The Role of Vitamin D in the Prevention of Breast Cancer

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Abstract

INTRODUCTION

Breast cancer is the most common cancer that affects women in the United States (excluding the skin cancers). One out of every 8 women will develop breast cancer in their lifetime.[1] Many women are diagnosed each year with breast cancer. In 2008 alone, it was estimated that 182,460 new cases of breast cancer were diagnosed.[1]

Commercials and billboards inundate women with thoughts of yearly mammograms and monthly self-breast exams. These methods of detection are excellent in finding early stage cancer of the breast, but what if medical science was able to prevent the onset of breast cancer rather than just treat it? Recent press has indicated that the so-called "sunshine vitamin" (vitamin D) may have a role in preventing breast cancer.

Prevention of breast cancer would save patients as well as medical assistance programs such as Medicare, thousands of dollars. Cost reduction for patients and insurance alike in itself gives this topic value to review in depth. In June of 2008, the Journal of the National Cancer Institute published a study evaluating Medicare's cancer treatment costs from 1991 to 2002. Breast cancer costs were found to have substantially increased from $4,189 to $20,964.[2] This study also noted that treatment of breast cancer with Avastin costs $55,000 per year for Medicare patients with a 20% copay. This would equal an $11,000 copay for the patient if they have no private insurance to cover the cost.[2]

Although breast cancer does occur in men and tends to be more aggressive, this review will focus on women only. Many risk factors for the development of breast cancer exist; however, this review will focus solely on women who are vitamin D deficient in comparison with those who have adequate serum storage. Cases included in the review will only include invasive ductal carcinoma of the breast and ductal carcinoma in situ. Rarer forms of breast cancer such as Paget's Disease and Inflammatory Carcinoma will be excluded. This evidenced-based medicine paper will discuss the proposed mechanism of action as well as recent studies evaluating the validity and role of vitamin D in prevention of breast cancer.

BACKGROUND

In 2007, the American Cancer Society estimated that 178,480 women were diagnosed with breast cancer and 40,460 more women died of this disease.[1] The chances of developing breast cancer increases with age to a lifetime risk of 1 out of every 8 women being diagnosed with this disease (Figure 1).[1] In addition, Caucasian and African American women have a higher rate of cancer when compared with other ethnicities.[1]

Figure 1

Figure 1: A women's probability increases over a lifetime to a 1 in 8 chance of developing an invasive breast cancer.

Age Specific Risk of Developing Invasive Breast Carcinoma

Risk of Invasive Breast Cancer By Age	
AGE	PROBABILITY
20	1 in 1,837
30	1 in 234
40	1 in 70
50	1 in 40
60	1 in 28
70	1 in 26
Lifetime Risk	1 in 8

Graphic Information Courtesy of: http://www.cancer.org/downloads/STT/BCFF-Final.pdf

The incidence of breast cancer may also be stratified by

state. In 2005, the Center for Disease Control and Prevention gathered information detailing the incidence of breast cancer diagnoses by state. The survey showed that the highest incidences were found in Alaska, Colorado, Connecticut, Delaware, Kansas, Maine, Massachusetts, Minnesota, New Hampshire, New Jersey, Oklahoma, Oregon, and Washington (Figure 2).[3] Noteworthy is the fact that many states included in the high rates are states which are further from the equator, although no specific correlation or study has shown any cause and effect relationship to date.

Breast cancer develops when normal breast tissue cells mutate and proliferate into malignant cells. This process can take place either in the epithelial lining of the ducts or lobules of the breast (Figure 3).[4] The carcinoma can be in situ or invasive (Figure 4).[5]
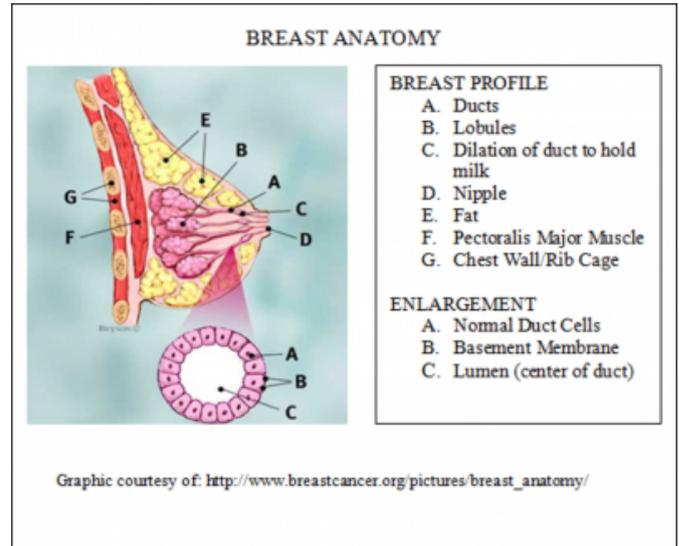
Figure 2

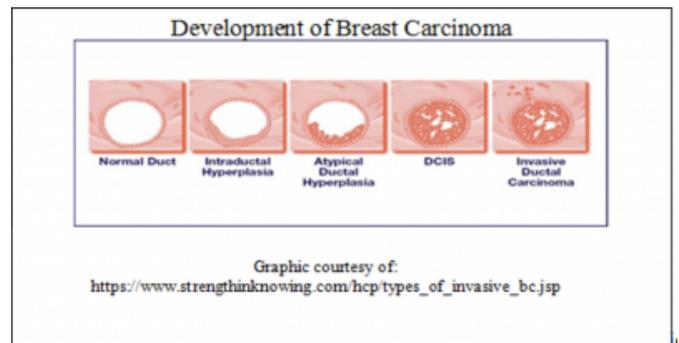Figure 2: Development of breast cancer per 100,000 women in 2005.
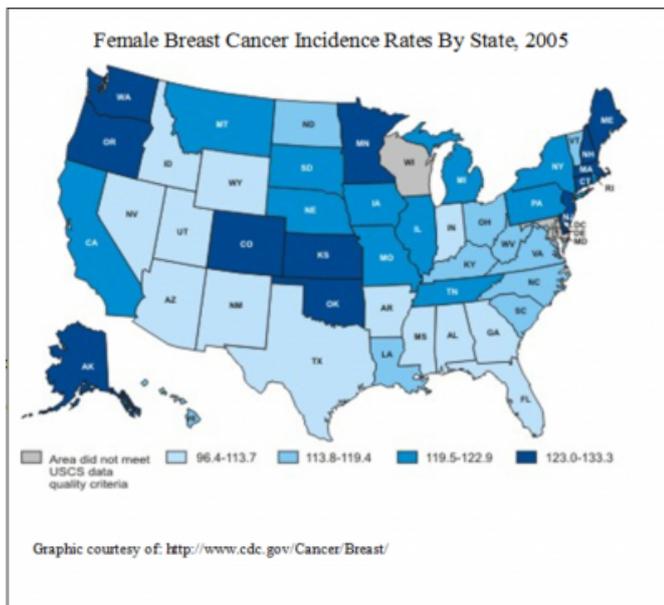
Figure 3

Figure 3: Anatomy of the female breast with an enlargement to view ductal lining.

Figure 4

Figure 4: Illustration of the development of an invasive breast carcinoma from normal tissue.

Figure 5

Figure 5: This figure shows the daily recommended intake of vitamin D supplementation that has been determined by the National Academy of Sciences. It is notable that this Academy has not yet increased their pediatric dosage, however the American Academy of Pediatrics has to 400 IU daily.8

Vitamin D Intake By Age Per National Academy of Sciences				
Adequate Intakes for Vitamin D				
AGE	CHILDREN	MEN	WOMEN	PREGNANT
Birth to 13 years	200 IU			
14-18		200 IU	200 IU	200 IU
19-50		200 IU	200 IU	200 IU
51-70		400 IU	400 IU	
over 71		600 IU	600 IU	

Graphic Information Courtesy of: http://ods.od.nih.gov/factsheets/vitamind.asp

Multiple risk factors for the development of breast cancer have been identified and include hereditary/genetic causes as well as environmental/lifestyle causes. Risk factors unable to be modified include female gender, early menarche, increasing age, BRCA1 or BRCA2 genetic mutations, a family or personal history of breast cancer, Caucasian or African American heritage, and dense breast tissue. Risk factors that can be influenced by an individual include late age of first pregnancy, not breastfeeding, use of hormonal therapy, sedentary lifestyle, obesity, and alcohol use.

Clinical presentation of breast cancer cases can be divided into early and late findings. Early findings include a single, non-tender mass with poorly-defined margins. Early breast cancers may not be physically palpable but found as a mammographic abnormality. Later in the development of this disease clinical signs may present as skin or nipple retraction, axillary lymphadenopathy, erythema, edema, or breast pain.

The most common differential diagnoses for breast cancer include fibroadenoma, intraductal papilloma, fat necrosis, fibrocystic breasts, or lipoma. Although each of these lesions may have similar presentations, carcinoma should always be evaluated and ruled out as the diagnosis.

Once a palpable lesion is identified in the breast, mammography is the initial standard for evaluation.

Although biopsy must be undertaken, a mammogram prior to biopsy allows for identification of other possible lesions as well as evaluation of the other breast. Before any treatment, a biopsy should always be obtained for histologic examination.[6] Three types of biopsies are available to the patient: fine needle, core needle, and open biopsy. Fine needle aspiration (FNA) and core needle biopsy are less expensive and less invasive; however, if either are undertaken and found to be non-diagnostic, an open biopsy must be obtained. From the obtained tissue, a histologic evaluation is performed which will identify the sample as benign or malignant. The tumor, if malignant by histology, will then be classified using the TNM system. This system assesses and classifies the primary tumor by size, lymph node involvement, and presence of distant metastases. Metastasis may be evaluated with the use of PET scanning and laboratory testing including alkaline phosphatase to identify liver or bone metastasis.[6] Following each classification is a number that identifies the stage of the lesion. Stage I is early and stage IV is late. By staging a cancer, the provider is able to provide treatment based on the severity and extent of spread within the body. In order to provide the clinician with more information, tissue samples are tested for the presence of estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (Her-2-Neu). This status, positive or negative, will dictate further treatment including the use of receptor blockers such as tamoxifen, Aromatase Inhibitors, and Herceptin.

Treatment of breast cancer includes the removal of malignant tissue by surgery. A woman may choose to have a mastectomy, or complete breast removal. Traditionally, axillary lymph nodes were also removed during mastectomy to evaluate the lymph nodes for metastasis. A sentinel lymph node (the first lymph node to which cancer cells spread) may be removed and evaluated for metastasis.[6] If this lymph node is negative, it is unnecessary to remove any further axillary lymph nodes.

The patient may opt to have a lumpectomy rather than a full mastectomy. This procedure involves only the removal of a segment of breast tissue where the carcinoma was found. This option is commonly followed by 5 to 7 weeks of radiation therapy, which is used to decrease the risk of recurrence of breast cancer by locally destroying any remaining malignant cells within the area irradiated.

Adjuvant chemotherapy is considered to further decrease the risk of recurrence. The most commonly used chemotherapy agents include Adriamycin, Cytoxan, and Taxotere. These

agents may be used in combinations such as AC (Adriamycin and Cytoxan), TC (Taxotere and Cytoxan), or TAC (Taxotere, Adriamycin, and Cytoxan). The fourth option for therapy is the use of hormonal chemotherapy and is based on the status (positive or negative) of hormonal receptors. Patients found to be ER or PR positive would be recommended to use tamoxifen or Aromatase Inhibitors (AI) for 5 years following initial treatment with surgery and/or radiation therapy. Tamoxifen is recommended for pre-menopausal women and Aromatase Inhibitors are recommended for post-menopausal women. Due to the fact that studies have shown a better effect using AI, menopausal status may be evaluated during treatment and a switch from tamoxifen to AI may be made (i.e., 3 years using tamoxifen followed by 2 years of Aromatase Inhibitors). For patients who are Her-2-Neu positive an agent known as Herceptin may be used. Both Adriamycin and Herceptin are known to decrease ejection fraction of the heart and must be used with caution together with regular interval MUGA scanning.

The attempt at breast cancer prevention incorporates pharmacologic research and study of lifestyle changes. Recent studies have evaluated the value of tamoxifen and raloxifene taken prophylactically.[6] One trial evaluating tamoxifen was able to show a 50% reduction in breast cancer for women under 50 years of age; however, this study found an increase of endometrial cancer and DVT in patients over the age of 50.[6]

Women as individuals are encouraged to make lifestyle modifications that may decrease their risk of cancer development such as increasing activity to lose weight, limiting alcohol consumption, and decreasing fat intake. Prevention can also include efforts to identify early stage disease. All patients are urged to perform monthly self-breast examination and to have clinical breast exams beginning in their 20s. The American Cancer Society recommends annual mammography beginning at age 40 for those at average risk for breast cancer. Earlier and more frequent evaluation by a clinician and imaging techniques may be used for those at increased risk.

Although breast cancer is the second most common cause of cancer deaths in women, much of the prognosis is based on stage of tumor at diagnosis.[1] The 2007-2008 Facts and Figures of Breast Cancer by the American Cancer Society makes the following statement about breast cancer prognosis; "Considering all races, 5-year relative survival is 98% for localized disease, 84% for regional disease, and 27% for distant-stage disease."[1]

Future research regarding breast cancer is beginning to focus more and more on preventative measures including the use of vitamin D.[7] Vitamin D is a fat-soluble vitamin, which can be obtained through ultraviolet sunlight or dietary supplementation. Due to the fact that vitamin D is found in a limited number of foods, it is often necessary for patients to obtain adequate supplies through sunlight exposure and/or supplementation in pill form.

The National Institute of Health Office of Dietary Supplements lists groups who are at risk of Vitamin D deficiency. These include older adults, breastfed infants, those with limited sun exposure, dark skinned individuals, obese people, and those who have fat malabsorption.[8]

Recommendations for vitamin D supplementation vary based on age and source. Two-thousand international units (2000IU) is noted as the upper limit of safe ingestion.[8] Recommendations are currently undergoing overhaul, with the American Academy of Pediatrics recently changing their recommendations from 200 IU daily to 400 IU daily.[8] For patients ages 51-70, a safe and acceptable dosage is 400 IU daily based on the National Academy of Sciences. Figure 5 shows the recommended values for all ages as per the Food and Nutrition Board of the National Academy of Sciences.[8]

Figure 5: This figure shows the daily recommended intake of vitamin D supplementation that has been determined by the National Academy of Sciences. It is notable that this Academy has not yet increased their pediatric dosage, however the American Academy of Pediatrics has to 400 IU daily.[8]

Vitamin D has the known properties of promoting calcium absorption leading to stronger bone density and bone growth. In relation to breast cancer, the article Vitamin D and breast cancer risk, published by Kay Colston, hypothesizes the mechanism of action of vitamin D on malignant tissues:

"In response to vitamin D compounds, cancer cells are commonly arrested in G0/G1 of the cell cycle in association with up-regulation of a number of cell cycle inhibitors, including p21 and p27. In some cancer cell lines- notably MCF-7 breast cancer cells-growth inhibition by vitamin D compounds is accompanied by induction of apoptosis." [7]

Another study by Abbas et al., notes that vitamin D has several actions including induction of cell differentiation,

inhibition of cell growth, and regulation of apoptosis.[9] In order to evaluate a patient's vitamin D stores, serum 25OH-D, which is the active metabolite of vitamin D, is measured.

Vitamin D receptors are found in various body tissues, including normal breast tissue. Vitamin D's active metabolite (25OH-D) has been shown to down-regulate estrogen receptor expression and limit induction of the progesterone receptor, as noted by Thomas Rohan, MD, PhD.[10] As estrogen attaches to the receptors in the 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.

This review will discuss the feasibility of vitamin D supplementation as a measure of breast cancer prevention.

METHODS

This paper asked the question, "Are women who have adequate vitamin D stores less likely to develop breast cancer in comparison to those who are vitamin D deficient?" which is a prevention question. This type of question is best answered by using a systematic review, meta-analysis, or randomized clinical trial. A computerized literature search for relevant studies was performed in the EBSCO Host and Science Direct databases. The literature search material was obtained by using the key words breast, cancer, vitamin D, and prevention in various combinations. Non-English papers were excluded because translations were not available. The restriction to English language studies is unlikely to cause any bias, as a recent assessment reported that non-English papers are likely to be of low quality and could introduce bias into a review. The most up-to date information was used so articles no older than 2005 were used in this paper. Only papers that involved humans and that were peer-reviewed were included. Three articles were ultimately chosen; two which were evidence ¬¬¬¬¬Level 1/A meta-analyses and one Level II/B case controlled study.

The first article chosen was a meta-analysis by Gissel et al., published in 2008. This study searched out and statistically analyzed 6 clinical trials containing original data dealing with vitamin D consumption and breast cancer.

The second article chosen was a case controlled study by Abbas et al., published in 2007. This study, although is considered a Level II/B evidence, gives a detailed methodology section so the reader is able to evaluate the validity of the results.

The third article chosen was a meta-analysis by Garland et al., published in 2007. This study pooled information from two case-controlled studies that evaluated serum 25OH-D levels and its association with breast cancer. A total of 1,760 individuals were included in these two studies.

Information was then extracted from all three articles and used to create an evidence-based medicine paper looking to provide an answer as to whether or not adequate vitamin D stores may statistically decrease the development of breast cancer.

DISCUSSION

The article Intake of vitamin D and risk of breast cancer – A meta-analysis by Gissel et al. evaluates the role of vitamin D in prevention of breast cancer by statistical analysis of 6 original trials.[11] This study searched Pubmed, Embase, and Web of Science on June 28, 2007 using the MESH terms breast cancer and vitamin D. They included only original epidemiological studies evaluating vitamin D intake by IU/daily and its association with breast cancer. Studies that did not report confidence intervals, or exact intake of vitamin D, were excluded from the meta-analysis. Five-hundred and eighty results were yielded from Pubmed, 116 from Embase, and 1092 from Web of Science. Of these references, only 6 were found to be eligible per the criteria outlined above. Estimators were used to calculate the relative risk of breast cancer. The estimators used were derSimonian and Laird. A meta-regression was performed using STATA 8.0 for Windows. Results showed no association between the amount of vitamin D and risk of breast cancer. The authors however, attribute this finding to low intakes of vitamin D in many of the evaluated studies because when a meta-regression was performed, it showed a declining trend in the risk of breast cancer with increasing vitamin D intake overall. The results were particularly significant when intake was greater than 800 IU/daily.

This article was found using Science Direct database. Science Direct is a reputable source that gives access to peer-reviewed literature about the sciences. The article was published in the Journal of Steroid Biochemistry and Molecular Biology, which is a peer-reviewed journal. This article thoroughly explains their methodology including providing specific data and analysis models used. They note the type of estimators used and the programs with which calculations were made. The authors noted which databases were searched and what terms were used so that the reader could obtain the information. The authors also evaluated

publication bias via use of funnel plots, which employed a scatterplot X-Y axis comparison of treatment effects versus study size. The article appropriately cited all of the literature included in the study and provided a reference list for the reader. The article was well-written and organized into appropriate sections, including charts of evaluated data.

A possible shortcoming of this analysis was the fact that a small number of studies were used in the final evaluation. The use of more original studies in the meta-analysis may have given the study more confidence in the results; whether supportive of vitamin D in prevention or against. The low intake of vitamin D in most of the evaluated studies was noted to be a weakness of the analysis by the authors.

The six studies used also included varying samples of women; for example, one study included only premenopausal women, while another included only postmenopausal women and another study included only Caucasian females in the study. Using a sample population of varying characteristics may have introduced bias, as postmenopausal women tend to be older, and age is a risk factor for the development of breast cancer alone. This age group also has a different amount of recommended vitamin D intake when compared to premenopausal females.

The study employed the method of evaluating vitamin D storage by intake values and not by serum 25OH-D, which is the active metabolite of vitamin D in the human body. A study done by Blum et al. found that vitamin D dosing may be based on body size; for example, a patient of smaller stature may need less daily intake of vitamin D to raise their serum 25OH-D to adequate levels and vice versa for a larger individual.[12] This shows that measuring daily intake may not accurately correspond to a therapeutic level of metabolized vitamin D.

Another shortcoming may be the fact that papers of all languages were included in the search and translated as necessary. Since a recent assessment has shown that non-English papers are likely to be of low quality, this could have introduced bias into a review, as there may be things that are misinterpreted during translation.

The article ultimately was unable to corroborate or reject the hypothesis and noted that more studies, specifically randomized clinical trials would be necessary to resolve this issue.

The second article Vitamin D and prevention of breast cancer: Pooled analysis by Garland et al., gathered information from two case-controlled studies evaluating the level of serum 25OH-D levels and its association with breast cancer.[13] A combined total of 1,760 participants were included in the studies. The data was elicited by a Pubmed database search. The terms used in the search were vitamin D, cholecalciferol, calcidiol and cohort, case-control, incidence, occurrence, or epidemiology. These terms were combined with the MESH terms human and breast neoplasms. Various combinations were used to elicit maximal responses. Inclusion criteria included publication in a medical journal, cohort or case controlled studies as well as measurement of association by quantiles. Studies were excluded if they did not meet the above criteria as well as lacking reproducible odds ratios. The information from the two chosen studies was pooled and divided into quintiles. The first study included 1,425 participants: 701 breast cancer patients and 724 controls. All patients included were of the same age, menopausal status, and hormone use status. The study drew monthly serum 25OH-D levels. The second study included 358 participants: 179 cases and 179 controls. The groups were matched by age, race, and the time of year that blood was drawn. A derSimonian-Laird test showed the results of the two studies to be homogenous. The results showed that patients with higher levels of 25OH-D had a lower risk of breast cancer. The study also showed that there was a 50% lower risk of breast cancer with a level of 25OH-D of 50ng/ml. The authors noted that this level would correspond with a daily intake of 4000 IU, double the recommended upper limit of safe ingestion per the National Academy of Sciences.

This article was found using Science Direct database. Science Direct is a reputable source that gives access to peer-reviewed literature about the sciences. The article was published in the Journal of Steroid Biochemistry and Molecular Biology, which is a peer-reviewed journal. Although this study uses pooled information from case-controlled studies, the lack of randomized controlled trials yet to be completed on this subject caused the level of evidence to be less than I/A value.

The article was a well-written and a cohesive source of information and described the methods used to obtain the information in detail. The authors gave a brief synopsis of each study used, but failed to provide the reader with specific data including how subjects were chosen, the inclusion and exclusion criteria, and how variables were controlled.

A definite shortcoming of this study was the extremely small

number of studies included and the number of overall participants. This flaw by itself limits the value of the study. By definition, case controlled studies tend to increase bias potential due to sampling of two populations without randomization or rigorous control methods.

The authors did note that the daily values found to be beneficial in the study were impractical, particularly since they were significantly higher than a published upper limit of safety dosage by the National Academy of Sciences. A reasonable assumption was made by the authors, however, who stated that this level could also be reached by a lower oral supplement intake of vitamin D and increased daily time exposed to the sun. They did note that this time would be dependent on latitude and weather restrictions.

In the end, the hypothesized connection between vitamin D and breast cancer prevention was accepted by the authors based on statistical analysis and feasibility of implementation.

The article Dietary Vitamin D and Calcium Intake and Premenopausal Breast Cancer Risk in a German Case-Control Study by Abbas et al., evaluated vitamin D status as well as calcium status in premenopausal German women.[9] Inclusion criteria were age less than 51 years, premenopausal status, and German speaking patients from one of two southern regions of Germany. A breast cancer case was considered as in situ or invasive breast cancer diagnosed between January 1992 and December 1995. The study identified cases by monitoring 38 local hospital's admissions, surgical schedules, and pathology reports. Nine-hundred and forty-four (944) total participants were included; 278 cases and 666 controls. The controls and cases were matched by age, BMI, education level, age of menarche, breast feeding history, family history of breast cancer, number of births, alcohol and tobacco usage, and physical activity. This information was obtained by a self-administered questionnaire. The mean ages were 41.7 years for cases and 41.6 years for controls. The article described the original numbers recruited and reasons why they were excluded, giving a final number of 944 subjects. The association of breast cancer with vitamin D and calcium status was evaluated using odds ratios and confidence intervals. These statistics were obtained by logistic regression with statistical software SAS version 9.1. All participants were accounted for at the conclusion of the study. Results showed that premenopausal women who had a vitamin D intake of 5 ug per day had a statistically significant lower risk of breast cancer. The authors also

noted that calcium ingestion was not associated with breast cancer development.

This article was found using the EBSCO Host database. EBSCO Host is a reputable source that gives access to peer-reviewed literature about the sciences. The article was published in Nutrition and Cancer, which is a peer-reviewed journal.

This article is not meant for the general public, but has value within the scientific community as the statistical analysis is quite detailed. This article gives all of the information that would be needed to reproduce the study. The article appropriately cited all of the literature included in the study and provides a reference list for the reader. The article was well-written and provided concise information.

A significant drawback to the validity of this study was the multiple variables within the participants of the study. This study attempted to evaluate too many breast cancer risks at once, using participants with varying BMI, age, health status, and personal/family history. The chosen number of cases versus controls was also significantly variable, with a more than two-fold greater amount of controls used in comparison to actual cases (666 versus 278).

Another shortcoming of this study was the fact that the participants themselves filled out the entrance questionnaire. The inclusion of patient opinion on their weight, alcohol and tobacco consumption, as well as education level may have lead to bias within the study. As discussed above with the pooled case-control study information, there was an inherent flaw in this study type by sampling two distinct patient populations.

The authors ultimately recommended a daily dietary intake of vitamin D, which was in support of their original hypothesis.

CONCLUSION

The hypothesis that vitamin D has the ability to alter gene mutations and ultimately prevent breast cancer has yet to be fully proven or refuted in any large-scale clinical trial. Current evidence based literature shows promise that vitamin D may, at minimum, play a role in lowering a patient's chance at developing breast cancer.[7]

Two of the articles reviewed in this evidenced based paper recommend dosages well above the currently recommended upper limit of safe value for daily vitamin D ingestion.[9,12] Controversy exists particularly in the area of advising

patients to obtain more sunlight exposure. Some scientists are concerned that this advice may lead to increasing rates of skin cancer, the current number one cause of cancer deaths in women.[1]

As a practitioner, the most value may be gained from assessing vitamin D storage by serum 25OH-D. If the patient is found to be vitamin D deficient, a regimen of daily vitamin D supplementation based on the current National Academy of Sciences recommendation, from 400 IU up to 800 IU daily is advised. Due to the fact that vitamin D has been shown to improve calcium absorption and deficiency has been linked to diseases such as diabetes, multiple sclerosis, and cancer, it is certainly an acceptable decision to advise oral supplementation for persons found to be deficient.

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