Vitamin D in the Breast Clinic

Tracey L. O’Connor, M.D.
Assistant Professor of Medicine
Roswell Park Cancer Institute
Buffalo, NY

Disclosures

- No relevant disclosures

Roswell Park Cancer Institute

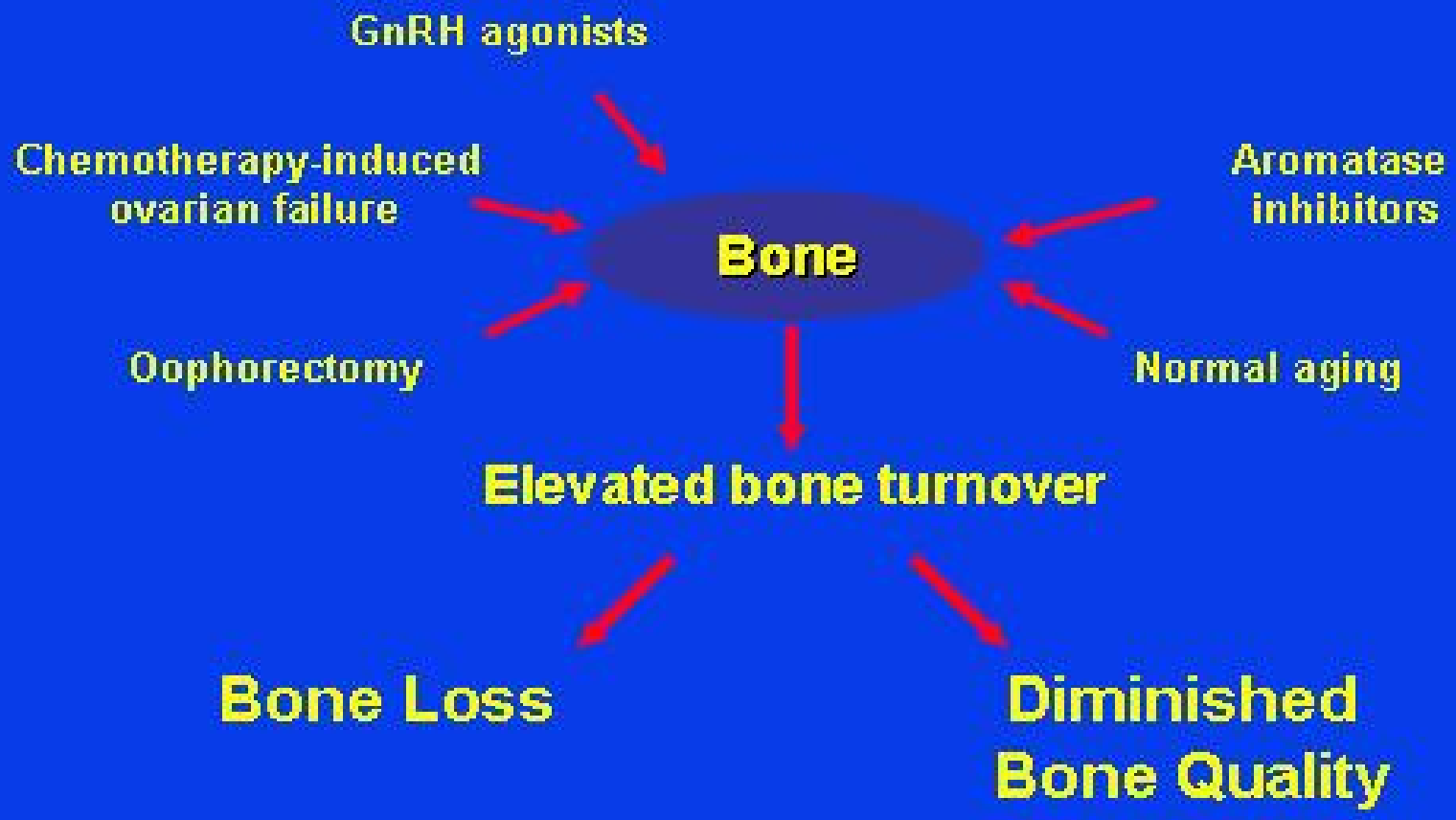
- 1st translational center in the US (founded in 1898)
- 3100 employees
- 300 faculty
- 7400 new cancer patients each year
- 1st NCI designated center
- Only NCI center in Upstate NY

ROSWELL PARK CANCER INSTITUTE

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



Pfeilschifter J et al. *J Clin Oncol.* 2000;18:1570-1593.

Gralow, ASCO 2008

A High Incidence of Vertebral Fracture in Women with Breast Cancer

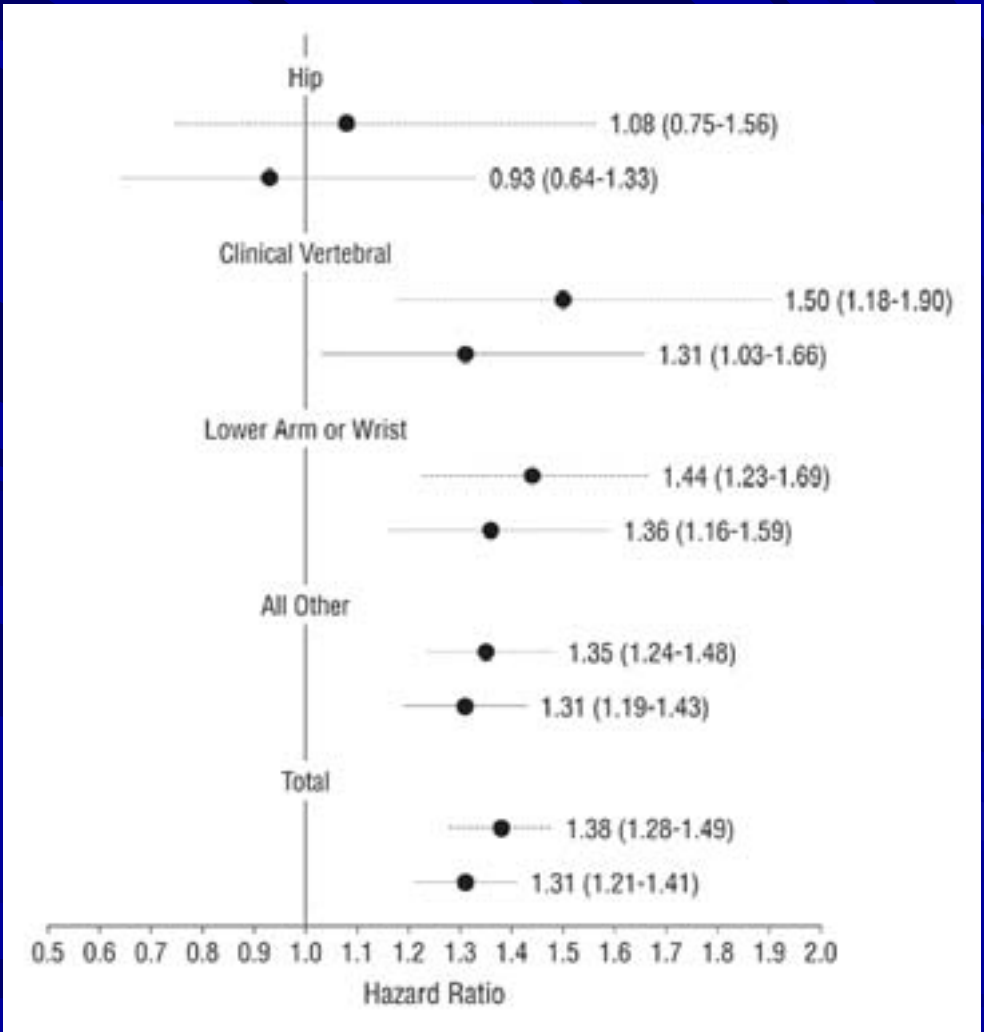
Kanis JA, et al. Br J Cancer 79:1179-1181, 1999.

- 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.

Fracture Risk Among Breast Cancer Survivors: Results from the Women's Health Initiative Observational Study Arch Intern Med 165: 552, 2005.

- 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



Chen, Z. et al. Arch Intern Med 2005;165:552-558.

ARCHIVES OF INTERNAL MEDICINE

2003 ASCO Guidelines on Bisphosphonates in Breast Cancer

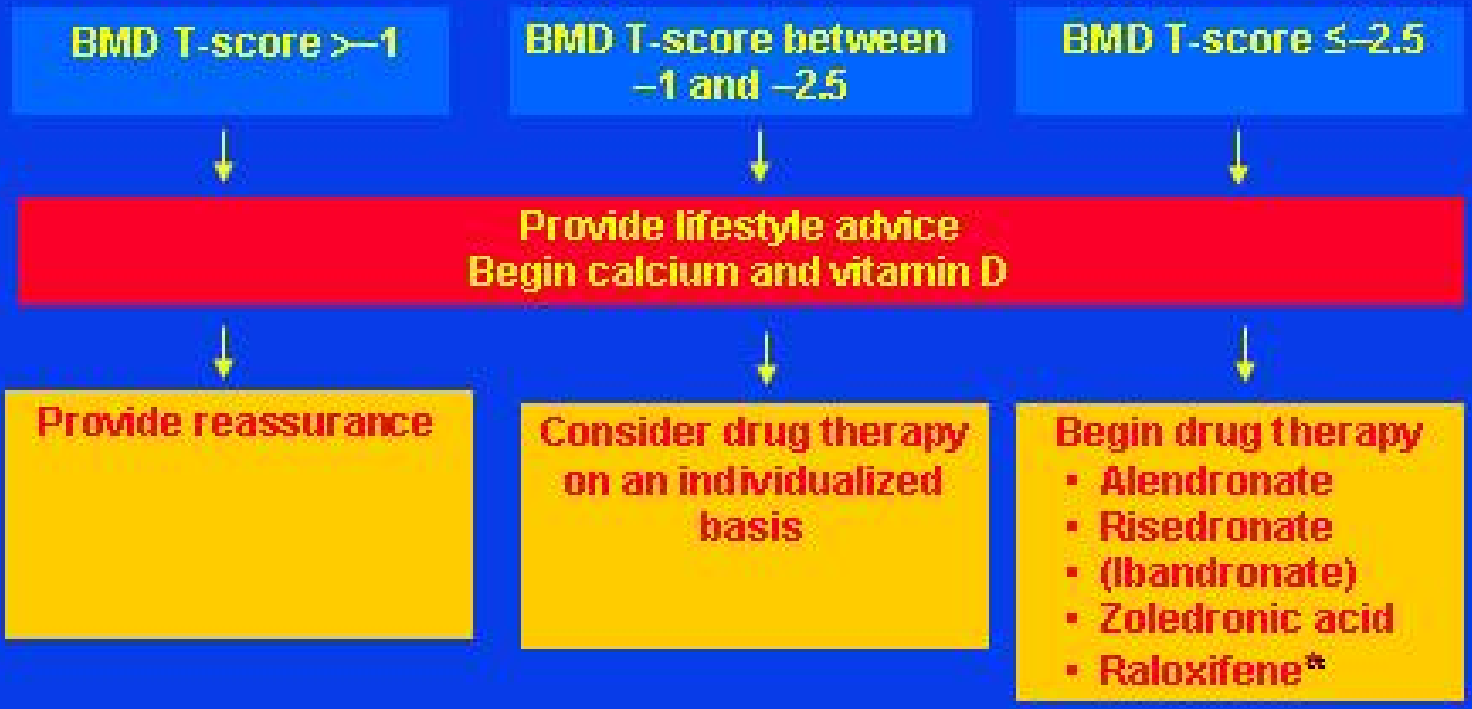
Hillner, B et al., JCO 21: 4042-4057, 2003

- 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

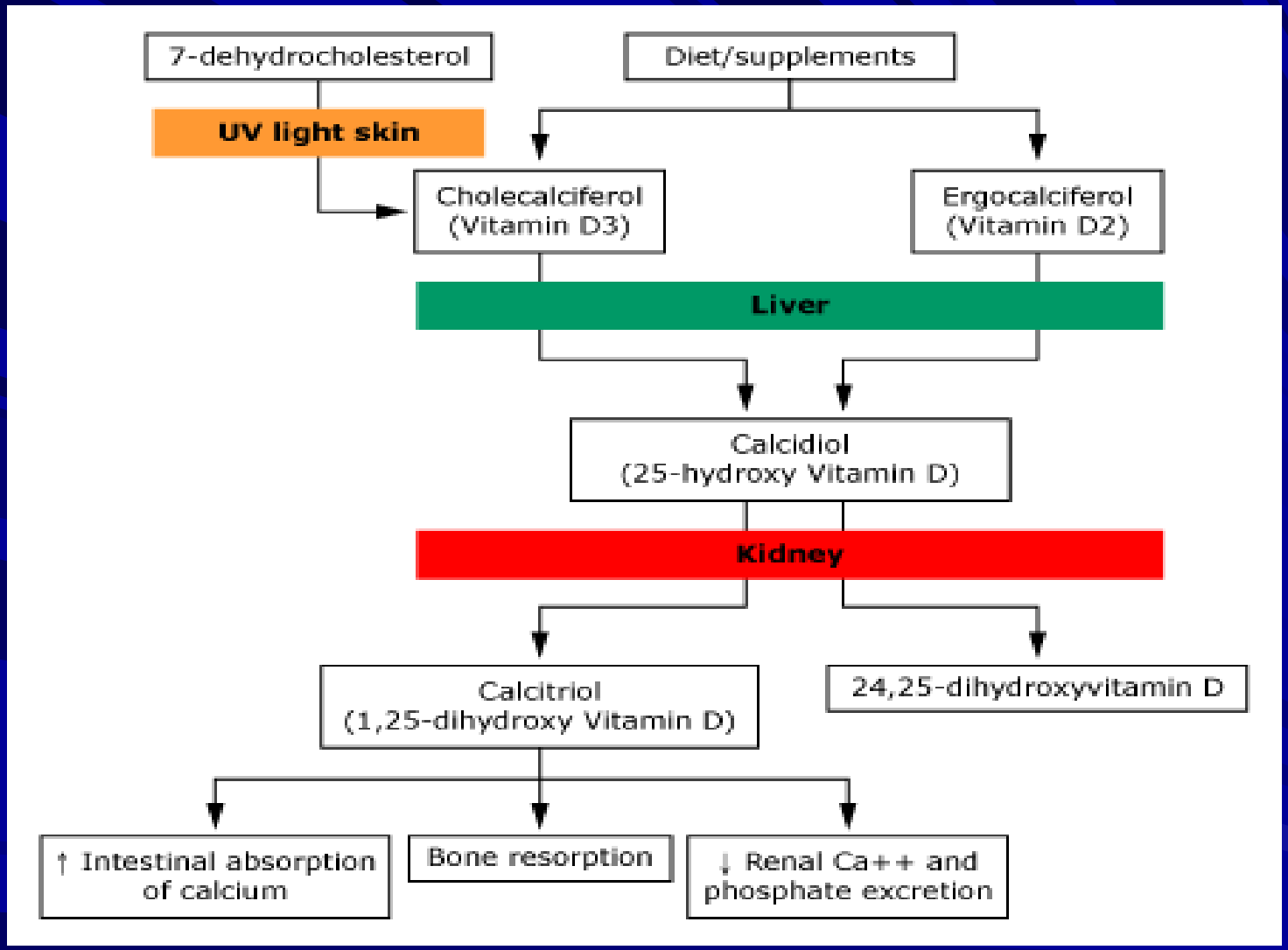
Treating Bone Density Loss in Breast Cancer Patients

Hillner BE at al, J Clin Oncol 21:4042-4057, 2004

ASCO Guidelines for Managing Bone Density in Breast Cancer



Gralow, ASCO 2008



UpToDate, 2009

Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D2 and D3

Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D_2 and D_3.*

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	About 300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D_3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D_3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D_2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D_2
Egg yolk	About 20 IU of vitamin D_3 or D_2
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	About 3000 IU of vitamin D_3
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D_3
Fortified orange juice	About 100 IU/8 oz vitamin D_3
Infant formulas	About 100 IU/8 oz vitamin D_3
Fortified yogurts	About 100 IU/8 oz, usually vitamin D_3
Fortified butter	About 50 IU/3.5 oz, usually vitamin D_3
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	About 100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D_3
Supplements	
Prescription	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D_2, or D_3‡
Vitamin D_3	400, 800, 1000, and 2000 IU

* 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 D_2; cholecalciferol or vitamin D_3 indicates that the product contains vitamin D_3.

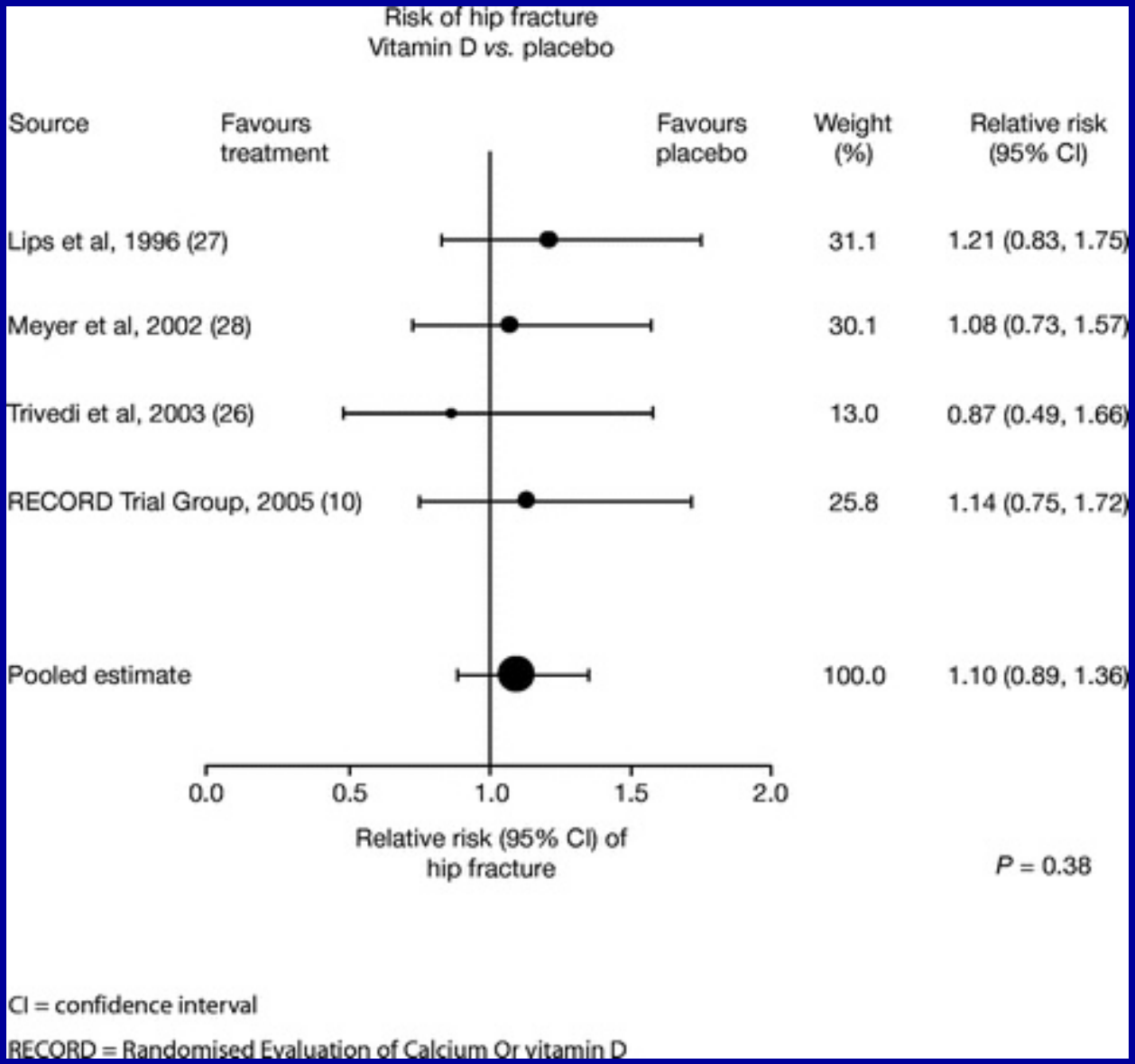
The NEW ENGLAND JOURNAL of MEDICINE

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]

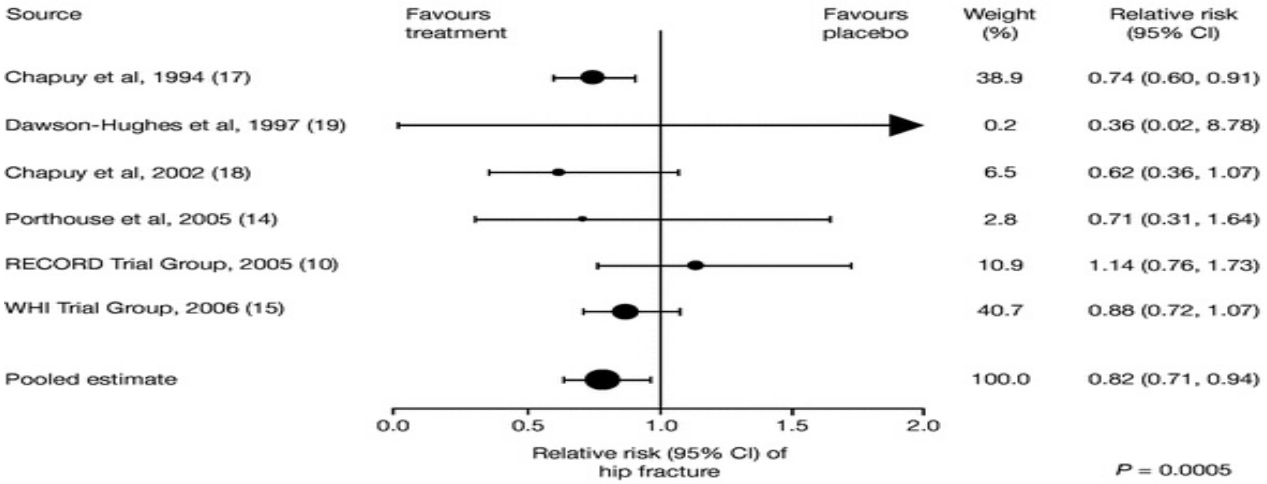
1.Villareal DT et al. J Clin Endocrinol Metab 1991; 72:628.

2. Bischoff-Ferrari HA, et al. Am J Med 2004; 116:634.



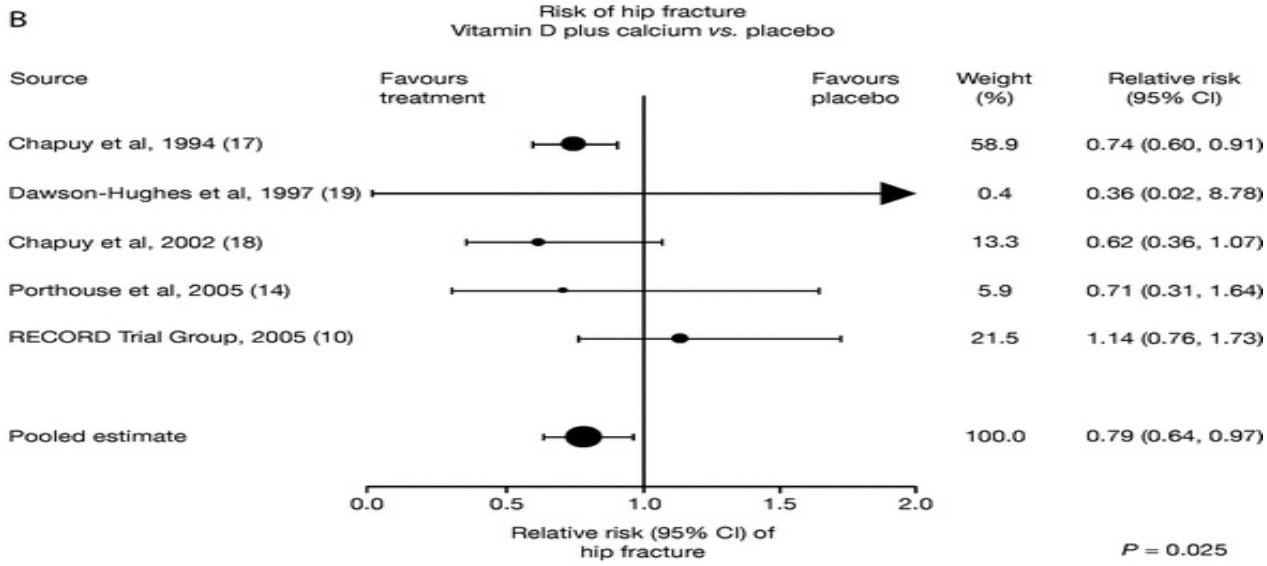
Boonen,S et.al J Clin Endocrinol Metab 92:1415, 2007

A



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

B



CI = confidence interval
RECORD = Randomised Evaluation of Calcium Or vitamin D

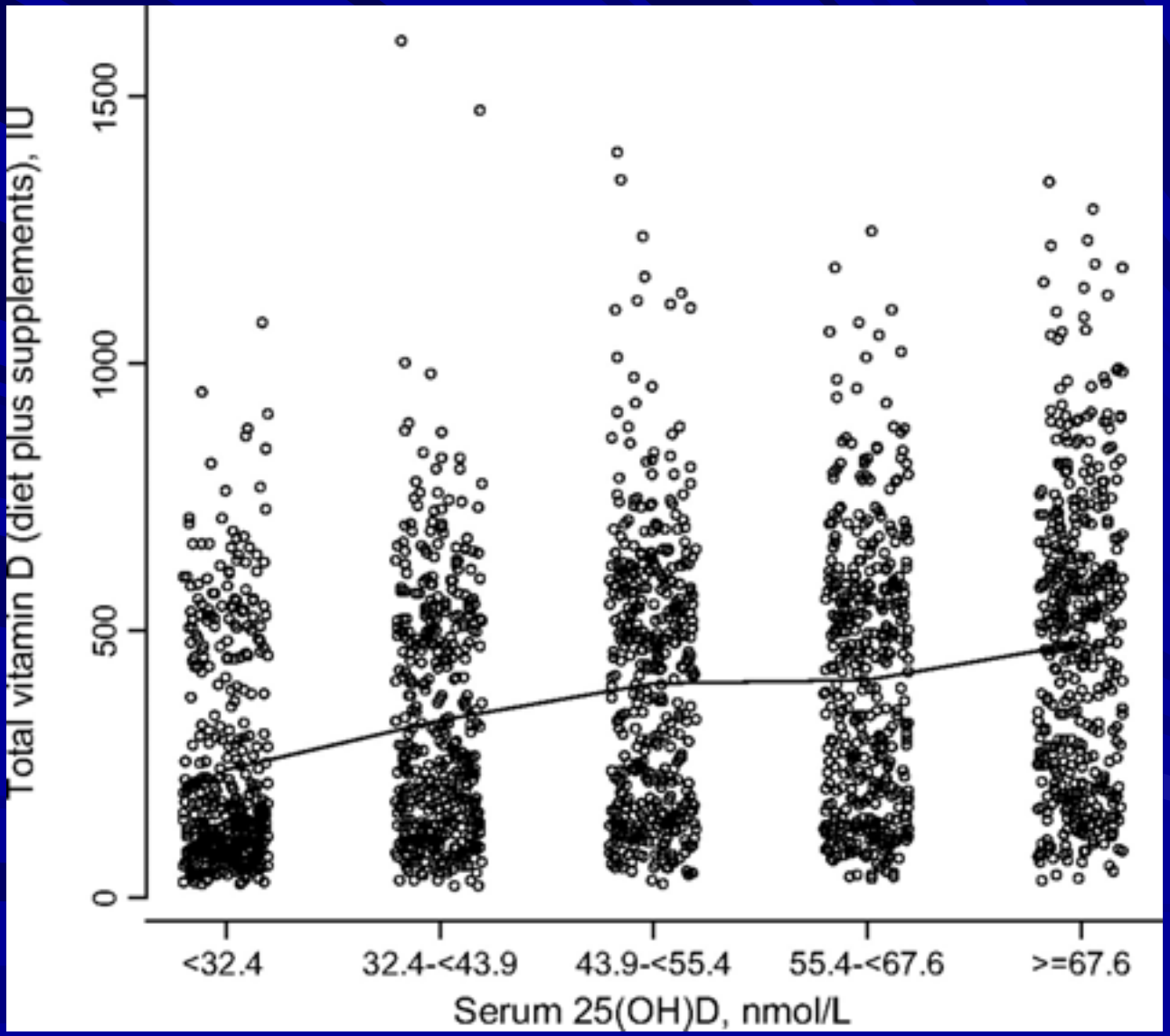
Vit D and bone health

- 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



Chlebowski, R. T. et al. J. Natl. Cancer Inst. 2008 100:1581-1591; doi:10.1093/jnci/djn360

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.

Freedman and Goodwin, ASCO educational book, 2009.

Vit D levels in Breast Cancer Patients

Goodwin J Clin Onc 2009	Diagnosis	512	Deficient < 20 ng/mL 37.5%	Insufficient 20-29 ng/mL 38.5%	Sufficient > 30 ng/mL 24%
Crew J Clin Onc 2009	Adjuvant chemotx and 400 IU	103	74%	20%	6%
Waltman Can Nurs 2009	On AIs	29	6.9%	79.3%	13.8%
RPCI unpub	Diagnosis	509	39.7%	41.4%	18.9% Goodwin ASCO 2009 adapted

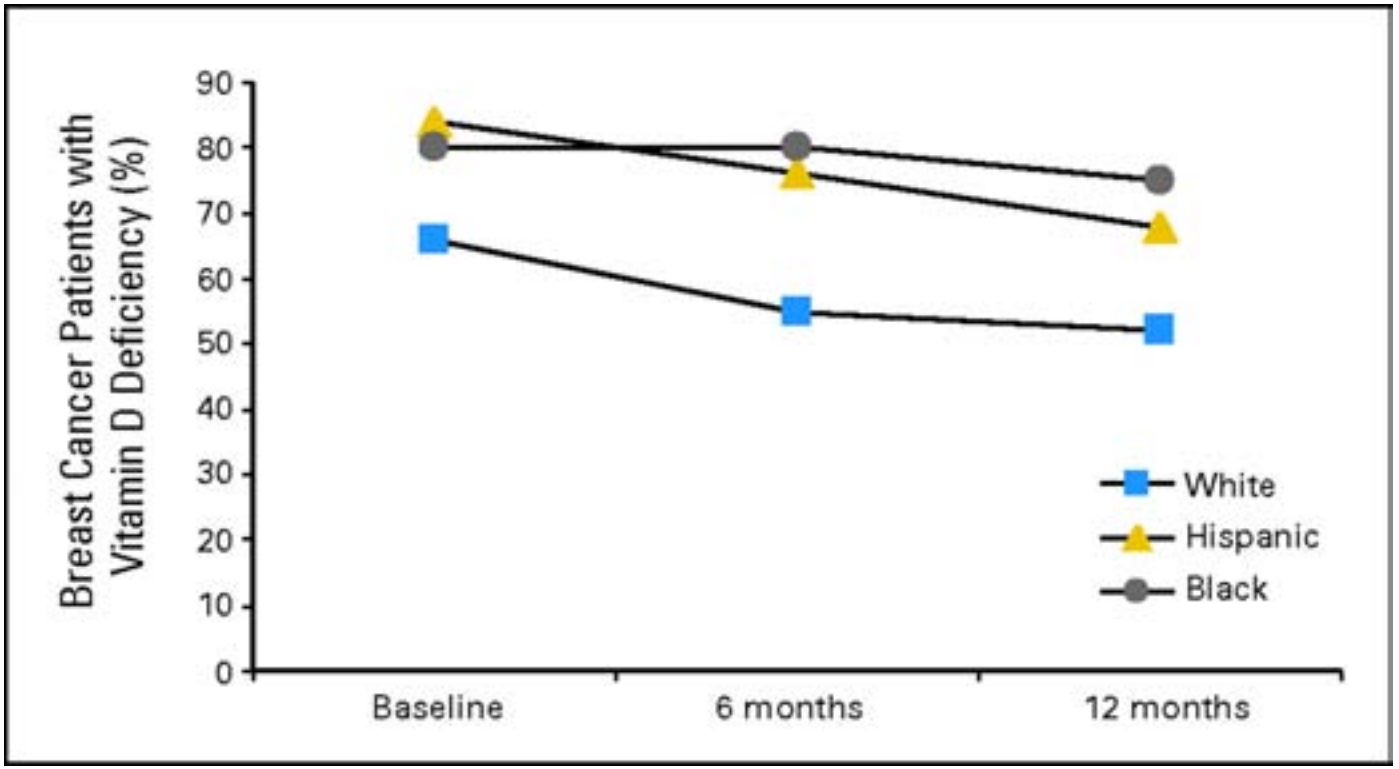
High Prevalence of Vitamin D Deficiency Despite Supplementation in Premenopausal Women with Breast Cancer Undergoing Adjuvant Chemotherapy
Crew et al, J Clin Oncol 27:2151, 2009

- 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



Crew, K. D. et al. J Clin Oncol; 27:2151-2156 2009

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.

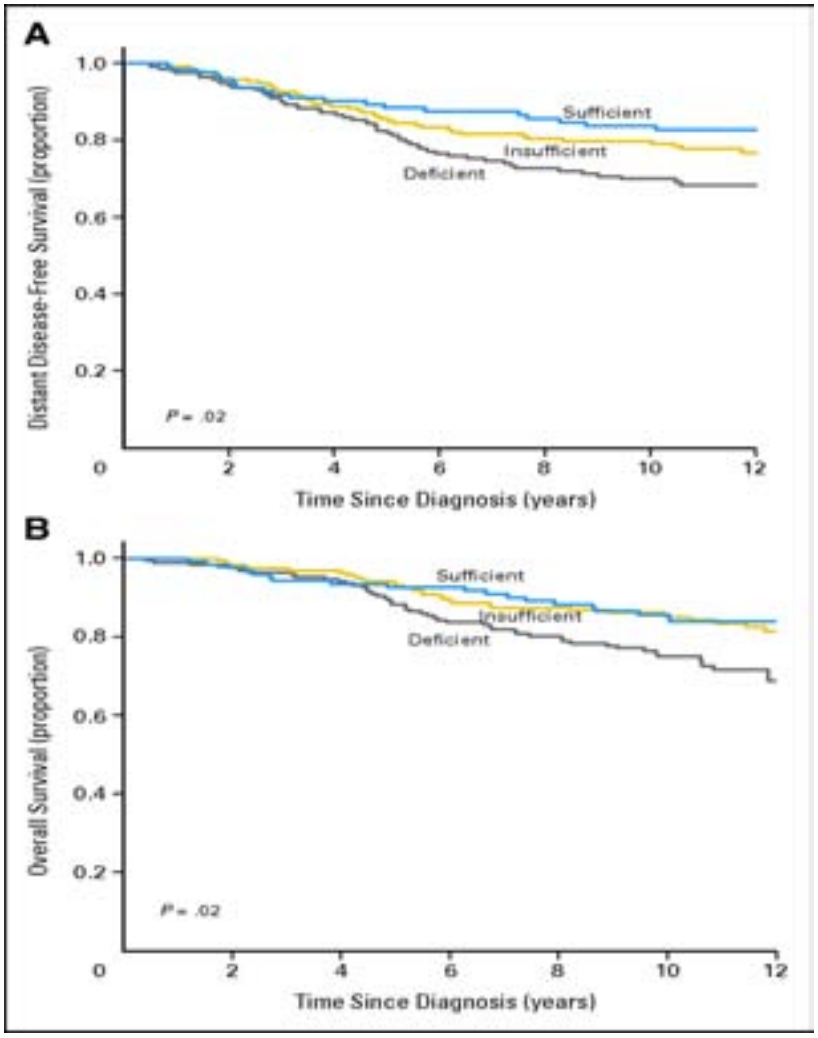
Prognostic Effects of 25-Hydroxyvitamin D Levels in Early Breast Cancer
Goodwin et al, J Clin Oncol 27:3757-3763

- 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

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

- 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



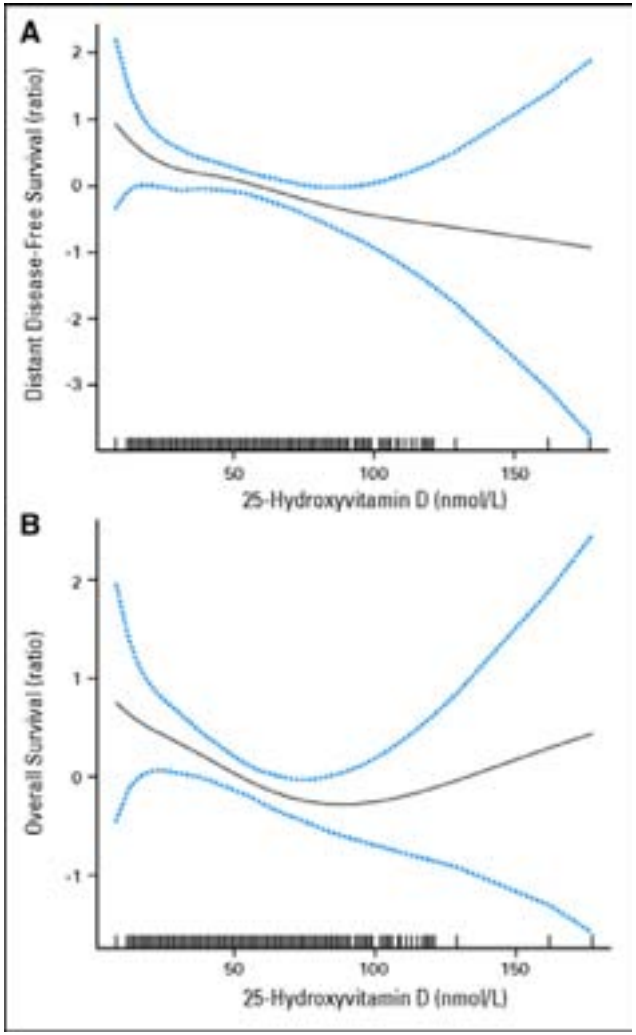
Goodwin, P. J. et al. J Clin Oncol; 27:3757-3763 2009

Distant Disease Free Survival
Goodwin et al, J Clin Oncol 27:3757-3763, 2009.

	deficient	insufficient	sufficient
HR (95% CI)	1.94 (1.16-3.25)	1.37 (0.80-2.33)	1.0
5 year	82%	85%	88%
10 year	69%	79%	83%

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)



Goodwin, P. J. et al. J Clin Oncol; 27:3757-3763 2009

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.

Vitamin D and Breast Cancer Subtypes

- 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?

Song Yao, PhD

Vitamin D and Breast Cancer Subtypes

- 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

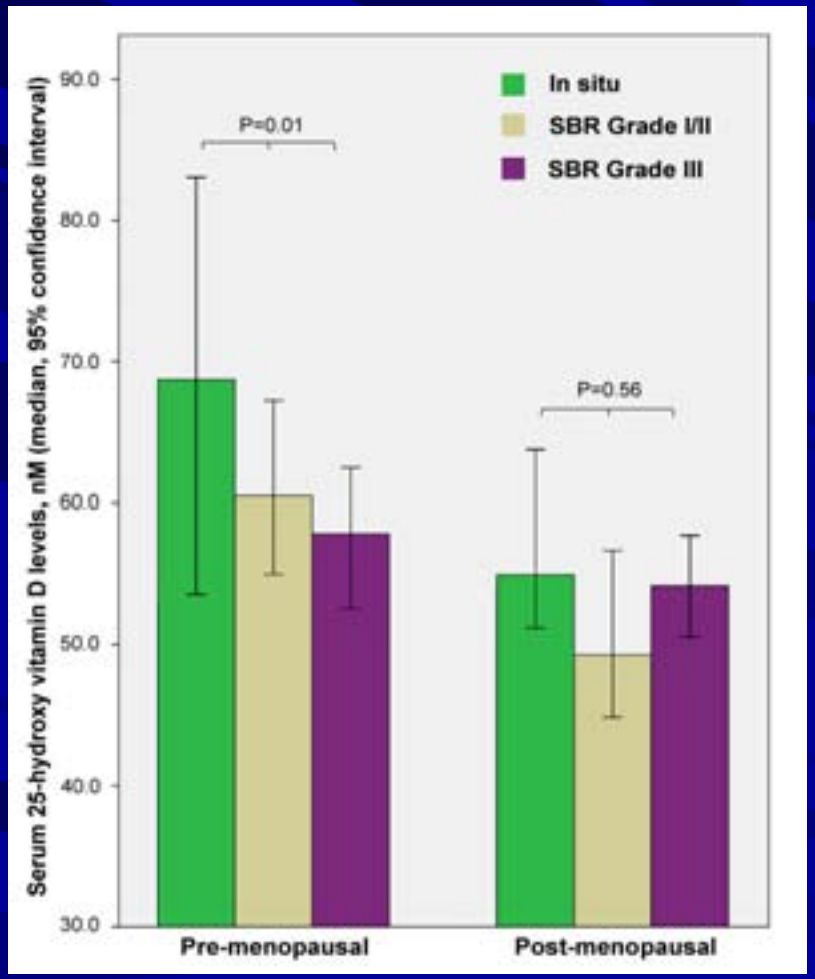
RPCI DataBank and BioRepository (DBBR)

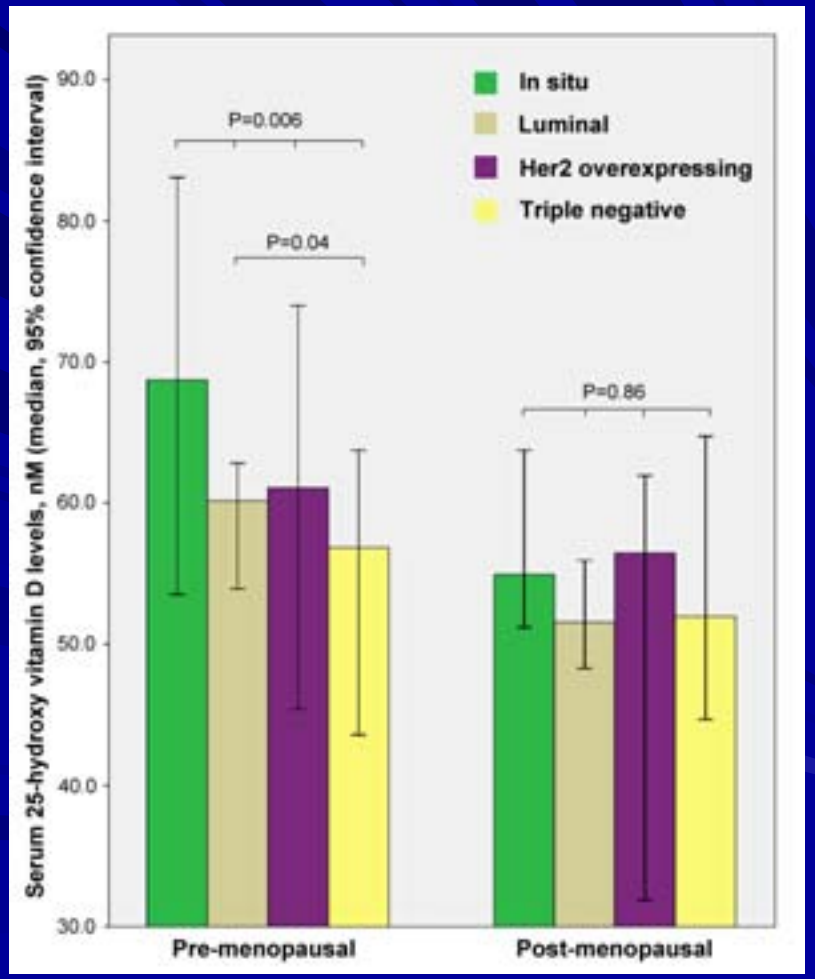
- Enrollment of newly diagnosed patients, prior to surgery
- Banked serum, plasma, RBCs, DNA
- Epidemiologic questionnaire completed
- Linkage with clinical data, tumor tissue
- Recruiting visitors as non-cancer controls

Breast Cancer Patients from RPCI DataBank and BioRepository (DBBR)

Characteristics	All cases (n=509)
ER status, n (%)	
Positive	347 (76.9)
Negative	104 (23.1)
PR status, n (%)	
Positive	291 (64.5)
Negative	160 (35.5)
Her2 status, n (%)	
Positive	74 (17.3)
Negative	354 (82.7)
Molecular subtype, n (%)	
Luminal (ER+ and/or PR+)	352 (79.3)
Her2 overexpressing (ER-, PR- and Her2+)	29 (6.5)
Basal-like (ER-, PR-, and Her2-)	63 (14.2)

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 D_3 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 D_3 can increase serum 25,OHD levels by about 10 ng/mL[1]
  - 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]

[1] Heaney, RP. et al: Human serum 25OHD response to extended oral dosing with cholecalciferol. Am J Clin Nutr 77: 204-210, 2003.

[2] Garland CF, et al. Vit D and prevention of breast cancer. Pooled analysis. J Steroid Biochem Mol Biol 103: 708-711, 2007.

Vitamin D Repletion

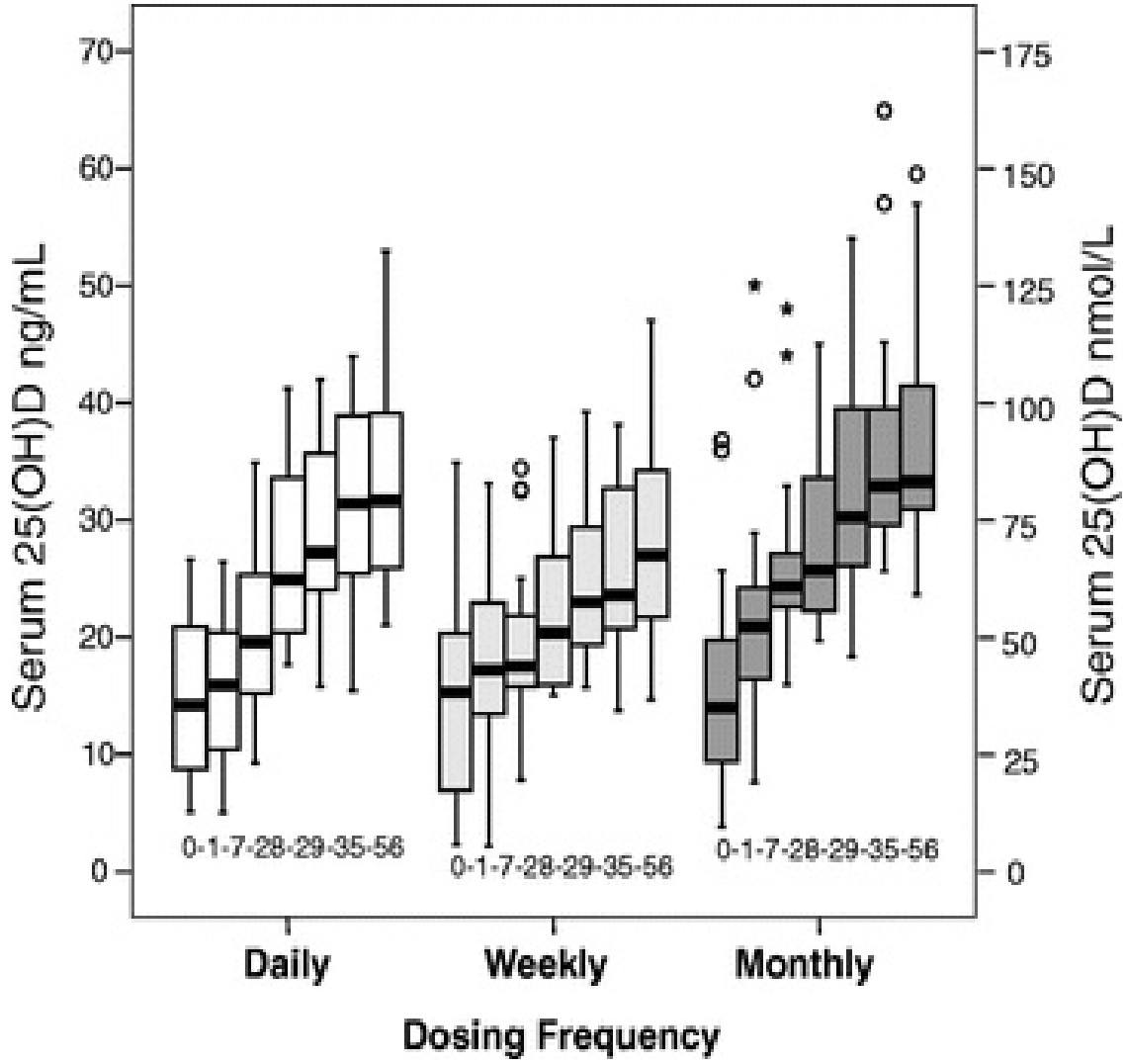
- Multiple dosing regimens treat deficiency effectively : frequency is less important than amount.
- Equal dose of Vit D_2 may be less effective at maintaining Vit D 25OH levels. Vit D_3 preferred.
- Adherence is key.
- We perform a baseline CMP/BMD for our patients and work up hypercalcemia if it is present.

Comparison of Daily, Weekly, and Monthly Vitamin D3 in Ethanol Dosing Protocols for Two Months in Elderly Hip Fracture Patients.

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

Journal of Clinical Endocrinology & Metabolism. 93(9):3430-3435, September 2008.

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

UpToDate, 2009, and Hollick, M. NEJM. 357:266-81,2007.

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.

[1] Pino AM, et al. Aromatase activity of human mesenchymal stem cells is stimulated by early differentiation, Vit D, and leptin. J Endocrinol 191: 715-725, 2006.

Vitamin D Repletion

- Up to 10,000 IU D_3 safe for 5 months[1]
- If very high doses required, we check CMP and 25OHD levels more frequently (monthly).

Vieth R Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. J Steroid Biochem Mol Biol 2004: 89-90;575-9.

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 D_3 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%).

UNDERSTAND PREVENT
& CURE CANCER

ROSWELL PARK
CANCER INSTITUTE

Ranked by the AARP as one of the 8 Best Cancer Hospitals in America