

# Micronutrients and Cancer Prevention

**Elena Martínez, M.P.H., Ph.D.**  
**Richard H. Hollen Professor of Cancer Prevention**



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# Micronutrients and Cancer Prevention

## Presentation Outline

- **Selenium**
- **Folate**
- **Calcium/Vitamin D**
- **Summary and Future Challenges**



# Randomized Controlled Trials of $\beta$ Carotene

| <b>Study</b>  | <b>PHS</b>                          | <b>ATBC</b>                                   | <b>CARET</b>                        | <b>Linxian</b>                                    |
|---|-------------------------------------|---|-------------------------------------|---|
| <b><math>\beta</math>-carotene dose<br/>(add'l agents)</b>                  | <b>50 mg qod<br/>(aspirin)</b>      | <b>20 mg<br/>(<math>\alpha</math>-tocoph)</b> | <b>30 mg<br/>(Vit A)</b>            | <b>15 mg<br/>(Se, <math>\alpha</math>-tocoph)</b> |
| <b>Follow-up (yrs)</b>  | <b>12</b>                           | <b>6</b>                                      | <b>4</b>                            | <b>5</b>  |
| <b>% ever smokers</b>   | <b>50</b>                           | <b>100</b>                                    | <b>98</b>                           | <b>30</b>   |
| <b>Plasma <math>\beta</math>-carotene<br/>post-intervention<br/>(ng/ml)</b> | <b>1200</b>                         | <b>3000</b>                                   | <b>2100</b>                         | <b>860</b>  |
| <b>RR lung cancer</b>   | <b>0.95 (incid)<br/>1.02 (mort)</b> | <b>1.18 (incid)<br/>1.08 (mort)</b>           | <b>1.28 (incid)<br/>1.17 (mort)</b> | <b>0.87 (mort, all<br/>cancers)</b>               |

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# SELENIUM

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# Selenium

## Background

- Trace mineral required in small amounts.
- Incorporated into proteins to make selenoproteins, which are important antioxidant enzymes.
- Forms: Sodium Selenite or Selenate, Selenomethionine, yeast forms.
- Deficiency: Keshan Disease
- Toxicity: Selenosis
- Adequate intake (AI): 55  $\mu\text{g}$  per day; UL: 400 $\mu\text{g}$  per day
- Selenium fortification of the food supply ongoing in Finland since 2003-2004.

# Selenium and Prostate Cancer in the NPC Trial\*

| Group                   | Se/Placebo | Adjusted HR (95% CI) |
|-------------------------|------------|----------------------|
| <b>Follow-up period</b> |            |                      |
| 1983-1993               | 13/35      | 0.35 (0.16-0.65)     |
| 1983-1996               | 22/42      | 0.48 (0.28-0.80)     |
| <b>Plasma selenium</b>  |            |                      |
| < 106.4                 | 2/15       | 0.14 (0.04-0.61)     |
| 106.4-123.2             | 7/16       | 0.33 (0.13-0.82)     |
| >123.2                  | 13/11      | 1.14 (0.51-2.59)     |

\*RCT of 1312 High Risk Non-Melanoma Skin Cancer Patients randomized to 200 µg Se (**baker's yeast**) vs. placebo



# *SELECT*

*Selenium and Vitamin E  
Cancer Prevention Trial*

- 32,000 men
- 200 micrograms ( $\mu\text{g}$ ) of selenium per day (**selenomethionine**)
- 400 International Units (IU) of vitamin E per day

**National Cancer Institute and  
Southwestern Oncology Group**

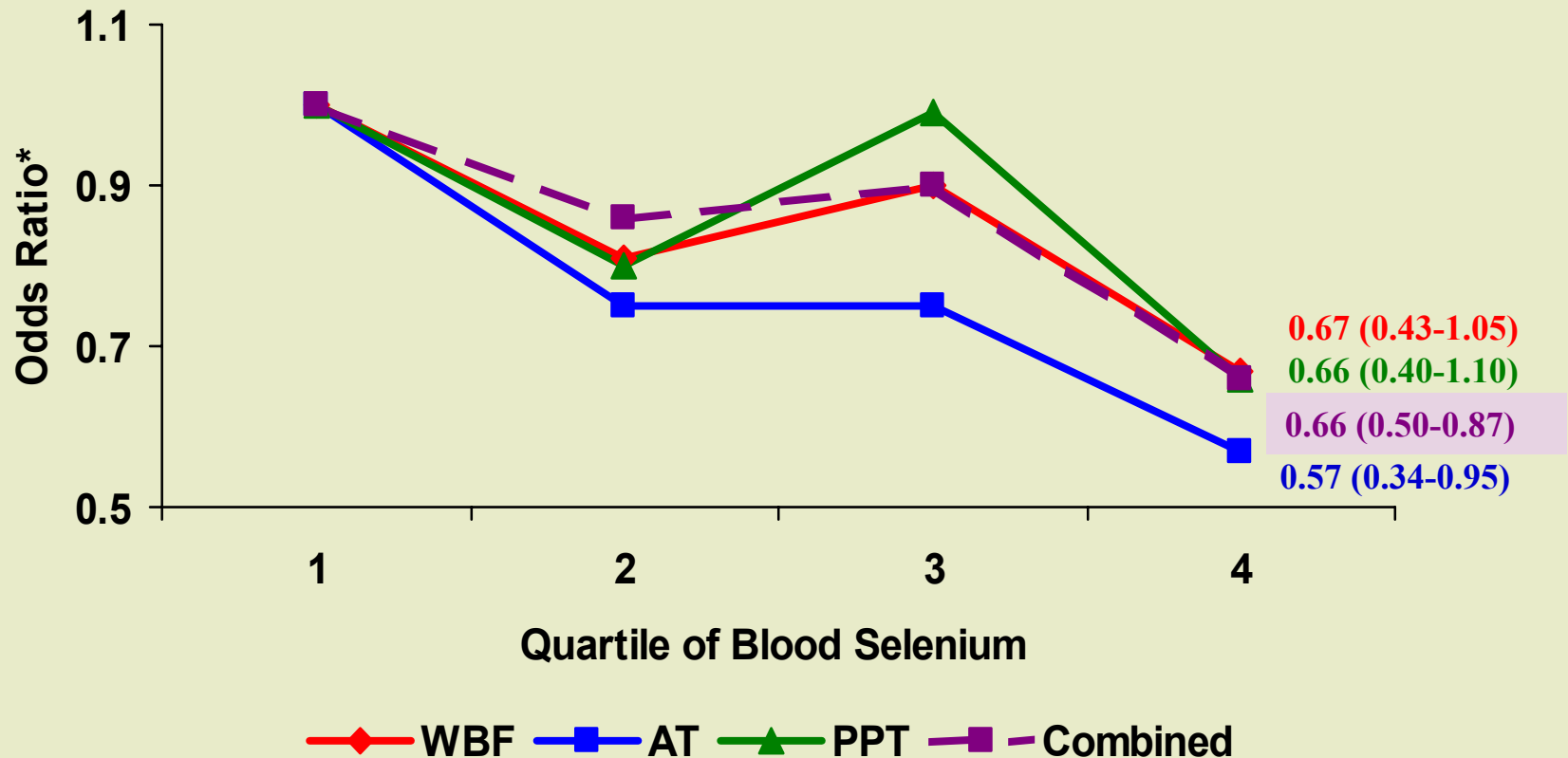
# Selenium Supplementation and Cancer Prevention in the NPC Trial

| <b>Endpoint</b>           | <b>Se</b> | <b>Placebo</b> | <b>↓ Risk (p-value)<br/>Clark, 1996</b> | <b>↓ Risk (p-value)<br/>Lillico, 2003</b> |
|---------------------------|-----------|----------------|---|---|
| <b>Tot. mortality</b>     | <b>17</b> | <b>31</b>      | <b>50% (0.002)</b>                      | <b>41% (0.008)</b>                        |
| <b>Tot. Incidence</b>     | <b>13</b> | <b>35</b>      | <b>37% (0.001)</b>                      | <b>25% (0.03)</b>                         |
| <b>Lung Incidence</b>     | <b>8</b>  | <b>19</b>      | <b>46% (0.04)</b>                       | <b>26% (0.26)</b>                         |
| <b>Prostate Incidence</b> | <b>9</b>  | <b>3</b>       | <b>63% (0.002)</b>                      | <b>52% (0.005)</b>                        |
| <b>CRC Incidence</b>      | <b>77</b> | <b>119</b>     | <b>58% (0.03)</b>                       | <b>54% (0.06)</b>                         |

# Selenium and Colorectal Neoplasia

| Author, year            | Study Design  | Endpoint        | No. cases | Result |
|-------------------------|---------------|-----------------|-----------|--------|
| Wallace, 2003           | Case-control  | Adenoma         | 276       | n/s    |
| Fernandez-Banares, 2002 | Case-control  | Cancer          | 24        | p<0.05 |
| Fernandez-Banares, 2002 | Case-control  | Adenoma         | 28        | n/s    |
| Lillico, 2002           | Intervention  | Cancer          | 28        | p<0.06 |
| Clark, 1996             | Intervention  | Cancer          | 27        | p<0.03 |
| Early, 2002             | Case-control  | Cancer          | 33        | n/s    |
| Early, 2002             | Case-control  | Adenoma         | 35        | n/s    |
| Ghadirian, 2000         | Case-control  | Cancer          | 402       | 0.009  |
| Psathakis, 1998         | Case-control* | Cancer survival | 106       | p<0.05 |
| Russo, 1997             | Case-control  | Adenoma         | 37        | p<0.06 |
| Nelson, 1995            | Case-control  | Cancer          | 25        | n/s    |
| Nelson, 1995            | Case-control  | Adenoma         | 139       | n/s    |
| Dworkin, 1988           | Case-control* | Cancer stage    | 97        | p<0.05 |
| Willett, 1983           | Case-control  | Cancer          | 13        | p<0.01 |

# Blood Selenium and Colorectal Adenoma Recurrence



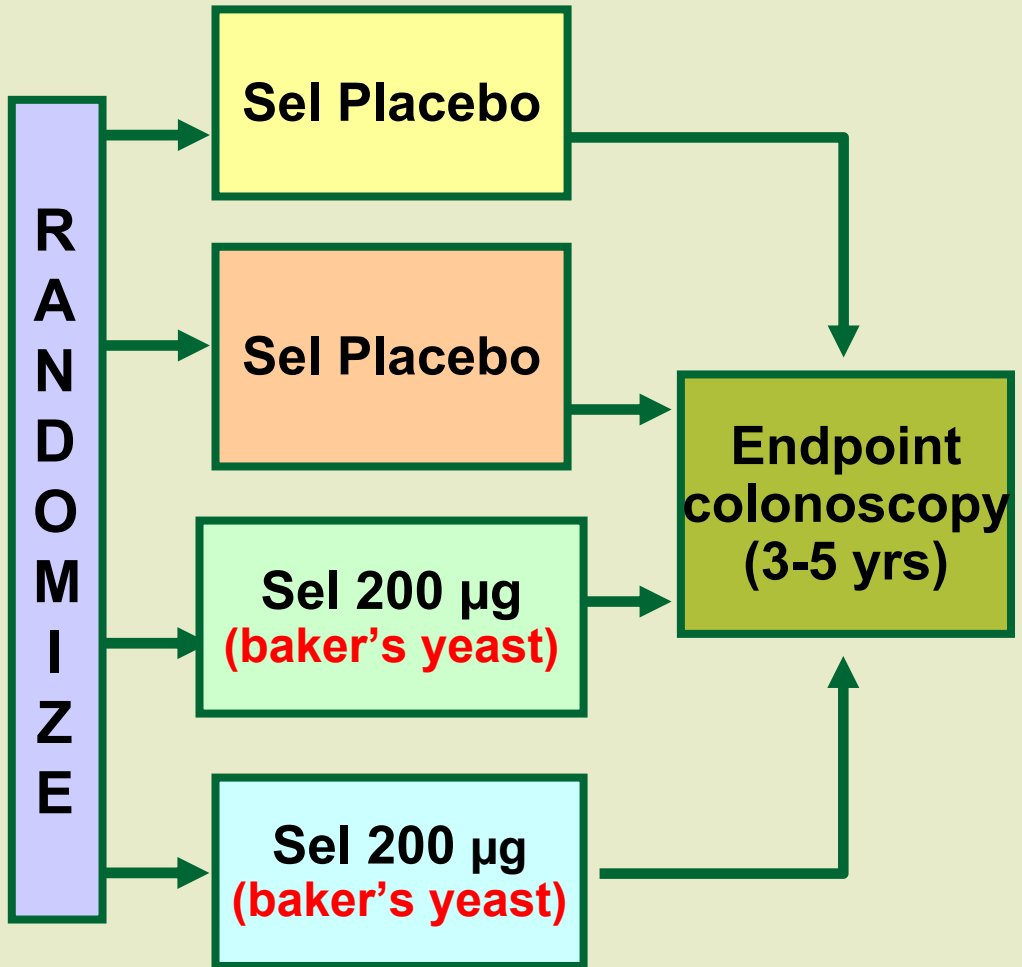
\*Study specific odds ratios adjusted for age, gender, and smoking status; OR for combined analysis includes study-specific covariates plus study site.

# Arizona Selenium Trial of Colorectal Adenoma

## Eligibility Criteria

- Removal of  $\geq 3$  mm adenoma
- 40-80 yrs old
- Adequate organ function
- Area resident
- No invasive cancer within 5 yrs
- No routine NSAIDs/  
Selenium use

4 wk  
Placebo  
Run-in



# Selenium and Cancer

## Summary

- Promising RCT results based on secondary endpoints.
- Trial results suggest benefit of selenium confined to individuals with low selenium levels.
- Mechanism(s) of action for chemopreventive effects not clear.
- Unknown whether all forms of selenium have similar chemopreventive properties.
- Await results of ongoing trials
  - ✓ SELECT
  - ✓ Arizona Selenium Trial
  - ✓ SELECT Colorectal Cancer Ancillary Study

# FOLATE



Photo by Bryan Castle, Arizona Cancer Center

# Folate and Folic Acid - Background

- Folate is a water soluble B-vitamin; functions as a coenzyme in single-carbon transfer in nucleic acid and amino acid metabolism.
- Only small amounts synthesized by intestinal microflora; must be obtained from exogenous sources.
- Folic acid is the fully oxidized monoglutamyl form of folate (synthetic form).
- Folic acid is used in supplements and fortified foods and is more bioavailable than natural form (1  $\mu\text{g}$  dietary folate=0.6  $\mu\text{g}$  of folic acid from fortified foods or 0.5  $\mu\text{g}$  supplement sources).
- Recommended intake: 400  $\mu\text{g}/\text{day}$ ; UL: 1000  $\mu\text{g}/\text{day}$ .
- Mandatory food fortification by US FDA in 1996 (NTD prevention), resulting in an additional 80-100  $\mu\text{g}$  of folic acid/day to women of childbearing age and 70-120  $\mu\text{g}$  to middle-aged and older adults.
- 30-60% of US population take multivitamins with folate.

# Meta-analysis of Dietary Folate and Breast Cancer

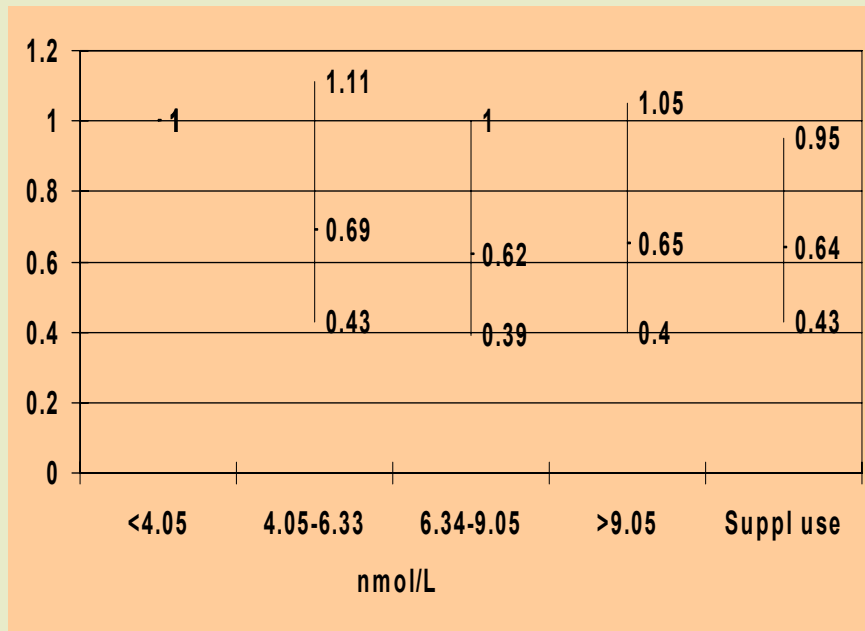
| <b>Study Type</b>              | <b>Total<br/>RR (95% CI)</b> | <b>Pre-menopausal<br/>RR (95% CI)</b> | <b>Post-menopausal<br/>RR (95% CI)</b> |
|--------------------------------|------------------------------|---------------------------------------|--|
| <b>Cohort<br/>(n=9)</b>        | <b>0.99 (0.98-1.01)</b>      | <b>1.01 (0.98-1.04)</b>               | <b>1.01 (0.98-1.05)</b>                |
| <b>Case-control<br/>(n=13)</b> | <b>0.91 (0.87-0.96)</b>      | <b>0.87 (0.78-0.97)</b>               | <b>0.92 (0.83-1.02)</b>                |

# Meta-analysis of Folate Intake and Colorectal Cancer

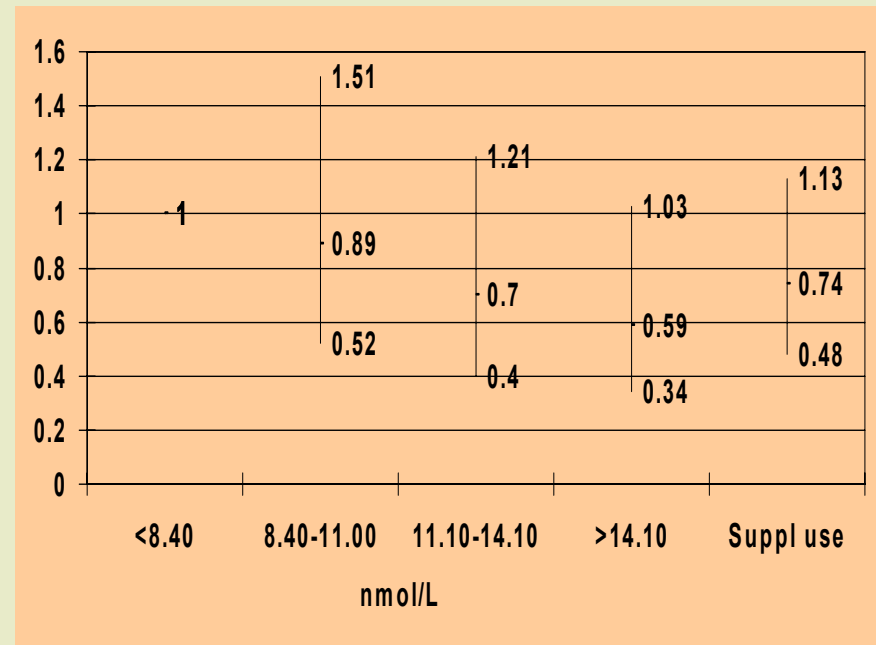
| <b>Study type</b>         | <b>Dietary Folate<br/>RR (95% CI)</b> | <b>Total Folate<br/>RR (95% CI)</b> |
|---------------------------|---------------------------------------|-------------------------------------|
| <b>Cohort (n=7)</b>       | <b>0.75 (0.64-0.89)</b>               | <b>0.95 (0.81-1.11)</b>             |
| <b>Case-control (n=9)</b> | <b>0.76 (0.60-0.96)</b>               | <b>0.81 (0.62-1.05)</b>             |

# Effect of Multivitamin Use According to Plasma Folate Levels

## Pre-fortification

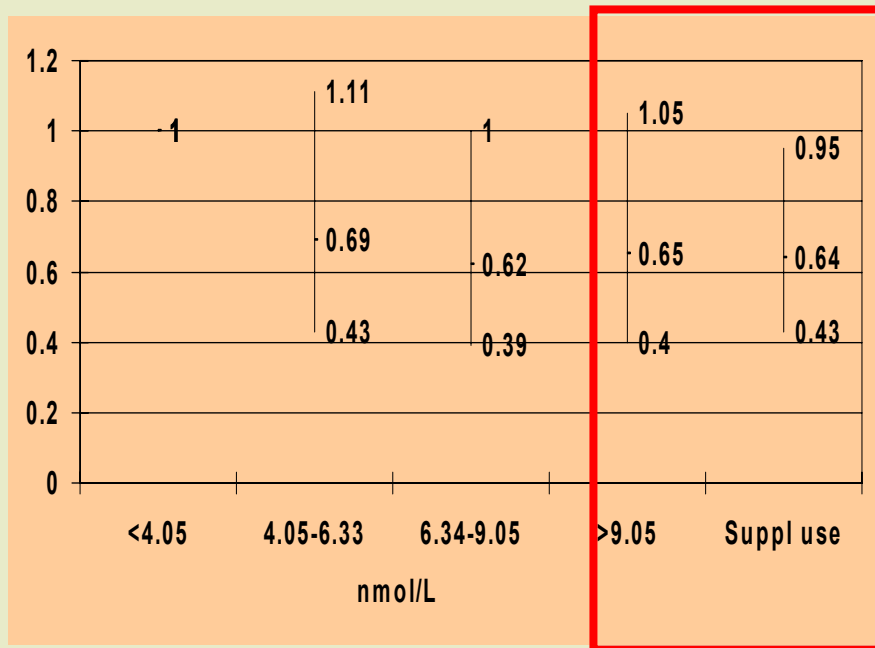


## Post-fortification



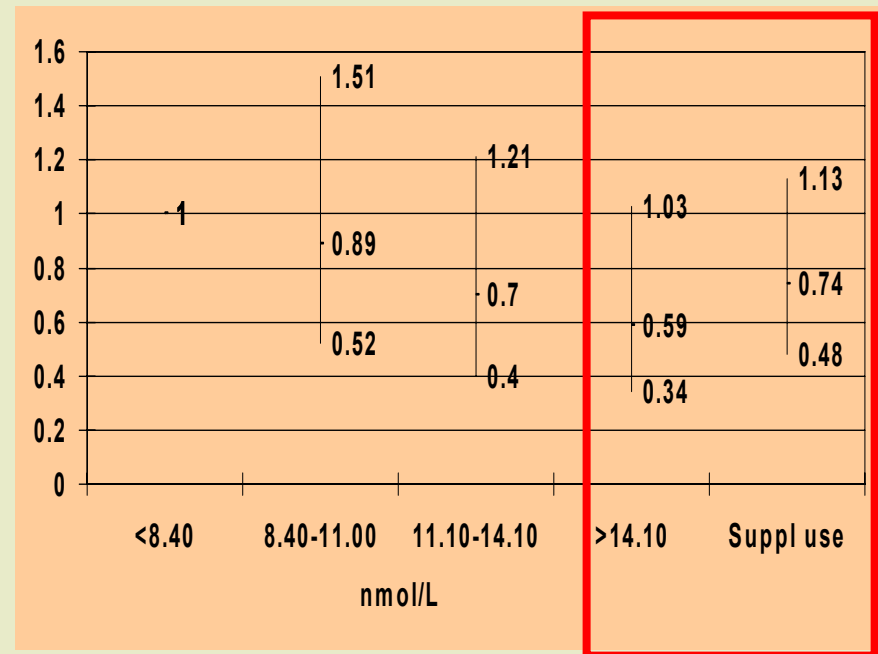
# Effect of Multivitamin Use According to Plasma Folate Levels

**Pre-fortification**



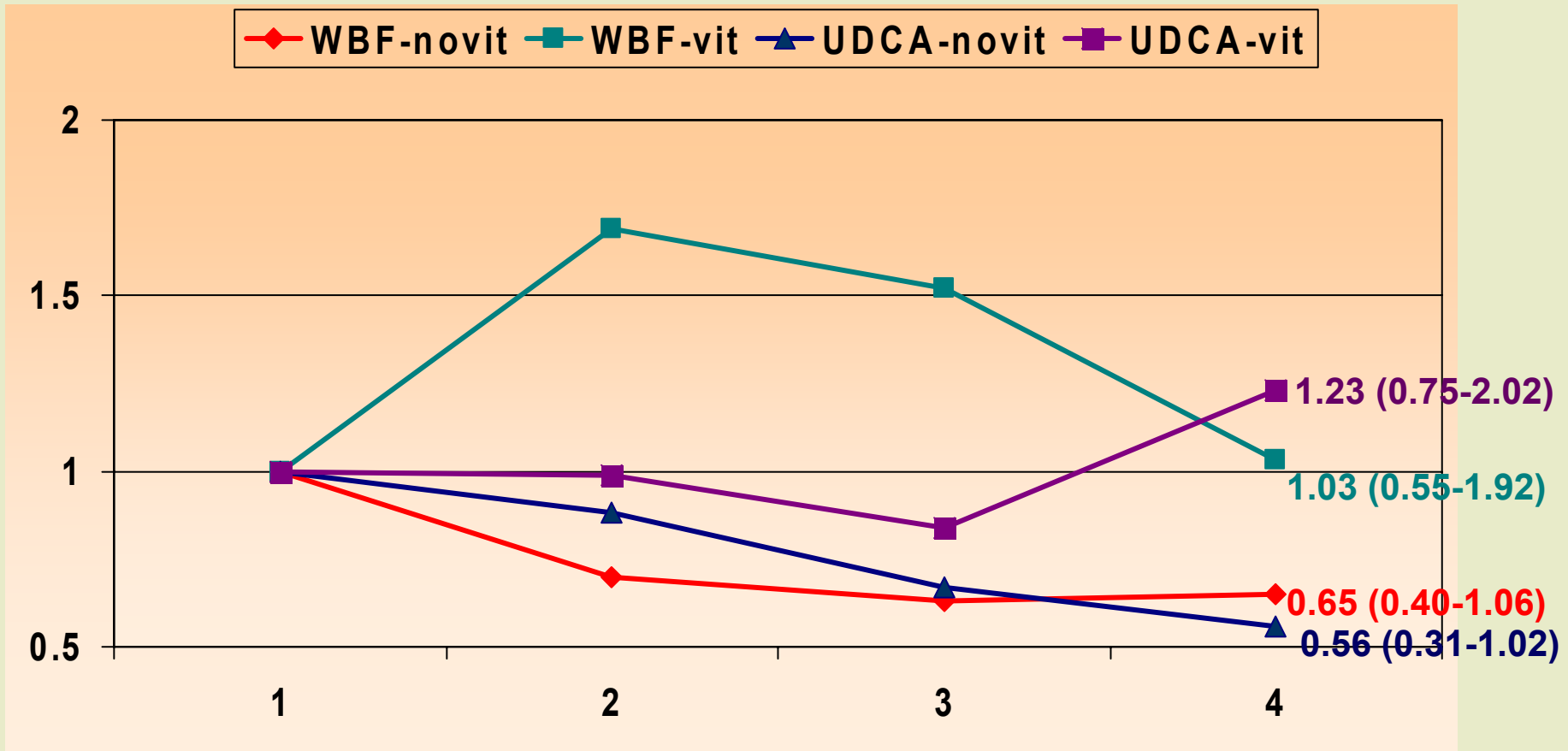
**No benefit for those with higher levels**

**Post-fortification**



**Possible higher risk for those with higher levels**

# Plasma Folate and Adenoma Recurrence in the WBF and UDCA Studies According to Vitamin Supplement Use



**Higher folate concentration is only protective among non-supplement users**

# Plasma Folate and Colorectal Cancer Risk in the Northern Sweden Health and Disease Cohort

| <b>Plasma Folate</b> | <b>Total Population<br/>RR (95% CI)</b> | <b>Studies &gt;4.2 yrs F/U<br/>RR (95% CI)</b> |
|----------------------|---|--|
| <b>Q1</b>            | <b>1.00 (Ref)</b>                       | <b>1.00 (Ref)</b>                              |
| <b>Q2</b>            | <b>1.72 (0.99-3.03)</b>                 | <b>2.15 (0.91-5.08)</b>                        |
| <b>Q3</b>            | <b>2.00 (1.13-3.56)</b>                 | <b>2.49 (1.04-6.00)</b>                        |
| <b>Q4</b>            | <b>1.87 (1.04-3.36)</b>                 | <b>2.64 (1.06-6.62)</b>                        |
| <b>Q5</b>            | <b>1.34 (0.72-2.50)</b>                 | <b>3.87 (1.52-9.87)</b>                        |

# Folic Acid Supplementation and Risk of Adenoma Recurrence\*

| <b>Recurrence Type</b> | <b>First Follow-up Risk Ratio (95% CI)</b> | <b>Second Follow-up Risk Ratio (95% CI)</b> |
|------------------------|--|---|
| <b>Total</b>           | <b>1.04 (0.90-1.20)</b>                    | <b>1.13 (0.93-1.37)</b>                     |
| <b>Advanced</b>        | <b>1.32 (0.90-1.92)</b>                    | <b>1.67 (1.00-2.80)</b>                     |
| <b>3+ adenomas</b>     | <b>1.20 (0.80-1.81)</b>                    | <b>2.32 (1.23-4.35)</b>                     |

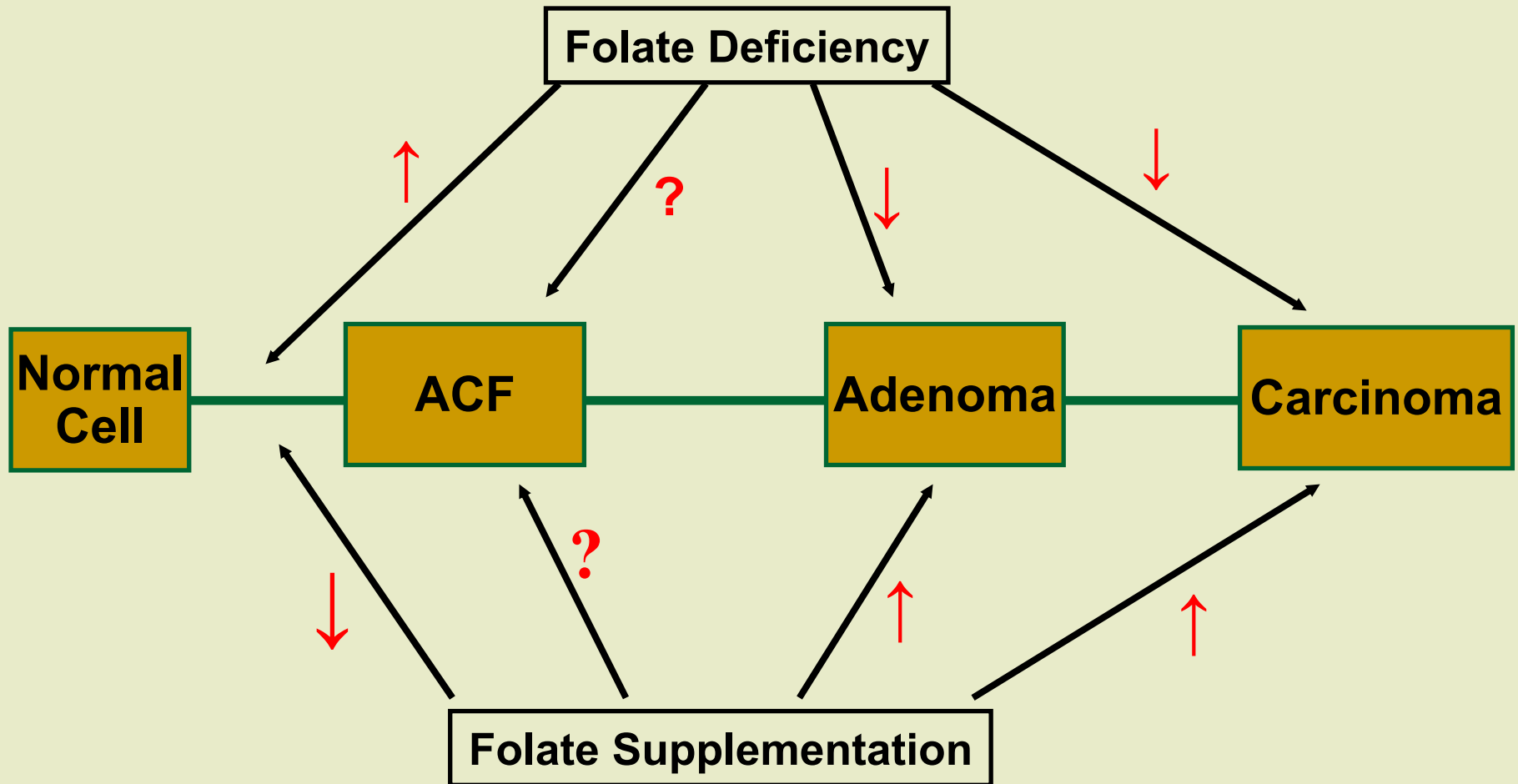
\*RCT testing 1 mg folic acid vs. placebo among 1,021 men and women

# Can Folate Promote Cancer?

## Timing and Dose are Important

- Folate plays an important role in DNA synthesis and replication
- In cancer cells, where DNA replication occurs at a high rate, interruption of folate metabolism causes ineffective DNA synthesis, resulting in inhibition of tumor growth (e.g., treatment with antifolate chemotherapy agents).
- In normal tissues, folate deficiency may predispose them to neoplastic transformation whereas *modest* folate supplementation suppresses tumor development.
- **Supplemental folate has a promoting effect on the progression of established neoplasms.**

# Opposing Effect of Folate on the Adenoma-Carcinoma Multi-stage Carcinogenesis Sequence



# Folate and Cancer

## Summary

- Human and animal studies indicate protective benefits of folate in the development of colorectal neoplasia.
- Safe and effective dose range for supplementation as well as optimal timing in human carcinogenesis sequence has not been fully established.
- Need to understand effects of excessive perinatal folic acid supplementation on epigenetic and other mechanisms that can alter disease risk.
- Assess safety of folic acid, particularly at higher levels and for longer periods of time.
- Some studies, including one RCT, suggest that higher doses or levels of folate increase risk of colorectal neoplasia.
- Supplemental doses on top of current fortification of the food supply is probably not beneficial.

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# CALCIUM AND VITAMIN D

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# Calcium and Vitamin D

## Background

### VITAMIN D

- Essential for maintaining normal calcium metabolism
- Can be synthesized in skin
- Recommended intake
  - ✓ 5-15 mcg/d (200-400 IU)
  - ✓ UL: 50 mcg/d (2000 IU)
- Deficiency
  - ✓ Classically defined as circulating 25-OHD < 10 ng/ml
  - ✓ Recently defined < 20 ng/ml
  - ✓ Rickets (children)
  - ✓ Osteomalacia (adults)
- Toxicity
  - ✓ Hypercalcemia
  - ✓ Deposition of calcium in soft tissues

### CALCIUM

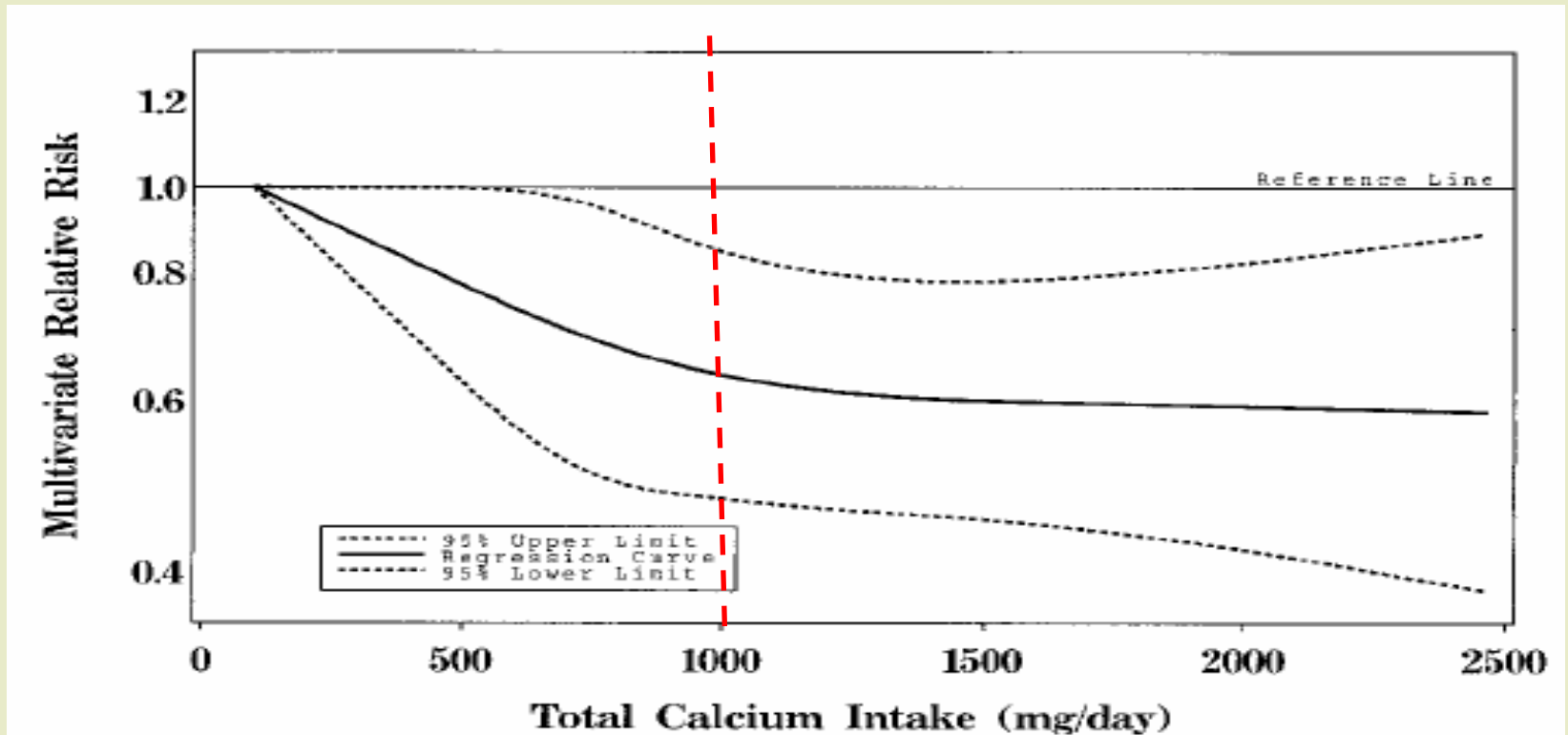
- 99% found in bones and teeth
- Blood and fluid levels tightly regulated
- Recommended intake
  - ✓ 1000-1200 mg
  - ✓ UL: 2500 mg
- Toxicity
  - ✓ Hypercalcemia
- Deficiency
  - ✓ Low blood levels usually due to abnormal parathyroid function
  - ✓ Low intake can lead to bone loss and osteoporosis

# Calcium and Adenoma Recurrence

| <b>Recurrence Type</b>     | <b>RR (95 % CI)</b>     |
|----------------------------|-------------------------|
| <b>Any Adenoma</b>         | <b>0.85 (0.74-0.98)</b> |
| <b>Advanced Adenoma</b>    | <b>0.65 (0.46-0.93)</b> |
| <b>Hyperplastic Polyps</b> | <b>0.82 (0.46-0.93)</b> |

**Baron et al., 1999**  
**Wallace et al., 2004**

# Pooling Project of Prospective Studies Calcium Intake and Colorectal Cancer



**Fig. 2.** Nonparametric regression curve for the relationship between total calcium intake and colorectal cancer. We excluded participants in the top 1% of total calcium intakes in each study to avoid excessive influence of extreme intakes and treated the studies as a single data set.

# WHI: Calcium and Vitamin D and Colorectal Cancer

- Aim: to determine whether calcium plus vitamin D supplementation would help prevent colorectal cancer (designated secondary aim).
- 36,282 post-menopausal women enrolled in the HRT and dietary modification study were invited to participate in the calcium/vit D trial.
- 1000 mg calcium carbonate and 400 IU vitamin D3 vs. placebo.
- Women were followed for a mean of 7.0 years.

# WHI: Calcium/Vit D and Colorectal Cancer

| Cancer type            | Cal/Vit D     | Placebo       | Hazard Ratio        |
|------------------------|---------------|---------------|---------------------|
| Inv. CRC               | 168 (0.13)    | 154<br>(0.12) | 1.08<br>(0.86-1.34) |
| CRC mortality          | 34<br>(0.03)  | 41<br>(0.03)  | 0.82<br>(0.52-1.29) |
| Total cancer mortality | 344<br>(0.72) | 383<br>(0.30) | 0.89<br>(0.77-1.03) |
| Total mortality        | 744<br>(0.58) | 807<br>(0.63) | 0.91<br>(0.83-1.01) |

## WHI: ORs for CRC by Serum 25-OH Vit D Levels

| <b>Baseline Vit D<br/>(nmol/L)</b> | <b>Main effect<br/>OR (95% CI)</b> | <b>Intervention<br/>OR* (95% CI)</b> |
|------------------------------------|------------------------------------|--------------------------------------|
| <b>&gt;=58.4</b>                   | <b>1.00</b>                        | <b>1.15<br/>(0.58-2.27)</b>          |
| <b>42.4-58.3</b>                   | <b>1.96<br/>(1.18-3.24)</b>        | <b>1.12<br/>(0.59-2.12)</b>          |
| <b>31.0-42.3</b>                   | <b>1.95<br/>(1.18-3.24)</b>        | <b>0.99<br/>(0.51-1.91)</b>          |
| <b>&lt;31.0</b>                    | <b>2.53<br/>(1.49-4.32)</b>        | <b>0.75<br/>(0.39-1.48)</b>          |

**\*Estimate of calcium/vit D intervention according to serum level**

# Calcium and Vitamin D and Colorectal Cancer – Implications from WHI Findings

- Personal use of calcium supplements was allowed throughout the study (54% at baseline and 69% at visit 9).
- Mean intake at baseline was 1151 mg/day for calcium and 367 IU/day for vitamin D.
- Recommended intake for vitamin D is probably higher than 400 IU/day.
- Tested the combined effect of calcium and vitamin D.

# Calcium, Vitamin D and Colorectal Cancer

## - Conclusions

- Observational data show that low calcium intake increases risk; unclear whether very high intakes further reduce risk (i.e., threshold effect at 600-1000 mg/day).
- WHI Findings:
  - ✓ Supplementation with 1000 mg of calcium combined with 400 IU of Vit D3 had no effect on the incidence of CRC among post-menopausal women.
  - ✓ Possible that doses of vitamin D were too low whereas calcium was too high.
- WHI Findings are not inconsistent with those of observational studies.
- WHI does not answer the question of whether calcium supplementation confers protection among individuals with low or moderately low calcium intakes.
- Public health message from vitamin D must balance the need for sunshine vs. risk of skin cancer.

## Should calcium and vitamin D be added to the current enrichment program for cereal-grain products?<sup>1,2</sup>

Harold L Newmark, Robert P Heaney, and Paul A Lachance

### ABSTRACT

Mean dietary intakes of calcium and vitamin D in the US adult population are far below the adequate intake (AI) values recommended by the Food and Nutrition Board, Institute of Medicine of the National Academy of Sciences, and thus substantial segments of the American population have inadequate intakes and elevated risks of osteoporosis and colon cancer. The current Code of Federal Regulations, Title 21, sets standards for the optional addition of moderate amounts of calcium and vitamin D in the enrichment of cereal-grain products, a provision that is essentially not used. We propose that the addition of calcium and vitamin D to currently enriched cereal-grain products be mandated in the United States: this would result in an increase in mean daily dietary intakes in the United States of  $\approx 400$  mg Ca and  $\geq 50$  IU (or possibly  $> 200$  IU) vitamin D. The benefits would be a significant reduction in the incidences of osteoporosis and colon cancer over time and overall improvement in health, with little risk and a modest financial cost because of the ability to capitalize on existing technology. We suggest a full scientific review of cereal-grain enrichment with calcium and vitamin D. *Am J Clin Nutr* 2004;80:264–70.

**KEY WORDS** Cereal-grain product enrichment, calcium, vitamin D, osteoporosis, colon cancer

Food Intake by Individuals is shown in **Figure 1** (2). After age 10 y, the data indicate that the mean intake of calcium does not achieve the recommended values for either females or males. After age 50 y, the mean intakes of calcium in females and males are only  $\approx 600$  and  $\approx 700$  mg/d, respectively, and the combined mean intake is only slightly over one-half of the recommended intake. Given normal population variability from the mean, the data indicate that large segments of the US population have inadequate dietary calcium intake.

Vitamin D is largely supplied by synthesis in the skin with sunlight exposure, and this synthesis may be adequate in white-skinned people who are active outdoors, especially in southern states. Older, less active people, especially those with heavily pigmented skin, are more prone to have vitamin D inadequacy. Thomas et al (3) showed that more than one-half the patients admitted to the Massachusetts General Hospital for general medical and surgical conditions had serum 25-hydroxyvitamin D<sub>3</sub> concentrations that were below the laboratory reference value. A recent publication from a group at the Centers for Disease Control and Prevention in Atlanta indicated a high prevalence of hypovitaminosis D in African American women ( $\approx 40\%$ ) and a lower prevalence in white women ( $\approx 4\%$ ) (4). The study was based on data from the third National Health and Nutrition



# Vitamin D: How do we decide on the optimal level?

- Recommended levels are outdated and not based on solid information
- Adequate Intakes: 10-15 mcg/day (200-400 IU/day).
- Upper Limit: 50 mcg/day (2000 IU/day).
- What should the optimal measure of status be:
  - ✓ Intake?
  - ✓ Serum 25-OHD?
  - ✓ PTH levels?
- What should the optimal measure be based on?
  - ✓ Deficiency (rickets, osteomalacia)?
  - ✓ Cancer?
  - ✓ Bone disease?
- What is the magic number for serum 25-OHD levels?
  - ✓ 80 nmol/liter, 32 ng/ml,
- Considerations
  - ✓ Latitude (i.e., Does southern AZ need more vitamin D?)
  - ✓ Race (Dark vs. light skin individuals)
  - ✓ Age (older vs. younger)
  - ✓ BMI (obese vs. non-obese)

# Lessons Learned, Moving Forward

**“As if we were searching for a new therapeutic compound, we have expected high doses of a single nutrient to reproduce the beneficial effects of the complex nutrient mixtures found in whole foods. Perhaps this basic assumption is wrong.”**

**T. Byers, CA Cancer J Clin, 1999**

**“..while the evidence (and prudence) most clearly supports modification of food patterns in order to lower cancer risk, we remain reductionists, forever seeking out the easiest solution, preferably a magic molecule in a pill.”**

**Taylor & Greenwald, 2005**

**“...should the opportunity arise, we should consider taking into account that, as is the case for many nutrients, individuals with lower rather than higher nutrient intakes are likely to benefit the most from supplementation...those who have already exceeded the threshold of prevention may exhibit no added protection.”**

**Martínez & Jacobs, 2006**

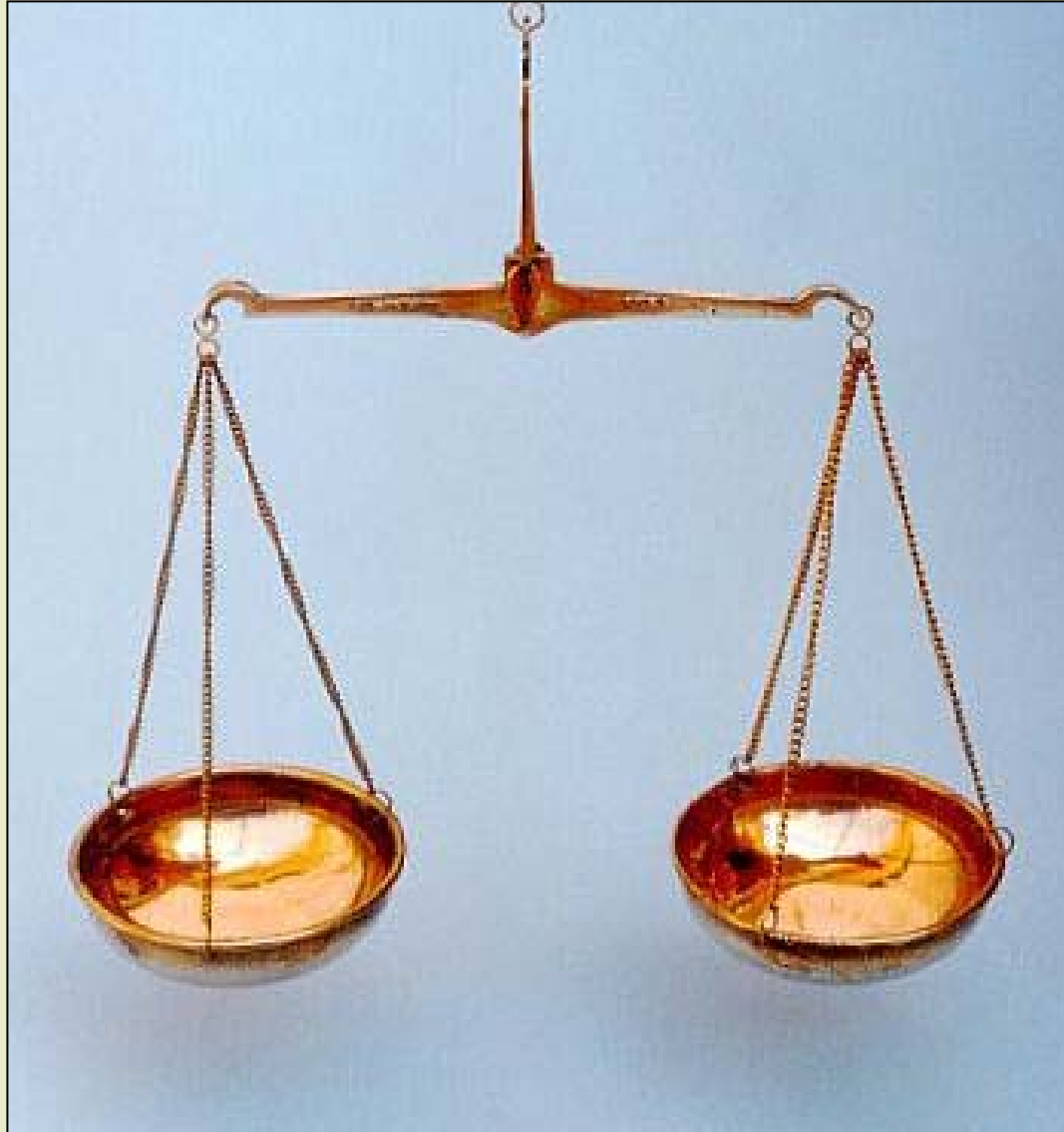


# Micronutrients and Cancer

## Summary and Future Challenges

- Decades of work in the area of micronutrients and cancer have resulted in mixed results.
- Do we continue searching for the “magic bullet”?
- All agents must be suspected of adverse effects; don’t just focus on their potential benefits.
- Must consider testing efficacy of nutrients in individuals with sub-optimal or deficient levels.
- We should critically appraise observational methodology as well as limitations of RCT design.
- Is fortification of the food supply the answer?

# Micronutrients and Cancer Prevention: It's all about Balance!!



# Acknowledgements

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## Clinical Staff

Liane Fales  
Dianne Parish  
Kris Koonce  
Amie Carrier  
Kelly Kaltenhauser

## Analysts

Ruiyun Jiang  
Erin Ashbeck

## Laboratory Staff

Julie Buckmeier  
Nancy Hart  
Mary Krutzch  
Lin Po  
Manuel Snyder

## Study/Data Management:

Fang Wang  
Stefanie Obara  
Jerilyn San Jose  
José Guillén

## BMSS

Ellen Graver  
Vern Hartz  
Robin Whitacre