the skin. A study utilizing a single fixed dose of ultraviolet B radiation noted that baseline circulating vitamin D_3 levels in African, white, Oriental and south Asian Americans were similar but that white and Oriental Americans had significantly higher levels of vitamin D_3 and of 25-hydroxyvitamin D_3 post-radiation than black or south Asian Americans (Hypponen and Power, 2007). However, post-radiation serum levels of 1α,25-dihydroxyvitamin D_3 were similar. African and white Americans exposed to sequentially increasing minimal erythemal doses of UVB had similar elevations of circulating 25-hydroxyvitamin D_3 although baseline levels were much lower in African than white Americans (Brazerol *et al.,*1988; Barnes *et al.,*2006).

In whites, decreasing vitamin D status is associated with increasing body mass index (see 7.3.3), low bone mass density (Cauley *et al*., 2008) and diabetes (Scragg *et al*., 1995). In blacks, vitamin D status is not associated with obesity (Epstein *et al.,*1986; Looker, 2005), bone mass density (Hannan *et al.,*2008) and diabetes (Scragg *et al.,*2004).

Limited data also suggests possible ethnic differences in terms of dietary vitamin D absorption or its endogenous conversion to 25-hydroxyvitamin D. A small study comparing circulating 25-hydroxyvitamin D levels between African and white Americans matched by age, gender and socio-economic status showed that African Americans had significantly lower basal levels but a much higher percentage increase after a single large oral bolus of vitamin D_2 (Matsuoka *et al.,*1995). These results suggest that in young healthy subjects with darker skin the reduced availability of circulating vitamin D may be compensated for by higher conversion rates of vitamin D into 25-hydroxyvitamin D by hepatic enzymes. It may be speculated that, low vitamin D concentrations may enhance the activity of the hepatic 25-hydroxylase (CPYP27A1), and that low 25-hydroxyvitamin D concentration may enhance the activity of renal 1α-hydroxylase.

These complex findings from a number of studies suggest notable ethnic differences in the vitamin D endocrine system. So, overall, if in general, Africans as a group have lower circulating levels of 25-hydroxyvitamin D than whites, it is not clear whether these differences have a clinical impact in adults. For example, although circulating 25-hyroxyvitamin D in African Americans could imply an increased risk for osteoporosis, compared to white Americans, their bone density is greater and rates of osteoporotic fracture is lower (Perry *et al.,*1996; Barrett *et al.,*1999; Aloia *et al.,*2008).

Thus, it remains to be determined whether circulating 25-hyroxyvitamin D level is a reliable indicator of ethnic variations in vitamin D status, and if there are different adaptive responses to varying vitamin D levels by ethnicity. Limited evidence suggests the likelihood of such adaptive responses (Harris, 2006). PTH promotes renal transformation of 25-hydroxyvitamin D in 1α,25-dihydroxyvitamin D and calcium resorption from bones. Black people are observed to have higher circulating levels of PTH and greater bone resistance against action of PTH. Black people therefore tend to have relatively high serum 1α,25-dihydroxyvitamin D levels that, together with greater bone resistance to PTH, would result in bone mineral content greater than that observed in other ethnic groups. A greater resistance to intestinal action of 1α,25-dihydroxyvitamin D would prevent hypercalcemia (Harris, 2006).

Evidence for adaptive mechanisms was also suggested by a 3-year randomised, double-blind, placebo-controlled trial with vitamin D supplementation at the level of 20 µg per day for the first 2 years and 50 µg per day for the third year. These supplementations had no effect on bone loss, bone turnover, or serum PTH levels in postmenopausal (50- to 75-year-old) black women (Aloia *et al.,*2005). Mean baseline 25-hydroxyvitamin D concentrations in placebo and vitamin D supplemented women were 17.2 and 19.2 ng/mL, respectively, but the lack of a vitamin D effect was observed even in the subset of women with lowest baseline 25-hydroxyvitamin D. Women in both the vitamin D and placebo groups were given calcium supplements to achieve total daily calcium intakes of 1.2 to 1.5 g per day, and it has been speculated that the consumption of calcium may have inhibited formation of the active metabolite of vitamin D and suppressed bone turnover independent of vitamin D status (Harris, 2006).

If different adaptive mechanisms exist according to ethnicity, their significance for vitamin D actions other than calcium and bone metabolism remain unknown.

7.4 Interferences with dietary sources

7.4.1 Dietary components

Vitamin D is fat soluble and just like other fat soluble nutrients, dietary vitamin D is primarily transported by chylomicrons via the lymph system. Vitamin A competes for receptor sites with vitamin D and high vitamin A doses may inhibit intestinal absorption of vitamin D. Vitamin A and retinols may antagonise the physiological action of vitamin D, mainly on bone. Two studies have reported a doubling of hip fracture rates among women with high retinol intakes from food or supplements (>1.5 mg per day) (Rothman *et al.,*1995; Melhus *et al.,*1998).

In addition, specific dietary components may also interfere with vitamin D bioavailability. For example, it has been shown that higher blood levels of mono- and polyunsaturated, but not saturated fatty acids may interfere with the affinity of vitamin D binding protein for vitamin D (Bouillon *et al.,*1992).

7.4.2 Dietary or injectable supplements

In subjects of all ages, dietary vitamin D supplements contribute to increasing the vitamin D status. The contribution of vitamin D supplements in vitamin D intakes vary considerably between populations, from zero % in Japan, to 12-24% in the UK, 30-40% in the USA, and 30 to 40% in Norway (Calvo *et al.,*2005). Iceland is situated between 64° and 66° latitude north, and UVB irradiation allowing endogenous vitamin D synthesis is absent 6 to 7 months of the year. In healthy Icelandic subjects aged 30 to 85 years of age, compared to subjects not taking supplements, around 12.5 µg per day of vitamin D supplements (cod liver oil or pill) is associated with serum 25-hydroxyvitamin levels nearly always above 18 ng/mL all the year round, lower serum PTH levels, and much less seasonal variation in serum 25-hydroxyvitamin levels (Figure 7.1)(Steingrimsdottir *et al.,*2005). In healthy subjects, vitamin D supplements are efficient for increasing vitamin D status all year round and for reducing the vitamin D winter gap.

Vitamin D supplements may be given as an intramuscular injection of vitamin D. This method became quite popular in the UK and was used in a number of trials (e.g., Trivedi *et al.,*2003). Earlier studies in a few elderly subjects aged 75 to 95 years old showed that intramuscular injection of 15 mg of vitamin D_3 could increase 25-hydroxyvitamin D level from less than 5 ng/mL before the injection to nearly 30 ng/mL 6 months after (Burns and Paterson, 1985).

7.4.3 Medications

Orlistat is used in the pharmacologic treatment of obesity. Orlistat reduces fat uptake by partial inhibition of the pancreas lipase which causes a malabsorption of dietary fat. Chronic fat malabsorption has been associated with a higher risk for vitamin D hypovitaminosis (Gotfredsen *et al.,*2001).

Comparing orlistat with placebo, Gotfredsen *et al.,*2001 found in both groups lower values for serum 25-hydroxyvitamin D between baseline and after one year of treatment. The differences between the groups were not statistically different, but deserve attention due to the usually low serum 25-hydroxyvitamin concentrations associated with obesity.

A second molecule is olestra (sucrose polyester), a non absorbable, non caloric fat substitute. Olestra is able to interfere with the absorption of fat-soluble vitamins[11].

7.4.4 Intestinal absorption disorders

Patients with fat malabsorption may be at risk of a decreased absorption of vitamin D and other fat soluble vitamins. However, data from selected animal studies suggest that if given orally, 25-hydroxyvitamin D may be absorbed from the proximal jejunum (Ovesen *et al.,*2003a,b), so that subjects with fat malabsorption may potentially be supplemented with this metabolite to enhance their vitamin D status, although no studies of this effect exist. Similar considerations may affect other distinct populations, such as iron deficient subjects whose fat soluble vitamin absorption mechanisms may be impaired.

The prevalence of low vitamin D status in patients with small intestinal resection (e.g., ileal bypass surgery for treatment of morbid obesity) can be very high. The aetiology is thought to be a result of fat soluble vitamin malabsorption due to steatorrhea, accompanied by a lower sunshine exposure and a reduced intake of dietary vitamin D (Haderslev *et al.,*2003; Compston and Creamer, 1977, Driscoll *et al.,*1982; Schoen *et al.,*1978; Jahnsen *et al.,*2002). A review on the impact of bariatric surgery in the treatment of obesity on nutritional status (Shah *et al.,*2006), reported a prevalence of low 25-hydroxyvitamin D levels of 51%. Malabsorption of fat due to the incomplete mixing of fat with pancreatic enzymes and bile salts as a result of bypassing the duodenum has been proposed as a mechanism for this low vitamin D status.

7.5 Comparisons between artificial UVB sources and oral supplementation

One cross-sectional study and three randomised trials compared changes in serum 25-hydroxyvitamin D induced by an artificial UVB source and oral vitamin D supplements.

A cross-sectional of 50 subjects who used a tanning bed at least once a week and 106 control subjects found serum 25-hydroxyvitamin D levels of 46 ng/mL in sunbed users and 24.1 ng/mL in control subjects (Tangpricha *et al.,*2004). The Working Group notes that biases could partly explain the results as the group of sunbed users and of non-users included 8% and 35% of non-white Americans (i.e., Asians and blacks), respectively. Assessment of vitamin D intakes was minimal, restricted to multivitamin use and milk drinking. Also, sunbed users used more vitamin supplements and had 62% more sun exposure than control subjects.

In a 12-week trial, Toss *et al.,* (1982) studied the effect of artificial UV exposure from an FS 40 lamp rich in UVB on 42 elderly nursing home residents 67-90 years of age (mean 81) compared to 11 µg of vitamin D_2 plus calcium 0.6 g daily, calcium alone, or placebo. Front and back were exposed to UVR for 1 minute each, then 2 minutes and followed by ten treatments of 3 minutes each. Serum 25-hydroxyvitamin D increased in the UV group from 11 to 24 ng/mL (difference = 13 ng/mL). In the vitamin D_2 and calcium group, the increase was from 8 to 17 ng/mL (difference = 9 ng/mL). There was no change in the control and calcium groups.

Lovell *et al.,* (1988) studied the effect of sun exposure in Caucasian elderly nursing home residents in Australia compared to a control group that had no extra sun exposure and usual meals, and two groups who received 7.2 or 26.7 µg vitamin D_3 supplements per day over a three month period. From March to May, median changes in serum 25-hydroxyvitamin D concentrations were 7.6 to 6.4, 13.0 to 22.8, 7.3 to 17.8, and 16.4 to 26.4 ng/mL in the control, sunlight, 7.2 µg and 26.7 µg vitamin D, respectively.

Chel *et al.,* (1998) investigated in The Netherlands the effect of artificial UVB irradiation in 45 elderly females of mean age 85 years. The majority of subjects were vitamin D deficient (<12 ng/mL). Subjects were randomised to receive UVB (one-half MED) three times per week, 10 µg vitamin D_3 or placebo per day for 12 weeks. Six areas of 4 cm2 were irradiated with UVB doses increasing from 30 to 140 mJ/cm2, and individual doses were adjusted according to skin sensitivity. After 12 weeks, the changes in serum 25-hydroxyvitamin D levels were 16.8, 14.8 and -0.2 ng/L in the UVB, supplement and control groups, respectively.

Therefore, overall, oral vitamin D supplements seem as effective as exposure to artificial sources of UVB for increasing serum 25-hydroxyvitamin D levels.

7.6 Relative contribution of multiple determinants on 25-hydroxyvitamin D serum level

Endogenous and exogenous vitamin D syntheses are influenced by different factors and have their own limiting rate mechanisms (see Chapter 4).

Dietary food sources of vitamin D show great international variation in intake level and are primarily limited to fatty fish, cod-liver oil, meat, eggs, milk and some fortified foods (Calvo, 2005). Food content and bioavailability of vitamin D has not been well studied but it is likely to represent a variable proportion of vitamin D requirements (Ovesen, 2003b). As such, daily dietary intake does not always correlate well with serum 25-hydroxyvitamin D levels. Vitamin D status seems better correlated with sun exposure, but this parameter is not easy to assess. For instance, very sun sensitive subjects tend to avoid sunlight, but the little UVB they receive on their skin is not at all blocked by pigment, and a little sun exposure of sun sensitive subjects may result in more vitamin D being produced than longer sun

exposure of dark skinned subjects. Also, there is great inter-individual variation in vitamin D synthesis in response to UVB exposure (see section 7.6). Therefore, evaluation of vitamin D status of populations have attempted to assess various factors known to influence serum 25-hydroxyvitamin D levels, and estimate their relative contribution to vitamin D status through the use of statistical models.

We found seventeen studies that used statistical modelling for evaluating the relative contribution of the different vitamin D endogenous and exogenous sources on vitamin D status[12]. Regression models used were linear in 14 studies (Lips *et al.,*1987; Jacques *et al.,*1997 in Massachusetts, USA; Brot *et al.,*2001 in Denmark; McNeill *et al.,*2002 in the UK; Brustad *et al.,*2003 in Norway; Andersen *et al.,*2005; Giovannucci *et al.,*2006a in the USA; van Dam *et al.,*2007 in the Netherlands; Burgaz *et al.,*2007 in Sweden; van der Meer *et al.,*2008 in the Netherlands; Egan *et al.,*2008 in the USA; Jacobs *et al.,*2008 in Arizona, USA; Hill *et al.,*2008 in Northern Ireland) and logistic in three studies, taking a cut-off for defining low and high serum 25-hydroxyvitamin D level (Holick *et al.,*2005 in the USA; Hyppönen and Power, 2007 in UK; MacDonald *et al.,*2008 in Scotland, UK).

Results were reported in many different ways, precluding an easy summary in tabular form. Also, assessment of sun exposure and of dietary vitamin D intakes used questionnaires and measurement error may have been high, which may dilute the associations observed.

The main finding of these modelling exercises was that both exogenous and endogenous pathways contributed significantly to vitamin D status (Figure 7.3). In many studies, use of vitamin D supplements and frequent intake of oily fish were as good predictors of serum 25-hydroxyvitamin D as outdoor activities, holidays in sunny areas and sunbed use. The relationship between vitamin D intake and vitamin D status is seasonally dependent, being stronger in the winter than in the summer (Andersen *et al.,*2005; SACN, 2007; MacDonald *et al.,*2008). During the winter period, the maintenance of vitamin D level is dependent on oral vitamin D intake and on the stores of vitamin D built up during the previous summer.

Multivariate regression models had R^2 ranging from a low 0.012 to 0.39, meaning that factors included in these models were not able to explain (or predict) most of the variation in serum 25-hydroxyvitamin D levels among individuals. Part of the unexplained variance (i.e., $1 – R^2$), could be due to measurement error of factors included in model, or to yet unknown factors that could influence vitamin D status.

In any case, results from statistical models of serum 25-hydroxyvitamin D levels do not support the statement that more than 90% of the vitamin D requirements come from exposure to sunlight (Holick, 2004) [13]. In many populations, the importance of exogenous sources of vitamin D found in diet and supplements is far from being negligible, especially in the winter. Exogenous sources of vitamin D are found in diet, vitamin D-fortified foods and supplements (Giovannucci *et al.,*2006a; Palomer *et al.,*2008). In diet, oily fish has a preponderant role as source of vitamin D.

7.7 Inter individual variations in serum 25-hydroxyvitamin D levels not explained by factors influencing vitamin D bioavailability

A striking feature of studies on serum 25-hydroxyvitamin D levels in healthy young adults who have extended summer sun exposure or are living in areas with high ambient sunlight, are the considerable variations in these levels among individuals. In 26 young adult males (presumably all were whites) with a mean 38 hours of summer sun exposure per week, serum 25-hydroxyvitamin D ranged from 20 to 90 ng/mL in late summer, and from 10 to 50 ng/mL in late winter (Berger-Lux and Heaney, 2002). Individual seasonal variation ranged from 10 to 30 ng/mL.

In Honolulu, Hawaii, 30 light-skinned females and 63 males of mean age 24 had on average 29 hours of sun exposure per week via outdoor sport (e.g., skate-board). 51% and 9% of them were found to have serum 25-hydroxyvitamin D below 30 ng/mL and 20 ng/mL, respectively (Binkley *et al.,*2007)(Figure 7.4). Thirty-seven subjects reported their race as white, 27 as Asian, 18 as multi-racial and 7 as Hawaiian/Pacific Islander. No black or Hispanic subject was included in the study sample.

Brisbane, Australia, is a city in a tropical area populated with highly sun sensitive light-skinned people that have the highest records of skin cancer in the world. A survey in 126 healthy subjects 18 to 87 years (median of 32 years) showed that 10% of participants had a serum 25-hydroxyvitamin D below 10 ng/mL and 41% had levels below 20 ng/mL at the end of the winter (Kimlin *et al.,*2007). Only 34% of this sample had a serum 25-hydroxyvitamin D of 75 ng/mL or more.

Santiago de Chile, Chile, is located at latitude 33° South and bright sunshine is present most of the year, thus subjects can synthesise vitamin D in skin all the year round. A survey of healthy volunteer women having normal sun exposure found a prevalence of serum 25-hydroxyvitamin D lower than 20 ng/mL in 27% of the premenopausal and 60% of the post-menopausal women (Gonzalez *et al.,*2007).

In sunbed studies already reviewed in this chapter (Lovell *et al.,*1988; Tangpricha *et al.,*2004; Thieden *et al.,*2008), increases in 25-hydroxyvitamin D levels were very variable across subjects, some of them had only marginal increases and stayed below 20 ng/mL. Six of 33 subjects with 8 sunbed sessions in the Danish study (Thieden *et al.,*2008) had no change in 25-hydroxyvitamin D levels. Strong variations in individual response of serum levels to UVB irradiation are also observed in elderly people, and these variations may also be due to inter-individual variations in age-dependent decreases in endogenous synthesis (Lovell *et al.,*1988).These observations demonstrate that high amounts of sun exposure do not guarantee high circulating 25-hydroxyvitamin D levels. Why such variability among individuals?

The simple answer would be that genetic differences exist in the amount of vitamin D necessary to maintain optimal physiologic function (Binkley *et al.,*2007). For instance, genetic variability in the vitamin D binding protein has been associated with differences in serum levels of 25-hydroxy and 1,25-dihydroxyvitmain D (Engleman *et al.,*2008). Genetic variations would be phenotypically apparent as inter -individual variations in limiting rates of vitamin D synthesis in the skin, hydroxylation in the liver and in the kidney, transport, metabolism, degradation that would ultimately influence individual vitamin D status. These genetic differences would also be reflected in the numerous variants of the VDR, some of which have different affinity to the 1α,25-dihydroxyvitamin D.

Considerable variation between individuals of the same skin complexion seems to exist, linked to variable regulation of skin production of vitamin D in response to UV radiation, or to variable regulation of degradation of vitamin D metabolites. Little is known about these genetic dependent variations, but they highlight that in many subjects, inadequate exposure to ultraviolet radiation is not the cause of apparently “low vitamin D status”.

Such genetic variations could also apply to ethnic differences in the vitamin D endocrine system mentioned earlier in this chapter that may reflect different evolutionary pathways and selection pressures, i.e., avoidance of vitamin D deficiency leading to rickets in light skinned populations living far from the equator, and avoidance of toxic levels of vitamin D in dark skinned populations living near the equator (Loomis *et al.,*1967).

7.8 Conclusions

In North America and Australia, latitude is a weak indicator of vitamin D status. In Europe, the use of latitude as a proxy indicator for skin vitamin D production is not relevant.

Exogenous sources of vitamin D found in diet, vitamin D-fortified foods and supplements are important sources of vitamin D, certainly in the winter when skin synthesis of vitamin D is low or non-existent.

Considerable inter-individual variations in serum 25-hydroxyvitamin D levels in health subjects having extended sun exposure suggest that genetic differences exist in the amount of vitamin D necessary to maintain optimal physiologic function.

The consequences of the worldwide epidemic of obesity on vitamin D status of populations merit attention. Better understanding of the effects of adiposity on circulating 25-hydroxyvitamin D concentration would have implications for vitamin D requirements.

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[9] An opposite cycle has been described for serum PTH.

[10] Melanin synthesis induced by exposure to ultraviolet radiation is the facultative melanin that acts as a low sun protection factor sunscreen for sunburn, and confers little protection against ultraviolet radiation DNA damage (IARC, 2007; Pedeux *et al.,*1998). The production of melanin (tanning) accounts for part of the protection against UV radiation, but there is mounting scientific evidence that facultative tan is triggered by UV-induced DNA damage in the skin (Pedeux *et al.,*1998; Gilchrest and Eller 1999 for a review). Facultative tanning is now considered a better indicator of inducible DNA repair capacity than of efficient photoprotective skin reaction. Inducible DNA repair capacity rather than pigmentation itself could result in the lower

incidence of skin cancer observed in darker skinned individuals (Young *et al.,*1998; Agar and Young, 2005; Bohm *et al.,*2005).

[11] For this reason, the Food and Drug Administration requires that all olestra-containing products include the addition of fat-soluble vitamins (Neuhouser *et al.,*2006).

[12] Some large studies reported results from univariate analysis only e.g., Martins *et al.,*2007 on NHANES III study. Other earlier studies were based on ecological type of approach and could not really evaluate the relative contributions of endo end exogenous pathways (Lawson *et al.,*1979).

[13] The scientific literature on human studies supporting the statement made my MF Holick on sun exposure contributing to 90% of vitamin D status could not be found by the Working Group.

Table 7.1 - Concentrations of 25-hydroxyvitamin D (25OHD) in obese and non-obese subjects

Reference	Population	Sample size (n)	BMI (kg/m²)	Age (years)	25OHD (ng/ml)§
Compston *et al.*,1981	both sexes	20	non obese	19 to 52	13.0 ± 5.9*
	both sexes	24	obese	40 to 64	10.0 ± 4.8*
Bell_*et al.*,1985	both sexes	14	non obese	24 ± 1*	20.0 ± 7.5*
	both sexes	12	obese	26 ± 1*	8.0 ± 3.4*
Liel *et al.*,1988	both sexes	13	nonobese	20 to 35	16.0 ± 2.0*
	both sexes	13	obese	20 to 35	11.0 ± 1.0*
Zamboni *et al.*,1991	both sexes	11	after weight loss	9.3 ± 1.2*	28.0 ± 6.3*
	both sexes	11	before weight loss	9.3 ± 1.2*	12.1 ± 4.7*
Scragg_*et al.*,1995	both sexes	96	<24.61	40 to 64	26.0 ± 11.8*
	both sexes	97	24.62-26.75	40 to 64	26.8 ± 11.8*
	both sexes	97	26.76-29.79	40 to 64	27.2 ± 11.8*
	both sexes	98	>29.79	40 to 64	26.4 ± 11.9*
Rockell *et al.*,2005	both sexes	875	<25	5 – 14	20.0 (18.4-21.6)***
	both sexes	422	25-29.9	5 – 14	20.0 (18.0-21.6)***
	both sexes	288	≥30	5 – 14	17.6 (15.6-19.6)***
Parikh *et al.*,2004	both sexes	148	25.6 ± 2.9*	36.6 ± 11.4*	31.0 ± 14.4*
	both sexes	154	37.3 ± 5.8*	37.6 ± 9.4*	23.5 ± 12.2*
Hypponen & Power,2006	both sexes	2522	<25	45**	21.8**
	both sexes	2974	25-29.9	45**	21.6**
	both sexes	1214	30-34.9	45**	19.1**
	both sexes	479	>35	45**	17.0**
Yanoff *et al.*,2006	both sexes	43	<30	39**	21.3 ± 10.4*
	both sexes	80	≥30	39**	16.1 ± 8.1*
	both sexes	104	<30	39**	31.2 ± 13.4*
	both sexes	152	≥30	39**	25.8 ± 11.9*
Hypponen & Power,2007	both sexes	3469	<30	45**	25.1 ± 9.6*
	both sexes	1066	≥30	45**	21.1 ± 8.7*
	both sexes	2129	<30	45**	17.1 ± 8.5*
	both sexes	674	≥30	45**	14.7 ± 6.9*
Reinehr *et al.*,2007	both sexes	35	after weight reduction	11.1 ± 2.3*	16.0 ± 9.0*
	both sexes	35	before weight reduction	11.1 ± 2.3*	11.0 ± 4.0*
Rockell *et al.*,2006	females	766	<25	15 and more	19.2 (18.0-20.4)***
	females	504	25-29.9	15 and more	19.6 (18.4-20.8)***
	females	334	≥30	15 and more	16.8 (15.2-18.0)***
	males	536	<25	15 and more	21.2 (19.6-22.4)***
	males	616	25-29.9	15 and more	20.8 (19.6-22.4)***
	males	190	≥30	15 and more	18.8 (16.4-21.2)***
Nesby-O'Dell *et al.*,2002	females/blacks	619	<25	15-49	18.8 ± 12.0*
	females/blacks	392	25-29.9	15-49	17.3 ± 12.7*
	females/blacks	471	≥30	15-49	16.6 ± 10.4*
	females/whites	829	<25	15-49	35.6 ± 20.7*
	females/whites	277	25-29.9	15-49	30.2 ± 16.0*
	females/whites	247	≥30	15-49	26.1 ± 10.7*
Martins *et al.*,2007	males/whites	15088	<25	20 and more	35.0**
	males/whites		25-29.9	20 and more	33.0**
	males/whites		≥30	20 and more	31.0**
	females/whites		<25	20 and more	33.0**
	females/whites		25-29.9	20 and more	29.0**
	females/whites		≥30	20 and more	26.0**
	males/blacks		<25	20 and more	21.0**
	males/blacks		25-29.9	20 and more	21.0**
	males/blacks		≥30	20 and more	20.0**
	females/blacks		<25	20 and more	19.0**
	females/blacks		25-29.9	20 and more	18.0**
	females/blacks		≥30	20 and more	17.0**

*mean and standard deviation; **mean; ***mean and 99% confidence interval; § multiply by ~2.50 for conversion in nmol/L

Table 7.2 - Concentrations of serum 25-hydroxyvitamin D (25OHD) in pigmented populations

Reference	Country	City	Population	Age	Males	Females	Serum (25OHD) ng/mL*		Hypovitaminosis	
							Estimate	Dispersion	Definition	Percent
Meddeb *et al.,* 2004	Tunisia	Tunis	random veiled women	20-60		78	14.0[1]		<15.0	70
			random unveiled women			183	17.0[1]		<15.0	49
Feleke *et al.,* 1999	Ethiopia	Addis Ababa	volunteers student nurses	19-40	24	6	9.4[1]	7.2-11.6[3]	<12.0	77
			volunteers pregnant women			31	10.0[1]	6.8-18.4[3]	<12.0	55
Cornish *et al.,* 2000	South Africa	Pietersburg	volunteers school for visual impaired	14-18	15		36.6[1]	1.4[5]		
Okonofua *et al.,* 1986	Nigeria		non-muslim non-purdah women			20	36.0[1]	27.2-60.0[3]		
	Nigeria		muslim purdah women			10	21.2[1]	14.8-25.6[3]		
Wejse *et al.,*2007	Guinea-Bissau		controls of a case-control study	≥16	239	255	34.1[1]	13.9[4]	<20.0	13
Skull *et al.,* 2003	Australia	Melbourne	African immigrants	≥16	116		7.7[1]			
					116		13.3[1]			
Gordon *et al.,* 2004	United States	Boston	volunteer black outpatients of a children's hospital	11-18	142				<15.0	36
			volunteer hispanic outpatients of a children's		78				<15.0	21,8
Harkness&Cromer, 2005	United States	Ohio	random black participants to National Institutes of Health study	12-18		234	17.2[1]		<11.0	26
Reed *et al.,* 2007	United States	Washington	volunteers Somali immigrants	≤21		12	13.5[1]		<12.0	12
				22-40		15	16.6[1]		<12.0	30
				41-50		14	13.8[1]		<12.0	18
				51-60		15	14.2[1]		<12.0	18
				≥61		15	13.7[1]	11.7-15.6[3]	<12.0	21
Aloia *et al.,* 2005	United States	Long Island	volunteers ambulant postmenopausal African women	60		104	17.2[1]	6.6[4]		
				60		104	19.3[1]	8.4[4]		
Harris&Dawson-Hughes,1998	United States	Boston	volunteers young American black women	20-40		51	12.1[1]	7.9[4]		
						51	16.4[1]	6.6[4]		
Nesby-O'Dell *et al.,*2002	United States	sample	random black participants to NHANES III	15-49		263	15.5[1]	1.0[5]	<15.0	46
				15-49		412	17.3[1]	0.6[5]	<15.0	29
				15-49		523	19.8[1]	0.3[5]	<15.0	46
				15-49		348	17.5[1]	0.7[5]	<15.0	52
Perry *et al.,* 1996	United States		volunteers premonopausal Africans	34.6		28	30.2[1]	2.1[5]		
			volunteers postmenopausal Africans	70.4		25	18.4[1]	3.4[5]		
Looker,2005	United States	sample	random black participants to NHANES III	12-29		925	18.2[1]			
				30-49		909	17.1[1]			
				50-69		458	20.0[1]			
				>70		183	19.3[1]			
Looker *et al.,* 2002	United States	sample	random black participants to NHANES III	12-29	340		20.0[1]		<15.0	32

				30-59	354		19.5[1]		<15.0	31
				>60	149		21.3[1]		<15.0	27
		sample	random hispanic participants to NHANES III	12-29	524		27.6[1]		<15.0	7
				30-59	521		25.4[1]		<15.0	13
				>60	370		26.3[1]		<15.0	9
		sample	random white participants to NHANES III	12-29	162		33.4[1]		<15.0	4
				30-59	314		30.0[1]		<15.0	7
				>60	329		30.2[1]		<15.0	5
		sample	random black participants to NHANES III	12-29		447	16.9[1]		<15.0	32
				30-59		447	16.7[1]		<15.0	48
				>60		143	18.8[1]		<15.0	43
		sample	random hispanic participants to NHANES III	12-29		560	23.1[1]		<15.0	19
				30-59		580	21.4[1]		<15.0	24
				>60		318	23.5[1]		<15.0	23
		sample	random white participants to NHANES III	12-29		181	29.9[1]		<15.0	6
				30-59		322	26.4[1]		<15.0	10
				>60		336	25.8[1]		<15.0	12
Zadshir *et al.,* 2005	United States	sample	random white participants to NHANES III	43	3086		33.2[1]	0.2[5]	<10.0	0.50
			random black participants to NHANES III		1999		20.9[1]	0.0[5]	<10.0	5.72
			random hispanic participants to NHANES III		2201		27.3[1]	0.2[5]	<10.0	1.24
		sample	random white participants to NHANES III	44		3602	30.4[1]	0.2[5]	<10.0	1.27
			random black participants to NHANES III			2360	18.1[1]	0.2[5]	<10.0	11.19
			random hispanic participants to NHANES III			2142	22.7[1]	0.2[5]	<10.0	3.71
Jacobs *et al.,* 2008	United States	Tucson and	white participants to a cohort study	40-80	539		26.7[1]	9.1[4]		
			hispanic participants to a cohort study		48		22.4[1]	7.3[4]		
			black participants to a cohort study		18		18.2[1]	7.5[4]		
			native participants to a cohort study		10		28.2[1]	8.6[4]		
Egan *et al.,* 2008	United States	southeast	black participants to a cohort study	40-79	99		17.0[2]	5.0-9.6[3]		
		southeast	white participants to a cohort study	40-79	99		27.8[2]	8.2-14.5[3]		
		southeast	black participants to a cohort study	40-79		99	14.2[2]	3.6-8.1[3]		
		southeast	white participants to a cohort study	40-79		98	25.9[2]	6.9-12.8[3]		
Harris *et al.,* 2001	United States	Boston	black volunteers living in subsidized housing units	75	89		20.1[1]	1.1[5]		
			white volunteers living in subsidized housing units	75	89		28.2[1]	1.5[5]		
Weiler *et al.,* 2007	Canada	Winnipeg	Canadian urban arboriginals	25-50		17	15.8[1]	5.0[4]		
				≥51		9	18.3[1]	7.0[4]		
			Canadian rural arboriginals	25-50		129	20.3[1]	10.2[4]		
				≥51		55	24.4[1]	9.8[4]		
			Canadian urban whites	25-50		87	26.6[1]	14.0[4]		
				≥51		59	28.8[1]	11.0[4]		

Van der Meer *et al.*,2006	Netherlands	The Hague	volunteers Moroccan immigrants	24,3		69	8.0[1]	5.4[4]	<10.0	81
Ford *et al.*, 2006	United Kingdom	Birmingham	volunteers Afro-Caribbean	53	125		16.0[1]	0.8[5]	<10.0	31
Van der Meer *et al.*,2007	Netherlands	The Hague	indigenous Dutch	18-65	102		26.8[2]	20.0-33.2[3]	<10.0	5.9
			volunteers Moroccan immigrants	18-65	96		12.0[2]	8.0-18.0[3]	<10.0	36.5
			volunteers sub-saharan africans	18-65	57		13.2[2]	10.0-18.0[3]	<10.0	19.3
Meulmeester *et al.*,1990	Netherlands	The Hague	volunteers indigenous Dutch	8	40		22.7[1]	6.2[4]		
			volunteers Moroccan immigrants	8			12.1[1]	5.6[4]		
		Rotterdam	volunteers indigenous Dutch	8	40		29.1[1]	5.6[4]		
			volunteers Moroccan immigrants	8			15.3[1]	5.7[4]		
M'Buyamba-Kabangu *et al.*, 1987	Zaïre		white volunteers in Zaïre		24		30.7[1]	22.8[4]		
	Zaïre	Kinshasa	black volunteers in Zaïre		33		26.0[1]	15.6[4]		
	Belgium		black volunteers in Belgium		22		13.5[1]	5.0[4]		

[1] Mean; [2] Median; [3] Range; [4] Standard deviation; [5] Standard error; * multiply by ~2.50 for conversion in nmol/L

Figure 7.1 – Iceland (64-66° North): seasonal variation in serum 25-hydroxyvitamin D by supplemental vitamin D intake (from Steingrimsdottir *et al.,* 2005, with permission).

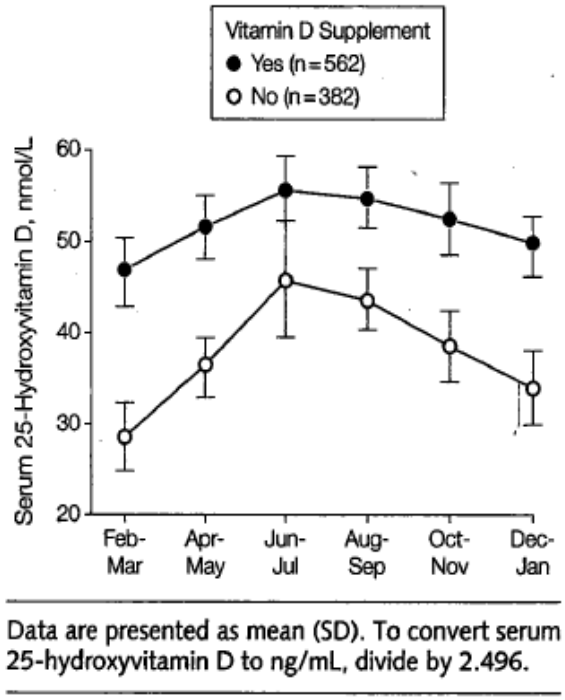


Figure 7.2 – *Original caption*: Mean (SD: SE) plasma 25-hydroxyvitamin D [25(OH)D] concentrations according to sex-specific tertiles of percentage body fat in 538 Dutch men (♦) and women (■) aged 60–87 y. Data were adjusted for age, season, and educational level by using ANCOVA. (van Dam *et al.*, Am J Clin Nutr. 2007;85(3):755-61. American Society for Nutrition.).

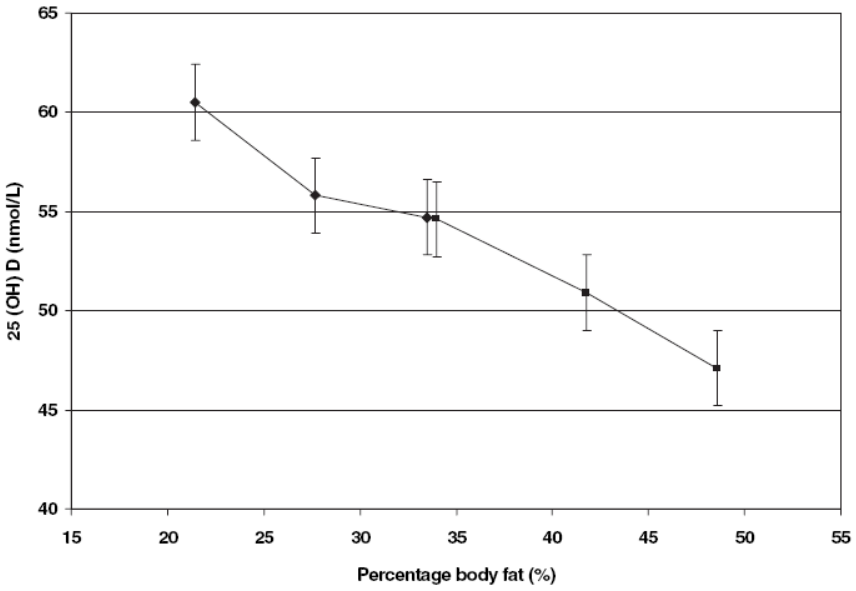


Figure 7.3 – *Original caption*: Geometric mean (95% CI) 25-hydroxyvitamin D [25(OH)D] concentrations by dietary and lifestyle indicators, standardised by sex and season. ; dark grey: winter and spring (December through May); light grey: summer and fall (June through November) in Great Britain. *December through May: log likelihood ratio test, $P < 0.0001$ for supplementation; log likelihood ratio trend test, $P < 0.0001$ for fish consumption and time spent watching television (TV) or using a personal computer (PC), $P < 0.002$ for sun protection. **June through November: log likelihood ratio test, $P < 0.0001$ for supplementation; log likelihood ratio trend test, $P < 0.0001$ for fish consumption, time spent outdoors, and time spent watching TV or using a PC, $P < 0.007$ for sun protection. All tests were adjusted for sex and month of measurement. 25(OH)D concentrations for time spent outdoors are presented for December through February, and those for all other indicators are presented for December through May. ***Number of unknown observations for December through May (first column) and for June through November (second column), respectively: supplementation, 95 and 75; fish consumption, 99 and 70; margarine use, 144 and 105; time spent outdoors, 336 and 251; sun protection, 319 and 244; and time spent using a PC or watching TV, 201 and 141 (Hyppönen and Power. Am J Clin Nutr. 2007;85(3):860-868. American Society for Nutrition).

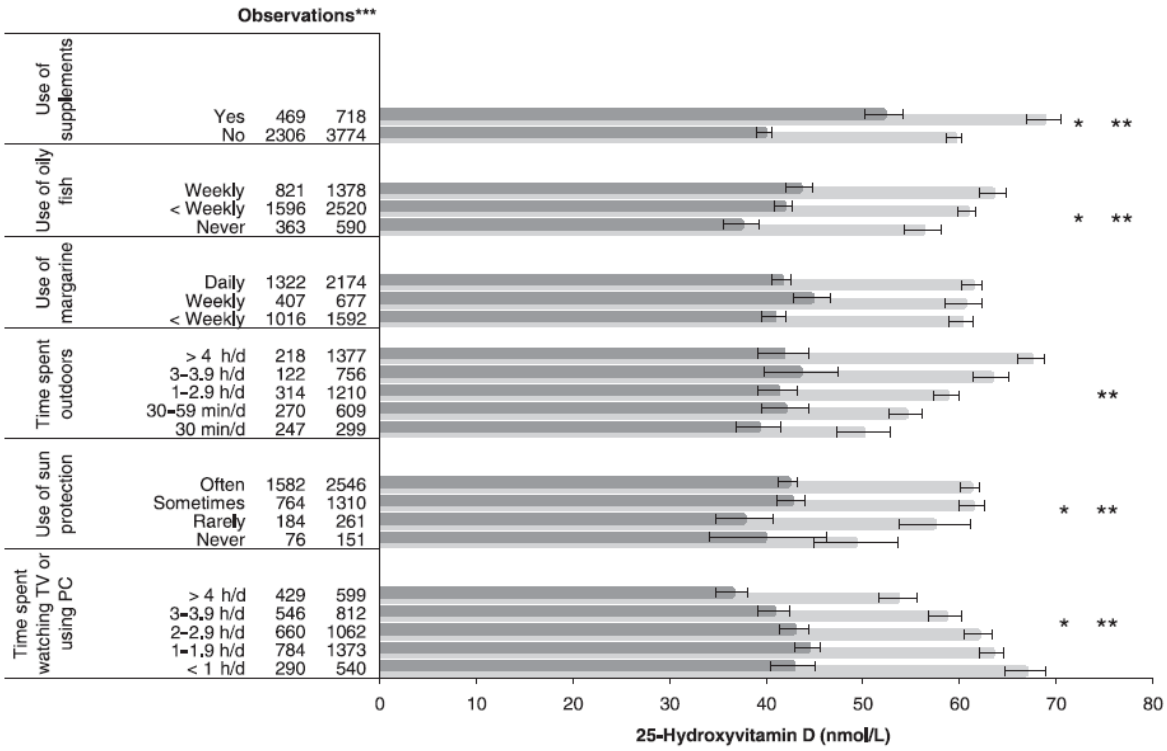
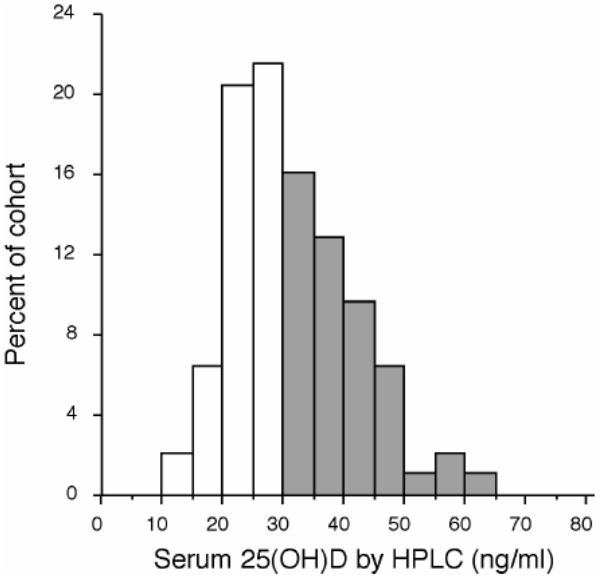


Figure 7.4 – *Original caption*: Low vitamin D status in highly sun-exposed subjects. When an accepted cut point of 30 ng/mL is used to define low vitamin D status, 51% of these subjects (open bar) are low (Binkley *et al.*, Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab. 2007:92(6):2130-2135. Copyright 2007, The Endocrine Society.).



Chapter 8 – Biological effects of vitamin D relevant to cancer

8.1 Introduction

In addition to bone mineralization and maintenance of calcium balance, 1α,25-dihydroxyvitamin D exerts physiological functions including regulation of growth and differentiation in a broad variety of normal and malignant cells (Chen, 1998; Reichrath and Holick, 1999; Lehmann *et al.,* 2004; Holick, 2006).

Basic information on biological processes possibly involved in anti cancerous properties of vitamin D metabolites, relevant to the report are briefly reviewed in this chapter. Readers interested in more details are invited to consult the more specialised literature (e.g., Dusso *et al.*, 2005; Ordonez Moran *et al.*, 2005; Deeb *et al.* 2007; Fleet, 2008).

8.2 Anti-neoplastic properties of the 1α,25-dihydroxyvitamin D

In vitro studies (mainly on human malignant cell lines) found that 1α,25-dihydroxyvitamin D and analogous compounds were capable of reducing cell proliferation, affect the cell cycle by inducing growth arrest in G0/G1 phase and promote cellular differentiation. For instance, an all mark of cancerous cell transformation is the acquisition of less differentiated characteristics, and 1α,25-dihydroxyvitamin D is able to stimulate differentiation of immature murine myeloid leukaemia cells. Apart from direct or indirect actions on the cell cycle, 1α,25-dihydroxyvitamin D can also suppress cancer growth by induction of apoptosis or inhibition of angiogenesis (which reduces the invasiveness of cancer cells).

These numerous *in vitro* observations suggested a potential role for 1α,25-dihydroxyvitamin D in the treatment of cancer patients. On the other hand, if 1α,25-dihydroxyvitamin D has such potent and coherent activity on cellular growth, then low serum levels of 1α,25-dihydroxyvitamin D or 1α,25-dihydroxyvitamin D resistance should predispose to cancer.

These *in vitro* results have been obtained using supraphysiological (i.e., pharmacological) concentrations of 1α,25-dihydroxyvitamin D. For instance the concentration of 1α,25-dihydroxyvitamin D needed for 50% growth inhibition exceeded in most cases the normal plasma concentration and in particular the concentration of free 1α,25-dihydroxyvitamin D (not bound to carrier proteins, i.e., the DBP). In many malignant cell lines, *in vitro* treatment with physiologic doses of 1α,25-dihydroxyvitamin D may even induce proliferation, rather than cause growth arrest (Frampton *et al.,* 1983). The cause for 1α,25-dihydroxyvitamin D-induced biphasic growth response, i.e., induction at low doses and inhibition at higher doses, is currently not clear. It is also unclear whether intra-organ production 1α,25-dihydroxyvitamin D is sufficient for reaching at local level the pharmacological concentrations observed in *in vitro* studies associated with anti-neoplastic activity.

Serum concentration levels of 1α,25-dihydroxyvitamin D is under tight control (see chapter 4) and does not vary much between healthy individuals. Also, only a few cell types have access to circulating 1α,25-dihydroxyvitamin D by expressing megalin that facilitates the uptake of DBP-bound 1α,25-dihydroxyvitamin D, for instance by mammary cells (Willnow and Kykjaer,2002; Nykjaer *et al.,*2001). Hence, at first sight, a physiological role of 1α,25-dihydroxyvitamin D on cellular growth and differentiation seemed quite limited. The interest in 1α,25-dihydroxyvitamin D and other biologically active vitamin D analogous in association with cancer emerged from two findings: evidence for extra-renal production of 1α,25-dihydroxyvitamin D, and expression of the VDR in many organs.

8.3 Extra-renal production of 1α,25-dihydroxyvitamin D

There is substantial evidence for extra-renal sites of 1α,25-dihydroxyvitamin D synthesis. *In vitro*, many non-renal cells, including bone, placenta, prostate, keratinocytes, macrophages, T-lymphocytes, dendritic cells and several cancer cells (e.g., from lung, prostate and skin) can enzymatically convert 25-hydroxyvitamin D to 1α,25-dihydroxyvitamin D (Zehnder *et al.,*2000; Hewison *et al.,*2007; Lehmann and Meurer,2003; Bikle *et al.,*1986). It should also be mentioned here that there are some tissues where the enzyme is undetectable, these include heart, liver, and adrenal cortex (Zehnder *et al.,*2001).

Extra-renal production of 1α,25-dihydroxyvitamin D has been demonstrated *in vivo* in both anephric humans (Barbour *et al.,*1981; Lambert *et al.,*1982) and animals (Littledike and Horst,1982), although the tissue source for circulating levels of 1α,25-dihydroxyvitamin D has not been established in these instances.

Extra-renal 1α-hydroxylase (CYP27B1) activity has been documented for patients with granulomatous diseases (sarcoidosis and tuberculosis) where locally synthesised 1α,25-dihydroxyvitamin D passes into the blood stream and may cause hypercalcemia. Most probably, disease-activated macrophages are responsible for extra-renal production of 1a,25-dihydroxyvitamin D in these granulomatous diseases (Bell,1998; Adams,1997). In addition to granulomatous diseases dysregulated extra-renal expression of CYP27B1 is associated with B-cell lymphoma, dysgerminomas and altered expression of CYP27B1 has been detected in different types of neoplasm including breast, prostate and colon cancers (Townsend *et al.,*2005; Evans *et al.,*2004; Hewison *et al.,*2003; Towsend *et al.*,2005).

Renal and extra-renal 1α-hydroxylase activity is due to a single gene product (CYP27B1) (Jones *et al.,*1999; Fu *et al.,*1997). However, there are substantial differences in the regulation of renal and extra-renal 1α,25-dihydroxyvitamin D synthesis. The biochemical reactions included in synthesis and catabolism of 1α,25-dihydroxyvitamin D are very similar in both renal and non-renal cells. However, in contrast to renal production, extra-renal synthesis of 1α,25-dihydroxyvitamin D is not regulated in a tight manner: PTH, calcium and 1α,25-dihydroxyvitamin D are, if any, weak regulators of extra renal CYP27B1. The catabolic enzyme CYP24A1 which regulates the intracellular concentration of 1a,25-dihydroxyvitamin D is stimulated by 1α,25-dihydroxyvitamin D itself. However, higher doses of 1α,25-dihydroxyvitamin D are required for stimulation of this enzyme in non-renal cells compared to renal cells (Bell, 1998; Adams 1997).

Hence, many normal and malignant cells express the 1α-hydroxylase (CYP27B1) which in theory enables them to produce their own 1α,25-dihydroxyvitamin D from circulating 25-hydroxyvitamin D. It is commonly assumed that most of the 1α,25-dihydroxyvitamin D formed by extra-renal cells serves an autocrine or paracrine regulation within the cells in which it is produced. The physiological function of the 1α-hydroxylase (CYP27B1) outside the kidney is still a matter of discussion, and the relative contribution of local versus systemic 1α,25-dihydroxyvitamin D for different cell functions is, however, not well established.

8.4 Extra-skeletal distribution of VDR

The second discovery suggesting involvement of 1α,25-dihydroxyvitamin D in extra-skeletal physiological function is the expression of the vitamin D receptor (VDR) in many types of cancer cells, including cells derived from tumours of the breast, prostate, pancreas, colon, bladder, cervix, thyroid, pituitary, skin (squamous cell carcinoma, basal cell carcinoma, and melanoma), glioma, neuroblastoma, leukaemia and lymphoma cells (Hannah and Norman,1994; Bouillon *et al.,*1995; Haussler *et al.,*1998; Bouillon *et al.,*2006).

The (VDR) is an intracellular hormone receptor that specifically binds the active form of vitamin D (1,25-dihydroxyvitamin D3 or 1α,25-dihydroxyvitamin D) and interacts with target-cell nuclei to produce a variety of biologic effects. Upon ligand activation, VDR binds specific nucleotide sequences (response elements) in target genes to activate or repress their expression.

Anti-neoplastic actions of 1α,25-dihydroxyvitamin D are partly mediated through VDR, which belongs to the superfamily of steroid/thyroid hormone receptors. Gene control by 1a,25-dihydroxyvitamin D and its analogues is highly complex and requires not only binding to the VDR but also heterodimerization of the VDR with the RXR, as well as the ability to induce phosphorylation of serine residues on the VDR (Haussler *et al.,*1994).

Physiological and pharmacological actions of 1α,25-dihydroxyvitamin D in various cells have indicated potential therapeutic applications of VDR ligands in inflammation, dermatological indications, osteoporosis, cancers, secondary hyperparathyroidism and autoimmune diseases (Nagpal *et al.,*2005; Pinette *et al.,*2003).

8.5 The VDR gene

The VDR gene (OMIM 601769) is located at chromosome 12q12q14. It includes 14 exons spanning approximately 75 kb (Figure 8.1). The noncoding 5' end includes exons 1A through 1F, while its translated product is encoded by 8 additional exons (MacLaughlin *et al.,*1982; CIE,2006; Norman,1998; Axelson,1991; Bekemeier,1966; Davie and Lawson,1980; Obi-Tabot *et al.,*2000; MacLaughlin and Holick,1985). Three unique mRNA isoforms are produced as a result of the differential splicing of exons 1B and 1C. The DNA sequence upstream to exon 1A is GC-rich and does not contain an apparent TATA box. Several potential binding sites for the transcription factor SP1 and other activators exist. Exons 2 and 3 of the VDR gene are involved in DNA binding, and exons 7, 8, and 9 are involved in binding to vitamin D.

Several single nucleotide polymorphisms (SNPs) have been identified. Most of the studies identified the restriction fragment length polymorphisms (RFLPs) Bb, Tt, Aa, and Ff, as defined by the endonucleases BsmI, TaqI, ApaI, and FokI, respectively. The lowercase allele contains the restriction site, whereas the uppercase allele does not.

The most frequently studied polymorphisms are:

- *Cdx2* (1e-1739G>A)
- *FokI* (exon2-Thr2Met)
- *BsmI* (IVS8+284G>A)
- *ApaI* (IVS8-48T>G)
- *Taq1* (exon10-Ile352Ile)

The Cdx2 polymorphism is located in the promoter region of the VDR gene, with the A-allele giving higher transcriptional activity of the gene.

The FokI RFLP is located in the coding region of the VDR gene and has an effect on the activity of the receptor.

The BsmI, ApaI and TaqI RFLPs are located in the 3' end of the gene.

In addition, there is also a 3’ untranslated region polyadenosine repeat (poly A) length polymorphism: long (18-22 repeats) or short.

Frequencies of VDR genetic variants differ according to ethnic groups. These polymorphisms modulate the activity of the VDR. It has been hypothesised that a less active VDR could be associated with either an increased susceptibility to cancer risk or to a more aggressive disease.

8.6 VDR-mediated and non VDR-mediated anti-neoplastic activities

Schematically, the active vitamin D metabolite 1α,25-dihydroxyvitamin D exerts its physiological activity via two ways: via influence of genomic transcription through activation of the vitamin D receptor (VDR), or via non-VDR, non-genomic associated mechanisms. The best known non-VDR related mechanism is the promotion of rapid calcium absorption in the jejunum.

At least eight major key cancer-relayed signaling pathways are targeted by 1α,25-dihydroxyvitamin D (Deeb *et al*.,2007). 1α,25-dihydroxyvitamin D regulates gene expression by binding to specific receptors, the vitamin D receptors (VDRs) of the nuclear receptor super-family, which are ligand- modulated transcription factors. Most cells of the body, including most cancer cells, express the VDR, and slightly supraphysiological concentrations of 1α,25-dihydroxyvitamin D have major effects on the cell cycle with a general but not complete G0/G1 cycle arrest (Bouillon *et al.,*2006). Very complex molecular mechanisms based on up– or down-regulation of several factors (p19, p21 and p27; TGFβ, IGF-BP3; c-myc, jun, c-fos and EGF receptor) are most probably responsible for the anti-proliferative effects of 1a,25-dihydroxyvitamin D and its analogues.

In some malignant cells, the cellular actions of 1α,25-dihydroxyvitamin D and its analogues do not require binding to the VDR (Kawa *et al.,*1996; Bhatia *et al.,*1995).

8.7 Effects on the immune system and on inflammatory processes

The effects of vitamin D on the immune system have been actively investigated, and, over the last years, potent new immunomodulatory effects of vitamin D analogs have been characterised (Adorini *et al.,*2003; Griffin and Kumar,2003; Van Etten *et al.,*2003). It has been demonstrated that various cell types involved in immunologic reactions (e.g. monocytes, T- and B-lymphocytes, and others) not only express VDR, but moreover possess the enzymatic machinery (25-hydroxyvitamin D_3-1α-hydroxylase) for the local synthesis of 1α,25-dihydroxyvitamin D (Van Etten *et al.,*2003). Today, the local synthesis of 1α,25-dihydroxyvitamin D in immune cells is considered to be of critical importance for the regulation and control of immune responses. Research on these immunomodulatory effects have led to the identification of new vitamin D analogues with reduced hypercalcemic activity, most likely to have a selective activity in inflammatory diseases (Zügel *et al.,*2002).

Inflammation critically enhances carcinogenic processes in several cancers (e.g., the colon, liver, stomach and prostate cancer). 1α,25-dihydroxyvitamin D would protect tissues from pro-inflammatory stresses that promote cancer, for instance by suppressing the prostaglandin signaling pathway (Fleet,2008).

The relationship between immunological processes associated with vitamin D cancer and other chronic diseases (e.g., cardiovascular diseases, neurological disorders) is a promising research avenue.

8.8 Cancer resistance to anti-neoplastic effects of 1α,25-dihydroxyvitamin D and analogues

Some malignant cells develop mechanisms to escape the anti-proliferative action of 1α,25-dihydroxyvitamin D. Such mechanisms include downregulation of the VDR by expression of SNAIL (Larriba and Muñoz,2005) or a decrease in the intracellular concentration of 1α,25-dihydroxyvitamin D by either downregulation of the CYP27B1 or amplification and/or overexpression of the catabolic CYP24A1 the pivotal enzyme in degradation of active 1α,25-dihydroxyvitamin D in inactive 24,25-dihydroxyvitamin D. Up regulation of CYP24A1 and downregulation of CYP27B1 has been found in high grade colon cancer (Cross, Bises *et al.*,2005). High increased copy numbers of the CYP24A1 were found in breast cancer tissues (Alberston *et al.,*2000). Other mechanisms for resistance against anti-proliferative actions of the 1α,25-dihydroxyvitamin D have been described. [14]

Reduced CYP27B1 activity in human prostate cancer cells correlates with decreased susceptibility to 1α,25-dihydroxyvitamin D-induced growth inhibition (Hsu *et al.,*2001). It is unclear, however, whether the loss of CYP27B1 activity is a factor contributing to the development of the tumour, or is a consequence of culture selection. Interestingly, several studies have indicated that different tumours will express and utilise CYP27B1 in different ways. This is perhaps best reflected by the varying levels of CYP27B1 expression in colon (Cross and Kállay,2005) and in prostate cancer (Puzas *et al.,*1987).

8.9 Animal models for vitamin D and cancer

In vitro studies show that 1α,25-dihydroxyvitamin D and its synthetic analogues have anti-proliferative effects on cancer cells. To date the strongest data in support of this property have been derived from the results of *in vivo* experimental animal studies. The majority of animal studies conducted in several experimental models of carcinogenesis, have indicated that various vitamin D analogues are capable of reducing the incidence of tumours and/or the risk of their development.

1a,25-dihydroxyvitamin D has been shown to prolong the survival time of mice inoculated with M1 murine myeloid leukemic cells, as well as inhibit tumour formation in a TPA-promoted skin cancer model (Wood *et al.,*1983). In contrast to other studies, however, administration of 1α,25-dihydroxyvitamin D increased the yield of tumours in the DMBA-induced skin cancer model (Wood *et al.,*1985). The reasons for these disparate effects of 1a,25-dihydroxyvitamin D in these studies on skin cancer remain unclear and warrant further study.

Many animal studies dealing with the chemopreventive effects of vitamin D analogues have used various experimental models of colonic carcinogenesis, and these studies provide most compelling evidence for anti-neoplastic properties of vitamin D. [15]

The role of vitamin D in carcinogenesis can now be better evaluated by analysis of mice with an engineered deletion of the vitamin D receptor (VDR). Mice deficient in key members of the vitamin D synthesis and catabolic pathway do not develop spontaneous cancer (Deeb *et al.*,2007). More specifically, VDR null (deficient) mice do not have a spontaneous increase in cancer, but show hyperproliferation and increased mitotic activity in the descending colon. These mice are also more prone to malignant transformation when challenged with oncogenes or chemical carcinogens (Welsh,2004; see Bouillon *et al.,*2008 for review). For instance, VDR null mice show altered mammary gland morphology and altered tumour characteristics, but tumour incidence, latency or multiplicity following exposure to the chemical carcinogen 7,12-dimetyl-benzanthracene (DMBA) were not different from those of wild type mice. VDR null mice exposed twice to DMBA develop more skin tumours and lymphomas than wild-type mice.

8.10 Cancer treatment with 1α,25-dihydroxyvitamin D_3 and analogous compounds

VDR ligands have been developed for therapeutic treatment of several diseases including psoriasis, osteoporosis and secondary hyperparathyreodism. The 1α,25-dihydroxyvitamin D_3 and several vitamin D analogues have shown promise as chemopreventive and/or chemotherapeutic agents in several experimental animal models of tumorigenesis (Brasitus and Bissonnette, 1999). Unfortunately, the application of 1α,25-dihydroxyvitamin D_3 as a therapeutic agent *in vivo* is limited by its tendency to cause hypercalcemia. Much effort has therefore been directed to identifying new vitamin D analogues with potent cell regulatory effects, but with weaker effects on calcium metabolism than those of 1α,25-dihydroxyvitamin D_3. Indeed, several newly available less-calcemic synthetic vitamin D analogues are more potent in their effects on cellular proliferation and/or differentiation than the standard compound 1α,25-dihydroxyvitamin D_3. Among other things, these analogues differ from 1α,25-dihydroxyvitamin D_3 in their ability to bind to DBP, to induce VDR-RXR-heterodimerization, DNA binding and transactivation.

Some investigators attempted to administer 1α,25-dihydroxyvitamin D_3 as a differentiating agent in myelodysplasia and acute leukaemia (Ferrero *et al.,*1996; Slapak *et al.,*1992; Hellström *et al.,*1990). Some patients seemed to respond to the therapy; these improvements were, however, not strong enough to encourage further trials. In addition, 20-30% of patients who received a daily dose of 1α,25-dihydroxyvitamin D developed severe forms of hypercalcemia.

Other studies have shown that administration of high-dose and vitamin D analogues can be safe and feasible (Deeb *et al.,*2007). Initial phase II studies and a single phase III study suggest that 1α,25-dihydroxyvitamin D_3 is an active agent in cancer therapy of prostate cancer (Deeb *et al.,*2007).

Although many less-calcemic analogues have been synthesised, they have not yet provided the desired separation between the therapeutic and calcemic action and truly non-calcemic vitamin D analogues are still elusive. In particular, the potentiation of several anticancer drugs such as the platinum derivates and taxanes support the continued development of 1α,25-dihydroxyvitamin D_3 and analogues as a anticancer drugs.

8.11 Conclusions

Altogether, it would appear that the physiologically active forms of vitamin D have a number of actions on important cellular processes mediated by VDR-dependent, and perhaps VDR-independent mechanisms that may contribute to their potential anticarcinogenic and chemotherapeutic actions. It remains to be shown, however, that in physiological conditions, sufficient quantities of 1α,25-dihydroxyvitamin D_3

Several rodent studies have shown that 1α,25-dihydroxyvitamin D_3 or its analogues can reduce the *in vivo* growth of cancer but studies in humans are still rare and in part contradictory (Bouillon *et al.,*2006).

The crucial point is to know whether properties suggested by basic and animal research do actually exists in humans, and when they exist, are they capable of influencing biological events involved in cancer occurrence and/or progression. Worries of the real existence of potentially

beneficial biological mechanisms described in this chapter are as legitimate as in the past, many cancer prevention or curative hypotheses were supported by considerable biological mechanistic data, and finally proved to be inefficient (e.g., fibrates, omega-3 fatty acids) or even hazardous (e.g., beta-carotenes, selenium, vitamin E-see chapter 5). New trials in humans for testing cancer preventive or chemotherapeutic properties of vitamin D and its analogues are thus warranted.

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[14] Other mechanisms include RAS-induced phosphorylation of RXRα on serin 260 in keratinocytes which results in inhibition of 1α,25$(OH)_2D_3$ signalling via VDR-RXR heterodimers (Solomon *et al.,*2001), increased expression of the VDR-interacting transcriptional repressor SMRT in prostate cancer cells (Khanim *et al.,*2004) or decreased expression of adhesion molecules (e. g. E-cadherin) (Peña *et al.,*2005).

[15]For instance, it was demonstrated that intragastric administration of alphacalcidol (1α-vitamin D_3) not only suppressed colonic tumours induced in rats by intrarectal instillation of N-methyl-N-nitrosourea, but also inhibited the promotion of tumours in these animals caused by lithocholic acid (Kawaura *et al.,*1989;1990).

Pence and Buddingh (Pence and Buddingh, 1988) demonstrated that in rats fed a high-fat diet, which promoted the development of 1,2-dimethyl-hydrazine (DMH)-induced colonic tumours, but not in rats fed a low-fat diet, supplemental dietary vitamin D_3 significantly reduced the incidence of colonic tumours. Similar results were obtained by Comer *et al.,* (Comer *et al.,*1993) who failed to detect a protective effect of supplemental dietary vitamin D_3 in rats fed a low-fat diet and administered a single sc dose of DMH (200 mg/kg body weight). Taken together, these findings indicate that dietary vitamin D_3, as well as intragastrically administered alphacalcidol, might serve to inhibit the promotion of colonic tumours, i. e. serve as antipromotors.

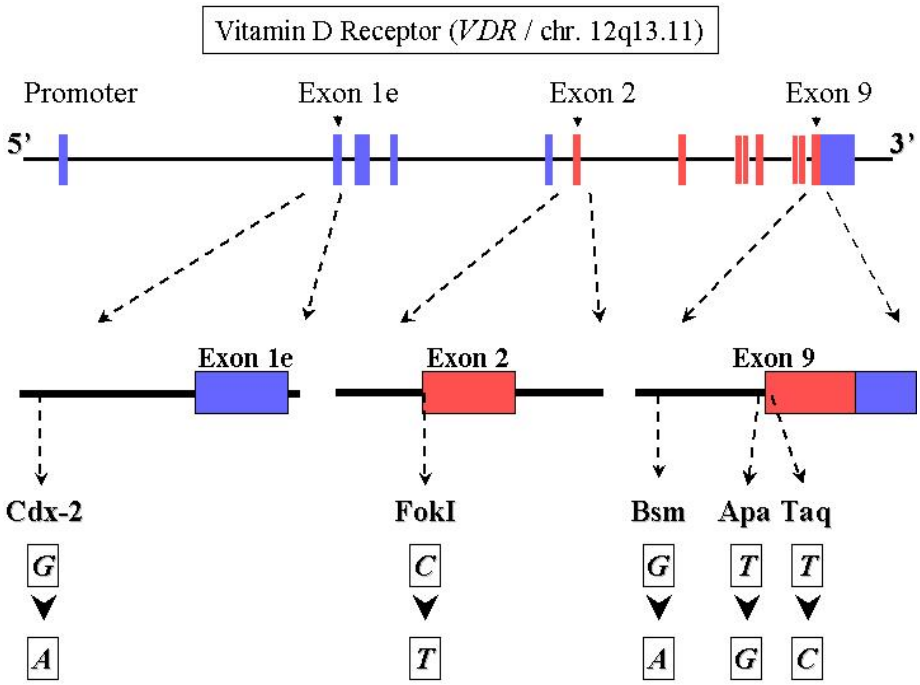
Table 8.1 - *In vitro* 1a,25-dihydroxyvitamin D synthesis in extrarenal cells (Jones *et al.,*1999; Adams,1997; Zehnder *et al.,*2000; Schwartz *et al.,*1998; Puzas *et al.,*1987; Bikle *et al.,*1986; Delvin *et al.,*1985; Cadranel *et al.,*1990; Lehman *et al.,*2001]

• Bone cells • Endothelial cells • Keratinocytes •Macrophages (alveolar/peritoneal) •Blood monocytes	• Placenta/Decidual cells • Prostate cells • T-Lymphocytes • Carcinoma cells (Sarcoma,Lymphoma, Melanoma, Lung and other tumours)

Further **tissues** with CYP27B1 activity (Goltzman and Henderson,1996):

Parathyroids – Pancreas – Adrenal medulla – Colon – Cerebellum – Lymph nodes – Hair follicle – Sweat glands

Figure 8.1 – The Vitamin D receptor gene



Source : www.genomos.eu

Chapter 9 – Ecological studies on sun exposure and cancer

9.1 Background and objective of the chapter

This chapter deals with (i) correlation studies between data related to geographical location of populations and cancer incidence or cancer mortality data gathered by registries, and (ii) with studies that examined the risk of cancer after a skin cancer using data from cancer or mortality registries, assuming that skin cancer was a proxy indicator for high lifetime exposure to solar ultraviolet radiation. Therefore assessment of sun exposure history was not done at the individual level.

9.2 Latitude and cancer incidence or mortality

With increasing latitude (i.e., increasing distance from the equator) the UVB abundance in the sunlight spectrum decreases. Therefore, latitude has often been used as parameter for examining the ecological association between sun exposure of populations living in specific areas and the burden of health conditions registered in these areas.

It was through the combination of clinical observations and ecological studies that the link between sun exposure and skin cancers was identified, with more skin cancer cases among populations residing in areas of high sun exposure (IARC, 1992). In a similar way, an opposite gradient for several cancers of solid organs was pinpointed, and possibly also for haematological malignancies, indicating a possible 'protective' effect of sun exposure for these tumours.

We performed a literature search in PubMed on "latitude" and "cancer", selecting ecological studies as defined above. Of all the articles found two were excluded, one because it was too difficult to appraise its results (Grant, 2001) the second was redundant (Grant, 2003).

Ecological studies on latitude and cancer are not so numerous (about 20), but some studies typically looked at all types of malignancies at the same time. As can be expected with the multiplicity of statistical testing, the incidence or mortality of some tumour types were significantly positively associated with increasing latitude when in reality no association existed (statistical type II or beta error).

Early ecological studies often simply plotted latitude of residence against cancer incidence and/or mortality rates and presented the strength of the correlation between these two factors. More sophisticated studies tried to infer UVB levels at the residential locations from several sources: satellites, ground-based UVB monitoring stations, heat zones, average hours of solar radiation, etc. Some of these studies adjusted for the prevalence of other cancer risk factors, such as food intake, income, race and physical activity, and also for factors influencing endogenous vitamin D synthesis (e.g., skin pigmentation).

9.2.1 Colorectal cancer

Most ecological studies found associations between increasing latitude and increasing colorectal cancer incidence or mortality (Boscoe and Schymura, 2006; Garland and Garland, 1980; Grant, 2002; Grant, 2007a; Grant, 2007b; Mizoue, 2004; Emerson and Weiss, 1992). One study correlating latitude with cancer mortality in Spain and adjusted for non-melanoma skin cancer, melanoma and lung cancer rates, did not find an association with colon cancer mortality for women, but did observe a positive association between latitude and mortality from rectal cancers for both sexes and for colon cancer for males (Grant *et al.,*2007b). Emerson and Weiss observed a trend in the USA with the annual average daily global radiation for the occurrence of cancers of the colon and rectum in males only, for females the trend was not significant (Emerson and Weiss, 1992).

9.2.2 Prostate cancer

All ecological studies found an association between increasing latitude and increasing burden of prostate cancer. (Boscoe and Schymura, 2006; Grant, 2002; Mizoue, 2004; Colli and Colli, 2006; Grant, 2004; Hanchette and Schwartz, 1992; Schwartz and Hanchette, 2006), except a study performed in Spain (Grant, 2007b). One study found such an association only for northern USA counties, in southern counties no significant association was observed (Schwartz and Hanchette, 2006).

9.2.3 Breast cancer

Ecological studies quite consistently reported inverse associations between measures of UVB exposure and female breast cancer mortality (Boscoe and Schymura, 2006; Grant, 2002; Garland *et al.,*1990; Gorham *et al.,*1990; Grant, 2002) or incidence (Boscoe and Schymura, 2006). Two studies did not observe any significant association between latitude and breast cancer mortality in Spain and China (Grant, 2007a; Grant, 2007b). A study comparing breast cancer mortality rates between regions of the USA, found increased relative risks for dying from breast cancer for women aged >50 years in the west, midwest and northeast, compared to the south, also after adjusting for known breast cancer risk and prognostic factors. For younger women, no significant differences in mortality were observed between these regions (Sturgeon *et al.,*1995).

9.2.4 Non-Hodgkin lymphomas (NHL)

Non-Hodgkin lymphomas tend to occur more often in patients that also develop skin cancers. For that reason, it was for a long time assumed that sun exposure was a risk factor for the development of non-Hodgkin lymphomas. However, most recent ecological studies seem to support the idea that low levels of ambient sun exposure might actually be associated with these cancers. One of the problems in studying non-Hodgkin lymphomas is the classification; over time the list of tumour types to be included under the heading 'non-Hodgkin lymphoma' has changed, and in different cancer registries the new coding rules have been adopted at different times. There are, however, a few ecological studies reporting on the association between levels of ambient sun exposure and the incidence (Bentham, 1996; Hu *et al.,*2004; Langford *et al.,*1998; Newton, 1997; McMichael and Giles, 1996) and/or mortality (Grant, 2002; Grant, 2007b; Freedman *et al.,*1997; Hartge *et al.,*1996) of non-Hodgkin lymphomas. Two of them, both from 1996, found a small, positive association between ambient sun exposure and NHL incidence (Bentham, 1996; McMichael and Giles, 1996). None of the other studies, published more recently, looking at NHL incidence found any significant associations, either with NHL on the whole or within ethnic groups (Hu *et al.,*2004; Langford *et al.,*1998), nor for primary cutaneous NHL only (Newton, 1997). Most of the ecological studies looking at mortality observed inverse associations between measures of UVB radiation and NHL mortality rates (Grant, 2002; Freedman *et al.,*1997; Hartge *et al.,*1996), which was usually, except for a study conducted in Spain, where a positive association was found, significant only for females (Grant, 2007b).

9.2.5 Ovarian cancer

Three ecological studies observed significant inverse gradients for UVB indicators and (estimated) ovarian cancer incidence in 175 countries (Garland *et al.,*2006) and mortality in the USA (Grant, 2002; Lefkowitz and Garland, 1994). Two other studies did not find any significant correlation with latitude in Spain (Grant, 2007b) and average hours of solar radiation in the area of residence in Japan (Mizoue, 2004).

9.2.6 Cervical and endometrial/uterine cancer

Three ecological studies reported on the association between cervical cancer and measures of solar irradiance, two from the USA, and one from China. Two studies indicated an inverse association between ambient sun exposure and cervical cancer or mortality (Grant, 2007a; Garland *et al.,*1990), the latter not being significantly associated. In contrast with these reports, Boscoe and Schymura (2006) observed a positive association with solar UVB exposure: the relative risks of cervical cancer for receiving annually 650 kJ/m^2 vs 1540 kJ/m^2 of solar UVB levels at the place of residence were 0.84 (0.80-0.89) for incidence and 0.89 (0.84-0.94) for mortality, respectively (Boscoe and Schymura, 2006). The same group observed inverse associations with solar UVB exposure for uterine cancer: RR incidence 1.49 (95% CI 1.45-1.53) and mortality 1.52 (1.46-1.58) for receiving annually 650 kJ/m2 vs 1540 kJ/m2 of solar UVB levels at the place of residence (Boscoe and Schymura, 2006). In line with this finding, a study on UVB irradiance adjusting for a large number of known or putative cancer risk factors and factors influencing endogenous vitamin D synthesis found an inverse association between UVB estimates and estimated incidence rates of endometrial cancer, also after correcting for other risk factors (Mohr and Garland, 2007). A report from Spain observed an inverse association between cancer of the corpus uteri and latitude (Grant, 2007b).

9.2.7 Other tumour types

Some publications report on ecological studies correlating measures of sun or UVB exposure with other types of cancer (Boscoe and Schymura, 2006; Grant, 2007a; Mizoue, 2004; Uehara *et al.,*2003; Mohr *et al.,*2006).

One study linked renal cancer incidence rates based on Globocan 2002 (Ferlay *et al.,*2004) with an algorithm for total solar UVB at the top of the atmosphere on the winter solstice and corrected this correlation for cloud cover and intake of calories from animal sources (Mohr *et al.,*2006). Renal cancer incidence rates were highest in countries situated at the highest latitudes, in men (R-square = 0.64, $p < 0.01$) and women (R-square = 0.63, $p < 0.01$). Multivariate analysis showed that UVB irradiance was inversely associated with renal cancer incidence rates (-0.45, $p = 0.0003$ for men and –0.11, $p=0.04$ for women). Cloud cover ($p = 0.003$) and intake of calories from animal sources ($p < 0.0001$) were independently positively associated.

9.3 Skin cancer and risk of subsequent cancer

9.3.1 Rationale for studying the risk of new primary cancer after skin cancer

It is well established that sunlight is the main environmental risk factor for non-melanoma skin cancer (NMSC) and also for cutaneous melanoma (see Chapter 3). Likewise, in many populations, the level of vitamin D in individuals is also related to their sun exposure (see Chapter 7). Therefore, if a high body level of vitamin D protects against cancer occurrence, as hypothesised, we could expect a reduced rate of second cancer occurrence in persons who have had skin cancer, and especially squamous cell carcinomas of the skin that are more related to lifetime, chronic type of exposure to solar UVB radiation (e.g., occupational exposure of farmers and construction builders, outdoor activities such as gardening, skiing, mountaineering, hiking). Such a protective effect would act in the context of other biological mechanisms that link NMSC and subsequent cancer occurrence, e.g. ultraviolet induced immune suppression and risk factors that are common to NMSC and other cancers, a genetic predisposition to both NMSC and other cancers, and increased surveillance in persons who have had skin cancer. Such mechanisms would expectedly act in the direction of increased occurrence of second cancers, i.e. in the opposite direction of a hypothesised protective effect of sunlight exposure and vitamin D.

We considered published studies where groups of patients with NMSC had been followed for occurrence of subsequent cancers. Cohort studies of patients with malignant melanoma were not included because this cancer is less strongly associated with cumulative sun exposure than squamous cell carcinoma [SCC]. One limitation of studies of second cancers following NMSC is that the majority of NMSC are basal cell carcinoma (BCC), which, like melanoma, appear to be related as much to pattern of exposure as to total amount of exposure (see Chapter 3).

We performed a search of the English literature on “skin cancer”, “squamous cell carcinoma”, basal cell carcinoma”, and “second primary cancer”. Where earlier studies had been updated, we only included the most recent publications.

9.3.2 The three major studies

Consortium of cancer registries

Tuohimaa *et al.,*(2007) reported the largest of the available studies. A collaboration of thirteen cancer registries in eleven countries accrued a cohort of 276,034 NMSC patients, yielding a total of 35,620 second cancers, excluding second NMSCs. The expected number, based on the population rates in the cancer registry populations, was 25,616, giving an overall SIR of 1.39 (95% CI: 1.38-1.41).

The SIR was elevated for all common types of cancer and all the increases were statistically significant ($p<0.05$). The SIR for lung cancer was 1.51 (1.47-1.54), which was slightly higher than the overall SIR. The SIR for prostate cancer was 1.27 (1.24-1.31).

When the cohort was stratified into two groups, representing sunny countries and less sunny countries, respectively, the patterns of second cancers differed significantly between the two groups of countries. In sunny countries (Spain and Singapore) the overall SIR for all cancers excluding skin cancer and cancer of the lip was 0.84 (0.78-0.92) but in the less sunny countries (Canada, Norway,

Denmark, Sweden, Finland, Iceland, Scotland, Slovenia) the SIR for all cancers excluding skin cancer and cancer of the lip was 1.35 (1.33-1.37). The lower than expected incidence in the sunny countries was consistent for most of the common types of cancer, and the higher than expected risk in less sunny countries was similarly consistent in all main types of cancer.

The authors describe the finding of a difference between sunny and less sunny countries as 'difficult to understand', but they concluded that 'vitamin D produced in the skin seems to decrease the risk of several solid cancers'.

Sunny countries were only represented by two cancer registries: Singapore (2.9 million) and Zaragoza, Spain (0.8 million), and the Working Group noted that the body of evidence from data from sunny countries represented a very small part of the overall data in this study, approximately 3% of the total person-years experience. It is difficult to assess whether the apparent difference was the result of an investigation of an a priori hypothesis, or whether the subgroup analysis was data driven. The Working Group considered that it would be useful to have further details on the relative contribution of these two areas to the overall estimate for sunny countries. Finally, the Working Group was not convinced that the finding of the stratified analysis study was generally supportive of the vitamin D hypothesis. Both the NMSC incidence rate and the production rate of vitamin D in the skin are expected to be limited by sun exposure in less sunny populations. Therefore, if vitamin D was significant in reducing cancer incidence, the reduction should be manifest not least in these countries. Further critiques of this study have been done by Grimsrud and Andersen (2008).

The Eindhoven cancer registry study

A cohort study was conducted in the Eindhoven Cancer Registry in The Netherlands comprising 12,121 patients with skin cancer (2,620 squamous cell carcinomas, 9,501 basal cell carcinomas, and 1,420 cutaneous malignant melanomas) followed until 2005 for the occurrence of prostate cancer (de Vries *et al.,*2007). The SIR for prostate cancer was 0.87 (0.77-0.98). The reduction in SIR for prostate cancer was most pronounced in patients who were 60 years or over at the time of NMSC diagnosis (0.84 [0.73-0.96]), or patients with NMSC in the chronically ultraviolet radiation-exposed head and neck region (0.85 [0.73-0.98]). The reduction was greatest for prostate cancers stage III or IV (0.73 [0.56-0.95]), and in the period immediately after NMSC, e.g. 0.53 (0.34-0.78) in the first year of follow-up. The authors reviewed seven previous studies on prostate cancer occurrence in NMSC patients. Only one of these studies (Bower *et al.,*2000) suggested a reduced SIR for prostate cancer of 0.85 (0.73-0.99). A meta-analysis of these seven studies and the de Vries *et al.,* study, conducted by the Working Group, gave an overall SIR for prostate cancer of 1.07 (1.03-1.12)(Table 9.1).

The group of investigators from Eindhoven subsequently published a similar analysis of colorectal cancer and breast cancer in patients who had had skin cancer (Soerjomataram *et al.,*2008). The cohort of skin cancer patients comprised 4,089 patients with SCC and 19,319 with BCC. The SIRs for colorectal cancer were 0.69 (0.50-0.94) for patients with SCC and 0.93 (0.81-1.06) for patients with BCC. Further analysis of the SCC cohort showed a particularly low SIR in the sub-group of patients who were 60 years or older when they had SCC (0.62 [0.43-0.87]). A similar pattern was suggested in the BCC cohort (0.90 [0.78-1.04]). For SCC and BCC combined, an analysis by period of follow-up showed that the lower than expected rate of colorectal cancer was confined to the first 3-4 years after skin cancer diagnosis. A review of five previous follow-up studies of patients with SCC or BCC (Nugent, Wassberg, Maitra, Friedman, Milan) did not suggest a general reduction in the incidence of colorectal cancer in patients with SCC or in the larger cohorts of patients with BCC. The analysis of breast cancer incidence did not suggest any material increase or decrease in persons who had had SCC (0.87 [0.54-1.31]) or BCC (0.99 [0.85-1.15]). A review of nine previous studies of breast cancer incidence in patients with skin cancer suggested a substantially increased rate of breast cancer subsequent to BCC.

The study by WB Grant

Grant (2007) collated twelve published studies of cohorts of NMSC patients followed for the occurrence of second cancers. He noted that the SIRs for many secondary cancers were higher than 1.0. Across the individual studies many SIRs were correlated with the SIR for lung cancer. He adjusted the SIR for each secondary cancer for the corresponding SIR for lung cancer, using a weighted, polynomial regression of the site-specific SIRs against the lung cancer SIRs, with study being the unit of analysis. In most of the individual studies, the SIR for lung cancer tended to be higher

than the SIR for other second cancers, and this adjustment for lung cancer SIR tended to give adjusted SIRs that were below 1.0. According to the author, this suggests a protective effect of NMSC on the development of second cancers, once lung cancer and risk factors associated with lung cancer are adjusted for.

Of the 21 cancer groups analysed and reported by Grant, 12 were below 1.0, four of these statistically significantly so (cervix cancer 0.71; oesophagus cancer 0.60; gastric cancer 0.67; rectal cancer 0.83).

The Working Group conducted its own meta-analyses of the studies collated by Grant, excluding one study that was considered to be of an incomparable design (Karagas *et al.,*1998). The study by Lindelof (1991) had no information about lung cancer and was excluded from the second meta-analysis. The pooled SIRs were 1.18 (1.17-1.20) for all cancer combined excluding NMSC, and 1.19 (1.15-1.23) for lung cancer (Tables 9.2 and 9.3).

The Working Group considered that the adjustment for lung cancer used by Grant is incorrect. It is accepted that a common risk factor or pre-deposition to both NMSC and lung cancer would lead to an excess of lung cancer in NMSC patients. One such factor is smoking, which is closely linked to lung cancer and possibly weakly linked to NMSC. The adjustment for lung cancer SIR implies that an SIR for a third cancer (e.g. cancer of the colon) would be reduced by the adjustment, even if that cancer was unrelated to smoking. It would only ever be appreciated as an excess incidence if the SIR for this cancer exceeded the SIR estimate for lung cancer. The effect of this inappropriate adjustment is to deflate the SIR estimates, in many cases from an estimate higher than 1.0 to a value below unity. Also, ecological adjusting for the lung cancer SIR is not equivalent to adjusting for smoking at the individual level (see 9.4.1).

Together with the new data assembled by Tuohimaa *et al.,*(2007), yielding 35,620 second cancers excluding NMSC, the publications collated by Grant (yielding 25,849 second cancers excluding NMSC), represents the largest volume of available data on the occurrence of second cancers after NMSC. There is a degree of overlap between the two datasets represented by the populations of Manitoba, Denmark, Sweden and Finland, which are included with new data in the Tuohimaa study as well as with a previously published study in the meta-analysis by Grant.

9.3.3 Other studies on skin cancer and second primary cancer

For the remainder of this section, the review of individual studies will emphasise observations and results that are not yet covered in the review of the three papers above (Tuohimaa; de Vries; Grant).

Lindelof *et al.,* (1991) reported a cohort study of 1,973 persons with BCC in Sweden. The study was included in the meta-analysis by Grant. The overall RR for a second cancer was 1.49 (1.32-1.68).

Frisch *et al.,* (1995) reported a cohort study of 5,100 persons with SCC in Denmark. This study was included in the meta-analysis by Grant. The overall SIR was 1.3 (1.2-1.4) for all cancers excluding NMSC. For lung cancer the SIR was 1.7 (1.4-2.0) and for prostate cancer it was 0.8 (0.6-1.1).

Frisch *et al.,* (1996) reported a cohort study of 37,674 persons with BCC in Denmark. This study was included in the meta-analysis by Grant. The overall SIR was 1.15 (1.11-1.19) for all cancers excluding skin cancer. For lung cancer the SIR was 1.40 (1.29-1.52) and for prostate cancer it was 1.10 (0.98-1.23).

Levi *et al.,* (1997) reported a cohort study of 4,639 persons with SCC in Switzerland. This study was included in the meta-analysis by Grant. The overall SIR excluding skin cancer was 1.0 (0.9-1.1). SIRs were 1.3 (1.0-1.6) for lung cancer and 1.1 (0.9-1.4) for prostate cancer.

Levi *et al.,* (1998) reported a cohort study of 11,878 persons with BCC in Switzerland. This study was included in the meta-analysis by Grant. The SIR for all cancers combined, excluding skin cancer, was 0.9 (0.8-1.0). For lung cancer the SIR was 0.9 (0.8-1.1) and for prostate cancer it was 1.1 (0.9-1.3).

Kahn *et al.,* (1998) reported an analysis of the 1.1 million people in the Cancer Prevention Study II in the United States and Puerto Rico. Overall cancer mortality was increased in persons with

NMSC with RR of 1.27 (1.20-1.33) in men and 1.24 (1.15-1.33) in women. RR for prostate cancer death was 1.28 (1.11-1.47). Of 46 site-sex specific analyses, 37 gave RRs that were higher than 1.0; 15 of these were statistically significant.

Wassberg *et al.,* (1999) reported a study of 25,947 patients with SCC in Sweden. There were increased SIRs for all sites excluding SCC (1.3 [1.2-1.3]) and lung cancer (1.7 [1.5-1.9]). Out of 27 second cancer sites reported, 24 had SIRs that were higher 1.0 and 20 of these were statistically significant.

Friedman and Tekawa, (2000) followed study of 3,164 persons with basal cell skin cancer in the Kaiser-Permanente Health Plan in California showed an RR of 1.2 (1.1-1.4) for any second cancer, 1.4 (1.0-1.8) for lung cancer, and 1.1 (0.9-1.4) for prostate cancer. This study was included in the meta-analysis by Grant. Of the 20 site-sex specific analyses, 16 showed an RR higher than 1.0; five of these were statistically significant.

Bower *et al.,* (2000) reported a cohort study of 13,961 cases of basal cell carcinoma (BCC) in south west England. This study was included in the meta-analysis by Grant. In this study, the occurrence of second primary cancers in BCC patients was generally below expectation. All non-cutaneous cancer: 0.90 (0.84-0.96); lung cancer 0.99 (0.88-1.12); and prostate cancer 0.85 (0.73-0.99). Of the 19 site-sex specific analyses, the majority (12) gave SIRs that were less than 1.0. Of these, four were statistically significant. The Working Group noted that the results from this study were systematically different from other relevant studies, including a similar study from another area in south England, in reporting many SIRs for second cancers that were less than 1.0.

Milan *et al.,* (2000) reported on the occurrence of second primary cancers in a cohort of 71,924 patients with BCC in Finland. This study was included in the analysis by Grant. The SIR for all cancers excluding NMSC was 1.19 (1.16-1.21). It was 1.12 (1.06-1.17 for lung cancer and 1.22 (1.15-1.29) for prostate cancer. Among 36 cancer sites reported, 34 had SIRs higher than 1.0; 18 of these were statistically significant.

Hemminki and Dong, (2000) reported a cohort study of 17,637 SCC patients in Sweden. This study was included in the meta-analysis by Grant. Excluding the first year of follow-up, SIRs were elevated for all cancers combined: men 1.9 (1.8-1.9); women 1.5 (1.4-1.7). Out of 26 site-sex specific analysis, 25 gave SIRs that were 1.0 or higher; 19 of these were statistically significant.

Troyanova *et al.,* (2002) followed 2,620 cases of NMSC in the Bulgarian National Cancer Registry for the occurrence of second primary cancer. The overall SIR was 1.01 (0.83-1.18) for all cancer. Increased incidence of second cancers was found for head and neck, thyroid, lung, larynx, bladder, colon, melanoma, non-Hodgkin's lymphoma, and leukaemia.

Efird *et al.,* (2002) reported a cohort study from the Kaiser-Permanente Health Plan in California. This study was included in Grant's meta-analysis. The RR was 1.4 (1.2-1.6) for all cancer excluding NMSC, 1.5 (0.8-2.7) for lung cancer, and 1.3 (0.9-2.0) for prostate cancer. Of the 14 site-specific estimates presented, 12 were higher than 1.0.

Brewster *et al.,* (2004) followed a cohort in Maryland, USA and compared the occurrence of second primary cancer in NMSC patients in people with different XPD genotypes. The DNA repair deficient genotypes Lys/Gln or Gln/Gln had a RR of 2.22 (1.30-3.76) for second primary cancer occurrence, compared with the Lys/Lys genotype.

Maitra *et al.,* (2005) followed 25,731 patients with squamous cell carcinoma (SCC) in the Thames Cancer Registry in south east England. The SIR for all cancers excluding NMSC was 1.22 (1.18-1.26). The SIR was 1.26 (1.17-1.35) for lung cancer and 1.0 (0.9-1.1) for prostate cancer. Of 47 site-sex combinations reported, 42 had SIRs higher than 1.0; 25 of these were statistically significant. Five SIRs were below 1.0: male breast; male bladder; female oesophagus; female liver; female Hodgkin's lymphoma. None of these were statistically significant.

Nugent *et al.,* (2005) examined long term cancer history 43,275 cases of NMSC in Manitoba included in the meta-analysis by Grant. SIRs were higher than 1.0 for all sites excluding NMSC (1.08 [1.05-1.10]), lung cancer (1.14 [1.07-1.22]) and prostate cancer (1.08 [1.01-1.14]).

Chen *et al.,* (2008) performed a cohort study in Maryland, USA and followed 19,174 subjects during 16 years. Compared with persons with no personal history of NMSC, subjects with past NMSC

had a risk of subsequent cancer other than NMSC of 1.99 (95% CI: 1.70-2.33) after adjusting for age, sex, body mass index, smoking status, and educational level (Chen *et al.,*2008). The association was observed for both basal cell carcinoma (multivariable-adjusted RR = 2.03, 95% CI: 1.70-2.42) and squamous cell carcinoma (multivariable-adjusted RR = 1.97, 95% CI: 1.50-2.59) of the skin. This study was a cohort study and contrary to studies with registry data, it did adjust for a number of confounding factors. This study should thus be classified in the chapter related to observational designs. However, the Working Group considered that the difference in design made little difference compared with the analysis of second primaries from cancer registries. On the contrary, it could easily be argued that the completeness of follow-up and ascertainment of second primaries is more complete and more systematic in the cancer registries. Also, this cohort study is quite small and does not add materially to the information already provided by cancer registries.

9.3.4 Discussion

Studies showed generally increased rates of second cancer occurrences in NMSC patients. The main exceptions from this general finding are reduced rates in the sub-group analysis of data from Singapore and Zaragoza (Spain) and in the analysis from south west England, and reduced rates of prostate cancer and colorectal cancer in sub-groups of the Eindhoven cohort. Grimsrud and Andersen (2008) have provided a criticism of ecological studies based on time associations between primary cancers diagnosed at different times as typically reported cancer registries. They recommended that epidemiological studies of potentially protective effects from carcinogenic ultraviolet rays should include individual information on solar exposure and vitamin D levels, as well as on other recognised and relevant risk factors.

The incidence of second cancers in individuals is elevated by several known and unknown mechanisms, including common aetiological factors and predispositions, and influenced by possible biases in the ascertainment of second cancers in the cancer registries. The net direction of these influences will mostly be in the direction of elevated occurrence of second cancers, against which a possible effect of sunlight and vitamin D (manifest through the occurrence of NMSC) could be difficult to detect with the type of cohort design that has been used in these studies and the lack of information on known risk factors in many of the studies.

9.4 Issues in interpreting ecological studies

9.4.1 Methodological problems

Ecological studies gave rise to the hypothesis that vitamin D is inversely associated with the risk of certain cancers. In 1941, Apperley reported an ecological analysis of cancer mortality in which the units of analysis were states in the USA and provinces in Canada. Skin cancer mortality was positively correlated with an index of solar radiation while total cancer mortality was negatively correlated with the index ($r = -0.626$). Almost forty years later, Garland and Garland (1980) reported that the mortality from colon cancer was highest in states of the USA that had the lowest levels of solar radiation and hypothesised that the association could be due to vitamin D.

Ecological studies have been useful for generating hypotheses about the potential effects of sunlight. Theobald Palm observed that rickets was uncommon in countries with abundant sunlight and in Britain was less common in rural parts of the country than in polluted cities and hypothesised that exposure to sunlight prevented the disease (Hardy 2003). Lancaster first observed that melanoma mortality was inversely related to latitude in Australia, New Zealand and the USA and hypothesised, correctly, that sunlight was a cause of melanoma, although he was unable to explain the anomaly in Europe whereby mortality was positively associated with latitude (Lancaster 1956).

Ecological studies have well known limitations with respect to making causal biological inferences. For example, some of the international ecological studies reviewed in section 9.3 found strong associations between per capita supplies of food items and constituents (e.g., dietary fat and calories from animal sources), which are reported by the Food and Agriculture Organization, and cancer mortality (Grant 2002b) and estimated incidence (Mohr *et al.,*2006, 2007), whereas in cohort studies in particular, few strong dietary associations with risk of cancer have been observed (World Cancer Research Fund/American Institute for Cancer Research 2007). Ecological studies together with studies showing that patients with skin cancer had increased risk of subsequent non-Hodgkin lymphoma led to the hypothesis that exposure to sunlight increases the risk of non-Hodgkin

lymphoma (McMichael and Giles, 1996), but several case-control studies that were initiated to test this hypothesis found either no association or an inverse association (see Chapter 16).

Ecological bias, which is also referred to as the ecological fallacy, is a major limitation of ecological studies. It occurs when associations for groups of individuals (e.g. countries) are not the same as those for individuals (Selvin 1958). In their ecological analyses, Apperley (1941) and Garland and Garland (1980) assessed the associations between average ambient solar radiation for each state or province and the corresponding average cancer mortality rates. Thus, every person in each state and province was assumed to have the same degree of exposure to solar radiation. These types of data, in which the joint distributions of exposure and outcome are unknown, are common to most ecological studies and can give rise to ecological bias if there is heterogeneity within the groups used in the analysis. The smaller the unit of analysis, the more homogenous it is likely to be, and the less chance there is for ecological bias. Thus, the studies in which the geographical groups were counties of the USA probably have less ecological bias than the international ecological studies.

Confounding is particularly problematic in ecological studies. In his analysis, Apperley (1941) considered the possibility that the association might be due to confounding attributable to greater availability of food such as green vegetables and raw foods in the southern regions of North America, but dismissed this as an explanation because cancer mortality rates in major cities, where, he speculated, availability of raw foodstuffs would be similar, showed a similar latitude gradient. Other potential confounders, such as physical activity (which was not known at the time to be associated with colorectal cancer), were not considered.

Many of the ecological studies controlled only for age, sex and race (usually by restriction). Others controlled for several possible confounding variables. The most comprehensive control was undertaken by Boscoe and Schymura (2006). Their model of cancer incidence and mortality in the USA included ecologic adjustment for age, poverty, income, smoking, exercise, alcohol, outdoor occupation, urban/rural residence and air quality. Unfortunately, even when confounders are measured accurately, ecological control for them might not reduce bias and a variable that does not confound an individual level exposure-outcome relationship may do so in an ecological analysis (Greenland and Morgenstern 1989).

Another source of potential bias is misclassification of exposure. Most investigators considered this possibility. For example, Garland and Garland (1980) analysed data separately for US states with and without major metropolitan areas on the grounds that in metropolitan areas, people would have less sun exposure because of indoor occupation and shading by buildings. Unlike in individual level studies, misclassification of exposures in ecological studies often biases the association away from the null (Brenner *et al.,*1992). This phenomenon is not well known by scientists as indicated by the statements of several authors of the ecological studies reviewed in this chapter that misclassification of exposure would have biased the associations between latitude or measures of UVB irradiance and cancer incidence or mortality towards the null (see, for example, Lefkowitz and Garland*.,* 1994). For some of the studies, estimated UVB irradiance was derived from a limited number of ground-based stations, with interpolation used to estimate UVB irradiance for wide areas. This can give rise to another source of ecological bias called “error propagation” in which faulty measurements are propagated and in which the estimates of exposure can be sensitive to the methods of interpolation (Portnov *et al.,*2006).

Incomplete ascertainment and misclassification of outcomes can bias associations, especially when the ascertainment varies systematically by the putative exposure. This is likely to be most problematic in studies that include resource poor countries.

In summary, ecological studies have many potential biases that affect the ability to draw conclusions from them about causality at the level of the individual person.

9.4.2 Validity of equating latitude to amounts of vitamin D synthesis

As discussed in detail in chapter 4, pre vitamin D is formed from 7-dehydrocholesterol when the skin is exposed to ultraviolet B radiation (MacLaughlin *et al.,*1982) and subsequently transformed to vitamin D by heat. Because latitude is inversely associated with terrestrial solar ultraviolet B irradiance (Diffey, 1991), latitude is also inversely associated with vitamin D synthesis.

Table 9.4 presents results of 11 studies that have examined the relationship between serum or plasma 25-hydroxyvitamin D and latitude; the results of one study were presented in two reports (Lips *et al.,*2006; Rizzoli *et al.,*2006). Studies were included if they included data from a range of latitudes. Studies from populations living at single latitudes were not included because of the likelihood that differences in measurement of 25-hydroxyvitamin D would render differences by latitude uninterpretable.

Few samples were population-based. The majority of studies involved women only, and most had elderly participants. In most studies, blood samples were taken in all seasons. In two studies (Lips *et al.,*2001; van der Mei, Ponsonby *et al.,*2007), more than one laboratory was used for the 25-hydroxyvitamin D assays, although the study by Lips *et al.,*(2001) used the same method for measurement of serum 25-hydroxyvitamin D. About half the studies adjusted for potential confounding variables such as age, sex, dietary vitamin D intake, use of supplements and BMI. Some additionally adjusted for personal sun exposure.

Within country studies

Within countries, there were generally inverse associations between latitude and mean 25-hydroxyvitamin D levels.

Within country studies in Europe

The mean values, adjusted for age and sex, were 20% lower in Scotland than in London and central and southwest England and Wales (Bates *et al.,*2003). A large cross-sectional survey in the UK (Hypponen *et al.,*2007) that included 7,437 white adults 45 years old found a significant north to south gradient in the prevalence of low vitamin D status, and this gradient was present for all seasons. In the winter, mean 25-hydroxyvitamin D concentrations were 17.04 ng/mL in south England and 14.6 ng/mL in Scotland. For the summer, these figures were 24.96 ng/mL and 20.36 ng/mL, respectively.

In France, a study found an increase in mean serum 25-hydroxyvitamin D levels from the north to the south of the country (Chapuy *et al.,*1997). The study was performed on a subsample of the SUI.VI.MAX randomised trial that tested health effects of antioxidant supplements. 1,569 adults 35 to 65 years old were selected from 15,000 healthy volunteers that were part of the trial. Volunteers that participated in the trial were healthier than the background French population of the same age (Hercberg, Preziosi *et al.,*1998), and no information was provided on how the subsample of 1,569 volunteers was selected for the vitamin D study. There is thus a high probability that the vitamin D status of these volunteers was higher than the average French population of same age.

In one study from northern Norway, latitude was not associated with 25-hydroxyvitamin D levels (Brustad, Alsaker *et al.,*2004).

Within country studies in the USA

In the Third National Health and Nutrition Examination Survey (NHANES III, 1988-94), blood samples were drawn during the summer in northern states and during the winter in southern states, making it impossible to compare serum 25-hydroxyvitamin D concentrations across latitudes (Looker *et al.,*2002).

A study was conducted in US patients with moderate and severe chronic kidney disease but not under dialysis (LaClair *et al.,*2005). No latitude gradient was found for serum 25-hydroxyvitamin D (from Illinois/Indiana to Florida). But these patients are known to have reduced capacity to produce vitamin D in the skin and to transform endogenous or exogenous vitamin D to 25-hydroxyvitamin D.

In the Health Professionals Follow-Up Study, the serum 25-hydroxyvitamin D level measured in 1,095 men somewhat varied with latitude, but after multivariate adjustment for potential predictors of vitamin D status, the south to north decrease was only 2.6 ng/mL for a difference in latitude of about 8 degrees (Giovannucci *et al.,* 2006b).

Serum 25-hydroxyvitamin D level was measured for 1,536 community-dwelling women of mean 71 (SD: 9) years of age between November 2003 and March 2004 (Holick *et al.,*2005). A weak, statistically non-significant association was seen between latitude and serum levels: Compared to women living below 35 degrees North, the prevalence of serum 25-hydroxyvitamin D below 30 ng/mL

was 11% (95% CI: -1%; 23%) higher for women living at ≥42 degrees latitude. Of note, the stepwise multivariate analysis reported by this study found eight variables significantly associated with vitamin D inadequacy: age (≥80 yr), race (non white), BMI (≥30 kg/m2), use of concomitant medicines known to affect vitamin D metabolism, use of vitamin D supplementation (≥ 10 µg daily), lack of exercise, absence of a previous discussion with a physician regarding the importance of vitamin D to bone health, and low education level. Latitudinal difference in areas of residence was not retained as a significant predictor of vitamin D status by this stepwise statistical process.

Within country studies in other countries

Strong inverse correlations between latitude and were seen in a study in Argentina (-0.81, p = 0.027) (Oliveri *et al.,*2004); this study did not control for any other variables.

A weak association was seen in an Australian study (van der Mei *et al.,*2007); in this study latitude explained only 3.9% of the variability in 25-hydroxyvitamin D levels, but season explained 16%. According to this study, a decrease of one degree in latitude would be associated with a 0.4 ng/mL change in mean serum hydroxyvitamin D level.

The mean 25-hydroxyvitamin D concentration was 17% higher in a sample of women from Hong Kong (22 N) than in a sample of women from Beijing (39 N) (Woo *et al.,*2008)

Studies involving several European countries

The three published international studies (van der Wielen *et al.,*1995; Lips *et al.,*2001; Lips *et al.,*2006) and one study performed within the context of this Report (see below) all reported positive correlations between 25-hydroxyvitamin D and latitude within Europe. The three published studies controlled for any potential confounding variables when examining the European data, and the study done within the context of this report controlled for age and sex.

Using blood samples drawn during the winter 1988-89 and a standard laboratory method for measurement of serum 25-hydroxyvitamin D level, the SENECA study (van der Wielen *et al.,*1995) found a south to north gradient in serum 25-hydroxyvitamin D concentrations, with levels in Nordic countries about two times higher than in Mediterranean countries. The higher vitamin D food supply in Nordic countries and the higher skin pigmentation in the south might account for this difference.

One large study assessed the serum 25-hydroxyvitamin D levels in women with osteoporosis (i.e., a bone mineral density below -2 Z-scores of female reference population 20-39 years old or two vertebral fractures) in 25 countries in 5 continents, using a standardised sampling method for patient inclusion and standardised laboratory essays (Lips *et al.,*2001). The mean age of these women was 66 years (SD = 7.1 years). The study found a strong south to north gradient in serum 25-hydroxyvitamin D levels of osteoporotic women living in Europe, with a 3.2 ng/mL mean increase in serum level per 10 degree-increase in latitude (Figure 9.2).

A systematic search of published articles reporting serum 25-hydroxyvitamin D levels in apparently healthy adult European populations was performed by members of the IARC Working Group on vitamin D and cancer (full methods and results are annexed to the report). Thirty-five studies were included in the analysis, representing 114 estimates of mean serum 25-hydroxyvitamin D derived from a total of 9,514 subjects 18 years old or more, including 1,887 males, 5,008 females, and 2,619 subjects of unknown sex. An increase in latitude was statistically significantly associated with an increase in serum 25-hydroxyvitamin D levels among subjects more than 65 years old (Figure 9.3). The analysis was adjusted for age and sex. Interactions between latitude, age and sex were assessed, and sensitivity analyses examined how inclusion or exclusion of the statistically most influential studies affected results. In younger subjects, no significant association with latitude was found. In subjects more than 65 years old, an increase in 10 degrees in latitude of residence was associated with an increase in mean serum 25-hydroxyvitamin D of 4.7 ng/mL, a figure quite close to the estimate of Lips *et al.,*(2001). Studies used various methods for measurement of serum 25-hydroxyvitamin D, but statistical variability introduced by utilisation of different methods could probably not explain the finding of a trend with increasing latitude.

One study found an inverse association between increasing latitude and mean serum 25-hydroxyvitamin D levels (Zitterman *et al.,*2006), and another found no association between latitude and mean serum 25-hydroxyvitamin D levels (Moan *et al.,*2007). These two studies had strong

limitations as they were not based on a systematic search of data in the literature, and included studies done in different continents, often including highly selected sub-populations (e.g., children, patients with a chronic condition) and with blood sampling sometimes done during summer. Thus results from these two studies were not interpretable.

9.4.3 Discussion of association between latitude and vitamin D status

It appears that national level surveys show higher mean serum 25-hydroxyvitamin D levels than at lower latitudes. The apparent contradiction is mainly observed in Europe between within and inter country latitude trends in serum 25-hydroxyvitamin D levels may be due to dietary habits in Europe that are known to be more homogeneous within than between countries (Slimani *et al.,*2002). Also, northern European countries are more inclined to fortify foods and recommend supplementation (see Chapter 6). Furthermore sun exposure habits differ between European populations: Northern populations who have lighter skin are usually more attracted by sunlight than more southern population who have darker skin and have less inclination for staying long in the sun (Peacey *et al.,*2006).

To explain the relationship between latitude and cancer burden in the USA, latitude has been viewed as a surrogate for exposure to solar ultraviolet-B radiation (UVB, 280-320 nm), and exposure to UVB has been equated to UVB-induced vitamin D synthesis in the skin (Holick, 1994). However, in the USA (and also in Australia), changes in serum levels according to latitude are quite small, and other variables are much better predictors of vitamin D status.

In Europe, mortality from breast, colorectal and prostate cancers follows a south to north gradient, with a peak in Denmark and then some decreases in Finland, Norway and Sweden (Table 9.5). The positive association found in the USA between mortality of these cancers and latitude is in fact inverted in Europe.

Therefore, causal inference from ecological studies on associations between sun exposure and cancer risk should be considered with great caution.

A number of physical and behavioural factors complicate the relationship between latitude (or UVB irradiance) and serum vitamin D levels. Season of the year, variations in stratospheric ozone, atmospheric aerosols and pollution, cloud cover, surface reflection and altitude all influence terrestrial ultraviolet B irradiance (Diffey 1991; International Agency for Research on Cancer 1992). All of the studies reviewed here used latitude rather than measured or modelled UVB irradiance.

People's exposure to ambient ultraviolet B radiation is influenced by the time that they spend outdoors, including the time of day, their clothing habits and use of sunscreen while outdoors, and particularly for people living at higher latitudes, holidays in sunny places. Because skin pigmentation strongly influences the skin's ability to synthesise vitamin D (Clemens *et al.,*1982 a), any differences in skin pigmentation by latitude would confound relationships between latitude and vitamin D levels. This has been suggested as one possible explanation for the positive association between 25-hydroxyvitamin D concentration and latitude in Europe. Use of sunbeds has also shown to be associated with 25-hydroxyvitamin D concentrations, presumably because of the small amount of UVB emitted by the lamps, and sunbed use may vary with latitude (IARC, 2007).

Finally, high dietary intakes of foods rich in vitamin D (particularly fatty fish and fish oils), fortification of foods with vitamin D and use of vitamin D supplements may also confound associations between latitude and serum vitamin D levels. In one study in Europe, dietary intake of vitamin D and use of supplements was much higher in northern Europe than southern Europe.

9.4.4 Alternatives to vitamin D synthesis

If results from ecological studies in the USA (but not in Europe) suggest that latitude is correlated with increased risk of colorectal cancer, and possibly of other cancers as well, it is not certain whether any protective effect of sunlight is mediated by vitamin D.

First, latitude could be associated with changes in factors other than solar irradiance. For instance, dietary patterns are known to be different in sunny and less sunny areas. Outdoor activities and physical activities could be higher in sunnier areas, and greater physical activity is a known

protective factor for many cancers, and colorectal cancer in particular. Overweight and obesity could be more prevalent in northern than in southern areas.

Second, potential effects of sun exposure might not be mediated by vitamin D. Observational studies of vitamin D and cancer are unlikely to provide definitive evidence because in many populations, sun exposure is the predominant source of vitamin D. Sunlight has a number of important systemic biological effects besides synthesis of vitamin D. These include immune suppression and regulation of circadian rhythms.

Melatonin

Visible light, transmitted through the eye, regulates the circadian rhythm in humans. Prospective cohort studies have found an inverse association between serum melatonin levels and the risk of breast cancer in postmenopausal women (Schenhammer *et al.,*2008). On the basis of "limited evidence in humans for the carcinogenicity of shift-work that involves night work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)", an IARC Working Group concluded that "shift-work that involves circadian disruption is probably carcinogenic to humans" (Straif *et al.,*2007).

Melatonin is a neurohormone produced by the pineal gland and regulated by the light-induced circadian mechanism. Its action spectrum lies in the blue region of visible light (446-477 nm) (Brainard *et al.,*2001). Suppression of melatonin production by exposure to light during the daily dark period has been proposed as a potential mechanism for the probable carcinogenic effect of shift work (Straif *et al.,*2007).

One study of melatonin and latitude was identified (Wetterberg *et al.,*1999). These authors conducted a study of 321 normal subjects from 19 medical centres in 14 countries. Overnight urine samples were collected on a monthly basis for 12 to 16 months. Melatonin was measured by radioimmunoassay and the values averaged for each subject. Urinary melatonin was positively correlated with latitude ($r = 0.20$, $p < 0.001$).

There are insufficient data to determine whether any effect of exposure to ambient sunlight on cancer risk may be mediated by melatonin. The only epidemiological study conducted across various latitudes suggests that people at higher latitudes have higher melatonin levels, which is not consistent with the hypothesis that night shift work increases the risk of cancer by suppressing melatonin production.

Seasonal affective disorder

Seasonal affective disorder is the term given to depressive symptoms that occur in winter but not other seasons. It appears to be most common in populations living at high northern latitudes and people with the condition respond favourably to daylight or bright light therapy (Magnusson and Partonen 2005).

Oerlemans *et al.,* conducted a systematic review and meta-analysis of 13 cohort studies of depression and subsequent risk of cancer (Oerlemans *et al.,*2007). None of the cohort studies included examined seasonal affective disorder and risk of cancer. The pooled relative risks were 1.12 (95% CI 0.99–1.26) for all cancer, 1.59 (0.74–3.44) for breast cancer, 1.37 (0.88–2.16) for lung cancer and 1.60 (0.40–6.50) for prostate cancer. There were insufficient data to examine colon cancer. Although the point estimates were elevated for some cancer sites, the overall evidence that depression is associated with an increased risk of subsequent cancer is weak.

Immunological effects

A plethora of immunologic mechanisms are involved in cancer control, and inflammatory processes change the course of cancer progression. UVB can influence immune response a local (skin) or systemic level, and also influences inflammatory processes (Norval, 2006; IARC, 2007). In this respect, in the USA, changes in UVB irradiance with latitude could account for latitudinal variations in the risk to die from some cancers.

Degradation of folic acid by UVB

Folic acid (also termed "folates") and its derivates act as methyl donors, and among other things, are necessary for the biochemical formation of thymidine, one of the four bases in DNA, and folic acid derivates are therefore an essential factor in DNA replication and cell division. Pharmacological agents counteracting the metabolic action of folic acid derivates such as metothrexate, are used as anticancer agents in clinical practice. The most common folate derivative in the human body, 5-methyltetrahydrofolate, is UV sensitive (Steindhal *et al.,*2007). The birth rate of children with neural tube defects, a disease closely related to dietary folate deficiency, varies with season. A proposed mechanism of this seasonality is UV induced folate degradation taking place in blood vessels situated in the dermis. It has thus also been proposed that the observed seasonal variation in survival rate of several types of cancer is due to photodegradation of folate by sun exposure (Steindahl *et al.,*2007), and also that folate deficiency could be associated with higher risk of cancer (Fairfield, 2002).

9.5 Conclusions of the Working Group on ecological studies

9.5.1 Studies on latitude and sun irradiance

The Working Group concluded that on the basis of methodological considerations alone, no cause-effect relationship could be made between latitude of residence and risk of being diagnosed with or dying from cancer

Studies in Europe, including a systematic review of these studies done by the Working Group showed a positive correlation between increasing latitude and increasing serum 25-hydroxyvitamin D levels. No similar systematic review has been done in other parts of the world.

Increasing latitude should not automatically be equated with decreasing vitamin D status, and the exposure to a number of cancer risk factors is known to vary with latitude.

9.5.2 Studies on second primary cancer after non-melanoma skin cancer (NMSC)

The Working Group considered that the overall body of evidence does not support the specific hypotheses of reduced prostate or colorectal cancer rates in subjects diagnosed with BCC or SCC.

The Working Group considered that the outlying and inconsistent observations from a minority of studies are plausibly attributable to chance or bias

Table 9.1 - Meta-analysis of eight studies on prostate cancer

	Observed	Expected	SIR	95 % CI	
				Lower bound	Upper bound
De Vries 2007	253	291	0.87	0.77	0.98
Milan 2000	1121	918.9	1.22	1.15	1.29
Levi 1998	155	142.2	1.09	0.93	1.28
Friedman 2000	108	98.2	1.1	0.9	1.4
Bower 2000	177	207.8	0.85	0.73	0.99
Maitra 2005	389	385.6	1.01	0.91	1.11
Levi 1997	74	64.8	1.14	0.9	1.43
Frisch 1995	49	61.3	0.8	0.59	1.06
Combined	2326	2169.6	1.07	1.03	1.12

Table 9.2 - Meta-analysis of 11 studies on cancer of all sites excluded NMSC

	Observed	Expected	SIR	95 % CI	
				Lower bound	Upper bound
Nugent 05	5944	5519.4	1.08	1.05	1.1
Frisch 95	562	432.3	1.3	1.19	1.41
Hemminki 2000	2391	1928.1	1.24	1.19	1.29
Levi 97	384	397.2	0.97	0.87	1.07
Efird 02	144	102.9	1.4	1.18	1.65
Frisch 96	3118	2711.3	1.15	1.11	1.19
Bower 2000	789	876.7	0.9	0.84	0.97
Milan 2000	9471	58.8	1.19	1.17	1.21
Lindeloff 91	282	189	1.49	1.32	1.68
Levi 98	975	1059	0.92	0.86	0.98
Friedman 2000	556	463.3	1.2	1.1	1.4
Combined	23458	19833.1	1.18	1.17	1.2

Table 9.3 - Meta-analysis of 10 studies on lung cancer

	Observed	Expected	SIR	95 % CI	
				Lower bound	Upper bound
Nugent 05	909	795.3	1.14	1.07	1.22
Frisch 95	113	66.5	1.7	1.4	2.04
Hemminki 2000	243	150.1	1.62	1.42	1.84
Levi 97	62	48.8	1.27	0.97	1.63
Efird 02	17	11.3	1.5	0.87	2.4
Frisch 96	589	420.7	1.4	1.29	1.52
Bower 2000	276	277.9	0.99	0.88	1.12
Milan 2000	1261	1125.9	1.12	1.06	1.18
Levi 98	128	139.1	0.92	0.77	1.09
Friedman 2000	72	51.4	1.4	1.1	1.76
Combined	3670	3087.1	1.19	1.15	1.23

Table 9.4 - Associations between latitude and circulating 25-hydroxyvitamin D concentration.

	Country	Participants			Season of blood draw	Measurement method	Adjust-ment	Results
		Sex	Age	Other				
(van der Wielen, Lowik *et al.,*1995)	11 European countries	414 men and 410 women	Elderly	Random samples	Winter	Competitive protein binding assay	None	Positive correlation between 25-hydroxyvitamin D and latitude [no estimates given, but paper has the data to do this].
(Lips, Duong *et al.,*2001)	25 countries, from 70 N to 43 S)	7564 women	Post-menopausal	Baseline data from participants in RCT for osteoporosis	All	RIA (INCSTAR Corp., Stillwater, MN); 2 labs, 1 Europe, 1 USA	None	Mean level, 70.8 (SD 30.9) nmol/L. "Serum 25-hydroxyvitamin D did not show a significant correlation with latitude on a global scale." Europe, r=0.65 (p<0.001). [note – the paper gives the data to calculate correlation with latitude]
(Lips, Hosking *et al.,*2006)	18 countries (latitudes 64 N to 3 N and 31-37 S)	2589 women	41-96	Recruited from outpatient practices, being treated for osteoporosis	All	Chemiluminescent assay (Nichols Institute Diagnostics, San Clemente, CA); one laboratory	None (for non-equatorial countries, winter and summer means presented separately)	Mean 25-hydroxyvitamin D 26.8 ng/mL. Within Europe, the mean 25-hydroxyvitamin D was positively associated with latitude. The means were lowest in the middle east. Equatorial countries had high means (although no higher than Sweden).
(Rizzoli, Eisman *et al.,*2006) [same study as Lips *et al.,*2006]	18 countries (latitudes 64 N to 3 N and 31-37 S)						Race (Asian, other, white), BMI, inadequate vitamin D supplement, general health, no discussion with doctor about vitamin D, difficulty tanning, no recent travel to sunny area	Mean 25-hydroxyvitamin D = 67.0 nmol/L. Odds ratio for 25-hydroxyvitamin D < 75 nmol/L, non-equatorial countries versus equatorial countries, 3.5 (2.8-4.6).
(Chapuy, Preziosi *et al.,*1997)	France (43 – 51 ° N)	765 men, 804 women	men 45–65; women 35–60	Randomly selected from 20 cities	Autumn-Spring (November to April)	RIA (Incstar Corp, Stillwater, MN); serum	None – age and sex not associated with 25-hydroxyvitamin D	Correlation with latitude, r = -0.79; p = 0.01. Mean 25-hydroxyvitamin D varied from 43 (SD 21) in the north to 94 (SD 38) in the southwest.
(Jacques, Felson *et al.,*1997)	USA	290 men and 469 women	67-95	Framingham heart study cohort	All	Competitive protein-binding assay	Sex, age, dietary vitamin D intake, supplemental vitamin D use,	Regression coefficients (nmol/L) for residing in Florida, California or Arizona for >= 3 months/year, by season of blood draw

							time spent outdoors, BMI, serum creatinine	Summer: 6.6 (SE 5.1 p = 0.20), autumn: 12.7 (SE 5.4 p = 0.02), winter 45.4 (SE 26.8 p = 0.10), spring 9.8 (SE 4.8 p= 0.05)
(Bates, Carter *et al.*,2003)	UK	773 men and women (180 in institutions)	65+	Nationally representative sample	All	RIA (DiaSorin, Minnesota, USA)	Age and sex	Adjusted mean values (nmol/L): Scotland 43.5, Northern England 45.2, Central & southwest England and Wales 51.9, London 52.1 (p =0.0004) [calcium intake was positively associated with 25-hydroxyvitamin D and was higher in the south than the north]
(Brustad, Alsaker *et al.*,2004)	Northern Norway (65- 71 N)	443 women	44-59	Random sample of participants in a cohort study	Late autumn to early summer	HPLC	Age, BMI, dietary vitamin d intake, vitamin D supplement use, resided in northern Norway during previous summer, hours in daylight week before blood draw, season, sun holiday, solarium use	Regression of log(25-hydroxyvitamin D). regression coefficient for latitude 0.007 p = 0.60 [limited latitude range]
(Oliveri, Plantalech *et al.*,2004)	Argentina, 7 cities (26º S to 55 º S)	226 women and 113 men; mostly Caucasian	65+	Living at home; relatives or guardians of patients attending hospitals or subjects included in hospital preventive programs	Mid August – mid October (late winter-early spring)	RIA-IDS	None	Mean serum 25-hydroxyvitamin D values (ng/mL) were: 20.7 (SD 7.4) in the north (26, 27 º), 17.2 (8.2) mid (33 and 34 º S), 14.2 (5.6) south (41+ º S) (p<0.001). correlation with latitude, -0.81, p = 0.027. calcium intake varied little by latitude
(Holick, Siris *et al.*,2005)	USA	1536 women	55+	Receiving osteoporosis medication	Autumn-early spring	Chemiluminescent assay (Nichols Institute Diagnostics, San Clemente, CA)	None	Odds ratio for 25-hydroxyvitamin D < 30 ng/mL. Latitude ≥ 42º N 0.89 (CI 0.77, 1.01), 35-42 º N, 0.97 (CI 0.85, 1.09) vs < 35 º N. Latitude not significant in multivariate model [results not given].
(van der Mei, Ponsonby *et al.*,2007)	Australia Tasmania 43 º S, Geelong 38 º S, southeast Queensland 27 º S)	1160 women and 509 men. 99% white	< 60	Population based samples	All	RIA (DiaSorin, Stillwater, MN, USA); different labs for each study centre	None; analyses restricted to women	Regression analysis of square root transformed 25-hydroxyvitamin D - mean 25-hydroxyvitamin D decreased by 1.0 nmol/L (CI 0.7–1.3) per degree of latitude, R2 = 3.9%. "Latitude remained significant after taking season into account (p<0.01)." For this model, R2 = 16.1%. The crude prevalence of 25-hydroxyvitamin D < 50 nmol/L was higher in Geelong than in Queensland. [use of different laboratories in the three centres may have affected the latitude gradient]
(Woo *et al.*,2008)	China, Hong Kong (22 N) and Beijing (39 N)	441 women	20–35	Recruited using flyers and mail-outs	February to May	RIA kit (DiaSorin Inc., Stillwater, MN, USA	None	Overall mean 32 nmol/L. Beijing had a lower mean (34 v. 29 nmol/L; P<0·001. Mean dietary Ca intake was higher in Beijing than Hong Kong (506 v. 448 mg/d; P<0·001) but vitamin D intake was higher in Hong Kong (3·4 v. 0·9μg/d; P<0·001)

Table 9.5 – Mortality from prostate, colorectal and breast cancer in Western, Southern and Northern European countries in 2002*

Country	Males		Females	
	Prostate	Colon and rectum	Colon and rectum	Breast
Iceland	23.0	12.8	13.2	19.6
Finland	18.0	11.5	9.8	17.4
Norway	28.4	20.1	16.8	17.9
Sweden	27.7	14.9	11.1	17.3
Denmark	22.6	23.3	19.2	27.8
United Kingdom	17.9	17.5	12.4	24.3
Ireland	19.7	23.6	13.7	25.5
The Netherlands	19.7	18.9	14.4	27.5
Germany	15.8	19.9	15.7	21.6
Belgium	20.3	18.7	14.1	27.7
Luxembourg	15.6	18.6	13.4	19.3
Austria	18.4	20.1	13.9	20.6
Switzerland	21.6	15.2	9.7	19.8
France	18.2	18.2	11.8	21.5
Italy	12.2	16.5	10.9	18.9
Spain	14.9	18.5	11.3	15.9
Greece	11.2	9.7	8.0	15.4

*Age Standardised mortality Rates (ASR), World Population Standard, Data source: Globocan 2002 (Ferlay *et al.*,2004).

Figure 9.1 – Relationship between mean serum 25-hydroxyvitamin D concentration and northern latitude in Europe in post-menopausal osteoporotic women. The relationship was very significant ($P < 0.001$). (Lips *et al.*, A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab. 2001;86:1212-21. Copyright 2001, The Endocrine Society.).

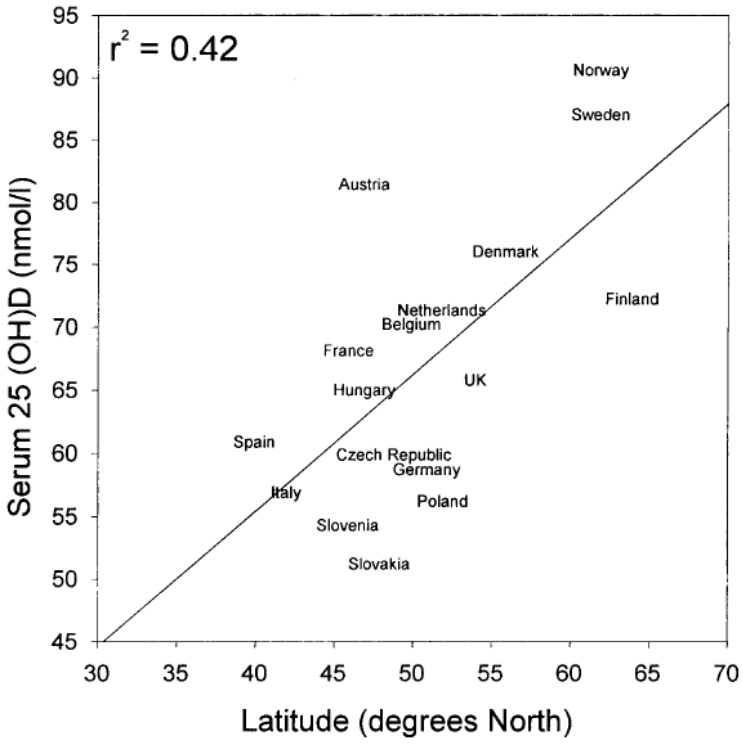
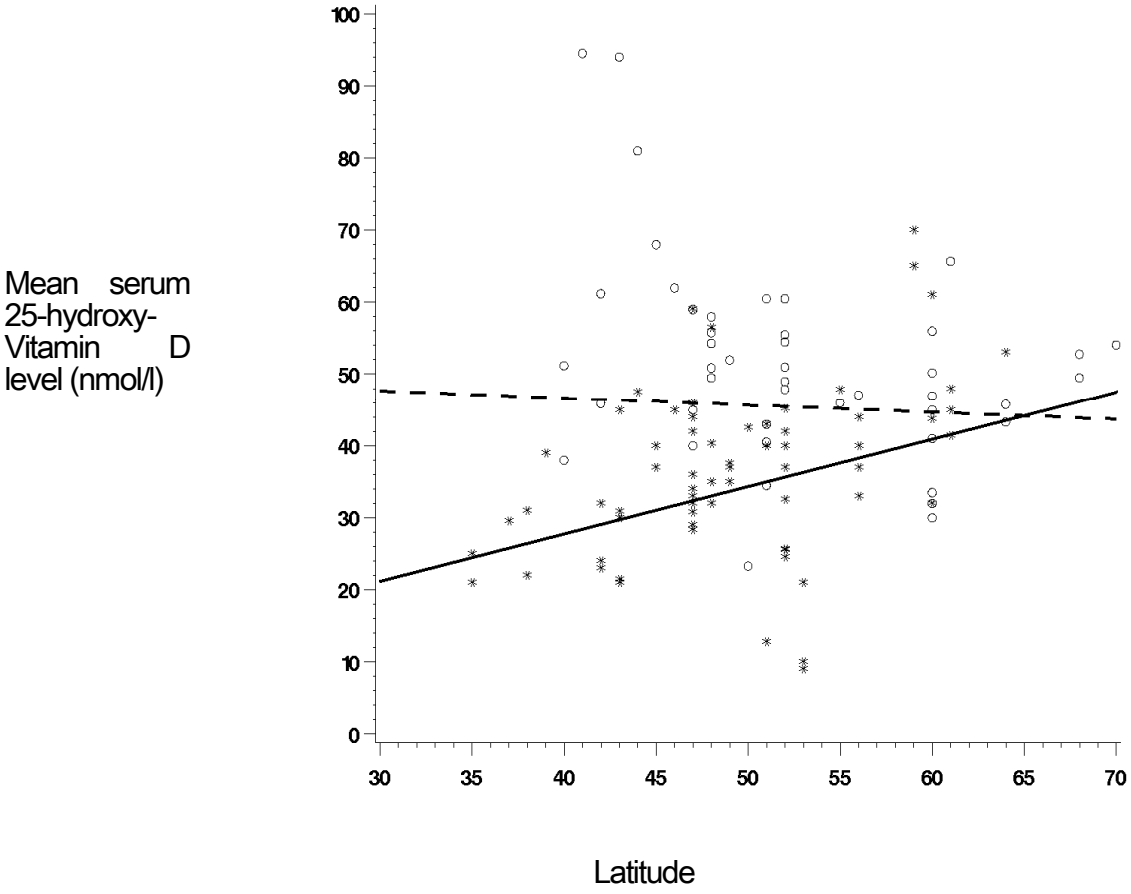


Figure 9.2 - Latitude and observed mean serum 25-hydroxyvitamin D level observed in European populations, totalling 114 studies including 9,514 subjects. Circles and dashed trend line represent values measured and predicted for populations with an average age lower or equal to 65 years. Stars and plain trend line represent values measured and predicted for populations with an average age greater than 65 years. The 3 outliers having levels greater than 80 nmol/l tend to lift-up the low latitude end of the trend line of younger subjects: two points from Chapuy (2007) and one point from D'Amore study (1984).



Chapter 10 – Observational studies on individual sun exposure and cancer

10.1 Background and objective of the chapter

Self-reported sun exposure or surrogates such as region of residence or sunburn history can be used in epidemiology studies. A number of ecologic studies have examined the vitamin D and cancer hypothesis at the population level by assuming that latitude of residence or sun exposure were surrogate measures for vitamin D status. These approaches were reviewed and commented on in chapter 9.

This chapter summarises and comments on the main study results on sun exposure and cancer assessed at an individual level. Studies reviewed in this chapter are summarised in Tables 10.1 and 10.2. This chapter does not address the association between sun exposure and skin cancer risk (see Chapter 3) or non-Hodgkin lymphoma (see Chapter 15).

10.2 Case-control studies

Kampman *et al.,*(2000) conducted a case control study on colon cancer and sun exposure in the Kaiser Permanente Medical Care Program of California, Utah and Minnesota (USA). Data was collected by a personal interview in 1,993 cases and 2,412 controls. Sun exposure was defined as the average number of hours per week spent outside in daylight. A logistic regression was conducted adjusting for age, body mass index, family history of colorectal cancer in first-degree relatives, lifetime vigorous physical activity, total energy intake, dietary fibre, and regular use of aspirin or non-steroidal anti-inflammatory drugs. Compared to the lowest quintile of exposure, the highest category of sun exposure had an OR of 0.9 (95% CI: 0.7-1.1) for men and 1.0 (95% CI: 0.8-1.4) for women.

A hospital-based case control study in the UK compared the sun exposure history of 210 histologically confirmed prostate cancer cases and 155 hospital controls diagnosed with a benign prostatic hypertrophy (Luscombe, Fryer *et al.,*2001). Recent sun exposure and sun exposure during childhood were recorded in a detailed questionnaire that was developed for skin cancer studies (Harvey *et al.,*1996). The risk of prostate cancer associated with each additional week of cumulative exposure was 0.998 (95% CI, 0.997-0.999). The decrease in prostate cancer risk was stronger for acute sun exposure such as a history of sunburn in childhood with an OR= 0.18 (95% CI: 0.08-0.38). This study was repeated in the 2001-2002 period and obtained similar results (Bodiwala *et al.,*2003b).

Bodiwala *et al.,*(2003a) made a pooled analysis of two hospital-based case control studies on prostate cancer conducted between 1999 and 2002 in the UK. The study included 453 cases and 312 controls that were men with benign prostatic hypertrophy (BPH) diagnosed in the same hospital. The analysis was based on a recursive partitioning of prostate cases and BPH according to various sun exposure measures: sunbathing, childhood sunburn and cumulative exposure. This created a "decision tree" made of a classification of branches with different proportions of cases and controls according to a series of nodes defined by exposure measurements. Age-adjusted logistic regression was later performed on the partitions identified. Another logistic regression was also done from the mean hours of cumulative exposure per year and occurrence of childhood sunburn. A significant decrease in prostate cancer risk was observed per 1 hour increase of sun exposure per year (OR=0.999; 95% CI: 0.999-1.000). A reduced risk of prostate cancer was also observed for having experienced childhood sunburn (OR=0.37; 95% CI: 0.24-0.56). Recursive partitioning identified significant associations of case-status with a number of sun exposure variables (sunbathing, childhood sunburn, cumulative exposure per year, and holidays abroad in a hot climate). [The Working Group considered that the analysis performed in this article could not provide a reliable risk estimate with appropriate confidence intervals. Indeed, the recursive partitioning method selects the "best" cut-off points that fit to the data. This selection should have been confirmed by either a bootstrap, or an analysis of independent test samples using cut-off points found during recursive partitioning. We suspect that another dataset could have given another selection of variables. The final logistic regression was based on a data driven selection of variables and cut-points, and confidence intervals could not be considered to account for the real variability. The Working Group noticed that this study was a reanalysis and thus not independent of two published studies: Luscombe, Fryer *et al.,*2001; and Bodiwala *et al.,*2003b.]

A large death certificate based case-control study examined associations between mortality from breast, ovarian, colon and prostate cancers, with residential and occupational exposure to sunlight (Freedman *et al.,*2002). Sun exposure based on residence was estimated from the state of residence and state of death, with states grouped into 3 categories according to data from the US Weather Bureau. Occupational exposure was estimated by an industrial hygienist from occupation mentioned on the death certificate and grouped into four categories. The cases consisted of all deaths from these cancers between 1984 and 1995 in 24 states of the United States. The controls were subjects who died from causes other than cancer and were age frequency matched to a series of cases. Occupation was extracted from the death certificate, socio-economic status and physical activity were based on occupation and sun exposure assessment was based on occupation and residence. Residential exposure to sunlight was negatively and significantly associated with mortality from female breast, ovarian, prostate, and colon cancer. Only female breast and colon cancer showed significant negative associations with jobs with the highest occupational exposure to sunlight OR= 0.82 (95% CI: 0.70-0.97) for female breast cancer, and OR= 0.90 (95% CI: 0.86-0.94) for colon cancer. For both cancers, the negative association with occupational sunlight was greatest in the geographical region of highest exposure to sunlight and was independent of occupational physical activity.

A population-based case-control study in San Francisco, USA, examined past exposure in men 40-79 years old diagnosed with advanced prostate cancer identified in the SEER cancer registry (John *et al.,*2005). Sun exposure was investigated in 450 cases and 455 controls using a questionnaire inquiring about past places of residence matched with information on the area-specific solar radiation from the National Weather Services Stations. A "sun exposure index" was used in the analysis and defined as the relative difference between constitutive and facultative skin pigmentation; this measure reflects cumulative lifetime exposure and requires skin reflectance spectroscopy measurements (Lock-Andersen *et al.,*1998). No association was observed between risk of prostate cancer and solar radiation by state of birth (p=0.9), duration of residence in states with low solar radiation (p=0.7), lifetime outdoor activities (p=0.8) or occupation (p=0.3). A significant decrease in prostate cancer risk was observed when comparing the high versus low index of sun exposure: OR=0.51 (95% CI: 0.33-0.80).

A population-based case control study in Ontario, Canada, made telephone interviews in 610 breast cancer cases randomly selected from the Ontario cancer registry and 1,135 controls (Knight *et al.,*2007). Sun exposure was assessed using a questionnaire on outdoor occupation activities, outdoor activities and outdoor exposure in summer, as well as sun protection habits. Information on breast cancer risk factors was also collected. The OR was 0.61 (95% CI 0.46-0.80) for outdoor occupation for more than 1 year at ages 10 to 19 years as compared to those never having had an outdoor job. A significant dose-response was also observed when considering outdoor activity episodes in summer ($p<0.0006$). However, these risk reductions were weaker for exposures between ages 20 to 29; and 45 to 54 years. When analyzing the association between outdoor activities and cancer, and stratifying for intensity of outdoor activity and age, the more important factor was age at exposure and not the intensity of exposure. [The Working Group noticed that the authors presented stratified results for age and intensity of exposure. Overall 115 statistical tests were reported without any adjustment for multiple testing. However, because of the high proportion of risk estimates being protective, the observed decrease of breast cancer risk associated with outdoor exposures can be considered as relatively reliable.]

10.3 Cohort studies

An analysis of breast cancer risk according to geographical place of residence was done in the Nurse's Health Study, USA (Laden *et al.,*1997). Between 1976 and 1992, 3,603 breast cancer cases were diagnosed among the 118,349 participating nurses. No baseline sun exposure was recorded, and only place of residence could serve as a comparison between nurses. A multivariate analysis was conducted to adjust for age, age at menarche, parity, age at first birth, use of oral contraceptive, menopausal status, use and duration of postmenopausal hormones, family history of breast cancer, personal history of benign breast disease and body mass index. When compared to southern states, a non-significant increase in breast cancer risk was observed for residents in the Midwest (RR=1.03; 95% CI: 0.91-1.17), Northeast (RR=1.05; 95% CI: 0.94-1.17), and California (RR=1.13; 95% CI: 0.99-1.29).

John *et al.,*(1999, 2004, 2007a, 2007b) investigated the potential association between sun exposure and breast and prostate cancer in the National Health and Nutrition Examination Survey I

(NHANES I) Epidemiologic Follow-up Study. This cohort consists of 5,811 men and 8,596 women aged 25-74 years, recruited between 1971 and 1975. They were contacted again and interviewed from 1992-1984, 1986-1987 and in 1992 with questions about health outcomes including breast and prostate cancer. Medical records were obtained for each individual and death certificates collected for participants found deceased during follow-up. After some exclusion such as missing follow-up information, prevalent breast cancer cases or non-white participants, the analysis cohort was based on 3,414 white men and 5,009 white women. Among this population, 191 breast cancer and 153 prostate cancers occurred during follow-up. Some cancer cases were obtained from death certificates, 14 breast and 33 prostate cancers. The analytic cohort also included self-reported cancers which were considered as sufficiently reliable (Bergmann *et al.,*1998). Usual sunlight exposure and residential sunlight exposure were recorded, asking proxy responders when subjects were dead. Analyses were based on a Cox proportional hazards regression adjusting for age, family history, fat intake and calcium intake for the analysis on prostate cancer; and adjusting for age, education, age at menarche, age at menopause, body mass index, alcohol consumption frequency and physical activity for the analysis on breast cancer. A decreased risk of prostate cancer was observed for individuals living in southern areas as compared to northeastern regions, RR= 0.68 (95% CI 0.41-1.13). The RR was 0.49 (95% CI 0.30-0.79) for the comparison of high solar radiation to low solar radiation at place of birth. For breast cancer, a non-significant decrease in risk was observed for recreational or occupational high sun exposure compared to low sun exposure, RR=0.67 (95% CI 0.42-1.06). This association was also observed, even if not significant, for region of residence: the comparison between south to northeast regions provided a RR of 0.71 (95% CI 0.44-1.09). Overall, the authors concluded that sun exposure during early life protects against prostate cancer (John, Koo *et al.,*2007). [Although organised within a cohort, this study more resembled a case-control study with a retrospective assessment of exposure. Bias may have been introduced by the self-reporting of prostate cancer and the use of proxy responders.]

Chen *et al.,*(2008) conducted an analysis of the risk of second cancer following a diagnosis of non-melanoma skin cancer in Maryland, USA. The CLUE (Give Us a Clue to Cancer and Heart Disease) II cohort study was composed of 32,894 participants recruited in 1989 followed by record linkage in the Maryland cancer registry. Among the 32,894 participants, 19,174 individuals with sufficient information on key variables of interest, no personal history of cancer and aged 25 years or more in 1989, were included in the analytic cohort. 769 individuals developed a non-melanoma skin cancer during follow-up, among which 181 developed a second cancer. The control groups consisted of the remaining cohort of 18,405 individuals among which 2,156 incident cancers occurred. The analysis was based on a Cox proportional hazard model adjusting for age, sex, body mass index, cigarette smoking status and year of education in 1989. A significant increased risk of a second cancer other than non-melanoma skin cancer was observed in the non-melanoma skin cancer patient cohort, RR= 1.99 (95% CI: 1.70-2.33). Analysis by site showed an increased risk for colorectal cancer RR=1.78 (95% CI: 1.12-2.82), breast cancer RR=1.64 (95% CI: 0.98-2.73), and prostate cancer RR=1.27 (95% CI: 0.88-1.82). [The Working Group noticed that whereas this study is a cohort study, the analysis strategy is similar to registry-based studies of second primaries as described in chapter 9. The cohort design in this study enabled an analysis of second primary risk adjusted for potential confounding factors. This adjustment does not remove all potential bias from that type of study.]

10.4 Discussion

Overall, case-control and cohort studies identified a protective effect of sun exposure on the risk of colon, breast, and prostate cancer. These protective effects are in line with some of the ecological studies (reported in chapter 9). Contrary to ecological studies, observational designs presented in this chapter are less sensitive to biases. In principle, confounding may be better controlled because typically more detailed information can be assessed on other covariates in analytic studies. In addition, the study population may be relatively homogenous, which may reduce the potential for residual or uncontrolled confounding that may not be captured by multivariate analysis. An advantage of these studies is the assessment of past sun exposures at points earlier in life, which for some cancers, may be more relevant than adult sun exposure. However, assessment of past sun exposure was indeed practically impossible when subjects were death at the moment of the assessment. An additional strength of such studies is that exposure is actually assessed for the individual, whereas in ecologic studies exposure is inferred for a whole population, when individuals' behaviours may be very different.

However, these studies remain limited. First, they do not directly assess vitamin D status, and some surrogates that have been used (such as sunburn) may represent acute short-term exposures to the sun rather than chronic exposure, the latter being more relevant for long term vitamin D status. In case-control studies, when assessing past exposures there may be measurement error and perhaps recall bias. Also, the assumption that sun exposure equates to vitamin D status is just a working hypothesis (See Chapter 9).

Second, geographical region of residence does not take into account the number of behaviours influencing the amounts of UVB actually received by individuals, such as sun protection, clothing habits and dress code, or sunlight avoidance (e.g., subjects always burning and never achieving a suntan) which can be a source of sun exposure misclassification.

Third, the studies summarised in this chapter are relatively sparse, and most of them explored the sun exposure-cancer relationship as a secondary intention and were thus not designed to investigate this association. This contrasts with the existence of hundreds of observational studies done around the world on sun exposure and cancer, mainly skin cancer. This means a publication bias should be suspected: other studies on individual sun exposure and non-skin cancer may exist, but these were not reported because of negative results.

Fourth, even if, in theory, case-control and cohort studies used individual measures of exposure, some studies, such as the NHANES I cohort were mainly recording place of residence, latitude and climatic difference, residential exposure, south vs. north, solar radiation at the longest residence, UV index, estimated ambient UV, and so on. Therefore, exposures were assessed for groups of cases and controls and in this respect, these so-called observational studies were not based on assessments of exposure at the individual level. These studies thus suffer from the same potential problems as described for ecological studies (See Chapter 9), and exposure assessment could just reflect exposure to a factor other than the sunlight that has a statistical distribution that follows a geographical pattern.

10.5 Conclusions

Published studies on sun exposure and cancer show limited evidence for an association between sun exposure and breast, colon and prostate cancer.

The existence of potential biases such as publication bias, lack of adjustment for confounders, improper measurement of sun exposure, and design issues specific to ecological studies could not be ruled out.

Table 10.1 - Case control studies on sun exposure and cancer (M=mortality; I=incidence; OR=Odds Ratio; 95% CI=95% Confidence Interval)

Author, year	Country	Cancer M/I	Case population	Control population	UV measure or proxy	OR (95% CI)	Adjustment for
Kampman, 2000	US	Colorectal, I, men	1993	2412	Sunshine exposure: high vs low.	0.9 (0.7-1.1)	Age, BMI, family history, physical activity, total energy intake, dietary fibre, use of aspirin or non-steroidal anti-inflammatory drugs
		Colorectal, I, women				1.0 (0.8-1.4)	
Luscombe, 2001	UK	Prostate, I	210	155	Chronic sun exposure.	0.998 (0.997-0.999)	Age
					History of sunburn in childhood.	0.18 (0.08-0.38)	
Freedman, 2002	US	Colon, M	153511	153502	Residence: high vs low exposure to sunlight, US Weather Bureau.	0.73* (0.71-0.74)	Age, sex, race, occupation, occupational physical activity, socio-economic status
		Prostate, M	97873	83421		0,90* (0,87-0,93)	
		Breast, M	130261	70081		0.74* (0.72-0.76)	
		Ovarian, M	39002	70081		0.84* (0.81-0.88)	
Bodiwala, 2003a	UK	Prostate, I	453	312	Increase of 1 hour of sun exposure per year.	0.999 (0.999-1.000	No adjustment but the analysis was based on recursive partitioning method [see comments in the text]
					Sunburn in childhood.	0.37 (0.24-0.56)	
John, 2005	US	Prostate, I	450	455	Lifetime outdoor activity: >19.9 h/wk vs <2.7h/wk	0.95 (0.62-1.45)	Age, family history
					Sun exposure index: high vs low	0.51 (0.33-0.80)	
Knight 2007	Canada	Breast, I	972	1135	Outdoor occupation for more than 1 year at ages 10 to 19 as compared to those never having had an outdoor job	0.61 (0.46-0.80)	Age, ethnicity, family history in first-degree relatives, ever breast-fed, education, age menarche, and age at first birth

Table 10.2 - Cohort studies on sun exposure and cancer (M=mortality; I=incidence; OR=Odds Ratio; 95% CI=95% Confidence Interval)

Author, year	Country	Cancer M/I	Population	Cancer occurrence	UV measure or proxy	RR (95% CI)	Adjustment for
Laden, 1997	USA, Nurses Health Study	Breast, I	118349	3603 diagnosed between 1976-1992	Place of residence in 1976, stratified into 4 regions reference: Southern states	Midwest: 1.03 (0.91-1.17) Northeast: 1.05 (0.94-1.17) California: 1.13 (0.99-1.29)	Age, age at menarche, parity, age at first birth, use of oral contraceptive, menopausal status, use and duration of postmenopausal hormones, family history of breast cancer, personal history of benign breast disease, and body mass index
John, 2004	USA, NHANES I	Prostate, I	3414 white men without history of prostate cancer	153 during follow-up	Place of residence: South vs North-east	0.68 (0.41-1.13)	Age, family history of prostate cancer, fat & calcium intake
					Solar radiation at longest residence: high vs low	0.62 (0.40-0.95)	
					Solar radiation at place of birth: high vs low	0.49 (0.30-0.79)	
		Breast, I	5009 white women without history of breast cancer	191 during follow-up	Recreational or occupational sun exposure: high vs low	0.67 (0.42-1.06)	Age, education, age at menarche, age at menopause, body mass index, frequency of alcohol consumption and physical activity
					Place of residence: South vs North-east	0.71 (0.44-1.09)	
Chen, 2008	US, CLUE II cohort	Second cancer other than non melanoma skin cancer, I	18405 individuals without skin cancer at baseline/ 769 individuals with skin cancer at baseline	2156 incident cancer in the control group/ 181 second cancer	Occurrence of second cancer	1.99 (1.70-2.33)	Age, sex, body mass index, cigarette smoking status, year of education in 1989
		Colorectal, I		231/21		1.78 (1.12-2.82)	
		Breast, I		345/16		1.64 (0.98-2.73)	
		Prostate, I		356/35		1.27 (0.88-1.82)	

Chapter 11 – Observational studies on dietary intakes of vitamin D and cancer

11.1 Background and methods

Most studies on vitamin D intakes and cancer have focused on the digestive tract, mainly the colon, rectum and colonic adenomas.

Observational research trying to detect a possible relation between vitamin D and gastro-intestinal cancers is hampered by the difficulties of measuring the exposure that encompasses the amounts of food eaten and quantity of vitamin D in each food item (See section 5.2). Many food composition databases do not include vitamin D and some databases do not report the origin of the estimates (Lamberg-Allardt, 2006). A second problem is that few foods contain vitamin D, and oily fish is a very important source. Oily fish is not eaten frequently, so food intake must be recorded for a longer period to obtain information about individual vitamin D intake. A third problem is the variability in concentrations of vitamin D in oily fish. Lu *et al.,*2007 found in farmed salmon only 25% of the vitamin D content present in wild salmon. Some countries fortify foods with vitamin D_2, for instance the USA and Canada. Other countries, like Finland fortify with vitamin D_3 (Lamberg-Allardt, 2006).

Therefore, studies on dietary vitamin D are vulnerable to errors in food intake assessment and to the uncertain reliability of vitamin D content of food items.

Absorption of vitamin D and metabolic action may be antagonised by other vitamins and nutrients, mainly vitamin A and the retinol compounds (Johansson and Melhus, 2001). Multivitamins are taken by millions of individuals and they contain vitamin A and retinol. To the best of our knowledge, only one observational study has taken this factor into account in their analysis of vitamin D intakes (Skinner *et al.,*2006).

Results of several observational studies are difficult to interpret, because they focus on supplements only (and not on other dietary sources), or the improper way results are reported, which is mainly a problem of older studies.

We performed a systematic search of observational studies on nutrition, diet and cancer with systematically using the MSEH term “vitamin D” in the search procedure.

11.2 Colonic adenomas and colorectal cancer (CRC)

Four case-control and nine cohort studies examined the relationship between vitamin D intake (sum of dietary vitamin D and supplement-intakes) and colonic adenomatous polyps (Table 11.1 and 11.2). When reported, we took results related to advanced adenoma (or large polyps), that are considered to be the true precursor lesions for CRC. Case-control studies provided no evidence for a decreased risk of adenoma with increasing vitamin D intakes. A significant protective effect of a high vitamin D intake against adenomas was found in one cohort study (Lieberman *et al.,*2003). A recent meta-analysis of observational studies found a borderline significant decrease (OR = 0.89, 95% CI: 0.78-1.02) in the risk of colorectal adenoma for the highest versus the lowest quintile of vitamin D intake, and although numbers were small, the association seemed stronger for advanced adenoma (Wei *et al*., 2008).

Of seven case-control studies, two had results compatible with a decrease in CRC risk with increasing vitamin D intakes (Pritchard *et al.,*1996; Marcus and Newcomb, 1998). One case-control study found a significantly reduced risk of colonic cancer with the highest vitamin D intake, but this association was restricted to males (Kampman *et al.,*2000).

Of twelve cohort studies, three found a significantly lower incidence of CRC in subjects with increasing high vitamin D intake (Garland *et al.,*1985; Kearney *et al.,*1996; McCullough *et al.,*2003) and one found lower incidence in males but not in females (Park *et al.,*2006). The study by Heilbrun *et al.,*(1985) was a letter to the editor that reported neither the method used for assessment of vitamin D intakes nor the estimated quantities of vitamin D intakes.

Of note, studies on colonic polyps or on colorectal cancer with results suggesting protective effect included subjects who tended to have high vitamin D intakes (often higher than 12 µg per day), while studies without evidence for a protective effect had quite low vitamin D intakes (often below 8 µg per

day). Also, case-control studies and cohort studies more often had results compatible with decreased adenoma or CRC risk with increasing calcium intakes. For instance, of the twelve cohort studies on CRC, six found a significant decrease with increasing calcium intakes, five found non-significant decreases and three found no association.

11.3 Other cancers of the digestive tract

A case-control study in an area of France with high incidence of oesophageal cancer found a non-significant lower risk of oesophageal cancer in the group with the highest intake of vitamin D (Launoy *et al.,*1998).

One report combined data from the Nurses' Health Study and the Health Professionals Follow-Up Study to examine total vitamin D intake (from diet and supplements) in relation to pancreatic cancer risk (Skinner *et al.,*2006, Table 11.2). This study found a linear inverse association, with a significant 41 percent reduction in risk comparing high (≥15 µg per day) to low total vitamin D intake (<3.75 µg per day), after adjustment for use of multivitamins.

11.4 Breast cancer

Two case-control studies (Levi *et al.,*2001; Abbas *et al.,*2007) and three cohort-studies (Shin *et al.,*2002; Robien *et al.,*2007; Lin *et al.,*2007) found data supporting a significant protective effect of a high vitamin D intake on breast cancer risk in pre-menopausal women, but not in post-menopausal women (Tables 11.1 and 11.2). All studies only included invasive breast cancers, but the Iowa Women's Health Study also included *in situ* cancer (Robien *et al.,*2007). In Abbas and Levi's studies, calcium intakes had no association with breast cancer risk. In the Women's Health Study (Lin *et al.,*2007) and in the Nurses Health Study (Shin *et al.,*2002), increasing calcium intakes was also protective against breast cancer in pre-menopausal women. In the Iowa Women's Health Study, no data on calcium intakes were reported and the borderline protective effect of vitamin intakes was confined to the *in situ* cancers (Robien *et al.,*2007).

A population based case- control study in Ontario, Canada of 972 breast cancer cases and 1,135 controls did not estimate vitamin D intakes but examined indicators related to vitamin D intakes and sun exposure, and found reduced risk with cod liver use, drinking of milk and hours of outdoor activities in the summer (Knight *et al.,*2007).

11.5 Prostate cancer

Two case-control studies (Bodiwala, Chan *et al.,*1998; Kristal *et al.,*2002) and one cohort-study (Park *et al.,*2007) did not support a role for vitamin D intake on prostate cancer risk.

11.6 Conclusions

Vitamin D intake, especially through diet, is measured with considerable error meaning results from observational studies on dietary vitamin D intakes and cancer is of low reliability. There is limited evidence suggesting that high intakes of foods containing vitamin D protect against colorectal cancer, but the number of studies is limited. Studies (including cohorts) on vitamin D intake and risk of breast and prostate cancer were generally negative. Too little data was available to examine the association between vitamin D intakes and other cancer sites (e.g., oesophagus, pancreas).

Table 11.1 - Case-control studies on vitamin D intake, and colonic polyps and cancer

First author	Year publication	Country	Study name or type of subjects	Sex	Participants	Total Vit D range of intake (µg/day)	Vit D intake category	Adjusted risk	95% CI	Trends in RR with increasing calcium intakes
Colonic adenomatous polyps §										
Neugut	1996	United States	Hospital based: Patients attending colonoscopy	Males	175 cases and 224 controls	-	Use of supplements versus no use	2	0.6-6.6	NR
				Females	122 cases and 281 controls	-		0.5	0.1-2.4	
Boutron	1996	France	Population-based	Males and females	208 subjects with large adenomas and 426 controls	<2.4 to >6.4	lowest	1.0	Ref.	No association
							2	1.3	0.7-2.4	
							3	1.1	0.6-2.0	
							4	1.2	0.6-2.4	
							highest	1.0	0.5-2.1	
Senesse	2006	France	Hospital based	Males and females	362 cases and 427 controls	<3 to >5.9	lowest	1.0	Ref.	NR
							2	1.0	0.7-1.4	
							3	0.8	0.5-1.2	
							highest	0.6	0.4-1.0	
Breuer-Katschinski	2001	Germany	Hospital-based	Males and females	182 subjects with polyps and 178 controls	Mean for all controls=4.2 (SD=3.0)	lowest	1.00	Ref.	No association
							2	1.18	0.61-2.30	
							3	0.67	0.33-1.38	
							4	0.94	0.47-1.88	
							highest	0.72	0.35-1.51	
Colorectal cancer										
Benito	1991	Spain	Hospital-based	Males and females	286 cases and 498 controls	Average intake of 1.06 to 1.27	lowest	1.00	Ref.	Increase
							2	1.27	NR	
							3	1.30	NR	
							highest	0.74	NR	
Peters	1992	USA	Population-based	Males and females	746 cases and 746 matched controls	<2.7 to >10.8	Increase in risk per quintile of 2.7 µg/day	1.08	0.97-1.20	Decrease
Ferraroni	1994	Italy	Hospital-based	Males and females	1,326 cases and 2,024 controls	<0.79 to >1.97	lowest	1.00	Ref.	No association
							2	1.11	0.89-1.39	
							3	0.99	0.78-1.24	
							4	1.11	0.88-1.40	
							highest	0.74	0.58-0.95	

Boutron	1996	France	Population-based	Males and females	171 cases and 426 controls	<2.4 to >6.4	lowest	1.0	Ref.	No association
							2	0.8	0.4-1.6	
							3	1.2	0.6-2.2	
							4	1.5	0.8-2.9	
							highest	0.8	0.4-1.6	
Pritchard	1996	Sweden	Hospital-based	Males and females	352 colon cancers and 512 controls	≤2.8 to ≥7	lowest	1.0	Ref.	No association
							2	0.8	0.5-1.2	
							3	0.9	0.6-1.4	
							highest	0.6	0.4-1.0	
					217 rectal cancers and 512 controls	≤2.8 to ≥7	lowest	1.0	Ref.	No association
							2	0.7	0.4-1.3	
							3	0.7	0.4-1.2	
							highest	0.5	0.3-0.9	
Marcus & Newcomb	1998	USA	Population-based	Males and females	348 colon cancer cases and 678 controls	<3.7 to ≥13.9	lowest	1.0	Ref.	Decrease
							2	0.8	0.5-1.2	
							3	0.8	0.5-1.3	
							4	0.6	0.4-0.9	
							highest	0.7	0.4-1.1	
					164 rectal cancer cases and 678 controls	<0.79 to >1.97	lowest	1.0	Ref.	Decrease
							2	0.7	0.4-1.3	
							3	1.2	0.7-2.1	
							4	0.6	0.3-1.1	
							highest	0.8	0.5-1.5	
Kampman	2000	United States	Hospital-based	Males	1,095 cases and 1,286 controls	3.6 to 11.2*	lowest	1.0	Ref.	Decrease
							2	1.4	1.1-1.8	
							3	1.1	0.8-1.4	
							4	1.1	0.8-1.5	
							highest	1.4	1.0-2.2	
				Females	888 cases and 1,114 controls	2.6 to 8.6*	lowest	1.0	Ref.	Decrease
							2	1.3	1.0-1.7	
							3	0.9	0.7-1.2	
							4	1.1	0.8-1.5	
							highest	1.0	0.8-1.4	
Breast Cancer										
Levi	2001	Switzerland	Population-based	Females, pre- and post-menopausal	289 cases and 442 controls	Median 1.0	Lowest	1.00	Ref.	
						Median1.9	2	1.06	0.68-1.64	
						Median 2.7	Highest	1.43	0.90-2.26	

Abbas	2007	Germany	Population-based	Females, premenopausal	278 premenopausal cases and 666 controls	<2 to ≥5	<2	1.0	Ref.
							2-<3.5	1.23	0.83-1.81
							3.5 - <5	0.85	0.50-1.44
							≥5	0.50	0.26-0.96
Oesophageal cancer									
Launoy	1998	France	Hospital-based	males	208 cases and 399 controls	<3 to >7	lowest	1	
							2	0.72	0.40-0.31
							3	0.61	0.29-1.28
							highest	0.70	0.32-1.54

NR: not reported

*The original report mentioned "mg of vitamin D intake per day, which was probably erroneous, and we corrected the units.

§ A study in Norway (Almedingen *et al.,*2001) was not included in the table, because of small numbers and serious design flaws

Table 11.2 - Prospective cohort studies on vitamin D intake and specific cancers

First author	Year publication	Country	Study name or subject selection	Sex	Participants	Average years of follow-up	No. cases	Total Vit D range of intake (µg/day)	Vit D intake category	Adjusted risk	95% CI	Trends in RR with increasing calcium intakes
Colonic adenomatous polyps (when reported, results for large polyps or advanced adenomas were selected)												
Kampman	1994	United States	Nurses' Health Study	Females	88,396	8	145 advanced adenomas	1.5 to 18.6	lowest	1.00	Ref.	No association
									2	1.47	NR	
									3	1.01	NR	
									4	0.89	NR	
									highest	1.67	NR	
			Health Professional Follow-up Study	Males	47,037	4	128 advanced adenomas	3 to 23.9	lowest	1	Ref.	No association
									2	1.04	NR	
									3	0.68	NR	
									4	1.02	NR	
									highest	0.85	NR	
Whelan	1999	United States	Hospital patients	Males and females	1,162	3	183 subjects with recurrent adenoma	Use of supplements	Use vs. no use	0.85	0.39-1.86	Decrease
Hartman	2005	United States	Polyp Prevention Trial	Males and females	1,905	4	125 large polyp recurrence	<3.4 to >11.7	lowest	1.00	Ref.	No association
									2	1.15	0.64-2.06	
									3	0.88	0.47-1.62	
									4	0.94	0.50-1.74	
									highest	1.34	0.76-2.39	

Kesse	2005	France	E3N cohort study	Females	100,000	7	175 subjects with high risk adenoma	<1.7 to >3.3	lowest 2 3 highest	1.00 1.24 1.24 1.00	Ref. 0.85-1.98 0.81-1.91 0.64-1.57	Decrease (NS)
Lieberman	2003	United States	Prospective study	Males and females	1,770	3	312 subjects with advanced adenoma	<4.5 to >16.7	lowest 2 3 4 highest	1.00 1.14 0.96 0.69 0.61	Ref. 0.77-1.69 0.65-1.47 0.45-1.07 0.39-0.97	Decrease
Martinez	2002	United States	Wheat Bran Fibre Trial	Males and females	1,304	3	665 subjects with recurrent adenoma	<2.2 to >11.4	lowest 2 3 highest	1.00 1.01 0.88 1.02	Ref. 0.72-1.43 0.62-1.25 0.71-1.47	Decrease
Oh	2007	United States	Nurses' Health Study	Females	48,115	22	1,064 subjects with large adenoma	<2.7 to >14.7	lowest 2 3 4 highest	1.00 0.73 0.82 0.77 0.82	Ref. 0.59-0.90 0.64-1.04 0.60-0.98 0.63-1.13	Decrease
Jacobs	2007	United States	UDCA trial	Males and females	1,190	3	504 subjects with recurrent adenoma	0.8 to 6.8	lowest 2 3 highest	1.00 1.18 1.07 1.00	Ref. 0.83-1.70 0.75-1.54 0.68-1.47	NR
Hubner	2008	United States	United Kingdom Colorectal Adenoma Prevention trial	Males and females	853	3	210 subjects with adenoma	NR, mean intake of 5.7/day	Low Medium High	1.00 0.81 0.96	Ref. 0.61-1.08 0.72-1.27	No association
Colorectal cancer											–	–
Garland	1985	USA	Western Electric Company's Hawthorn Works	Males	1,954	19	49 CRC	0.04 to 5.2 per 1000 kcal/day, i.e., ~0.1 to 13 µg/day	lowest 2 3 highest	1.00 1.27 0.47 0.53	NR NR NR NR	Decrease
Heilbrun*	1985	Japan	Hospital patients	Males	6,000	13 to 16	100 colon cancers	NR	lowest 2 3 highest	0.81 1.13 1.12 1.00	NR NR NR NR	No association
							59 rectal cancers	NR	lowest 2 3 highest	1.00 0.66 2.34 1.00	NR NR NR NR	No association

									lowest	1.00	Ref.	Decrease (NS)
										0.77	0.51-1.16	
Bostick	1993	United States	Iowa Women's Health Study	Females	41,837	4	212 CRC	<4 to >15.5		0.83	0.55-1.27	
										0.93	0.61-1.41	
									highest	0.73	0.45-1.18	
									lowest	1.00	Ref.	Decrease (NS)
									2	1.06	0.70-1.60	
Kearney	1996	United States	Health Professionals Follow-up Study	Males	51,529	6	203 CRC	<4 to ≥15.3	3	0.85	0.55-1.31	
									4	0.68	0.43-1.08	
									highest	0.66	0.42-1.05	
									lowest	1.00	Ref.	Decrease (NS)
									2	1.03	0.80-1.35	
Martinez	1996	United States	Nurses' Health Study	Females	89,448	12	501 CRC	<2.3 to >11.9	3	0.84	0.63-1.11	
									4	0.78	0.59-1.03	
									highest	0.88	0.66-1.16	
									lowest	1.00	Ref.	Decrease
Zheng	1998	USA	Iowa Women's Health Study	Females	34,702	9	144 rectal cancers	<5.6 to ≥11.9	2	0.71	0.47-1.08	
									highest	0.76	0.50-1.16	
									Lowest	1.0	Ref.	Decrease
Pietinen	1999	Finland	ATBC Study	Male smokers	27,111	8	185	Quartiles (medians of intake): 2.6 to 8.6	2	1.0	0.6-1.4	
									3	0.8	0.5-1.2	
									Highest	1.0	0.7-1.5	
									lowest	1.00	Ref.	Increase (NS)
Jarvinen	2001	Finland	Social Insurance Institution's Mobile Clinic	Males and females	9,959	24	72	<2.6 to >4.9	2	1.19	0.59-2.41	
									3	1.37	0.67-2.82	
									highest	1.74	0.82-3.68	
									lowest	1.00	Ref.	Decrease (NS)
									2	0.98	0.78-1.23	
McCullough	2003	United States	Cancer Prevention Study II Nutrition Cohort	Males and females	133,749	5	683	<2.3 to >11.9	3	0.90	0.72-1.14	
									4	0.78	0.61-1.01	
									highest	0.80	0.62-1.02	
									lowest	1.00	Ref.	Decrease
									2	0.96	0.75-1.22	
Terry	2002	Sweden	mammography program	Females	61,463	3	572 CRC	<2.6 to >3.8	3	0.95	0.75-1.21	
									highest	1.05	0.83-1.33	
									lowest	1.00	Ref.	Decrease (NS)
									2	1.11	0.74-1.67	
Kesse	2005	France	E3N cohort study	Females	100,00	7	172 CRC	<1.7 to >3.3	3	0.85	0.55-1.31	
									highest	0.89	0.58-1.36	

									lowest	1.00	Ref.	Decrease
									2	1.01	0.85-1.20	
				Males	85,903		1,138 CRC		3	0.89	0.74-1.07	
									4	0.82	0.68-0.98	
Park	2006	United States	Multiethnic Cohort Study			7		1 to >6.9 per 1000 kcal/day, i.e., ~2.5 to 17 µg/day	highest	0.66	0.54-0.81	
									lowest	1.00	Ref.	Decrease
									2	0.93	0.74-1.16	
				Females	105,108		972 CRC		3	0.82	0.65-1.03	
									4	0.89	0.67-1.19	
									highest	0.89	0.63-1.27	

Breast cancer

									Lowest	1	Ref.
									2	0.90	0.72-1.13
									3	0.87	0.68-1.11
							827 cases in pre-menopausal	≤3.75 to ≥12.5	4	0.79	0.60-1.05
									5	0.76	0.56-1.03
									6	0.77	0.60-0.99
Shin	2002	USA	Nurse's Health Study	Females	88,691	16			Highest	0.72	0.55-0.94
									Lowest	1	Ref.
									2	1.04	0.90-1.20
									3	1.04	0.89-1.21
							2,345 cases in post-menopausal	≤3.75 to ≥12.5	4	0.94	0.79-1.11
									5	1.11	0.94-1.32
									6	1.01	0.87-1.17
									Highest	0.94	0.80-1.10
									Lowest	1	Ref.
									2	0.74	0.52-1.05
					10,578 premenopausal	10	276 cases in pre-menopausal	<4 to ≥13.7	3	0.59	0.41-0.86
									4	0.59	0.40-0.88
									Highest	0.65	0.42-1.00
Lin	2007	USA	Women's Health Study	Females					Lowest	1.00	Ref.
									2	1.53	1.19-1.96
					20,909 post-menopausal	10	743 cases in post-menopausal	<4 to ≥13.7	3	1.52	1.19-1.96
									4	1.45	1.12-1.88
									Highest	1.30	0.97-1.73

Robien	2007	USA	Iowa Women's Health Study	Females, post-menopausal	34,321	18	2,440 cases (280 *in situ*)	<10 to ≥20	Lowest 2 Highest	1.00 0.95 0.89	Ref. 0.87-1.04 0.77-1.03
Pancreas cancer											
Skinner	2006	United States	Health Professionals Follow-up Study pooled with Nurses' Health Study	Males and females	112,128	16	365 cases	<3.8 to ≥15	lowest 2 3 4 highest	1 0.78 0.57 0.56 0.59	 0.59-1.01 0.40-0.83 0.36-0.87 0.59-0.88

NR: not reported; CRC: colorectal cancer; NS: not statistically significant

*The report was a letter to the editor without details on methodological aspects

Chapter 12 – Observational studies on serum 25-hydroxyvitamin D, cancer and all-cause mortality

12.1 Prospective studies of serum 25-hydroxyvitamin D and cancer risk

Some studies have examined plasma or serum 25-hydroxyvitamin level in relation to cancer risk, especially for colorectal cancer and for prostate cancer. There are a few other studies of other endpoints, including breast, ovarian and pancreatic cancers. The studies based on circulating 25-hydroxyvitamin D level are arguably the "gold standard" among observational studies for testing the vitamin D cancer hypothesis because 25-hydroxyvitamin D accounts not only for skin exposure to UVB radiation, but also for total vitamin D intake and for factors such as skin pigmentation. All these factors influence vitamin D status. In addition, 25-hydroxyvitamin D has a relatively long half-life ($t_{1/2}$) in the circulatory system of about 2-3 weeks, and thus can provide a fairly good indicator of long-term vitamin D status. For example, in one study of middle-aged to elderly men, the correlation of two 25-hydroxyvitamin D measures approximately three years apart was 0.7 (Platz *et al.,*2000). However, it is not clear how the consistency of 25-hydroxyvitamin D would be across different populations. In epidemiologic studies, circulating 25-hydroxyvitamin D has typically been based on a measure in archived blood samples in a nested case-control study. Because the sample is taken before the diagnosis of cancer, in some cases over a decade before, it is unlikely that any association observed is due to reverse causation, that is, spuriously due to the cancer influencing the blood level. One complexity is that in studies of 25-hydroxyvitamin D typically only one measurement is made, and levels fluctuate seasonally throughout the year due to variances in sun exposure. Several studies have been based on the measurement of 25-hydroxyvitamin D in individuals already diagnosed with cancer; these studies need to be interpreted very cautiously because of the potential for the phenomenon of reverse causation. For example, during the treatment period for cancer, exposure to sunlight is likely to be very skewed (due e.g., to hospitalisations, disability, change in lifestyle) and dietary habits are often different than before. Thus, studies that had blood sampled at about the time of cancer detection (like cross-sectional studies or case-control studies in which the blood sample was drawn at about the time of diagnosis [16]) are not summarised in detail hereafter (e.g., Niv *et al.,*1999; Janowski *et al.,*1999; Sieg *et al.,*2006).

12.2 Studies of predicted serum 25-hydroxyvitamin D and cancer risk

A study can use known predictors of 25-hydroxyvitamin D level based on data on the individual level to formulate a predicted 25-hydroxyvitamin D score. For example, based on an individuals' reported vitamin D intake, region of residence (surrogate of UVB exposure), outdoor activity level, skin colour and body mass index, a quantitative estimate of the expected vitamin D level can be made. The predicted 25-hydroxyvitamin D approach may have some advantages and disadvantages compared to the use of a single measurement of circulating 25-hydroxyvitamin D in epidemiologic studies. The measurement of 25-hydroxyvitamin D is more direct, intuitive, and encompasses some of the sources of variability of 25-hydroxyvitamin D not taken into account by the score. The most important of these is actual sun exposure behaviours, such as type of clothing and use of sunscreen. However, in some aspects, the predicted 25-hydroxyvitamin D measure may provide a comparable or superior estimate of long-term vitamin D status over a single measurement of circulating 25-hydroxyvitamin D. Most importantly, some factors accounted for by the predicted 25-hydroxyvitamin D score are immutable (for example, skin colour) or relatively stable (region of residence, body mass index). In contrast, circulating 25-hydroxyvitamin D level has a half-life of two to three weeks, and thus a substantial proportion of variability picked up by a single blood measure would likely be due to relatively recent exposures that are not necessarily representative of long-term exposure. The predicted 25-hydroxyvitamin D approach has been rarely used.

12.3 Specific cancer sites

12.3.1 Colorectal cancer

Measured serum 25-hydroxyvitamin D level

Studies that have examined 25-hydroxyvitamin D levels prospectively in relation to risk of colorectal cancer or adenoma have generally supported an inverse association (Garland *et al.,*1989;

Tangrea *et al.,*1997; Feskanich *et al.,*2004; Levine *et al.,*2001; Peters *et al.,*2001; Platz *et al.,*2000/JNCI; Grau *et al.,*2003; Braun *et al.,*1995; Wactaski-Wende *et al.,*2006; Wu *et al.,*2007; Otani *et al.,*2007; Freedman *et al.,*2007; Mazda *et al.,*2008).

The largest studies are the Nurses' Health Study (NHS)(Feskanish *et al.,*2004), the Women's Health Initiative (WHI)(Wactawski-Wende *et al.,*2006) and the European Prospective Investigation into Cancer (EPIC) study (Mazda *et al.,*2008).

The NHS study was based on 193 incident cases of colorectal cancer. Two controls were matched per case on year of birth and month of blood draw. After adjusting for age, body mass index, physical activity, smoking, family history, use of hormone replacement therapy, aspirin use, and dietary intakes, the RR decreased monotonically across quintiles of plasma 25-hydroxyvitamin D concentration, with a RR of 0.53 (CI, 0.27-1.04) for quintile 5 versus 1. The median 25-hydroxyvitamin D concentration in quintile 5 was approximately 20 ng/mL higher than that in quintile 1.

In the WHI, there were 322 total cases of colorectal cancer. A similar inverse association was observed between baseline 25-hydroxyvitamin D level and colorectal cancer risk, though detailed analyses on potential confounders was not done. The WHI was primarily a randomised placebo-controlled trial of 10 µg vitamin D plus 1000 mg a day of calcium in 36,282 post-menopausal women; however, as discussed below, the interventional component of this study did not support a protective role of vitamin D intake.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 1,248 colorectal cancer cases were identified and matched to 1,248 control subjects by age, gender, study centre, follow-up time and fasting status/time of day of blood donation (Jenab *et al*., 2008). Conditional logistic regression models (adjusted for body mass index, total energy intake, smoking status/duration/intensity, physical activity, education level, as well as consumption of fruits, vegetables and meats) were used to estimate relative risks. Compared to a serum 25OHD concentration of 50.0-75.0 20-29 ng/mL, lower levels of a 25OHD concentration were associated with an increase in colorectal cancer risk (<25.0 10 ng/mL: OR=1.32, 95%CI=0.87-2.01; 10-19 ng/mL: OR=1.28, 95%CI=1.05-1.56), whereas higher concentrations were associated with a decreased risk of colorectal cancer (30-39 ng/mL: OR=0.88, 95%CI=0.68-1.13; ≥40 ng/mL: RR=0.77, 95%CI=0.56-1.06).

Similar reduced risks of colorectal cancer were confirmed in the Health Professionals Follow-Up Study (HPFS)(Wu *et al.,*2007). That study showed a non-statistically significant inverse association between higher plasma 25-hydroxyvitamin D concentration and the risk of colorectal cancer and a statistically significant inverse association for colon cancer (highest versus lowest quintile: odds ratio (OR) = 0.46, 95% CI = 0.24 to 0.89). After pooling the results from the HPFS and NHS, higher plasma 25-hydroxyvitamin D concentrations were statistically significantly associated with decreased risks of both colorectal cancer (highest versus lowest quintile, OR = 0.66, 95% CI = 0.42 to 1.05) and colon cancer (highest versus lowest quintile, OR = 0.54, 95% CI = 0.34 to 0.86). Inverse associations with plasma 25-hydroxyvitamin D concentration did not differ by location of colon cancer (proximal versus distal), but the number of patients was small and none of the associations was statistically significant. Opposite relationships between plasma 25-hydroxyvitamin D levels and the risk of rectal cancers were found among men (positive) and women (inverse), though the number of cases were small for each.

The association between plasma 25-hydroxyvitamin D and subsequent colorectal cancer incidence risk by a nested case-control study was examined in The Japan Public Health Centre-based Prospective Study (Ottani *et al.,*2007). This study covered 375 newly diagnosed cases of colorectal cancer from 38,373 study subjects during an 11.5-year follow-up after blood collection. Two controls were matched per case on sex, age, study area, date of blood draw, and fasting time. In a conditional logistic regression model with matched pairs adjusted for smoking, alcohol consumption, body mass index, physical exercise, vitamin supplement use and family history of colorectal cancer, plasma 25-hydroxyvitamin D was not significantly associated with colorectal cancer in men or in women. However, the lowest category of plasma 25-hydroxyvitamin D was associated with an elevated risk of rectal cancer in both men (OR = 4.6; 95% CI: 1.0-20) and women (OR, 2.7, 95% CI: 0.94-7.6), compared with the combined category of the other quartiles.

In a recent study, Freedman *et al.,* (2007) examined this hypothesis in 16,818 participants in the Third National Health and Nutrition Examination Survey (NHANES III). The subjects were 17 years or

older at enrolment and were followed from 1988-1994 through 2000. Levels of serum 25-hydroxyvitamin D were measured at baseline. Cox proportional hazards regression models were used to examine the relationship between serum 25-hydroxyvitamin D levels and cancer mortality. Colorectal cancer mortality (n = 66 cases) was inversely related to serum 25-hydroxyvitamin D level, with levels 32.5 ng/mL or higher associated with a 72% risk reduction (95% CI: 32% to 89%) compared with lower than 20 ng/mL.

Thus, based on multiple studies of circulating 25-hydroxyvitamin D and colorectal cancer risk, individuals in the high quartile or quintile of 25-hydroxyvitamin D had about half the risk of colorectal cancer as did those in the lowest group. The dose-response appears fairly linear up to a 25-hydroxyvitamin D level of at least 35-40 ng/mL, and controlling for multiple covariates had little influence on the findings. The results are somewhat inconsistent in distinguishing whether the association is stronger for colon cancer or for rectal cancer, possibly due to small numbers.

Several studies that have examined circulating vitamin D levels and the risk of colorectal adenoma, which are well accepted precursors to colorectal cancer. On the whole, these studies suggest an inverse association with 25-hydroxyvitamin D and possibly 1,25-hydroxyvitamin D (Levine *et al.,*2001; Peters *et al.,*2001; Platz *et al.,*2000/CEBP;Grau *et al.,*2003; particularly for advanced adenomas (Wallace *et al.,*2004; Grau *et al.,*2005). With regard to the required 25-hydroxyvitamin D level to optimally reduce colorectal cancer risk, no threshold was suggested in any of the studies.

Predicted serum 25-hydroxyvitamin D level

An approach to estimate predicted 25-hydroxyvitamin D and then relating this score to risk of colorectal cancer was used in the HPFS (Giovannucci *et al.,*2006a). The analysis required two steps. First, in a sample of 1,095 men who had 25-hydroxyvitamin D levels measured, multiple linear regression was used to develop a predicted 25-hydroxyvitamin D score based on geographical region, skin pigmentation, dietary intake, supplement intake, body mass index, and leisure-time physical activity (a surrogate of potential exposure to sunlight UVB) as the independent variables (Giovannuci *et al.,*2007). Then, the score, after being validated, was calculated for each of approximately 47,000 cohort members, and this variable was examined in relation to a subsequent risk of cancer. For colorectal cancer, based on 691 cases diagnosed from 1986 to 2000, a predicted 10 ng/mL increment in 25-hydroxyvitamin D was associated with a reduced risk (multivariable RR=0.63; 95% CI 0.48-0.83). This association persisted when controlled for BMI or physical activity.

12.3.2 Prostate Cancer

Higher 25-hydroxyvitamin D level has not been clearly associated with a reduced risk for prostate cancer, although some of the studies suggest weak inverse associations (Braun *et al.,*1995; Corder *et al.,*1993; Gann *et al.,*1996; Nomura *et al.,*1998; Platz *et al.,*2004; Jacobs *et al.,*2004). Two case-control studies, conducted in Nordic countries, supported an inverse association for 25-hydroxyvitamin D (Ahonen *et al.,*2000; Tuohimaa *et al.,*2004). However, the second study also found an increased risk in men with the highest 25-hydroxyvitamin D values, suggestive of a U-shaped relationship (Tuohimaa *et al.,*2005). Although 1,25-hydroxyvitamin D that is produced intracellularly is believed to be more important than circulating 1,25-hydroxyvitamin D, several studies found supportive (Corder *et al.,*1993) or suggestive (Gann *et al.,*1996) inverse associations for circulating 1,25-hydroxyvitamin D and aggressive prostate cancer, particularly in older men. With further follow-up in the Physicians' Health Study, men with both low 25-hydroxyvitamin D and 1,25-hydroxyvitamin D were at higher risk of aggressive prostate cancer (RR = 1.9)(Li *et al.,*2007). In the Health Professionals Follow-up Study, both lower 25-hydroxyvitamin D and 1,25-hydroxyvitamin D appeared to be associated, surprisingly, with lower (mostly early stage) prostate cancer risk (Platz *et al.,*2004) but possibly with higher risk of advanced prostate cancer, although the numbers of advanced cases were limited (n=60). Thus, overall the studies of circulating 25-hydroxyvitamin D have been equivocal for prostate cancer and in general have not tended to support a robust association.

A nested case-control study within the Health Professionals Follow-up Study included 684 prostate cancer cases and found a increased risk with decreased serum 25-hydroxyvitamin D level (Mikhak *et al.,*2007)[17]. The study reported an OR of 0.62 (95% CI: 0.43-0.91) for serum 25-hydroxyvitamin D level lower or equal to 15 ng/mL, as compared to higher levels.

Another nested case-control study within the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial found no evidence for reduced risk of prostate cancer with decreased serum 25-

hydroxyvitamin D, but found higher levels to be associated with more aggressive disease (Ahn *et al.,*2008).

For prostate cancer, the data on circulating 25-hydroxyvitamin D are thus equivocal and sometimes contradictory (e.g., about the association with aggressive prostate cancer), suggesting no association or at least an association of a much weaker magnitude than has been observed for colorectal cancer. It is plausible that for prostate cancer, vitamin D level much longer before the time of diagnosis is most relevant, consistent with the notion that the process of prostate carcinogenesis encompasses a very long time period. Prostate cancer cells appear to lose 1-alpha-hydroxylase activity early in carcinogenesis, so it is plausible that exposure to vitamin D early in life (during very early stages of carcinogenesis) is most relevant. In addition, determinants of prostate cancer incidence may differ from prostate cancer progression and ultimately mortality and most of the available data have assessed incident prostate cancer, as opposed to aggressive or fatal prostate cancer.

12.3.3 Breast cancer

There have been relatively few studies of 25-hydroxyvitamin D level and the risk of breast cancer. One nested case-control study based on 96 breast cancer cases found no association between pre-diagnostic 1α,25-hydroxyvitamin D concentration and the risk of breast cancer; circulating 25-hydroxyvitamin D, which could be the more relevant compound, was not examined.

In one case-control study, breast cancer cases had lower 25-hydroxyvitamin D levels than did controls (Colston *et al.,*2006). Biases may explain these results as cases and controls were recruited in hospitals, and control women were volunteers, and thus not a control group constituted according to the habitual standards for case-control designs. Also blood samples were collected after diagnosis in cases, and thus reverse causation may also explain results.

In the Nurses' Health Study, stored plasma samples were assessed in 701 breast cancer cases and 724 controls (Bertone-Johnson *et al.,*2005). Cases had a lower mean 25-hydroxyvitamin D level than controls (P=0.01), and women in the highest quintile of 25-hydroxyvitamin D had a RR of 0.73 compared with those in the lowest quintile. The association was stronger in women age 60 and older, suggesting that vitamin D may be more important for post-menopausal breast cancer.

A large case-control study in Germany including 1,394 postmenopausal women with breast cancer and 1,365 controls matched on year of birth and month of blood sampling found a strong inverse correlation between serum 25-hydroxyvitamin D level and breast cancer risk, with a OR of 3.2 (95%CI: 2.4-4.2) for levels below 12 ng/mL compared to levels equal to or greater than 30 ng/mL (Abbas *et al.,*2007). Biases may explain these results: blood samples were available for a portion of subjects, and the median time difference between the diagnosis and time of blood collection in cases was 66 days. Thus reverse causation may partly explain the results. Furthermore, of the 17,093 controls who met the inclusion criteria, only 7,421 (43.4%) participated. Finally, it remains difficult to understand how the final case and control groups were constituted from much larger numbers of eligible cases (n=5,970) and controls (n=17,099).

The Prostate, Lung, Colorectal, and Ovarian cancer screening trial identified 1,005 incident breast cancer cases during a mean 3.9 years follow-up of women 55 to 74 years of age at baseline (Freedman *et al.,*2008). The RR of breast cancer for the highest versus lowest quintile of serum 25-hydroxyvitamin D concentration was 1.04 (95% CI: 0.75-1.45). Similarly, the breast cancer RR for the highest quintile of serum 1α,25-dihydroxyvitamin D level compared with the lowest was 1.23 (95% CI: 0.91-1.68). The statistical analysis in this study used season-specific quintiles (December-February, March-May, June-August, and September-November), for identifying the first quintile of measurements for each season and combined them to constitute a first quintile for the study. Then the second quintile for each season was identified and combined to constitute the second quintile and so on, for all five quintiles. Then, risk was assessed based on this combined quintile categorisation.

A small nested-case control study in California (USA) including 96 women 55 years old and over and matched controls found no association with serum 1α,25-dihydroxyvitamin D level measured in blood samples drawn 15 years before diagnosis (Hiatt *et al.,*1998).

12.3.4 Pancreatic cancer

Measured 25-hydroxyvitamin D level

There is one report of a prospective study of serum 25-hydroxyvitamin D in relation to pancreatic cancer risk. This study was based on the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort of male Finnish smokers (Stolzenberg-Salomon *et al.,*2006). This study was based on 200 cases of exocrine pancreatic cancer and 400 controls. This study found a significant positive association between higher 25-hydroxyvitamin D levels and increased risk of pancreatic cancer. Higher vitamin D concentrations were associated with a 3-fold increased risk for pancreatic cancer (highest versus lowest quintile, >27 versus <13 ng/mL: OR: 2.92; 95% CI: 1.56-5.48). This association persisted in multivariate analysis and after excluding cases early in follow-up (to avoid reverse causation). Of note, all the men in this study were smokers, and smoking is a strong risk factor for pancreatic cancer.

Predicted 25-hydroxyvitamin D level

As described above, one analysis based on the Health Professionals Follow-up Study used a surrogate of 25-hydroxyvitamin D to examine risk of total cancer (Giovannucci *et al.,*2006a). Based on 170 cases of pancreatic cancer, a 10 ng/mL increment in predicted 25-hydroxyvitamin D was associated with a 51% reduction in pancreatic cancer incidence (RR = 0.49; 95% CI = 0.28-0.86).

12.3.5 Ovarian cancer

Tworoger *et al.,* (2007) conducted a nested case-control study of plasma 25-hydroxyvitamin D in relation to the risk of epithelial ovarian cancer using data from three prospective cohorts: the Nurses' Health Study (NHS), NHSII, and the Women's Health Study (WHS). The analysis had 224 cases and 603 controls. No significant association between 25-hydroxyvitamin D (top versus bottom quartile: OR=0.83; 95% CI: 0.49-1.39) and ovarian cancer risk was observed. When the first two years of follow-up were excluded, a suggestive inverse association was noted for 25-hydroxyvitamin D levels equal or greater than 32 ng/mL (OR= 0.67, 95%CI: 0.43-1.05). Study-specific associations were not statistically significant and no statistical heterogeneity existed between the studies (χ^2 for heterogeneity: P=0.66 for 25-hydroxyvitamin D; P=0.40 for 1,25-dihydroxyvitamin D). However, there was a significant inverse association among overweight and obese women for 25-hydroxyvitamin D levels (OR=0.39; 95% CI: 0.16-0.93), and women with 25-hydroxyvitamin D below 32 ng/mL had a modestly decreased risk of serous ovarian cancer (RR= 0.64; 95% CI: 0.39-1.05).

12.3.6 Oesophageal and gastric cancer

Linxiam is an area in central China with very high incidence of oesophageal squamous cell carcinoma (ESCC) and gastric cardia adenocarcinoma, and also with widespread nutritional deficiencies. A cohort study in subjects with low and very low vitamin D status (serum 25-hydroxyvitamin D level was below 8 ng/mL in 25% of adult subjects), including 545 oesophageal squamous cell carcinomas (ESCC), 353 gastric cardia adenocarcinomas, and 81 gastric noncardia adenocarcinomas, found that higher serum 25-hydroxyvitamin D concentrations were associated with monotonically increasing risk of ESCC in men, but not in women (Chen *et al.,* 2007a). Men in the fourth quartile of serum 25-hydroxyvitamin D concentrations compared to the first had a hazard ratio of 1.77 (95% CI: 1.16–2.70). No associations were found for gastric cardia or noncardia adenocarcinoma. A companion study on the same cohort found that higher serum 25-hydroxyvitamin D concentrations were associated with significantly increased risk of squamous dysplasia of the oesophagus, and these lesions are considered as precursors of ESCC (Abnett *et al.,*2007). In this study, all blood samples were drawn during the spring.

12.4 Total cancer

Measured serum 25-hydroxyvitamin D level

Freedman *et al.,*(2007) examined cancer risk in 16,818 participants in the Third National Health and Nutrition Examination Survey (NHANES III) who were 17 years old or older at enrolment and who

were followed from 1988-1994. Through 2000, 536 cancer deaths were identified in 146,578 person-years. Total cancer mortality was unrelated to baseline serum 25-hydroxyvitamin D level, although a non-significant inverse trend (P = .12) was observed in women only. Among specific cancer sites, colorectal cancer mortality was inversely related to serum 25-hydroxyvitamin D level (discussed above), and there was a non-significant inverse association for breast cancer, though based on only 28 cases.

The NHANES study is sometimes difficult to interpret because all northern states had blood samples taken in the summer while in southern states, blood samples were taken in the winter (Looker *et al.,*2002). However, an analysis stratified by season of blood drawing obtained the same results (Freedman *et al.,*2007).

A cohort study of 3,299 German patients referred to coronary angiography recorded during a median 7.8 years of follow-up 736 deaths, among which 95 were attributed to a cancer (Pilz *et al.,*2008a). After adjusting for common confounders (e.g., sex, age, obesity, smoking status, physical exercise) the study found a two-fold increased risk (95% CI: 1.01-3.8) for cancer death in patients with serum 25-hydroxyvitamin D level below 15 ng/mL, as compared to patients with higher serum concentrations. Cancer death risk did not vary in serum level categories higher than 15 ng/mL. No association was found between serum 1α,25-dihydroxyvitamin D level and cancer death. The number of cancer deaths was small, but this study computed quartiles of serum 25-hydroxyvitamin D levels for each month of blood draw.[18]

Predicted serum 25-hydroxyvitamin D level

In the HPFS cohort of men, predicted serum 25-hydroxyvitamin D level was examined in relation to total risk of cancer (Giovannucci *et al.,*2006a). Predicted serum 25-hydroxyvitamin D level ranged from 15 to 36 ng/mL. From 1986 through January 31, 2000, 4,286 incident cancers (excluding organ-confined prostate cancer and non-melanoma skin cancer) and 2,025 deaths from cancer were documented in the cohort. From multivariable models, an increment of 10 ng/mL in predicted 25-hydroxyvitamin D level was associated with a 17% reduction in total cancer incidence (multivariable RR= 0.83, 95% CI: 0.74 to 0.92) and a 29% reduction in total cancer mortality (RR = 0.71, 95% CI: 0.60 to 0.83). The reduction was largely confined to cancers of the digestive tract, showing a 45% reduction in mortality (RR = 0.55, 95% CI: 0.41 to 0.74). Results were similar when further controlled for body mass index or physical activity level.

12.5 All-cause mortality

In the Netherlands, the Longitudinal Aging Study has examined during a 6-year follow-up the risk of death of 1,260 community dwelling people 65 years old and more according to serum 25-hydroxyvitamin D levels measured at baseline (Visser *et al.,*2006). 380 deaths were recorded. Subjects with serum 25-hydroxyvitamin D levels lower than 20 ng/mL had mortality risk associated with steadily lower levels (log-rank test: $p < 0.0001$). However, after adjustments for health and lifestyle variables and several frailty indicators, the relationship between serum 25-hydroxyvitamin D levels and mortality was no longer statistically significant. Figure 12.1 shows the successive adjustments done: the more variables were entered in the model, the lower the increased risk with lower serum 25-hydroxyvitamin D levels. A subtle “U-shaped” risk curve seemed to emerge with successive adjustments, but none of the relative risks were statistically significant.

The 13,331 adults 20 years or older from the Third National Health and Nutrition Examination Survey (NHANES III, USA) were followed during a median 8.7 years (Melamed *et al.,*2008). 1,806 deaths occurred, including 777 from cardiovascular disease (CVD) and 424 from cancer. In multivariate adjusted models, compared with the highest quartile, being in the lowest quartile of serum 25-hydroxyvitamin D level (i.e., below 17.8 ng/mL) was associated with a 26% increased rate of all-cause mortality (mortality rate ratio (95% CI: +8%;+46%). Figure 12.2 summarises risk of death from any cause, including CVD and cancer. U-shaped risk curves are noticeable, mainly for cancer and CVD deaths, with increased risk for lower levels, but also some increase when levels are above 32.1 ng/mL.

12.6 Discussion

These studies are discussed at end of chapter 13, after the outline of results of the meta-analysis done for colorectal, breast and prostate cancer, and for colonic adenomas.

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[16] Usual case-control designs and nested case-control designs are considerably different: the (usual) case-control design compares past exposure of subjects with a disease (the "cases") with subjects not having the disease (the "controls"), and exposure assessment is thus retrospective. The nested case-control study is a case-control study embedded within a prospective cohort study, where data on exposure (e.g., serum 25-hydroxyvitamin D level) was collected before disease onset (e.g., a colorectal cancer diagnosed years after the blood sample was taken). In this respect, the nested case-control design is an integral part of the prospective cohort design, while the (usual) case-control design is typically a retrospective design, far more vulnerable to biases and reverse causation (i.e., the disease has modified the exposure, rather than the exposure existing before the disease).

[17] Other studies were done on the same data set were reported by other authors, e.g., Li *et al., (*2008).

[18] The same cohort found a decreased risk of death from heart failure (116 patient) and of sudden cardiac arrest ((188 patients) associated with serum 25-hydroxyvitamin D level below 10 ng/mL, as well as with low serum 1α,25-dihydroxyvitamin D level (Pilz *et al.,*2008b). A third publication from the same cohort study showed an inverse relationship between serum 25-hydroxyvitamin D and 1α,25-dihydroxyvitamin levels and risk of stroke (42 patients) (Pilz *et al.,*2008). It was not clear from the two latter reports, however, how results were adjusted for season of blood draw. A fourth paper, using classification of serum 25-hydroxyvitamin D level as in Pilz *et al.,*2008a) reported decreased survival with decreasing serum 25-hydroxyvitamin D level (Dobnig *et al.,*2008, see Chapter 15).

Figure 12.1 - Risk of death in elderly people according to baseline serum 25-hydroxyvitamin D in the Longitudinal Aging Study (Visser et al., 2006). Subjects with 20 to 29.9 ng/ml levels are the referent category

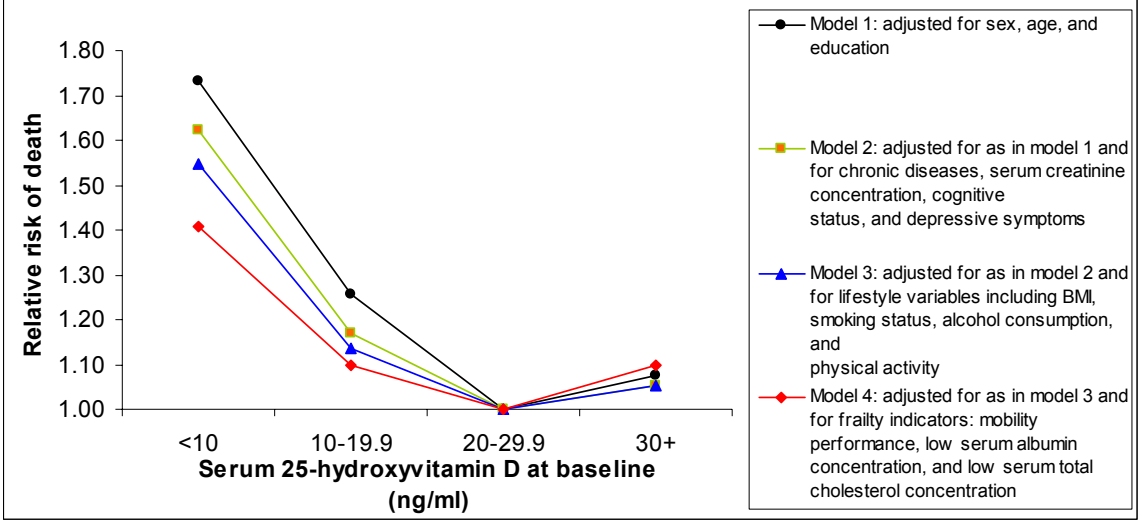
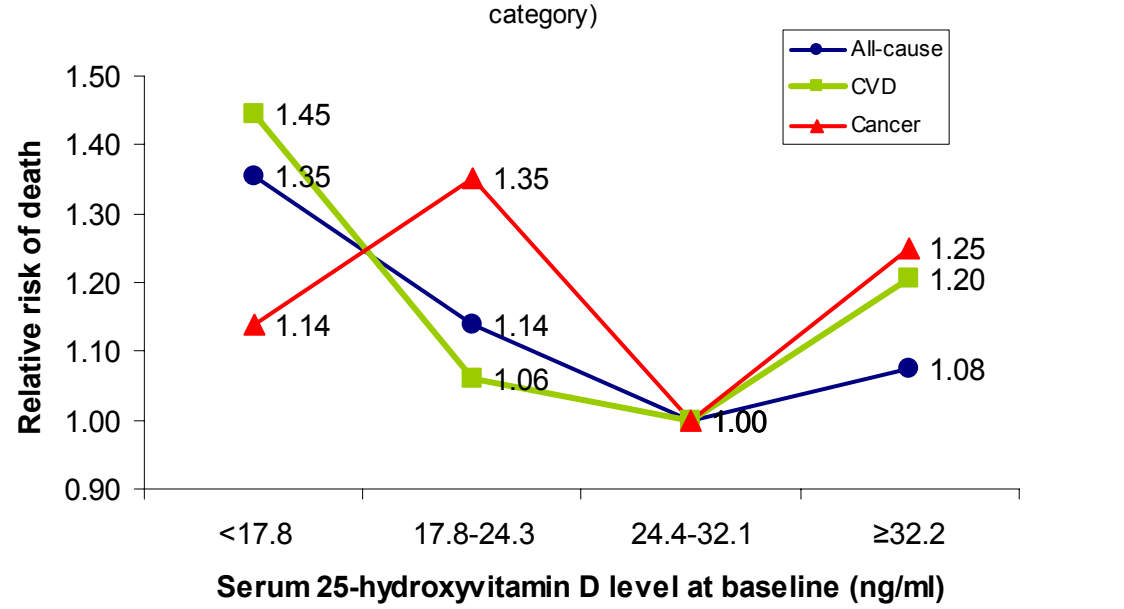


Figure 12.2 - Relative risk of dying from all-cause, cardiovascular disease (CVD) or cancer in the NHANES III study according to serum 25-hydroxyvitamin D level at baseline (24.4 to 32.1 ng/ml is the reference category)



Chapter 13 – Meta-analysis of observational studies on vitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma

13.1 Objective

The objective was to estimate the relative risk of cancer associated with variations in vitamin D status as measured by serum levels of the biomarker 25-hydroxyvitamin D, using the results of all the observational studies done on the topic to date. The meta-analysis was restricted for colorectal, breast and prostate cancers, and to colonic adenoma, as little or no observational studies have been done on vitamin D status and other cancers (see Chapter 12).

Ideally, 25-hydroxyvitamin D is measured years before the diagnosis of cancer. In this respect, relative risk estimates derived from meta-analytic methods will be done for all observational studies, and only for cohort and nested-case controls studies, as reverse causation is always a potential bias in (classic) case-control studies.

13.2 Background

Two meta-analyses have been published on vitamin D status and colorectal cancer and breast cancer. The first one from Gorham *et al.,* (2007) on colorectal cancer was based on results from 5 studies. The second one, from Garland *et al.,* (2007) was based on results from 2 studies. For both meta-analyses, a dose-response analysis was also carried out, but based on an artificial reconstruction of the individual data using the midpoints of the 25-hydroxyvitamin D intervals. Thus, confounding factors could not be included and the variability of association was limited by the case and control group size of the original studies. The authors did not attempt to include the actual variability from the confidence intervals reported in the paper. A significant decreasing risk of colorectal cancer (RR=0.49) and breast cancer (RR=0.50) was found for the highest quintiles of 25-hydroxyvitamin D as compared to the lowest quintile. However, these quintiles were not based on the actual adjusted RR reported in the original studies but defined as a linear interpolation of the dose-response curve obtained with artificial reconstruction of individual data. In both meta-analyses, the statistical methods were not appropriate: Peto's method is not recommended as a default approach for meta-analysis because it could result in biased estimates (Greenland and Salvan 1990); heterogeneity between studies was not accounted for; intra-correlation between quintiles of exposure to the reference category were not taken into account (Greenland and Longnecker, 1992); no publication bias was investigated and finally no sensitivity and heterogeneity analysis was performed.

Finally, recent studies have been published, in 2007 and 2008, based on larger sample sizes, were not included in these two meta-analyses.

13.3 Methodology for literature search

The literature search was conducted in the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded) and Embase, up until May 2008. The following keywords were used in searching: "breast cancer", "breast neoplasm", "colon cancer", "colorectal cancer", "rectal cancer", "prostate cancer" and "colorectal adenoma". To define the exposure, the following key words were used: "vitamin", "vitamin D", "25-hydroxyvitamin D", "25-Hydroxyvitamin D", "cholecalciferol", "calcidiol", "calcitriol" and "vitamin D receptors". We searched for the key words in the headers and in the abstract, when available. We also performed a manual search of references cited in the selected articles and published reviews. All participants of the Working Group were asked to report on any additional published or submitted studies. No language restrictions were applied. The search was limited to human studies.

Primary inclusion criteria were developed for the selection of relevant articles, which were: case-control and cohort studies published as an original article, which reported relative risk estimates or crude data of serum 25-hydroxyvitamin D levels. Ecological studies, case reports, reviews and editorials were not considered eligible. As a second step, further inclusion criteria were identified to select studies with the minimum necessary information for relative risk estimates:

1. Sufficient information to estimate the relative risk and 95% confidence intervals for the different quantiles used to categorise serum 25-hydroxyvitamin D levels (odds ratios, relative risks or crude data and corresponding standard errors, variance, confidence intervals or P-value of the significance of the estimates).

2 The studies had to be independent in order to avoid double weighting some studies.

When several articles published results using the same subjects, results from the publication on the largest sample were preferred; when the populations did not change the RRs with the best adjustments are chosen.

Selected articles were then reviewed and the data abstracted by means of a standardised data-collection protocol. The abstraction was performed independently by two readers per cancer site. For each study the following information was retrieved:

- General information: year of publication, study design, study location and the latitude of the region;
- Exposure information: values used for categorisations, units used to quantify 25-hydroxyvitamin D, season, methods of blood collection and distance from blood collection to diagnosis were collected;
- Case-controls information: number and source of cases and controls for each category of vitamin D levels, mean age and gender of cases and controls; exclusion of subgroups (black people, vitamin supplementation, and so on); incidence or mortality; recurrence of adenoma.
- Statistical information: statistical methods used, adjustments for confounding variables (demographic factors such as age and sex, BMI, intake of supplementation, and so on) and type of effect estimates (odds ratio, relative risk and standardised incidence ratio) with corresponding measures of precision, according the specific exposure category. When possible, the fully adjusted estimates were abstracted.

Information on serum vitamin D levels was extracted across all published categories in order to evaluate a dose-response model. When data were reported by gender, the estimates were extracted separately for both men and women.

13.4 Selection of data and methods of analysis

(a) Evaluation of serum levels of 25-hydroxyvitamin D

Estimates of all published quantiles of serum levels of 25-hydroxyvitamin D were evaluated for each study. Studies reporting data only on 1,25OHD were excluded.

Most studies presented the data using ng/mL as units. When the 25OHD levels were presented in nmol/L they were converted in ng/mL using a correction factor of 0.401.

(b) Estimates of risk

Since cancer is a relatively rare disease, we ignored the distinction between the various estimates of relative risk (i.e., odds ratio, rate ratio, risk ratio) and all measures were interpreted as odds ratios. Every measure of association, adjusted for the maximum number of confounding variables, and corresponding confidence intervals were transformed into log RRs and the corresponding variance was calculated using the formula proposed by Greenland (1987). When no estimates were given, crude estimates were calculated from tabular data, using the asymptotic Mantel-Haenszel estimates to calculate the 95% CI of the log odds ratio.

Most estimates included all subjects, combining sexes. Some studies presented results separately for women and men; these estimates were preferred in order to be able to evaluate the variability by these factors. A study identification number was set as a random effect, since some of these estimates came from the same study.

The homogeneity of the effects across studies was assessed using the large sample test based on the Chi-squared statistic (Chi). Since the Chi-square test has limited power, we considered

statistically significant heterogeneity at the P=.10 level of association. A further measure of heterogeneity I^2, that is the square-root of the Chi-squared divided by its degrees of freedom, has been considered in order to make comparisons between heterogeneities regarding different numbers of pooled studies. Greater values of I^2 indicate larger heterogeneity (Higgins and Thompson, 2002).

Pooled estimates of the effect of 25-hydroxyvitamin D levels on the risk were based on a two-step procedure. First, a linear model was fitted within each study to estimate the relative risk per unit increase of serum 25-hydroxyvitamin D. When sufficient information was published (the number of subjects at each serum level category), the model was fitted according to the method proposed by Greenland and Longnecker, which provides the natural logarithm of the RR, and an estimator of its standard error, taking into account the fact that the estimates for separate categories depend on the same reference group. When the number of subjects at each serum level category was not available from the publications, coefficients were calculated ignoring the correlation between the estimates of risk at the separate exposure levels (Greenland and Longnecker, 1992).

Second, the summarised RR was estimated by pooling the study-specific estimates of the mixed effects models in order to be conservative and to generalise the results. (Greenland, 1987) PROC MIXED in SAS (SAS Institute Inc. SAS Windows version (8.02), 1999, Cary, NC.), with maximum likelihood estimates, was used to take into account two sourced of variations: between-study variability and the correlation of estimates that come from a single study (van Howelingen *et al.,*2002). The final summary RR expressed the risk of an increase in 25-hydroxyvitamin D of 1 ng/mL. A further estimate is presented considering a 10 ng/mL increase corresponding to the average between 25-hydroxyvitamin D quartiles across all the studies included.

(c) Sensitivity analyses

Several sensitivity analyses were conducted to evaluate the stability of the pooled estimates. We excluded single studies that could influence the final results. Two further methodological choices were evaluated to verify the generalisation of the results and the variability of the estimates: 1) the analyses were carried out on the RRs for “highest” versus (vs) “lowest” quantiles; 2) application of the classical Dersimonian and Laird random effects models on dose–response estimates.

To verify whether publication bias might affect the validity of the estimates, funnel plots were investigated considering the regression of Ln(RR) on the sample size, weighted by the inverse of the pooled variance (Macaskill *et al.,*2001).

(d) Heterogeneity and sensitivity analyses for colorectal cancer

Meta-regressions and subgroup analyses (Colditz *et al.,*1995) were carried out to investigate between-study heterogeneity for colorectal cancer, the cancer site with the greatest number of estimates. Heterogeneity was investigated by looking at all the possible factors that could influence the estimates (cancer sub-sites, type of study, adjustments, categories used for exposure, and features of the population).

A further summary estimate was obtained from RRs obtained by collapsing gender categories and cancer sub-sites.

13.5 Description of the main characteristics of studies included in the meta-analysis

(a.1) Study characteristics for colorectal cancer.

An overview of the 9 studies included in the analysis (for a total of 2630 cases) is given in Table 13.1. The first was published in 1989 and last one sent for publication in 2008. Three case-controls studies were found: 2 carried out in the USA and one in Turkey. Only the Turkish one was a hospital-based case-control study. Only one article presented results on mortality, it was a cohort study (Freedman *et al.,*2007). We included 5 nested case control studies: 2 carried out in the USA, one multicentric in Europe, one in Finland and one in Japan (Otani, 2007). The multicentric study (Jenab 2008) was made available from the first author before its publication. Tangrea *et al.,*1997 included only men and Wactaski-Wende *et al.,*2006 only women. The median latitude of the study centres was 40º (range 35º-64º). The median age in both cases and controls was 59 (range 44-70). The median reference category was 19 ng/mL (range 10-25 ng/mL) and for the upper quantile 32 ng/mL (range

19-100 ng/mL). Methods used for the measurement of 25-hydroxyvitamin D are displayed in Table 13.4.

Jacobson *et al.,*2007 and Grau *et al.,*2003 were excluded because they investigated only recurrences of colorectal cancer. Niv *et al.,*1999 and Sieg *et al.,*1996 did not publish estimates of risk nor crude data with numbers of cases and controls by serum levels. Giovannucci *et al.,*2006a and Feskanich *et al.,*2004 were excluded from the analysis of colorectal cancer because they were not independent from Wu *et al.,*2007 that is a nested case-control study pooling data extracted from the NHS and HPFS cohort studies.

(a.2) Type of estimates presented in studies that analysed colorectal cancer

Risk estimates were extracted separately for colon and rectum when feasible. The adjustments used are shown in Table 13.2.

For Wactawski-Wende *et al.,*2006 we calculated dose-response estimates from the crude data of the placebo group. One study Yaylim-Eraltan *et al.,*2007 presented data for only two categories (>50nmol/L versus <50nmol/L), all the other studies presented data for at least 3 categories; Braun *et al.,* Garland *et al.,* and Jenab *et al.,* used quintiles. For Wu *et al.,*2007 we included the estimates from the HPFS and the NHS separately in order to obtain estimates by cancer sub-site. All the studies presented estimates on incidence, except for one cohort study that published RRs for mortality, Freedman *et al.,*2007.

Tangrea *et al.,* (1997) presented estimates by ng/l but, given the values, it was reasonable to suppose that it was meant to be ng/mL and the data was taken without modifying the units.

(b.1) Study characteristics for colorectal adenoma.

The 7 studies included in the analysis (for a total of 2,126 cases) are summarised in Table 13.1. The first was published in 2000 and last one sent for publication in 2007. Three case-control, 3 nested case-control studies and data extracted from a trial were found: all were conducted in USA. Platz *et al.,*2000 included data for women only. The median age of both cases and controls was around 60 (range 54-63). Jacobs *et al.,*2007 and Grau 2003 investigated recurrences of colorectal adenoma. Grau 2003 published the results of a placebo control randomised trial on calcium supplementation and presented an estimated increased risk of 12 ng/mL circulating 25-hydroxyvitamin D levels. The overall estimate, for the two treatment arms together, was extracted.

(b.2) Type of estimates presented in studies that analysed colorectal adenoma

Adjustments are indicated in Table 13.2. Peters 2001 and Peters 2004 reported estimates expressed as risk per increase of 10 ng/mL of 25-hydroxyvitamin D. Peters 2001 did not present the estimates for all categories and could not be included in the comparison between high versus low levels of 25-hydroxyvitamin D. Levine 2001 and Platz 2000 presented data for four categories, Miller 2007 and Jacobs 2007 in 3 categories. For Jacobson 2007 we included estimates of recurrences/non-recurrences that occurred only after the blood draw for 25-hydroxyvitamin D analyses. Data from colonoscopies prior to blood draw were not used for these RR estimates.

(c.1) Study characteristics for breast cancer.

An overview of the 5 studies included in the analysis (for a total of 3,307 cases) is given in Table 13.1. The first (published in 2005) and last (published in 2008) studies included were published only 3 years apart.

Two European case-control studies were found: one in the UK and one in Germany, which was only of pre-menopausal women. The remaining studies were 2 nested case control studies and a cohort study carried out in the USA.

Lowe *et al.,*2005 was excluded from the analysis on breast cancer because it was not independent from Colston *et al.,*2006.

(c.2) Type of estimates presented in studies that analysed breast cancer

Adjustments are indicated in Table 13.2. One study, Colston *et al.,*2006 presented crude data (a rough histogram of cases and controls for each categories) for quartiles, and the other studies presented, for quintiles, estimates adjusted for all of the important confounders (BMI, parity, family history, age at menarche, and age at menopause).

(d.1) Study characteristics for prostate cancer.

Overall 7 studies were included in the analysis (for a total of 1,909 cases) as given in Table 13.1. The first was published in 1995 and the last in 2008.

All but one study were conducted in the USA. Ahonen 2000 was conducted in Finland. All but one of the studies were nested case-control studies. Freedman 2007 was a cohort study. Gann 1996, Li 2007 and Platz 2004 were excluded from the analysis on prostate cancer because they were not independent from Mikhak *et al.,*2007 that published the most updated results. Tuohimaa 2004, which presented results for Norway, Finland and Sweden, published the estimates considering the middle quintile as the reference category but with no crude data. This study was excluded and replaced by Ahonen 2000, which reported the crude data for Finland.

All nested case-control studies were matched by age and the median age in both cases and controls was 66 (range 58-68). The median reference category was 24 ng/mL (range 11-34 ng/mL) and 33 ng/mL (range 15-48 ng/mL) for the upper quantile.

(d.2) Type of estimates presented in studies that analysed prostate cancer

Adjustments are indicated in Table 13.2. One study, Ahonen *et al.,*2000, presented relative risk using the highest category as the reference and so we calculated the relative risk from the crude data by quartiles.

13.6 Information and adjustment on season of blood draw

Serum 25-hydroxyvitamin D levels vary much with season, being lowest at the end of the winter and highest at the end of the summer (see Chapter 7). The time of the year when blood was drawn can be an obvious source of bias if, for instance, blood was more frequently taken during the winter in cancer patients than in non-cancer subjects. This distortion would lead to a falsely increased risk of cancer with low vitamin D status. Table 13.3 summarises strategies adopted for coping with seasonal variations. Few studies did not report how they dealt with this problem. The most frequent strategy in nested case-control studies was to match cases and controls by month or season of blood draw, or to take all blood samples during a limited period.

13.7 Results of the meta-analysis

13.7.1 Pooled estimates

Results of the meta-analysis on all included published studies are shown in Table 13.5 and forest plots are displayed in Figures 13.1 to 13.5. We also calculated relative risks after excluding case-control studies where reverse causation was possible, as for instance for Colston (2006) and Abbas (2007) for breast cancer (see Chapter 12). Relative risks restricted to cohort or nested-case control studies are displayed in Figures 13.1 to 13.5.

For colorectal cancer, analyses were carried out on the estimates by gender and cancer sub-site when the data were available in order to investigate heterogeneity, and for the overall population, a forest plot and summary RR are presented (Figure 13.2).

A significant protective effect was indicated by the summary RR for colorectal cancer and colorectal adenoma. For breast cancer the pooled estimates did not reach significance even though the magnitude of the association was similar to the estimates of colorectal cancer. For prostate cancer the results did not show any association with 25-hydroxyvitamin D levels. Between-study heterogeneity was statistically significant in all analyses.

13.7.2 Heterogeneity analysis

We investigated several factors that could potentially influence the summary relative risk for colorectal cancer: adjustment for confounders, publication year, latitude, mean age of controls or population of exposure, mean age of cases, European versus not-European countries, gender, cancer sub-site for colorectal cancer, study design, years since blood was drawn, lowest values of the upper categories and upper values of the reference category. None of the factors considered in the subgroups and meta-regression analyses explained the between-study variability of both relative risk estimates evaluated: dose-response model and highest versus lowest exposure. Estimates from the subgroup analyses are presented in Table 13.6.

For breast cancer, adenoma and prostate cancer there were few studies available and the factors considered were not very different across studies: for example all studies of colonic adenoma were from the USA, and the age of cases or controls and values of reference categories or upper quartiles were in narrow ranges.

13.7.3 Sensitivity analyses and publication bias investigation

A series of further analyses were performed to test the stability and sensitivity of the analysis for colorectal cancer. We excluded the estimate from the cohort study on mortality (Freedman *et al.,*2007), the Otani *et al.,* (2007), that was the only oriental study, and Yaylim-Eraltan *et al.,* 2007, which presented estimates for only two categories (greater than the median). The pooled RR, for the dose-response model, increased and showed wider confidence intervals. The data are summarised in Table 13.7.

For colorectal cancer, colorectal adenoma, breast and prostate cancers, the funnel plot regression of dose-response estimates gave no indication of publication bias (P=0.19, 0.38, 0.77, and 0.97 respectively).

Considering high versus low levels of 25-hydroxyvitamin D we had an indication of a protective effect only for colorectal cancer, and the decreased risks for colonic adenoma and breast cancer were only of borderline statistical significance (Table 13.8). For colorectal cancer, funnel plot regression on highest versus lowest RRs gave no indication of publication bias (P=0.27).

Results from Dersimonian and Laird random effect models indicated a protective effect for all cancer sites except for prostate cancer (data not shown).

13.8 Discussion

The EPIC study (Jenab *et al.,* 2008) showed that standardization of serum 25-hydroxyvitamin D according to the month of blood draw did not affect the observed inverse colorectal cancer risk association with serum 25-hydroxyvitamin D concentration. The seasonal variations were of similar magnitude for both colorectal cancer patients and controls.

Some studies had recourse to subgroup analysis for finding statistically significant results when no association was found for the more aggregated cohort (e.g., Otani *et al.,* 2007).

13.9 Conclusions

Observational studies provide evidence of a decreased risk of colorectal cancer associated with higher serum 25-hydroxyvitamin D. This evidence is supported by a decrease in colonic adenoma with higher serum 25-hydroxyvitamin D.

A non-significant decreased risk of breast cancer risk was associated with higher serum 25-hydroxyvitamin D, but study results were very heterogeneous. Further cohort studies are warranted.

Observational studies provide no evidence for an association between higher serum 25-hydroxyvitamin D and prostate cancer risk.

The data for other cancers are too sparse to allow a proper meta-analysis.

Table 13.1 - Study features of studies included in the meta-analyses

Disease	First Author, PY	Country	Study design	Fup years	N. cases	N. controls	Age cases¥	Age controls¥	Reference category†	Upper quantile#
Colorectal cancer										
	Garland, 1989	USA	CC	9	34	67	63	63	19	42
	Braun, 1995	USA	CC		2757	114			17	30
	Tangrea, 1997	Finland	NCC[2]	8	146	290	59	60	10	19
	Yaylim-Eraltan, 2006	Turkey	CC		26	52	59	52	20	20
	Wactawski-Wende, 2006	USA	NCC[3]	12	306	306	70	63	12	24
	Freedman, 2007	USA	Cohort	12	66	16818		44	20	32
	Otani, 2007	Japan	NCC	14	375	750	57	57	20	30
	Wu, 2007	USA	NCC	9	372	739	66	66	16	40
	Jenab, 2008	EU	NCC	9	1248	1248	58	58	10	40
Colorectal adenoma										
	Platz, 2000	USA	NCC	7	326	326			16	38
	Levine, 2001	USA	CC		473	507	62	62	15	34
	Peters, 2001	USA	CC		236	218	60	57	**	
	Grau, 2003‡ [1]	USA	Cohort	4	202/174	405/398	61	61	***	
	Peters, 2004	USA	NCC	6	394	397	63	62	**	
	Jacobs, 2007[1]	USA	NCC	3	210	568		66	17	36
	Miller, 2007	USA	CC		111	238	60	54	21	34
Breast cancer										
	Bertone-Johnson, 2005	USA	NCC	7	701	724	57	57	22	42
	Colston, 2006	UK	CC		179	179	58	58	20	60
	Abbas, 2007	Germany	CC		1394	1365	64	64	12	30
	Freedman, 2007	USA	Cohort	12	28	16818		44	25	25
	Freedman, 2008	USA	NCC	12	1005	1005		62	18	34
Prostate cancer										
	Braun, 1995	USA	NCC	17	61	122	59	59	24	41
	Nomura, 1998	USA	NCC	28	136	136	58	58	34	48
	Ahonen, 2000	Finland	NCC	14	149	566			12	22
	Jacobs, 2004	USA	NCC	19	83	166	67	67	25	33
	Freedman, 2007	USA	Cohort	12	47	16818		44	25	25
	Mikhak, 2007	USA	NCC	14	684	692	66	66	15	15
	Ahn, 2008	USA	NCC	10	749	781	68	68	11	44

PY: publication year; Fup: maximum Follow up; NCC: Nested Case-control study; CC: Case-control study. [1] Adenoma recurrence. [2] Nested in ATBC trial. [3] Nested in WHI trial. ** OR reported as risk per increase of 10 units of 25-hydroxyvitamin D; *For cohorts: the study size; ¥Mean age. †Upper bound in ng/mL and mean values when upper level not available; #Lower bound in ng/mL and mean values when lower level not available. ‡ Clinical trial on calcium intake and risk for recurrence of adenoma, with number of subjects in each arms. *** OR reported as risk per increase of 12 units of 25-hydroxyvitamin D;

Table 13.2 – Factors adjusted for in colorectal cancer and colon adenoma studies

Disease	First Author, PY	Matching and adjustments
Colorectal cancer	Garland, 1989	Match.: age, sex, race and date of blood draw.
	Braun, 1995	Match.: age, race, sex and date of blood draw.
	Tangrea, 1997	Match.: age, study clinic and date of blood draw.
	Yaylim-Eraltan, 2006	Crude
	Wactawski-Wende, 2006	Match.: age, centre, race and date of blood draw.
	Freedman, 2007	Adj.: Age, sex, race and smoking.
	Otani, 2007	Match.: age, sex, time since last meal, study centre and date of blood draw. Adj.: Smoking, alcohol, BMI, physical exercise, Vitamin supplem., family history
	Wu, 2007	Match.: age and date of blood draw. Adj: Smoking, alcohol, BMI, physical exercise, Vitamin supplem., family history, calcium, alcohol, red meat intake, retinol intake.
	Jenab, 2008	Match: incidence density sampling by age (±6 months at recruitment), gender, study centre (to account of centre specific differences in questionnaire design, blood collection procedures etc.), time of the day at blood collection, and fasting status at the time of blood collection (<3, 3-6, >6 hours). Adj: Smoking status/duration/intensity, alcohol, BMI, physical activity, fruit, vegetables, meat intake, level of education
Colorectal adenoma	Platz, 2000	Adj.: BMI, physical activity, aspirin use, cigs smoked, alcohol, red meat and methionine intake, folic acid intake and postmenopausal status hormone use. Match.: period of on endoscopy, age, indication for endoscopy, time period of first or most recent endoscopy and date of blood draw.
	Levine, 2001	Adj.: Age, gender, race, clinic, sigmoidoscopy date, tot calories, BMI, tot dietary fibre intake, saturated fat intake, multi-vitamin use and ca/phosphorus ratio.
	Peters, 2001	Adj.: Age, sex and season.
	Grau, 2003	Adj.: Age, sex, centre, smoking status and alcohol intake
	Peters, 2004	Adj.: Age, gender, ethnic origin, study centre, month of blood drawn
	Jabobs, 2007	BMI, number of colonoscopies, previous polyps, date of blood draw and gender.
	Miller, 2007	Adj.: Age, sex, race and date of blood draw.
Breast cancer	Bertone-Johnson, 2005	Match.: age, menopausal status, use of hormone, fasting status and date blood draw. Adj.: BMI, parity, family history, age at menarche and at menopause, alcohol, hormone therapy, date blood draw…
	Colston, 2006	Match.: age, menopausal status and date blood draw
	Abbas, 2007	Match.: age, time of blood collection and study region. Adj.: BMI, parity, family history, age at menarche and at menopause, alcohol, date of blood draw, smoking, hormone therapy, education…
	Freedman, 2007	Adj.: Age, race and smoking.
	Freedman, 2008	Match.: age and date blood draw, Adj.: BMI, age at menarche, age at menopause, HRT benign breast disease, family history, alcohol, smoking, date blood draw …
Prostate cancer	Braun, 1995	Match.: age.
	Nomura, 1998	Match.: age, month and year of examination (blood draw).
	Ahonen, 2000	Match.: age, residence and time of blood draw. Adj.: Smoking, bmi, HDL, treatment, age and time of blood draw.
	Jacobs, 2004	Match.: Selenium dose, age and clinic. Adj.: Age at blood, BMI, smoking and clinic.
	Freedman, 2007	Adj.: Age, sex, race and smoking history.
	Mikhak, 2007	Match.: age, time of blood draw, history of PSA test. . Adj.: race, FH of cancer, quadrant of US, BMI, tobacco, vit E, dietary Ca, tomato sauce, energy, fish and alpha-linolinic acid.
	Ahn, 2008	Match.: age, times since initial screening, year. Adj.: BMI, physical activity, total calcium intake, history of diabetes and study centre.

PY: publication year; Adj.: adjustments for. Match.: Matched by.

Table 13.3 - Information on how studies dealt with month or season of blood draw

Disease	First Author, PY	Actions
Colorectal cancer	Garland, 1989	Blood draw from September to the end of November. Matched by blood draw.
	Braun, 1995	Blood draw from late August to November (from Comstock 1991). Matched by blood draw.
	Tangrea, 1997	Blood draw at randomisation (1985-1993). Matched by blood draw.
	Yaylim-Eraltan, 2006	No information on blood drawn. Blood draw probably after cancer diagnosis.
	Wactawski-Wende, 2006	Blood draw at randomisation (1993-1998). Matched by blood draw.
	Freedman, 2007	Blood draw at southern latitudes from November to March. At northern latitudes from April to October. No adjustment for season. Authors stratified analyses by seasons and found no significant changes.
	Otani, 2007	Blood draw at health check-up (1990-92, 1993-95). Matched by blood draw. Checked stratified analyses by seasons: No significant changes
	Wu, 2007	Blood draw at recruitment (1993-95). Matched by blood draw. Adjustments for season.
	Jenab, 2007	Blood draw at recruitment (1992-98). Adjusted for seasons as confounder but not included in final models. Difference in serum 25-hydroxyvitamin D between cases and controls was found irrespective of seasonal variation in cases and controls, and amplitude of seasonal variation was similar in cases and controls. Findings presented with and without standardization of serum 25-hydroxyvitamin D for month of blood draw.
Colorectal adenoma	Platz, 2000	Blood draw at recruitment: May 1989 through June 1991. Matched by blood draw. Checked stratified analyses by seasons: No significant changes.
	Levine, 2001	No information on blood draw.
	Peters, 2001	Adjustment for season. Blood draw very close to cancer diagnosis.
	Grau, 2003	Blood draw at recruitment: November 1988 to April 1992. No adjustment for date blood draw. Month of blood draw as a covariate did no change the RRs.
	Peters, 2004	Blood draw at recruitment: September 1993 to September 1999. Adjustment for date blood draw. Season-specific cut points for quintiles (December to May and June to November) were used.
	Jabobs, 2007	Adjustment for date blood draw.
	Miller, 2007	Blood draw at recruitment: August 1998 to March 2000. Adjustment for date blood draw.
Breast cancer	Bertone-Johnson, 2005	Blood draw between 1989 and 1990. Matched by blood draw. Adjustment for date blood draw. Season-specific cut points for quintiles (February-April, May-July, August-October, November-January) were used.
	Colston, 2006	Matched by blood draw.
	Abbas, 2007	Matched by blood draw. Adjustment for date blood draw.
	Freedman, 2007	Blood draw at southern latitudes from November to March. At northern latitudes from April to October. No adjustment for season. Checked stratified analyses by seasons: No significant changes.
	Freedman, 2008	Matched by blood draw. Adjustment for date blood draw. Season-specific cut points for quintiles (December to February, March to May, June to August and September to November) were used.
Prostate cancer	Braun, 1995	Blood draw at recruitment: August to November 1974. Checked distribution of cases and controls by month of serum collection.
	Nomura, 1998	Blood draw at II examination, two years after recruitment. Matched by blood draw. Relationships between case-controls differences and month of the exams were analysed and not trends were found.
	Ahonen, 2000	Blood draw at recruitment: 1981-1982. Matched by blood draw. Adjustment for date blood draw.
	Jacobs, 2004	Blood draw at recruitment: 1983-1991.
	Freedman, 2007	Blood draw at southern latitudes from November to March. At northern latitudes from April to October. No adjustment for season. Checked stratified analyses by seasons: No significant changes.
	Mikhak, 2007	Blood draw at recruitment: 1993-2000. Matched by time of blood draw. Adjustment for season.
	Ahn, 2008	Blood draw at recruitment: 1993-2001. Quintiles of season standardised values of 25-hydroxyvitamin D were calculated. Subgroup analyses by season of blood collection (no significant differences were found).

Table 13.4 - Features of measurements of 25-hydroxyvitamin D for colorectal cancer

First Author, PY	Blood collection before diagnosis#	Method of 25-hydroxyvitamin D detection
Garland, 1989	1	High-performance liquid chromatography and UV absorbance detection
Braun, 1995	13	A radioimmunoassay method
Tangrea, 1997	3	A radioimmunoassay method
Yaylim-Eraltan, 2006	0*	Enzyme-linked immunoassay
Wactawski-Wende, 2006	10	Chemiluminescent radioimmunoassay system
Freedman, 2007	9	A radioimmunoassay method
Otani, 2007	10	Competitive protein-binding assay of Haddad and Chyu
Wu, 2007	7	A radioimmunoassay method
Jenab, 2008	6	Enzyme immunoassay method

#Years in average. *Before treatment.

Table 13.5 - Dose-response Pooled estimates for increasing serum levels of 25-hydroxyvitamin D

Disease	Units of increase	RR and 95%C.I.	P heterogeneity*	I^2
Colorectal cancer	1 ng/mL	0.983 (0.976, 0.990)	0.004	55
	10 ng/mL	0.85 (0.79, 0.91)		
Colorectal adenoma	1 ng/mL	0.993 (0.987, 0.999)	0.003	69
	10 ng/mL	0.93 (0.88, 0.99)		
Breast cancer	1 ng/mL	0.984 (0.966, 1.002)	<0.001	92
	10 ng/mL	0.85 (0.71, 1.02)		
Prostate cancer	1 ng/mL	0.998 (0.992, 1.005)	0.032	56
	10 ng/mL	0.98 (0.92, 1.05)		

*Chi-square test

Table 13.6 - Subgroups analyses for colorectal cancer.

Factor	N. estimates	I^2	Pooled RR* and 95%C.I.	P for factor‡
Cancer sub-site				
Colon	8	57	0.987 (0.979, 0.994)	0.86
Rectum	6	61	0.985 (0.969, 1.002)	
Gender				
Men	4	48	0.991 (0.97, 1.012)	0.69
Women	5	69	0.987 (0.972, 1.002)	
Type of study				
CC	3	39	0.982 (0.967, 0.997)	0.79
NCC or CO¥	14	59	0.984 (0.976, 0.991)	
Adjustment for BMI				
No	7	3	0.977 (0.966, 0.988)	0.12
Yes	10	65	0.986 (0.979, 0.994)	
Mean age cases				
<60	9	57	0.985 (0.977, 0.994)	0.96
≥60	6	56	0.985 (0.976, 0.995)	
Mean age controls/pop				
<60	8	69	0.983 (0.973, 0.992)	0.68
≥60	8	40	0.985 (0.975, 0.995)	
Publication Year				
<2000	4	0	0.985 (0.968, 1.001)	0.82
≥2000	13	64	0.983 (0.974, 0.992)	
Reference category				
<16 ng/mL	6	0	0.983 (0.973, 0.993)	0.85
≥16 ng/mL	11	69	0.984 (0.975, 0.993)	
Upper category				
≤32 ng/mL	10	64	0.980 (0.968, 0.992)	0.50
>32 ng/mL	7	44	0.985 (0.976, 0.995)	

* for 1 mg/ml units of increase of 25-hydroxyvitamin D; ‡ from meta-regression;

¥ Co: cohort studies, NCC: Nested case-controls studies.

Table 13.7 - Overall Pooled estimates for colorectal cancer excluding single studies

Excluded studies	RR and 95%C.I.	I^2
Freedman, 2007	0.985 (0.978, 0.991)	52
Yalim-Eraltan, 2006	0.984 (0.977, 0.991)	48
Otani, 2007	0.980 (0.975, 0.986)	37

Table 13.8 - Overall Pooled estimates for Highest *vs.* Lowest serum 25-hydroxyvitamin D values

Disease	RR and 95%C.I.	P heterogeneity*	I^2
Colorectal cancer	0.56 (0.42, 0.74)	0.02	47
Colorectal adenoma	0.76 (0.56, 1.02)	0.09	48
Breast cancer	0.46 (0.21, 1.03)	<0.001	90
Prostate cancer	0.83 (0.61, 1.12)	0.18	33

*Chi-square test

Forest plots

Figure 13.1 - Dose-response relative risks for colorectal cancer due to an increase of 1 unit of ng/mL serum level of 25-hydroxyvitamin D. The relative risk "pooled Co or NCC" is calculated after exclusion of case-control studies (C is colon, R is rectum, Co is cohort studies, NCC is nested case-control studies)

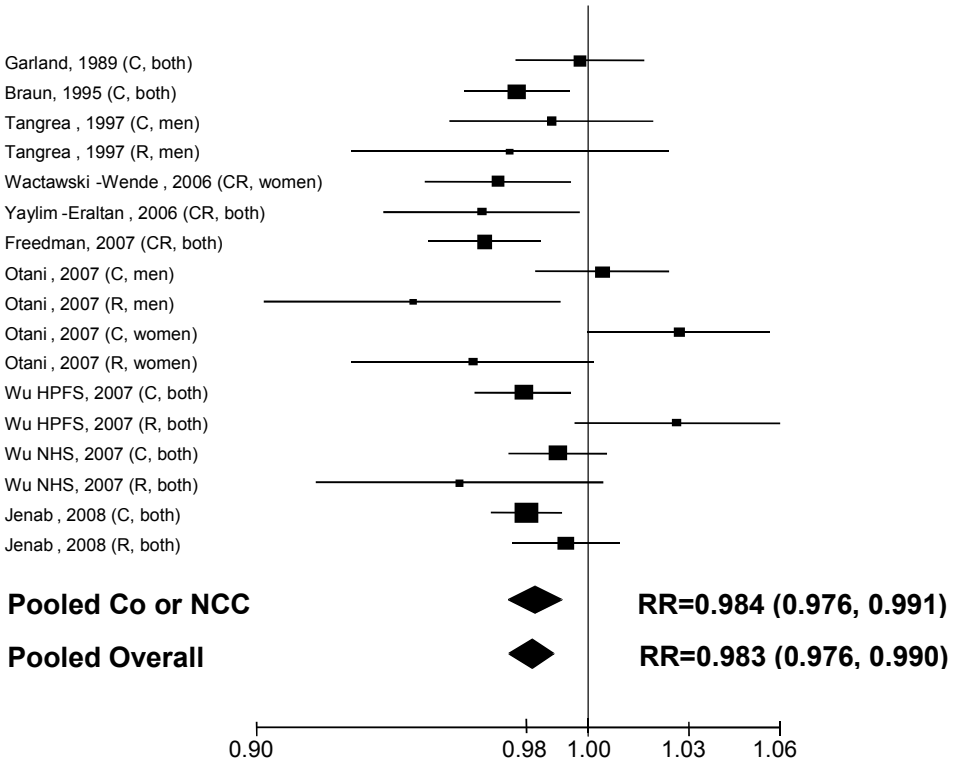


Figure 13.2 - Dose-response relative risks for colorectal cancer due to an increase of 1 unit of ng/mL serum level of 25-hydroxyvitamin D. Aggregated estimates. The relative risk "pooled Co or NCC" is calculated after exclusion of case-control studies (C is colon, R is rectum, Co is cohort studies, NCC is nested case-control studies)

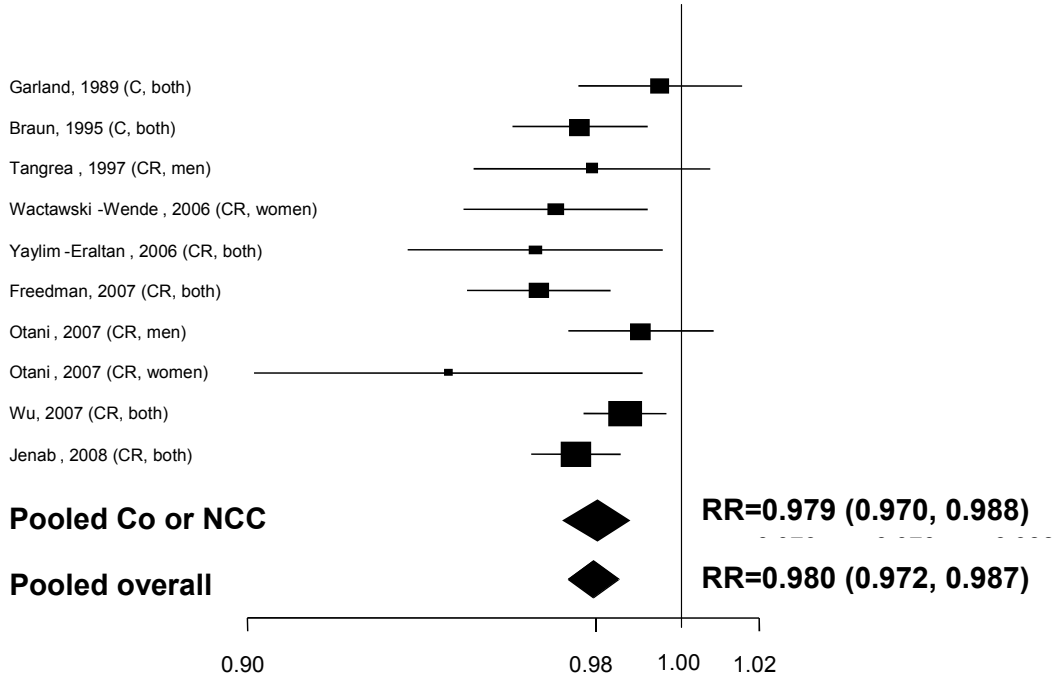


Figure 13.3 - Dose-response relative risks for colorectal adenoma due to an increase of 1 unit of ng/mL serum level of 25-hydroxyvitamin D. The relative risk "pooled Co or NCC" is calculated after exclusion of case-control studies (Co is cohort studies, NCC is nested case-control studies)

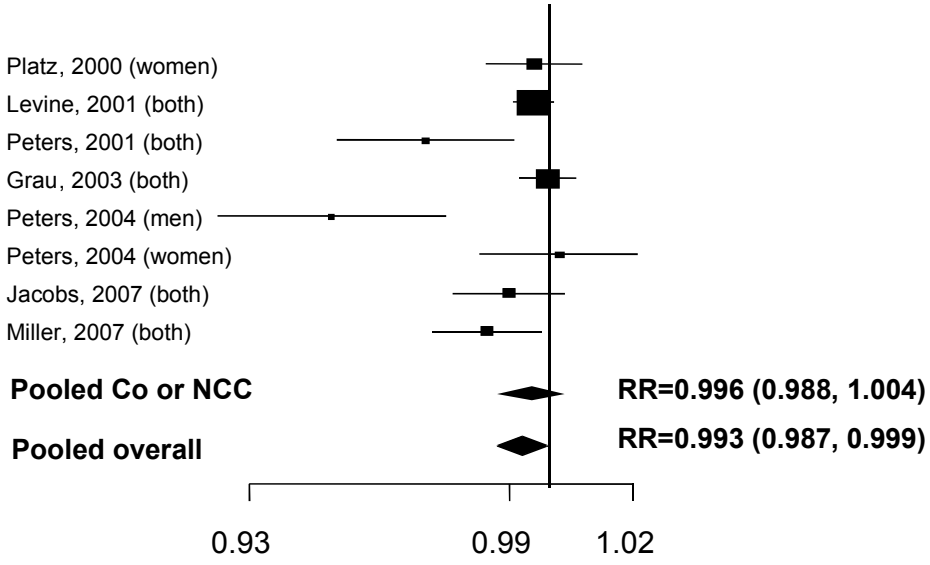


Figure 13.4 - Dose-response relative risks for breast cancer due to an increase of 1 unit of ng/mL serum level of 25-hydroxyvitamin D. All studies are on breast cancer incidence, but Freedman *et al.*,2007, that used breast cancer mortality as endpoint. The relative risk "pooled Co or NCC" is calculated after exclusion of case-control studies (Co is cohort studies, NCC is nested case-control studies)

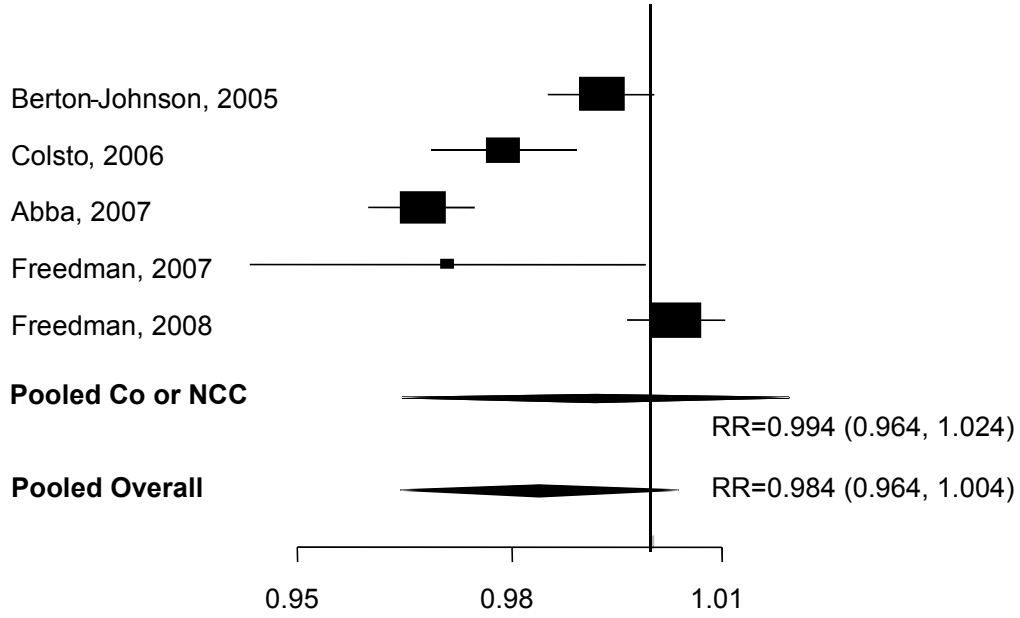
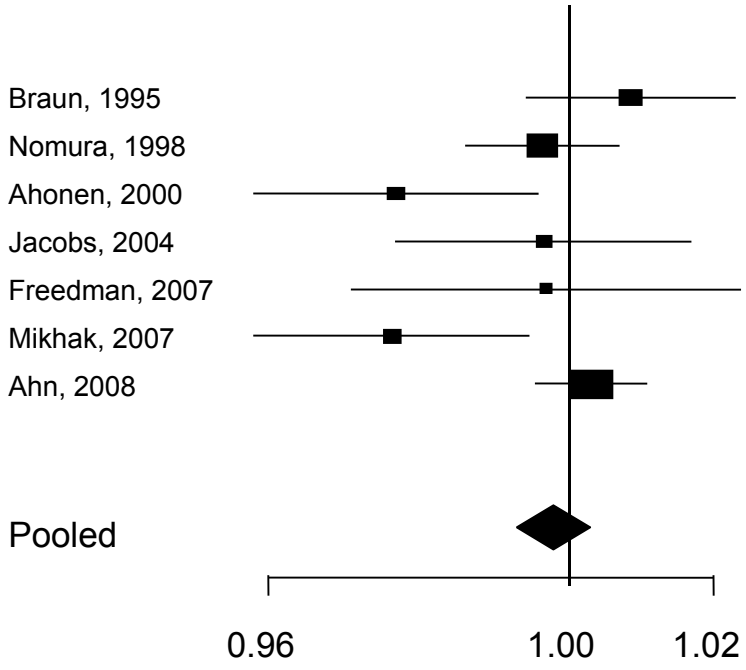


Figure 13.5 - Dose-response relative risks between 25-hydroxyvitamin D and prostate cancer. All studies were cohort or nested-case control designs.



Chapter 14 – Randomised trials on vitamin D, cancer and mortality

14.1 Rationale for randomised trials

A double-blinded, placebo controlled, randomised trial is the "gold standard" in establishing a causal association because in theory, confounding factors have been evenly distributed among randomisation groups (including the yet unknown confounding factors) and endpoint assessment is not influenced by knowledge of whether a subject is taking the active drug or the placebo. Trials with vitamin D have mainly been organised for the prevention of fracture in elderly people, usually in association with calcium supplements. Prevention studies with vitamin D have rarely been done in the context of vitamin D and cancer. In practice, these trials have practical limitations, including selection of the effective dose, varying baseline levels of subjects before randomisation, compliance with the intervention, contamination of the placebo group (i.e., taking of vitamin D supplements by subjects allocated to the placebo group), and unknown lag time between start of the intervention and disease onset. Thus, when these studies show a null association, caution must be taken to not over-interpret the results. In addition to the absence of a true association, one or more of the limitations mentioned above could produce a null association. If a significant association is found, double blind, placebo controlled randomised trials are the strongest evidence of a causal association.

14.2 Randomised trials on vitamin D supplements and cancer incidence

Three double-blind, placebo-controlled randomised trials have examined the influence of vitamin D and calcium supplements on cancer risk (Table 14.1).

14.2.1 UK trial for the prevention of osteoporotic fractures

The trial by Trivedi *et al.,* (2003) had as its primary objective the reduction of fracture risk and used the equivalent of 41 µg vitamin D per day, without calcium supplements. It found a significantly reduced risk of fracture, but no reduction in colorectal or in all-cancer risk. Baseline serum 25-hydroxyvitamin D levels were not known. Blood draw in samples during the trial showed that subjects in the intervention group had serum 25-hydroxyvitamin D level on average 40% higher than subjects in the control group.

14.2.2 The Women's Health Initiative Trial

Within the Women's Health Initiative (WHI) in the USA (Wactawski-Wende *et al.,*2006), a randomised trial was organised having as its stated objective the influence of 10 µg of vitamin D per day and 1 g of elementary calcium on colorectal cancer incidence. 36,282 women were included in the trial, and mean follow-up duration was 7 years. Results of the trial were negative for an impact on colorectal cancer risk or on all cancer risk (Table 14.1). No impact was noticeable on stage of colorectal cancer. Also, published results showed strictly no divergence during the entire trial period in the cumulative incidence of colorectal cancer occurrence between the two groups.

A nested case-control study organised within the WHI trial including 317 colorectal cancer cases and 317 matched controls (matching on age, race, centre, and date of blood sample), showed that the risk of colorectal cancer increased with decreasing serum 25-hydroxyvitamin D levels at baseline, before use of supplements or placebo. Results were suggestive of a possible interaction between baseline serum 25-hydroxyvitamin D levels and vitamin D supplement intake i.e., the impact of supplements on colorectal cancer risk increased with decreasing baseline levels, but the interaction term was not statistically significant (p =0.54). However, to fully examine such an interaction, this nested-case-control study should have included at least ten times more subjects. All together, results of the WHI trial suggest that vitamin D status would be a predictor of colorectal cancer occurrence, but not a causal agent, since supplementation did not influence colorectal cancer occurrence.

The WHI trial also analysed breast cancer incidence according to assignation to vitamin D and calcium supplements, or to placebo (Chlebowski *et al.,* 2008). No association was found with treatment allocation, and stage distribution of breast cancer at diagnosis was similar in the two groups. However, in the intervention group, the mean size of invasive breast cancer was 1.54 cm (SD: 1.23) versus 1.71 cm (SD: 1.29) in the control group (P=0.05).

For non-cancer endpoints, results of vitamin D and calcium supplementation on diabetes (de Boer *et al.,*2008), coronary events (Wang *et al.,*2008), blood pressure (Margolis *et al.,*2008), physical functioning (Brunner *et al.,*2008) and risk of benign proliferative breast disease (Rohan *et al.,*2008) were all negative.

14.2.3 The Nebraska trial

A 4-year, population-based, double-blind, randomised placebo-controlled trial of vitamin D and calcium was conducted with the primary outcome being fracture incidence, and the principal secondary outcome cancer incidence (Lappe *et al.,*2007) The subjects in the study were 1,179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged 55 and over in a 9-county rural area of Nebraska, USA. Subjects were randomly assigned to receive each day 1.4-1.5 g supplemental elementary calcium alone (Ca-only), supplemental calcium plus 27.5 µg vitamin D_3 (Ca + D), or placebo. When analysed by intention to treat, cancer incidence was lower in the (Ca + D) women than in the placebo control subjects ($P < 0.03$). Authors concluded that improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women (Lappe *et al.,*2007).

14.2.4 Vitamin D supplements and mortality

A meta-analysis of 18 randomised trials on intakes of vitamin D and calcium supplements found that 12 to 15 µg per day of vitamin decreased all-cause mortality (Autier and Gandini, 2007). These doses were similar to those tested in the WHI trial (Wactawski-Wende *et al.,*2006) and in the UK trial on elderly people (Trivedi *et al.,*2003). Mean baseline serum 25-hydroxyvitamin D level in eight trials ranged from 8.8 to 30.1 ng/mL, but was lower than 20 ng/mL in seven trials. Eight of these trials reported increases in serum 25-hydroxyvitamin D level in the intervention group but variations ranged from a factor 1.4 to 5.2 mainly because of compliance issues (Autier and Gandini, 2007). There was also some suggestion for a lower increase induced by vitamin D supplements when baseline levels were higher. The decrease in mortality risk was associated with vitamin D supplements and not with calcium supplements. The meta-analysis could not identify specific causes of mortality that contributed to reduction in all-cause mortality.

Table 14.2 shows fatal events in the Wactawski-Wende *et al.,* (2006) and Trivedi *et al.,* (2003) trials. While no change at all between intervention and placebo groups was perceptible when considering cancer risk, all-cause mortality was decreased with borderline significance, and data also suggested decreased mortality from all cancers and from colorectal cancer, although the two latter results were not statistically significant. But trial sizes were not sufficient for reaching statistically significant results with all-cancer and colorectal cancer mortality. Also, no other randomised trial on vitamin D supplementation and any health condition (e.g., fracture risk) reported details on specific causes of death.

14.3 Discussion

14.3.1 Reasons for the negative result of the WHI trial

Commentaries on the negative findings of the WHI trial invoke too low vitamin D doses and too short trial duration (Holick, 2006; Giovannucci, 2006).

1/ The WHI trial was of insufficient trial duration, and time between vitamin D action and change in colorectal cancer occurrence could be longer than 7 years. However, in the last years of the WHI trial, there was no indication in the data for an eventual start of a reduction in colorectal cancer incidence. Data even showed that at the end of the trial, there was slightly more colorectal cancer diagnosed in women supplemented with vitamin D and calcium than in women receiving placebo.

2/ Compliance to supplementation was low. Throughout the entire trial duration, only 50 to 60% of women took 80% of the scheduled supplementation regimen (Wactawski-Wende *et al.,*2006). The same WHI trial with calcium and vitamin D that took fracture risk as its endpoint did an analysis restricted to women adhering to the regimen, and found that in these women, the hip fracture risk was reduced by 29% (95% CI: -48%;-3%) (Jackson *et al.,*2006). Probably the reduction in hip fracture risk was due more to calcium than to vitamin D supplements (see Chapter 16 and Tang *et al.,*2008).

3/ Doses of vitamin D supplements were insufficient. Answering this question is hampered by the absence of baseline and in-study measurement of serum 25-hydroxyvitamin D levels in the WHI trial, which would have given information on real changes in serum 25-hydroxyvitamin D level induced by the intervention. The lack of this information also hampers examination of whether vitamin D supplements would be beneficial in subjects with low vitamin D status at baseline.

4/ The reduction of colorectal cancer incidence would have occurred in subjects with low vitamin D status at baseline. A lack of serum 25-hydroxyvitamin D level at baseline hinders knowing whether vitamin D supplements would be beneficial in subjects with low vitamin D status at baseline. The nested case-control study organised within the WHI trial did not include sufficient numbers of cases and control subjects to explore the possibility of an interaction between supplementation with vitamin D and serum 25-hydroxyvitamin D levels at baseline. If true, in the context of the null result of the WHI trial, this hypothesis would imply that in subjects with high vitamin D status at baseline, vitamin D supplements could increase the likelihood of colorectal cancer.

5/ Many interactions seem to exist between vitamin D and other substances, for instance, menopause hormone therapy (MHT) and calcium. The WHI trial was initially mounted for testing the impact of MHT on various health conditions. So, the trial organised with vitamin D and calcium supplementation randomised women some of whom were already assigned to taking active MHT and others already assigned to taking the MHT placebo. Reanalysis of the WHI trial results found that concurrent active MHT led to increased colorectal cancer risk associated with calcium plus vitamin-D supplementation (HR=1.50, 95% CI: 0.96–2.33) while placebo MHT led to decreased colorectal cancer risk associated with calcium plus vitamin-D supplementation (HR= 0.71, 95% CI: 0.46–1.09) (p value for-estrogen-interaction = 0.018) (Ding *et al.,* IJC, 2007). Consistent interaction was also found by reported estrogen use (p interaction = 0.037). These results suggest that biological interactions between vitamin D, calcium and estrogens at the cellular level may have reduced the potential beneficial influence of vitamin D and calcium supplementation in the prevention of colorectal cancer.

Calcium is another compound of possible interaction. For instance, randomised trials have shown that calcium supplements in the order of 1.2 to 2.0 g of elemental calcium per day during 3 or 4 years may decrease the recurrence of colonic adenoma (Weigarten *et al.,* 2008). This protective effect on polyps and also on colorectal cancer was more pronounced when serum 25-hydroxyvitamin D levels were high (Grau *et al.,*2003; Jenab *et al.,*2008). We do not know whether 25-hydroxyvitamin D levels obtained in the intervention group in the WHI trial were high enough to influence the effect of calcium.

6/ Individual vitamin D status as measured by serum 25-hydroxyvitamin D level may be more of a risk marker than a risk factor. That is, low vitamin D status would reflect an individual's propensity to develop diseases. This propensity would be associated with lifestyle, e.g., obesity, smoking, low physical activity. If the risk marker hypothesis is grounded, then serum 25-hydroxyvitamin D level would be a predictor of disease occurrence and of poorer survival. If the risk factor hypothesis is true, then supplementation with vitamin D should reduce disease occurrence and improve survival. The failure of two randomised trials to show a decreased incidence of cancer and mainly of colorectal cancer favours the risk marker hypothesis. The discovery by the a nested case-control study organised within the WHI trial that women developing a colorectal cancer had lower serum vitamin D at baseline than women who did not develop this cancer further supports the risk marker hypothesis. Furthermore, in the WHI trial, the influence of supplementation with vitamin D and calcium on colorectal cancer risk did not change across strata of lifestyle factors known to be associated with low vitamin D status, e.g., high body mass index or current smoking (Wactawski-Wende *et al.,*2006).

14.3.2 Critiques of the Nebraska trial

Results from the Nebraska trial (Lappe *et al.,*2007) accredited the hypothesis of insufficient vitamin D supplement doses in the WHI trial. However, the statistical analysis of this trial was not correct. For instance, subjects that received (Ca-only) had a decrease in cancer risk of similar magnitude to subjects receiving (Ca + D). Thus a correct intent-to-threat analysis comparing the (Ca + D) group with (Ca-only pooled with placebo) shows no significant decrease in cancer risk (Table 14.1). In contrast, an intent-to-threat analysis of (Ca + D pooled with Ca-only) versus placebo shows a significant reduced cancer risk due to calcium supplements (Table 14.1). The methodology and statistical analysis of this trial have been much criticised (Sood *et al.,*2007; Bolland *et al.,*2007; Ojha *et al.,*2007; Shabas *et al.,*2008). For instance, the cancer incidence was unusually high in the placebo

group, a bias that undermined the trial's findings (Shabas *et al.,*2008). In conclusion, the design of the Nebraska trial was biased, and its results were negative for vitamin D.

14.3.3 Another look at the vitamin D dose issue

Ordinary doses of vitamin D supplements as used during trials for the prevention of fractures (Avenell *et al.,*2005; Cranney *et al.,*2007; Tang *et al.,*2008 – See Chapter 17), or in the WHI trial did not reduce the incidence or the mortality from all cancers, colorectal cancer, breast cancer, and cardiovascular diseases. Decreases in disease-specific mortality could not be investigated by randomised trials on vitamin D supplements as they were neither designed nor sufficiently powered for that objective, and meta-analysis was limited by the absence of reporting of specific causes of mortality by the majority of these trials.

Another way to look at the dose issue is the fact that daily vitamin D doses in the range of 10 to 20 µg per day were able to significantly decrease all-cause mortality by 7% (Autier and Gandini, 2007). The negative results, or the unknown results, on specific causes of death diseases, but positive results on all-cause mortality support the notion that apparently "low doses" of vitamin D nevertheless have significant physiological impact.

The likelihood of the mortality reduction associated with the use of 10 to 20 µg per day of vitamin D supplements is supported by recent observations that patients with chronic kidney disease receiving vitamin D supplements have better overall survival (see Chapter 16). The biological mechanisms underlying the gain in life expectancy remain obscure but are probably not (mainly) mediated by a reduction in cancer risk.

The apparent beneficial impact of ordinary doses of vitamin D supplements on all-cause mortality is in sharp contrast with trials on anti-oxidants showing increasing all-cause mortality (see Chapter 5).

14.4 Conclusions

Results from three double-blind, placebo controlled randomised trials provided no evidence that supplementation with vitamin D in the range of 10 to 21µg per day could change the incidence of colorectal and breast cancer or of all cancers.

Results from a meta-analysis including 18 randomised trials provided evidence that supplementation with vitamin D in the range of 12 to 15 µg per day could significantly decrease all-cause mortality. The contribution of specific causes of mortality to the reduction in all-cause mortality remains unknown. Data from two trials that reported specific causes of death suggest the possibility that vitamin D supplements could have more impact on death from cancer than on cancer incidence.

Table 14.1 - Summary of randomised trials on vitamin D and invasive cancer

Study reference and endpoint	Type of randomised trial	Vitamin D daily dose	Elementary calcium daily dose	Mean trial duration (years)	No. in intervention group	No. in control group	Age at inclusion	No. cases in intervention group	No. cases in control group	RR	95% CI
Wactawski-Wende *et al.*,, 2006	Double-blind, placebo controlled	10µg	1.0 g	7	18,176 women	18,106 women	50-79				
Colorectal cancer								168	154	1.08	0.86-1.34
Colon cancer								128	126	1.00	0.78-1.28
Rectal cancer								44	30	1.46	0.92-2.32
SEER stage of invasive CRC											
Localised								71	63	1.11	0.79-1.56
Regional								68	62	1.09	0.77-1.54
Distant								21	21	0.97	0.53-1.78
All cancers								1634	1655	0.98	0.91-1.05
Chlebowski *et al.*,, 2008)	id.	id.	id.	id.	id.	id.	id.				
Breast cancer								528	546	0.96	0.85-1.09
SEER stage of breast cancer								No difference between the two groups (data not reported)			
Trivedi *et al.*,, 2003	Double-blind, placebo controlled	21 µg	No calcium supplement	5	1345 men and women	1341 men and women	65-84				
Colorectal cancer								28	27	1.02	0.60-1.74
All cancers								144	130	1.11	0.86-1.42
Lappe *et al.*,, 2007	Double-blind, placebo controlled	27.5 µg	1.5 g	4			>55				
All cancers (intervention is vitamin D supplements)					446 women	733 women		13	37	0.59	0.32-1.10
All cancer (intervention is calcium supplements)					891 women	288 women		30	20	0.50	0.29-0.87

Table 14.2 - Mortality in two trials on vitamin D supplements and cancer

	WHI trial*		Trivedi *et al.*,, 2003		Both trials					
	Vitamin D and calcium group	Placebo group	Vitamin D and calcium group	Placebo group	Vitamin D and calcium group	Rate per 1,000	Placebo group	Rate per 1,000	Relative risk	95% CI
No. subjects in group	18176	18106	1345	1341	19521		19447			
Deaths from colorectal cancer	34	41	7	11	41	2.1	52	2.7	0.79	0.52-1.18
Deaths all cancers	344	382	63	72	407	20.8	454	23.3	0.89	0.78-1.02
Deaths all causes	744	807	224	247	968	49.6	1054	54.2	0.91	0.84-1.00§

*Wactawaski-Wende *et al.*,, 2006 - § p = 0.050.

Chapter 15 – Vitamin D, cancer prognostic factors and cancer survival

15.1 Variation in cancer survival by season of diagnosis

Studies in individual subjects have suggested that sun exposure may have an impact on the survival and outcome from breast, colon and prostate cancer. In Norway, pronounced seasonal and latitudinal variations in UVB irradiation exist that are paralleled by a north to south gradient in the incidence of squamous cell cancer of the skin. A series of epidemiological investigations done by the same Norwegian group indicate that compared to cancer patients diagnosed during the winter season, cancer patients diagnosed during summer and autumn have an improved survival rate (Moan *et al.,*2005; Robsahm *et al.,*2004; Porojnicu *et al.,*2008). This was observed for prostate cancer (46,205 patients, mean follow-up of 3 years; Lagunova *et al.,*2007), breast cancer (49,821 patients, 7.2 years of follow-up; Porojnicu *et al.,*2007), lung cancer (45,681 patients, mean follow-up 18 months; Porojnicu *et al.,*2007), colon cancer (37,745 patients, mean follow-up 3 years; Moan *et al.,*2005; 2007) and Hodgkin lymphoma (3,139 patients, 10 years follow-up; Porojnicu *et al.,*2005). Overall, in autumn compared to winter, 30% decreases in mortality in the 3 years following diagnosis of colon, breast and prostate cancer are observed (Porojnicu *et al.,*2007).

An American study (Zhou at al., 2005) investigated the effect of the season in which surgery took place as well as the effect of vitamin D intake on the survival of patients with non small cell lung cancer. The authors reported a beneficial effect of diagnosis in the summer season combined with vitamin D intake.

In the United Kingdom, a cancer-registry based study involving 588,435 men and 606,127 women diagnosed with cancer found seasonality in cancer survival (Lim *et al.,*2006). Compared to the winter, mortality hazard rate observed in the summer was 0.86 (95 % CI: 0.88-0.89) for cancer of the breast, 0.94 (CI: 95 % 0.91-0-97) for colorectum, 0.95 (95 % CI: 0.92-0.97) for lung cancer, and (0.94 ; 95 %CI: 0.93-0.95) for all cancer sites combined

In Australia, 2,710 deaths occurred among 25,845 cases of melanoma followed during 63 months (Boniol *et al.,*2006). More melanomas were diagnosed in the summer than in the winter. There was also a 16% (95% CI: -6%;-28%) decrease in the multivariate adjusted fatality rate between winter and summer after adjustment for Breslow thickness, suggesting a reason other than earlier diagnosis for the survival advantage, for instance, a late promotional effect of greater exposure to UV in the summer.

15.2 Individual measurement of serum 25-hydroxyvitamin D levels

Recent studies have examined the survival of cancer patients according to individual serum 25-hydroxyvitamin D level measured years before disease onset.

In a study in Massachusetts (USA), 234 deaths occurred in 447 patients with early-stage Non–Small-Cell Lung Cancer followed during a median of 72 months (Zhou *et al.,*2008). The adjusted overall survival rate was 0.74 (95% CI: 0.50 to 1.10) in all patients and of 0.45 (95% CI, 0.24 to 0.82) in patients with stage IB-IIB disease for highest versus lowest quartile of serum 25-hydroxyvitamin D level.

In the Nurses' Health Study and the Health Professionals Follow-Up Study (USA), among 304 participants who were diagnosed with colorectal cancer, patients in the highest quartile when compared with the lowest quartile, had an age-stage-adjusted HR of 0.52 (95% CI: 0.29 to 0.94) for overall mortality. A trend toward improved colorectal cancer–specific mortality was also seen (HR=0.61; 95% CI: 0.31 to 1.19) (Ng *et al.,* 2008).

Studies in diseases other than cancer also show improved survival with higher serum 25-hydroxyvitamin D level measured at baseline. A prospective cohort study in Germany followed, during a median follow-up period of 7.7 years, 3,258 male and female patients who underwent coronary angiography. 737 patients died during follow-up, including 463 deaths from cardiovascular causes (Dobnig *et al.,*2008). Multivariate-adjusted hazard ratios (HRs) for patients in the lower two 25-hydroxyvitamin D quartiles (median, 7.6 and 13.3 ng/mL) were higher for all cause mortality (HR= 2.08; 95% CI: 1.60-2.70; and HR= 1.53; 95% CI: 1.17-2.01; respectively) and for cardiovascular

mortality (HR= 2.22; 95% CI, 1.57-3.13; and HR, 1.82; 95% CI, 1.29-2.58; respectively) compared with patients in the highest 25-hydroxyvitamin D quartile (median, 28.4 ng/mL). Similar results were obtained for patients in the lowest 1,25-dihydroxyvitamin D quartile. These effects were independent of the presence of coronary artery disease, physical activity level, co-morbidities and functional capacity. The same cohort found an increased risk of fatal cancer in patients with low baseline serum 25-hydroxyvitamin D level (Pilz *et al.,*2008, see Chapter 12). An advantage of this study was that quartiles of baseline serum 25-hydroxyvitamin D level were computed from quartile distributions within each month of blood draw, a method likely to control for seasonal differences in patients included in the study.

15.3 Skin solar elastosis and survival of patients with cutaneous melanoma

Solar elastosis is considered as a strong marker of chronic sun exposure during lifetime, as for instance commonly observed in older adults and elderlies that had outdoor occupation during most of their life. The association between solar elastosis and cutaneous melanoma has been investigated primarily to assess the importance of chronic sun exposure on cutaneous melanoma occurrence. It has been further proposed that presence and extent of solar elastosis in skin specimens or biopsies could also be considered as an indicator of high vitamin D status during long periods of life. Essential characteristics of these studies are shown in Table 5.1. Four follow-up studies of patients with cutaneous melanoma found an association between survival of melanoma patients and solar elastosis, a histological indicator of chronic sun damage to the skin (Knutson *et al.,*1971; Heenan *et al.,*1991; Barnhill *et al.,*1996; Berwick *et al.,*2005). This association was not found in three studies (Larsen and Grude 1979; Sondergaard and Schou, 1985; Vollmer, 2007). The study of Vollmer (2007) included 1,234 cutaneous melanoma cases, and both the studies of Vollmer (2007) and Sondergaard and Schou (1985) adjusted survival hazard estimates on other melanoma prognostic factors (e.g., clinical stage, site of the lesion, thickness of the lesion, level of invasion, ulceration). There is thus little support for an association betwee vitamin D status and survival of melanoma patients. This negative conclusion is supported by an Italian study that found significantly increased survival in melanoma patients who had intermittent sun exposure before dagnosis, while melanoma patients who had an history of outdoor occupation had (non significant) decrease in survical (Rosso *et al*., 2008).

15.4 Serum 25-hydroxyvitamin D levels and cancer prognostic factors

A small cross-sectional study of 84 patients diagnosed with colorectal cancer and 30 healthy controls found equal levels of serum 25-hydroxyvitamin D levels by cancer stage, but decreasing levels of 1alpha,25-dihydroxyvitamin D with advancing stage: from mean 73 pg/ml in stage I cancer to 34 pg/ml in stage 4 cancer (Niv *et al.,*1999). The serum PTH levels were increased with advancing stage. A small study in 204 women found that serum levels of 25-hydroxyvitamin D were significantly higher in patients with early-stage breast cancer than in women with locally advanced or metastatic disease (Palmieri *et al.,*2006). In these two studies, however, the possibility of reverse causation cannot be ruled out as 25-hydroxyvitamin D levels were assessed in patients who already had cancer.

15.5 Discussion

In Norway, the largest seasonal difference in colon and prostate cancer survival was observed for cancer diagnosed in people living in the most northern area of the country. However, in latitudes around 69 degrees North in Norway, little variation in serum 25-hydroxyvitamin D levels was observed, with a decrease of only 6% between September and February in a sample of healthy volunteers (Brustad *et al.,*2007). Other studies show an absence of marked seasonal variations in serum 25-hydroxyvitamin D level in Norwegian women older than 65 years (Moan *et al.,*2007) and in Norwegian men and women 31 to 80 years old (Porojnicu *et al.,*2006). These observations are in contradiction with the seasonal variations in survival from colon and breast cancer in women 65 and older (Moan *et al.,*2007; Porojnicu *et al.,*2007); and in survival of men with prostate cancer (Lagunova *et al.,*2007). The absence of clear parallelism between seasonal variation of serum 25-hydroxyvitamin D level and survival according to season suggests that (unknown) factors other than vitamin D status are involved.

Seasonal variation in the risk of death, including risk of dying from cardiovascular or respiratory or infectious disease is well documented. In Europe, compared to the April-November period, mortality rates in the December-March period are 28% and 21% greater in Portugal and Spain, respectively, for

10 and 12% in Finland and Denmark, respectively (Healy, 2003). If seasonal variation in UVB irradiation had an influence, then seasonal contrast in mortality should be more pronounced in northern than in southern countries. New Zealand extends from 34 to 47 degrees of latitude. Statistically significant seasonal variations in mortality from 7 out of the 14 main WHO ICD-10 chapters for disease classification exist, whereas latitudinal differences are not associated with differences in mortality (Davie *et al.,*2007). No seasonal variation in cancer mortality was found (RR=1.03; 95% CI: 0.98-1.08). In studies on serum 25-hydroxyvitamin D level and cancer or cardiovascular disease in German patients undergoing coronarography, dying from cardiovascular disease was found to be higher in the winter period than in the summer period (Pilz *et al.,*2008b). This suggests that seasonal variation in survival of cancer patients could largely be influenced by the more general impact of season on mortality and survival of patients diagnosed with potentially fatal disease.

A last comment relates to the hazard of equating seasonal variations in disease or death occurrence and survival to fluctuations in serum 25-hydroxyvitamin D level throughout the year (See Chapter 9). Seasonal variations in a myriad of health events have been described. The underlying reasons are unknown for most of them and it would be very difficult to establish with reasonable certainty if the seasonal variation in vitamin D status could explain these phenomena.

15.6 Conclusions

Season of diagnosis is a predictor of survival from cancer, but the reasons underlying seasonality patterns remain to be established

The few studies on cohorts of cancer patients (and in patients with cardiovascular disease) suggest that a low serum 25-hydroxyvitamin D level could be associated with decreased survival, but it remains to be established whether the association is a causal one.

Mortality from many frequent, serious, health conditions and total all-cause mortality follow a similar seasonal pattern, suggesting that other, non-cancerous conditions could influence survival of cancer patients.

Studies that examined the survival of melanoma patients according to skin solar elastosis yielded inconsistent results.

Table 5.1 – Essential characteristics of studies on solar elastosis and Survival of patients diagnosed with cutaneous melanoma.

Study	No. of patients	RR was adjusted on main known melanoma prognostic variables
Studies that found higher survival associated with solar elastosis		
Knutson *et al.,* 1971	230 (type?)	No
Heenan *et al.,* 1991	382 stage I	No
Barnhill *et al.,* 1996	548 localized	No
Berwick *et al.,* 2005	528 localized	Yes
Studies that found no association between solar elastosis and survival		
Larsen & Grude 1979	669 localized	No
Sondergaard & Schou, 1985	2012	Yes
Vollmer, 2007	1234 localized	Yes

Chapter 16 – Special topics: non-Hodgkin lymphoma and VDR genetic variants

16.1 Sun exposure, vitamin D and risk of haemopoietic cancers

16.1.1 Non Hodgkin lymphoma (NHL)

Patients diagnosed with melanoma or non-melanoma skin cancer are at an increased risk of developing NHL (Levi *et al.,*1996). Likewise, the risk of melanoma is increased after a diagnosis of NHL (Levi *et al.,*1996). A meta-analysis of 7 studies found a risk of 2.0 (95% CI 1.8-2.2) of developing NHL in melanoma survivors, and a risk of 1.4 (95% CI 1.3-1.6) of developing melanoma in NHL survivors (Lens and Newton-Bishop, 2005). It has been postulated that the association between the NHL and skin cancers may be due to common etiologic determinants (Hall *et al.,*1995). Since UV radiation exposure is a major risk factor for skin cancers (IARC, 1992), sun exposure and other sources of UV radiation have also been investigated as a potential cause of NHL, too (Cartwright *et al.,*1994).

Total or recreational exposure to UV radiation

A population based case-control study based on 704 NHL cases and 694 population controls from 2 states of Australia, found an inverse relation between total reported sun exposure hours and risk of NHL (Hughes *et al.,*2004). Relative to the lower quartile of total sun exposure hours, the OR in subsequent quartiles were 0.72 (95% CI 0.53-0.98), 0.66 (95% CI 0.48-0.91) and 0.65 (95% CI 0.46-0.91), Strong inverse relations were also found for sun exposure during nonworking days (OR=0.47, 95% CI 0.34-0.66 for the 4th versus 1st exposure quartile) and sun exposure on vacation (OR=0.60, 95% CI 0.43-0.85 for the 4th versus 1st exposure quartile). The associations were stronger for women and in childhood.

In the Scandinavian lymphoma aetiology (SCALE) study, a large population based case-control study including over 3,000 NHL and a similar number of controls, conducted in Denmark and Sweden between 1999 and 2002, the risk of NHL was reduced by 30-40% according to various indicators of recreational UV exposure (Smedby *et al.,*, 2005). The OR was 0.7 (95% CI 0.6-0.9) for sunbathing ≥4 times/week in summer at age 20 years compared to never sunbathing, 0.6 (95% CI 0.5-0.8) for ≥2 sunburns/year at age 20 years versus no sunburns. Similar results were found for sunbathing or sunburn 5-10 years before interview, number of sun vacations abroad or use of solaria/sun lamps. No clear difference emerged between NHL lymphoma subtypes.

A population based case-control study conducted between 1998 and 2000 in four Surveillance, Epidemiology, and End Results (SEER) registries (Iowa, Los Angeles County, metropolitan Detroit and metropolitan Seattle) and based on 551 NHL cases aged 20-74 years and 462 controls selected by random digit dialling (age <65 years) or Medicare/Medicaid rosters (age 65-74 years) found ORs ranging between 0.73 and 0.78 in the highest exposure category compared to the lowest one, for hours spent in the mid-day sun during summer in different periods of life, although none of these estimates was statistically significant (Hartge *et al.,*2006). No clear association emerged with use of sunlamps or tanning booth (where prevalence of use was low) or with number of month per year with a tan as teenager or in the past 10 years. Subjects with a history of 5 or more blistering sunburns had an OR for NHL of 0.68 (95% CI 0.47-0.97) compared to subjects without a history of blistering sunburns.

In a population based case-control study conducted in 6 regions of Germany (Weihkopf *et al.,*2007) on 554 B-NHL (including 76 multiple myelomas) and 35 T-NHL and an equal number of individually matched controls there was an inverse association between cumulative days spent at sun-exposed location and B-HNL risk: compared to subjects with <350 cumulative days, the OR for those with >1,190 days was 0.6 (95% CI 0.4-0.9), although no association emerged for cumulative hours of outdoor leisure activities excluding vacation (OR=1.3, 95% CI 0.9-2.0 for >53,000 hours vs ≤ 24,000 hours) or occupational sunlight UV exposure (see below). A use of sunbeds >118 times relative to never use was associated with an OR of 0.6 (95% CI 0.4-0.9). No clear association emerged for T-NHL.

In a population based case control study conducted in Connecticut (Zhang *et al.,*2007) between 1996 and 2000 on 601 women with incident NHL and 717 control women, cumulative duration of

suntan was directly related to NHL risk (OR=1.5, 95% CI 1.0-2.4 for the highest vs the lowest exposure tertile) as was spending time in strong sunlight during summer (OR=1.7, 95% CI 1.2-2.4).

Kricker *et al.,* (2008) examined the relationship between sun exposure and NHL in a pooled analysis of 10 studies participating in the International Lymphoma Epidemiology Consortium (InterLymph). Ten case-control studies (including the 5 previously discussed) which covered 8,243 cases and 9,697 controls in the USA, Europe and Australia, contributed original data to the pooled analysis. The participants were of European origin. Four kinds of measures of self-reported personal sun exposure were assessed at interview (outdoors and not in the shade in warmer months or summer; in the sun in leisure activities, in sun light, sun bathing in summer). Eight studies provided data to estimate a composite index (time-weighted average) of total sun exposure, for a total of 4,499 NHL cases and 5,583 controls. Compared to the lowest quartile of exposure, the OR was 0.92 (95% CI 0.71-1.20) in the second, 0.90 (95% CI 0.76-1.07) in the third and 0.87 (95% CI 0.71-1.05) in the fourth quartile. When only recreational sun exposure was considered, the OR in subsequent quartiles of exposure became 0.88 (95% CI 0.74-1.04), 0.85 (95% CI 0.69-1.04), and 0.76 (95% CI 0.63-0.91), respectively. Similar patterns were seen for exposure in different periods of life. No clear differences emerged between men and women, B- or T-cell NHL or subtypes of B-NHL.

In a hospital based case-control study on lymphoid malignancies conducted in France between 2000 and 2004 (Grandin *et al.,*2008), including 395 NHL cases and 748 controls no association emerged for frequency of outdoor activities since leaving school (OR=0.9, 95% CI 0.6-1.4 for >6 vs <1 hours/week) or in the last 10 years (OR=0.8, 95% CI 0.6-1.3 for >7.5 vs <1-5 hours/week) or for all uses of artificial UV radiation (OR=1.0 for yes vs no).

Occupational exposure to UV radiation

A few studies have considered indirect measures of UV exposure, such as occupation.

In a case-control study of NHL and skin cancer deaths conducted in 24 states of the USA, potential occupational exposure to sunlight was inferred from the occupation derived from the death certificate (Freedman *et al.,*1997). The OR of NHL for occupational exposure to sunlight was 0.88 (95% CI 0.81-0.96). For comparison, that of skin cancer was 1.14 (95% CI 0.96-1.36). In the same study, residence in the states with the highest sun exposure was directly associated to melanoma (OR=1.12, 95% CI 1.06-1.19) and skin cancer (OR=1.30, 95% CI 1.18-1.43), but inversely with NHL (OR=0.83, 95% CI 0.81-0.86).

A cohort study from Sweden found an increased risk of NHL for subjects residing in southerly latitudes, but no association for sun exposure inferred from job titles (Adami *et al.,*1999).

Similarly, no increase in risk of NHL was observed for sun exposure in a cohort of electric utility workers from the US (van Wijngaarden and Savitz 2001). In a Swedish cohort of construction workers, sunlight exposure was associated with an increased risk of NHL (Hakansson *et al.,*2001).

In an Italian case-control study including 446 cases of NHL and 1295 hospital controls the odds ratio for patients reporting ever occupational UV exposure was 1.0 (95% CI 0.7-1.4), and the risk was similar for duration of exposure longer than 10 years (Tavani *et al.,*2006).

Most of the studies described in the previous section also reported data on occupational exposure to UV radiation.

The Australian case-control study found an OR of NHL of 1.21 (95% CI 0.87-1.69) in the highest tertile of lifetime occupational sun exposure compared to subjects never exposed to sun at work (Hughes *et al.,*2004).

In the Scandinavian lymphoma aetiology (SCALE) study, the risk of ever having had an outdoor occupation was 1.1 (95% CI 1.0-1.2) (Smedby *et al.,*2005).

In the population based case-control study conducted in 6 regions of Germany (Weihkopf *et al.,*2007) no association emerged between cumulative hours of occupational sunlight UV-exposure and NHL risk: for B-NHL the OR was 0.9 (95% CI 0.6-3.9) for >7,600 cumulative hours of exposure vs none, and 0.9 (95% CI 0.3-3.5) for T-NHL.

Vitamin D and Cancer

In the population based case control study conducted in Connecticut (Zhang *et al.,*2007) on 601 women with incident NHL, having an outdoor occupation was associated with an OR of 1.8 (95% CI 1.0-3.4).

In the Interlymph pooled analysis (Kricker *et al.,*2008), 6 of the studies provided data to estimate a composite index (time-weighted average) of non-recreational (working days) sunlight exposure, including the studies from Australia (Hughes *et al.,*2004), the SCALE study (Smeby *et al.,*2005), the study from Germany (Weihkopf *et al.,*2007) and the one from Connecticut (Zhang *et al.,*2007). Compared to the lowest quartile of exposure, the estimated ORs were 1.06 (95% CI 0.94-1.19) for the second, 0.98 (95% CI 0.81-1.20) for the third and 1.01 (95% CI 0.89-1.15) for the fourth quartile. No association with NHL risk emerged even when non-recreational sun exposure at different ages or time periods was considered.

Indicators of host susceptibility to UV radiation

The SCALE study (Smedby *et al.,*2005) did not find an association with hair colour (OR=1.0 for blond, and 0.8 for red vs dark brown), and found an increased risk for lighter eye colour (OR=1.2, 95% CI 1.0-1.4 for blue vs brown or black)

In the US SEER study (Hartge *et al.,*2006) an inverse association, significant for eye colour (OR=0.47, 95% CI 0.30-074 for green/blue green vs dark brown) and not significant for complexion (OR=0.75, 95% CI 0.41-1.40 for light vs dark), was found. Skin reaction to sun exposure was not associated with NHL.

In the French study (Grandin *et al.,*2008) no association emerged between NHL and eye colour (OR=0.9, 95% CI 0.7-1.2, for blue/gray/green vs hazel/brown/black), hair colour (OR=1.2 for blond/red vs other) or skin colour (or=1.1 for very fair/fair vs olive/brown), nor with propensity to burn or tan.

Dietary vitamin D intake

In a population based case-control study from Sweden (Chang *et al.,*2006) including 591 NHL and 460 population controls dietary vitamin D intake was not associated with risk of all NHL (OR=1.3, 95% CI 0.8-2.1 for the highest vs the lowest quartile of intake), or any common subtypes other than T-cell lymphoma (OR=5.0, 95% CI 1.2-19.). The latter result was based on few cases only.

In the case-control study form the USA, Hartge and colleagues (Hartge *et al.,*2006) also investigated the association of HNL risk with total intake of vitamin D from diet and supplements and with consumption of foods rich in vitamin D, including milk and fish. Neither total vitamin D (OR=1.10, 95% CI 0.72-1.67, for the highest vs the lowest intake quartile) nor milk (OR=1.01, 95% CI 0.67-1.52) consumption was associated with NHL risk. Tuna and other types of oily fish showed a non-significant inverse association (OR= 0.80, 95% CI 0.53-1.20).

In a hospital-based case-control study (Polesel *et al.,*2006) conducted in Italy of 190 incident histologically-confirmed NHL cases and 484 controls admitted to hospital for acute non-neoplastic diseases, dietary vitamin D intake was inversely associated with NHL risk (OR=0.6, 95% CI 0.4-0.9 for the highest vs the lowest tertile of intake). The effect was stronger in women and for follicular NHLs, while no difference emerged across strata of age, smoking habits and alcohol consumption.

Serum vitamin D levels

Giovannucci and colleagues (Giovannucci *et al.,*2006a) investigated the association between predictors of vitamin D status and cancer incidence and mortality in the Health Professional Follow-Up Study cohort, consisting of 47,800 US male dentists, osteopaths, pediatrists, pharmacists and veterinarians aged 40-75 years in 1986 and followed up until 2000. The relation between the identified determinants (dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence and leisure-time physical activity) and plasma 25-hydroxyvitamin D levels was determined in a subsample of 1095 men through linear regression models (r^2=0.28). The model was tested by comparing measured and estimated plasma 25-hydroxyvitamin D levels in an independent sample of 542 men with satisfactory results. During the follow-up of the cohort 330 NHL cases were identified. The estimated adjusted RR of NHL for an increment of 25 mmol/L in predicted plasma 25-hydroxyvitamin D was around 0.75 (95%CI 0.50-1.15; RR and CI estimated from a figure).

Among 16,818 participants in the Third National Health and Nutrition Examination Survey (NHANES III) followed up from 1988-1994 through 2000 there were 40 deaths from NHL/leukaemia (Freedman *et al.,*2007). No clear association emerged between serum 25-hydroxyvitamin D levels and risk of NHL/leukaemia death.

16.1.2 Other lympho-hematopoietic cancers

Besides NHL, some studies discussed above also included cases with other lympho-hemopoietic diseases.

The Danish/Swedish SCALE study included 618 Hodgkin lymphoma (HL) cases, and found inverse associations between various indicators of recreational UV exposure and HL risk, similar to those found for NHL (Smedby *et al.,*2005).

In the case-control study from Germany 116 HL cases were also studied. HL risk was inversely associated with cumulative number of days spent at sun-exposed locations, but not with hours of outdoor leisure activities, occupational UV exposure or use of sunbeds (Weihkopf *et al.,*2007).

In the hospital based case control study from France 147 cases of HL, 103 of multiple myeloma (MM) and 168 of lymphoproliferative syndrome (LPS, i.e. 132 chronic lymphocytic leukaemia's and 36 hairy cell leukaemia's) were also included (Grandin *et al.,*2008). HL but not MM or LPS risk was directly related to various indicators of host susceptibility to UV radiation, and the OR was 3.4 (95% CI 1.4-8.4) for subjects with blond red hair and a propensity to burn after sun exposure, as compared to those with brown/black hair and no propensity to burn. A significant inverse trend in risk emerged between frequency of outdoor activities and MM risk, and the OR was 0.5 (95% 0.2-1.3) for >6 hours/week as compared to <1.

In the Health Professional Follow-Up Study cohort (Giovannucci *et al.,*2006a) a significant inverse relation emerged between predicted plasma 25-hydroxyvitamin D and leukaemia (RR=0.44 for a 25 mmol/L increment, 95% CI 0.20-1.00), bases on 82 cases. For MM the RR was around 1.15 (95%CI 0.55-2.40; RR and CI estimated from a figure), based on 97 cases.

Finally, a case-control study on 138 children with acute lymphoblastic leukaemia (ALL) and 138 control children from northern California, US, did not find any association between maternal vitamin D intake during pregnancy and risk of ALL in the child (Jensen *et al.,*, 2004).

16.1.3 Conclusions

In conclusion, the epidemiologic evidence does not confirm the hypothesis that UV exposure is a risk factor for NHL. If anything, some studies, including the Interlymph pooled analysis of 10 case-control studies (Kricker *et al.,*2008), found a protective effect of sun exposure, and particularly recreational sun exposure.

No clear association emerged between NHL and occupational sunlight exposure, even in studies where recreational exposure was associated with a decreased risk. Potential confounding by social class or other occupational exposures possibly related to NHL for some job categories (e.g. viruses or pesticides for farmers) may have influenced the results in some studies. On the other hand, it is also possible that the inverse relation found for recreational UV radiation exposure may be the result of (residual) confounding by socioeconomic status, physical activity or some other factor. It has also been suggested that intermittent sun exposure would result in a greater net vitamin D production than continuous exposure, given the tight regulation of vitamin D synthesis in the human body (Hughes *et al.,*2004, Kricker *et al.,*2008).

No clear association emerged in the few studies that investigated risk of NHL associated to indicators of host susceptibility to UV radiation like skin, eye or hair colour, or propensity to burn or tan.

Data on the association between dietary intake or serum level of vitamin D and NHL risk, or between any vitamin D status indicator and the risk of other hemo-lymphopoietic malignancies were too scanty to allow any meaningful conclusion.

16.2 VDR genetic variants and cancer

More than one hundred studies have investigated the association of one or several VDR polymorphisms, or haplotypes, with cancer risk and / or clinical outcome, mostly for prostate, breast and colon cancers, and to a lesser extent for non-Hodgkin lymphoma, renal carcinoma and melanoma.

16.2.1 VDR polymorphisms and cancer risk

16.2.1.1 Prostate cancer

Numerous studies have yielded conflicting results in different populations. The most recent ones are summarised in Table 8.4.1.

Two recent meta-analyses have been conducted. A meta-analysis of 14 studies with TaqI genotyping (1870 prostate cancer cases; 2843 controls), 6 studies with poly(A) repeat genotyping (540 cases; 870 controls), 5 studies with BsmI genotyping (987 cases; 1504 controls), and 3 studies with FokI genotyping (514 cases; 545 controls) shows that these four polymorphisms are unlikely to be major determinants of susceptibility to prostate cancer on a wide population basis (Ntais, 2003). A second meta-analysis of 26 studies evaluating the association between vitamin D receptor TaqI, poly(A), BsmI, ApaI, and/or FokI polymorphisms, and prostate cancer risk suggest that the vitamin D receptor TaqI, poly(A), BsmI, ApaI and FokI polymorphisms are not related to prostate cancer risk. (Berndt *et al.,*2006).

Few studies have explored the joint association of circulating vitamin D levels with VDR polymorphisms. Vitamin D status, measured by 25-hydroxyvitamin D in plasma, interacts with the VDR FokI polymorphism and modifies prostate cancer risk. Men with the less functional FokI ff genotype (14% in the European-descent population) are more susceptible to this cancer in the presence of low 25-hydroxyvitamin D status and may have an increased risk of more aggressive cancer (Li, 2007).

16.2.1.2 Breast cancer

Twenty studies published in the last ten years found no overall association between selected VDR gene polymorphisms and postmenopausal breast cancer risk and older studies indicative of association of some VDR polymorphisms with risk of breast cancer, were not confirmed in more recent results. Thus, it is unlikely that VDR polymorphisms may be major determinants of breast cancer risk (Table 8.4.2).

Results are conflicting, and associations between VDR genotypes and risk of breast cancer may be influenced by dietary factors such as calcium intake. Thus, BsmI bb genotype has been associated with an increased risk in Caucasians (Trabert, 2007), but no association was found in the large Nurses' cohort (Chen, 2005), and an association with a reduced risk was found in patients with higher than median calcium intake (McCullough, 2007). The same interaction with calcium intake has been noticed for TaqI T allele (McCullough, 2007).

The start codon polymorphism FokI is generally not associated with breast cancer risk, but an increased risk is associated with FokI ff in the large Nurses' cohort (Chen, 2005).

16.2.1.3 Colorectal cancer

Few studies have investigated the association between VDR polymorphisms and colorectal cancer risk or prognosis. The studies have yielded limited evidence for a role of these polymorphisms (it should be noted that several different publications actually refer to the same study, e.g. 5 publications result from 2 large US case control studies of colon and rectal cancer). These studies are summarised in Table 8.4.3.

It appears that BsmI bb or haplotypes containing b, and FokI (start codon) f increase colorectal cancer risk, but that the VDR genotype effect may be modified by dietary calcium and fat: e.g. there is no association between FokI genotype and colorectal cancer among subjects with higher than

median calcium or dietary fat. In addition, the short SS variant of polyA may reduce colorectal cancer risk.

Four studies have investigated the association of Fok1 and Bsm1 VDR genetic polymorphisms and risk of sporadic colorectal adenoma, and found no direct association (Kim *et al.,*2001, Ingles *et al.,*2001, Peters *et al.,* Boyapati *et al.,*2003). However, it has generally been shown that higher calcium and vitamin D intake are associated with a modest reduction in risk of colorectal adenoma, the VDR genotype influence on adenoma development may be modified by calcium intake and vitamin D status and this relationship may be strongest among those who have at least one vitamin D receptor BsmI b allele (Boyapati *et al.,*2003). In addition, it was shown that those with the BB BsmI VDR genotype may be at reduced risk of colorectal adenoma in the presence of lower calcium and vitamin D intake (Kim *et al.,*2001).

The risk of large (>1 cm) adenomas decreases with increasing copies of the FokI f allele, and FokI genotype is more strongly related to large adenoma risk among subjects with low dietary calcium or vitamin D intake, which suggests that VDR FokI genotype influences development of colorectal adenomas. and that the effect may be modified by calcium and vitamin D status (Ingles *et al.,*2001).

16.2.1.4 0ther cancers

Three VDR gene polymorphisms (*Bsm*I, *Taq*I, *Fok*I) were studied in a US population-based case-control study of non-Hodgkin's lymphoma. *Bsm*I B and *Taq*I t alleles were associated with an increased risk (Purdue *et al.,*2007a, 2007b).

Few studies have investigated variants of the VDR gene in relation with melanoma and non-melanoma skin cancers. Two recent meta-analyses have explored this relation and found comparable results (Gandini *et al.,*2008, Mocellin *et al.,*2008): both identified an association of *Bsm*I *b* variant with melanoma risk, pooled RR being 0.78 (0.65-0.92) and 0.75 (0.59-0.95) for the *bB* and *BB* versus wild-type of *Bsm*I, respectively, (Gandini *et al.,*2008). In addition, Gandini *et al.,* found a positive association of *Fok*I *f* allele with melanoma, SOR: 1.13 (1.01-1.25), and found the same associations between *Bsm*I *b* and *Fok*I *f* alleles and non-melanoma skin cancers. Further studies on the role of vitamin D in skin cancer development could be useful to clarify these associations.

16.2.2 Vitamin D_3 receptor and cancer prognosis

The vitamin D receptor is expressed in normal and tumour cells. VDR is down-regulated during colon tumourigenesis, and absence or low levels of VDR expression correlate with poor prognosis (Evans *et al.,*1998).

Two studies have evaluated the relationship between Vit D 3 receptor (expression) in relation to bladder cancer and cervical cancer survival (Sahin *et al.,*2005; Frederich *et al.,*2002). The first one found that transitional cell carcinoma of the bladder expresses VDR and that there is a positive correlation between VDR expression and disease progression. The second did not corroborate the association between VDR expression and cervical cancer survival.

A third study measured the frequency of VDR in 68 patients with breast cancer. The presence of the receptor was not associated with significant differences in survival or metastasis free survival (Freake *et al.,*1984). Moreover, certain polymorphisms have been associated with metastasis, recurrence, treatment response or prognosis of breast cancer, and prostate cancer (Guy *et al.,*2004; Berndt *et al.,*2006)

A fourth study analysed the association between polymorphisms of VDR and survival in early-stage lung cancer in 373 non-small cell lung cancer patients (Zhou *et al.,*2006). The study included the polymorphisms of Cdx-2n G>A, FokI C>T and Bsm I C>T with overall survival (OS) and recurrence free survival (RFS).

For the joint effects of the three polymorphisms, subjects with two or more protective alleles had better OS. The adjusted hazard ratio of 0.20 (95% CI, 0.09-0.48), 0.40 (95% CI, 0.19-0.87) and 0.43 (95%CI 0.19-0.97) respectively, for subjects with two, three, four or more protective alleles when compared with subjects with 0 or one “protective” allele.

A similar study, including *BsmI* polymorphism of VDR, found in 101 melanoma patients and 101 healthy controls (blood donors) an association between the polymorphism and mm status (Santonocito *et al.,*2007).

The active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3, binds with vitamin D receptor, which forms a complex with retinoid X receptors alpha, beta and gamma to manifest antitumour effects. A study examined the expression of vitamin D receptor and retinoid X receptors in renal cell carcinoma and elucidated the prognostic significance of these receptors in nephrectomised specimens of 68 patients with renal cell carcinoma for a mean follow-up of 68.2 months. No significant correlation was found between the expression of vitamin D receptor, retinoid X receptor alpha or beta and clinicopathological parameters. In contrast, retinoid X receptor gamma expression correlated significantly with tumour stage ($p = 0.009$) and distant metastasis ($p = 0.005$). The 5-year cancer specific survival rate was higher in patients with retinoid X receptor gamma positive renal cell carcinoma than those with retinoid X receptor gamma negative renal cell carcinoma (79.3% vs 40.0%, $p < 0.05$) (Obara *et al.,*2007)

One study has cross-sectionally analysed the association between colon cancer growth and proliferation and Vit D levels in 84 consecutive colorectal carcinomas and 30 healthy asymptomatic controls. Serum Vit D_3 levels were significantly lower in patients with more advanced stages of the disease (Niv *et al.,*1999). A similar study considered serum 25 hydroxyvitamin D levels in early and more advanced breast cancer (Palmieri *et al.,*2006). The study was carried out in 279 Caucasian women with invasive breast cancer, 204 women with early stage disease and 75 women with locally advanced or metastatic disease. Patients with early stage breast cancer had significantly higher circulating levels of 25-hydroxyvitamin D in comparison with the other two groups (Palmieri *et al.,*2006).

Similarly, a study evaluated the circulating levels of 25-hydroxyvitamin D in relation to early-stage non-small cell lung cancer survival in 447 patients. After 72 months, with 161 disease recurrence and 234 deaths, the investigators found a 25% reduction in risk of death for the highest versus lowest quartile of the serum vitamin levels (Zhou *et al.,*2007).

With 1,066 prostate cancer cases, Li *et al.,* (2007) have observed a significant interaction between 25-hydroxyvitamin D levels and VDR FokI genotype. Compared with those with plasma 25-hydroxyvitamin D levels above the median and with the FokI FF or Ff genotype, men who had low Vit D levels and the less functional FokI had an increased risk of total (OR=1.9, 95% CI1.1.-3.3) and aggressive prostate cancer (OR=2.5, 95% CI1.1-5.8).

Table 16.1 - VDR polymorphisms and prostate cancer risk/outcome

Population / Place	Type of study	Cases	Controls	Polymorphisms/Haplotypes studied	Main Results	Remarks	Reference
Seattle-Puget Sound cancer registry 1993-1996	Population based, case control	630 incident cases 40-64 years old	565 age matched	22 common VDR polymorphisms	Homozygotes at 2 VDR loci: rs2107301 OR 2.47 (1.52-4.0) rs2238135 OR 1.95 (1.17-3.26)	Haplotypes not associated with cancer risk	Holick *et al.*,2007
Mexico	Comparative study	68	48	Taq1	Taq1 TT associated with better histological prognosis		Patino-Garcia *et al.*,2007
USA Health Professionals Follow Up Study	Nested case control			Cdx2, Fok1, Bsm1	NO association of SNPs or haplotypes with susceptibility to prostate cancer	Haplotypes A-f-b and A-F-B associated with reduced risk of aggressive cancer. Interaction with plasma levels of VitD	Mikhak *et al.*,2007
USA Physicians Health Study	Nested case control	1,066 (including 496 with aggressive disease	1,618 age- and smoking-matched	Fok1	Interaction with 25-hydroxyvitamin D plasma levels: low 25-hydroxyvitamin D levels and Fok1ff genotype : increased risk of total (OR = 1.9, 95%CI 1.1-3.3) and aggressive prostate cancer (OR = 2.5, 95% CI 1.1-5.8)	Ff genotype not associated with risk when 25-hydroxyvitamin D levels above median.	Li *et al.*,2007
Cleveland, USA	Family based case control study	918		6 common variants: Cdx2, FokI, BsmI, ApaI, TaqI, and the poly-A microsatellite, and FBAT haplotypes	Fok1 FF: OR = 0.56 (0.31-1.01) among men with less advanced disease. Apa1 AA or Aa: OR = 0.64 (0.39-1.03). FBAt haplotype: OR =0.48 (0.30-0.76) FbaT haplotype: OR = 0.60 (0.38-0.95)	Inverse association between disease and FBAt and fbaT haplotypes stronger among men with more advanced disease.	Cicek *et al.*,2006
Sweden	Comparative study	137 incident cases	176	Taq1	No difference between cases and controls		Andersson *et al.*,2006
Martinique, West Indies	Case control	253		Poly(A) sequences	Heavy allele associated with increased risk of poor prognostic tumour		Veronique-Baudin *et al.*,2006
UK				SNPs in haplotype block sub-regions C2 and C1	In men with very low ultraviolet exposure, various haplotypes in both sub-regions are associated with increased risk (OR 1.95 to 2.37)		Rukin *et al.*,2007
Taiwan	Case control	416	502 age-matched controls, 189 non-matched BPH patients	Fok1	No association with overall prostate cancer risk.	Marginal association of Fok1 F allele with cancer risk in younger patients: OR = 2.08 (1.00-4.34). FF associated with more aggressive cancer: OR = 2.47 (1.20-5.08).	Huang *et al.*,2006
Thailand	Comparative study	28	44 BPH, 30 controls	Bsm, Apa1, Taq1	No variations in distribution between the 3 groups.		Chaimuangraj *et al.*,2006
San Francisco Bay area, Ca, USA	Population-based case control study	426 Non-Hispanic Whites, 40-79 y.o.	440	Cdx-2, Fok1, Taq1, BglI	Reduced risk of advanced prostate cancer associated with high sun exposure: OR = 0.51 (0.33-0.80), high outdoor activity: OR = 0.73 (0.48-1.11), and high activity alleles FF or Ff, tt, BB in the presence of high sun exposure (Ors 0.46 to 0.67).	Sun exposure measured by reflectometry of sun-protected and sun exposed skin.	John *et al.*,2005
India	Comparative study	128, 43-89 y.o.	147 age-matched,	Fok1	FF, Ff and ff genotype frequency distribution different in cancer patients and controls		Mishra *et al.*,2005
New South Wales, Australia	Population-based case control	812	713	3' region g.60890 5' region g.27823	No difference in genotypes distribution between cases and controls.		Hayes *et al.*,2005

Table 16.2 - VDR polymorphisms and colorectal cancer risk/outcome

Population / Place	Type of study	Cases	Controls	Polymorphisms/Haplotypes studied	Main Results	Remarks	Reference
Germany	Population-based case control	1,048	2,612	FokI, TaqI, VDR-5132 Cdx2	None of the polymorphisms associated with overall risk for postmenopausal breast cancer. TaqI t associated with increased risk of ER+ tumours (OR = 1.18 1.00-1.38). Haplotype FtCA associated with increased risk by comparison with the most frequent haplotype FTCG (OR = 1.43 1.00-2.05)		Abbas *et al.*,2008
Seattle, USA	Population based case control	1,631 35-64 y.o.	1,435	BsmI, poly(A)	BsmI bb genotype: increased risk in Caucasians (OR = 1.53 1.04 – 2.27) no association in African-American No association with poly (A) genotype.	Smoking status modifies associations.	Trabert *et al.*,2007
San Francisco Bay Area, California, USA	Population based case control	1,788	2,129	FokI, TaqI, BglI	VDR genotype does not modify association with sun exposure	High sun exposure (reflectometry) associated with increased risk of advanced breast cancer (OR = 0.53, 0.31 – 0.91)	John *et al.*,2007
Sweden	Population based case control	1,502	1,510	Poly (A)	Association depends on cut-off value for long/short. Cut-off 18/19: - 2 short alleles = reduced risk - 2 long alleles = increased risk of more advanced cancer. Cut-off <21: - OR = 1.26 (1.04-1.51).	Interaction between VDR genotype and parity.	Wedren *et al.*,2007
Cancer Prevention Study II Nutrition Cohort, USA	Nested case control	500	500 matched	Bsm1,Apa1,Taq1, and Fok1, poly(A) microsatellite, and associated haplotypes (baTL and BAtS)	Incident breast cancer not associated with any genotype. BsmI bb with higher than median Ca intake: reduced risk (OR = 0.61, 0.38-096)	Interaction with calcium intake	McCullough *et al.*,2007
USA	Case control	220 African-American and whites	192		No association between VDR genotypes and breast cancer risk	Polymorphisms not associated with bone mass.	VandeVord *et al.*,2006
Nurses' Health Study; USA	Nested case control	1,234 1,180	1,676 1,547	FokI BsmI	Increased risk of breast cancer among carriers of FokI ff: OR = 1.34, 1,06-1.39. No association with BsmI genotype		Chen *et al.*,2005
UK	Case control	179	179	BsmI	Increased risk in subjects with low 25-hydroxyvitamin D levels and bb genotype: OR 6.82, 2.31-14.7.	Low levels 25-hydroxyvitamin D alone or in combination with BsmI genotype increase breast cancer risk.	Lowe *et al.*,2005
UK	Retrospective case control	398	427	BsmI, poly(A), FokI	bb and LL genotypes associated with increased risk: ORs = 1.92, 1.20-3.10 and 1.94, 1.20-3.14 FokI not associated.	FokI modulates associations with bb/LL genotypes: one F allele increases risk.	Guy *et al.*,2004
Austria	Case control	396 breast cancer 154 fibroadenoma	1936	BsmI	No association		Hefler *et al.*,2004
Finland	Case control	483	482	ApaI, TaqI	ApaI a associated with decreased risk: OR = 0.73, 0.54-0.98	Association stronger in women with family history of	Sillanpää *et al.*,2004

					TaqI T non significantly associated with reduced risk.	breast cancer.	
Turkey	Comparative study	78	27	TaqI, BsmI	No differences between patients and controls.		Buyru *et al.*,2003
Germany	Case only	183	-		ApaI AA: 1.7 fold increased risk of bone metastases. TaqI TT: 0.5 fold risk of bone metastases		Schöndorf *et al.*,2003
Taiwan	Comparative study	34	46 benign tumours 169 controls	ApaI, BsmI, TaqI	Trend for association of AA with increased risk, and Aa with decreased risk. TaqI not associated.		Hou *et al.*,2002
UK	Comparative study	181	241	BsmI, FokI	Bb genotype associated with increased risk: OR = 2.32, 1.23-4.39. FokI not associated	BsmI in linkage disequilibrium with poly(A) and L associated with increased risk.	Bretherton-Watt *et al.*,2001
US Latinas	Comparative study	143	300	BsmI, poly(A), FokI	Trend for increasing risk with BsmI B and poly(A) S alleles: ORs 1.5 to 3.2. Start codon FokI not associated.		Ingles *et al.*,2000
Australia	Comparative study	135	110	ApaI, TaqI, FokI	ApaI and TaqI variants associated with increased risk (ORs 1 ;56 and 1.45). Alleles frequencies of FokI not different in the study population.		Curran *et al.*,1999
East Anglia, UK	Comparative study	951 (incident and prevalent cases)	627	TaqI	No association. ORs = 1.01, 0.81-1.27 for heterozygotes, and 0.97, 0.71-1.32 for homozygotes.		Dunning *et al.*,1999
Sweden	Comparative study	111 <37 y.o.	130	TaqI	No overall association with risk of breast cancer. Patients without TaqI site (TT) have increased risk of lymph node metastasis (RR = 1.8, 1.3-2.6), and tendency toward increased survival in ER+ tamoxifen treated tt patients.		Lundin *et al.*,1999
Italy	Comparative study	88 50 primary tumours, 38 relapses.	167	BsmI	No difference in distribution of genotypes between group with primary tumours and controls. BB genotype twice more frequent in metastatic patients than in controls.		Ruggiero *et al.*,1998

Table 16.3 - VDR polymorphisms and colorectal cancer risk/outcome

Population / Place	Type of study	Cases	Controls	Polymorphisms/Haplotypes studied	Main Results	Remarks	Reference
USA	2 case control studies	Colon:1,574 Rectum: 791	1,970 999	Cdx2 and haplotypes including Cdx2	Cdx2 not associated with either colon or rectal cancer. bLFA haplotype associated with increased risk OR = 2.45 (1.38-4.38) BSFA haplotype associated with a reduced risk of rectal cancer but not colon OR = 0.71 (0.52-0.97)		Slattery *et al.,*2007

Germany	Case control	256	256	Cdx2, FokI, BsmI, Tru91, ApaI, TaqI	No association between any single variant and colorectal cancer.
					Haplotypes BsmI G # TaqI C
					and BsmI A # TaqI T inversely associated with colorectal cancer
					ORs = 0.067 (0.016-0.284) and
					0.188 (0.077-0.461)
							Flügge *et al.,*2007

Turkey	Comparative study	26	52	TaqI, FokI	Frequency of TTFf or TtFf genotypes very low among patients: OR = 0.112 (0.030-0.419)	Limited numbers of cases and controls.	Yaylim-Eraltan I *et al.,*2007
Northern California, Utah and Minnesota, USA	2 case control studies	Colon: 1,698 Rectum: 752	1,861 960	FokI	Lowest colon cancer risk with FF/ff genotypes and low sucrose to fibre ratio. Rectal cancer risk increased with red meat consumption and FF genotype.	Interaction with dietary risk factors	Murtaugh *et al.,*2006
Bulgaria	Comparative study	140	94	BsmI	Increased risk for colorectal cancer in bb carriers: OR = 1.8 (0.81-4.05)		Kadiyska *et al.,*2006
USA	2 case control studies	Colon: 1,811 Rectum: 905	 1,451 679	Haplotypes BsmI, polyA, FokI	Common bLF and rare BLF haplotypes associated with increased risk of colon cancer: ORs = 1.15 (1.03-1.28) and 2.40 (1.43-4.02).	No differences for rectal cancer.	Sweeney *et al.,*2006
South Korea	Population-based case control	180	318	Start codon 27823 C>T	C/C genotype and C containing haplotype associated with increased risk, T/T genotype and T containing haplotype associated with decreased risk.		Park *et al.,*2006
USA	2 population-based case control studies	Colon: 1174 Rectum:785	1174 1000	BsmI, polyA, FokI	Greater risk of colon cancer in obese if they have SS or BB or ff genotypes (ORs 2.6 to 3.5). greater risk among less physically active who have ff genotype (OR 3.46)	Study designed to investigate interactions between VDR genotype and factors affecting energy balance	Slattery *et al.,*2004
USA	2 population-based case control	2,306	2,749	Bsm1, polyA	SS genotype reduces the risk of colorectal cancer in men (OR = 0,71 0.55-0.92)		Slattery *et al.,*2004b
Singapore Chinese	Nested case control	217	890	FokI	Ff or ff increase risk (+ 51 and 84%), OR = 2.5 in low calcium intake individuals.	VDR genotype effect modified by dietary calcium and fat. No association FokI genotype colorectal cancer among subjects with higher than median calcium or dietary fat.	Wong *et al.,*2003
Hungary	Case only (rectum)	56	-	BsmI	B allele associated with overexpression of erbB-2, b allele associated with lower erbB-2 expression.		Speer *et al.,*2001
Hungary	Case only (rectum)	59	-	BsmI	B allele associated with expression of erbB-2	BsmI polymorphism may influence rectal cancer development and prognosis by influencing erbB-2 oncogene expression.	Speer *et al.,*2000

Chapter 17 – Vitamin D and cancer in specific populations or conditions

17.1 Introduction

Some specific populations are known to be at increased risk for low vitamin D status or to have a higher than average vitamin D status. Lower vitamin D status may be conferred by the presence of a chronic disease, like end-stage renal disease; or by racial or ethnic characteristics, such as being African-American. Higher vitamin D status may be conferred by important exposures to sources of ultraviolet radiation, for instance, in psoriasis patients. In this chapter, we explore the scientific evidence linking chronically changed vitamin D status with cancer risk in a number of these special populations.

17.2 Search strategy

Using MEDLINE (National Library of Medicine, Washington, D.C.) we identified studies published between 1966 and October 2008 corresponding to the MeSH keywords related to chronic conditions of interest, combined with the MeSH terms for "Vitamin D" or "Vitamin D analogs" and "Cancer". In addition to the MEDLINE search, we also systematically examined the list of references in the identified articles. When several articles were published from the same study, we used the most recent report or the one providing the most detailed information. To be considered, studies had to provide results on either breast, colorectal or prostate cancer. Studies that just reported the incidence or mortality of all cancers or with too few details on cancer types (e.g., skin versus non-skin cancers) were not considered.

17.3 African, Hispanic and Native Americans

It has long been known that African-Americans have higher cancer incidence rates and higher cancer mortality rates than whites, with a larger difference for mortality than for incidence. African-Americans in general, and particularly African-American women, have been found to have lower levels of 25-hydroxyvitamin D than white Americans, which prompted the hypothesis that the higher melanin content of the skin might block vitamin D synthesis in response to sunlight (See Chapter 7). In spite of this lower vitamin D status, after the age of 50, African Americans have lower rates of osteoporosis and of fracture than white Americans (Harris *et al.,* 2006).

There is a possibility that low vitamin D levels mediate some of the increased cancer risk among African-Americans. Giovannucci *et al.,* (2006b) used data from the Health Professionals Follow-up Study collected from 1986-2002 to examine the relationships between risks factors for vitamin D deficiency other than race and cancer incidence and mortality for African-Americans and whites. Risks factors previously linked to vitamin D deficiency included residence in the northeastern United States, vitamin D intake <10 µg daily, BMI>25 kg/m^2 and physical activity level below the median. Adjusting for other risk factors, the study confirmed a higher cancer incidence (RR=1.32, 95% CI: 1.08-1.61) as well as a higher cancer mortality (RR=1.89, 95% CI: 1.40- 2.56) among African-American compared to white men. The higher cancer mortality was particularly striking for cancers of the digestive system (RR=2.24, 95% CI: 1.35-3.70). When the results were stratified by both race and risk factors for vitamin D deficiency, compared to whites with one or fewer risk factors for vitamin D deficiency, African-Americans with two or more risk factors had a particularly high risk for cancer incidence and mortality in general, and for digestive system cancers in particular (Table 17.1). This study had several limitations. First, there were only 99 cancer cases among 481 black men versus 7,019 cancer cases in 43,468 white men. Second, vitamin D status was not measured directly but predicted using a combination of factors associated with low serum 25-hydroxyvitamin D levels in a subsample (n=1,095) of the entire cohort.

Descriptive epidemiological data do not support a link between low vitamin D status and high cancer burden in African-Americans. Hispanics, Native Americans and Asian Americans have darker skin complexions than white Americans, and UVB-induced vitamin D skin synthesis may not be as easy as in white Americans. Hispanic Americans have serum 25-hydoxyvitamin D levels intermediate to those of white and African-Americans (see Chapter 7 and Zadshir *et al.,* 2005; Bishoff-Ferrari *et al.,*2004). Table 17.2 shows that cancer incidence and mortality rates for all cancers, colorectal cancer, prostate cancer and breast cancer are lower in Hispanics/Latinos, Native Americans and Asian

Americans (Trapido *et al.,*1995; Jemal *et al.,*2008; MMWR, 2002; Howe *et al.,*2006). Therefore, differences in vitamin D status among ethnic groups in the USA do not correspond with differences in cancer burden.

Cancer mortality rates in Indian Americans are also lower than in white and African Americans. But too few data were available on serum 25-hydroxyvitamin D levels in this ethnic group to allow comparisons to other ethnic groups (see Chapter 7).

In the Third National Health and Nutrition Survey (NHANES III), where 16,818 subjects were followed from 1988-1994 through 2000, Freedman *et al.,*(2008) found a statistically elevated risk of total cancer mortality in non-Hispanic blacks compared with non-Hispanic whites that was not reduced by adjusting for serum 25-hydroxyvitamin D levels. If the lower vitamin D status of African-Americans conferred a higher risk of cancer deaths than in white-Americans, then statistical adjustments on serum 25-hydroxyvitamin D levels should have reduced the cancer mortality difference.

Alternative explanations for the higher cancer risk in African-Americans refer to the lower socio-economic status of many African-Americans, which is known to be strongly associated with higher cancer mortality (Albano *et al.,*2007). Lower socio-economic status may be a marker for factors associated with both decreased vitamin D status and increased cancer risk factors like smoking, obesity and unhealthy dietary habits.

In summary, the available data conflict regarding whether vitamin D deficiency might be a causative factor for the higher risk of cancer incidence and mortality among African-Americans.

17.4 Asian and North African migrants in Europe

Asian migrants in Europe have (much) lower serum 25-hydoxyvitamin D levels than local populations (see Chapter 7). The cancer incidence rates in Asian migrants living in England (Dunningan *et al.,*1990; Harding and Rosato, 1999) are much lower than those of white English natives. The same relationship has been observed for cancer mortality rates, particularly for colorectal cancer mortality (Swerdlow *et al.,*1995).

17.5 End stage renal disease

Patients with chronic kidney disease (CKD) commonly develop phosphate retention, deficiency in circulating 25-hydroxyvitamin D and in 1,25-dihydroxyvitamin D deficiency once the glomerular filtration rate (GFR) falls below 60 mL/minute (LaClair *et al.,*2005; Khan *et al.,*2007). Consequences include reductions in ionised calcium and secondary hyperparathyroidism with resultant renal osteodystrophy (Khan, 2007; Cheng *et al.,*2007). Patients with advanced chronic kidney disease are often prescribed phosphate binders and activated preparations of vitamin D to combat the development of renal osteodystrophy. Activated vitamin D analogues are prescribed (instead of the vitamin D) because the activity of the 1α-hydroxylase is reduced due to the kidney disease. These activated vitamin D analogues are also called VDRA for “vitamin D receptor activator”.

Patients with advanced CKD, and particularly patients on dialysis, are known to have high mortality rates, particular from cardiovascular disease (Levin *et al.,*2005). Recently, a modest increase in the incidence of some cancers has been described among patients on dialysis in a retrospective, multi-national cohort study (Maisonneuve *et al.,*1999). During a mean follow-up of 2.5 years, the overall standardised incidence ratio for cancer incidence among the dialysis patients compared to the populations from which they were drawn was 1.18 (95% CI: 1.17- 1.20), with the higher risk concentrated among younger patients and in cases of kidney, bladder, thyroid, and other endocrine cancers. An increase in non-melanoma skin cancer was also found. Cancers of the lung, colorectum, prostate, breast and stomach were not consistently increased. These observations are consistent with the higher cancer risk conferred by the conditions that caused the CKD or by a higher susceptibility to some infectious agents such as the human papilloma virus. Chronic low vitamin D status does not seem to influence cancer risk in other organs. This international study did not address cancer mortality, nor stratify dialysis patients based on whether they were receiving activated vitamin D as part of their treatment.

A recent trend in the management of patients with CDK is the more systematic prescription of injections of 1α,25-dihydroxyvitamin D_3 (calcitriol) or of other activated vitamin D analogs (e.g., the

paricalcitriol) for the prevention of renal osteodystrophy (Khan *et al.,* 2007). Teng *et al.,* (2005) have performed a series of large historical ("retrolective") observational cohort studies of dialysis patients in the United States addressing the relationship between the administration of activated injectable vitamin D (principally calcitriol and paricalcitol) and mortality. In fact, at 2 years, mortality rates were 13.8 /100 person years among 37,137 vitamin D users and 28.6/100 person years among 13,864 nonusers (adjusted hazard ratio 0.80, 95% CI: 0.73-0.83). However, significant cause-specific reductions were only noted for cardiovascular diseases and infections, and cancer death rates were not reported (Teng *et al.,*2005). In a similar large study comparing mortality with paricalcitol versus calcitriol use among dialysis patients, adjusted mortality was lower with paricalcitol use, but the lower mortality appeared attributable to cardiovascular disease and infections, with no report of cancer mortality rates (Teng *et al.,*2003).

The challenge of examining the relationship between vitamin D and cancer mortality among dialysis patients is nicely illustrated in a small non-experimental study by Shoji *et al.,* (2004), which examined mortality among just 242 Japanese dialysis patients depending on whether they were taking an oral vitamin D_3 preparation. Over approximately 5 years of follow-up, 53 deaths occurred: 31 due to cardiovascular causes, 11 due to infections, 8 due to other causes, and just 3 due to cancer. Cancer deaths are greatly overshadowed by cardiovascular deaths in this population, and even large observational studies like those by Teng and colleagues may have insufficient power to detect clinically important differences in cancer mortality between groups based on activated vitamin D levels or use.

More recent reports have shown increased survival in non-dialyzed CKD patients treated with vitamin D (Kovesdy *et al.,*2007; Shoben *et al.,* 2008).

A meta-analysis of trials of vitamin D and vitamin D analogues for controlling phosphorus and calcium disturbances in CKD patients found no impact on total mortality but the authors underlined that randomised trials with sufficient power for assessing the influence of these compounds on mortality in these patients are still to be done (Palmer *et al.,*2007).

In summary, currently no evidence links activated vitamin D deficiency to a higher risk of cancer among patients with advanced chronic kidney disease. Similarly, there is no current evidence that prescription of activated vitamin D preparations mitigates cancer risk in this population. Observational data consistently suggest that such prescription may decrease all-cause mortality, mainly of cardiovascular origin, but randomised trials are needed to confirm this (Vervloet *et al.,*2008).

17.6 Psoriasis

Psoriasis is a chronic skin disease of unknown origin, involving complex immunological processes. It can be treated with topical vitamin D preparations, which occasionally have systemic effects (Menter and Griffiths, 2007). Ultraviolet therapy through sun exposure in very sunny and dry areas has been promoted for patients with severe disease (i.e., the Dead-Sea therapy). Treatment with PUVA, i.e., oral intake of oral 8-methoxypsoralen followed by sessions of UVA irradiation or with narrowband UVB were introduced in the 1980s, for PUVA and in the late 1990s for narrowband UVB. Some psoriasis patients receive numerous PUVA or narrowband UVB sessions during their lifetime. PUVA has a limited impact on vitamin D status because of the UV spectrum used, although minute amounts of UVB lead to increased serum levels of 25-hydroxyvitamin D and 1α,25-dihydroxyvitamin D (Rogers *et al.,*1979; Gilhou *et al.,*1990). Narrow band UVB consistently increases serum vitamin D levels and thereby suppresses PTH levels in some patients (Osmancevic *et al.,*2007). Psoriasis patients have a great inclination for indoor tanning and intense sun exposure (Farr *et al.,*1998; Clark *et al.,*1998; Su *et al.,*2005). As a result of the numerous occasions of exposure to various sources of ultraviolet radiation, psoriasis patients are likely to have a higher vitamin D status than average.

Several cohort studies from different populations in different countries have suggested patients with psoriasis have a higher risk of other malignancies, mainly of non-melanoma skin cancer and lymphoproliferative malignancies (Olsen *et al.,* 1992; Hannuksela-Svahn *et al.,* 2000; Margolis *et al.,* 2001; Gelfand *et al.,* 2003). The mechanisms of these possibly increased risks are unclear, although concerns about whether some psoriasis treatments, particularly methotrexate, ultraviolet phototherapy, or PUVA photochemotherapy might be carcinogenic have been raised (Stern, 2006). Cohort studies that have attempted to determine whether the higher risk of lymphoproliferative

disorders among psoriasis patients might be attributable to methotrexate use have yielded conflicting results (Gelfand *et al.,* 2006; Stern, 2006).

Five studies reported more detailed results on cancer occurrence in psoriasis patients (Olsen *et al.,*1992; Hannuksela-Svahn *et al.,*2000; Boffetta *et al.,*2001) and in PUVA-treated patients (Lindelof *et al.,*1991; Stern *et al.,*1997). Some of these studies found slight increases in the risk of breast (Stern *et al.,*1997; Boffetta *et al.,*2001), colorectal (Olsen *et al.,*1992; Lindelof *et al.,*1991), and oral cavity or laryngeal cancer (Olsen *et al.,*1992; Hannuksela-Svahn *et al.,*2000; Boffetta *et al.,*2001) probably linked to higher tobacco use and alcohol intakes by psoriasis patients (Lindelof *et al.,*1991; Olsen *et al.,*1992; Stern *et al.,*1997; Hannuksela-Svahn *et al.,*2000; Boffetta *et al.,*2001). No study found changes in prostate cancer risk.

In conclusion, psoriasis patients are likely to have high vitamin D status due to frequent exposure to medical and non-medical artificial, and also solar ultraviolet radiation. We found limited evidence for a slight increase in cancer risk among these patients, and more evidence for increased risk of non-melanoma skin cancer, and myeloproliferative disorders. We found no studies linking vitamin D levels or specific vitamin D-related therapies to cancer incidence or mortality among psoriasis patients.

17.7 Crohn's and celiac diseases

Crohn's disease is a chronic inflammatory condition of the small bowel, and celiac disease is caused by intolerance to the gluten contained in most wheat products. Both diseases often develop early in life, and Crohn's disease peaks in adolescence. Patients with Crohn's or celiac disease have low intestinal absorption of fats and thus of lipid soluble vitamin D. In Crohn's disease, malabsorption of calcium and of vitamin D increases with increasing length of small bowel resection (van Hogezand *et al.,*2006). Hypovitaminosis D is frequent among Crohn's disease patients (Sentongo *et al.,*2002; Papa *et al.,*2006; Gilman *et al.,*2006), and in patients with celiac disease (Scott *et al.,*2000; Green *et al.,*2007). Crohn's disease patients are frequently prescribed calcium and vitamin D supplements to mitigate steroid-induced bone disease (Bernstein *et al.,*2005). Osteomalacia, due to severe hypovitaminosis D can appear in celiac disease (Basu *et al.,*1999). Thus patients with these conditions have a long lasting history of low vitamin D status.

Studies of vitamin D levels among patients with Crohn's Disease have yielded conflicting results. Older studies suggested that 25-hydroxyvitamin D levels are low among Crohn's disease patients (Harries *et al.,*1985;Vogelsang *et al.,*1989), while a newer study has reported normal 25-hydroxyvitamin D levels but elevated 1,25-dihydroxyvitamin D levels (Abreu *et al.,*2004).

Patients with Crohn's Disease have a higher risk of small bowel and colorectal cancer (Jess *et al.,*2005) and lymphoma (von Roon *et al.,*2007). The risk of cancer outside the gastro-intestinal tract is slightly increased, by about 23%, probably because of corticosteroid and other immuno-suppressive therapies (von Roon *et al.,*2007).

Three studies that reported detailed cancer risk in celiac disease patients found a higher risk of gastro-intestinal cancer, no change in prostate cancer risk and a decreased risk of breast cancer (Logan *et al.,*1989; Askling *et al.,*2002; West *et al.,*2004).

We found no studies linking serum 25-hydroxyvitamin D level or vitamin D therapy with cancer incidence and mortality among patients with Crohn's or celiac disease.

17.8 Obesity

Overweight (body mass index between 25 and 29.9 kg/m^2) and obesity (body mass index $\geq$ 30 kg/m^2) are strongly associated with low serum 25-hydroxyvitamin D levels (See Chapter 7).

Obesity is associated with higher mortality, mainly of cardiovascular origins (Bender *et al.,*2006). An IARC working group found that overweight and obesity were consistently associated with oesophageal adenocarcinoma, colorectal cancer, breast cancer in post-menopausal women, cancer of the corpus uteri and kidney cancer (IARC, 2002). This systematic review concluded that there was not sufficient evidence for an association of overweight or obesity with prostate or gallbladder cancer.

17.9 Obese patients treated with bariatric surgery

Bariatric surgery is an increasingly common treatment for morbid obesity (Shah *et al.,*2006). Bariatric surgery, particularly "malabsorbtive" procedures such as gastric or intestinal bypass surgery, have been associated with postoperative low vitamin D status, even among patients prescribed calcium and vitamin D supplements (Carlin *et al.,*2006; Shah *et al.,*2006;Abbassi *et al.,*2007). Three longitudinal studies suggest that in morbid obesity, vitamin D depletion is already present before bariatric surgery (Compston *et al.,*1981; Ybarra *et al.,*2005; 2007). Nevertheless, low vitamin D status is a common finding after bariatric surgery as well (Teitelbaum *et al.,*1977; Hey *et al.,*1979; Hey *et al.,*1982; Rickers *et al.,*1984; Clements *et al.,*2006; Compher *et al.,*2007; Poitou-Bernert *et al.,*2007; Mahlay *et al.,*2008). A randomized trial shows that correction of vitamin depletion after bariatric surgery necessitates doses vitamin D of 180 µg per day in addition to usual daily supplementation of 20 µg (Carlin *et al.*, 2008).

Three large cohort studies from Canada (Christou *et al.,*2004), Sweden (Sjonström *et al.,*2007) and the United States (Adams *et al.,*2007) have reported substantial reductions in overall mortality following bariatric surgery, with fewer cancer deaths reported after surgery in all three studies.

However, we found no data linking vitamin D levels with cancer incidence or mortality among obese patients after bariatric surgery.

17.10 Conclusions

Chronic conditions associated with low or high vitamin D status over long periods of time seemed not to be associated with higher or lower risk of breast, colorectal, prostate and overall cancer, except cancers occurring in organs affected by the chronic condition, or lympho-proliferative disorders and cancer directly related to treatments.

Available data on vitamin D status are not correlated with the variable cancer incidence and mortality rates observed in the different ethnic groups in the USA and the reasons for the greater cancer burden in African Americans remain to be established.

Table 17.1 - Relative risk (RR) of cancer incidence and mortality of Blacks compared to Whites by risk factors for vitamin D deficiency in the Health Professionals Follow-Up Study 1986-2002 (Reproduced with permission of Giovannucci, E., from Cancer incidence and mortality and vitamin D in black and white male health professionals. Giovannucci et al. Cancer Epidemiol Biomarkers Prev. 2006;15:2467-2472. Copyright 2006; permission conveyed through Copyright Clearance Centre, Inc.).

	Cancer Incidence			
	Total		Digestive System	
	n (cases)	RR (95% CI)	*n* (cases)	RR(95% CI)
Whites (≤1 risk factor)	1,821	1.00	465	1.00
Whites (≥2 risk factors)	2,820	1.08 (1.01-1.04)	819	1.21 (1.08-1.36)
Blacks (≤1 risk factor)	18	0.95 (0.60-1.51)	4	0.84 (0.32-2.26)
Blacks (≥2 risk factors)	45	1.57 (1.16-2.11)	19	2.59 (1.63-4.11)
	Cancer Mortality			
	Total		Digestive System	
	n (cases)	RR (95% CI)	*n* (cases)	RR(95% CI)
Whites (≤1 risk factor)	874	1.00	268	1.00
Whites (≥2 risk factors)	1,349	1.09 (1.00-1.18)	398	1.02 (0.87-1.20)
Blacks (≤1 risk factor)	14	1.55 (0.91-2.62)	3	1.06 (0.34-3.31)
Blacks (≥2 risk factors)	30	2.27 (1.57-3.28)	13	2.99 (1.70-5.26)

NOTE: Cox proportional hazards modelling was used to control for multiple variables simultaneously and to compute hazard ratios to estimate RR and 95% confidence intervals. Age was controlled for in 1-year increments and time period in 2-year intervals. The following covariables were included in the models: height, region, BMI, physical activity, smoking history, alcohol, total calories, red meat, calcium, vitamin retinol and total fruits and vegetables. Each of the following was considered a risk factor for hypovitaminosis D: residence in the Northeastern United States, total vitamin D intake <10 µg/d, BMI >25 kg/m^{2,} and physical activity below the median.

Table 17.2 – Cancer incidence and mortality in the USA, by race and ethnicity, 2000-2004*

	white Americans (WA)	African Americans (African-Americans)	Ratio African-Americans/WA	Hispanic/ latino (Hispanic-Americans)	Ratio Hispanic-Americans/WA	American Indians and Alaska Natives (IA)	Ratio IA/WA	Asian American and Pacific Islanders (APA)	Ratio APA/WA
Cancer incidence									
All sites									
Males	556.7	663.7	1.19	421.3	0.76	321.2	0.58	359.9	0.65
Females	423.9	396.9	0.94	314.2	0.74	282.4	0.67	285.8	0.67
Breast (female)	132.5	118.3	0.89	89.3	0.67	69.8	0.53	89	0.67
Colon & Rectum									
Males	60.4	72.6	1.20	47.5	0.79	42.1	0.70	49.7	0.82
Females	44	55	1.25	32.9	0.75	39.6	0.90	35.3	0.80
Prostate	161.4	255.5	1.58	140.8	0.87	68.2	0.42	96.5	0.60
Cancer mortality									
All sites									
Males	234.7	321.8	1.37	162.2	0.69	187.9	0.80	141.7	0.60
Females	161.4	189.3	1.17	106.7	0.66	141.2	0.87	96.7	0.60
Breast (females)	25	33.8	1.35	16.1	0.64	16.1	0.64	12.6	0.50
Colon & Rectum									
Males	22.9	32.7	1.43	17	0.74	20.6	0.90	15	0.66
Females	15.9	22.9	1.44	11.1	0.70	14.3	0.90	10.3	0.65
Prostate	25.6	62.3	2.43	21.2	0.83	21.5	0.84	11.3	0.44

*Jemal *et al.*,, 2008; rates per 100,000 population, age-adjusted to the 2000 US standard population.

Chapter 18 – Vitamin D: predictor or cause of cancer and of other chronic health conditions?

18.1 Low vitamin D status: marker or cause of poor health status?

Low vitamin D status has been associated with a large number of chronic conditions such as cancer, high blood pressure, coronary heart disease, congestive heart failure, stroke, cognitive impairment, depressive symptoms, reduced mobility, fractures, falls, incontinence, and more.

A central question is whether low vitamin D status is a causal factor for increased risk of cancer, other chronic health conditions and death, or simply an indicator of impaired health status, and thus just a predictor of increased risk for cancer, other chronic diseases, or premature mortality. Many patients suffering from or more prone to a chronic condition would have poorer health status than average, and vitamin D status (as reflected by serum 25-hydroxyvitamin D level) could simply reflect this poorer health status.

The ill health marker hypothesis is supported by a number of observations:

1/ Low vitamin D status is associated with a number of factors that are themselves known risk factors for chronic diseases, including ageing, overweight and obesity, smoking, low physical activity, absence of outdoor activities and an unhealthy diet (See Chapter 7).

2/ In NHANES III and in the Longitudinal Aging Study, successive adjustments of factors known to be associated with both vitamin D status and increased mortality (e.g., body mass index, smoking, low physical activity, outdoor activities) resulted in a decreased relative risk of deaths from all causes (and from CVD or cancer in the NHANES III study) associated with either steadily lower or higher serum 25-hydroxyvitamin D levels (See Chapter 12).

3/ Several studies show a relationship between low vitamin D status and declining health status. For instance, in the Dutch cohort of elderly people that found increasing risk of death with decreasing serum 25-hydroxyvitamin D levels, successive adjustments for health and lifestyle variables and several frailty indicators decreased the serum levels-mortality association that was no longer significant after all co-variates had been included in the statistical model (Visser *et al.,*2006 – See Chapter 12.5). A study in 408 community dwelling subjects 75 to 96 years of age in Aberdeen, UK, reported serum 25-hydroxyvitamin D levels ranging from 2.4 to 32.8 ng/mL (McNeil *et al.,*2002). A 114 item questionnaire was used to explore a wide range of potential dietary and other risk factors for micronutrient deficiencies. Only four items were statistically associated with low iron status, five with low folate and six with low vitamin C, while twenty-five items were strongly statistically associated with low vitamin D status. These 25 items were mostly related to decaying health, including frailness, poor appetite, weight loss, low intake of oily fish, poor general health, depression, and physical inactivity. Such observations are also found in areas with abundant sunshine all year. For instance in Israël, levels of serum 25 hydroxyvitamin D below 15 ng/mL were significantly more prevalent in elderly people with reduced mobility and/or suffering from chronic conditions (Hochwald *et al.,*2004).

4/ Patients with congestive heart failure have different profile of vitamin D associated life-style factors (Zittermann *et al.,* 2003; Zittermann *et al*., 2007). The question is whether it would be some of these factors that would be causally associated with congestive heart failure, while vitamin D status would just be an indicator of presence or absence of these factors in individuals.

If the hypothesis that low vitamin D status is a general marker of poor health is true, then vitamin D supplementation will not improve health status or protect against conditions found by observational studies to be associated with low vitamin D status. If the hypothesis that low vitamin D status is a causal factor for several chronic conditions is correct, then supplementation with vitamin D is likely to reduce occurrence of and/or mortality from these conditions, and improve health status.

18.2 Results in favour of vitamin D status being an indicator of poor health or a predictor of chronic disease

Failure of the two randomised trials of vitamin D supplements (see Chapter 14) to decrease the incidence of cancer, particularly of colorectal cancer, favours the “indicator/predictor” hypothesis. The

nested case-control study organised within the WHI trial found that women developing a colorectal cancer had lower serum vitamin D status at baseline than women who did not develop this cancer. This contrast between the results of the experimental and observational components of the WHI trial further supports the "indicator" hypothesis.

One could assume that vitamin D would be more causally linked to disease when vitamin D status is low. In the WHI trials, the risk if colorectal cancer or of cardiovascular event and supplementation with vitamin D and calcium did not change with obesity or being a smoker (Wactawski-Wende *et al.,*2006; Hsia *et al.,*2007), two characteristics known to be associated with lower vitamin D status (see Chapter 7).

Other arguments favouring the "indicator" hypothesis come from randomised trials for prevention of fractures with supplements of vitamin D and calcium. Low vitamin D status in elderly people is associated with greater risk of fracture and with postural instability. However, randomised trials showed that calcium supplements decreased fracture risk, while vitamin D supplements did not.[19] This means vitamin D status was probably more an indicator than a cause of frailness and higher risk of fracture. Calcium supplements were more active in these subjects, while provision of vitamin D supplements did not change the risk of fracture.

Similar findings were done for physical functioning and falls in elderly people [20]: declining vitamin D status is associated with decreasing muscle strength, increasing postural instability and falls. However randomised trials provide only mixed evidence that vitamin D supplementation can improve muscle strength, postural stability and decrease rates of falls (Cranney *et al.,*2007 and endnote 18).

18.3 Results in favour of vitamin D status being a causal factor for poor health and chronic disease occurrence

The main hard evidence currently existing for a causal impact of vitamin D on health is a meta-analysis showing that vitamin D supplementation in older subjects with low vitamin D status may decrease all-cause mortality (Autier & Gandini, 2007). This study could not identify which cause of death was reduced due to the use of vitamin D supplements, and the results of this meta-analysis need to be confirmed by a randomised trial with all-cause mortality as the main outcome.

The only way to disentangle the issue of "indicator or predictor" versus "causal factor" is to mount new randomised trials for verifying the impact of vitamin D on all-cause mortality and on the incidence and mortality from common cancers and other conditions.

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[19] Meta-analyses of double blind placebo controlled randomised trials showed weak evidence that vitamin D and calcium supplements can prevent fractures and falls in elderly people (Cranney *et al.,*2007; Avenell *et al.,*2005), but vitamin D alone seems not able to reduce fracture (Avenell *et al.,*2005). The meta-analysis done by Bischoff-Ferrari *et al.,* (2005) suggesting that daily supplements of 20 µg of vitamin D may reduce fracture risk in elderly people did not include several large randomised trials.

In contrast, calcium supplements decrease fracture risk by 12% (95% CI: -17%;-5%), and by 20% (-28%;-11%) if daily dose of elementary calcium is 1200 mg or more (Tang *et al.,*2007). Calcium supplements proved to have greater prevention capacity when serum 25-hydroxyvitamin D level was below 10 ng/mL (RR = 0.86; 95%CI: 0.78-0.93) than when serum 25-hydroxyvitamin D level was 10 ng/mL and higher for (RR = 0.94; 95% CI: 0.90-0.99) (interaction p value = 0.06)(Tang *et al.,*2007). At the same time, adding vitamin D to calcium supplements did not change the influence of calcium supplements, even when given at doses of 20 µg per day (Tang *et al.,*2007). In theory, vitamin D supplementation should be more beneficial to subjects with low serum 25-hydroxyvitamin D level at baseline, and but trial results are not in favour of this supposition (Avenell *et al.,*2005).

Hip fracture is known to occur in frail elderly people who are in poorer health than subjects of same sex and age. Half of hip fractures occur after 79 years of age. Therefore, in elderly people, hip fracture is often the health event that will precipitate death. The prevalence of low vitamin D status among elderly people with hip fractures in the United States and Great Britain has been found to be very high (Holick,1994; Holick,2006; Lips *et al.,*1988). These studies were cross-sectional (exposure and outcome measured about at the same time), and thus reverse causation is possible, meaning that low vitamin D status could be a marker of frail, poor health and physical inactivity.

Prospective studies on vitamin D status measured well before fracture occurrence have yielded inconsistent results, and at present there is no clear temporal association between low vitamin D status and future occurrence of fracture, mainly the hip fracture. A cohort study in the USA, part of the WHI-OS study, found decreased serum 25-hydroxyvitamin D levels associated with hip fracture (Cauley *et al.,*2008), but this study was conducted in relatively young patients for hip fracture (only one third were more than 70 years old when the median of hip fracture patients is usually 80 years old) and did not collect data on bone mineral density. It could thus not adjust for this important predictor of fracture also associated with vitamin D status. These prospective observations reinforce the likelihood that many cross-sectional observations were due to reverse causation.

In the logic of recent meta-analyses of vitamin D and calcium supplements and fracture occurrence after 50 years of age (Avenell *et al.,*2006; Cranney *et al.,*2007; Tang *et al.,*2008;), the decreased hip fracture risk found in the WHI randomised trial among women fully adherent to the vitamin D and calcium supplementation could well be due to the calcium and not to vitamin D.

[20] The low vitamin D status of many elderly people is associated with low physical functioning and muscle weakness (Kenny *et al.,*2003). A 9-month double double-blind placebo-controlled randomised trial including 65 men and women in geriatric ward of mean age 82 with mean baseline serum 25-hydroxyvitamin D levels below 16 ng/mL and supplemented with 225 µg vitamin D_2 per day succeeded in increasing serum levels to 40 to 50 ng/mL but failed to improve the capacity to perform essential activities of daily living (Corless *et al.,*1985). A 6-month double-blind placebo-controlled randomised trial including 65 community-dwelling men of 65 to 87 years old with mean baseline serum 25-hydroxyvitamin D levels of 25 (SD: 7) ng/mL succeeded in increasing serum levels by about 10 ng/mL with 25 µg vitamin D per day but failed to improve muscle strength or physical performance or health perception (Kenny *et al.,*2003). It can however not be excluded that the high vitamin D status and good health at baseline probably precluded a positive action of vitamin D supplements. In the UK, a randomised, double-blind, placebo-controlled trial found that in the 6 months following a single intramuscular injection of 600,000 i.u. ergocalciferol (i.e., 83 µg per day), 139 elderly people ≥65 years of age with a history of falls and with serum 25-hydroxyvitamin D ≤12 ng/mL at baseline had no increased muscle strength or reduced rates of falls (Dhesi *et al.,*2004). Attempts with 1α,25-dihydroxyvitamin D were not more successful (Grady *et al.,*2001).

Chapter 19 – Should recommendations for sun protection and vitamin D intakes be changed?

19.1 On the concepts of "deficiency", "insufficiency" and "optimal" vitamin D status

The concepts of "deficient", "insufficient", "adequet" or "optimal" should not be defined according to results of ecological or observational studies for the following reason: if a disease is due to deficiency of some substance, then restoration of sufficiency of that substance should be followed by disappearance of the disease. This simple logical rule has been observed worldwide for rickets and osteomalacia, as these diseases are caused by vitamin D deficiency and are cured by vitamin D supplementation or sun exposure.

We do not know whether this simple logical rule also applies for the numerous conditions found by mainly ecological and some observational studies to be associated with low vitamin D status. It is only when demonstrated that restoration of some adequate vitamin D status is followed by decreasing incidence and/or mortality from health conditions hypothetically associated with low vitamin D status that one could acknowledge that maintenance of adequate vitamin D status is associated with lower disease burden, longer life expectancy, and absence of serious side effects. Only randomised trials may demonstrate this, and to date, trials have not been supportive of relatively low doses of vitamin D and calcium supplements in the prevention of colorectal and breast cancer, coronary heart disease, diabetes, and so on (see Chapter 14).

For the time being, the definition of vitamin D deficiency should be maintained as they are now, i.e., related to the prevention of rickets, osteomalacia or muscular pain.

19.2 Should recommendations for vitamin D intakes be changed?

The lower limit usually considered for serum 25-hydroxyvitamin D level is 10 g/mL, as below this level, rickets in children and osteomalacia in adults may occur. Increased blood PTH levels are regarded as markers of vitamin D insufficiency for adequate bone metabolism, and serum 25-hydroxyvitamin D level between 10 and 19 ng/mL are often associated with undesirably high levels of this peptidic hormone. However, the upper limit for PTH clearance in the blood is still a matter of debate (see e.g., Lips 2001).

Setting a lower limit of "adequate" serum 25-hydroxyvitamin D levels at 20 or 30 ng/mL is currently inappropriate since there are no results from randomised trials suggesting that maintenance of such "adequate" serum 25-hydroxyvitamin D level actually prevents any cancer and any other chronic condition.

Also, it would be premature to change current recommendations on vitamin D intakes, as at present, there is insufficient evidence of a lack of harm due to long term higher levels of vitamin D [21].

19.3 Should recommendations for sun protection of light-skinned populations be changed?

Discussions on sunlight and vitamin D often mix quite diverse issues: there is a difference between Muslim veiled women living in northern Europe and suntan worshippers spending hours on Mediterranean beaches, preferably around noon. The former would most probably benefit from some more sun exposure, while the latter would most probably benefit from restricting overexposure. There is a difference between elderly people not longer eager to go outside and adults spending most of their time indoors but who are eager to maximise time spent in the sun when on holidays. Again, the former would most probably benefit from some more sun exposure, while the latter would most probably benefit from following sun protection recommendations.

Over-simplified messages on sun exposure timing, duration and potential for improving vitamin D status need to be questioned through an evidence-based approach (Kimlin *et al.,*2007). Answering this question would rest on answering first the two preliminary questions:

1/ Do increase in vitamin D status decrease the risk of cancer or other chronic condition?

2/ If the answer to question one was affirmative, then the next question would be about the safest way to increase vitamin D status. Given the well-established link of skin cancer risk and UV radiation on light-skinned populations, and the still increasing incidence of skin cancer in most light-skinned populations, use of oral supplements of vitamin D would probably represent the safest way for increasing vitamin D status.

UVB radiation doses implicated in skin cancer occurrence (mainly the squamous cell cancer) are much higher than doses involved in endogenous vitamin D production. Maximum vitamin D_3 synthesis occurs within a relatively short period of UVB exposure (less than one minimal erythemal dose); beyond this period, further synthesis of vitaminD_3 ceases (see Chapter 4). For children and adults, everyday casual exposure to sunlight provides vitamin D requirements (Holick, 1995). Best estimates are that at around 40° of latitude during a sunny summer day, a fair-skinned person could achieve maximum pre–vitamin D_3 production in 5 to 10 minutes of exposure two or three times a week of the face and forearms to mid-day sunlight (Holick, 1995, 2001; Gilchrest, 2008).

[21] In contrast, (and this is beyond the scope of the objective of this Report), there is sufficient evidence from other trials, expert consensus, reviews and studies outside the cancer domain, that adequate vitamin D status according to current recommendations should be maintained for optimal bone health and defence against infectious diseases, essentially among children and women in childbearing age (Cranney *et al.,*2007). The evidence is less clear in elderly subjects (Avenell *et al.,*2006; Cranney *et al.,*2007). The question of whether for bone health, elderly people in areas above 40-42° of latitude should take doses of vitamin D supplement of about 25 µg per day for maintaining serum 25-hydroxyvitamin D summer levels during the winter (Viljakainen *et al.,*2006) is still an open question beyond the scope of this report.

Chapter 20 – Further research: a plea for new randomised trials on vitamin D

Vitamin D is a drug, more precisely a hormone. The experience accumulated in the last twenty years with chemoprevention and hormonal substances shows that no compound should be recommended for cancer chemoprevention if its efficacy and side effects have not been evaluated in large, randomised trials. Ideally, these trials should be double-blind and placebo controlled. Laboratory data and observational studies should only be considered as indicative of potential for chemopreventive use. Reasons for such stringent methodological requirements are summarised in an endnote,[22] together with some examples of wrong assumptions on the efficacy and safety of several compounds.[23]

Randomised trials using ordinary doses of vitamin D (i.e., 10 to 20 µg per day) have shown no influence on cancer risk, particularly colorectal cancer. However, these ordinary doses seem to reduce all-cause mortality. In addition findings from prospective cohort studies on colorectal cancer risk and on mortality constitute pieces of evidence strong enough to consider that randomised trials of vitamin D use and cancer risk (or risk of other chronic conditions) may not have correctly addressed the question, and that new double-blind, placebo controlled randomised trials should be organised.

However, as seen in Chapter 5, no data exists on the health effects of intakes of high doses of vitamin D (say, 30 µg per day or more) over the long term. Also, U-shaped curves between serum 25-hydroxyvitamin D and all-cause mortality and cardiovascular events have been reported recently, suggesting that both low and (too) high vitamin D status would be detrimental for health (See Chapters 5 and 12).

Trials must be organised that will test higher dosages of vitamin D supplements. Failure to conduct such trials before issuing new recommendations on vitamin D intakes would be an error. Such recommendations could result in repeating the story of anti-oxidants or hormone replacement therapy (or other similar stories - see endnotes and Chapter 5), where randomised trials finally showed the absence of health benefit or even the substantial hazards associated with taking some of these compounds.

Some groups advocate increasing vitamin D status (e.g., above 30 ng/mL of serum 25-hydroxyvitamin D) through more exposure to ultraviolet radiation or through taking high doses of vitamin D supplements (i.e., more than 50 µg per day or more). But as for any drug, before issuing claims on health benefit and promoting recommendations for increasing substantially the vitamin D status of millions of individuals, the alleged claims must be tested via randomised controlled trials for evaluation of efficacy on primary endpoint(s) and assessment of all-cause mortality and incidence of other major diseases (e.g., cardiovascular events, self-inflicted violence).

Trials should preferably be double-blind, placebo-controlled randomized trials. Analysis of health impact according to serum 25-hydroxyvitamin D level at baseline should be done. Side effects may be rare but highly undesirable since chemoprevention is likely to be followed by millions of healthy individuals. Therefore, these trials must be large and allow the possibility to include data in pooled analysis (statistical analysis of data of each individual from more than one randomised trial). Data should be collected on key outcomes such as total mortality, main causes of death, and incidence of other major cancerous, cardiovascular, metabolic, or neurological diseases and on violence, suicide and psychiatric disorders. For data pooling purposes, the trials should use standard definitions for outcome assessment, mainly for conditions other than cancer.

The example to follow with vitamin D is probably the series of double-blind, placebo controlled trials that were organised since the 1980s with the statins, a family of powerful hypocholesterolemic drugs able to substantially reduce cardiovascular and all cause mortality.

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[22] Rationale for randomised controlled trial for chemopreventive agents:

First, chemopreventive agents are pharmacological compounds, that is, substances that will interact with several biological receptors which eventually reduction in cancer risks, and also, other effects due to other physiological activity. This notion also applies to apparently "natural" substances such as vitamin D. Current standards issued by regulatory agencies (e.g., FDA in USA, EMEA in Europe) stipulate that any new proposed indication for a pharmaceutical compound must be first tested through a randomised trial for verification that the compound will be efficient when used for the new indication and with which side effects.

Second, the formidable complexity of biological phenomenon makes it easy for laboratory experiments to find that a compound is associated with biological mechanisms that could reduce cancer risk. Laboratory experiments will never exhaust the numerous biological pathways in which any substance is involved, and will often not be able to indicate potential adverse events dangers due to long-term use, mainly when used at doses substantially higher than those found in usual diet. So, again verification through randomised trials is the only way to verify whether biological properties translate in a health benefit or not in humans, and if side effects unforeseen by laboratory research would not show up.

Third, case-control and cohort studies have often yielded results suggestive of anti-cancer activity, but biases and failure to control for unknown confounding factors may have accounted for most observed effects. Observational studies may be misleading on true effect on health of taking regularly (e.g., daily) physiologically significant doses of drugs or micronutrients over long periods of time (e.g., more than one year). It is thus critical to tests adverse effects counterbalancing eventual decrease in cancer risk, for instance, the increase in other diseases or in mortality. Many examples are now available of chemopreventive agents which appear to have a beneficial effect in observational studies, but which have failed in randomised trials (see below). The most dangerous source of error in observational studies is the "bias by indication" that leads to reduced cancer risk in users of the compound (or in those having high serum levels of a compound) because they have personal characteristics that are associated with both a greater inclination to use the compound (or to have high serum levels) and a reduced risk of cancer. For instance, higher socio-economic status is associated with lower risk of several cancers. If more affluent people are more inclined to have a particular diet or usage of a pharmaceutical product, then that diet or pharmaceutical product may appear as conferring protection against these cancers. This socio-economic issue has been particularly relevant for the apparent positive cardiovascular effects of hormone replacement therapy in observational studies faded away in randomised trials (HERS and WHI trials).

[23] Chemopreventive compounds for which randomised controlled trials demonstrated lack of efficacy and sometimes significant rate of adverse event:

Vitamin B6, B12, and folic acid for the prevention of cardiovascular diseases

Observational studies provided convincing data on increased risk of CVD in subjects with mildly elevated serum homocysteine levels (Loscalzo, 2006). Because vitamin B6, B12 and folic acid are involved in homocysteine metabolism, it was hypothesised that high serum homocysteine levels were probably due to some deficiency in these vitamins that could lead to raised cardiovascular risk. A large body of basic science and physiological studies supported that hypothesis. However, three large randomised trials demonstrated that effective lowering of serum homocysteine levels with supplementation with vitamin B6 and B12, folic acid did not lead to reductions in incidence and mortality from major cardiovascular events, and that supplementation with folic acid, vitamin B6 and B12 increases (rather than decreases) the risk of fatal cardiovascular events (Toole *et al.,*2004; HOPE 2, 2006; Bonaa *et al.,*2006).

Menopause hormonal therapy (MHT)

During three decades, duration of menopause hormone therapy has been steadily extended because clinical and observational studies suggested that these compounds could lower CV risk, fracture risk and preserve cognitive functions. When doubts started to be raised about the safety of MHT mainly revealed by higher breast cancer risk among MHT users (CGHFBC, 1997), large scale randomised trials were organised as well as cohort studies designed and sufficiently large for detecting eventual adverse effects. At the end of the 1990s, two large-scale double-blind randomised placebo-controlled trials in the USA, the HERS and HERS II trials (Hulley *et al.,*2002) and the Women's Health Initiative (WHI) trial (Rossouw *et al.,*2002; Chlebowski *et al.,*2003; Anderson *et al.,*2004) and several large cohort studies (mainly the Million Women Study in the UK, (Million Women Study Collaborators, 2003) were initiated to try to answer the numerous puzzling questions regarding HRT use. These studies demonstrated that women taking MHT for one year or more had higher risk of breast cancer, myocardial infarctions, cardiovascular diseases, deep venous thrombosis, stroke and decline of cognitive functions. Reduced risks for fractures and colorectal cancer were found when MHT was taken for five years or more. The overall conclusion of these trials and large cohort studies was that increased disease risks associated with the MHT use largely outweigh the benefits.

Omega-3 fatty acids

Omega-3 fatty acids are mainly found in oily fish, and were deemed to protect against oxidative reactions involved in cancer and cardiovascular diseases. Systematic reviews of prospective cohort studies and of randomised trials found no evidence for a protective effect of these fatty acids on either cancer (including colorectal and breast cancer) or cardiovascular diseases (Hooper *et al.,*2006; MacLean *et al.,*2006).

Dietary fibre

A systematic review of 13 prospective cohort studies found no effect of dietary fibre intakes on colorectal cancer incidence (Park *et al.,*2005). In five randomised trials, dietary supplementation with wheat bran or other types of fibre did not affect the rate of recurrence of colorectal adenomas (MacKeown-Eissen *et al.,*1994; Schatzskin *et al.,*2000; Mac Lennan *et al.,*1995; Alberts *et al.,*2000; Bonithon-Kopp *et al.,*2000). The randomised trial by Bonithon-Kopp *et al.,*(2000) found that subject assigned in the intervention arm (ispaghula husk 3.5g per day) had in fact a significant increased risk of adenoma recurrence.

Table 21.1 - Variable characteristics of randomized trials on vitamin D

Dose per day	Primary endpoint	Duration active intervention	Interactions	Selection subjects
Ordinary doses 10-20 µg	Cancer-specific incidence	2-4 years	Baseline 25(OH)D	Any healthy
High doses 25-35 µg	All cancer incidence	5-9 years	Baseline vitD intakes	Any healthy with baseline < say 15 ng/ml
Very high doses >35 µg	Cancer+CVD+Diabetes incidence	10-14 years	With Calcium intakes	Patients with cancer or CVD or diabetes
Dose escalation: e.g., 1 group placebo/1 group 10-20 µg/ 1 group 40 µg	Cancer-specific mortality		Statin use	
	All cancer mortality		Hormone Therapy	
	CVD mortality			
	Non cancer, non-CVD disease mortality			
	All-cause mortality			

Chapter 21 – Overall conclusions of the IARC Working Group on vitamin D and cancer

Overall conclusion 1: colorectal cancer

The epidemiological evidence from observational studies for an inverse association between serum 25-hydroxyvitamin D levels and the incidence of colorectal cancer and sporadic colorectal adenoma was consistent and persuasive. There is however only limited evidence of a causal link due to possible confounding by other dietary or lifestyle factors.

Results from randomised controlled trials to date have not demonstrated an effect of vitamin D supplementation on colorectal cancer risk. However, due to several issues (doses, interaction, duration), they cannot be judged as contradictory to the evidence from observational studies either.

Overall conclusion 2: breast cancer

The epidemiological evidence from observational studies suggest an inverse association between serum 25-hydroxyvitamin D levels and the incidence of breast cancer, but the differences between studies are large, and the overall evidence is weak when case-control studies are not included in the meta-analysis.

New cohort studies on serum 25-hydroxyvitamin D levels and breast cancer risk are warranted.

Overall conclusion 3: prostate cancer

Observational studies have provided evidence of little or no effect of serum 25-hydroxyvitamin D on the incidence of prostate cancer.

Overall conclusion 4: other cancers

The evidence available to the Working Group for incidence of other cancers was insufficient for evaluation.

Overall conclusion 5: all-cause mortality

Results from observational studies and randomised trials suggest that vitamin D supplements may lower all-cause mortality. The specific health conditions for which mortality would be reduced remain to be established.

Overall conclusion 6: adverse events

There is no data available on the health hazards of long-term maintenance of high 25-hydroxyvitamin D serum levels in healthy subjects over long periods.

Past experiences with other compounds (e.g., several anti-oxidants and hormone replacement therapies) have shown serious adverse effects of the chronic use of supplements or long-term maintenance of high serum levels.

Overall conclusion 7: The need for new randomised controlled trials

Hypotheses on vitamin D status and colorectal cancer, cardiovascular diseases and all-cause mortality should be tested in appropriately designed randomised controlled trials.

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Annex

Latitude of residence in Europe and serum 25-hydroxyvitamin D levels: a systematic review

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Abstract

The increasing breast, colorectal and prostate cancer mortality rates found with increasing latitude by ecological studies in the USA and in Europe has been equated to lower vitamin D status with increasing latitude. We examined in Western, Northern and Southern Europe the association between latitude of residence and serum 25-hydroxyvitamin D levels. We performed a systematic search of published articles reporting serum 25-hydroxyvitamin D levels in apparently healthy adult European populations. Using results of selected studies, we fitted a random effects model based on standard deviations of means of serum 25-hydroxyvitamin D concentrations. Thirty-five studies were included in the analysis, representing 114 estimates of mean serum 25-hydroxyvitamin D derived from a total of 9,514 subjects 18 years old or more, including 1,887 males, 5,008 females, and 2,619 subjects of unknown sex. Increase in latitude was statistically significantly associated with increase in serum 25-hydroxyvitamin D levels among subjects more than 65 years old. In younger subjects, no significant association with latitude was found. In subjects more than 65 years old, an increase in 10 degrees in latitude of residence increases mean serum 25-hydroxyvitamin D by 11.8 nmol/L. Between European countries, increase in latitude is associated with increase in serum 25-hydroxyvitamin D concentrations. Reasons other than vitamin D status may explain the relationship between increasing latitude and cancer mortality rates observed in the USA and in Europe.

Introduction

Ecological studies in the United States and in Europe indicate that mortality rates from several cancers including breast, colorectal and prostate cancer increase with increasing latitude, i.e., increasing distance from the equator (Garland 1990; Grant 2002, 2003; Grant EJC 2008). Results from several observational case-control and cohort studies on latitude of residence and cancer are compatible with these ecological observations (van der Rhee et al, 2006). For explaining the relationship between latitude and cancer burden, latitude has been viewed as a surrogate for exposure to solar ultraviolet-B radiation (UVB, 280-320 nm), and exposure to UVB has been equated to UVB-induced vitamin D synthesis in the skin (Holick 1994).

Vitamin D is stored in skin adipose tissues or hydroxylated in the liver in 25-hydroxyvitamin D, that is further hydroxylated in the kidneys for production of the physiologically active metabolite 1α,25-dihydroxyvitamin D. Only the latter metabolite is physiologically active and plays a crucial role in calcium metabolism and bone formation. Because of marked seasonal variations in UVB exposure, 25-hydroxyvitamin D serum levels are usually highest after the summer and lowest at the end of the winter. In spite of seasonal variations, the serum level of 25-hydroxyvitamin D is more stable than serum level of vitamin D and of 1α,25-dihydroxyvitamin D (Adams et al, 1982). Therefore, 25-hydroxyvitamin D serum level during the winter until beginning of spring is considered as the best indicator of individual vitamin D status.

Laboratory experiments have shown that in addition to its action on calcium and bone metabolism, the 1α,25-dihydroxyvitamin D inhibits cellular proliferation, and promotes differentiation and apoptosis, all properties compatible with antineoplastic action. The discovery of extra-renal production of 1α,25-dihydroxyvitamin D coupled with existence of vitamin D receptors (VDR) in various tissues has led to the hypothesis that autocrine or paracrine production of 1α,25-dihydroxyvitamin D could prevent several cancers (e.g., prostate, colon, breast, pancreas, ovary) and attenuate their progression. All together, these elements support the hypothesis that high serum 25-hydroxyvitamin D status would contribute to decrease the risk of cancer (Giovannucci, CCC).

If ecological studies on latitude and mortality from cancer have been instrumental for triggering new researches on vitamin D, these studies never presented data on serum 25-hydroxyvitamin D status of populations. In this paper, we examine ecological associations between 25-hydroxyvitamin D serum levels in European populations according to latitude of residence.

Methods

We made a systematic search of published data on serum 25-hydroxyvitamin D measurement in European populations from 1970 until December 2006, using MEDLINE, ISI Web of Knowledge, Science Citation Index Expanded and Cochrane Library. The search was done without language restriction with using combinations of the following keywords: “serum 25-hydroxyvitamin D”, “25-hydroxy-serum 25-hydroxyvitamin D”, “1 alpha,25-dihydroxy-serum 25-hydroxyvitamin D”, “survey”, “cross-sectional”, “epidemiology”, and “latitude”.

We selected studies that had among their objectives the evaluation of the prevalence of serum 25-hydroxyvitamin D levels in a sample of the population. In many instance, specific age groups were sampled.

The literature search found 150 articles, for which full copies were obtained. A first selection round was performed as follows: Studies were not selected if (i) they did not report mean values, but rather percentages of subjects below specific cut-off values for serum 25-hydroxyvitamin D. (ii) If they focused on serum 25-hydroxyvitamin D status in subjects with a specific disease (e.g., patients with osteoporosis or kidney diseases) or in convenient samples of selected subjects (e.g., volunteers for assessment of seasonal variations, of for metabolic studies on bone turnover) or in selected sub-populations likely to have serum 25-hydroxyvitamin D levels different from the general population of same age (e.g., servicemen). (iii) We also excluded studies conducted in non-Caucasian populations or in population younger than 18 years old. We did not exclude surveys done in institutionalized elderly people.

This first selection identified 72 articles that were subjected to a second selection round: two of us (PM and PA) completely read these articles for selecting results related to serum 25-hydroxyvitamin D measured from November until May. Several studies reported serum levels during different seasons, and we only selected data of serum levels assessed from November until May. Studies were not selected if months or period of blood sampling were not indicated. Data from relevant articles were abstracted in a table summarizing key variables and results. Whenever possible, we abstracted data for men and women separately, in other case data was abstracted for both sexes together.

The webtable 1 provides reasons for exclusion of studies or of results during the second selection round, and webtable 2 lists studies that were included in the analysis. Full references of articles selected after the first selection round can be found after the webtables in the additional material.

Statistical analysis

We retrieved from original papers the average age of populations. When age was only presented in intervals or range, we took the middle value. Then after, we categorised populations in two age groups: with an average age lower or equal to 65 years old *versus* populations with an average age greater than 65 years.

For latitude, when the articles specified the city where the study was realized we took the latitude of that city. When the authors did not publish a description of the geographical area for data collection, we took an average estimate of latitude of the country from the website www.tageo.com (last accessed in October 2007).

We fitted a random effects model based on means of serum 25-hydroxyvitamin D concentration considering studies as random effect, taking into account heterogeneity between studies as well as correlation within studies. Age, gender and latitude were considered as fixed effects in the model. When only percentiles of the serum 25-hydroxyvitamin D concentration were reported as a measure of variance, we estimated the standard deviation under the normal assumption. For the study by van der Wielen and co-workers (1995), no indication of variance was available. We estimated an average standard deviation for each mean serum 25-hydroxyvitamin D level reported for each sample included in this study based on the linear correlation between sample size and variances found in all other studies.

Age was included in models as a two-category variable (18-65 and >65 years old) since a better fit was obtained than with inclusion of age as a continuous variable. Latitude was included as a continuous variable.

Stratified analysis showed that serum 25-hydroxyvitamin D levels according to gender and latitude were influenced by age. We therefore included in the full model an interaction term between age and gender as well as an interaction term between age and latitude.

We conducted sensitivity analyses with inclusion and exclusion of the following studies: (i) The study by Van der Wielen et al (2005) did not report standard deviations and in samples drawn in some countries seemed to include small selected population (e.g., in Belgium). (ii) The study by Chapuy et al (1997) measured serum 25-hydroxyvitamin D in a selection of subjects that were themselves volunteers for a randomized trial testing the influence of antioxidants on health. Selection of subjects for serum measurements was not explained. (iii) Three studies (D'Amore 1984, Moreiras 1992, Schrijver 1985) used methods for serum 25-hydroxyvitamin D measurement that were not clearly described or used ancient type analysis of poor reliability (e.g., the "Buhlman's method" reported by D'Amore et al, 1984).

We carried out another sensitivity analysis in order to verify whether estimations of latitudes attributed to countries or regions did affect results. We evaluated if the estimates coming from publication with no indication of the city where the study was conducted, or important latitude span (5 degrees or more), were significantly different from the others.

A result was labeled as "significant when the p value associated with a two-sided statistical test was lower than 0.05.

Results

Thirty-five studies were included in the analysis (webtable 1), representing 114 estimates of mean serum 25-hydroxyvitamin D derived from a total of 9,514 subjects 18 years old or more, including 1,887 males, 5,008 females, and 2,619 subjects of unknown sex. Twenty-four of these studies were published after 1994. The median sample size for which an estimate of serum 25-hydroxyvitamin D was reported was 42 (range 11-357). The range of ages in samples was 18 to 85, and the median of the average ages of the samples was 71. Sixty-seven estimates (out of 114) were derived from samples having an average age greater than 65. The median latitude of populations was 49.5° North ranging from 35° North (Greece) to 70° North (Norway).

The distribution of mean serum 25-hydroxyvitamin D levels was close to Normal (Figure 1) with a mean concentration of 42.7 nmol/l (SD=14.7). We noticed three outliers with serum 25-hydroxyvitamin D level greater than 80 nmol/l, two in Chapuy (1997) and one in D'Amore study (1982).

In the model with all studies, all factors and interactions terms between age and sex and between age and latitude showed that being an older subject was the most important predictor of mean serum 25-hydroxyvitamin D levels (Table 1). There was a significant interaction between gender and age.

A significant interaction was also found between age group and latitude. In subjects 18-65 years old, the mean serum 25-hydroxyvitamin D levels slightly decreased with increasing latitude, with an average decrease of 3.4 nmol/l between latitudes 35° North and 70° North (Figure 2). In subjects more than 65 years old, the mean serum 25-hydroxyvitamin D levels increased with increasing latitude, with an average increase of 23.1 nmol/l between latitudes 35° North and 70° North.

Sensitivity analyses in Table 1 showed no change in the beta coefficient for latitude after exclusion of the study by Van der Wielen et al (1994). This stability in estimates indicates that the standard deviation for results in the study of Van der Wielen et al (1994) we calculated on the basis of sample size and variances of other studies did not influence the results. Exclusion of the study of Chapuy et al (1997) had a certain impact on all estimates: the relationship between mean serum 25-hydroxyvitamin D level and latitude in young population was reversed with a significant, slight average increase of 3.9 nmol/l between latitude 35 and 70 ° N. This observation was also found when excluding both studies of Van der Wielen et al (1995) and of Chapuy et al (1997).

Exclusion of the three studies for which the serum 25-hydroxyvitamin D measurement method was not clearly described or prone to error did not affect the estimates.

Distribution of residuals from all the models was Normal (data not shown), and there was no correlation between residuals with latitude or with age (data not shown). This indicates that the model was not influenced by mean serum 25-hydroxyvitamin D levels found in highest latitude or among oldest population. The studies of D'Amore et al (1994) and Chapuy et al (1997) were systematically outliers in residuals distribution (data not shown).

From the main model regression coefficients in Table 1 one can estimate that in subjects >65 years old, an increase in 10 degrees in latitude of residence increases mean serum 25-hydroxyvitamin D by 11.8 nmol/L (i.e., 10*[1.3 – 0.12]). This main model also allows estimating the mean gender-specific serum 25-hydroxyvitamin D level of European populations according to latitude. For instance, a sample of men younger than 65 years old living at a latitude of 43° North, the mean serum level would be [52.3+(-5.6)+(-0.12*43)] = 41.54 nmol/l. A sample of women older than 65 years old living a latitude of 51 ° North would have a mean serum 25-hydroxyvitamin D level of

[52.3+(-94.4)+2.1+(-0.12*51)+18.4+(1.3*51)] = 38.58 nmol/L.

Detailed results from the main model displayed in Table 2 show that female subjects in study samples more than 65 years old had mean serum 25-hydroxyvitamin D levels much lower than female subjects in study samples with average age equal or lower than 65 years. Such difference was not apparent between younger and older males.

Table 3 displays estimates of mortality for year 2002 for colorectal, breast and prostate cancer extracted from the Globocan database (Ferlay et al, 2004). A South to North gradient is noticeable for prostate cancer mortality. For colorectal and breast cancer mortality, an inverse U-shaped association is observed, with lowest rates in southern countries, highest rates in Western European countries, and decreased rates in Northern countries. Serum 25-hydroxyvitamin D levels are higher in Norway than in Greece, Spain and Italy, while mortality rates for the three cancers are higher in Norway.

Discussion

This study was a systematic review of all surveys on serum 25-hydroxyvitamin D levels in Western, Northern and Southern Europe conducted in apparently adult healthy subjects in which blood samples were drawn during the cold seasons. The main findings are first, the positive association between latitude and serum 25-hydroxyvitamin D levels in European subjects more than 65 years old, and an absence of association in younger subjects. Thus latitude of residence does not necessarily equate to vitamin D status. Second, in Europe, there is little association between the South to North gradient in serum 25-hydroxyvitamin D concentration and geographical variations in age-standardized mortality rates. For comparing the cancer burden in European countries, we choose mortality data because incidence data are more influenced by between country variations in implementation of screening techniques.

Our study has several limitations: first, methods used for measurement of serum 25-hydroxy-vitamin D level may vary according to study, and few larger studies (e.g., Van der Wielen et al, 1994) used standard method across countries. Other studies such as d'Armore et al (1984) used uncommon method. Such variation in measurement may have introduced random noise in the data, and if all measurements had been done using a single method, the association we found between latitude and serum 25-hydroxy-vitamin D levels would have been statistically more significant.

Second, in some studies, it is not clear whether sampled subjects were representative of the general population they belonged to. For instance, samples included relatively few subjects (e.g.,

Belgium in van der Wielen et al, 1994) and the published report did not clearly outline how these subjects were sampled. The estimates of mean serum 25-hydroxyvitamin D level in various populations in France (Chapuy et al, 1997) were made on a subsample of the SUI.VI.MAX randomized trial that tested health effects of antioxidant supplements. 1,569 adults 35 to 65 years old were selected from 15,000 healthy volunteers that were part of the trial. Volunteers that participated to the trial were healthier that the background French population of same age (Hercberg et al, 1998), and no information was provided on how the subsample of 1,569 volunteers were selected for the vitamin D study. There is thus a high probability that the vitamin D status of these volunteers was higher than the average French population of same age. Therefore, a sensitivity analysis was performed, examining results after exclusion/inclusion of studies for which there were doubts as to the laboratory or subject sampling method.

Vitamin D status has been often investigated in patients suffering from chronic conditions such as osteoporosis or other bone disease, and chronic kidney diseases. We excluded studies on patients with chronic conditions as they were not likely to reflect the vitamin D status of the general population, and were often conducted in very dissimilar types of patients. One large study assessed the serum 25-hydroxyvitamin D levels in women with osteoporosis (i.e., a bone mineral density below -2 Z-scores of female reference population 20-39 years old or two vertebral fractures) in 25 countries in 5 continents, using standardized sampling method for patient inclusion and standardized laboratory essays (Lips et al, 2001). The mean age of these women was 66 years (SD = 7.1 years). The study found a strong South to North gradient in serum 25-hydroxyvitamin D levels of osteoporotic women living in Europe, with an increase of serum level of 8.0 nmol/L per 10 degree increase in latitude, a figure quite close to our estimate of 11.8 nmol/L per 10 degree increase in latitude.

One study found an inverse association between increasing latitude and mean serum 25-hydroxyvitamin D levels (Zitterman et al, 2006), and another found no association between latitude and mean serum 25-hydroxyvitamin D levels (Moan et al, 2007). These two studies had strong limitations as they were not based on systematic search of data in the literature, and picked up studies done in different continents, often including highly selected sub-populations (e.g., children, patients with chronic condition) and with blood sampling sometimes done during summer period. Thus results from these two studies are not interpretable.

We are not aware of studies in the United States that tried to compare latitudinal trends in serum 25-hydroxyvitamin D concentrations. The only study we found was conducted in US patients with moderate and severe chronic kidney disease but not under dialysis (LaClair et al, 2005). No latitude gradient was found for serum 25-hydroxyvitamin D (from Illinois/Indiana to Florida). However these patients are known to have reduced capacity to produce vitamin D in the skin.

A recent large cross-sectional survey in the UK (Hypponen et al, 2007) included 7,437 white adults 45 years old at the moment of the survey. Like in the French study (Chapuy et al, 1997) that included adult subjects less than 65 years old, a South to North gradient in serum 25-hydroxyvitamin D levels was found. It seems that when done at the national level, surveys show a North to South gradient serum 25-hydroxyvitamin D levels. The apparent contradiction between within and between country latitude trends in serum 25-hydroxyvitamin D levels may be due to dietary habits in Europe known to be more homogeneous within than between countries (Slimani et al, 2002). Also, sun exposure habits differ between European populations: Northern populations who have lighter skin are usually more attracted by sunlight than more Southern population who have darker skin and have less inclination for staying long in the sun (Peacey et al, 2006).

The few studies that performed multivariate adjustments of factors predicting serum 25-hydroxyvitamin D levels have shown that latitude is only one among a number of predictors, including intakes of oily fish, outdoor activity, obesity, smoking status, socio-economic status (van der Mei et al, 2007; Hypponen et al, 2007; Giovannucci et al, 2006). Also, all factors other than latitude considered together are much better predictors of vitamin D status than latitude.

Results from this study indicate that changes in latitude should not necessarily be equated with vitamin D status. Latitude gradient of other factors having an influence on cancer mortality could represent alternative explanation of ecological studies in the USA. For instance, hours of daylight, melatonin and cancer, latitudinal variations in dietary patterns or lifestyle that would be associated with higher cancer mortality rates.

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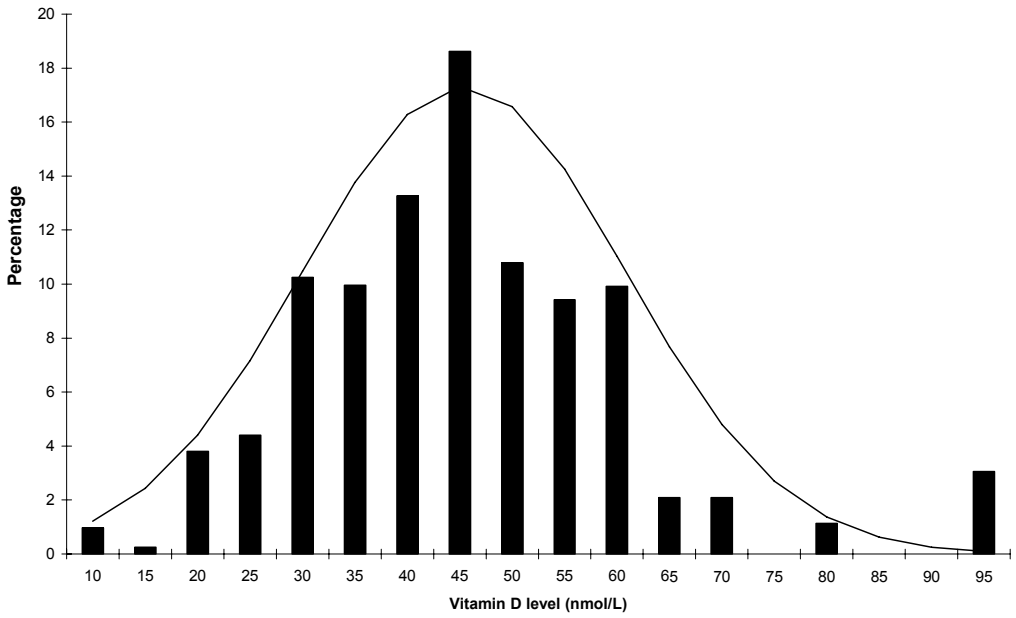

Figure 1 – Histogram and curve showing the distribution of the mean serum 25-hydroxyvitamin D levels reported in 35 studies (114 samples including 9514 subjects ≥ 18 years old) in Europe. Mean concentration was 42.7 nmol/l (SD=14.7). Three outliers have levels greater than 80 nmol/l: two points from Chapuy's (9) and one point from D'Amore' study (10).

Table 1 – Predictors of mean serum 25-hydroxyvitamin D levels in Europe from 35 studies including 114 samples including a total of 9,514 subjects 18 years old and more. Entries are changes in serum 25-hydroxyvitamin D in nmol/l.

Variables	Change in nmol/l	95% CI		Exclusion of studies of:			
				van der Wielen et al, 1995	Chapuy et al, 1997	van der Wielen et al, 1995 and Chapuy et al, 1997	D'Amore [ref], 1985 Moreiras et al, 1992[ref], Schrijver et al, 1985[ref]
Intercept	52.3*	14.6	90.1	52.34	36.66	36.66	48.1
Age							
≤65	Reference			Reference	Reference	Reference	Reference
>65	-94.4*	-149.5	-39.3	-117.03	-78.72	-101.35	-87.22
Gender							
Unknown	Reference			Reference	Reference	Reference	Reference
Male	-5.6	-18.2	6.9	-5.62	-1.54	-1.54	-4.65
Female	2.1	-8.7	12.9	2.1	5.49	5.49	2.88
Latitude (per degree)	-0.12	-0.79	0.54	-0.12	0.1	0.1	-0.06
Interaction between age >65 and gender							
Male and >65	32*	14.5	49.5	32.69	27.88	28.61	31.9
Female and >65	18.4*	3.3	33.5	18.58	15.02	0	18.38
Interaction between latitude and age>65 (per degree)	1.3*	0.3	2.3	1.7	1.06	1.48	1.16
Studies with results being outliers according to model residual analysis	D'Amore et al, 1994			D'Amore et al, 1994	D'Amore et al, 1994	D'Amore et al, 1994	Chapuy et al, 1996

* $P < 0.05$.

Table 2 - Mean serum 25-hydroxyvitamin D levels estimated from least square means analysis *

Gender	Age ≤ 65	Age > 65
Male	40.4* (30.8-50.1)	42.4 (33.8-51.0)
Female	48.2 (40.3-56.1)	36.6 (30.3-42.8)
Unknown Sex	46.1 (37.7-54.4)	16.0 (8.0-24.1)

* Entries in Table are estimates of mean serum 25-hydroxyvitamin D levels (nmol/l) and (95% confidence intervals) derived from a full random effect model including age, gender, latitude, an interaction term between age and gender and an interaction term between age and latitude.

Table 3 – Mortality from prostate, colorectal and breast cancer in Western, Southern and Northern European countries in 2002*

Country	Males		Females	
	Prostate	Colon and rectum	Colon and rectum	Breast
Iceland	23.0	12.8	13.2	19.6
Finland	18.0	11.5	9.8	17.4
Norway	28.4	20.1	16.8	17.9
Sweden	27.7	14.9	11.1	17.3
Denmark	22.6	23.3	19.2	27.8
United Kingdom	17.9	17.5	12.4	24.3
Ireland	19.7	23.6	13.7	25.5
The Netherlands	19.7	18.9	14.4	27.5
Germany	15.8	19.9	15.7	21.6
Belgium	20.3	18.7	14.1	27.7
Luxembourg	15.6	18.6	13.4	19.3
Austria	18.4	20.1	13.9	20.6
Switzerland	21.6	15.2	9.7	19.8
France	18.2	18.2	11.8	21.5
Italy	12.2	16.5	10.9	18.9
Spain	14.9	18.5	11.3	15.9
Greece	11.2	9.7	8.0	15.4

*Age Standardized mortality Rates (ASR), World Population Standard, Data source: Globocan 2002 (13).

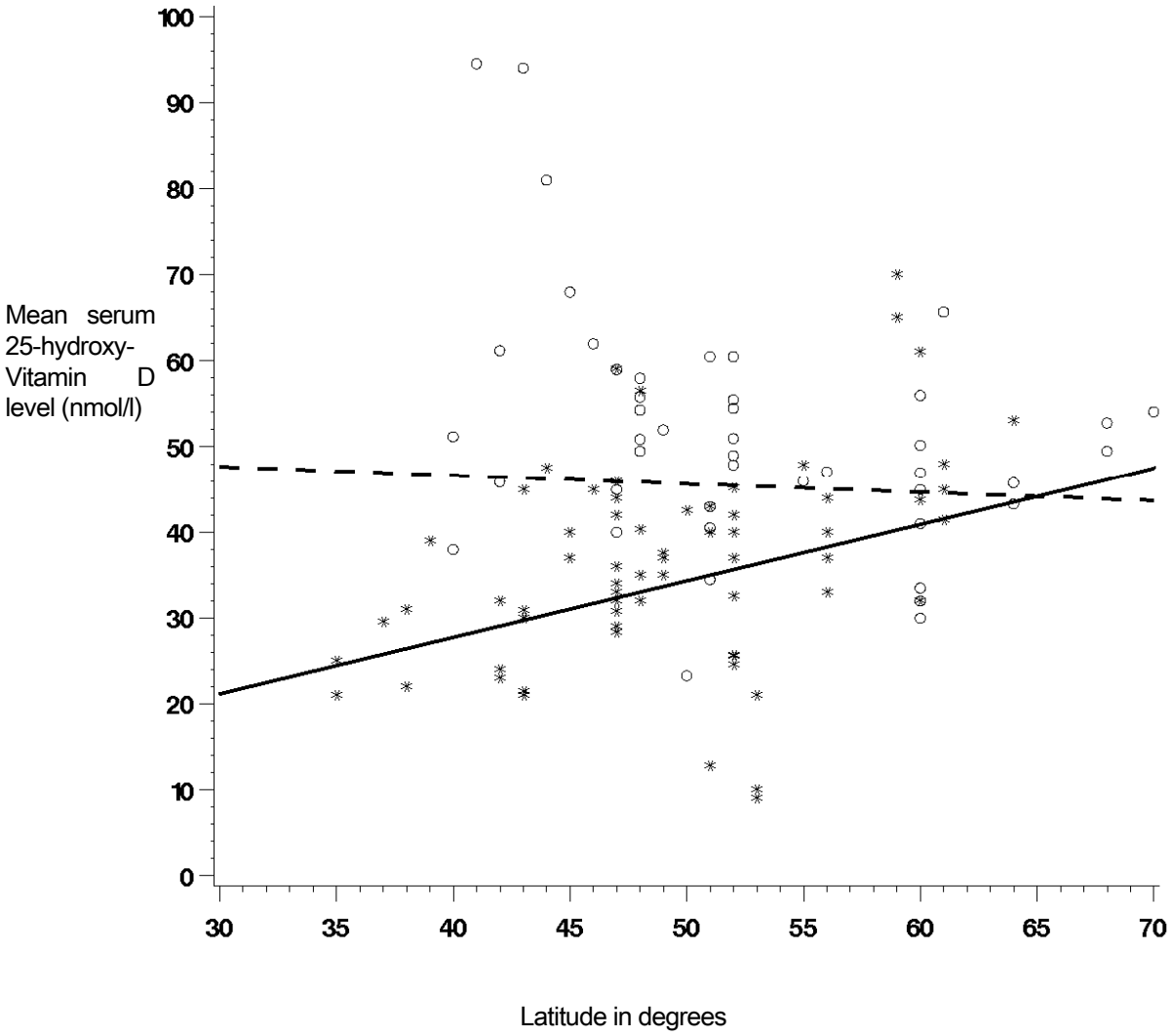

Figure 2 - Latitude and observed mean serum 25-hydroxyvitamin D level observed in European populations, totalizing 114 samples including 9514 subjects. Circles and dashed trend line represent values measured and predicted for populations with an average age lower or equal to 65 years. Stars and plain trend line represent values measured and predicted for populations with an average age greater than 65 years. The 3 outliers having levels greater than 80 nmol/l tend to lift-up the low latitude end of the trend line of younger subjects: two points from from Chapuy (9) and one point from D'Amore study (10).