Vitamin D and breast cancer

Tara Bergren, MS, RD
Roschelle Heuberger, PhD, RD
Practical Guidelines for Clinicians Vitamin D and Breast Cancer Prevention

Vitamin D deficiency has been hypothetically linked to a number of diseases (Gissel, Rejnmark, Mosekilde, & Vestergaard, 2008), including cancer (Grant, 2002, 2003), and recent research has shown that adequate amounts of vitamin D may help prevent breast cancer (Crew et al., 2009). One theory regarding the protective properties of vitamin D centers on the biologically active form of the vitamin, 1,25 dihydroxyvitamin D. Vitamin D is converted to this active form mostly in the kidneys, but also in target tissues, such as breast tissue (Tangpricha et al., 2001; Zehnder et al., 2001). In addition, data from clinical studies suggest that the biologically active form of vitamin D prevents rapid cell growth in breast tissue that could lead to cancer (Christakos, Ravil-Pandya, Wernyj, & Yang, 1996; Danielsson et al., 1997; Love-Schimenti, Gibson, Ratnam, & Bikle, 1996). When a woman is deficient in vitamin D these effects are limited, which may increase her risk of cancer. The focus of this article is to provide practical guidelines for clinicians regarding vitamin D deficiency and breast cancer risk.

Vitamin D: The Basics

Vitamin D comprises a group of fat-soluble compounds found naturally only in a few foods, including fish-liver oils, fatty fish, mushrooms, egg yolks and liver. The two major physiologically relevant forms of vitamin D are D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is photosynthesized in the skin of vertebrates by ultraviolet B (UVB) radiation on a precursor (7-dehydrocholesterol); vitamin D2 is produced by UV irradiation of ergosterol, which occurs in molds, yeast and higher-order plants. Vitamin D from either source circulates in the blood for 1 to 2 days, and is then stored in fat cells or metabolized in the liver. In the liver, it is converted to 25-hydroxyvitamin D, which must be further activated in the kidneys (and to a small extent in the breast and other tissues) to 1,25-dihydroxyvitamin D. This is is the form thought to be responsible for most, if not all, of the biologic functions of vitamin D.

Active vitamin D functions as a hormone, and its main function is to maintain serum calcium and phosphorus concentrations.
within the normal range by enhancing the efficiency of the small intestine to absorb these minerals from the diet. While it’s too early to draw any definitive conclusions, the vitamin that was once best known for building strong bones also appears to be associated with a number of cancers, as well as cognitive changes, autoimmune diseases and the development of heart disease (Nagpal, Na, & Rathnachalam, 2005).

What the Data Tell Us About Cancer
Animal research provided initial evidence for the inverse association between vitamin D and breast cancer. Removal of the vitamin D receptor caused an abnormal increase in breast cells in studies conducted on animals (Zinser, Suckow, & Welsh, 2005; Zinser & Welsh, 2004). An animal study conducted in 2008 examined whether supplementing a Western diet with increased vitamin D and calcium would have an effect on the mammary glands of mice (Kurihara, Fan, Thaler, Yang, & Lipkin, 2008). The mice fed the standard Western diet showed an accumulation of cells in ducts of the mammary gland and increased duct cell growth (see Box 1). Additional animal studies provided similar findings (Lipkin & Newmark, 1999). Over the past decade, most of the research on vitamin D and breast cancer has been done using case-control and cohort studies. A recent large, population-based case-control investigation by Crew et al. (2009) examined the association between levels of 25-hydroxyvitamin D and breast cancer incidence. The study utilized in-person interviews and blood samples of 25-hydroxyvitamin D from more than 1,000 breast cancer cases and controls. Women with 25-hydroxyvitamin D levels above 40 ng/mL were less likely to develop breast cancer than women with a vitamin D deficiency, defined as 25-hydroxyvitamin D levels <20 ng/mL—suggesting that optimal levels of 25-hydroxyvitamin D for breast cancer prevention may be ≥40 ng/mL (Crew et al.). Other studies have also provided evidence of an inverse relationship between active vitamin D levels and breast cancer risk (John, Schwartz, Dreon, & Koo, 1999; McCullough et al., 2005; Nunez, Carbajal, Belmonte, Moreiras, & Varela, 1996; Shin et al., 2002).

Lin et al. (2007) used a prospective study to evaluate the
association between calcium and vitamin D relative to breast cancer occurrence in pre- and postmenopausal women. The women were at least 45 years old and did not have cancer at the beginning of the study. Food frequency questionnaires were used to assess dietary intake. The premenopausal women who consumed more calcium and vitamin D were found to have a lower risk of premenopausal breast cancer. This inverse relationship was not seen in the postmenopausal women. Another study found that women were less likely to die of breast cancer if they had 25-hydroxyvitamin D levels ≥25 ng/mL (Garland, Gorham, Baggerly, & Garland, 2008).

Current Vitamin D Recommendations

Recommendations for vitamin D intake are available as Dietary Reference Intakes (DRI), published by the Institute of Medicine of the National Academies (Institute of Medicine [IOM], 1997). From birth to age 50, the adequate intake (AI) is 200 international units (IU) with no increased need during pregnancy or lactation. The AI increases to 400 IU for adults over age 50 and to 600 IU for those over 70 years of age. However, recent research suggests that levels of vitamin D above 400 IU may aid in prevention of breast cancer. A meta-analysis by Gissel et al. (2008) reviewed studies that contained original data on the association between vitamin D intake and breast cancer risk. The researchers concluded that although there appears to be a trend toward a lower incidence of breast cancer with increased intake of vitamin D, further research is needed to confirm these findings.

370 © 2010, AWHONN http://nwh.awhonn.org
Tara Bergren, MS, RD, is a clinical dietitian and diabetes educator at Mercy Hospital in Cadillac, MI. Roschelle Heuberger, PhD, RD, is a professor at Central Michigan University in Mount Pleasant, MI. The authors report no conflicts of interest or relevant financial relationships. There is no discussion of off-label drug or device use in this article.
Address correspondence to: taraj711@hotmail.com.
DOI: 10.1111/j.1751-486X.2010.01575.x
• Recent research suggests an inverse association between vitamin D intake and breast cancer risk.
• Current recommendations for vitamin D intake are likely too low with regard to chemoprevention.
• Strategies for increasing vitamin D intake include the consumption of fatty fish and fortified foods, supplementation and sensible exposure to sunlight.

Bottom Line

October November 2010 Nursing for Women’s Health 371

of vitamin D ≥400 IU/day, many of the studies included in the meta-analysis were of poor quality.

To date, the exact amount of vitamin D needed for chemoprevention is still unknown. However, some experts believe that at least 1,000 IU/day is needed by most adults (Holick, 2008). Currently, the tolerable upper intake levels (ULs) are 1,000 IU from birth to 12 months and 2,000 IU for all others. The IOM defines the UL as “the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects” (IOM, 1997).

Who’s at risk?

Monitoring vitamin D should become the standard of care among primary care practitioners. Measurement of 25-hydroxyvitamin D is the best indicator of one’s overall vitamin D status (Moyad, 2009) as it reflects vitamin D levels in the body from all sources, including diet, supplements, and sunlight (Moyad; Rajakumar, Greenspan, Thomas, & Holick, 2007). The test should ideally be ordered in the winter when vitamin D levels are typically lower due to limited sun exposure (Moyad). There is currently disagreement about the lower limit of optimal vitamin D levels, but most experts believe that levels lower than 20 ng/mL are undesirable and that the lower limit is likely <30 ng/mL (Weng, Shults, Leonard, Stallings, & Zemel, 2007). Note that the IOM has defined vitamin D deficiency as a concentration less than 12 ng/mL (IOM, 1997).

Those at risk for vitamin D deficiency include older adults, those with limited sun exposure, individuals with dark skin, people with fat absorption disorders and individuals with a body mass index (BMI) ≥30 (Vilarrasa et al., 2007). In women, the risk for breast cancer should also be taken into account. The Breast Cancer Risk Assessment Tool may also be useful in determining current risk for breast cancer. The tool was developed at the National Cancer Institute as part of the National Surgical Adjuvant Breast and Bowel Project and is useful in determining
breast cancer risk (see Get the Facts).

Getting Enough Vitamin D

Food Sources

Helping patients achieve optimal vitamin D status requires that they understand the various sources of vitamin D, starting with food sources (see Box 2). Very few foods in nature contain vitamin D. The flesh of fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources, with small amounts of vitamin D found in beef liver and egg yolks.

Fortified foods provide most of the vitamin D in the American diet. For example, almost all of the U.S. milk supply is fortified with 100 IU/cup of vitamin D (50 percent of the AI level for ages 14-50 years). Other dairy products made from milk, such as cheese and ice cream, are generally not fortified.

Ready-to-eat breakfast cereals may contain added vitamin D, as do some brands of orange juice, yogurt, and margarine. In the United States, foods allowed to be fortified with vitamin D include cereal flours and related products, milk and products made from milk, and calcium-fortified fruit juices and drinks.

Maximum levels of added vitamin D are specified by law.

Sunlight

Sunlight is another source of vitamin D. Known for years as the "sunshine vitamin," vitamin D is partially activated when UVB

BOX 1

Measurements of Epithelial Cells in Ducts

Western Diet With Increased Calcium and Vitamin D in Dried Elemental Calcium Carbonate

Diet group Western Diet—Mean Yogurt Powder—Mean and Vitamin D3—Mean

Small 13.6 10.6 11.1

Medium 28.8 24.6 25.0

Large 95.4 80.0 78.4

Average 33.2 27.4 27.8

Source: Kurihara et al. (2008).

Monitoring vitamin D should become the standard of care among primary care practitioners
radiation from sunlight hits cholesterol compounds in the skin, converting them to vitamin D precursors. These precursors travel to the liver and kidneys, where they are converted to the active form of vitamin D. The total amount of vitamin D synthesized depends not only on sun exposure, but also on the season (winter is less desirable than summer), skin color (darker tones absorb less UVB) and residence (the farther from the equator, the less UVB is available). In fact, North Americans who live north of 42 degrees latitude—which would include residents of Boston, Milwaukee and Seattle—don’t get enough UVB from roughly mid-October to mid-March, regardless of how much time they spend outdoors (Looker, Dawson-Hughes, Calvo, Gunter, & Sayhoun, 2002).

According to Moyad (2009), a 21-year-old who spends 15 to 20 minutes exposed to summer UVB rays will produce 10,000 IU of vitamin D; continued exposure beyond 20 minutes will not produce additional vitamin D. This assumes that the sun exposure occurs without sunscreen, as even low levels of sun protection factor in sunscreen may block the synthesis of vitamin D. Other factors that affect the skin’s ability to produce vitamin D include age, skin color, latitude, time of day, season, and cloud/pollution cover (Litchford, 2009).

Past studies have shown that some sun exposure may be a beneficial approach to preventing breast cancer. An inverse relationship has been found between sunlight exposure and death from breast cancer (Garland, Garland, Gorham, & Young, 1990). Another study showed that breast cancer incidence decreased as sun exposure increased (Gorham, Garland, & Garland, 1990). Recent research shows similar findings. Data from the Women’s Health Initiative Observational Study (WHIOS) showed that women who reported limited sun exposure were 20 percent more likely to have breast cancer compared with those who spent much time outside each day (Millen et al., 2009).

Another recent study looking at large groups of people found an inverse relationship between high levels of UVB rays and age-standardized breast cancer rates in 107 countries.
(Mohr, Garland, Gorham, Grant, & Garland, 2008). These research conclusions are supported by others as well, who agree that the minimum requirement to maintain a circulating level of 25-hydroxyvitamin D of more than 20 ng/mL is 1,000 IU/day, a level that is difficult to achieve from diet alone (Holick, 2008). But even this level is well below the >40 ng/mL thought to be necessary for chemoprevention. While 15 to 20 minutes

**BOX 2**

**Selected Food Sources of Vitamin D**

*Nursing for Women’s Health Volume 14*

<table>
<thead>
<tr>
<th>Food</th>
<th>IU per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 tablespoon</td>
<td>1,360</td>
</tr>
<tr>
<td>Salmon (sockeye), cooked, 3oz</td>
<td>794</td>
</tr>
<tr>
<td>Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3oz (not yet commonly available)</td>
<td>400</td>
</tr>
<tr>
<td>Mackerel, cooked, 3oz</td>
<td>388</td>
</tr>
<tr>
<td>Tuna fish, canned in water, 154 drained, 3oz</td>
<td>154</td>
</tr>
<tr>
<td>Milk, nonfat, reduced fat, and 115 to 124 whole, vitamin D-fortified, 1 cup</td>
<td>115 to 124</td>
</tr>
<tr>
<td>Orange juice fortified with 100 vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)</td>
<td>100</td>
</tr>
<tr>
<td>Yogurt, fortified with 20% of 80 the DV for vitamin D, 6oz (more heavily fortified yogurts provide more of the DV)</td>
<td>80</td>
</tr>
<tr>
<td>Margarine, fortified, 1 tablespoon</td>
<td>60</td>
</tr>
<tr>
<td>Sardines, canned in oil, drained, 2 sardines</td>
<td>46</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3.5oz</td>
<td>46</td>
</tr>
<tr>
<td>Ready-to-eat cereal, fortified 40 with 10% of the DV for vitamin D, 0.75 to 1 cup (more heavily fortified)</td>
<td>40</td>
</tr>
</tbody>
</table>
fortified cereals might provide more of the DV)
Egg, 1 whole (vitamin D is found 25 in yolk)
IU = International Units DV = Daily Value
October November 2010 Nursing for Women’s Health 373
Patients should be advised that a circulating level of 40 ng/mL 25-hydroxyvitamin D may be required to prevent diseases such as breast cancer. You should explain the importance of sun exposure to the patient, including information about the fact that 15 to 20 minutes of sun exposure (without sunscreen) is desirable. This exposure should be in direct sunlight and include exposure to the face and arms. It is also important to explain that vitamin D production should not extend beyond 20 minutes and that lengthy sun exposure may increase the risk of skin cancer.
If sun exposure is not possible, vitamin D intake from diet and supplementation will be required. It might be necessary to prescribe levels as high as 50,000 IU once per week for 6 to 8 weeks if a mild to moderate deficiency (8-12 ng/mL) is observed. The prescription may be increased to twice per week for a severe deficiency (<8 ng/mL) (Litchford, 2009). When prescription strength vitamin D is taken for any period of time, the patient should be monitored for signs of toxicity (Joshi, 2009) (see Box 3). Signs and symptoms of vitamin D toxicity are listed in Box 4. Follow-up blood tests should be obtained to monitor vitamin D status and further recommendations made accordingly. Once an individual reaches the desired level, a maintenance dose of 800 to 1,400 IU may be given (Shils, et al., 2005). This can come from a multivitamin with 400 IU plus 400 to 1,000 IU from an additional vitamin D supplement.
Conclusion
Much of the research currently supports vitamin D deficiency as a risk factor for breast cancer. However, more tightly controlled randomized clinical trials are needed to substantiate this association. Areas for further research include investigation into
the amount of vitamin D needed to have a protective benefit against breast cancer, differential protective effects by source of vitamin D and alterations in risk stemming from chemical isoforms of vitamin D. As this is a public health concern, the of daily sun exposure may be of benefit, it is important not to forget other issues such as the risk of skin cancer. It’s important to balance the risks versus the benefits and consider all factors.

Supplementation
When considering supplementation, the amount of vitamin D obtained from other sources such as diet and sun exposure should be taken into account. While both vitamin D2 and D3 are available as over-the-counter supplements, D3 is the preferred form for supplementation as it is better able to bind the receptors in human tissue and is more effective at elevating and maintaining blood levels (Moyad, 2009). Of note is that vitamin D2 is the only form available by prescription in the United States (Holick, 2007).

Patient Recommendations
The IOM is currently conducting a review of the DRIs for vitamin D and calcium. Until then, clinicians should use their judgment about prescribing supplements based on the patient’s medical history, current 25-hydroxyvitamin D level, and current disease state (i.e., people with conditions that interfere with fat absorption may have higher needs). Risk for cancer and the tolerable UL for vitamin D should also be considered when making any recommendations. If a patient is tested and found to be vitamin D deficient, then a health care practitioner might prescribe a dose well above the UL, monitor the patient for signs of toxicity, check blood levels and adjust the dose as needed (see Box 3).

Fortified foods provide most of the vitamin D in the American diet.

BOX 3
Dietary Reference Intake for Vitamin D
Age Group (Years) Adequate Intake
0 to 1 200 IU or 5 mcg
2 to 50 200 IU or 5 mcg
51 to 70 400 IU or 10 mcg
> 70 600 IU or 15 mcg
1 mcg = 40 IU.
Source: Institute of Medicine of the National Academies (2010).
374 Nursing for Women’s Health Volume 14 Issue 5


American Public Health Association, World Health Organization, Public Health Foundation and several other public health organizations will likely become involved in promoting research in this area.

Lichtenstein et al. (2000) have studied the association between genetics and cancer and suggest that diet plays a stronger role than genetics. They cite statistics showing that 33 percent to 66 percent of cancer cases could be prevented by implementing dietary changes highlighting the importance of taking a proactive approach to cancer prevention. Clearly the reactive nature of Western medicine clearly has not been successful, as the United States currently has an overweight/obesity rate of 67 percent (Centers for Disease Control and Prevention, 2009).
Sufficient vitamin D and other dietary changes may be very influential in preventing cancer. It's our job and responsibility to help educate and aid our patients in making healthful changes before they develop disease, whenever possible. NWH References


http://nwhTalk.awhonn.org

BOX 4

Signs and Symptoms of Vitamin D Toxicity

Source: Joshi (2009).

Signs

Increased thirst

Increased urination

High blood pressure

Excess blood calcium

Excess calcium in the urine

Symptoms

Dehydration

Vomiting

Poor appetite

Constipation

Fatigue

October November 2010 Nursing for Women’s Health 375


Get the Facts
American Cancer Society
http://www.cancer.org/docroot/NWS/content/NWS_1_1x_Can_Vitamin_D_Prevent_Cancer.asp
American Dietetic Association
http://www.eatright.org/
Institute of Medicine
http://www.iom.edu/Activities/Nutrition/DRIVitDCalcium.aspx

National Cancer Institute
http://www.cancer.gov/bcrisktool

Office of Dietary Supplements