WHI

Dietary Modification (DM) Trial
WHI – DM Trial

Leslie Ford, MD
Session Moderator

Associate Director of Clinical Research
Division of Cancer Prevention,
National Cancer Institute
National Institutes of Health
Rockville, Maryland
Carolyn Clifford  1941-2001
DM Trial Morning Session I
The Intervention

- Background
- Hypothesis and Design
- The Dietary Change Program
- Personal Accounts of Dietary Change Participants
- Audience Questions
DM Trial
Background and Hypothesis

☐ Background
Maureen Henderson, OBE, MD, DPH

☐ Hypothesis and Design
Ross Prentice, PhD
Dietary Modification Trial

Background

Maureen Henderson, OBE, MD, DPH
Past Principal Investigator
Seattle Clinical Center

Emeritus Professor of Epidemiology and Medicine
University of Washington
Seattle, Washington
Breast Cancer Rates by Country

Breast cancer incidence per 100,000 women 55-69 years of age

Cancer Incidence in Five Continents vol. V. WHO, IARC, 1987
Feasibility & Safety of the Intervention

- **Feasibility**
  - Low-fat eating patterns can be achieved and maintained by women of all ages, income, breast cancer risk levels, and racial and ethnic backgrounds.

- **Safety**
  - No serious side effects during either two year study or among a sample of study women 2 years later.
  - Eating 5+ servings of fruit and vegetables and 6+ servings of grains were made into specific goals for the WHI instead of recommendations as in the two pilot studies.

Women’s Health Trial Vanguard 1984 and Women’s Health Trial: Feasibility in Minority Populations 1995
Colorectal Cancer
Coronary Heart Disease

- WHI designed primarily for breast cancer
- However, WHT pilot studies showed:
  - A persistent reduction in:
    - Total fat intake
    - Saturated fat intake
    - Total blood cholesterol
  - No increase in polyunsaturated fats
- For safety reasons no further changes in P/S ratio were proposed for the WHI
## Women’s Health Trial Vanguard Pilot Study: Intervention Group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat, percent of calories</td>
<td>39.1%</td>
<td>21.6%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Saturated fat, percent of calories</td>
<td>13.8%</td>
<td>7.0%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Blood cholesterol</td>
<td>221 mg/dL</td>
<td>207 md/dL</td>
<td>210 mg/dL</td>
</tr>
</tbody>
</table>

*Prev Med. 1990; 19: 115-133*
Dietary Modification Trial
Hypothesis and Design

Ross Prentice, PhD
Principal Investigator
Clinical Coordinating Center

Member, Public Health Sciences Division
Fred Hutchinson Cancer Research Center
Seattle, Washington
Premise of the DM Trial

International comparisons, time trend and migrant studies, motivated the trial, and led to the basic trial hypothesis for a 20% versus a 40% energy from fat diet.
Feasibility study data were used to specify an adherence assumption.
Breast Cancer Incidence
Age-Adjusted

## Dietary Fat & Postmenopausal Breast Cancer

### Case-control Studies
- **Howe et al (1990, JNCI)**
  - Fat Consumption Quintile: 1 1.20 1.24 1.24 1.46 (p<.0001)

### Cohort Studies
  - Fat Consumption Quintile: 1 1.01 1.12 1.07 1.05 (p=0.21)

**Ability to adequately characterize and adjust for measurement error?**
Underreporting of Energy and Protein

DM Eligibility & Assumptions

- Women having FFQ% energy from fat <32% were excluded.
- National breast cancer incidence rates projected for control group.
- Loss to follow-up and competing risk assumptions incorporated.
- Assumptions combine to give a projected 14% lower breast cancer incidence in the intervention (I) versus the comparison (C) group.
Some Elements of Study Design

- Target sample size 48,000
- Excludes women with prior breast or colorectal cancer
- Age and ethnicity goals
- 40% Intervention; 60% Comparison
- Projected power
  - Invasive breast cancer 86%
  - Colorectal cancer 90%
  - Coronary heart disease 86%
- Dietary intervention program based on NCI-sponsored feasibility studies
DM Trial
Dietary Change Session

☐ Dietary Change Program
  Deborah Bowen, PhD

☐ Predictors of Change
  Lesley Tinker, PhD, RD
The Dietary Change Program

Deborah J. Bowen, PhD
Co-investigator
Clinical Coordinating Center

Professor – University of Washington
Member - Fred Hutchinson Cancer Research Center
Seattle, Washington
Dietary Change Goals: Intervention Group

- 20% energy from fat
- 5 or more fruit and vegetable servings daily
- 6 or more grain servings daily

Photos courtesy of USDA Agricultural Research Service
Packaging the Strategies: Structure of the Intervention

**CORE**
- 18 group sessions
  - Year 1

**BASELINE**
- Motivational Interviewing – 3 personal contacts
- Targeted Messaging – Mailing

**AUGMENTATIONS**
- Tailored Feedback: Personal Evaluation of Fat Intake – Group sessions
- Tailored Feedback: Personal Evaluation of Fat Intake – Mailing
- Clinical Center augmentations

**END OF DM TRIAL**
- Quarterly maintenance sessions
  - Year 2 and beyond
Fats of Life – Fats in Foods

Higher fat meal = 49 fat grams
- Fried chicken breast (3 oz)
- Potato salad (1/2 cup)
- Green beans and bacon (1/2 cup)
- Cornbread (3 by 3 1 inches)

Lower fat meal = 10 fat grams
- Roast chicken breast no skin (3 oz)
- Brown rice (1/2 cup)
- Green beans (1/2 cup) with 1 tsp seasoned oil
- Whole wheat roll, 1 medium
Nutritional strategies

- Fat identification
- Food purchasing
- Food preparation
- Fat budgeting
Behavioral strategies

- Self-Management
- Cognitive behavioral strategies
- Social support and interaction
- Relapse prevention
- Self-determination and self-efficacy
Adherence strategies

- Regular contact
- Record keeping
- Reinforcement of progress

Women’s Health Initiative Picture Tracker

5 or more Fruits/Vegetables – Circle

6 or more Grains - Circle

Low fat foods eaten...

High fat foods eaten...
Augmented interventions

- Motivational interviewing techniques
- Enhanced intervention messages
- Enhanced interventions for special populations
Predictors of Dietary Change

Lesley Tinker, PhD, RD
Co-investigator
Clinical Coordinating Center

Nutrition Scientist
Fred Hutchinson Cancer Research Center
Seattle, Washington
What Have We Learned?

- More lowering of % calories from fat among:
  - *** Women who attended more dietary sessions
  - *** Women who self-monitored their food intake
  - Women less than 65 years of age at baseline
  - White women compared to African American women
  - Women with BMI <35
  - White women compared to Hispanic women
  - Women with household incomes above $20,000 annually
  - Women also randomized to the HT Trial

J Am Diet Assoc. 2004; 104: 654-658
Some of the effect of emotional well-being on fat intake is mediated by session attendance and self-monitoring.

Dietary & Emotional Predictors of Dietary Change

- Higher session attendance or self-monitoring during Year 1
- Higher emotional well-being at baseline
- Lower fat intake at Year 1

J Am Diet Assoc. 2002; 102: 789-800
## Changes in Grams of Fat from Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Baseline</th>
<th>Yr 1 - Base</th>
<th>Yr 2 - Yr 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added fats</td>
<td>16.1</td>
<td>-12.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Meats</td>
<td>13.6</td>
<td>-6.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Desserts</td>
<td>7.1</td>
<td>-6.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Milk, cheese</td>
<td>5.7</td>
<td>-3.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Mixed dishes</td>
<td>6.0</td>
<td>-2.3</td>
<td>0.1</td>
</tr>
<tr>
<td>High-fat breads, salty snacks</td>
<td>3.7</td>
<td>-2.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*J Am Diet Assoc. 2003; 103: 454-460*
DM Trial
Personal Accounts from Participants

Facilitators:
Yasmin Mossavar-Rahmani, PhD (NYC)
Linda Snetselaar, PhD, RD (Iowa)

Participants:
Dolores Buckley (Worcester)
Betty Cintas (Stanford)
Sylvia Grendisa (Buffalo)
Olga Lamarche (Seattle)
Marcia Mazur (George Washington University)
Audience Questions

Leslie Ford, MD

Associate Director of Clinical Research
Division of Cancer Prevention,
National Cancer Institute
National Institutes of Health
Rockville, Maryland
DM Trial – The Results

- Overview and Baseline Demographics
  Norman Lasser, MD, PhD

- Dietary Assessment
  Cynthia Thomson, PhD, RD

- Dietary Change and Biomarkers
  Bette Caan, DrPH
DM Trial – The Results

- Breast Cancer
  Ross Prentice, PhD

- Colorectal Cancer
  Shirley Beresford, PhD

- Heart Disease and Stroke
  Linda Van Horn, PhD, RD

- Summary and Dietary Implications
  Peter Greenwald, MD, DrPH

- Audience Questions
  Leslie Ford, MD (Moderator)
Recruitment, Retention, and Baseline Demographics

Norman Lasser, MD, PhD
Principal Investigator
Newark Clinical Center

Professor of Medicine
University of Medicine and Dentistry of New Jersey, New Jersey Medical School
Newark, New Jersey
373,092 completed the eligibility screening form

56,139 eligible

48,835 randomized

316,953 excluded (refused, low fat intake, info not avail)

7,304 excluded (staff/participant reevaluation, history of breast cancer, other)

Intervention 19,541
Status 3/31/05
17,674 alive & retained
1,867 lost, deceased, or withdrew
19,541 included in analysis

Comparison 29,294
Status 3/31/05
26,677 alive & retained
2,667 lost, deceased, or withdrew
29,294 included in analysis
WHI DM Trial: Race and Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Intervention</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>81.4</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Am. Indian</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

Percent of participants
WHI DM Trial: Age at Baseline

Average age 62.3 years

Percent of participants

Intervention
Comparison

50-59
60-69
70-79
Baseline Physical Characteristics

- **Waist circumference**: 89 cm
- **Physical activity**: 10 METS
- **Smoking**: 93% never or past, 7% current
- **Alcohol**: 28% never or past, 72% current
- **Calories**: 1790

Body Mass Index (BMI) distribution:
- <25
- 25-<30
- 30-<35
- ≥35

Graph showing distribution of participants across BMI categories for Intervention and Comparison groups.
Overlap with WHI Hormone or Calcium Vitamin D Trials

**Hormone Trials**  
- HT - no  
- E-alone active  
- E-alone placebo  
- E+P active  
- E+P placebo  

**Calcium plus D Trial**  
- CaD - no  
- CaD active  
- CaD placebo

- DM Intervention  
- DM Comparison

Percent of participants

- Hormone Trials $p=0.05$
- Calcium plus D Trial $p<0.001$
Generalizability
Baseline characteristics DM and OS

Percent of participants

DM Trial
Observational Study

White Black Hispanic Asian/ Native Am Unknown 50-59 60-69 70-79 BMI
How Was Diet Measured?

Study Start
- Food Frequency Questionnaire All
- 4-day food records Case only analysis

Year 1
- Food Frequency Questionnaire All
- 4-day food records 4.6% of participants

Year 2→Close-out
- Food Frequency Questionnaire Rotating 1/3 of participants
- Repeat (x2) 24 hr Recalls 4.6% of participants
- 24 hour recalls 1% of participants

Year 3,6,9
- Assess change in intake over time
- Assess intervention effects
- Calibrate with other diet measures

Dietary
WHI Food Frequency Questionnaire

<table>
<thead>
<tr>
<th>Type of Food</th>
<th>How Often Did You Eat the Food (Mark one)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never or less than once per month</td>
<td>Medium Serving Size</td>
</tr>
<tr>
<td></td>
<td>1 per month</td>
<td>1 per week</td>
</tr>
<tr>
<td></td>
<td>2-3 per week</td>
<td>2-3 per week</td>
</tr>
<tr>
<td></td>
<td>1 per day</td>
<td>1 per day</td>
</tr>
<tr>
<td></td>
<td>2-5 per day</td>
<td>2-5 per day</td>
</tr>
<tr>
<td></td>
<td>5+ per day</td>
<td>5+ per day</td>
</tr>
</tbody>
</table>

During the last three (3) months...

<table>
<thead>
<tr>
<th>Type of Food</th>
<th>How Often Did You Eat the Food (Mark one)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never or less than once per month</td>
<td>Medium Serving Size</td>
</tr>
<tr>
<td></td>
<td>1 per month</td>
<td>1 per week</td>
</tr>
<tr>
<td></td>
<td>2-3 per week</td>
<td>2-3 per week</td>
</tr>
<tr>
<td></td>
<td>1 per day</td>
<td>1 per day</td>
</tr>
<tr>
<td></td>
<td>2-5 per day</td>
<td>2-5 per day</td>
</tr>
<tr>
<td></td>
<td>5+ per day</td>
<td>5+ per day</td>
</tr>
</tbody>
</table>

**FRUITS AND JUICES**

<table>
<thead>
<tr>
<th>Fruit Type</th>
<th>How Often Did You Eat the Food (Mark one)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apples and pears</td>
<td>1 medium or 1/2 cup</td>
<td>Medium Serving Size</td>
</tr>
<tr>
<td>Banana</td>
<td>1 medium</td>
<td>Medium Serving Size</td>
</tr>
<tr>
<td>Peaches, nectarines and plums (fresh or canned)</td>
<td>1 medium or 1/2 cup</td>
<td>Medium Serving Size</td>
</tr>
<tr>
<td>Cantaloupe, orange melon, muskmelon, mango and papaya</td>
<td>1/4 melon or 1 cup</td>
<td>Medium Serving Size</td>
</tr>
<tr>
<td>Watermelon and red melons</td>
<td>1 medium or 1 cup</td>
<td>Medium Serving Size</td>
</tr>
<tr>
<td>All other melon, such as honeydew</td>
<td>1 medium slice or 1 cup</td>
<td>Medium Serving Size</td>
</tr>
</tbody>
</table>
# Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Food Frequency</th>
<th>Records</th>
<th>Recalls</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Long term eating</td>
<td>- Short term eating</td>
<td>- Short-term eating</td>
</tr>
<tr>
<td>- Low participant burden</td>
<td>- More detail</td>
<td>- More detail</td>
</tr>
<tr>
<td>- Administer by mail</td>
<td>- Participant burden</td>
<td>- Less report bias</td>
</tr>
<tr>
<td>- Cost-effective</td>
<td>- Completeness</td>
<td>- Ability to make contact</td>
</tr>
<tr>
<td></td>
<td>- Behavior change</td>
<td>- Ability to recall</td>
</tr>
<tr>
<td></td>
<td>- More costly</td>
<td>- More costly</td>
</tr>
</tbody>
</table>

- Limited foods
- Less detail
- Ability to recall
- Report bias

- Participant burden
- Completeness
- Behavior change
- More costly

- Participant burden
- Ability to make contact
- Ability to recall
- More costly
Dealing with Uncertainty

- Multiple measures of self-report
- Biomarkers
  - Double-labeled water – caloric intake
  - Urinary nitrogen – protein
  - Plasma carotenoids – fruit and vegetable intake
- Composite of self-report and biomarkers
- WHI DM Nutritional Biomarkers Study
  - Assess factors that influence the accuracy of self-report
  - Develop mathematical formulae for improving self-report of caloric intake
Dietary Intake: Percent Calories from Fat

Howard BV et al. JAMA Feb 2006

C-I, actual = 10.7
C-I, design = 13

C-I, actual = 8.2
C-I, design = 11
Dietary Changes in the Intervention Group: Types of Fat

- Monounsaturated: Baseline 12.7, Year 2 8.9, Year 5 10.8
- Saturated: Baseline 7.8, Year 2 5.2, Year 5 9.5
- Polyunsaturated: Baseline 0.6, Year 2 0.7, Year 5 0.7
- P/S Ratio: Baseline 0.7

JAMA 2006; 295; 655-666
Dietary Intake: Fruits and Vegetables

<table>
<thead>
<tr>
<th>Year</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Yr 1</td>
<td>3.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Year 2</td>
<td>3.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Yr 3</td>
<td>3.8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

JAMA 2006; 295; 655-666
Dietary Intake:
Grains & Whole Grains

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Yr 1</th>
<th>Year 2</th>
<th>Yr 3</th>
<th>Yr 4</th>
<th>Yr 5</th>
<th>Yrs 5, 6, 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grains</strong></td>
<td>4.8</td>
<td>5.1</td>
<td>4.2</td>
<td>4.1</td>
<td>4.0</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Whole Grains</strong></td>
<td>1.1</td>
<td>1.4</td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1</td>
</tr>
</tbody>
</table>

JAMA 2006; 295; 655-666
# Nutrient Intakes & Blood Biomarkers

<table>
<thead>
<tr>
<th>Daily Nutrient Intakes</th>
<th>Baseline</th>
<th>Baseline-Year 3, Inter-Cont</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate (dietary), μg</td>
<td>259</td>
<td>+ 62 (+24.5%**)</td>
</tr>
<tr>
<td>Fiber, g</td>
<td>15.4</td>
<td>+ 3.1* (+20.0%)</td>
</tr>
<tr>
<td>Red meats, servings</td>
<td>0.9</td>
<td>- 0.2 (-22.0% **)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarkers in Blood</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>224</td>
<td>- 3.3 *</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>133</td>
<td>- 3.6 *</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>60.1</td>
<td>- 0.4</td>
</tr>
<tr>
<td>Total carotenoids, μg/dL</td>
<td>0.88</td>
<td>+ 0.04 (+ 5% )</td>
</tr>
<tr>
<td>Gamma tocopherol, μg/dL</td>
<td>2.3</td>
<td>- 0.21 *</td>
</tr>
</tbody>
</table>

* p<.05
** p<.001

JAMA 2006; 295; 629-642; JAMA 2006; 295; 642-654; JAMA 2006; 295; 655-666
Changes in Body Weight

Mean Difference (kg)

Years of Intervention

Intervention
Control

JAMA 2006; 295; 39-49
Breast Cancer

Ross Prentice, PhD
Principal Investigator
Clinical Coordinating Center

Member, Public Health Sciences Division
Fred Hutchinson Cancer Research Center
Seattle, Washington
## Risk of Breast Cancer and Other Major Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intervention Cases = 655</th>
<th>Comparison Cases = 1072</th>
<th>Hazard Ratio (95% CI)</th>
<th>Unweighted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>0.42%</td>
<td>0.45%</td>
<td>0.91 (0.83-1.01)</td>
<td>.07</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.77 (0.48-1.22)</td>
<td>.26</td>
</tr>
<tr>
<td><strong>Total cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>1.23%</td>
<td>1.28%</td>
<td>0.96 (0.91-1.02)</td>
<td>.15</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.28%</td>
<td>0.29%</td>
<td>0.95 (0.84-1.07)</td>
<td>.41</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.60%</td>
<td>0.61%</td>
<td>0.98 (0.91-1.02)</td>
<td>.70</td>
</tr>
<tr>
<td>Global index</td>
<td>1.30%</td>
<td>1.35%</td>
<td>0.96 (0.91-1.02)</td>
<td>.16</td>
</tr>
</tbody>
</table>

JAMA 2006; 295; 629-642

Dietary
**Breast Cancer: Cumulative Hazard Ratios**

1,727 total diagnoses
3.5% of all DM participants

HR, 0.91 (95% CI, 0.83-1.01)

*Comparison*

*Intervention*

JAMA 2006; 295; 629-642
Blood Hormone Concentrations

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reduced</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>0.85</td>
<td>1.09</td>
</tr>
<tr>
<td>Estrone</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Estrone-sulfate</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Sex hormone binding globulin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative Change from Baseline

JAMA 2006; 295; 629-642
### Hazard Ratios by Dietary Factors

<table>
<thead>
<tr>
<th>Baseline Quartiles (4DFR)</th>
<th>Inter Cases</th>
<th>Comp Cases</th>
<th>Mean I-C % cal fat</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% energy from fat (kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 27.9</td>
<td>144</td>
<td>222</td>
<td>-9.7</td>
<td>0.97 (0.79, 1.20)</td>
<td>0.04</td>
</tr>
<tr>
<td>27.9 - &lt; 32.3</td>
<td>186</td>
<td>259</td>
<td>-10.4</td>
<td>1.08 (0.89, 1.30)</td>
<td></td>
</tr>
<tr>
<td>32.3 - &lt; 36.8</td>
<td>160</td>
<td>283</td>
<td>-11.7</td>
<td>0.85 (0.70, 1.03)</td>
<td></td>
</tr>
<tr>
<td>≥ 36.8</td>
<td>151</td>
<td>291</td>
<td>-12.2</td>
<td>0.78 (0.64, 0.95)</td>
<td></td>
</tr>
<tr>
<td>Vegetables and fruits (sv/day)</td>
<td></td>
<td></td>
<td>sv/day</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>&lt; 2.3</td>
<td>155</td>
<td>259</td>
<td>1.3</td>
<td>0.90 (0.73, 1.09)</td>
<td></td>
</tr>
<tr>
<td>2.3 - &lt; 3.3</td>
<td>158</td>
<td>268</td>
<td>1.3</td>
<td>0.88 (0.72, 1.07)</td>
<td></td>
</tr>
<tr>
<td>3.3 - &lt; 4.6</td>
<td>144</td>
<td>264</td>
<td>1.2</td>
<td>0.82 (0.67, 1.00)</td>
<td></td>
</tr>
<tr>
<td>≥ 4.6</td>
<td>197</td>
<td>276</td>
<td>1.0</td>
<td>1.08 (0.90, 1.29)</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline Quartiles (4DFR)**

**Cases = 655**

**Cases = 1072**

**% cal fat**

**Hazard Ratio (95% CI)**

**Interaction**

*JAMA 2006; 295; 629-642*
Interpretation

- Intensive intervention resulted in significant and sustained dietary fat reduction and vegetable and fruit increase.
- Observed 9% lower breast cancer rate (15% among “adherent women”) may be attributable to chance.

JAMA 2006; 295; 629-642
Interpretation (continued)

- Longer follow-up needed for a more definitive evaluation of low-fat eating pattern and breast cancer hypothesis:
  - Power reduced by 8.1 rather than 9 years of average follow-up and by less than targeted adherence.
  - Greater evidence of breast cancer reduction among women having higher baseline % energy from fat.

JAMA 2006; 295; 629-642
Colorectal Cancer

Shirley A.A. Beresford, PhD
Principal Investigator
Seattle Clinical Center

Professor, Epidemiology – University of Washington
Member - Fred Hutchinson Cancer Research Center
Seattle, Washington
Colorectal Cancer

Objective:

To evaluate the effects

- of a low-fat dietary pattern
- on risk of colorectal cancer
- in postmenopausal women
Colorectal Cancer: Cumulative Hazard Ratios

480 total diagnoses (1% of all DM participants)

JAMA 2006; 295; 642-654
Colorectal Cancer: Annualized Rates and Hazard Ratios

HR = 1.08
(0.90, 1.28)

HR = 1.25
(0.96, 1.61)

HR = 0.86
(0.56, 1.19)

HR = 1.11
(0.77, 1.61)

Cases per year per 10,000 women

Total Proximal Distal Rectal

HR = 1.08
(0.90, 1.28)

HR = 1.25
(0.96, 1.61)

HR = 0.86
(0.56, 1.19)

HR = 1.11
(0.77, 1.61)

JAMA 2006; 295; 642-654
Bowel Examinations: Polyps/Adenomas

Examination Rate, Percent

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Rectal Exam</th>
<th>Hemoccult guaiac</th>
<th>Sigmoidoscopy/flex. sig/colonoscopy</th>
<th>Barium enema x-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>35.0</td>
<td>25.0</td>
<td>15.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Year 2</td>
<td>33.0</td>
<td>23.0</td>
<td>14.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Year 3</td>
<td>31.0</td>
<td>21.0</td>
<td>13.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Year 4</td>
<td>29.0</td>
<td>19.0</td>
<td>12.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Year 5</td>
<td>27.0</td>
<td>17.0</td>
<td>11.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Year 6</td>
<td>25.0</td>
<td>15.0</td>
<td>10.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Year 7</td>
<td>23.0</td>
<td>13.0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Year 8</td>
<td>21.0</td>
<td>11.0</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Year 9+</td>
<td>19.0</td>
<td>9.0</td>
<td>7.0</td>
<td></td>
</tr>
</tbody>
</table>

JAMA 2006; 295; 642-654

HR, 0.91
95% CI, 0.87-0.95
### Colorectal Cancer Hazard Ratios by Baseline Participant Characteristics

<table>
<thead>
<tr>
<th>Study Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at enrollment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 yr</td>
<td>0.87 (0.67-1.12)</td>
<td>0.18</td>
</tr>
<tr>
<td>60-69 yr</td>
<td>1.00 (0.82-1.23)</td>
<td>0.92</td>
</tr>
<tr>
<td>70-79 yr</td>
<td>1.44 (1.07-1.94)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Aspirin use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.90 (0.70-1.16)</td>
<td>0.54</td>
</tr>
<tr>
<td>&lt; 325 mg</td>
<td>1.24 (0.98-1.58)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt; 325 mg</td>
<td>1.10 (0.89-1.35)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Baseline current E-alone user or randomized to E-alone active arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.62 (0.40-1.00)</td>
<td>0.19</td>
</tr>
<tr>
<td>No</td>
<td>1.19 (0.89-1.58)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Baseline current E+P user or randomized to E+P active arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.62 (0.40-1.00)</td>
<td>0.19</td>
</tr>
<tr>
<td>No</td>
<td>1.19 (0.89-1.58)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

JAMA 2006; 295; 642-654
Colorectal Hazard Ratios by Baseline Dietary Factors

**Dietary energy (kilocalories)**
- <1391.8
- 1391.8 – <1663.6
- 1663.6 – <1958.7
- 1958.7 +

**Dietary percent energy from fat**
- <27.9
- 27.9 – 32.3
- 32.3 – 36.8
- 36.8 +

**Alcohol intake**
- Never Drinker
- Past Drinker
  - < 1 drink per day
  - 1+ drink per day

<table>
<thead>
<tr>
<th><strong>P Value</strong></th>
<th><strong>Hazard Ratio</strong></th>
<th><strong>95% CI</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

JAMA 2006; 295; 642-654
The low fat dietary pattern intervention did not reduce the risk of colorectal cancer over 8.1 years.

Reduction in polyps and adenomas associated with the intervention suggest longer follow-up is needed before long term effects can be ruled out.
Cardiovascular Disease
(Heart Disease and Stroke)

Linda Van Horn, PhD, RD
Principal Investigator
Chicago Northwestern Clinical Center

Professor,
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Definitions

- **Coronary heart disease (CHD):**
  Heart attack, heart bypass surgery, stent, or angioplasty

- **Stroke:**
  Lack of blood flow to the brain or bleeding in the brain leading to weakness or paralysis, and impairment of speech or other functions

JAMA 2006; 295; 655-666
Coronary Heart Disease: Cumulative Hazard Ratios

MI, CHD death or Revascularization

HR, 0.97 (95% CI, 0.90-1.06)

2,549 total diagnoses (5% of all DM participants)

Hazard ratio = 0.97 (95% CI = 0.90-1.06)

JAMA 2006; 295; 655-666
Stroke: Cumulative Hazard Ratios

1,076 total diagnoses
(2% of all DM participants)

Hazard Ratio = 1.02
(95% CI = 0.90-1.15)

JAMA 2006; 295; 655-666
## Changes in Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Baseline</th>
<th>Difference at year 3 (I-C)</th>
<th>* p&lt;.05; ** p&lt;.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>133</td>
<td>- 3.6 *</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76</td>
<td>- 0.3 **</td>
<td></td>
</tr>
<tr>
<td>Factor VIIC, %</td>
<td>131</td>
<td>- 4.9 **</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mg/dL`</td>
<td>139</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>60</td>
<td>- 0.4</td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>100</td>
<td>- 1.1</td>
<td></td>
</tr>
<tr>
<td>Insulin, µIU/mL</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*JAMA 2006; 295; 655-666*
# Changes in Types of Fat

<table>
<thead>
<tr>
<th>Type of fat</th>
<th>Baseline</th>
<th>Difference: Yr 1 (I-C)</th>
<th>Difference: Yr 6 (I-C)</th>
<th>* p&lt;.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat, % calories</td>
<td>12.7</td>
<td>- 3.7 *</td>
<td>- 2.9 *</td>
<td></td>
</tr>
<tr>
<td>Trans fat, % calories</td>
<td>2.7</td>
<td>- 0.8 *</td>
<td>- 0.6 *</td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated fat, % calories</td>
<td>7.8</td>
<td>- 2.0 *</td>
<td>- 1.5 *</td>
<td></td>
</tr>
<tr>
<td>P/S ratio</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* JAMA 2006; 295; 655-666
Additional Analyses: Heart Disease Risk

Intake at Year 1

- Saturated fat <6.1% calories
- Trans fat <1.1% calories
- Fruit/vegetable ≥6.5 servings

Decreased Risk

JAMA 2006; 295; 655-666
Cardiovascular Disease: Conclusions

- Postmenopausal women who initiated a low fat dietary pattern had no significant reductions in coronary heart disease, stroke, or cardiovascular disease (CVD) after 8.1 years.

- Some CVD risk factors were modestly improved, especially among women with greater adherence to dietary recommendations.

- Interventions on specific dietary factors known to influence risk of CVD and potentially initiated younger in life may be needed to improve risk factors and CVD risk.

JAMA 2006; 295; 655-666
Women’s Health Initiative
The Dietary Modification Results
Summary & Dietary Implications

Peter Greenwald MD, DrPH
Division of Cancer Prevention
National Cancer Institute, NIH
February 28, 2006
## Women’s Health Initiative
### Dietary Fat & Breast Cancer

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

Breast Cancer Prognosis
Women’s Health Initiative

Fabulous study, BUT some limitations

1. Reductionist thinking hinders dietary research
2. Public message may ↓ reporting of fat intake
3. Lack of lab measures to validate intake
4. Carcinogenesis takes many years
The Causes of Cancer

Diet 35%
Other Factors 35%
Tobacco 30%
What is the Right Message?

Reduce consumption of fat (especially saturated fat) and cholesterol

Consume nutritionally adequate and varied diets, based primarily on foods of plant origin

Choose a diet low in fat, saturated fat, and cholesterol

U.S. Department of Agriculture
U.S. Department of Health and Human Services
One Size Doesn’t Fit All
Steps to Healthier You

- Make smart choices from every food group
- Find your balance between food and physical activity
- Get the most nutrition out of your calories
Nutrigenomics & Beyond
Mapping Individual Health

DIET &
  - Gene polymorphisms
  - Nutritional Epigenomics
  - Transcriptomics
  - Proteomics
  - Metabolomics
1. ↑ Basic Nutritional Science
   • …omics ↔ …ologies
2. Truly Validated Markers of Dietary Intake, Effect (Molecular Targets) & Susceptibility
   • At various times of life
3. ↑ Research on Bioactive Food Compounds
4. ↑ Research & Development of Engineered Foods
5. ↑ Dietary Intervention Trials
6. ↑ Robust Nutritional Science at NIH
   • Intramural & Extramural
7. Long-term Follow-up of WHI Participants
Nutrition “is the ultimate biochemical interaction – the human organism reacting with the environment, daily, in a very intimate sense. And it’s been starved for research funding.”

Bernadine Healy, 2004
Audience Questions

Leslie Ford, MD

Associate Director of Clinical Research
Division of Cancer Prevention,
National Cancer Institute
National Institutes of Health
Rockville, Maryland