BCUK Background Briefing | Vitamin D & Breast Cancer

SUMMARY

Most studies have found low levels of circulating vitamin D are linked to an increased breast cancer risk. The body produces adequate levels of vitamin D if skin is exposed to sufficient sunlight. Other sources include diet or supplements. Studies have not demonstrated that taking vitamin D supplements reduces breast cancer risk, although taking these can restore serum vitamin D levels to a healthy state and are recommended for those unable to achieve sufficiency through sunshine and diet. The main function of vitamin D is maintaining extracellular calcium levels. It may help prevent breast cancer through its actions on cellular differentiation, breast cell growth, programmed cell death, reduction of cancer cell growth and tumour blood vessel formation and its effects on oestrogen pathways.

Introduction

Breast cancer is the most common cancer in women globally [1]. In the UK there are around 55,500 new cases of breast cancer in women and 370 in men, every year [2]. A person's risk of developing breast cancer depends on many factors, including those associated with age, hormones (in particular oestrogen), genetics, diet, lifestyle and the environment [3]. In 1990, scientists first reported an inverse association between total average annual sunlight and breast cancer mortality [4]. Since then, numerous studies have examined whether low levels of circulating vitamin D increase breast cancer risk and breast cancer mortality. In this brief, we evaluate recent studies on this topic. We also discuss how the body synthesises vitamin D and its mode of action and explain why it is difficult to establish whether or not taking vitamin D supplements is protective against breast cancer.

What is vitamin D and where does it come from?

Vitamins are essential organic compounds needed in small amounts for normal bodily function. Most cannot be made by the body and are obtained from the diet [5]. Vitamin D is an exception as it can be synthesised by the body provided there is sufficient exposure to sunlight, making intake from food unnecessary [6].

Vitamin D refers to a group of fat-soluble secosteroids (open ring steroids) [7] synthesised in skin cells in humans and some animals. It is naturally present in some foods, added to others (see Table 1) and may be taken as a dietary supplement [8].

Vitamin D production in the skin is the primary natural source of vitamin D. Synthesis is triggered when the sun's ultraviolet (UV) rays interact with skin [9]. According to Yale Medicine, vitamin D derived from sunlight is functionally the same as that obtained from supplements; both can provide healthy vitamin D levels [10]. There is some evidence that the vitamin D you synthesise from sunlight stays active in your body longer than the vitamin D obtained from supplements [11]. Furthermore, it is not possible to produce toxic levels of vitamin D from sunlight, whereas it is possible from supplements [12].

Table 1: Vitamin D content of selected foods [13]

Food	Vitamin D (µg/100g)
Foods	
Naturally occurring	
Herring	7.8 – 25.0
Salmon	16.0
Egg yolk	5.6
Mackerel	4.0
Egg, whole	2.9
Margarine	2.5 – 7.5
Chanterelle mushroom	2.1
Button mushroom	1.9
Liver, beef	1.7

Gouda cheese, 45% fat (dry matter)	1.3
Butter	1.2
Calf's liver	0.3
Whole milk, 3.5% fat	0.1
Fortified	
Multivitamin Whole Fresh Milk	2.2
Wholegrain oats (Ready Brek)	4.3
Almond milk	0.8
Soy milk	0.8

In foods and dietary supplements, vitamin D has two main forms, D_2 (ergocalciferol) and D_3 (cholecalciferol), that differ chemically only in their side-chain structures (Figure 1). Vitamin D_2 is present only in fungi (e.g., wild mushrooms or UVB-treated cultivated mushrooms, and UVB-treated yeasts), while D_3 comes mainly from animal sources. Some foods like milk and cereal are vitamin D_2- and D_3-fortified, while most vitamin D supplements contain vitamin D_3. As vitamin D is fat-soluble it is better absorbed if eaten with fat [8] .

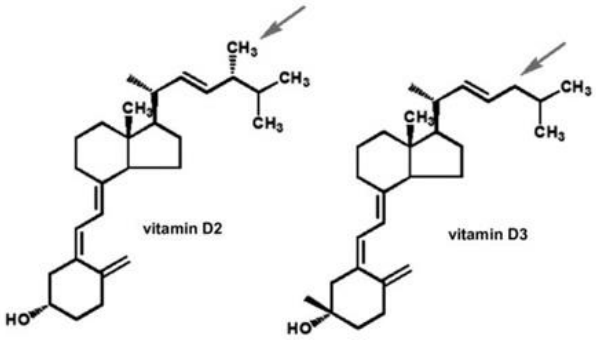

Figure 1: Structures of vitamin D_2 (ergocalciferol, from fungi) and vitamin D_3 (cholecalciferol, made by animals or given sunlight), showing vitamin D_2 has an additional methyl group (CH_3) (see arrows) [14].

Vitamin D synthesis and function

After vitamin D is synthesised in the skin upon exposure to UV light or acquired from food or supplements, it is stored in the body's fat cells. Here it remains inactive until it's needed. Through a process called hydroxylation, it is converted in the liver and kidney to the metabolically active form, 1,25-Dihydroxyvitamin D_3, commonly known as calcitriol (Figure 2).

Synthesis begins when 7-dehydrocholesterol (provitamin D_3), derived from cholesterol in the liver and found in the skin, is broken down to previtamin D_3 upon exposure to UV-B light. Previtamin D_3 is then converted to vitamin D_3, transported to the blood by vitamin D binding protein and subsequently to the liver, wherein it is hydroxylated to 25-hydroxyvitamin D_3 ($25(OH)D_3$). This is the major circulating metabolite and the storage form of vitamin D, mainly located in the skin, liver, skeletal muscle and fat tissue [15]. Similarly, dietary vitamin D_2 or vitamin D_3 are converted to $25(OH)D_3$ in the liver. Vitamin D status is normally based on serum levels of $25(OH)D_3$. To be biologically active, $25(OH)D_3$ needs to be converted to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), which occurs in the kidney [16] (see also table 2).

$1,25(OH)_2D_3$ acts as a steroid hormone [17] which exerts its action by binding to an intracellular nuclear receptor, the vitamin D receptor (VDR). This receptor, first identified in a breast cancer cell line in 1979, regulates gene expression by acting as a transcription factor (DNA-binding protein involved in transcribing DNA into RNA). In addition to its main function of maintaining extracellular calcium levels, activation of VDR influences up to 200 genes that mediate cellular growth, differentiation and apoptosis (programmed cell death) [18].

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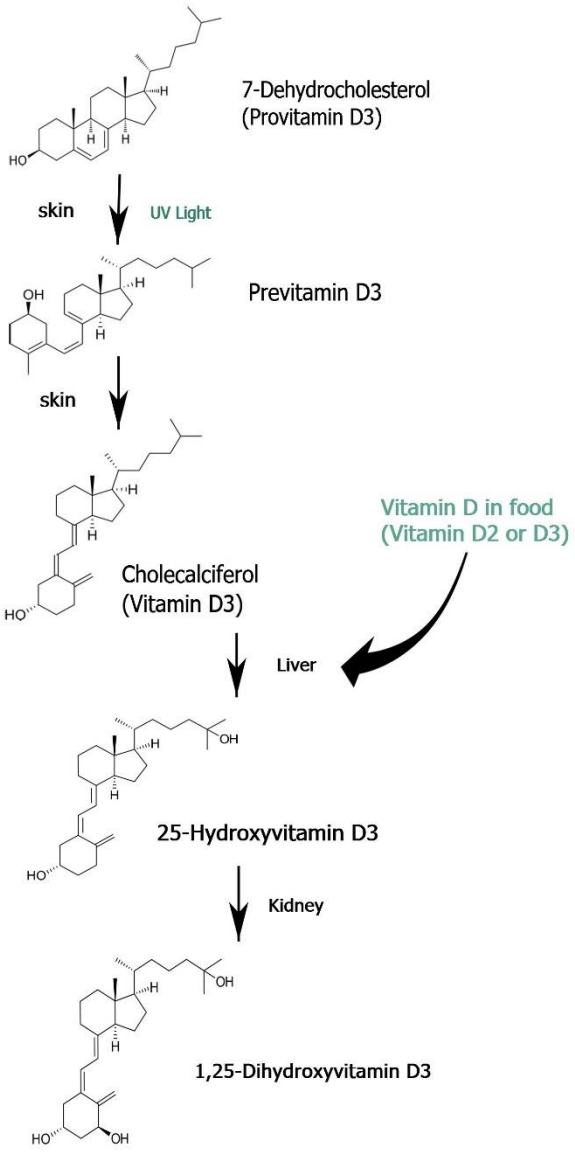

Figure 2: Vitamin D synthesis. Vitamin D can be synthesized in the skin (vitamin D_3) or provided in the diet (vitamin D_2 or D_3). It is converted by reactions occurring first in the liver (making 25-Hydroxyvitamin D_3) and then kidney (making 1,25-Dihydroxyvitamin D_3, the active form) [19].

Table 2: Nomenclature of Vitamin D

Vitamin D	Synonyms	Abbreviation	Comments
Provitamin D3	7-Dehydrocholesterol	7-DHC	Photochemically converted to vitamin D3 in the skin
Vitamin D3	Cholecalciferol	-	Synthesised in skin when exposed to sunlight Found in foods of animal origin (e.g. oily fish), fortified foods and dietary supplements
Vitamin D2	Ergocalciferol	-	Found in mushrooms (grown in UV light), fortified foods and dietary supplements
25-Hydroxyvitamin D3	Calcidiol/ Calcifediol	$25(OH)D_3$	Best reflects vitamin D status
1,25-Dihydroxyvitamin D3	Calcitriol	$1,25\text{-}(OH)_2D_3$	Active form of vitamin D

Vitamin D has several functions in the body. It promotes calcium absorption in the gut, maintains adequate serum calcium and phosphate concentrations to enable normal bone mineralisation and is needed for bone growth. Without sufficient vitamin D bones can become thin. Together with calcium, vitamin D helps protect older adults from osteoporosis. Vitamin D reduces inflammation and modulates processes such as cell growth, neuromuscular and immune function and glucose metabolism. Many genes encoding proteins that regulate cell proliferation, differentiation and apoptosis are modulated in part by vitamin D [20]. Vitamin D has been investigated for its potential role in reducing the risk of many diseases, including cardiovascular disease and cancer, including breast cancer [21].

What is a healthy level of vitamin D?

Your vitamin D level depends on many factors such as how much time you spend outdoors, what you eat, what medications you take, but also on your age

and skin type [20]. Most people in the northern hemisphere can make enough vitamin D from daily sun exposure with their forearms, hands or lower legs uncovered (without [1]sunscreen) from late March to the end of September (e.g. Caucasians across the UK need 10-15 minutes; for darker skin types, 25-40 minutes is recommended [22]). The vitamin D is stored by the body and helps maintain adequate levels in winter. Diet, for example liver, eggs or oily fish - such as salmon or herring, can provide small amounts of vitamin D [9].

According to the NHS, serum 25(OH)D_3 levels of >50 nmol/L[2] are adequate and sufficient for bone health in most people [23].

Vitamin D deficiency and use of supplements

If you are healthy and regularly spend time outdoors, you are unlikely to be vitamin D deficient. However, due to limited sunlight, especially during winter months, this deficiency is common in the UK population; with 19% children aged 11-18 years, 16% adults aged 19-64 years and 13% adults aged 65 years and over (although higher in institutionalised older people) considered vitamin D deficient [24]. Vitamin D deficiency in infants can lead to rickets, which causes bone deformities, although this condition is rare in the UK. In adults, deficiency can result in osteomalacia, a condition causing bone pain, and in older adults, osteoporosis [25]. Vitamin D supplements are used to prevent and treat these conditions.

To detect vitamin D deficiency, a laboratory blood test is necessary. The NHS defines a deficiency as circulating levels of 25(OH)D_3 below 25 nmol/L [23]. Other countries define vitamin D deficiency differently, for example Germany, which considers levels below 30 nmol/l as deficient [26].

Who is most at risk of vitamin D deficiency?

Those at higher risk of vitamin D deficiency include:

- people around 65 years of age or older; the skin's ability to produce vitamin D often decreases with age
- people who rarely get outside, due to illness, the need for care or other reasons
- babies who need to be protected from direct sunlight in the first year of life
- women who cover their bodies when outside their homes for cultural or religious reasons
- people with coloured skin who cannot produce enough vitamin D due to insufficient exposure to sunlight, for example those who reside in northern Europe
- people with certain diseases, for example, intestinal diseases which impair absorption of vitamin D (from dietary sources) [27].
- people carrying variants of certain genes involved in the metabolism, catabolism, transport, or binding of vitamin D to its receptor, which result in low vitamin D levels [28].

How much vitamin D should be taken as supplements?

A daily supplement containing 10 µg of vitamin D (400 IU)[3] is recommended by the NHS (see here for details) [9].

Vitamin D toxicity

While you can't get too much vitamin D through sunshine you can through supplements, which can lead to health problems such as hypercalcaemia, where excess calcium builds up in the body. This can

[1] Excessive exposure to sunlight can cause sunburn and may lead to skin cancer.

[2] Serum concentrations of 25(OH)D_3 are reported in both nanomoles per litre (nmol/l) and nanograms per millilitre (ng/ml). One nmol/l = 0.4 ng/ml & 1 ng/ml = 2.5 nmol/l.

[3] The amount of vitamin D can be expressed as International Units (IU), where 1 µg of vitamin D is equal to 40 IU.[29].

lead to weakened bones and damage kidneys and the heart [12]. Ingesting more than 4000 IU per day (100 µg/day) increases the risk of harmful health effects, for example kidney damage. Serum 25(OH)D_3 levels of more than 125 nmol/l are linked to adverse effects, especially if levels exceed 150 nmol/l [8].

Association between low vitamin D levels and an increased breast cancer risk [4]

Most studies have found low serum vitamin D is associated with increased breast cancer risk.

Observational studies

Observational studies are those which investigate the rate of an outcome in groups that were differently exposed to a risk factor. They are used to assess associations but the potential for biases means that these associations might not be causal. [30]. However, all of the studies discussed here included adjustment for the following confounders (in simple words: something, other than the thing being studied, that could be causing the results seen in a study), among others: race/ethnicity, education, hormonal birth control use, hormone therapy use, menopausal status, physical activity, BMI, alcohol consumption, parity and BMI.

Of the observational studies which were conducted in the chosen time period[4], two found that a vitamin D deficiency was associated with an increased risk of breast cancer [31, 32], one found high serum vitamin D levels were associated with a lower risk of getting breast cancer [33], while one found no association [34].

Three reviews and meta-analyses, combining the results of several observational studies, concluded that a 25(OH)D_3 deficiency was linked to an increased breast cancer risk [17, 35, 36], and three suggested a protective relationship between high circulating vitamin D and breast cancer [37–39]. Although one 2014 meta-analysis found that healthy vitamin D status was only weakly associated with low breast cancer risk, breast cancer survival showed a strong association [40]. A 2018 analysis of two randomised controlled trials and one observational study (see below for descriptions of different types of studies) concluded that women with serum levels of 25(OH)D_3 above 150 nmol/l, (although considered toxic), had one-fifth of the risk of breast cancer compared to those with less than 50 nmol/l [38]. It is important to mention that some meta-analyses show between-study heterogeneity [41] (variation between studies is referred to as heterogeneity; studies in a systematic review usually vary among themselves due to different populations, interventions or measurement methods). Large systematic differences between studies limit the trustworthiness of the pooled overall result.

Mendelian randomisation studies

In contrast to the above findings, one large Mendelian randomisation study found no causal effect of circulating 25(OH)D_3 on breast cancer risk [42]. Mendelian randomisation is a research method that provides evidence about causal relations between modifiable risk factors and disease, using genetic variants. This study took advantage of the fact that some people are born with gene variations that predispose them to low vitamin D levels. A Mendelian randomisation study is less likely to be affected by confounding factors (those that make it difficult to isolate the effect of the intervention) than other types of observational studies.

Observational studies of breast cancer and vitamin D have shown inverse associations between increased sunlight exposure and reduced breast

[4] We looked at studies from the years 2010-2021.

cancer incidence as well as breast cancer mortality [4, 43–47].

In summary, most observational studies suggest that healthy vitamin D levels are protective against breast cancer risk, however one large study, the mendelian randomisation study, did not provide evidence for this.

How could vitamin D protect against breast cancer?

Vitamin D may affect breast cancer development through several mechanisms of action, which are summarised in Figure 3.

Vitamin D is converted to $1,25(OH)_2D_3$ in several different tissues, including breast tissue (Figure 2). $1,25(OH)_2D_3$, in turn, binds to VDR, which regulates many genes, some of which are linked to cancer, including the oncogene *ID1.* An oncogene is a gene that has the potential to cause cancer if mutated or overexpressed. Overexpression of ID1 is associated with mammary tumour growth and metastasis [48].

In studies of breast cancer cells grown *in vitro* and of tumours in mice, vitamin D has been found to slow or prevent the development of breast cancer by promoting cellular differentiation (a process in which healthy cells become specialised so that they can carry out their function in the body), cancer cells often reproduce very quickly and don't fully differentiate); controlling normal breast cell growth, decreasing cancer cell growth; stimulating apoptosis and reducing tumour blood vessel formation (angiogenesis). It also exhibits anti-inflammatory effects and decreases the expression of aromatase, an enzyme responsible for oestrogen synthesis. Oestrogens increase the risk of developing breast cancer, mainly because of their ability to increase rates of cell division and promote growth of oestrogen-responsive tumours. Vitamin D also downregulates oestrogen receptor (ER)-alpha, a nuclear receptor that mediates the actions of oestrogen. In addition, VDR knockout mice (genetically modified mice carrying an inactivated VDR gene) exhibit enhanced cancer development [49]. Other important functions of vitamin D include suppression of metastasis (cancer spread) [50] and regulation of the immune system [51, 52].

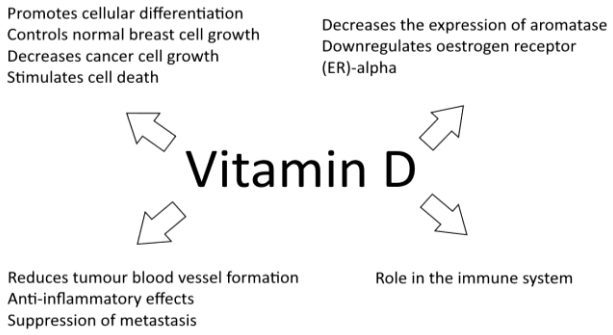

Figure 3: Summary of the mechanisms of action of vitamin D in breast cancer.

Epidemiological studies[5] that examine whether vitamin D supplements reduce breast cancer risk

Randomised controlled trials and meta-studies

Large randomised controlled trials (RCTs) are the reference standard for studying causal relationships between interventions and outcomes (i.e. if one event causes another event to occur) as they eliminate much of the bias within other study designs [53]. Most randomised RCTs do not support a protective effect of vitamin D supplements [54–57].

Of the five RCTs we looked at, four found no association between vitamin D supplementation and a reduced breast cancer risk [54–57]. Two RCTs found a reduced risk for *in situ* ductal carcinoma of the breast (a non-invasive breast cancer) [58] and vitamin D supplementation [56, 59]. One RCT reported an increased risk for invasive breast cancer when vitamin D supplement intakes exceeded >600 IU/day [56].

[5] We looked at studies from the years 2010-2021.

Three meta-analyses combining the results of multiple RCTs concluded that vitamin D supplements had no effect on reducing breast cancer risk [60–62]. A meta-analysis is statistically stronger than the analysis of any single study, due to increased numbers of participants and greater diversity among them [63].

Observational studies

Of the observational studies we considered, two studies concluded that vitamin D supplements decrease breast cancer risk [32, 33], while one found no effect [64].

One review found an inverse relationship between total vitamin D from foods and supplements and a reduced breast cancer risk [35].

In summary, most epidemiological studies do not demonstrate that taking vitamin D supplements reduces breast cancer risk.

Why aren't findings more conclusive?

Despite observational studies suggesting that a higher vitamin D status is associated with a lower incidence of breast cancer, most RCTs do not support a protective effect of vitamin D supplementation. There are several explanations for why the findings are not definitive.

One lies in study design. Observational studies can only indicate a possible association and cannot scientifically prove a causal link between vitamin D deficiency and breast cancer. Although RCTs are considered the gold standard of study designs, even these may have flaws. For example, an inadequate dose of vitamin D may have been provided or the follow-up time was too short.

Studying the role of vitamin D in the diet and its effect on breast cancer is challenging because some foods that contain vitamin D also contain calcium (e.g. milk), which helps lower breast cancer risk [65].

It is difficult to measure the amount of sunlight a person is exposed to.

There are many types of breast cancer and vitamin D may not be important for all types [66].

Breast cancer often takes more than a few years to develop, so it may be important to take vitamin D for many years (> 5) to see benefits [67].

Many factors can influence the development of breast cancer. Diet, exercise, lifestyle choices, environmental factors and genetics all play a role [68]. Numerous confounding factors must therefore be accounted for within the study design.

The serum 25(OH)D_3 level is not only dependent on vitamin D intake and production in the skin, but also on genetic factors [69].

It is still unclear what vitamin D dose (or serum 25(OH)D_3 level) is needed to potentially reduce cancer risk. One analysis of nine prospective studies suggested that circulating 25(OH)D_3 levels ranging from 67.5 to 87.5 nmol/l were associated with breast cancer risk reduction in postmenopausal women [70]. However, two RCTs provided no information on final serum 25(OH)D_3 concentrations [56, 59]. Therefore, the lack of any observed effects on breast cancer risk might be due to inadequate vitamin D supplementation.

On the other hand, if the threshold for serum 25(OH)D_3 at which supplementation might be beneficial is well below 75 nmol/L, then the participants' vitamin D status before the start of the study might be adequate and getting additional vitamin D would be of no benefit. Indeed, in three of the five RCTs we looked at, the mean baseline serum 25(OH)D_3 level was above 30 nmol/l [54, 55, 57]. Two RCTs provided no information on baseline serum 25(OH)D_3 [56, 59].

Conclusion

Most, but not all, epidemiological studies support an inverse association between low levels of serum vitamin D and increased breast cancer risk. Despite this finding, randomised controlled trials have not demonstrated that taking vitamin D supplements reduces breast cancer risk. Further studies are needed to clarify this finding and determine serum levels that may result in increased risk. Vitamin D deficiency is common in the UK and the global population and can lead to diseases in children and adults. Vitamin D supplements can restore serum vitamin D levels to a healthy state and are recommended for those unable to achieve sufficiency through sunshine and diet.

About Breast Cancer UK

Who are we?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them

For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk
To view this information in a more accessible format or to provide feedback, please contact us.

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This brief is for information purposes only and does not cover all breast cancer risks. Nor does it constitute medical advice and should not be used as an alternative to professional care. If you detect a lump or have any concerns, seek advice from your GP. Breast Cancer UK has made every effort to ensure the content of this leaflet is correct at the time of publishing but no warranty is given to that effect nor any liability accepted for any loss or damage arising from its use.

We welcome your feedback, if you have any comments or suggestions about this brief please contact us at info@breastcanceruk.org.uk or on 0845 680 1322

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