

Vitamin D and prevention of breast cancer: Pooled analysis

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Abstract

Background: Inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence and mortality rates of breast cancer in ecological and observational studies, but the dose–response relationship in individuals has not been adequately studied.

Methods: A literature search for all studies that reported risk by of breast cancer by quantiles of 25(OH)D identified two studies with 1760 individuals. Data were pooled to assess the dose–response association between serum 25(OH)D and risk of breast cancer.

Results: The medians of the pooled quintiles of serum 25(OH)D were 6, 18, 29, 37 and 48 ng/ml. Pooled odds ratios for breast cancer from lowest to highest quintile, were 1.00, 0.90, 0.70, 0.70 and 0.50 (p trend < 0.001). According to the pooled analysis, individuals with serum 25(OH)D of approximately 52 ng/ml had 50% lower risk of breast cancer than those with serum <13 ng/ml. This serum level corresponds to intake of 4000 IU/day. This exceeds the National Academy of Sciences upper limit of 2000 IU/day. A 25(OH)D level of 52 ng/ml could be maintained by intake of 2000 IU/day and, when appropriate, about 12 min/day in the sun, equivalent to oral intake of 3000 IU of Vitamin D₃.

Conclusions: Intake of 2000 IU/day of Vitamin D₃, and, when possible, very moderate exposure to sunlight, could raise serum 25(OH)D to 52 ng/ml, a level associated with reduction by 50% in incidence of breast cancer, according to observational studies.

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1. Background

A wide range of ecological studies have linked low levels of sunlight or ultraviolet B irradiance with high breast cancer rates [1–6], and studies of markers of ultraviolet B exposure individuals have supported this association [7]. However, until recently, it was not possible to estimate the dose–response relationship. Vitamin D status is assessed by the level of 25(OH)D in the serum. This is the predominant Vitamin D metabolite in the circulation because its half life is

far greater than that of Vitamin D or 1,25-dihydroxyvitamin D (1,25(OH)D) [8].

The serum 25(OH)D concentration is determined mainly by exposure to sunlight [9], although oral intake of Vitamin D increases it by about 10 ng/ml per 1000 IU [10]. The serum concentration of 25(OH)D is important because it is the substrate for conversion to 1,25(OH)D in the tissues by 1-alpha-hydroxylase enzyme, and its concentration is regarded as a limiting factor in 1,25(OH)D biosynthesis [11].

It is thought that the most probable mechanism linking UVB irradiance with lower risk of breast cancer is increased photosynthesis of Vitamin D due to increased UVB irradiance, and a resulting increase in the circulating 25(OH)D concentration [12,13], making more of this substrate avail-

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able to the epithelial tissues of the terminal ductal lobular unit of the breast.

2. Methods

A PUBMED search for 1966–2006 was performed by two investigators studies. The search was performed by using the terms (“Vitamin D” or “cholecalciferol” or “calcidiol” or “calcitriol”), and (“cohort” or “case–control” or “case–cohort” or “incidence” or “occurrence” or “epidemiology” or “clinical trial”) and “human” as medical subject heading (MeSH) terms and words in the abstract, combined with the subject term “breast neoplasms”. Articles were included if they were published in medical journals, were either cohort, case–control or case–cohort studies of breast cancer, and included measures of association by quantiles. Two studies reporting odds ratios for breast cancer by quantiles of serum 25(OH)D in association with breast cancer risk were identified, those of Bertone-Johnson et al. [14], and Lowe et al. [15]. Data from these studies were pooled and divided into quintiles of serum 25(OH)D. One study that examined the association did not report odds ratios but reported no effect [16]. Two studies examined circulating 1,25(OH)D. One found a strong inverse association with risk of breast cancer [17] and the other found no association [16].

Findings from the two studies that reported on risk of breast cancer by quantiles of 25(OH)D were pooled and divided into quintiles with median values of 6, 18, 29, 37 and 48 ng/ml. The DerSimonian–Laird test was used to assess heterogeneity [18]. The results of the two studies

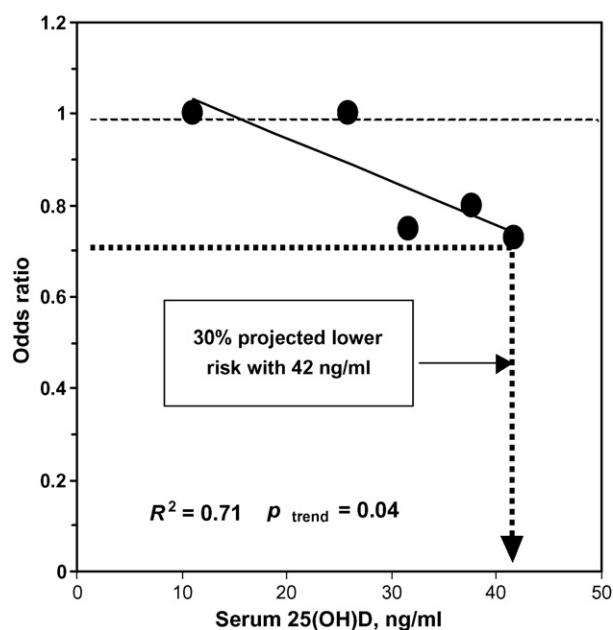


Fig. 1. Dose–response gradient of risk of breast cancer according to prediagnostic serum 25-hydroxyvitamin D concentration, Harvard Nurses' Health Study (source [14]).

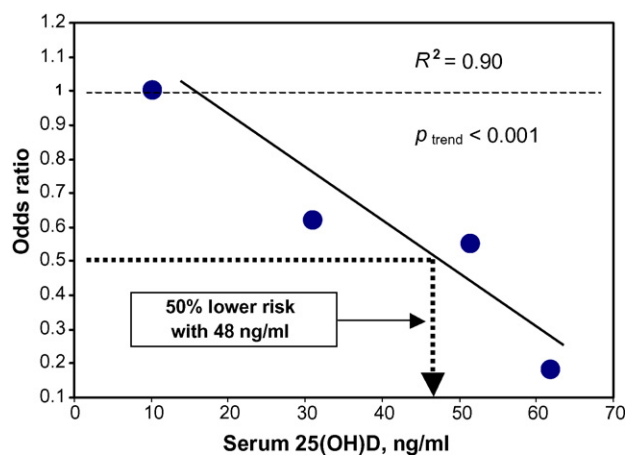


Fig. 2. Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, St. George's Hospital, London, study (source [15]).

were homogenous according to the DerSimonian–Laird test. Ordinary and Mantel–Haenszel [19] odds ratios were calculated. The lowest quintile was used as the reference group. Dose–response curves were plotted based on five odds ratios, one for each quintile of the pooled data. Details of the two studies are provided below:

Study 1. This was a nested case control study by Bertone-Johnson et al. of the Harvard Nurses Health Study cohort of prediagnostic serum from 701 cases of breast cancer and 724 controls, matched on age, menopausal status, replacement hormone use and month blood was drawn [14].

Study 2. This was a case–control study by Lowe et al. of 179 cases of breast cancer diagnosed in London and matched to 179 controls on age, race and time of year of blood draw [15].

3. Results

Both studies found lower risk of breast cancer in individuals with higher levels of 25(OH)D (Figs. 1 and 2). When

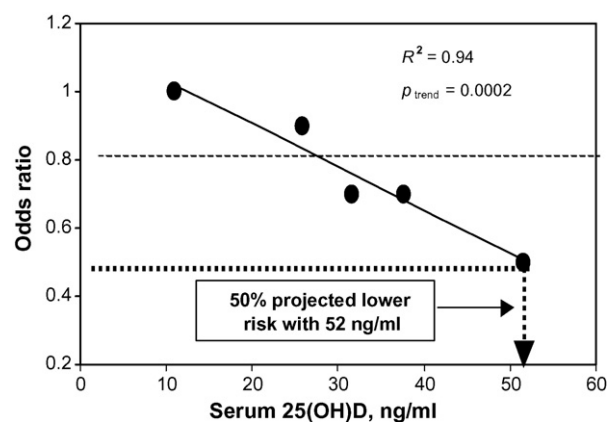


Fig. 3. Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, pooled analysis.

Table 1

Projected annual number of breast cancer cases prevented, according to serum 25-hydroxyvitamin D level and corresponding oral intake of Vitamin D₃, United States

Vitamin D ₃		Serum 25(OH)D		Projected		Comment
mcg/day*	IU/day*	ng/ml†	nM†	Prevented (%)‡	Number of cases prevented	
25	1000	22	53	21	45,000	Widely recommended intake
50	2000	32	77	31	66,000	Present NAS [§] upper limit
60	2400	36	87	35	74,000	NAS NOAEL [¶]
75	3000	42	102	40	86,000	
95	3800	50	121	48	103,000	NAS lowest toxicity level**
100	4000	52	126	50	107,000	Proposed revised upper limit†

* Note: Intake above 50 mcg/day (2000 IU) is not presently endorsed by National Academy of Sciences [25].

** Lowest intake associated with any report of illness, according to National Academy of Sciences (see above). Actual lowest threshold may be considerably higher (source [26]).

† All serum levels are within normal laboratory limits (source [26]). Assumes baseline 25(OH)D of 12 ng/ml.

‡ Value shown is the product of the percentage that could be prevented by maintaining the specified serum 25(OH)D level, based on the pooled observational data, times the total number of new cases in 2006 ($N=214,000$). The source of the total new cases is American Cancer Society [27].

§ NAS, National Academy of Sciences (source: National Academy of Sciences, see above).

¶ NOAEL, No Adverse Effect Level (source: National Academy of Sciences, see above).

results of these studies were pooled, the odds ratios for the pooled serum 25(OH)D studies, from lowest to highest quintile, were 1.00, 0.90, 0.70, 0.70 and 0.50 (p trend < 0.001). The dose–response relationship is shown in Fig. 3. The serum 25(OH)D concentration accounted for 90% of the variation in risk of breast cancer ($p < 0.001$).

4. Discussion

A 50% lower risk of breast cancer was associated with a serum 25(OH)D level of 50 ng/ml, compared to ≤ 10 ng/ml. Since 25(OH)D increases by 10 ng per 1000 IU, this serum level would correspond to intake of 4000 IU/day, assuming baseline 25(OH)D of 10 ng/ml [10]. This exceeds the current National Academy of Sciences upper limit of 2000 IU/day [20]. However, a proposal has been made to establish an upper limit of 4000 IU/day [21,22]. Given the low background levels of 25(OH)D in US women during the winter months [23], such an intake would be necessary to maintain a serum level of 50 ng/ml. In the meantime, it is probably impractical to recommend intake of 4000 IU/day.

If the oral dose must be kept at or below 2000 IU/day, a 50 ng/ml concentration of 25(OH)D could be achieved by oral intake of 2000 IU/day and, if appropriate and climate allowing, about 12 min/day in the noontime sun on a clear day with 50% of skin area exposed to the sun. Twelve minutes is only 60% of a minimal erythemal dose in a typical fair-skinned Caucasian individual, and would be a suberythemal dose for all but the most photosensitive persons. Despite this, such a sun exposure in whites at mid-latitudes in the US would be roughly equivalent to oral intake of 3000 IU of Vitamin D₃ [24]. Of course, photosynthesis would be inadvisable for individuals with primary photosensitivity disorders, those of mainly Celtic descent, people taking photosensitizing medicines, such as tetracycline or psoralens, or those with photosensitivity illnesses, such as xeroderma pigmentosum,

systemic lupus erythematosus and others and anyone with a personal or close family history of skin cancer or who has actinic keratosis. Of course, the face should be protected with a broad-brimmed hat at all times when in the sun. While there are many exceptions to the assumption of a safe 12 min sunlight exposure, most people in the world could benefit from Vitamin D photosynthesis with minimal risk, including persons of African, Asian or Eastern Indian ancestry, and others who can tan readily.

Based on the pooled results of the observational studies, it is possible to estimate the number of cases of breast cancer than could be prevented by various serum levels of 25(OH)D and oral intake of Vitamin D, assuming no increase in sun exposure. There are 214,000 new cases and 41,000 deaths from breast cancer each year in the US. The predicted associations of various serum 25(OH)D concentrations with incidence rates of breast cancer in the US are summarized in Table 1. A serum 25(OH)D level of 50 ng/ml would be associated with 50% lower incidence of breast cancer, compared to a baseline of < 10 ng/ml. Maintenance of this serum level of 25(OH)D would require oral intake of 4000 IU/day of Vitamin D₃. An alternative for some individuals would be a combination of 2000 IU/day of oral intake of Vitamin D₃ and very moderate exposure to the sun.

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