Vitamin D in the Breast Clinic

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Buffalo, NY
Disclosures

- No relevant disclosures
Roswell Park Cancer Institute

- 1st translational center in the US (founded in 1898)
- 3100 employees
- 300 faculty
- 7400 new cancer patients each year
- 1st NCI designated center
- Only NCI center in Upstate NY
Vitamin D in the Breast Clinic?

- Bone Health
- Vitamin D levels in Breast Cancer Patients
- Breast Cancer Recurrence and Vitamin D
- Repletion strategies
Causes of Breast Cancer Treatment-Induced Bone Loss

GnRH agonists
Chemotherapy-induced ovarian failure
Oophorectomy
Aromatase inhibitors
Normal aging

Elevated bone turnover

Bone Loss
Diminished Bone Quality


Gralow, ASCO 2008
A High Incidence of Vertebral Fracture in Women with Breast Cancer

- Premenopausal women with BC history have higher-than-average rates of bone loss and fracture as they age.
- Lifetime risk of vertebral fractures nearly 5 times that of the general population.
- 50% of the population in this study were taking clodronate, a bisphosphonate, shown to decrease fracture rates.

- Post menopausal survivors (5298) vs. patients without BC history (80,848).
- Self-reporting, hip fractures researched.
- Breast cancer survivors reported a 15% higher fracture risk than women without a history.
- Of interest: post menopausal BC occurs more often with increased BMD.
Hazard ratios (95% confidence intervals) of fractures among breast cancer survivors compared with the reference group

Recognizes that women with breast cancer are a high-risk group for the development of osteoporosis.
- Age
- Treatment

Oncology specialists asked to take responsibility to ensure routine and regular assessment of the osteoporosis risk in these patients.

High risk patients
- Post-menopausal women (any age) receiving AIs.
- Premenopausal women with therapy associated premature menopause
- Recommends yearly BMD assessments in high risk patients
Treating Bone Density Loss in Breast Cancer Patients
Hillner BE et al, J Clin Oncol 21:4042-4057, 2004

ASCO Guidelines for Managing Bone Density in Breast Cancer

<table>
<thead>
<tr>
<th>BMD T-score ≥ -1</th>
<th>BMD T-score between -1 and -2.5</th>
<th>BMD T-score ≤ -2.5</th>
</tr>
</thead>
</table>
| Provide reassurance | Provide lifestyle advice Begin calcium and vitamin D | Consider drug therapy on an individualized basis Begin drug therapy
  - Alendronate
  - Risedronate
  - (Ibandronate)
  - Zoledronic acid
  - Raloxifene* |

*Not recommended after TAM or with AIs.
UpToDate, 2009
Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D2 and D3

<table>
<thead>
<tr>
<th>Source</th>
<th>Vitamin D Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natural sources</strong></td>
<td></td>
</tr>
<tr>
<td>Salmon</td>
<td>About 600–1000 IU of vitamin D3, or D2</td>
</tr>
<tr>
<td>Fresh, wild (3.5 oz)</td>
<td></td>
</tr>
<tr>
<td>Fresh, farmed (3.5 oz)</td>
<td></td>
</tr>
<tr>
<td>Canned (3.5 oz)</td>
<td>About 300–600 IU of vitamin D3</td>
</tr>
<tr>
<td>Sardines, canned (3.5 oz)</td>
<td>About 300 IU of vitamin D3</td>
</tr>
<tr>
<td>Mackerel, canned (3.5 oz)</td>
<td>About 230 IU of vitamin D3</td>
</tr>
<tr>
<td>Tuna, canned (3.6 oz)</td>
<td>About 230 IU of vitamin D3</td>
</tr>
<tr>
<td>Cod liver oil (1 tsp)</td>
<td>About 400–1000 IU of vitamin D3</td>
</tr>
<tr>
<td>Shiitake mushrooms</td>
<td></td>
</tr>
<tr>
<td>Fresh (3.5 oz)</td>
<td>About 100 IU of vitamin D3</td>
</tr>
<tr>
<td>Sun-dried (3.5 oz)</td>
<td>About 1600 IU of vitamin D3</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>About 20 IU of vitamin D3 or D2</td>
</tr>
<tr>
<td><strong>Fortified foods</strong></td>
<td></td>
</tr>
<tr>
<td>Fortified milk</td>
<td>About 100 IU/8 oz, usually vitamin D3</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>About 100 IU/8 oz vitamin D3</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>About 100 IU/8 oz vitamin D3</td>
</tr>
<tr>
<td>Fortified yogurts</td>
<td>About 100 IU/8 oz, usually vitamin D3</td>
</tr>
<tr>
<td>Fortified butter</td>
<td>About 50 IU/3.5 oz, usually vitamin D3</td>
</tr>
<tr>
<td>Fortified margarine</td>
<td>About 430 IU/3.5 oz, usually vitamin D3</td>
</tr>
<tr>
<td>Fortified cheeses</td>
<td>About 100 IU/3 oz, usually vitamin D3</td>
</tr>
<tr>
<td>Fortified breakfast cereals</td>
<td>About 100 IU/serving, usually vitamin D3</td>
</tr>
<tr>
<td><strong>Supplements</strong></td>
<td></td>
</tr>
<tr>
<td>Prescription vitamin D3 (ergocalciferol)</td>
<td>50,000 IU/capsule</td>
</tr>
<tr>
<td>Drisdol (vitamin D3) liquid supplements</td>
<td>8000 IU/ml</td>
</tr>
<tr>
<td><strong>Over the counter</strong></td>
<td></td>
</tr>
<tr>
<td>Multivitamin</td>
<td>400 IU vitamin D3, D2, or D2‡</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>400, 800, 1000, and 2000 IU</td>
</tr>
</tbody>
</table>

IU denotes international unit, which equals 25 ng. To convert values from ounces to grams, multiply by 28.3. To convert values from ounces to milliliters, multiply by 29.6.

† About 0.5 minimal erythemal dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure (depending on the time of day, season, latitude, and skin sensitivity of the arms and legs to direct sunlight.

‡ When the term used on the product label is vitamin D or calciferol, the product usually contains vitamin D3; cholecalciferol or vitamin D2 indicates that the product contains vitamin D2.
Vitamin D and bone health

Calcium and vitamin D are necessary for normal skeletal homeostasis.

Postmenopausal women with low serum concentrations of 25OHD have lower bone density compared to those with normal or high levels.¹

In the NHANES III study, higher 25OHD levels were associated with greater BMD throughout the reference range, with a plateau at 36-40 ng/mL (90-100 nmol/L).²

### Risk of hip fracture

**Vitamin D vs. placebo**

<table>
<thead>
<tr>
<th>Source</th>
<th>Favours treatment</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lips et al, 1996 (27)</td>
<td></td>
<td>31.1</td>
<td>1.21 (0.83, 1.75)</td>
</tr>
<tr>
<td>Meyer et al, 2002 (28)</td>
<td></td>
<td>30.1</td>
<td>1.08 (0.73, 1.57)</td>
</tr>
<tr>
<td>Trivedi et al, 2003 (26)</td>
<td></td>
<td>13.0</td>
<td>0.87 (0.49, 1.66)</td>
</tr>
<tr>
<td>RECORD Trial Group, 2005 (10)</td>
<td></td>
<td>25.8</td>
<td>1.14 (0.75, 1.72)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td>100.0</td>
<td>1.10 (0.89, 1.36)</td>
</tr>
</tbody>
</table>

**P = 0.38**

CI = confidence interval

**RECORD** = Randomised Evaluation of Calcium Or vitamin D

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A

Risk of hip fracture
Vitamin D plus calcium vs. placebo

<table>
<thead>
<tr>
<th>Source</th>
<th>Favours treatment</th>
<th>Favours placebo</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy et al, 1994 (17)</td>
<td></td>
<td></td>
<td>38.9</td>
<td>0.74 (0.60, 0.91)</td>
</tr>
<tr>
<td>Dawson-Hughes et al, 1997 (19)</td>
<td></td>
<td></td>
<td>0.2</td>
<td>0.36 (0.02, 8.78)</td>
</tr>
<tr>
<td>Chapuy et al, 2002 (18)</td>
<td></td>
<td></td>
<td>6.5</td>
<td>0.62 (0.36, 1.07)</td>
</tr>
<tr>
<td>Porthouse et al, 2005 (14)</td>
<td></td>
<td></td>
<td>2.8</td>
<td>0.71 (0.31, 1.64)</td>
</tr>
<tr>
<td>RECORD Trial Group, 2005 (10)</td>
<td></td>
<td></td>
<td>10.9</td>
<td>1.14 (0.76, 1.73)</td>
</tr>
<tr>
<td>WHI Trial Group, 2006 (15)</td>
<td></td>
<td></td>
<td>40.7</td>
<td>0.88 (0.72, 1.07)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td></td>
<td>100.0</td>
<td>0.82 (0.71, 0.94)</td>
</tr>
</tbody>
</table>

Relative risk (95% CI) of hip fracture

$P = 0.0005$

CI = confidence interval
RECORD = Randomised Evaluation of Calcium Or vitamin D
WHI = Women’s Health Institute

B

Risk of hip fracture
Vitamin D plus calcium vs. placebo

<table>
<thead>
<tr>
<th>Source</th>
<th>Favours treatment</th>
<th>Favours placebo</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy et al, 1994 (17)</td>
<td></td>
<td></td>
<td>58.9</td>
<td>0.74 (0.60, 0.91)</td>
</tr>
<tr>
<td>Dawson-Hughes et al, 1997 (19)</td>
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<td>0.4</td>
<td>0.36 (0.02, 8.78)</td>
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<tr>
<td>Chapuy et al, 2002 (18)</td>
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<td>13.3</td>
<td>0.62 (0.36, 1.07)</td>
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<tr>
<td>Porthouse et al, 2005 (14)</td>
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<td>5.9</td>
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<td>21.5</td>
<td>1.14 (0.76, 1.73)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td></td>
<td>100.0</td>
<td>0.79 (0.64, 0.97)</td>
</tr>
</tbody>
</table>

Relative risk (95% CI) of hip fracture

$P = 0.025$

CI = confidence interval
RECORD = Randomised Evaluation of Calcium Or vitamin D
Vit D and bone health

- Data on hip fracture mixed, although the combination of Calcium and Vit D appears to reduce fracture risk and increase BMD.
- Post menopausal women 1200-1500 mg of calcium daily, premenopausal women 1200 mg.
- Calcium citrate recommended in patients on PPI, achlorhydria, otherwise calcium carbonate with meals.
- Upper limit of calcium should not exceed 2000 mg/day.
Vitamin D 25, OH (25-hydroxyvitamin D)

- Main circulating form of vitamin D
- Inactivated, has to be activated in kidneys to the biologically active 1,25 Vitamin D
- Vitamin D 25, OH levels in blood reflect the Vitamin D exposure over the past 3 months.
Self-reported individual vitamin D intake (diet plus supplementation) and serum 25-hydroxyvitamin D levels at baseline

Dosing of Vitamin D

- Probably should be based on blood levels of Vitamin D 25, OH
  - Many factors affect Vit D 25, OH availability
    - Age, pigmentation
    - % body fat

- Target blood level = whole answer?
  - Hormone & growth factor influences on VDR
  - VDR polymorphisms

Fabian, ASCO 2009
Vit D sufficiency defined on basis of 25, OH levels for Bone Health

- At a 25, OH level of 30-32 ng/mL (75-80 nmol/L) PTH is close to undetectable indicating optimal circulating calcium.
- > 30 ng/mL considered sufficient
- 20 to < 30 ng/mL considered insufficient
- < 20 ng/mL considered deficient
- Optimal levels 40-60 ng/mL
- > 150 ng/mL can be associated with hypercalcemia and toxicity

Fabian, ASCO 2009
Vitamin D and Breast Cancer

- Vitamin D is an essential nutrient; the vitamin D receptor is active in the transcription of genes responsible for cell cycle control, apoptosis, and metastasis.
- Vitamin D deficiency is common in breast cancer patients.
- Treatment with standard doses of vitamin D can lead to variable levels; serum monitoring is preferred.

## Vit D levels in Breast Cancer Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Group Description</th>
<th>N</th>
<th>Deficient (&lt; 20 ng/mL)</th>
<th>Insufficient (20-29 ng/mL)</th>
<th>Sufficient (&gt; 30 ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodwin J Clin Onc 2009</td>
<td>Diagnosis</td>
<td>512</td>
<td>37.5%</td>
<td>38.5%</td>
<td>24%</td>
</tr>
<tr>
<td>Crew J Clin Onc 2009</td>
<td>Adjuvant chemotx and 400 IU</td>
<td>103</td>
<td>74%</td>
<td>20%</td>
<td>6%</td>
</tr>
<tr>
<td>Waltman Can Nurs 2009</td>
<td>On AIs</td>
<td>29</td>
<td>6.9%</td>
<td>79.3%</td>
<td>13.8%</td>
</tr>
<tr>
<td>RPCI unpub</td>
<td>Diagnosis</td>
<td>509</td>
<td>39.7%</td>
<td>41.4%</td>
<td>18.9%</td>
</tr>
</tbody>
</table>

*Goodwin ASCO 2009 adapted*
103 patients from the northeast US with Stage I-III breast cancer treated with adjuvant chemotx and 1 year ZA.

- All prescribed Vit D$_3$ 400 IU and 1000 mg calcium carbonate daily.
- Baseline, 6 and 12 month BMD assessments and 25OHD levels.
High Prevalence of Vitamin D Deficiency Despite Supplementation in Premenopausal Women with Breast Cancer Undergoing Adjuvant Chemotherapy
Crew et al, J Clin Oncol 27:2151, 2009

- Median 25 OHD levels at baseline, 6, 12 months: 17 ng/mL, 18 ng/mL, 19 ng/mL.
- 74% patients were Vit D deficient (<20 ng/mL) at baseline, 65% at 6, 60% at 12m.
- Only 6% patients had sufficient levels (>30 ng/mL) at baseline, only 11% had sufficient levels after 1 year of Vit D supplementation.
Fig 2. Prevalence of vitamin D deficiency (defined as serum 25-hydroxyvitamin D < 20 ng/mL) over time with vitamin D supplementation for 1 year, stratified by ethnicity

Prognostic Effects of 25-Hydroxyvitamin D Levels in Early Breast Cancer
Goodwin et al, J Clin Oncol 27:3757-3763

- Prospective study of 512 women with early stage breast cancer enrolled between 1989-1996.
- Vitamin D levels measured in stored blood from the time of diagnosis
- Clinical, pathological, and dietary data collected and examined for prognostic effects of Vit D.
Vit D levels deficient (37.5%) insufficient (38.5%) and sufficient (24%)
No patients in toxic range
Vitamin D levels lower in women with higher BMI
No change with physical activity
Higher in peri-post menopausal women than in premenopausal women.
Vit D supplement associated with inc level
Vitamin D 25,OH levels significantly lower in women with high grade tumors

Vit D 25,OH levels significantly lower in women who received chemotherapy (in part reflecting younger women).
Fig 2. (A) Distant disease-free and (B) overall survival in women with sufficient, insufficient, and deficient vitamin D levels.

Distant Disease Free Survival

<table>
<thead>
<tr>
<th></th>
<th>deficient</th>
<th>insufficient</th>
<th>sufficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>1.94 (1.16-3.25)</td>
<td>1.37 (0.80-2.33)</td>
<td>1.0</td>
</tr>
<tr>
<td>5 year</td>
<td>82%</td>
<td>85%</td>
<td>88%</td>
</tr>
<tr>
<td>10 year</td>
<td>69%</td>
<td>79%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Goodwin, ASCO 2009
Fig 3. The log hazard for vitamin D as estimated using a smoothing spline (solid line), with point-wise 95% CIs (dotted lines)

Prognostic Effects of 25-Hydroxyvitamin D Levels in Early Breast Cancer
Goodwin et al, J Clin Oncol 27:3757-3763

- No evidence of a plateau above which further increases in Vitamin D would not be beneficial.
- For overall survival, suggestion that maximum benefit occurred with Vitamin D levels 80-110 nmol/L (32-45 ng/mL), not statistically significant.
Inconsistent study results on relationship between Vitamin D, Vitamin D receptor and risk of breast cancer

Possible that effects are on breast cancer progression, rather than etiology?
In rodent models, treatment with vitamin D inhibits proliferation of breast cancer cells, induces apoptosis, and prevents carcinogenesis.

Vdr knock-out mice more likely to develop Er/Pr negative tumors than wild type littermates.

Inhibits expression of myoepithelial markers (P-cadherin, N-cadherin); reverts their myoepithelial trans-differentiation associated with tumor invasion.
Enrollment of newly diagnosed patients, prior to surgery

Banked serum, plasma, RBCs, DNA

Epidemiologic questionnaire completed

Linkage with clinical data, tumor tissue

Recruiting visitors as non-cancer controls
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All cases (n=509)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>347 (76.9)</td>
</tr>
<tr>
<td>Negative</td>
<td>104 (23.1)</td>
</tr>
<tr>
<td>PR status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>291 (64.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>160 (35.5)</td>
</tr>
<tr>
<td>Her2 status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>74 (17.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>354 (82.7)</td>
</tr>
<tr>
<td>Molecular subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>Luminal (ER+ and/or PR+)</td>
<td>352 (79.3)</td>
</tr>
<tr>
<td>Her2 overexpressing (ER-, PR- and</td>
<td></td>
</tr>
<tr>
<td>Her2+)</td>
<td>29 (6.5)</td>
</tr>
<tr>
<td>Basal-like (ER-, PR-, and Her2-)</td>
<td>63 (14.2)</td>
</tr>
</tbody>
</table>

Breast Cancer Patients from RPCI DataBank and BioRepository (DBBR)
Vitamin D levels according to clinical characteristics by menopausal status
The data may be confounded, but patients don’t need to be. . .

- Individuals with higher Vit D 25OH levels tend to have:
  - Good health
  - Healthy BMI
  - Increased activity levels

These “confounders” are important for breast cancer survivors to address.
Current Recommendations in US

- 200, 400, 600 IU/day dietary allowance vitamin D₃ in individuals under 50, 50-70, older than 70.
- Evidence that these doses associated with decreased mortality and improved bone health.
- Evidence that this is inadequate dosing in breast cancer patients.
Vitamin D Repletion

- Oral daily intake of 1000 IU vitamin D₃ can increase serum 25,OH-D levels by about 10 ng/mL¹
  - Varies with sunlight, BMI, dietary intake.
- Circulating levels of 32 ng/mL are associated with normal mineral metabolism, optimal levels for breast cancer prevention exceed 40-50 ng/mL.²

Vitamin D Repletion

- Multiple dosing regimens treat deficiency effectively: frequency is less important than amount.
- Equal dose of Vit D$_2$ may be less effective at maintaining Vit D 25OH levels. Vit D$_3$ preferred.
- Adherence is key.
- We perform a baseline CMP/BMD for our patients and work up hypercalcemia if it is present.

Ish-Shalom, Sophia; Segal, Elena; Salganik, Tina; Raz, Batia; Bromberg, Irvin; Vieth, Reinhold
FIG. 1

Effects of the same cumulative dose of vitamin D3, equivalent to 1500 IU/d, but given once daily, once weekly, or once monthly (28 d), on serum 25(OH)D concentration in women followed up for hip fracture. Samples were taken on the number of days after the first dose of vitamin D, after baseline (d 0), as indicated by the numbers below the box plots. Each cluster of boxes shows results for samples taken repeatedly from the one group of patients. Boxes show quartile values; whiskers show the high and low, non-outlier values, whereas the open circles and stars are individual values determined by SPSS software as outliers. From d 7 onward, the serum 25(OH)D concentration was significantly higher than baseline for all groups.
Vitamin D Repletion

Nutritional Deficiency (25OHD <20 ng/mL [< 50 nmol/L])
- 50,000 IU Vit D2 /D3 orally once a week for 2-3 months, check level. If < 30 ng/mL, continue for additional 2-3 months. Once replete, Vit D3 1000-2000 IU/day. Many patients require higher doses.

Insufficiency (25 OHD 20 to 30 ng/mL [50-75 nmol/L]) 1000 – 2000 IU Vitamin D3 orally daily. Many patients will require higher doses.

Alternative dosing schedule for those who prefer less frequent dosing: 50,000 IU D2 orally once every 2-4 weeks

Vitamin D Repletion

- Monitor levels approximately q 3m until desired level (~ 40-60 ng/mL).
- Rather than endorsing a single dose, recommend measurement of blood levels of 25OHD.
- Very high levels may be of concern at present in breast cancer survivors as high levels reported to stimulate aromatase activity.¹
  - May increase estrogen levels, of concern in our patients on aromatase inhibitors.

Vitamin D Repletion

- Up to 10,000 IU D₃ safe for 5 months

- If very high doses required, we check CMP and 25OHD levels more frequently (monthly).

Effect of Vit D supplementation on 25OHD levels, joint pain and fatigue in women starting adjuvant letrozole for breast cancer. Khan QJ, Breast Ca Research and Treatment Aug 2009

- **Baseline:** Ca + Vit D with letrozole
- 4 weeks later, if level < 40 ng/mL, women treated Vit D₃ 50,000 IU weekly X 12 weeks.
- 25OHD levels >40 ng/mL in all 42 patients.
- After 16 weeks, women with levels > 66 ng/mL (median) reported no disability from joint pain (52% vs 19%).
Ranked by the AARP as one of the 8 Best Cancer Hospitals in America