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Intake of vitamin D and risk of breast cancer—A meta-analysis

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ABSTRACT

Vitamin D insufficiency has been shown to be associated with a number of conditions including diabetes, multiple sclerosis and the overall risk of cancer. We aimed at studying the association between vitamin D intake and risk of breast cancer in a meta-analysis. We searched Pubmed, Embase, and Web of Science using the MESH terms “vitamin D” and “breast cancer”. A total of 1731 studies were identified, but only 6 studies contained original data on the association between intake of vitamin D and risk of breast cancer. Overall there was no association between amount of vitamin D and risk of breast cancer (RR = 0.98, 95% CI: 0.93–1.03, test for heterogeneity $p < 0.01$). However, most studies reported on very low intakes of vitamin D (typically in the range 100–400 IU/day). Restricting the analyses to intakes ≥ 400 IU/day yielded a more homogenous result with a trend towards less breast cancer with ≥ 400 IU/day vs. the lowest intake (typically < 50 –150 IU/day), RR = 0.92, 95% CI: 0.87–0.97, p for heterogeneity 0.14.

In conclusion there may be a trend towards fewer cases of breast cancer with higher intakes of vitamin D (≥ 400 IU/day). However, more research is needed, preferably in the form of randomized-controlled trials.

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1. Introduction

In recent years vitamin D has been demonstrated to be more than a vitamin of significance to calcium turnover [1]. Vitamin D deficiency has been linked to a number of diseases spanning from type 1 diabetes [2], over multiple sclerosis [3], rheumatoid arthritis [4], and inflammatory bowel disease [5], to overall cancer mortality [6,7], although overall cancer mortality did not seem linked to serum vitamin D except for colon cancer where a trend was present [8]. Overall survival seemed linked to vitamin D status in a meta-analysis of randomized-controlled trials on vitamin D intervention [9].

An anticancer effect of vitamin D may be explained by the fact that vitamin D is activated in many cancer cells by a local 1- α -hydroxylase that converts 25-hydroxyvitamin D (25OHD) to the biological active 1,25-dihydroxyvitamin D (1,25(OH)₂D) metabolite [10,11]. In vitamin D insufficiency, the local conversion may be impaired. As 1,25(OH)₂D inhibits estrogen-induced cell proliferation and increases the differentiation of human breast cancer cell lines [12–14], low intracellular levels of 1,25(OH)₂D may increase risk of cancer. The anti-proliferative effects of 1,25(OH)₂D have been linked to suppression of growth stimulatory signals and potentia-

tion of growth inhibitory signals, which lead to changes in cell cycle regulators [15,16].

Regarding cancer occurrence some of the studies on the influence of vitamin D have been indirect using exposure to UVB radiation from the sun and relying on area data in an ecological design [6,7]. In a recent randomized-controlled trial 4 years of supplement with calcium or calcium plus 1100 IU vitamin D/day caused a significant reduction in cancer incidence [17].

A pooled analysis of two studies on the relationship between serum 25OHD levels and breast cancer have reported that patients with serum 25OHD levels above 130 nmol/l had a 50% reduction in breast cancer risk compared to those with serum 25OHD levels below 32.5 nmol/l [18]. In theory a serum 25OHD level of 130 nmol/l would require intakes of vitamin D of around 4000 IU/day (or 2000 IU/day in dietary intake and 12 min of sun exposure per day) [18]. However, no specific analysis on the effects of intake of vitamin D on risk of breast cancer was presented in this pooled analysis [18].

Consequently, it may be of interest to study if breast cancer is linked to intake of vitamin D. We therefore performed a meta-analysis with the aims of studying:

- (1) Is the risk of breast cancer linked to total intake of vitamin D from food or supplements?
- (2) Is there a dose–response relationship for the intake of vitamin D and risk of breast cancer?

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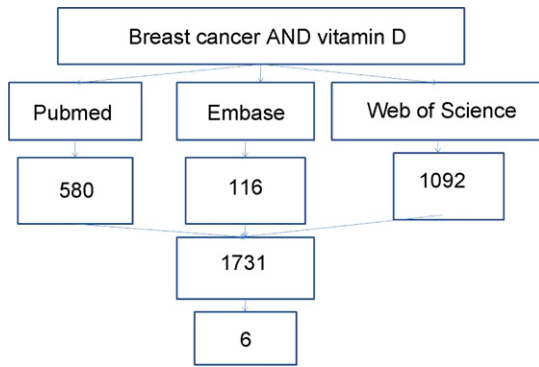


Fig. 1. Details of literature search. The MESH terms used were “breast cancer” and “vitamin D”, and the number of references retrieved from each database (Pubmed, Embase, and Web of Science) who were searched using these terms have been shown. Due to overlap, 1731 unique citations were retrieved, but only 6 contained original data from clinical trials.

2. Material and methods

The study was performed as a meta-analysis. The search date was 28 June 2007. The Pubmed (1958 and onwards), Embase (1974 and onwards), and Web of Science (1945 and onwards) were searched using the MESH terms “breast cancer” and “vitamin D”. Fig. 1 gives details of the search. The inclusion criteria were original studies reporting on the association between intake of vitamin D in IU per day (expressed as total intake or intake via food and supplements) and risk of breast cancer. Eligible studies were epidemiological studies (cross-sectional, case-control or cohort studies) or randomized-controlled trials. The risk was expressed as relative risk (RR), odds ratio (OR) or prevalence proportion ratio. Exclusion criteria were studies not reporting confidence intervals of the risk estimates or in whom it was not possible to calculate confidence intervals from the data provided. Furthermore, papers not reporting the exact estimated intake of vitamin D (e.g. just stating vitamin D supplements vs. no supplements) were excluded. All papers in all languages were eligible. Papers in foreign languages were translated where appropriate.

The search was performed by TG and PV supported by a research librarian. TG and PV screened and retrieved papers judged to be of interest. Discrepancies were solved through discussion. The full text of papers judged to fulfill the inclusion criteria from the abstracts were retrieved, and reference lists from papers retrieved in full text were also screened for papers of potential interest. No contact was made with authors of papers. Potential publication bias was examined using funnel plots.

2.1. Statistics

A weighted estimate for the relative risk of breast cancer was calculated using a derSimonian and Laird estimator [19]. The weights of the studies were based on the standard error of the mean of the relative risk estimates from the individual studies [19]. The meta-regression was based on a model with between-study variation as a random effect [20,21].

The calculations were performed using RevMan 4.0 and Microsoft Excel 2000. A meta-regression using the relative risk of breast cancer vs. the daily intake of vitamin D was performed using STATA 8.0 for Windows. The effect of publication bias was evaluated using funnel plots.

3. Results

Six original studies were retrieved (Fig. 1 and Table 1). Using all six available studies, there was no association between amount of

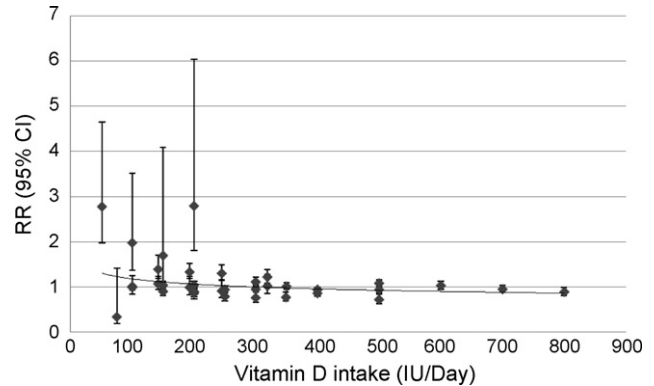


Fig. 2. Association between daily intake of vitamin D expressed in IU and relative risk of breast cancer. The abscissa is the intake of vitamin D per day in IU, and the ordinate is the relative risk (RR) and 95% confidence intervals (95% CI) of breast cancer in patients with the actual daily vitamin D intake vs. those with the lowest vitamin D intake (see also Table 1).

vitamin D and risk of breast cancer (RR=0.98, 95% CI: 0.93–1.03, test for heterogeneity $p < 0.01$, six studies). However, most studies reported on very low intakes of vitamin D (typically in the range 100–400 IU/day).

A meta-regression demonstrated a non-significant declining trend in risk of breast cancer with increasing vitamin D intake (slope of regression $(-8.9 \pm 10.2) \times 10^{-5}$, p for slope 0.38, intercept 0.984 ± 0.039 , p vs. 1 was 0.66). The vitamin D intake for which a significant decline in relative risk of breast cancer was seen was theoretically 461 IU/day. It did not change the significance of the meta-regression to shift from a linear model to an exponential model (Fig. 2).

Restricting the analyses to intakes ≥ 400 IU/day yielded a more homogenous result with a trend towards less breast cancer with ≥ 400 IU/day vs. the lowest intake (typically < 50 –150 IU/day), RR=0.92, 95% CI: 0.87–0.97, p for heterogeneity 0.14, three studies. For studies with a vitamin D intake lower than 400 IU/day the RR was 1.01, 95% CI: 0.94–1.07, p for heterogeneity 0.01, six studies with data.

Funnel plots did not reveal signs of publication bias.

4. Discussion

In this meta-analysis we have demonstrated a trend towards fewer cases of breast cancer in women with intakes of vitamin D above 400 IU (10 μg)/day. Only few data were available for the higher intakes (especially above 800 IU/day). The meta-analysis supports that high intakes of vitamin D may be preventive against breast cancer. However, more research is needed especially in terms of large population-based randomized-controlled trials using high doses of vitamin D supplements (800 IU or more per day).

The heterogeneity for the entire analysis may stem from variations in vitamin D intake, but other variables such as smoking, parity, and age at menarche and menopause known to be associated with the risk of breast cancer may also play a role.

In our model an intake of vitamin D above 400 IU/day was associated with an 8% reduction in the risk of breast cancer. Although modest, this may have significant impact on the incidence of breast cancer in high risk populations. It must be stressed that this meta-analysis is not designed to assess the effects of vitamin D in treatment of breast cancer.

Extrapolating from our meta-regression showed a RR of breast cancer of 0.63 at an intake of 4000 IU/day using the linear model, and 0.55 using the exponential model (Fig. 2), i.e. a little less than the RR of 0.5 predicted by the prior meta-analysis using

Table 1
Details of studies reporting on the association between intake of vitamin D and risk of breast cancer

| Reference | Study characteristics | Exposure ^a (IU vitamin D/day) | Breast cancer | RR | Lower 95% CI | Upper 95% CI |
|-----------|--|--|---------------|--------------|--------------|--------------|
| [32] | 4747 women, 179 had breast cancer | <100 | 86 | Reference | | |
| | | 100–199 | 51 | 1.01 | 0.69 | 1.49 |
| | | ≥200 | 40 | 0.86 | 0.61 | 1.20 |
| [33] | 2885 postmenopausal women with breast cancer | <100 | 529 | Reference | | |
| | | 100–199 | 826 | 0.99 | 0.88 | 1.10 |
| | | 200–299 | 326 | 0.90 | 0.78 | 1.03 |
| | | 300–399 | 220 | 0.95 | 0.81 | 1.11 |
| | | 400–499 | 241 | 0.86 | 0.73 | 1.00 |
| | | 500–599 | 304 | 1.08 | 0.93 | 1.24 |
| | | 600–699 ≥700 | 206 203 | 1.03 0.95 | 0.87 0.81 | 1.21 1.13 |
| [34] | 10,578 premenopausal women | <142 | 77 | Reference | | |
| | | 142–193 | 55 | 1.39 | 0.98 | 1.99 |
| | | 193–245 | 47 | 0.99 | 0.67 | 1.46 |
| | | 245–319 | 50 | 0.91 | 0.61 | 1.35 |
| | | >319 | 47 | 1.02 | 0.69 | 1.53 |
| | 20,909 postmenopausal women | <142 | 107 | Reference | | |
| | | 142–193 | 167 | 1.07 | 0.83 | 1.38 |
| | | 193–245 | 168 | 1.33 | 1.04 | 1.69 |
| | | 245–319 | 151 | 1.30 | 1.02 | 1.66 |
| | | >319 | 150 | 1.22 | 0.95 | 1.55 |
| [35] | 3482 women (827 premenopausal) | <150 | 268 | Reference | | |
| | | 150–199 | 111 | 0.90 | 0.72 | 1.13 |
| | | 200–249 | 88 | 0.87 | 0.68 | 1.11 |
| | | 250–299 | 66 | 0.79 | 0.60 | 1.05 |
| | | 300–349 | 55 | 0.76 | 0.56 | 1.03 |
| | | 350–500 | 115 | 0.77 | 0.60 | 0.99 |
| | | >500 | 124 | 0.72 | 0.55 | 0.94 |
| | 3482 women (2345 postmenopausal, and 310 with unknown menopause status) | <150 | 526 | Reference | | |
| | | 150–199 | 312 | 1.04 | 0.90 | 1.20 |
| | | 200–249 | 272 | 1.04 | 0.89 | 1.21 |
| | | 250–299 | 211 | 0.94 | 0.79 | 1.11 |
| | | 300–349 | 209 | 1.11 | 0.94 | 1.32 |
| | | 350–500 | 411 | 1.01 | 0.87 | 1.17 |
| | | >500 | 404 | 0.94 | 0.80 | 1.10 |
| | | 75–99 | 1 | 0.34 | 0.05 | 2.45 |
| | | 100–149 | 8 | 1.97 | 0.78 | 4.99 |
| | | 150–199 | 3 | 1.69 | 0.45 | 6.37 |
| ≥200 | 4 | 2.79 | 0.85 | 9.14 | | |
| [36] | 34,321 women (99% Caucasian) | <400 | 212 | Reference | | |
| | | 400–799 | 565 | 0.95 | 0.87 | 1.04 |
| | | ≥800 | 1088 | 0.89 | 0.77 | 1.03 |
| [22] | 148 women with breast cancer, 322 controls, and a random population based sample of 1141 women | <50 | 13 | Reference | | |
| | | 51–74 | 11 | 2.77 | 1.19 | 6.44 |
| | | 75–99 | 1 | 0.34 | 0.05 | 2.45 |
| | | 100–149 | 8 | 1.97 | 0.78 | 4.99 |
| | | 150–199 | 3 | 1.69 | 0.45 | 6.37 |
| | | ≥200 | 4 | 2.79 | 0.85 | 9.14 |

RR: relative risk, CI: confidence interval, IU: international units (40 IU = 1 µg vitamin D).

^a Total intake from foods and supplements combined.

serum vitamin D, but still within the range of a 50% reduction in risk [18].

The main weaknesses of this meta-analysis are the low number of studies, and the low intake of vitamin D reported in most trials. Bias from diet reports by breast cancer patients in case-control studies cannot be eliminated although one of the trials who looked into this did not find evidence of such bias [22].

The results from our study needs to be corroborated from further studies following large cohorts of women for an extended period of time and using large doses of vitamin D as exposure and breast cancer as outcome. If an effect is corroborated the doses of vitamin D that are needed can only be determined from such studies as our results rely on extrapolation. However, existing studies seem to corroborate that doses as high as 4000 IU/day may be necessary to obtain reductions of 50% in the risk of breast cancer [18]. The prior meta-analysis focused on serum values of 25OHD [18], and thus not on intakes as in our study. The serum levels are the result of complex interactions between vitamin D intake (which may be modified through dietary habits and absorption in the intestine), dermal production of vitamin D through sunlight (which may be modified through clothing and sunbathing habits including use of sun screen), distribution in the body (which may be modified by body composition in particular the distribution between fat tissue and lean tissue as vitamin D tends to accumulate in fatty tissue). Our meta-analysis focused on the intake and corroborated that intake was linked to breast cancer. This is important as the contribution from sunlight may be limited in many parts of the world, and supplementation with vitamin D may be needed.

The increase in relative risk of breast cancer with low daily intakes of vitamin D (Fig. 2) is not readily explainable. However, a dual pattern may be present: At very low vitamin D intakes the substrate for the cancer cells is lacking, thus perhaps slowing cancer development, but otherwise being detrimental.

It has been shown that a number of different cancer cells including breast, colon and prostate cancer cells and leukaemic cells express VDR and that calcitriol (1,25(OH)₂D) has an inhibitory effect on these cells [1]. The effect mechanisms have not been fully elucidated but include regulation of cell cycle, stimulation of differentiation, impairment of growth stimuli, inhibition of angiogenesis and increased apoptosis of malignant cells [23–25].

Breast tissue express VDR and both vitamin D status and genetic variations in VDR can affect the risk of developing breast cancer [26,27]. 1,25(OH)₂D increases the differentiation of human breast cancer cell lines [28,29]. Furthermore, pre-clinical studies suggest that vitamin D derivatives can reduce breast cancer development in experimental animals.

Partial or complete deficiency in 1- α -hydroxylase leads to a decreased production of 1,25(OH)₂D and thus potentially an increased risk of development breast cancer [30]. The production of 1,25(OH)₂D may take place both in the kidney but also locally in the tissues [31].

At insufficient levels, cancer development may take place, and is not controlled by adequate serum 25OHD levels, whereas at high levels, processes involved in cancer development may be suppressed by exogenous vitamin D. This pattern may give rise to concern, but further research is needed to corroborate this hypothesis. Our study has dealt with intake of vitamin D, however it may be that both native vitamin D and activated vitamin D and vitamin D analogues may be effective in preventing breast cancer, but this requires further studies.

In conclusion increasing the intake of vitamin D above 400 IU/day may be preventive against breast cancer. However, more research in the field is needed.

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