The Women's Health Initiative randomized trial of calcium plus vitamin D: Effects on breast cancer and arthralgias.

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Type of Session: Plenary

Background
- In 12 of 16 retrospective observational studies, calcium (Ca) and vitamin D (D) have been associated with reduced breast cancer risk, decreased breast density, and decreased arthralgias
- Question: Would prospective Ca and D supplementation decrease risk of breast cancer?

Materials and Methods
- Double-blind, placebo-controlled study of 32,282 women randomized to:
  - Ca/D arm (n=18,176): 1000 mg Ca as calcium carbonate + 400 IU vitamin D3
  - Placebo arm (n = 18,106)
- The Ca/D study was part of a larger study that included patients on two other studies:
  - a dietary modification intervention study Hormone therapy vs. placebo (54% of these patients)
    - conjugated equine estrogen + medroxyprogesterone (or estrogen alone for those with hysterectomy)
- Criteria:
  - post-menopausal, life expectancy > 3 yr, no breast cancer in last 10 yr
  - excluded hypercalcemia, kidney stones, corticosteroid use
- Endpoints:
  - Primary: Hip fractures
  - Secondary: Invasive breast cancer incidence, Colorectal cancer
- Allowed personal use of Vit D supplementation
  - Initially 600 IU, subsequently increased to 1000 IU
  - Serum vit D levels were measured in a subset of participants

Results
- Groups were well balanced, including baseline Ca and D intake, Gail risk
- Semi-annual contact to assess adherence
  - 60-63% in first year
- Terminated after 7 yr
- There was no difference in invasive breast cancer incidence
  - 528 Ca/D vs. 546 placebo
  - HR 0.96 (95% CI 0.85-1.09)
  - No difference in non-invasive breast cancers either
- Subgroups analyses revealed a possible benefit from Ca/D to lower invasive breast cancer risk
  - Adherence-adjusted favored Ca/D (HR=0.91, p=0.09)
  - Subgroup not taking supplement at baseline (HR=0.82, p=0.008)
- Invasive breast cancers were smaller in Ca/D arm
  - 1.54 +/- 1.23 cm Ca/D vs. 1.71 +/- 1.29 cm placebo (p=0.05)
- Total vit D baseline intake was associated with lower breast cancer risk in the placebo group
- Baseline vit D deficiency was common as measured in serum
Not correlated with joint pain symptoms
- Joint symptoms did correlate with hormone therapy (p<0.01), but did not differ between Ca/D and placebo arms
- Kidney stones were more frequent in Ca/D arm

Author's Conclusions
- Supplementation with Ca/D did not decrease incidence of breast cancer, but tumors were somewhat smaller
- Ca/D did not decrease joint pain symptoms

Clinical/Scientific Implications
- Although retrospective studies and pre-clinical data would predict that Ca/D could lower breast cancer incidence, supplementation as used in this study did not confer a benefit
- Possible explanations for the lack of effect on breast cancer incidence:
  - Too much baseline Vit D use (~750 IU) compared with level of intervention (400 IU) to see an effect from intervention
  - Not enough Vit D intervention? Need about 3000 IU to achieve serum level of 42 ng/mL, which has been correlated with greatest breast cancer risk decrease
  - Too much baseline Ca use (mean intake was 1165 mg, which is close to optimal amount, 1200 mg)
  - Participation in hormone therapy trial may have confounded effect
  - Intervention in the right age group?
- At the present time, Ca and Vit D supplementation can not be recommended to prevent breast cancer