

# Cancer Association of South Africa (CANSA)



## Fact Sheet On Vitamin D

### Introduction

Although vitamin D is firmly enshrined as one of the four fat-soluble vitamins, it is not technically a vitamin. True, it is essential for health and only minuscule amounts are required. It breaks the other rules for vitamins because it is produced in the human body, it is absent from all natural foods except fish and egg yolks and even when it is obtained from food, it must be transformed by the body before it can do any good.

[Picture Credit: Vitamin D]



Vitamin D is one of the 13 vitamins discovered in the early 20th century by doctors studying nutritional deficiency diseases. Ever since, scientists have defined vitamins as organic (carbon-containing) chemicals that must be obtained from dietary sources because they are not produced by the body's tissues. Vitamins play a crucial

role in the body's metabolism, but only tiny amounts are needed to fill that role.

(Picture Credit: Rickets)



Vitamin D was discovered in 1920, culminating the long search for a way to cure rickets (see picture of X-ray of 2-year old with rickets), a painful childhood bone disease. Within a decade, the fortification of foods with Vitamin D was introduced and rickets became rare. But solving the problem of rickets was only the beginning of research into vitamin D. Research suggest that vitamin D may have an important role in many aspects of human health, from bone fractures to prostate cancer, from cardiovascular disease and neuromuscular problems to diabetes (Harvard Medical School).

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Page 1

Currently, there is a lot of scientific debate about how much Vitamin D individuals need each day (Institute of Medicine).

Low levels of vitamin D have been implicated in a wide variety of health issues including cancer, diabetes and cardiovascular disease (IARC; Deeb, *et al.*; Scragg). For most humans, the majority of vitamin D<sub>3</sub> is derived from sunlight. Dietary intake of vitamin D is usually low as natural foods containing a significant amount of vitamin D are rare (Meinhardt-Wollweber & Krebs, 2012).

Vitamin D deficiency is now recognised as a pandemic. The major cause of vitamin D deficiency is the lack of appreciation that sun exposure in moderation is the major source of vitamin D for most humans. Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child's or an adult's vitamin D requirement. Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults. Vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases. A circulating level of 25-hydroxyvitamin D of >75 nmol/L, or 30 ng/mL, is required to maximise vitamin D's beneficial effects for health. In the absence of adequate sun exposure, at least 800–1000 IU vitamin D<sub>3</sub>/d may be needed to achieve this in children and adults. Vitamin D<sub>2</sub> may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations (Holic & Chen, 2008).

### **Vitamin D Status in South Africa**

In a study by Poopdi, *et al.*, (2011) of three hundred and eighty-five (385) children in the Greater Johannesburg area, White children had significantly higher 25(OH)D than their black peers (120.0(sd 36.6)nmol// v. 93.3 (sd 34.0) nmol/l, respectively). Seasonal variations in 25(OH)D levels were found only in white children, with 25(OH)D levels being significantly higher in White than in Black children during the autumn and summer months. In multiple regression analysis, season, ethnicity, sex and total fat mass were the factors found to have an influence on 15(OH)D. Vitamin D deficiency (7%) and insufficiency (19%) were uncommon among the 10-year-old children.

### **The Vitamin D Status of 10-year-old South African Children**

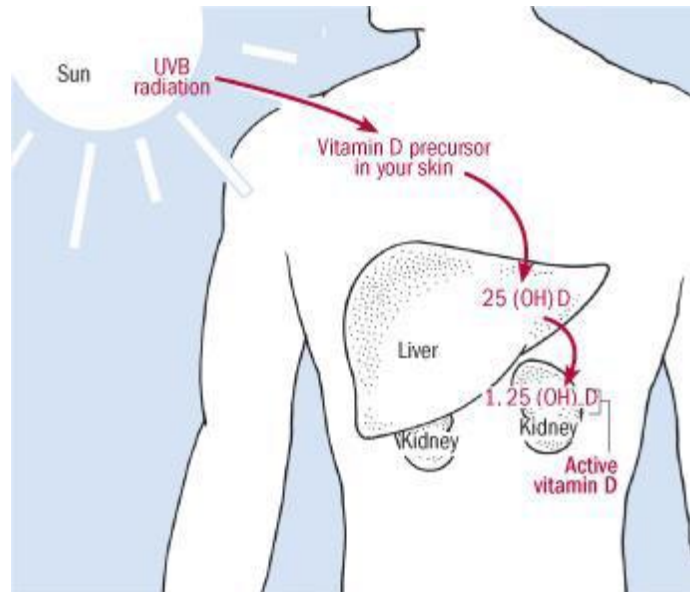
In a study by Poopedi, Norris and Pettifor of 385 children in the Greater Johannesburg area of South Africa who form the Bone Health sub-cohort of the longitudinal Birth to Twenty cohort it was found that White children had significantly higher 25(OH)D than their black peers (120.0 (sd 36.6) nmol/l v. 93.3 (sd 34.0) nmol/l, respectively). Seasonal variations in 25(OH)D levels were found only in white children, with 25(OH)D levels being significantly higher in white than in black children during the autumn and summer months. In multiple regression analysis, season, ethnicity, sex and total fat mass were the factors found to have an influence on 25(OH)D. Vitamin D deficiency (7 %) and insufficiency (19 %) were uncommon among the 10-year-old children.

The study concluded that Vitamin D supplementation or fortification was not warranted in healthy children living in Johannesburg. However, further studies needed to confirm this in other regions of the country, especially in those living further south and with less sunshine during the winter months.

## Sources of Vitamin D

The best source of vitamin D is from sunlight on our skin. Vitamin D is made by our body in the skin in reaction to direct sunlight.

[Picture Credit: UVB Radiation]



Vitamin D production is different for skin regions with different optical properties. For forearm skin, production from solar irradiation is most efficient in the viable layers of the epidermis and in the spectral range from 300–315 nm. More than 90% of the production in volar forearm skin is produced in the range from 301–313 nm with a maximum at 305 nm. The depth range at which 90% of pre-vitamin D is produced is between 15 and 85  $\mu\text{m}$  with a most effective production at 54  $\mu\text{m}$ . Only about 11.5% of the total production is from the dermis i.e. at depth  $>75 \mu\text{m}$  in this model, the stratum spinosum contributes most (50%) to the overall production, followed by the stratum basale (22%) and the superficial layers (stratum corneum and stratum granulosum, 16.5%). As the attenuation of vitamin D-efficient radiation is weaker in the lighter skin of the inner side of the forearm, overall vitamin D production is higher here than on the outer side of the forearm.

The stronger pigmentation at the outer side of the arm also causes a slight shift ( $\sim 0.5 \text{ nm}$ ) of efficient production towards higher wavelengths and towards the surface as more than 90% are produced at depths between 3 and 78  $\mu\text{m}$  with a maximum around 49  $\mu\text{m}$ . The strong attenuation of ultraviolet radiation in the skin is the major limiting factor for the depth at which effective pro-vitamin D conversion is still possible. At a depth of 100  $\mu\text{m}$ , less than 1% (15%) of the incident radiation in the range below 300 nm (315 nm) is still available even in the weakly pigmented skin of the inner side of the forearm (Meinhardt-Wollweber & Krebs, 2012).

Vitamin D is also found in small quantities in a number of foods. Good food sources include:

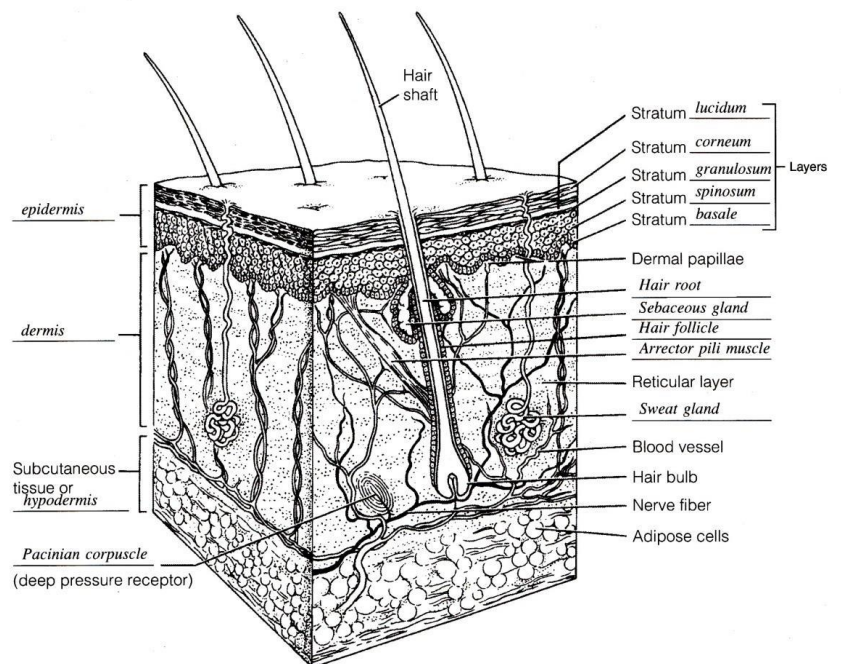
- oily fish, such as salmon and sardines
- egg yolk
- fortified fat spreads
- fortified breakfast cereals
- fortified powdered milk

(NHS UK).

According to Meinhardt-Wollweber & Krebs (2012) the following pertains to the formation of Vitamin D in the body. According to their research:

[Picture Credit: The Skin]

- Vitamin D<sub>3</sub> is formed within the skin
- 16,5% of Vitamin D<sub>3</sub> is formed in the stratum corneum and stratum granulosum of the skin
- 22% of Vitamin D<sub>3</sub> is formed in the stratum basale of the skin
- 50% of Vitamin D<sub>3</sub> is formed in the stratum spinosum of the skin
- More than 90% of Vitamin D<sub>3</sub> is produced at depths between 3 and 78 μm within the skin with a maximum around 49μm



- At the depth of the basal layer, Vitamin D production becomes negligible, even though the substrate, i.e. provitamin D, concentration is the highest here
- Their findings support the hypothesis that skin phototype or pigmentation have a considerable effect on individual Vitamin D production

Vitamin D is fat-soluble. This means that one's body can store extra amounts of vitamin D.

It is important to get enough vitamin D from one's diet because it helps the body absorb and use calcium and phosphorus for strong bones and teeth. Vitamin D can help protect older adults against osteoporosis.

Recent reports have supported a role for 1,25(OH)(2)D(3) in mediating normal function of the innate and adaptive immune systems. Crucially, these effects seem to be mediated via localised autocrine or paracrine synthesis of 1,25(OH)(2)D(3) from precursor 25-hydroxyvitamin D<sub>3</sub>, the main circulating metabolite of vitamin D. The ability of vitamin D to influence normal human immunity is highly dependent on the vitamin D status of individuals and may lead to aberrant response to infection or autoimmunity in those who are lacking vitamin D (Hewison, 2010).

It may help reduce the risk of developing chronic diseases such as multiple sclerosis and certain types of cancer, such as colorectal cancer but this is still being studied.

According to the National Institute of Health there are several food sources of Vitamin D. These include:

Food	International Units per Serving	Percent Daily Value
Cod liver oil – 1 tablespoon	1 360	340
Swordfish (cooked) – 90ml	566	142
Salmon (sockeye) (cooked) – 90ml	447	112
Tuna fish (canned in water and drained) – 90ml	154	39
Orange juice (fortified with Vit D) – 125ml (check label)	137	34
Milk (fortified with Vit D) – 125ml (check label)	115 - 124	29 – 31
Yogurt (fortified with Vit D) – 180ml (check label)	80	20
Margarine (fortified with Vit D) – 15ml (check label)	60	15
Sardines (canned in oil) - sardines	46	12
Beef liver (cooked) – 90ml	42	11
Egg (1 large) – Vit D found in yolk	41	10
Cheese (Swiss) – 30ml	6	2

Daily Value (DV). DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet. The DV for vitamin D is currently set at 400 IU for adults and children age 4 and older. Food labels, however, are not required to list vitamin D content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.

### Is Unprotected Sun Exposure Necessary to Prevent Vitamin D Deficiency?

This is a highly controversial issue (Lim, et al. 2005; Wolpowitz & Gilchrest, 2006). Vitamin D is synthesised when the skin is exposed to ultraviolet radiation (UVR). Its active form, 1,25-dihydroxy Vit D<sub>3</sub>, regulates calcium metabolism, essential for bone and muscle health, and recent epidemiologic studies have shown that individuals with adequate serum vitamin D levels had a lower incidence of internal cancers and multiple sclerosis. However, the action spectrum for cutaneous vitamin D synthesis is in the UVB range, known to be photocarcinogenic. To make the active form, vitamin D<sub>2</sub> and vitamin D<sub>3</sub> are modified in the liver to produce 25-hydroxyvitamin D, which travels through the blood to the kidneys, where it is modified further to make 1,25-dihydroxyvitamin D (National Cancer Institute).

Therefore, for individuals at risk for vitamin D insufficiency, such as the elderly, homebound, or dark-skinned individuals, a balanced diet with adequate intake of food rich in vitamin D (e.g., salmon and fortified milk) is the most appropriate way to maintain a good vitamin D level. If necessary, vitamin D supplements can be added. Because of its harmful effects, intentional, unprotected sun exposure should not be used as a way to increase vitamin D levels.

In the southern hemisphere, residents of Buenos Aires (Brazil) and Cape Town (South Africa) can make far less vitamin D from the sun during their winter months (June through August) than they can during their spring and summer (Solar-Facts-and-Advice).

### Vitamin D and Sunburn

High doses of vitamin D taken one hour after sunburn significantly reduce skin redness, swelling, and inflammation, according to double-blinded, placebo-controlled clinical trial out of Case Western Reserve University School of Medicine and University Hospitals Cleveland Medical Center. The trial results were recently published in the *Journal of Investigative Dermatology*.

In the study, 20 participants were randomized to receive a placebo pill or 50,000, 100,000, or 200,000 IU of vitamin D one hour after a small UV lamp "sunburn" on their inner arm. Researchers followed up with the participants 24, 48, 72 hours and 1 week after the experiment and collected skin biopsies for further testing.

[Picture Credit: Sunburn]



Participants who consumed the highest doses of vitamin D had long-lasting benefits -- including less skin inflammation 48 hours after the burn. Participants with the highest blood levels of vitamin D also had less skin redness and a jump in gene activity related to skin barrier repair. (Science Daily).

### **Ideal Sunshine Exposure**

Although ultraviolet (UV) solar radiation contributes to the development of sun erythema, cancer and aging of the skin, it also reduces blood pressure, synthesises vitamin D and improves the treatment of several diseases.

Now, the Solar Radiation Research Group at the Polytechnic University of Valencia (UPV) has analysed the exposure time needed to obtain the recommended doses of vitamin D without damaging our health. The results have been published in the journal 'Science of the Total Environment'.

Spanish researchers have estimated the duration of solar radiation exposure required in order to obtain the recommended doses of vitamin D. While in spring and summer 10 to 20 minutes in the sun are enough, in the winter months almost two hours would be needed, therefore for the vast majority of the population it is difficult to achieve the optimal values. (Science Daily).

### **How Much Vitamin D Does the Body Need?**

Most people should be able to get all the vitamin D they need by eating a healthy balanced diet and by getting some exposure to sunlight. However, certain groups of the population may be at risk of not getting enough vitamin D. They are:

- pregnant and breastfeeding women
- babies and young children under five years
- older people aged 65 years and over
- people who are not exposed to much sun, such as people who cover up their skin when outdoors or those who are housebound or confined indoors for long periods
- people who have darker skin such as people of African, African-Caribbean and South Asian origin

(NHS UK).

According to the National Institute of Health the following is the recommended dietary allowances for Vitamin D:

Age	Male	Female	Pregnancy	Lactation
0 – 12 months*	400 IU (10mcg)	400 IU (10mcg)		
1 – 13 years	600 IU (15mcg)	600 IU (15mcg)		
14 – 18 years	600 IU (15mcg)	600 IU (15mcg)	6000 IU (15 mcg)	600 IU (15mcg)
19 – 50 years	600 IU (15mcg)	600 IU (15mcg)	600 IU (15mcg)	600 IU (15mcg)
51-70 years	600 IU (15mcg)	600 IU (15mcg)		
>70 years	800 IU (20mcg)	800 IU (20mcg)		

(\*) = Adequate intake

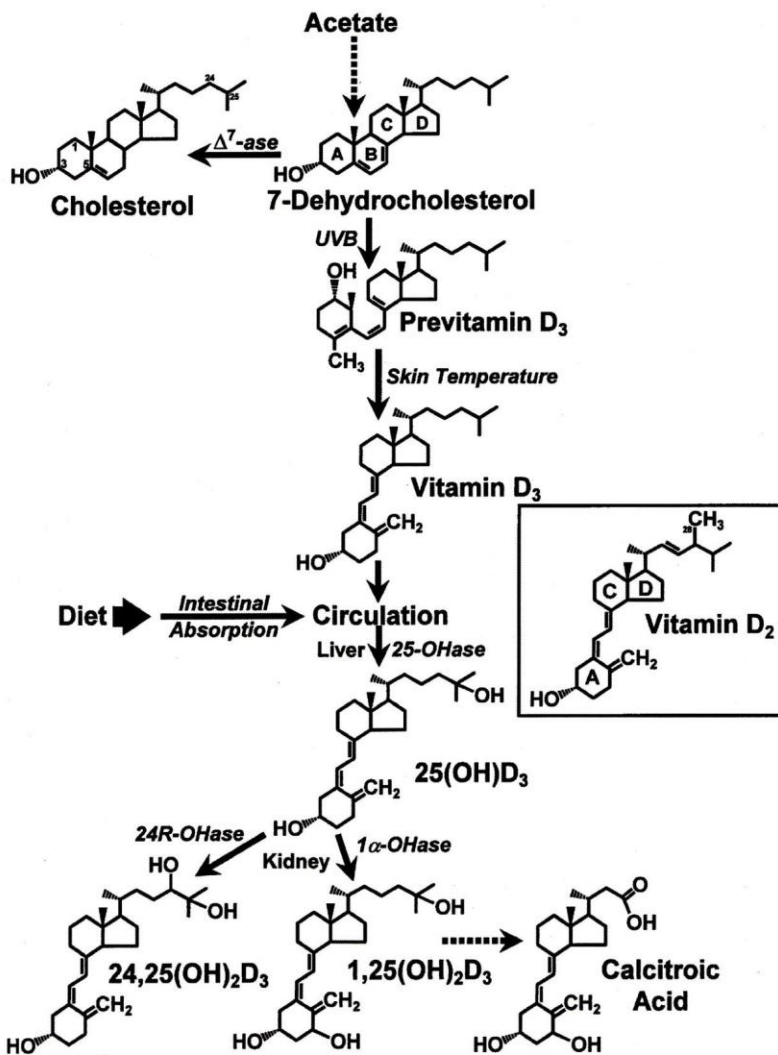
### The Photochemical, Thermal and Metabolic Pathways for Vitamin D<sub>3</sub>

Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D is converted to 25-hydroxyvitamin D, the major circulating form of vitamin D and then to 1,25-dihydroxyvitamin D, the active form of vitamin D, by enzymes in the liver and kidney. 1,25-dihydroxyvitamin D binds to the intracellular vitamin D receptor to activate vitamin D response elements within target genes. The half-life of 1,25-dihydroxyvitamin D is four to six hours, compared with two to three weeks for 25-hydroxyvitamin D and 24 hours for parent vitamin D.

Dietary vitamin D is fat soluble and is absorbed in the small intestine incorporated into chylomicrons. Dietary vitamin D travels to the liver, bound to vitamin D-binding protein and in continued association with chylomicrons and lipoproteins, where it and endogenously synthesized vitamin D<sub>3</sub> are metabolized. The hepatic enzyme 25-hydroxylase places a hydroxyl group in the 25 position of the vitamin D molecule, resulting in the formation of 25-hydroxyvitamin D or calcidiol.

The association of oral vitamin D with chylomicra and lipoproteins permits more rapid hepatic delivery when compared with endogenously synthesized or parenterally administered hormone, which circulates exclusively on vitamin D-binding protein. This difference results in a rapid but less sustained increase in plasma 25-hydroxyvitamin D (25OHD) levels obtained with oral as opposed to parenteral administration or endogenous synthesis (Up-to-date).

The photochemical, thermal and metabolic pathways for Vitamin D<sub>3</sub> is diagrammatically indicated in the accompanying diagram (According to Holick, 1996).



### Vitamin D and Reducing the Risk for Cancer

Higher serum levels of the main circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D), are associated with substantially lower incidence rates of colon, breast, ovarian, renal, pancreatic, aggressive prostate and other cancers. It is projected that raising the minimum year-around serum 25(OH)D level to 40 to 60 ng/mL (100-150 nmol/L) would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year and 75% of deaths from these diseases in the United States and Canada, based on observational studies combined with a randomized trial. Such intakes also are expected to reduce case-fatality rates of patients who have breast, colorectal, or prostate cancer by half. There are no unreasonable risks from intake of 2000 IU per day of vitamin D<sub>3</sub>, or from a population serum 25(OH)D level of 40 to 60 ng/mL. The time has arrived for nationally coordinated action to substantially increase intake of vitamin D and calcium. (Garland, *et al.*; Harvard School of Public Health).

High levels of vitamin D are associated with protection against bladder cancer, according to a multidisciplinary study coordinated by molecular biologists and epidemiologists from the Spanish National Cancer Research Centre (CNIO), the conclusions of which were published in the *Journal of National Cancer Institute (JNCI)*.



Increasing vitamin D levels may lower risk for developing cancer, according to a study conducted by Creighton University with cooperation from the University of California San Diego. The results of the study were released on 28 March 2017 in the *Journal of the American Medical Association*. The study, funded by the National Institutes of Health, was a randomised clinical trial of the effects of vitamin D supplementation on all types of cancer combined. Women who were given vitamin D3 and calcium supplements had 30% lower risk of cancer. This difference in cancer incidence rates between groups did not quite reach statistical significance. However, in further analyses, blood levels of vitamin D, specifically 25-hydroxyvitamin D (25(OH)D), were significantly lower in women who developed cancer during the study than in those who remained healthy. (Science Daily).

### **Vitamin D and Cancer Mortality**

A meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States was published during June 2014 in the *British Medical Journal* (BMJ). In this large consortium of eight cohort studies, the bottom 25(OH)D [Vitamin D] quintile was associated with increased all-cause and cardiovascular mortality and with cancer mortality in subjects with a history of cancer but not in subjects without a history of cancer.

This means that in cancer survivors Vitamin D may play an important role in cancer prognosis (outlook) and that individuals with a history of cancer and who have low levels of 25(OH)D [Vitamin D] also have a higher mortality rate than those individuals without a history of cancer (Consortium on Health and Ageing).

In patients with stage I to III colorectal cancer, postoperative plasma vitamin D is associated with clinically important differences in survival outcome, higher levels being associated with better outcome. We observed interactions between 25-OHD level and VDR genotype, suggesting a causal relationship between vitamin D and survival. The influence of vitamin D supplementation on colorectal cancer outcome requires further investigation (Zgaga, *et al.*).

### **Vitamin D and General Health**

A growing body of research suggests vitamin D may play an important role in the prevention of several diseases that previously weren't believed to have a vitamin D connection, including multiple sclerosis, cardiovascular disease, Parkinson's disease, dementia, diabetes, hypertension, obesity, and several types of cancers. Among all the possible associations between vitamin D and disease prevention, the one concerning vitamin D and cancer risk appears to be the most widely studied.

Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation (Institute of Medicine; Holick, *et al.*; Norman & Henry). Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D (Institute of Medicine). Low blood levels of Vitamin D is linked to headaches (Kjaergaard, *et al.*, 2012).

Professor Michael F Holick (Professor of Medicine, Physiology and Biophysics, Boston University Medical School) in his book entitled *The vitamin D Solution*, has the following to say about Vitamin D:

- There is evidence from mouse studies that a patient may respond better to chemotherapy, have less tumour growth and have less metastatic activity, if his/her 25-hydroxyvitamin D level is raised to 40-60 ng/ml of blood
- Ageing markedly decreases the body's ability to make Vitamin D in the skin. When comparing a 70-year old to a 20-year old, the 70-year old only makes about 25% of the Vitamin D compared to the 20-year old
- We could probably decrease health care costs across the board by 25% if everybody had optimal Vitamin D status

Scientists at London's Kingston University have uncovered evidence that lack of a particular form of vitamin D is associated with Alzheimer's disease. Working in collaboration with researchers from Brighton and Sussex Medical School and the Sussex Partnership NHS Foundation, the Kingston researchers spent six months analysing blood samples from patients with Alzheimer's. They compared test results from those not being treated with any drugs to those from people on medication and a further group who did not have the condition.

A study led by researchers from the University of California, San Diego School of Medicine has found a correlation between vitamin D3 serum levels and subsequent incidence of Type 1 diabetes. The six-year study of blood levels of nearly 2,000 individuals suggests a preventive role for vitamin D3 in this disease (University of California).

It is estimated that one billion people worldwide do not have sufficient vitamin D. This deficiency is thought to be largely due to insufficient exposure to the sun and in some cases to poor diet. As well as being a well-known risk factor for rickets, there is a growing body of evidence that vitamin D deficiency also increases an individual's susceptibility to auto-immune conditions such as multiple sclerosis (MS), rheumatoid arthritis and type 1 diabetes, as well as certain cancers and even dementia (University of Oxford).

Vitamin D, specifically vitamin D's active form (a potent steroid hormone known as calcitriol), exerts its effects on the body by binding to what is called a vitamin D receptor (VDR). Vitamin D receptors are located on the surface of living cells throughout the human body. Zinc has been found to modulate steroid hormone receptor-DNA interactions and one of the ways it does so is to bind to VDR, enabling its influence over the activity of vitamin D dependent genes in cells (Craig, *et al.*).

High body mass index (BMI), smoking, and being of African American or Hispanic descent are all factors linked with lower vitamin D levels. (Yao, *et al.*, 2016).

### **Vitamin D and Hormone Disruptors**

Environmental exposure to phthalates and bisphenol A (BPA) may impact circulating 25-hydroxyvitamin D (25[OH]D) levels in adults, according to recent research published in the *Journal of Clinical Endocrinology & Metabolism*.

Nearly every person on the planet is exposed to BPA and another class of endocrine-disrupting chemicals called phthalates, so the possibility that these chemicals may even slightly reduce vitamin D levels has widespread implications for public health. Vitamin D

plays a broad role in maintaining bone and muscle health. In addition, low vitamin D levels have been implicated in outcomes of numerous conditions such as cardiovascular disease, diabetes and cancer. (Johns, *et al.*, 2016).

### **Vitamin D and Hypertension Risk**

In a recent study involving 108 173 individuals Vimalleswaran, *et al.*, (2014) found that increased blood concentration levels of 25(OH)D was associated with decreased systolic blood pressure and reduced odds for hypertension, but not with decreased diastolic blood pressure. Each 25(OH)D-increasing allele of the synthesis score in meta-analysis was associated with a significant change of 0.10 mmHg in systolic blood pressure and a significant change of 0.08 mmHg in diastolic blood pressure.

### **Vitamin D and Prostate Cancer**

Research has shown that there is a link between prostate cancer and vitamin D. Studies have found that men with prostate cancer tend to have lower levels of vitamin D. However, the relationship between prostate cancer and vitamin D is complex and still being researched.

Vitamin D receptors are found on the surface of a cell and vitamin D can attach themselves to these receptors. By binding to a receptor, vitamin D sends chemical signals that direct a cell to do something, such as divide or die.

There are vitamin D receptors in prostate tissue, and vitamin D can bind to these receptors. This may cause cancerous cells to die, stop growing, or stop from spreading to other parts of the body. Therefore, it is thought that vitamin D may help in protecting against the progression of prostate cancer.

Cells in the prostate are able to take the inactive form of vitamin D and activate it. Some of the cancerous cells in the prostate lose this ability, but they still have receptors for vitamin D, which could mean that supplementing with vitamin D may help to slow the growth of cancerous cells. (Vitamin D Council).

### **Vitamin D and Breast Cancer**

Recent research has shown that Vitamin D deficiency is indicative of inferior survival among patients with breast cancer. Sufficient vitamin D levels are defined as at least 30 ng/mL. Deficient levels are said to be below 20 ng/mL. (Yao, *et al.*, 2016)

### **Vitamin D and Bladder Cancer**

Deficiency of vitamin D, which is linked to insufficient sunlight exposure and some dietary choices, may increase one's risk of developing bladder cancer, according to a study published in *Endocrine Abstracts*.

Vitamin D deficiency has previously been associated with other forms of cancer. To determine whether such deficiency is linked to bladder cancer, researchers appraised 7 research papers evaluating the synthesis of 1,25-dihydroxyvitamin D and vitamin D signalling in bladder epithelial cells.

Five of the 7 studies showed an increased rate of bladder cancer among those with vitamin D deficiency.

[Picture Credit: Bladder Cancer]



The researchers note, however, that 1,25-dihydroxyvitamin D synthesis is linked to local immune response: with increased vitamin D levels, greater amounts of 1,25-dihydroxyvitamin D are synthesized, leading to a greater immune response to cancer cell proliferation.

With adequate levels of vitamin D, the authors conclude, bladder epithelial cells are more able to respond to bladder cancer growth. If this finding is verified, it may be useful in both bladder cancer treatment and prevention.

(Bland, *et al.*, 2016).

### **Medical Disclaimer**

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

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