The Role of Clinical Trials in Nutrition Research

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North Bethesda, MD; Nov. 16, 2016
Learning Objectives

- Levels of Evidence
- Clinical Trials: Pros & Cons
- Importance of Age at Exposure
- Examples of Clinical Trials – Eating Behavior; Vitamins/Minerals; Physical Activity
- Multi-Endpoint Prevention Research
Best Evidence & Frequency

- Randomized Controlled Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Ideas, Opinions

Randomized Controlled Double Blind Studies
Dietary Clinical Trials

Pros

- Strongest basis for inference
- Gives definitive evidence of effect (phase III)
- Builds on epidemiology, basic science, & safety/biomarker end-point trials (phase I-II)
Dietary Clinical Trials

Cons

- Cannot study diet over a life-span
- Participant selection may make it hard to generalize or address disparities
- Not good for rare endpoints/outcomes
Linxian Nutrition Intervention Trial
Linxian China

Consumption of pickled vegetables
### Linxian Nutrition Intervention Trial

**General Population Trial – Linxian**

**Treatment factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Micronutrients</th>
<th>Dose/day</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Retinol</td>
<td>5000 IU</td>
</tr>
<tr>
<td>A</td>
<td>Zinc</td>
<td>22.5 mg</td>
</tr>
<tr>
<td>B</td>
<td>Riboflavin</td>
<td>3.2 mg</td>
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<tr>
<td>B</td>
<td>Niacin</td>
<td>40 mg</td>
</tr>
<tr>
<td>C</td>
<td>Ascorbic acid</td>
<td>120 mg</td>
</tr>
<tr>
<td>C</td>
<td>Molybdenum</td>
<td>30 μg</td>
</tr>
<tr>
<td>D</td>
<td>Selenium</td>
<td>50 μg</td>
</tr>
<tr>
<td>D</td>
<td>β-carotene</td>
<td>15 mg</td>
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<tr>
<td>D</td>
<td>Vitamin E</td>
<td>30 mg</td>
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</tbody>
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### Linxian Nutrition Intervention Trial

#### Population & Study design

<table>
<thead>
<tr>
<th><strong>Population:</strong></th>
<th>29,594 adults 40-69 yr</th>
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<tbody>
<tr>
<td><strong>Design:</strong></td>
<td>½ x 2⁴ fractional factorial, randomized, double-blind, placebo-controlled</td>
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<td><strong>Intervention:</strong></td>
<td>4 different combinations of 9 vitamins, minerals</td>
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<td><strong>Duration:</strong></td>
<td>5¼ yr</td>
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<td><strong>Primary endpoint:</strong></td>
<td>Esophageal cancer incidence, mortality</td>
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*Li et al, Ann Epidemiol 1993*
Linxian Nutrition Intervention Trial
General Population– Linxian
Summary of significant trial results

Selenium, beta-carotene, and vitamin E (factor D) reduced:
- Total mortality (decreased 9%)
- Total cancer mortality (decreased 13%)
- Total gastric cancer mortality (decreased 21%)

Retinol and zinc (Factor A) reduced:
- Gastric non-cardia cancer mortality (decreased 41%)

Blot et al, JNCI 1993
Linxian Nutrition Intervention Trial

**Total mortality by factor D (N=9727)**

Factor D (Selenium, β-carotene, Vitamin E)

Log-rank P=0.001
RR=0.88

Log-rank P=0.443
RR=0.98

Taylor, P. et al., 2006
Linxian Nutrition Intervention Trial

**Cancer mortality by factor D (N=3242)**

Factor D (Selenium, β-carotene, Vitamin E)

- **Log-rank P=0.003**
- **RR=0.85**

- **Log-rank P=0.591**
- **RR=1.02**

Taylor, P. et al., 2006
Linxian Nutrition Intervention Trial

**Stomach cancer mortality by factor D (N=1199)**

Factor D (Selenium, β-carotene, Vitamin E)

Log-rank P=0.044  
RR=0.83

<55 years

Log-rank P=0.326  
RR=0.93

55+ years

Taylor, P. et al., 2006
Linxian Nutrition Intervention Trial

Esophageal cancer mortality by factor D (N=1515)

Log-rank P=0.024
RR=0.83

<55 years

Log-rank P=0.045
RR=1.14

55+ years

Factor D (Selenium, β-carotene, Vitamin E)

Taylor, P. et al., 2006
Women’s Health Initiative
The Dietary Modification Results
Women’s Health Initiative
Clinical Trial Components

Hormone Replacement Therapy vs. Coronary Heart Disease
n=25,000

Calcium/Vitamin D vs. Fractures
n=45,000

Dietary Modification vs. Cancer of Breast, Colon
n=48,000

n=57,000
Invasive Breast Cancer
Dietary Fat: Cumulative Hazard

### Women’s Health Initiative

#### Dietary Fat & Breast Cancer

<table>
<thead>
<tr>
<th>Studied</th>
<th>Did Not Study</th>
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<tr>
<td>Eating Fat</td>
<td>Being Fat</td>
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<tr>
<td>% Calories from Fat</td>
<td>Grams of Fat</td>
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<td>Total Fat</td>
<td>Type of Fat</td>
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<td>Post-menopausal</td>
<td>Pre-menopausal</td>
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<tr>
<td>Breast Cancer Risk</td>
<td>Exercise</td>
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<td>Breast Cancer Prognosis</td>
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Women’s Health Initiative

Fabulous study, BUT some limitations

1. Reductionist thinking may hinder dietary research
2. Public message may ↓ reporting of fat intake
3. Lack of lab measures to validate intake
4. Carcinogenesis takes many years
The VITamin D and OmegA-TriaL (VITAL)
The **VIT**amin D and Omeg**A-3** Tria**L** (**VITAL**): Design

25,874 Initially Healthy Men and Women (Men ≥50 yrs; Women ≥55 yrs)

- Vitamin D<sub>3</sub> (2000 IU/d); N=12,937
  - EPA+DHA (1 gm/d); N=6468
  - Placebo N=6469

- Placebo N=12,937
  - EPA+DHA (1 gm/d); N=6468
  - Placebo N=6469

Mean Treatment Period = 5.0 years
5107 African Americans

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Contents: 31 capsules of vitamin D₃ (2000 IU) or placebo (smaller capsule) and 31 capsules of Omecor® fish oil/ EPA+DHA (1gram/840mg) or placebo (larger capsule).
Take both capsules by mouth each day. Store in a cool, dry place, at temperature not greater than 77° F. Avoid direct sunlight. Do not freeze. Keep out of the reach of children.

Caution: Limited by federal law to investigational use.

VITAL Study: Brigham and Women's Hospital / Harvard Medical School
Toll-free phone: (800) 388-3963
Packaged by: GPSI, Hauppauge, NY GPSI.com
Mechanisms by Which Marine Omega-3 Fatty Acids May Lower Cancer and CVD Risk

Marine Omega-3 Fatty Acids

↓ Cell Proliferation
↑ Apoptosis
↓ Inflammation
↓ Triglycerides
↓ Blood Pressure
↓ Cardiac Arrhythmias
↓ Angiogenesis
↓ Thrombosis

Cancer Prevention
CVD Prevention
Ancillary Studies in VITAL

**Funded**
- Cognitive Function
- Diabetes/Glucose Tolerance
- Hypertension
- Autoimmune Disorders
- Asthma/Respiratory Diseases
- Fractures
- DXA/Bone Microarchitecture
- Diabetic Nephropathy
- Mood Disorders/Depression
- Infections
- 2D Echocardiogram
- Macular Degeneration
- Dry Eye Syndrome
- Anemia
- Atrial Fibrillation
- Adiposity (DXA)
- Mammographic Density
- HTN-related kidney disease

**Supplements**
- Diversity/Race/Ethnicity (NCI)
- Magnesium/Vit D (ODS/NCI)

**Pending**
- Vitamin D Genomics
- Telomere Biology
- Heart Failure
Dear VITAL participant,

Thanks to your collaboration, VITAL is fast becoming one of the most extensive resources in the world for the study of the health effects of vitamin D and omega-3 fatty acids. The primary goal of VITAL is to determine whether these supplements can prevent cancer, heart disease, and stroke, but a number of sub-studies—20 and counting—are focusing on other health outcomes or conditions. The newest sub-study, which received funding from the National Institute of Diabetes and Digestive and Kidney Diseases in April 2015, will examine whether vitamin D and fish oil favorably affect kidney function in men and women with high blood pressure. Two sub-studies that are already well underway are highlighted on page 2 of this newsletter. (Please note that VITAL participants who are eligible for certain sub-studies on the basis of their medical history receive separate invitation letters to join those sub-studies. Participation in sub-studies is optional and does not affect participation in the main trial.) We very much appreciate your continuing support of VITAL. If you have any questions or comments, please feel free to contact us at 1-800-388-3963, vitalstudy@partners.org, or the postal address on page 4. Thank you!

JoAnn Manson, MD
Professor of Medicine
Harvard Medical School
Brigham and Women’s Hospital

Julie Buring, ScD
Professor of Medicine
Harvard Medical School
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**VITAL Q&A**

The Q&A column, a regular feature of the newsletter, takes center stage in this issue.

**Q.** A couple of my friends are taking high-dose vitamin D supplements (that is, more than 800 IU per day) or omega-3 fatty acids (fish oil), but I am not because I am committed to VITAL. Some of my friends think that vitamin D and/or fish oil have already been proven to be beneficial. What should I tell them?

**A.** The reality is that the jury is still out, and that is why VITAL is so important! No previous large randomized clinical trials were designed to test whether vitamin D or fish oil supplements can prevent cancer, heart disease, and stroke in people without a history of these conditions. Many studies on vitamin D and omega-3 fatty acid supplements to date have been observational studies, comparing the health experience of people who self-select to take these supplements to the health experience of non-users. However, other factors in the lifestyles of people who choose to take these supplements may be responsible for the apparent health benefits of vitamin D or omega-3 fatty acids seen in some observational studies. Press reports, particularly headlines, often do not make this clear. Only a large randomized trial such as VITAL can provide clear answers as to whether vitamin D or fish oil are beneficial or are merely markers for healthier lifestyles.

**Q.** I’m in good general health, eat a balanced diet, and do not have osteoporosis, but my doctor has recommended that I take a vitamin D supplement (1000 IU per day) for “insurance,” saying that “it can’t hurt and it might help.” Your thoughts, please?

**A.** VITAL guidelines permit the use of non-study supplemental vitamin D in doses of up to 800 IU per day, which is consistent with the current recommended dietary allowance (RDA) of 600-800 IU per day for adults. If your doctor feels strongly that you should be taking a higher dose, it might be worth discussing your individual health risks and benefits with your doctor.

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VITAL receives a lot of media coverage. For a sample, please take a look at the recently updated “VITAL in the News” section of the VITAL website, www.vitalsudy.org.
Physical Activity
Physical Activity
Clinical Trials are a powerful basis for evidence-based dietary guidelines

There are insufficient clinical trials of eating behavior & cancer risk

Studies of eating behavior over your lifespan require epidemiologic studies linked with laboratory research
Future Outlook

- Biochemical, Immunologic, Molecular & Genetic Cancer Prevention Studies
- Identify & Validate Biomarkers of Exposure & Surrogate End-Points
- Clinical Trials are one part of the Totality of Evidence
- Communicate Successful Prevention Strategies