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Prevalence of vitamin D insufficiency among breast cancer survivors

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Prevalence of Vitamin D Insufficiency Among Breast Cancer Survivors

By

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ABSTRACT

The objective of this study was to determine if vitamin D deficiency is a prevalent problem for female breast cancer survivors (BCS) who have completed treatment for breast cancer. Ninety-nine breast cancer survivors and a control population of fifty-five women with no history of breast cancer participated in this study. Serum 25-hydroxy vitamin D concentrations were measured throughout 2007. Dietary and supplement intake of vitamin D was assessed by a food frequency questionnaire. Zip code of residence was used to evaluate potential for skin production of vitamin D. Vitamin D deficiency (<32ng/mL) was observed in 76 of 99 (77%) of BCS, and 51 of 55 (93%) of controls. Women taking vitamin D supplements were less likely to exhibit vitamin D deficiency, but supplementation did not guarantee sufficiency. Vitamin D deficiency appears to be prevalent among both groups. Vitamin D status should be routinely evaluated for all women as part of regular preventive care.

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Chapter 1: Introduction

In recent years, vitamin D insufficiency has been documented as a common problem among a wide variety of populations across the globe. Studies have linked low vitamin D levels with increased rates of certain cancers, including breast cancer. Vitamin D is known to play a critical role in the prevention of bone disease such as rickets, osteomalacia, and osteoporosis and is currently being investigated for its role in cancer development and immune function. Low vitamin D levels increase the risk of osteoporosis, and improving vitamin D levels has been shown to reduce the risk of osteoporotic fractures. There are a few explanations for why osteoporosis is known to affect breast cancer survivors at higher rates than women who have not had breast cancer. Chemotherapy and radiation are known to damage bone formation cells. Hormonal therapies to treat breast cancer often decrease estrogen levels, which adversely affect bone health. Women may also reach menopause earlier due to breast cancer treatments. All of the above factors result in a higher occurrence of osteoporosis for breast cancer survivors. Finally, women who survive breast cancer may have a long life expectancy and therefore could be impacted by osteoporosis, a disease that affects mobility and quality of life. The goal of this study was to determine if vitamin D insufficiency was a problem for women who have survived breast cancer and therefore remain at high risk for osteoporosis compared to postmenopausal women with no history of breast cancer.

Chapter 2: Literature Review

Vitamin D deficiency was thought to be a problem of the past in the United States. Humans and other mammals can produce vitamin D when exposed to ultraviolet blue (UVB) light, typically provided by sunlight. In addition, fortification of cow's milk and supplementation of vitamin D through multivitamins and calcium tablets is common. However, recent studies have documented a surprisingly high prevalence of deficiency across all age groups worldwide, particularly in infants,[1] the elderly,[2] persons of color,[3] and those residing at higher latitudes.[4]

Vitamin D and Incidence of Disease

Recent epidemiological data have shown that inadequate vitamin D status is correlated with diseases other than rickets, osteomalacia, and osteoporosis. The discovery of vitamin D receptors (VDR) in more than 30 body tissues has provided data as to how vitamin D may play a role in the development of a number of conditions, including cancer.[5] Epidemiological evidence has shown a correlation between higher levels of sunlight exposure and decreased mortality from breast, colon, and prostate cancers. The geographical patterns of mortality from these types of cancer are similar to the occurrence of rickets, a disease of vitamin D deficiency.[6]

Factors Influencing Vitamin D status

Several factors affect vitamin D status, including dermal synthesis after UVB exposure, food intake, and dietary supplements. When analyzing vitamin D concentrations, it is critical to evaluate how these factors impact the dermal production of vitamin D (age, skin melanin concentrations, and obesity). Since vitamin D is easily manufactured by the skin after sunlight exposure, it is important to note the seasonal variability of vitamin D insufficiency. In many parts of the United States, UVB radiation does not penetrate the atmosphere during winter months (November through February), thus preventing skin production of vitamin D. Even those persons who live in year-round sun-drenched areas, such as Florida, may be at risk for vitamin D insufficiency if they have limited sun

exposure. In addition, the use of topical sunscreen and covering of the skin with a variety of types of clothing can completely block vitamin D production.[7] Aging decreases the skin's ability to create vitamin D. It is estimated that the ability of the skin to synthesize vitamin D after an equivalent dose of UVB radiation decreases by 50 ng/mL between ages 20 and 70 years. This age-related drop in vitamin D production is likely linked to reductions in 7-dehdyrocholesterol in the skin. As age increases, blood flow to the skin decreases, which may also diminish dermal clearance of vitamin D.[8]

Dietary Intake of Vitamin D and Vitamin D Status

Food does not generally provide adequate amounts of vitamin D. Milk is fortified with approximately 100 IU vitamin D per cup in the United States. Fatty fish such as salmon, tuna, mackerel, and sardines contain about 350 IU per 3.5 ounce serving.[9] One egg provides only about 20 IU of vitamin D. Though the current DRI for vitamin D is 400 IU, it has been documented that dietary intakes equal to 400 IU daily do not result in adequate vitamin D status without additional vitamin D being provided from skin production or supplemental intake.[10]

Supplemental Intake of Vitamin D and Vitamin D Status

Since vitamin D is a fat-soluble vitamin, supplements of vitamin D are best absorbed when taken with a meal that contains some type of fat. Vitamin D supplements are available in two forms, ergocalciferol (D_2) and cholecalciferol (D_3). Controversy exists as to which supplemental form of vitamin D is most effective. However, a growing consensus points to cholecalciferol (D_3) as the most potent form of vitamin D. It has been shown that vitamin D_3 not only has a longer serum half-life but also greater affinity than vitamin D_2 for the vitamin D binding protein, hepatic vitamin D hydroxylase, and vitamin D receptors.[11,12]

Race and adiposity are two other variables that are associated with risk and survival of breast cancer as well as vitamin D status. As skin melanin concentrations increase, greater quantities of UVB exposure are needed to produce equivalent amounts of vitamin D in the dermis. According to

the NHANES III, which surveyed 18,875 persons, circulating concentrations of serum 25(OH)D are lower in African Americans than Caucasian Americans.[4] The Women's Health Initiative (WHI) study of more than 150,000 women investigated differences in breast cancer incidence and found that African Americans are disproportionately at risk for breast cancer mortality.[13] Grann et al.[14] analyzed epidemiological data and also noted that mortality from breast cancer was higher in African Americans even after controlling for several variables (socioeconomic status, insurance coverage, age, cancer stage/type). Obese individuals have been shown to have lower concentrations of circulating 25(OH)D vitamin D since it is stored deep in adipose tissue.[15] Markers of poor vitamin D status such as elevated parathyroid (PTH) concentrations have also been shown to be low in obese subjects.[16]

Cancer and Vitamin D

Current theories as to how vitamin D may affect cancer development and growth focus on its effects on cell cycle growth regulation, activation of apoptotic cell death, and modulation of growth factor signaling.[17,18] These actions have been documented in several cell lines including breast cancer cells.[19,20] In addition, some studies have suggested that low vitamin D concentrations increase parathyroid hormone and androgen concentrations and that this might lead to breast cancer development.[21,22]

Breast cancer is the most common type of cancer diagnosed in American females and is responsible for the deaths of more than 40,000 women in the United States each year. Female breast cancer survival has been correlated with season of diagnosis and with cumulative sunlight exposure in the months preceding diagnosis. Women diagnosed in summer or autumn experienced improved survival compared with those diagnosed in winter.[23] Increased dietary intake of vitamin D and sunlight exposure is associated with reduced risk of breast cancer occurrence.[24]

There are several mechanisms by which vitamin D can affect the development and progression of cancer. Mammary tissue is known to contain both vitamin D receptors and the 1-alpha-hydroxylase enzyme needed to convert vitamin D into its active form.[5] Vitamin D has also been found to have anti-proliferative effects against cancer in addition to inducing differentiation and apoptosis and encouraging cellular maturation.[5]

Since many women with breast cancer can expect a long survival time post-diagnosis, maintaining quality of life after treatment is an important goal. Women who have undergone treatment for breast cancer are at higher risk for osteoporosis than other postmenopausal women due to the detrimental effects of chemotherapy, radiation, and hormonal therapy on bone cells. Since improving vitamin D deficiencies is known to reduce the risk of osteoporosis, improvement of vitamin D concentrations in breast cancer survivors may improve long term quality of life.

Determination of Insufficient Concentration of Vitamin D

Vitamin D status is best measured by determining serum 25(OH)D concentrations since it is reflective of both oral intake and subcutaneous production of vitamin D. A consensus has not been reached as to the definition of insufficient or adequate vitamin D status. Vitamin D deficiency was defined in the past as the level below which rickets or osteomalacia develops due to inadequate bone mineralization. This is equivalent to a serum concentration of 25(OH)D of <12.5 nmol/L, but may be as high as <25nmol/L.[5,8]

When serum vitamin D concentrations are low, the parathyroid gland releases parathyroid hormone (PTH) to stimulate synthesis of calcitriol in the kidney. Therefore, vitamin D insufficiency has also been described as the concentration at which PTH is elevated. Elevated PTH concentrations occur more often as 25(OH)D concentration decreases, especially below 50 nmol/L.[25] Low vitamin D concentrations in adults <32ng/mL (80nmol/L) lead to poor intestinal calcium absorption and decreased calcium resorption in the kidney, which increases fracture risk and

osteoporosis. The risk of falling was found to be increased in persons with 25(OH)D concentrations that were equal to 68nmol/L or lower.[26] Low vitamin D levels have also been correlated with higher risk of certain cancers, including breast. Thirty-two ng/mL (80nmol/L) has recently been considered to be the threshold for vitamin D deficiency due to the cumulative evidence that vitamin D is important in regard to aspects of health besides bone health.

Prevalence of Insufficiency

Among healthy adult women in Boston, 30% of participants were found to have insufficient vitamin D concentrations after winter and 20% after summer.[3] A study by Rucker et al.[27] that examined 188 healthy, ambulatory adults in Calgary (Alberta, Canada) found that vitamin D insufficiency varied between 60-95% during the year when 80 nmol/L was used as the cutoff for minimally adequate vitamin D concentrations. In a study of European postmenopausal women, the prevalence of 25(OH)D inadequacy was 79.6% when the same cutoff of 80 nmol/L was used.[28]

Vitamin D and Breast Cancer

Though research has correlated risk of breast cancer with low vitamin D intake and sunlight exposure, few of these studies have measured serum concentrations of vitamin D. Some studies[29-38] in persons with breast cancer have examined 1,25(OH)$_2$D concentrations and/or 25(OH)D concentrations and found an association between breast cancer risk and vitamin D concentration.

Hiatt et al.[29] found no significant differences in 1,25(OH)$_2$D concentrations that were determined 15 years before diagnosis when BCS were compared to controls. Another study reported significant mean differences in 1,25(OH)$_2$D in breast cancer subjects versus controls but no differences in 25(OH)D concentrations.[30] Bertone-Johnson et al.[31] found BCS to have a lower serum 25(OH)D concentration compared to controls before diagnosis but similar 1,25(OH)$_2$D concentrations between groups. However, results were not statistically significant. Mawer et al.[32] measured the 1,25(OH)$_2$D concentrations in 129 breast cancer patients and found constant

concentrations in those with stable disease or disease responding to therapy. However, concentrations of 1,25(OH)$_2$D dropped in subjects with progressive disease. It was concluded that since 1,25(OH)$_2$D is not a good measure of vitamin D status, research that analyzed 25(OH)D concentrations may be more useful in understanding the relationship between vitamin D and breast cancer. More recently, Freedman et al.[33] measured 25(OH)D concentrations 4-14 years prior to breast cancer diagnosis and found the breast cancer relative risk decreased for women who were in the highest quintile of 25(OH)D concentration versus the lowest.

Abbas et al.[34] found that serum concentrations of 25(OH)D were inversely associated with post-menopausal breast cancer risk. A study by Lowe et al.[35] found that women with a serum 25(OH)D that was <50nmol/L were more likely to have current breast cancer than women with concentrations of >50nmol/L. Colston et al.[36] compared current breast cancer patients to controls and found that women with cancer were significantly more likely to have a 25(OH)D concentrations of <50nmol/L than women without cancer. Research by Palmieri et al.[37] determined that patients with advanced breast cancer disease had significantly lower concentrations of 25(OH)D than those with early breast cancer.

Most recently, Neuhouser et al.[38] assessed 25(OH)D concentrations in breast cancer survivors and found that 75.6% exhibited low vitamin D concentrations, indicating that the prevalence of vitamin D insufficiency was high in this population.

Bone Health, Vitamin D, and Breast Cancer Survivors

Women who have received treatment for breast cancer are acutely at risk for osteoporosis for several reasons. Osteoporosis has been shown to be a common disease in postmenopausal women, with one in 3 women over the age of 50 worldwide being affected with this condition. Estrogen is a key factor in bone turnover, and the reduction in estrogen concentrations after menopause has been shown to cause the rate of bone loss to increase by two- to four-fold. Women

who reach menopause earlier due to ovarian failure induced by chemotherapy may be especially at risk for developing osteoporosis due to a longer post-menopausal lifespan.[39] In addition, since 60-70% of breast cancers in postmenopausal women are hormone-receptor positive, they are often treated by estrogen deprivation. Toxic effects of chemotherapy have also been shown to damage bone formation cells.[39.40] Vitamin D is critical in the protection of bone health, and an insufficient concentration of vitamin D is known to increase the risk of fracture and osteoporosis.[41] Breast cancer survivors have been shown to have significantly lower bone mineral density than controls after adjusting for age, race, and years since menopause.[40] Assessment of vitamin D status in breast cancer survivors could provide data to better manage the risk of osteoporosis in this population.

Chapter 3: Research Design and Methodology

This study was designed to document the prevalence of vitamin D insufficiency in breast cancer survivors (BCS) and compare these rates to those found in healthy female controls.

Subjects

Ninety-eight BCS who had completed their treatment at least 6 months before initiation of the present study and 55 control subjects were recruited for the present study. The BCS who participated in the present study were women with no active cancer growth after completion of their chemotherapy or radiation treatments and who returned for follow-up analysis at the Cancer Treatment Centers of America (CTCA) at Midwestern Regional Medical Center (MRMC), Zion, IL. Controls were age and menopausal matched healthy female volunteers who were employees of the CTCA.

Prior to taking part in the study, all participants had to provide informed consent (Appendix C). Eighty-three percent of participants in both groups were Caucasian. Ethnic distribution was different between the two groups, with slightly more Asians in the control group and slightly more African Americans in the BCS group (Table 1). There was no significant difference in age or body mass index (BMI) between the two groups.

Table 1. Demographic Characteristics of Breast Cancer Survivors (BCS) and Controls

Characteristics	BCS (n=99)	Controls (n=54)
Age (y), mean ± SD	55.8 (9.2)	52.7 (14.9)
Body Mass Index (BMI), mean ± SD	29.2 (7)	27.3 (5.7)
Race (n)		
African American	10	5
Asian	0	6
Caucasian	87	40
Hispanic	2	2
Native American	0	1

The majority (80%) of the BCS had been diagnosed with stage one or stage two breast cancers (Table 2). Seventy-two percent of the BCS had estrogen-receptor positive (ER+) tumors, 60% had progesterone-receptor positive (PR+) tumors, and 80% had HER2/neu negative tumors. Most of the BCS had received surgery followed by chemotherapy or radiation as their treatment for cancer. One subject had undergone a stem cell transplant. A majority of the BCS (73%) were not taking hormonal therapy for breast cancer at the time of the study (Table 2).

Table 2. Descriptive Characteristics of Breast Cancer Survivors (BCS)

Characteristics	**Percentage**
Estrogen Receptor Positive (ER+)	72%
Progesterone Receptor Positive (PR+)	60%
HER2/neu Receptor Positive (HER2/neu+)	20%
Inflammatory Breast Cancer	6%
Stage of Breast Cancer	
1	28%
2	52%
3	15%
4	5%
Surgery as treatment for cancer	93%
Chemotherapy as treatment for cancer	88%
Radiation as treatment for cancer	77%
Stem cell transplant as treatment for cancer	1%
Hormonal treatment for cancer	27%

Persons with the following medical conditions were excluded from the study: undergoing current dialysis treatment, elevated liver enzymes, primary hyperparathyroidism, hypercalcemia, hypercalciuria, or Paget's disease.

The MRMC Institutional Review Board and the Eastern Michigan University Human Subjects Committee approved this study (Appendices D, E.)

Research Design

The present research project was an observational, case-controlled study that was conducted over a twelve-month period. Subjects were recruited from a group of BCS who had scheduled follow-up appointments at MRMC in 2007. These potential subjects were mailed an invitation to participate in the study prior to their appointment. Control women were employees of MRMC and were recruited using a public email invitation. All participants provided a blood sample at MRMC that was tested for 25-hydroxy vitamin D. They also completed a food frequency questionnaire that included a list of current vitamin and mineral supplements and their consumption rate and also provided their present zip code of residence.

Biochemical Analysis

All BCS provided a one-time non-fasting serum sample for determination of 25(OH)D concentration during their appointment at MRMC. The control group provided serum samples either during the months of April (n=27) or October (n=28) 2007. Serum was collected at the MRMC laboratory, packed in coolpacks, and sent to the Laboratory Corporation of America (Raleigh, NC), where a chemiluminescence procedure was used to measure 25(OH)D.[16] 25(OH)D measurements included both D_2 and D_3 in serum. Serum samples were incubated with antivitamin-D coated microparticles and isoluminol derivative-conjugated 25(OH)D before measurement of chemiluminescent signals.[16] Analysis was completed within 48 hours of collection.

Survey Instrument

All participants were surveyed when they visited MRMC to obtain demographic information and medical history. The principal investigator (a registered dietitian) met with each participant to review and collect all surveys upon completion and to answer any questions regarding the study and the survey.

Demographic information collected included each subject's age, sex, race, height, weight, and zip code of residence. Medical histories included non-cancer-related medical information; type, stage, and date of breast cancer diagnosis; completed cancer treatment regimens, and current medications (Appendix A). Medical records were used to obtain pertinent health and cancer treatment related information when subjects could not answer relevant questions.

Sunlight Exposure Calculations

Amount of exposure to ultraviolet blue (UVB) radiation was approximated for each participant based on latitude of residence. Zip codes of residence were used to determine the latitudes of residence. Zip code information was obtained in the demographic questionnaire (Appendix A). No data were collected regarding sunscreen use or time spent outdoors.

Food Frequency Questionnaire

Dietary intake of vitamin D was determined using data from a modified food frequency questionnaire originally developed by Blalock et al.[42] (Appendix B). This questionnaire provided data regarding calcium and vitamin D intake as well as intake of other vitamins, minerals, and herbal supplements.

Statistical Analysis

Participants were stratified for statistical analysis on the basis of age, race, stage of cancer, BMI, approximate level of UVB exposure, level of dietary intake of vitamin D, level of supplemental intake of vitamin D, and date of last cancer treatment. One-way analysis of variance (ANOVA) and the student's paired t-test as well as basic averages and medians were performed to compare these groups for differences in vitamin D status. Analysis was completed using the Java Memory Profiler (JMP) 5.1 software developed by the SAS Institute, Cary, North Carolina. A P value$\leq$0.05 was considered to be statistically significant.

Chapter 4: Results

The majority of BCS and controls had unusually low concentrations of serum 25(OH)D. Vitamin D deficiency, as defined by a serum concentration that is below 32ng/mL, was observed in 77% of the BCS and 93% of the controls. The controls (women with no history of breast cancer) had significantly lower serum concentrations of 25(OH)D (including serum D_2 and D_3) than the BCS by one-way ANOVA and paired *t* test ($P<0.0175$). The mean concentration of serum 25(OH)D for controls was 19.5ng/mL, and the mean for BCS was 24.2ng/mL (Figure 1).

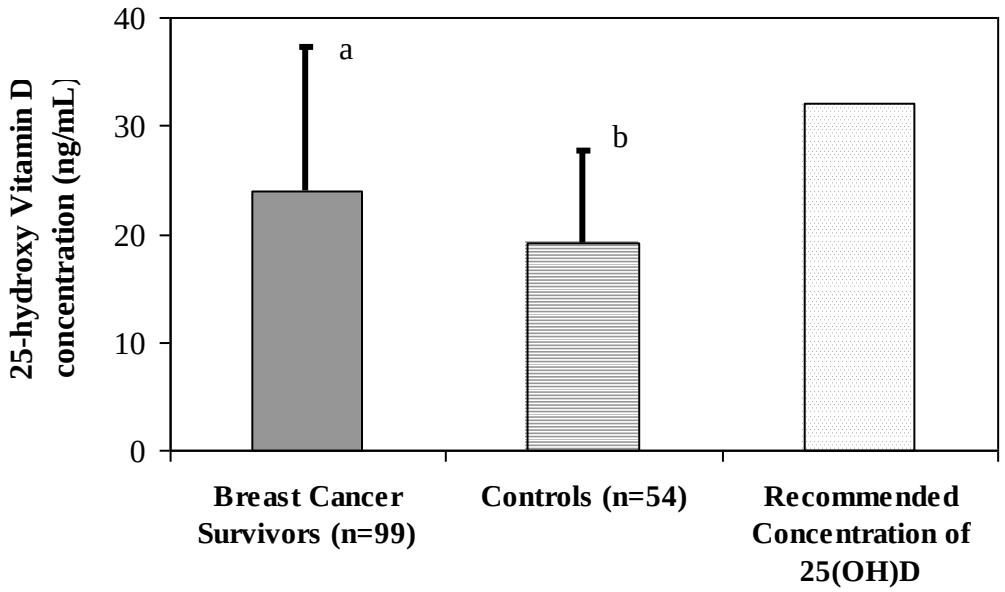

Figure 1. Mean serum 25(OH)D concentrations of breast cancer survivors (BCS) and controls as compared to recommended concentrations of 25(OH)D (including serum D_2 and D_3). Error bars indicate SD. Bars with different superscripts were significantly different at ($P\leq0.0175$).

When serum 25(OH)D concentrations were analyzed according to geography and location and possible annual sun exposure, only 7 of 96 breast cancer survivors (none of the controls) were found to live in zip code areas where year-round skin production of vitamin D is possible. There were no differences in vitamin D concentrations throughout the 12 months of the year (Figure 2).

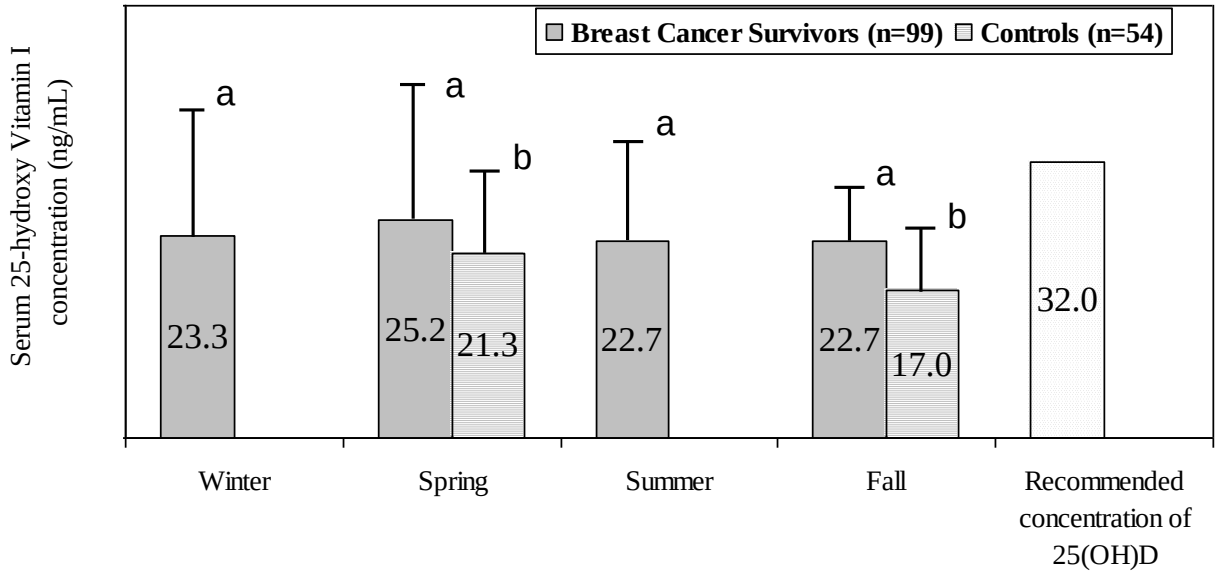

Figure 2. A comparison of recommended concentrations of 25(OH)D to serum 25(OH)D concentrations of Breast Cancer Survivors (BCS) and controls according to seasons of the year. Error bars indicate SD. Note: Controls were tested only during the spring and fall time periods. Bars with the same superscript indicate no significant difference between 25(OH)D concentrations between seasons at ($P \leq 0.05$). Bars with different superscripts were significantly different at ($P \leq 0.05$).

Dietary Vitamin D Intake

The majority of BCS and controls did not consume adequate amounts of dietary vitamin D. The dietary reference intake (DRI) for vitamin D is 400 IU daily. Average daily intake of vitamin D among BCS was 140 IU/day; whereas among controls it was 135 IU/day. Only 9 subjects met the DRI for vitamin D solely with food intake (8 BCS, 1 control). Eight of these women consumed fatty fish regularly (about one serving/day). One woman consumed 72 oz. of whole milk daily.

Supplemental Vitamin D Intake

Supplement intake varied widely and explained only 31% of the variation in serum 25(OH)D status. Average vitamin D intake from supplements was significantly different ($P \leq 0.094$) between

groups, with BCS consuming 1,013 IU/day and controls consuming 421 IU/day. A majority of all participants (73% of cases, 89% of controls) took supplements containing vitamin D. Most vitamin D supplements were consumed as multivitamin/calcium supplements. Few participants consumed separate vitamin D supplements. Most subjects consumed 1000 IU vitamin D/day or less from supplements. One BCS had a vitamin D intake of 14,000 IU/day that was prescribed by her physician as a 100,000IU weekly supplement. No difference was seen in serum vitamin D concentrations between those who took vitamin D supplements with food and those who took vitamin D only with water.

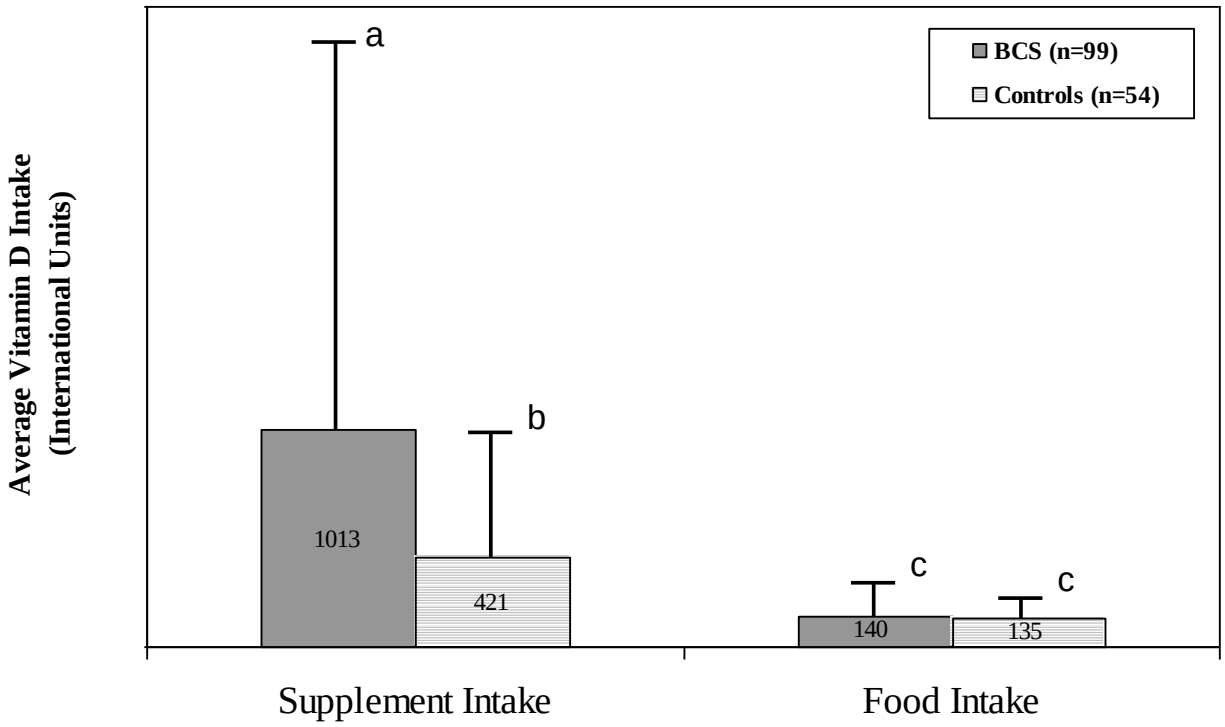

Figure 3. Supplemental intake of vitamin D and dietary intake of vitamin D between BCS and controls. Bars with the same superscript indicate no significant difference between vitamin D intake between BCS and controls at ($P \leq 0.05$). Bars with different superscripts were significantly different at ($P \leq 0.05$).

Finally, both groups were asked about their current bone health in the medical questionnaire. Breast cancer survivors had a significantly higher burden of bone disease (osteopenia or osteoporosis) than controls (32% vs. 13%) ($P<0.0331$).

Chapter 5: Discussion

Finding a majority of participants to be deficient in vitamin D was not surprising, considering the epidemic of vitamin D deficiency in the general population.[43] The finding of exceptionally high rates of vitamin D deficiency were consistent with other results reported in research studies that compared healthy women and BCS.[27,28,38] Tangpricha et al.[3] found that 20-30% of their cohort were deficient in vitamin D when ≤20ng/dL was used as a cutoff for deficiency. Kakarala et al.[44] found 67% of uninsured Michigan women to be deficient in vitamin D by serum vitamin D concentrations. One explanation for the discrepancy in rates of serum vitamin D deficiency may be that the cutoff values for vitamin D deficiency and insufficiency are not standard. The current general consensus defines serum vitamin D deficiency as a concentration <32ng/mL.[45] A review of literature on the prevalence of vitamin D deficiency in various populations reveals that a myriad of cutoff values are being used, thus leading to discrepancies in how common this condition actually is. For instance, many studies use <20ng/mL as the cutoff value for vitamin D insufficiency (rather than <32ng/mL), which results in a much smaller percentage of persons being labeled "insufficient."

However, it was not expected that controls would have lower serum vitamin D concentrations than BCS. Since dietary intake and sunlight exposure were not significantly different between groups, one explanation might be that BCS were more likely to take higher doses of vitamin D supplements than controls (1025 IU vs. 436 IU, respectively). But only 31% of the variability in 25(OH)D concentrations was explained by vitamin D supplements. Not all women taking vitamin D supplements reached sufficient concentrations of vitamin D. It was disconcerting that one participant was taking a 100,000 IU vitamin D supplement prescribed by her primary care provider without prior testing of her serum 25(OH)D concentration.

No seasonal variability was detected in vitamin D status in either group. This was unusual, as most studies have found vitamin D concentrations to vary with the seasons.[46] One limitation of the study is that sun exposure and sunscreen use were not explicitly measured. Participants provided only their zip code of residence. Overall, as no variability in vitamin D concentration was seen between seasons, it is hypothesized that participants did not receive sun exposure adequate to significantly affect vitamin D concentrations even during the summer months.

Dietary intake of vitamin D was not significantly different between BCS and controls (140 IU vs. 135 IU, respectively) and did not provide even half of the DRI for vitamin D. This result was similar to that found in a population of postmenopausal women in the United Kingdom.[47] It is well known that there are not many significant dietary sources of vitamin D, and therefore inadequate dietary intake of vitamin D should not be surprising.[13,14]

Supplemental intake of vitamin D was one area where significant differences were found between BCS and controls. BCS had significantly higher levels of vitamin D intake from supplements (1013 IU vs. 421 IU). Studies suggest that persons who have survived cancer are more likely to take vitamin or mineral supplements than persons who have no history of cancer.[48] A more recent survey of cancer survivors found that 73% took supplements of some type. Caucasian women were most likely to take supplements compared to other races and to men. Vitamin D supplements are also one of the most commonly taken nutritional supplements.[49] In addition, CTCA is a unique hospital in that patients typically meet with both their dietitian and naturopathic doctor along with their oncologist as part of each follow-up visit. Recommendations from these complementary and alternative medicine (CAM) providers may increase the likelihood of supplementation. Patients who choose to use CAM may also be more likely to self-select cancer care and follow-up care at CTCA. Though vitamin D intake from supplements was greater among BCS, women taking supplements did not always reach vitamin D sufficiency. It is possible that some

women chose vitamin D supplements of low doses inadequate to reach sufficient concentrations of vitamin D. Also, it is possible that vitamin D supplements were not well absorbed. It has been theorized that fat is necessary to absorb vitamin D as it is a fat-soluble vitamin. However, research by Tangpricha et al.[50] did find that vitamin D absorption was equivalent when vitamin D supplements were taken with fat-free or fat-rich beverages. Finally, individuals do exhibit different vitamin D receptors, but this is beyond the scope of this research study.

Age and BMI can both affect vitamin D status as our skin production of vitamin D declines four-fold between ages 20-70 and because vitamin D is stored in adipose tissue and is therefore unavailable for use. However, neither variable was different between groups or predicted vitamin D status in this study.

It may have been expected to see differences in 25(OH)D concentrations between ethnic groups due to differences in skin melanin levels, but no variability was seen. This is most likely due to the extremely low concentrations of vitamin D of all participants and the probable lack of sunlight exposure among all participants. The study population was also mostly Caucasian, which may not have permitted an adequate sample size of any other ethnic group to see differences.

The findings of significantly more bone disease in BCS is not remarkable, as it is known that decreases in estrogen due to cancer therapies that promote earlier menopause as well as that chemotherapy and radiation negatively impact bone health. It is known that vitamin D is critical in maintaining adequate calcium stores.[26] This highlights an important opportunity for clinicians to protect bone health by assessing vitamin D status and correcting deficiencies in BCS.

Overall, the majority of both populations were deficient in vitamin D. A predictor of adequate vitamin D status in this study was vitamin D supplement intake >2000 IU daily.

Chapter 6: Conclusions

Vitamin D insufficiency is prevalent in both BCS and healthy women. Assessment of vitamin D status should be part of a regular nutrition assessment for most women. Food intake of vitamin D and intake of vitamin D supplements of less than 1000 IU daily did not prevent vitamin D deficiency in this study. It is unlikely that increasing vitamin D intake from food would be an effective method of preventing vitamin D deficiency due to the large amounts of food that would have to be eaten on a daily basis. The current DRI of 400 IU was not adequate to prevent vitamin D deficiency in this population. Sun exposure did not appear to significantly contribute to vitamin D status in this cohort of women. Overall, vitamin D supplementation in amounts >1000 IU daily appears to be the best strategy to prevent vitamin D deficiency. Women found to be deficient in vitamin D through this study were recommended to take 8000 IU vitamin D_3 daily for 8 weeks as advised by Holick.[25]

Suggestions for Future Research

It would be valuable for further studies to investigate if breast cancer recurrence can be affected by maintenance of vitamin D adequacy and to determine what serum concentration of vitamin D is optimal for health. In addition, more data are needed regarding what conditions are optimal for vitamin D absorption from food and supplements.

Considering the relationship of low vitamin D concentrations and many disease states, including polycystic ovary syndrome, cardiovascular disease, diabetes, autoimmune disease and bone health, assessing vitamin D status and correcting vitamin D deficiencies is a critical goal.

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APPENDICES

Appendix A: Sample Demographic Survey Form

Vitamin D Study – Demographic and Medical Questionnaire

Please answer the following questions about you and your medical history.
All information will be kept confidential.

Today's Date:_____

Demographic Data:

Participant Number:_____
Age:_____
Sex:_____
Height: _____
Weight:_____ BMI_____ (RD will calculate)
I consider my race to be:_____

State and zip code of residence:_____
How long have you resided in this area?_____

If you have resided in this area less than 2 years, please provide previous state(s) and zip code(s)of residence and time of residence in those
locations._____
_____
_____

Medical Data:

Date of breast cancer diagnosis (month/year):_____

Type of breast cancer:_____ (ER+/-, PR+/-, Her2Neu+/-, Inflammatory)

Stage of breast cancer at diagnosis:_____

Types of treatment you have received for breast cancer AND dates that you received these treatments:_____
_____
_____
_____
_____
_____

When was your last treatment for cancer (month/year)?_____

What other medical conditions do you have?_____
_____
_____

What medications are you currently taking?_____
_____
_____

Appendix B: Sample Dietary Survey Form

SHORT FOOD QUESTIONNAIRE

This form asks about your *usual* eating habits over the past year.

First: For each food listed, mark the column to show how often, on the average, you ate the food during the past year.
Please BE CAREFUL which column you put your answer in.

Second: Mark whether your usual serving size is small, medium, or large. Please DO NOT OMIT serving size.

Additional Comments:

- Please DO NOT SKIP any foods. If you never eat a food, mark "Never or less that once a month."
- A small serving is one-half the medium serving size shown, or less.
- A large serving is about one-and-a-half times the medium serving size shown, or more.

Sample: **This person ate a medium serving of rice about twice per month and never ate squash.**

	HOW OFTEN									**HOW MUCH**			
Type of Food	Never or Less than Once Per Month	1 Per Month	2-3 Per Month	1 Per Week	2 Per Week	3-4 Per Week	5-6 Per Week	1 Per Day	2+ Per Day	Medium Serving	Your Serving Size		
													L
Rice			X							¾ cup		X	
Winter squash, baked squash	X									½ cup			

HOW OFTEN										HOW MUCH			
Type of Food	Never or Less than Once Per Month	1 Per Month	2-3 Per Month	1 Per Week	2 Per Week	3-4 Per Week	5-6 Per Week	1 Per Day	2+ Per Day	Medium Serving	Your Serving Size		
													L
Pudding made with milk										½ cup			
Soy nuts										¼ cup			
Cod liver oil										1 Tbsp.			
Shittake mushrooms, dried										4 dried mushrooms			
Common white mushrooms, raw										½ cup			
Mackerel										3 oz. (deck of cards)			
Sardines										1 sardine			
Eel										3 oz. (deck of cards)			
Herring, pickled										1 piece			
Herring, kippered										1 piece			
Catfish										3 oz. (deck of cards)			
Halibut										3 oz.(deck of cards)			
Oysters										6 medium			
Shrimp										3 oz. (deck of cards)			
Pink salmon										3 oz. (deck of cards)			
Tuna, tuna salad, tuna casserole										½ cup			

HOW OFTEN										HOW MUCH			
Type of Food	Never or Less than Once Per Month	1 Per Month	2-3 Per Month	1 Per Week	2 Per Week	3-4 Per Week	5-6 Per Week	1 Per Day	2+ Per Day	Medium Serving	Your Serving Size		
													L
Liver, including chicken livers										4 ounces			
Eggs, egg yolks or egg substitute										1 egg or ¼ cup egg sub or 1 yolk=small 2 eggs=medium			
Dry breakfast cereals										¾ to 1 cup			

Please Note: Below are some beverages you may drink. When marking how often you drink a beverage, please read each column heading carefully. They are different from those above.

HOW OFTEN										HOW MUCH			
Type of Beverage	Never or Less than Once Per Month	1-3 Per Mon	1 Per Week	2-4 Per Week	5-6 Per Week	1 Per Day	2-3 Per Day	4-5 Per Day	6+ Per Day	Medium Serving	Your Serving Size		
													L
Cow's milk: whole, 2%, 1% or skim (include milk used on cereal)										8 oz. glass			
Orange juice fortified with Vitamin D (do not include regular orange juice)										8 oz. glass			

Nonfat dry milk powder (1/4 cup dry)										8 oz. glass			
Milk in coffee or tea										1 tablespoon			
Milkshakes										12 oz. = small 22 oz. = large			
Soy milk fortified with Vitamin D										8 oz. glass			
Rice milk fortified with Vitamin D										8 oz. glass			
Almond milk fortified with Vitamin D										8 oz. glass			

The following questions ask about your use of dietary supplements in the form of foods, beverages or pills

1. Do you regularly consume any type of meal replacement beverages such as *Ensure, Boost, Carnation Instant Breakfast*, or *Slim Fast*?
   _____ Yes _____ No
   If yes, please answer the following questions.

   Which beverage(s) do you consume?_____

   How often do you consume this beverage?_____

   How much do you consume of this beverage?_____

2. Do you regularly consume any type of protein bar, energy bar, or meal replacement bar such as *PowerBar, Clif Bar, Luna Bar, Slim Fast Bar, Ensure Bar, Glucerna Bar*?
   _____ Yes _____ No
   If yes, please answer the following questions.

   Which bar(s) do you consume?_____

How often do you consume this bar?_____

How much of this bar do you consume?_____

3. If you take any type of vitamin, mineral or herbal supplement that contains vitamin D, please show the bottle or package label to the interviewer at this time. The following questions should be answered for each supplement with vitamin D that you take.

   How often do you take this supplement?_____

   What time of day do you usually take this supplement?_____

   Do you consume this supplement with any food or beverage?_____

   Do you consume this supplement with any other supplements?_____

Appendix C: Consent Form

CANCER TREATMENT CENTERS OF AMERICA
Midwestern Regional Medical Center, Zion, IL

CONSENT TO PARTICIPATE IN STUDY

PROTOCOL:

IRB Approval:
IRB Review: 12/06/06

A Prospective Survey Evaluating the Prevalence of Vitamin D Insufficiency Among Breast Cancer Survivors

This disclosure is an effort to make you better informed, so you may give or withhold your consent to participate in clinical research.

Why Is This Survey Being Done?
This survey is being done to measure the blood level of vitamin D among survivors of breast cancer under the care of oncologists at Midwestern Regional Medical Center. Currently the medical community has little information on the levels of vitamin D in breast cancer survivors. Data obtained from this study will help us learn more about how vitamin D may affect breast cancer. In addition, vitamin D is critical in the prevention of osteoporosis and many survivors of breast cancer are at high risk of osteoporosis. Improvements in vitamin D levels may help survivors protect bone health. The investigators of this study will also use this data to prioritize future research regarding vitamin D as it relates to breast cancer.

DESCRIPTION OF PROCEDURES
If you take part in this survey, you will be asked to answer a series of questions regarding your consumption of vitamin D foods, vitamin D supplements and sunlight exposure upon your follow-up visit. A blood sample taken during your routine follow-up blood draw will also be analyzed for the level of vitamin D.

HOW LONG WILL YOU BE IN THE STUDY?
Your participation is scheduled for one visit only. The survey will take approximately 30 minutes to complete. You can stop participating at any time. If you choose not to participate or complete the study, no loss of benefits in your care will occur.

WHAT ARE THE RISKS OF THE STUDY?
There are no physical risks associated with this research other than the risks of routine venipuncture. Venipuncture is the process of drawing blood from a vein with a needle and is typically done by a phlebotomist or nurse. When the needle is inserted, you may feel moderate pain or only a prick or stinging sensation. Afterward, you may bruise easily in this area. Risks associated with venipuncture include excessive bleeding, fainting, hematoma (blood accumulating under the skin), infection (a slight risk anytime the skin is broken), and

multiple punctures to locate veins. This test will require an additional 2mL of blood compared to the routine blood draw.

All data collected in this study will be kept confidential and no patient identifiers will ever be used in reportable analysis.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with cancer in the future. A complimentary 30 minute appointment with a registered dietitian will be offered to participants. Those persons found to be deficient in vitamin D will be counseled on appropriate actions to resolve deficiency as a normal part of counseling by the nutrition department at MRMC.

WHAT ABOUT CONFIDENTIALITY?

AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

Section 1 Introduction

This form is provided to you because you have agreed to participate in a clinical research study. You have received a separate informed consent form describing the study and seeking your consent to take part.

In the course of the study, medical information will be created about each person who takes part. This form will explain how your medical information will be used and who may see it. If you wish to allow your medical information to be collected, used and shared with certain persons involved in the study, you will be asked to sign this form. If you do not sign this form, you will not be able to take part in the study.

Read this information carefully and please ask the study doctor or the study staff if you have any questions.

Section 2 Authorization to Collect, Use and Disclose Your Medical Information

The following sections explain how your medical information will be collected, used and shared with certain other persons involved in the study and describe your rights, including your right to see your medical information.

Section 3 Purpose of This Authorization

You are being asked to permit the collection, use and sharing of your medical information so that the safety and effectiveness of the study drug can be evaluated as described in the informed consent form.

Section 4 What Does Medical Information Mean?

Your medical information is information about your physical or mental health or condition. It includes your previous medical records and information about you created or collected during the

study (for example, the dates or results of various tests or examinations). This information may identify you because it may contain, for example, your name, address, telephone number, photograph, date of birth, social security number, race or ethnic origin or other unique identifiers.

Section 5 Use and Disclosure of Your Medical Information

If you sign this form, you allow the study doctor to collect and use your medical information to carry out this study. You also allow the study doctor to share your medical information with:

- other doctors and health care professionals who are involved in the study;
- the Institutional Review Board (IRB) that watches over the study; and
- government agencies overseeing this study or the study drug, including the Food and Drug Administration (FDA), other Department of Health and Human Services agencies, and government agencies in the United States and other countries.

Section 6 Will Persons Looking At Your Medical Information Be Able to Identify You?

That part of your medical information sent by the study doctor to the other institutions listed above ("study data") usually does not identify you personally (for example, by name, address, or social security number. However, an example of data that may be sent to another institution is your date of birth). Instead, the study doctor uses your initials and a code number on the study data sent to other institutions. However, authorized personnel from the FDA, other Department of Health and Human Services agencies, government agencies in other countries, the Institutional Review Board and other supervising bodies may look at all your medical information at the study doctor's site. The reason these persons may look at your medical information is to make sure the study has been done properly and that study data has been collected correctly, or for other reasons allowed by law.

Section 7 Notice on Redisclosure of Your Medical information and Confidentiality

Federal law provides that the study doctor can only share your medical information with those persons whom you have permitted to see it. However, if you sign this form, those persons may share your medical information with other persons. Federal law does not protect you against this. (The laws of your state may provide additional privacy protection.)

Section 8 Publication of Study Results

Except as explained in this form, your medical information will be kept confidential. The data and results from this study may also be presented at meetings or in publications, but in those presentations people taking part in the study will not be identified by name.

Section 9 Your Right to See and/or Copy Your Medical Information

You have the right to see and copy your medical information related to the study for as long as the study doctor holds this information. However, you may not be able to see some of your records related to the study until after the study has been completed, otherwise it could spoil the study.

Section 10 Withdrawing Your Authorization

You may withdraw your Authorization (permission) regarding your medical information at any time by writing to the study doctor at the following address: 2520 Elisha Avenue, Zion, IL 60099. If you

withdraw this Authorization, the study doctor will no longer use your medical information or share it with others under the Authorization for this study, unless the study doctor needs to do so to protect the study data. However, your study doctor may still use information about you that was shared with him or her before you withdrew your Authorization.

If you withdraw your Authorization, you cannot continue to take part in the study. However, this will involve no penalty or loss of benefits to which you are otherwise entitled.

Section 11 Expiration of Your Authorization

Your Authorization will expire once there is no longer a need to examine the data related to the study.

Section 12 AUTHORIZATION:

I, _____(name of subject)**, HAVE READ AND I UNDERSTAND ALL THE INFORMATION IN THIS AUTHORIZATION FORM. I HAVE BEEN GIVEN THE OPPORTUNITY TO DISCUSS IT AND ASK QUESTIONS. ALL MY QUESTIONS HAVE BEEN ANSWERED TO MY SATISFACTION. I VOLUNTARILY CONSENT TO PARTICIPATE IN THIS PROGRAM. I UNDERSTAND I WILL RECEIVE A COPY OF THIS INFORMATION AND CONSENT FORM.**

I AUTHORIZE THE COLLECTION, USE AND DISCLOSURE OF MY MEDICAL INFORMATION IN ACCORDANCE WITH THIS FORM TO THE SPONSOR (INCLUDING ITS CONTRACTORS AND AGENTS), THE FDA AND OTHER GOVERNMENT AGENCIES, AND THE MIDWESTERN REGIONAL MEDICAL CENTER INSTITUTIONAL REVIEW BOARD FOR RESEARCH AND ETHICS

_____ _____

Signature of Subject **Date of Signature (Month/Day/Year)**

_____

Printed name of Subject

_____ _____

Signature of Person Administering this Authorization **Date of Signature (Month/Day/Year)**

_____

Printed Name of Person Administering this Authorization

WHAT ARE THE COSTS?

There are no costs to you.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this survey is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

You are free to withdraw your consent to participate in this study at any time without prejudice to your subsequent care.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions about your rights as a research participant, contact **Dr. Harlan Verrill ,** Chairman of the Institutional Review Board of Research and Ethics at Midwestern Regional Medical Center (which is a group of people who review the research to protect your rights) at 847-872-6147.

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

Signatures

You have read all of the above, asked questions, received answers concerning areas you did not understand, and willingly give your consent to participate in this program. Upon signing this form you will receive a copy.

Signature of Patient (or legal representative)	Date
Name of Patient's Guardian or next of kin	Date
Signature of Patient's Guardian or next of kin (if participant is unable to sign)	Date
Name of person administering the Survey	Date
Signature of person administering the Survey	Date

Appendix D: MRMC IRB Approval Letter

Midwestern Regional Medical Center
Institutional Review Board
2520 Elisha Avenue
Zion, IL 60099
tel 847-872-6286
fax 847-872-7126
web cancercenter.com

December 13, 2006

Kristen Trukova, RD, LDN, CNSD
Nutrition Department
Midwestern Regional Medical Center
2520 Elisha Avenue
Zion, IL 60099

Re: Protocol CTCA 06-11: A Prospective Survey Evaluating the Prevalence of Vitamin D Insufficiency Among Breast Cancer Survivors.

Dear Kristen:

On December 6, 2006, the Institutional Review Board of Midwestern Regional Medical Center held its 4th Quarter meeting. The above mentioned research project was reviewed during the meeting and approved contingent on the following revisions:

- Pages of the Informed Consent Document are numbered 1 of 7, should read: 1 of 3.
- Page 2 and 3 the header of the Informed Consent, list CTCA 06-09, should read CTCA 06-11.
- Page 3 of the Informed Consent, change IRB contact phone number to (847) 872-6286.
- Once these revisions have been incorporated, please revise the Version and Date on the Informed Consent Document.
- Prior to start of the study submission of the Grant Application is required for IRB review.

As principal investigator of this research study, you are responsible for reporting any adverse events, serious adverse events, revisions or amendments to the Institutional Review Board for Research of this institution. You are also responsible for submitting a progress report on the status of the research project and on any patients enrolled. This may be done by fully completing the Continuing Review Form provided to you by the IRB Coordinator, prior to the next IRB meeting.

If you have any questions or concerns regarding the above, please feel free to contact Gloria Flesher or myself at (847) 872-6286.

Sincerely,

Harland L. Verrill, Ph.D.
IRB Chairman