Plenary 5: Long-term Influence of the WHI Dietary Modification Trial Intervention on Chronic Disease Incidence and Mortality

Opening Remarks/ Introductions

Mortality from and mortality after cancer diagnoses in the Dietary Modification Trial with long-term follow-up

Rowan Chlebowski, MD, UCLA

Cardiovascular disease and total mortality in the Dietary Modification Trial with long-term follow-up

Ross Prentice, PhD, Fred Hutchinson Cancer Research Center

Long-term effects of the Dietary Modification Trial intervention on diabetes incidence and severity

Barbara Howard, PhD, Medstar
Hormone Therapy Trials: Coronary Heart Disease & Fractures. Adverse effect for Breast Cancer?

Calcium/Vitamin D Trial: Fractures & Colorectal Cancer

Dietary Modification Trial of Low-fat diet compared to usual diet: Breast & Colorectal Cancers & Coronary Heart Disease

Observational Study

161,808 postmenopausal women
1993-2005
2005-2010: n = 115,407
2010-2015: n = 93,558
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**
- **Year 3,6,9**
  - Repeat (x2) 24 hr Recalls
  - 4.6% of participants

**24 hour recalls**
- 1% of participants

Assess change in intake over time
- Assess intervention effects
- Calibrate with other diet measures
# The Women’s Health Initiative: Scholarly Productivity

<table>
<thead>
<tr>
<th>Publications/Studies</th>
<th>Total Number to Date</th>
</tr>
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<tbody>
<tr>
<td>WHI Publications</td>
<td>1,498</td>
</tr>
<tr>
<td><strong>Diet/Nutrition Publications</strong> (1996-2017; 16% of total)</td>
<td></td>
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<tr>
<td>Cancer</td>
<td>56 (23%)</td>
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<tr>
<td>Cardiovascular</td>
<td>43 (18%)</td>
</tr>
<tr>
<td>Ca/D Bone/Osteoporosis</td>
<td>22 (9%)</td>
</tr>
<tr>
<td>Diet Assessment/Methods</td>
<td>26 (11%)</td>
</tr>
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WHI Dietary Modification Trial: Percent Calories from Fat

Howard BV et al. *JAMA* Feb 2006
Dietary Changes in the Intervention Group: Types of Fat

- Monounsaturated: 14.4, 12.7, 8.9, 10.8, 9.5
- Saturated: 7.8, 5.2, 8.1, 6.1
- Polyunsaturated: 0.6, 0.7, 0.7
- P/S Ratio: 0.7

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>
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<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>
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<tr>
<th>Biomarkers in Blood</th>
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<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
Coronary Heart Disease: Cumulative Hazard Ratios

MI, CHD death or Revascularization

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

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

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

Intake at Year 1

- Saturated fat
  \(<6.1\% \text{ calories}

- Trans fat
  \(<1.1\% \text{ calories}

- Fruit/vegetable
  \(\geq 6.5\text{ servings}

Howard JAMA 2006; 295; 655-666
Subsequent Diet Publications Including OS (mostly)/DM/CaD/HT

Examples:

- Dietary Patterns and Adherence: HEI, AHEI, DASH, Mediterranean, Inflammatory Index (Belin, 2011, Van Horn, 2012; Tabung, 2016; Orchard, 2016)
- Diet and Heart Failure (Belin, 2011; Levitan, 2013)
- Diet and Cancer (DM–Post Stop) (Thomson, 2014)
- Other diet/lifestyle studies (Mossavar-Rahmani, 2013; Bertoia, 2014)
Hypothesis: Mediterranean and DASH diets, foods and nutrients affect cholesterol, inflammation, the development of atherosclerosis, and risk SCD.

OBJECTIVE: Examine associations between the Mediterranean and DASH dietary patterns and risk of SCD (occurred within 1 h of symptom onset).

DESIGN: Prospective cohort of 93,122 WHI participants followed 10.5 y. FFQ scored based on adherence to each dietary pattern

RESULTS: Higher Mediterranean diet score associated with lower risk of SCD (HR: 0.64; 95% CI: 0.43, 0.94) comparing highest/ lowest quintiles (adjusted). Higher DASH diet score not associated with risk of SCD. (Sodium intake, a DASH focus, not well quantified by FFQ)

CONCLUSION: Mediterranean dietary pattern may be associated with lower risk of SCD

Mediterranean and DASH Diet Scores and Mortality in Women With Heart Failure: WHI

Levitan, E; Lewis, C; Tinker, L; Eaton, C; Ahmed, A; Manson, J; Snetselaar, L; Martin, L; Trevisan, M; Howard, B; Shikany, J

Background: Recommended diet for prevention/treatment of heart failure (HF) are inconclusive and derived from non-HF populations; influence of dietary patterns, e.g, Mediterranean and DASH diet scores on HF mortality is limited.

Methods and Results: participants followed from HF hospitalization through date of death or last contact before August 2009. Mediterranean and DASH diet scores calculated from FFQ data. Cox proportional hazards models adjusted for demographics, health behaviors, and health status used to calculate hazard ratios and 95% CI. Over 4.6 years of follow-up, 1385 of 3215 (43.1%) of HF ptps died. Multivariable-adjusted hazard ratios were 1 (reference), 1.05 (95% CI, 0.89–1.24), 0.97 (95% CI, 0.81–1.17), and 0.85 (95% CI, 0.70–1.02) across quartiles of the Mediterranean diet score (P trend=0.08) and 1 (reference), 1.04 (95% CI, 0.89–1.21), 0.83 (95% CI, 0.70–0.98), and 0.84 (95% CI, 0.70–1.00) across quartiles of the DASH diet score (P trend=0.01).

CONCLUSIONS: Higher DASH diet scores were associated with modestly lower mortality in women with HF, and there was a nonsignificant trend toward an inverse association with Mediterranean diet scores. Vegetables, nuts, and whole grains inversely associated with mortality.

Circ Heart Fail. 2013;6:1116-1123.
Risk of Heart Failure Among Postmenopausal Women
A Secondary Analysis of the Randomized Trial of Vitamin D Plus Calcium of the Women’s Health Initiative

M. Donneyong; C Hornung; K Taylor; R Baumgartner; J Myers; C Eaton; E Gorodeski; L Klein; L Martin; J Shikany; Y Song; W Li; J Manson

**CONCLUSIONS:** CaD supplementation did not significantly reduce HF incidence in the overall cohort, but was beneficial among postmenopausal women without major HF precursors and little value in high-risk subgroups.

*Circ Heart Fail.* 2015;8:49-56.
Nutrient and Physical Activity Biomarkers in the WHI
Ross Prentice, Fred Hutch and University of Washington

Nutrient Biomarker Study: 544 women completed two-week DLW protocol with urine and blood collection and with FFQ and other questionnaire data collection (50% intervention, 50% control). A 20% reliability subsample repeated protocol separated, by about 6 months from original data collection. (NBS)

Nutrition and Physical Activity Assessment Study Biomarker study among 450 women in the WHI Observational Study for calibrating baseline FFQ, 4DFR, and PA questions, and for evaluating measurement properties of prominent dietary and physical activity assessment approaches (frequencies, records, and recalls) and their combination. (NPAAS)
Women’s Health Initiative Nutrition Research Gaps

1. ↑ Basic Nutritional Science to complement diet data
   • targeted metabolomics and other “omics”
2. Validated Biomarkers of Dietary Intake, Effect (Molecular Targets) & Susceptibility at various times of life
3. Validated calibration of WHI FFQ data
4. ↑ Research on Bioactive/Engineered Food Compounds
5. ↑ Diet Intervention/Feeding Studies (Lampe, 2016)
6. Diet quality and longevity 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
Acknowledgements

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