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Vitamin D and its Use in the Prevention of Breast Cancer

Lesley Rae Kurowski
St. Catherine University

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Cancer is one of the most dreaded diagnoses from a physiological, psychological, social and spiritual standpoint, and is the second leading cause of death in the United States (Zhou, Stoitzfus, & Swan, 2009). Currently, breast cancer is the leading cause of cancer morbidity and mortality among women and accounts for thirty one percent of all female cancers. Approximately 1,150,000 cases and 410,000 deaths occur globally each year from breast cancer (Mohr, Garland, Gorham, Grant, and Garland, 2008). In addition, it is also well documented that breast cancer survival rates vary considerably from one geographic area to another (Sariego, 2009). Breast cancer death rates tend to be higher in areas with low winter sunlight levels and lower in sunny areas (Garland et al, 2006). This raises the question, is there an inverse relationship between the incidence of breast cancer and vitamin D supplementation?

Vitamin D deficiency is an epidemic health problem. In the United States, twenty five to fifty eight percent of adolescents and adults are vitamin D deficient. The prevalence of vitamin D deficiency among people diagnosed with cancer is much higher, approaching ninety percent (Zhou, Stoitzfus, &Swan, 2009). The high risk of vitamin D deficiency, combined with the discovery of increased risks of certain types of cancer in those who are deficient, suggests vitamin D deficiency may account for several thousand premature deaths from different types of cancer annually (Garland et al, 2006).

Populations living farther from the equator have higher overall cancer death rates compared to those living closer to the equator, thus suggesting an increase in sun exposure, and an increase in vitamin D, have lead to decreased cancer-associated mortality (Vijayakumar et al., 2006). The highest mortality rates occur in the northeast while the lowest mortality occurs in the south. This suggests solar radiation may be protective against breast cancer, as it leads to vitamin D synthesis (Vijayakumar et al., 2006).

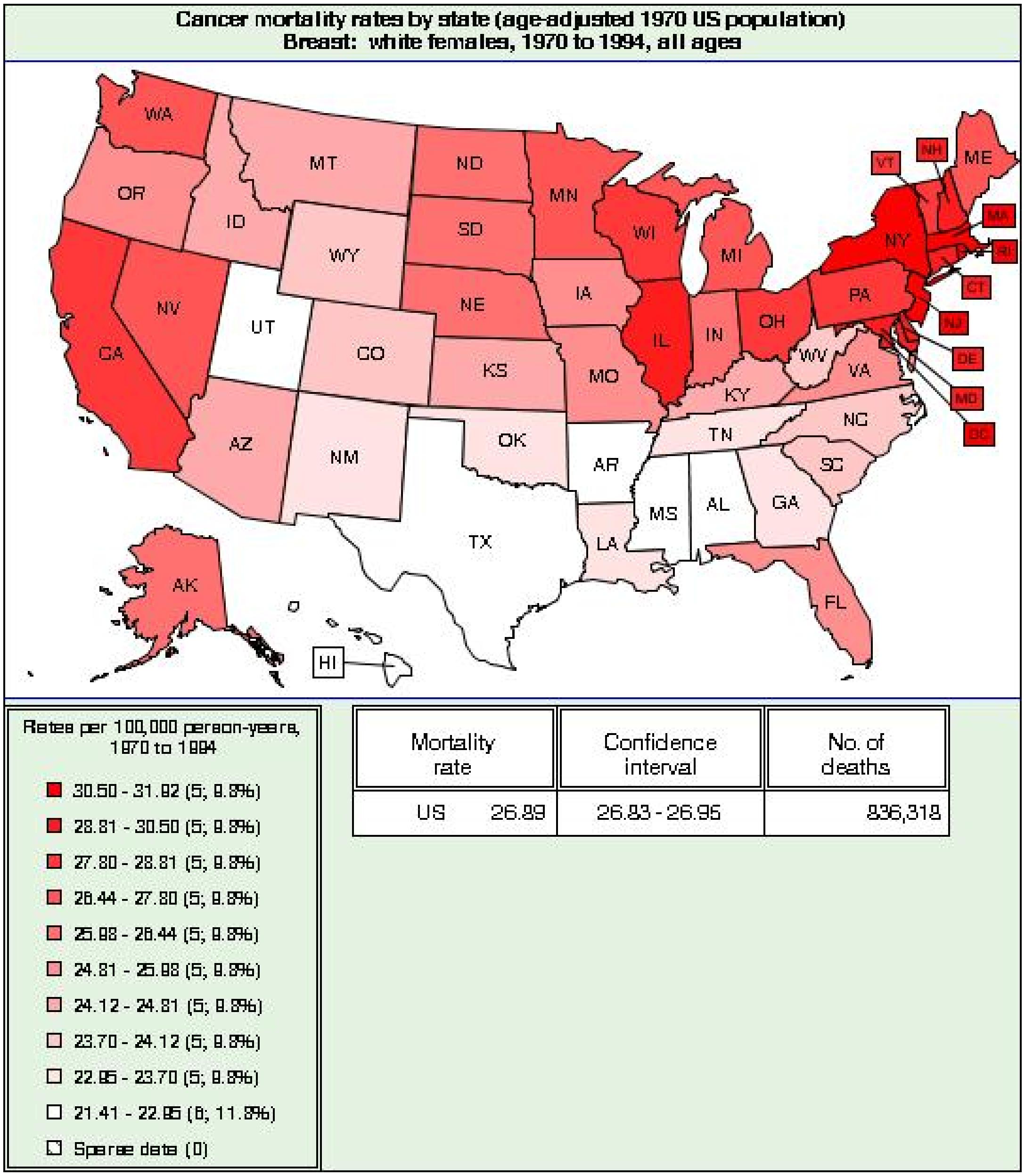

FIGURE 1 – Age adjusted breast cancer mortality rates by state, United States, 1940-1994. Source: NCI Cancer Mortality Maps and Graphs (available at: http://cancercontrolplanet .cancer.gov/atlas/index)

Pathophysiolgy of Vitamin D and Breast Cancer

Breast cancer is a malignant tumor that starts from cells of the breast. A malignant tumor is a group of cancer cells that may grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body (American Cancer Society, 2009). Progression from normal tissue to invasive cancer is thought to take place over five to twenty years and is influenced by hereditary genetic factors as well as somatic genetic changes (Calvo, Petricoin,& Liotta, 2005). The disease occurs almost entirely in women, but men may develop it as well (American Cancer Society, 2009).

Vitamin D is an essential vitamin the body needs to regulate the amount of calcium and phosphorus in the body. It is best known for its role in using calcium to help build bones and keep them strong. Vitamin D participates in a feedback loop to maintain calcium levels within the regulated range (Lin et al, 2007). Vitamin D affects many other tissues of the body, including the kidneys, intestines, and parathyroid glands. Some experts note that vitamin D acts more like a hormone than a vitamin, in part because the body can make its own vitamin D if the skin gets enough ultraviolet (UV) rays from sunlight. Vitamin D is needed to keep a balance between calcium and phosphorus in the body by controlling how much of these nutrients are absorbed from foods or taking them from bones when needed. While known for its role in building bones and keeping them strong, the exact function of vitamin D in other cells and organs is not fully known (American Cancer Society, 2009).

Vitamin D receptors are found in multiple places throughout body tissues, including normal breast tissue. The active metabolite of vitamin D (25OH-D) has been shown to down-regulate estrogen receptor expression and limit induction of the progesterone receptor. As estrogen attaches to the receptors in breast tissue and causes cell proliferation during each menstrual cycle, the down regulation of this receptor by vitamin D analogs ultimately lowers breast cell proliferation, a major factor in the development of cancers (Yanuskiewicz, 2010). Vitamin D and its metabolites reduce the incidence of many types cancer by inhibiting tumor angiogenesis, which stimulates mutual adherence of cells and enhances intercellular communication through gap junctions (Garland et al, 2006).

Vitamin D can be ingested through a few natural food sources such as dairy foods and supplements or can be obtained through UV radiation for conversion of 7-dehydrocholesterol into vitamin D in the skin. It is then hydroxylated in the liver to produce 25-hydrocholecalciferol. The circulating 25-hydroxycholecalciferol is then further converted into 1,25-dihydroxyvitamin D, which is the active form of vitamin D that binds to vitamin D receptors in target tissues such as the mammary gland (Lin et al, 2007).

Vitamin D deficiency is defined as a low serum level of 25-hydroxyvitamin D, which is the principal form of circulating vitamin D, and is the main marker of vitamin D deficiency. The range in which 25-hydroxyvitamin D is considered deficient is less than 15 to 20 ng/mL (Garland et al, 2006).

Literature Review

A complete list of the effects vitamin D can have on the body is unknown. Evidence for an association between vitamin D and breast cancer has not been consistent in previous studies, which show an inverse association only in premenopausal women, in postmenopausal women with estrogen-receptor positive tumors, or no association at all (Abbas, Linseisen, &Chang-Claude, 2007).

Authors Garland, Garland, Gorham, Lipkin, Newmark, Mohr, & Holick searched PubMed in December of 2004 for epidemiological studies of vitamin D, sunlight, ultraviolet radiation, and latitude (2004). The search yielded 63 studies including 30 of colon cancer, 13 of breast cancer, 26 of prostate cancer, and 7 of ovarian cancer. Twenty of the 30 studies of colon cancer found a statistically significant benefit of vitamin D, sunlight exposure, its serum metabolites, or another marker of vitamin D status on cancer risk or mortality and incidence of adenomatous polyps. Of the 13 studies of breast cancer, 9 studies reported an association of vitamin D markers or sunlight with cancer risk. Of the 26 studies of prostate cancer, 13 found a statistically significant association with vitamin D and cancer risk. Five of the seven studies of ovarian cancer found a higher mortality associated with lower regional sunlight or lower vitamin D intake (Garland et al, 2006).

Total calcium and vitamin D intake was evaluated in relation to breast cancer incidence in a study conducted by Lin, Manson, Lee, Cook, Buring, and Zhang. The above was evaluated among 10,578 premenopausal and 20,909 postmenopausal women who were cancer and cardiovascular disease free at baseline in the Women's Health Study. The participants dietary intake was assessed by the food frequency questionnaire. The authors used Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals. Results showed during an average of 10 years of follow up, 276 of the premenopausal women and 743 postmenopausal women had a confirmed diagnosis of invasive breast cancer. In premenopausal women, intakes of both calcium and vitamin D were moderately associated with a lower risk of breast cancer, however intakes of both nutrients were not inversely associated with the risk of breast cancer among postmenopausal women (Lin et al, 2007).

Authors Lappe, Travers-Gustafson, Davies, Recker, and Heaney (2007) conducted a 4 year, population based, double-blind, randomized placebo-controlled trial to analyze the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types. The subjects consisted of 1,179 community-dwelling women who were randomly selected from a population of healthy postmenopausal women aged 55yrs and older in a rural area of Nebraska. The subjects were randomly assigned to receive 1400-1500mg calcium supplementation, supplemental calcium plus 1100 IU vitamin D3, or placebo. Results of the study showed improving calcium and vitamin D nutritional status substantially reduces all cancer risk in postmenopausal women. By evidence of use of logistical regression, results showed the cancer incidence was lower in the calcium plus vitamin D3 subjects than the placebo subjects ($P<0.03$), (Lappe et al, 2007).

Also, authors Robien, Culter, and Lazovich (2007) evaluated the association between vitamin D intake and breast cancer risk among women in a large prospective cohort study. A total of 34,321 postmenopausal women who had completed a questionnaire that included diet and supplement use were followed for breast cancer incidence from 1986 to 2004. Adjusted relative risks for breast cancer were calculated for dietary, supplemental, and total vitamin D intake among all women. The adjusted relative risk of breast cancer for women consuming >800 IU/day versus <400 IU/day total vitamin D was 0.89 with 95% confidence interval ranging from 0.77-1.03. Results overall showed that vitamin D intake of >800 IU/day appeared to be associated with a small decrease in risk of breast cancer among postmenopausal women.

However, more studies evaluating all sources of vitamin D are still needed to fully understand the association between vitamin D and breast cancer risk (Robien, Culter, and Lazovich, 2007).

Contrary to the previous studies, authors Chlebowski, Johnson, Kooperberg, Pettinger, Wactawski-Wende, Rohan, Rossouw, Lane, O'Sullivan, Yasmeen, Hiatt, Shikany, Vitolins, Khandekar, & Hubbell (2008) evaluate a randomized clinical trial in examining calcium plus vitamin D supplementation and the risk of breast cancer. Postmenopausal women (N= 36,282) who were enrolled in a Women's Health Initiative clinical trial were randomly assigned to 1000mg of calcium with 400 IU of vitamin D daily or placebo for a mean of seven years. Baseline serum 25-hydroxyvitamin D levels were assessed in a nested case-control study of 1,067 care patients and 1,067 control subjects. Researchers used a Cox proportional hazards model to estimate the risk of breast cancer association with random assignment to calcium and vitamin D. Associations between 25-hydroxyvitamin D serum levels and total vitamin D intake, body mass index, recreational physical activity, and breast cancer risks were evaluated using logistical regression models. Results showed invasive breast cancer incidence was similar in both groups (528 participants in supplement group vs 546 participants in the placebo group; hazard ratio = 0.96; 95% confidence interval = 0.85 to 1.09). Conclusions made showed calcium and vitamin D supplementation did not reduce invasive breast cancer incidence in postmenopausal women (Chlebowski et al, 2008).

A population based case control study by Knight, Lesosky, Barnett, Rabound, and Vieth was conducted to assess the evidence for a relationship between sources of vitamin D and breast cancer (2007). During the study, women with newly diagnosed invasive breast cancer were identified from the Ontario Cancer Registry. Women without breast cancer were identified through randomly selected residential telephone numbers. Telephone interviews were completed for 972 cases and 1,135 controls. Odds ratios and 95% confidence intervals for vitamin D related variables were estimated using unconditional logistic regression with adjustment for potential confounders. Results showed reduced breast cancer risks were associated with increasing sun exposure from ages 10 to 19. The authors concluded they found strong evidence to support the hypothesis that vitamin D could help prevent breast cancer. However, results suggested that exposure earlier in life may be most relevant and that more studied needed to be conducted to confirm results (Knight et al, 2007).

The next article reviewed, Dietary Vitamin D and Calcium Intake and Premenopausal Breast Cancer Risk in a German Case-Control Study was by Abbas, Linseisen, and Chang-Claude. The researchers conducted a population based case-control study. Participants were recruited from two study regions in southern Germany. Two controls per case, latched by exact age and study region were selected from a random list of residents provided by the population registries. The cases n= 706, controls n= 1,020. All study participants gave informed consent and the study was reviewed and approved by the ethics committee of the University of Heidelberg. Researchers assessed the association of dietary vitamin D and calcium and premenopausal breast cancer risk by means of logistic regression with stratification according to age. Odds ratio estimates and their 95% confidence intervals were calculated with SAS statistical software. Results show breast cancer risk was significantly inversely associated with vitamin D intake but not calcium intake.

Lastly, authors Mohr, Garland, Gorham, Grant, & Garland investigated the relationship of modeled and measured serum 25-hydroxyvitamin D levels with age standardized incidence rates of breast cancer in 107 countries (2008). A multiple regression approach was used to show the contributions of ultraviolet B irradiance to age standardized incidence rates of breast cancer in the 107 countries. Results showed increasing increments in serum 25-hydroxyvitamin D were associated with incrementally lower incidence rates of breast cancer (Mohr, Garland, Gorham, Grant, & Garland, 2007).

Counseling and Education

Generally, throughout the United States, the estimated daily solar exposure needed to maintain a serum 25(OH)D level of 30 ng/mL is 15 minutes in summer and 20 minutes in early fall or late spring from 11am to 2pm under clear skies with full exposure of arms, shoulders and back (Garland et al, 2006). Unfortunately, during November to March north of 37 degrees latitude in the Northeastern and mid Atlantic regions, no amount of sun exposure is sufficient . Therefore, oral supplementation of vitamin D is needed through food consumption or vitamin supplements. Based on its review of data of vitamin D needs, a committee of the Institute of Medicine concluded that persons are at risk of vitamin D deficiency at serum 25(OH)D concentrations <30 nmol/L (<12 ng/mL) (Office of Dietary Supplements, National Institutes of Health, 2011).

There are only a few foods that are good sources of vitamin D. Suggested dietary sources of vitamin D by AlgaeCal are listed below.

Food	**International Units(IU) per serving**	**Percent DV DailyValue)***
Pure Cod liver oil, 1 Tablespoon (Note: most refined cod liver oils today have the vitamin D removed! Check your label to be certain.)	1,360	340
Salmon, cooked, 3½ ounces	360	90
Mackerel, cooked, 3½ ounces	345	90
Tuna fish, canned in oil, 3 ounces	200	50
Sardines, canned in oil, drained, 1¾ ounces	250	70

Milk, nonfat, reduced fat, and whole, vitamin D fortified, 1 cup	98	25
Margarine, fortified, 1 Tablespoon	60	15
Pudding, prepared from mix and made with vitamin D fortified milk, ½ cup	50	10
Ready-to-eat cereals fortified with 10% of the DV for vitamin D, ¾ cup to 1 cup servings (servings vary according to the brand)	40	10
Egg, 1 whole (vitamin D is found in egg yolk)	20	6
Liver, beef, cooked, 3½ ounces	15	4
Cheese, Swiss, 1 ounce	12	4

Figure 2: Selected Food Sources of Vitamin D. Source AlgaeCal (available at http://www.algaecal.com/vitamin-d/vitamin-d-sources.html)

The Food and Nutrition Board established a Recommended Dietary Allowance (RDA) for vitamin D representing a daily intake that is sufficient to maintain bone health and normal calcium metabolism in healthy people. Even though sunlight may be a major source of vitamin D for some, the vitamin D RDAs are set on the basis of minimal sun exposure (Office of Dietary Supplements, National Institutes of Health, 2011). The current recommendations for vitamin D supplementation by the National Institute of Health are as follows:

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

Age	Male	Female	Pregnancy	Lactation
	(15 mcg)	(15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

* Adequate Intake (AI)

Figure 3: Recommended Dietary Allowances (RDAs) for Vitamin D. Source Office of Dietary Supplements, National Institute of Health. (available at :http://ods.od.nih.gov/factsheets/VitaminD/)

Summary Recommendations

Though the chart above shows the recommended daily dosages, the studies examined in this paper show a need to increase the daily dosage of vitamin D in order to produce a chemopreventative effect on breast cancer. It has been suggested that 1000 IU/d of vitamin D intake is needed to achieve adequate vitamin D concentrations in the body (Lin et al, 2007). In the study by Robien, Cutler, and Lazovich (2007) it was not until vitamin D intakes reached >800 IU/day for it to show a small decrease in the risk of breast cancer among postmenopausal women. Garland et al go as far as to say the lower limit for any benefit of vitamin D would correspond to 2000 IUs of vitamin D for the first meaningful increment of breast cancer prevention (2007). It has also been shown that vitamin D dosages of up to 1000 IU per day are not likely to produce toxicity and the National Academy of Sciences-Institute of Medicine has indicated that 2000 IU per day is the safe upper limit of vitamin D intake (Garland et al, 2006). Toxicity of vitamin D generally only occurs when the daily dose exceeds 10,000 IU on a chronic basis (Garland et al, 2007).

Studies on whether or not vitamin D has a preventative effect against breast cancer have been inconclusive as the studies in the literature review demonstrate. However, with that being said, strong evidence indicates that intake or synthesis of vitamin D in increased amounts is associated with reduced incidence and death rates of breast cancer along with multiple other types of cancer. Also, vitamin D status differs by latitude, with residents in the northeastern United States being at increased risk of deficiency (Garland et al, 2007). More studies examining the effects of higher doses of vitamin D and its effect against breast cancer are needed before recommended intakes of vitamin D can be made.

Trusted Resources for Patient Education and Vitamin D Information

1. Office of Dietary Supplements/ National Institute of Health at:

   http://ods.od.nih.gov/factsheets/VitaminD

2. The Mayo Clinic at: http://www.mayoclinic.com/health/vitamin-d/NS_patient-vitamind
3. Medline Plus at: http://www.nlm.nih.gov/medlineplus/ency/article/002405.htm

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