Women’s Health Initiative (WHI)

Clinical Trials (CT)

- Diet Modification (DM)
- Hormone Replacement Therapy (HRT)
- Calcium + Vitamin D (CaD)

Observational Study (OS)
WHI Organizational Chart

- **NHLBI Director**
- **Data & Safety Monitoring Board**
- **Consortium of NIH Directors**

**WHI Program Office**

- **Working Group** (NHLB Advisory Council)
- **Performance Monitoring Committee (PMC)**

**WHI Steering Committee (SC)**

- [40 Clinical Center (CC) PIs + CCC PI + PO rep.]
- Executive Committee (8 members)

**Coordinating Center (CCC)**

- FHCRC

**4 Regional Groups of 9-12 CCs**

- CC PIs; Lead Staff Groups (5/Reg)

**Advisory Committees**

- DM, HRT, CaD, OS
- Special Pop., Behavioral
- D&A, P&P, M&M
WHI CT Sample Size, Outcomes, Follow-up

Diet Modification (DM) Trial
- Primary Outcomes: Breast & Colorectal Cancer
- Secondary Outcome: CHD

Hormone (HRT) Trial
- Primary Outcome: CHD
- Secondary Outcomes: Hip Fracture, Breast Cancer

DM
48,836
Average Follow-up 8.5 years
11.8% Overlap

HRT
27,347
Average 8.4 years

Women, aged 50-79  Total CT = 68,133
Background for Diet/Cancer Hypothesis

- USA National Cancer Act of 1971
- Symposium on Nutrition and Causes of Cancer (AACR, 1975) National Cancer Institute & American Cancer Society
- Diet, Nutrition, and Cancer, 1982, National Academy of Science
- Scientific Evidence from many types of studies (Descriptive, Correlation, Special Exposure Groups, Migrant, Case-Control, Cohort, and Controlled Trials) was evaluated and rated as Convincing, Probable, Possible, or Insufficient to make judgements on causal relationships of dietary factors: decreases risk, increases risk, or no relationship
WHI Diet Trial: Intervention Goals
40% of DM Sample (N=19,542)

溘 Total Fat Intake $\leq$ 20% of Daily Calories
  Saturated Fat $\leq$ 7% of Daily Calories

溘 Vegetable+Fruit intake $\geq$ 5 servings/day

溘 Grains, Cereals, Legumes $\geq$ 6 servings/day

溘 Maintain these dietary changes for 9 years
Background for HRT Study Hypothesis

<table>
<thead>
<tr>
<th>•Observational Studies</th>
<th>•Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>🌺 LRC Prevalence Study (1983,1987)</td>
<td>🌺 PEPI (1995) post-m. women, aged 45-64. HRT improved HDL (ERT &gt; PERT), LDL, and fibrinogen, but increased TG.</td>
</tr>
<tr>
<td>🌺 Nurses’ Health Study (1985, 91)</td>
<td>🌺 HERS (1998) women with CHD, aged 50-79. No benefit from HRT (CEE+MPA) in reducing fatal+non-fatal MI; incr. DVT, PE, gallbladder disease</td>
</tr>
<tr>
<td>🌺 Framingham Study (1985)-reversed</td>
<td>🌺 WHI (2005)</td>
</tr>
<tr>
<td>🌺 Nurses’ Health Study (1997) PERT</td>
<td></td>
</tr>
<tr>
<td>🌺 &gt; 20 other Observational Studies HRT users vs nonusers (generally): fewer smokers, more physically active, leaner, healthier, at lower risk, more educated, higher SES</td>
<td></td>
</tr>
</tbody>
</table>
WHI HRT Trial (N=27,347): Treatments
Adherence < 80% initiates Intensive Adherence Program

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>Women with a Uterus (55% by design): Actual = 60.7% (N=16,608)</th>
<th>Women with a Hysterectomy (45%): Actual = 39.3% (N=10,739)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen with Progestin (50%)</td>
<td>Conjugated Equine Estrogen (CEE) - 0.625 mg/day + Medroxyprogesterone Acetate - 2.5 mg/day (daily MPA)</td>
<td>Estrogen only (50%)</td>
</tr>
<tr>
<td>or Placebo (50%)</td>
<td></td>
<td>or Placebo (50%)</td>
</tr>
</tbody>
</table>
WHI CT: Baseline Age Distribution
Mean ± S.D.: DM = 62.3 ± 6.9; HRT = 63.4 ± 7.2

Goal: 50-54=10%; 55-59=20%; 60-69=45%; 70-79=25%

- 50-59
  DM=37%; HRT=32%
- 60-69
  DM=47%; HRT=45%
- 70-79
  DM=17%; HRT=22%
WHI CT (DM+HRT): Minority Distribution
Total CT = 68,133   Minorities = 12,462 (18.3%)

- Black: 10.3%
- Hispanic: 4.2%
- Asian/PI: 2.2%
- Native American: 0.4%
- Other: 1.1%

CT (81.5% Whites; 0.2% Unspecified)
WHI CT: Baseline Body Mass Index (kg/m²)

Mean BMI: DM = 29.1 ± 6.0; HRT = 29.1 ± 6.1

Percent Overweight or Obese

<table>
<thead>
<tr>
<th>Category</th>
<th>Percent</th>
<th>DM</th>
<th>HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 19</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Normal</td>
<td>19-24.9</td>
<td>25.0</td>
<td>24.7</td>
</tr>
<tr>
<td>Overweight I</td>
<td>25-29.9</td>
<td>27.0</td>
<td>26.7</td>
</tr>
<tr>
<td>Obese I</td>
<td>30-34.9</td>
<td>28.0</td>
<td>27.7</td>
</tr>
<tr>
<td>Obese II</td>
<td>35-39.9</td>
<td>28.0</td>
<td>27.7</td>
</tr>
<tr>
<td>Obese III</td>
<td>≥ 40</td>
<td>28.0</td>
<td>27.7</td>
</tr>
</tbody>
</table>

% Overwt or Obese
DM: 74.0   HRT: 73.3
WHI CT: Hormone Use & Uterine Status

History of Hormone Use

- Never
- Former
- Current

Hysterectomy Status

- Uterus
- HysterX

Percent

DM

HRT
WHI CaD: Outcomes, Relationship to CT

Total CT = 68,133

HRT 27,347

DM 48,836

Calcium + Vitamin D (CaD)
- Primary Outcome: Hip Fracture
- Secondary Outcomes: Other Fractures, Colorectal Cancer

at 1st (or 2nd) Annual Visit

CaD 36,282
WHI CaD Trial (N = 36,282): Treatments
Adherence < 80% initiates Intensive Adherence Program

Supplement* (50%)
Calcium carbonate 1000 mg/day + Vitamin D 400 IU/day (daily RDA)
or
Placebo (50%)

* Women may decide whether to take “Chewable” or “Swallowable” pill.
Women are instructed to take one pill in the morning and one at night
WHI CT : Baseline Age Distribution

Mean ± SD: DM = 62.3 ± 6.9; HRT = 63.4 ± 7.2; CaD = 62.4 ± 6.9
WHI CT: Baseline Body Mass Index (kg/m²)
Mean ± SD: DM = 29.1 ± 6.0; HRT = 29.1 ± 6.1; CaD = 29.0 ± 5.9

Percent Overweight or Obese
DM: 74.0  HRT: 73.3  CaD: 73.5
WHI CT: Hormone Use & Uterine Status

History of Hormone Use

- Never
- Former
- Current

Hysterectomy Status

- Uterus
- HysterX

Legend:
- DM
- HRT
- CaD
**WHI: Major Study Phases (Challenges)**

<table>
<thead>
<tr>
<th>Recruitment of 165,000 Women aged 50-79* within 3-4 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Age-Specific Goals; CT Goal = 20% Minorities</td>
</tr>
<tr>
<td>DM: Initial Diet ≥ 32% calories from fat; CT: medical, willingness</td>
</tr>
</tbody>
</table>

**Screening & Baseline (Data Collection & Management)**

**Randomization to CT or Enrollment into OS**

<table>
<thead>
<tr>
<th>DM: 40% Diet Change; 60% Diet Comparison (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT: 50% Active Hormone Pills*; 50% Placebo</td>
</tr>
<tr>
<td>*with Uterus: Estrogen+Progestin; Hysterectomy: Estrogen only</td>
</tr>
<tr>
<td>CaD: 50% Active Supplements; 50% Placebo [1st Ann. Visit]</td>
</tr>
</tbody>
</table>

**Interventions (Adherence & Safety Concerns)**

**Follow-up Visits (Retention) & Outcomes Ascertainment**
WHI CT: Percent of Initial Goal; Overlap
Total CT = 68,133  (53.3% are in CaD)*

DM
48,836
(101.7%)

HRT
27,347
(99.4%)

CaD
36,282

16.5% of DM are in HRT
11.8% CT in DM+HRT
29.4% of HRT are in DM
37.0% CT in DM +CaD
51.6%
58.8%
23.6% CT in HRT+CaD
7.3% CT in DM+HRT+CaD
Dietary Goals

- Total Fat Intake ≤ 20% of Daily Calories
  Saturated Fat ≤ 7% of Daily Calories
- Vegetables + Fruits ≥ 5 servings/day
- Grain, Cereals, Legumes ≥ 6 servings/day
- Maintain these dietary changes for 9 years

Compliance Monitoring: Choice of Several Self-Monitoring Tools

Class Attendance Goals (average 15 women/class)

- Once a week for 6 weeks (Initial Sessions: Fat Goals, F&V)
- Once every other week for 6 weeks (Grains, Roadblocks)
- Once a month for 9 months (Behavioral Issues)
- Maintenance: Once every 3 months until Study Ends
WHI DM Change: Class Attendance, Fat Scores

Class Attendance, Session Completion, Scores

% attendance

First Year Maintenance

% attendance

1 3 5 7 9 11 13 15 17 5F 5Sp

- ATTENDED
- COMPLETED
- SUBMITTED FAT SCORES
WHI DM Change Group: Daily Fat Grams

Submitted Fat gram Scores in DM Change

Average Goal = 25 grams

Year 1

Maintenance
WHI DM Change Group: Food Scores

Submitted Vegetable/Fruit and Grain Scores

Goal ≥ 6 grains/day
Goal ≥ 5 V&F/day

Number Daily Servings

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Maintenance</th>
</tr>
</thead>
</table>

Vegetables + Fruits
Grains

1 3 5 7 9 11 13 15 17 5F 5Sp
### WHI: Annual Clinic Visits

- HRT participants are contacted semi-annually and attend annual follow-up clinic visits, involving:
  - Breast exam (Annual Mammogram is also required)
  - Pelvic Exam (for those with a uterus only)
  - PAP smear (Baseline & Years 3,6, 9)
  - ECG (Baseline & Years 3,6,9)
  - Pill Collection to assess Adherence
  - Risk counseling with any new information
  - A subset of women have endometrial aspirations and blood draws every 3 years (for later analyses)
WHI CT: Follow-up Clinic Visits

Percent Annual Visits Conducted in DM and HRT

AV1
AV2
AV3
AV4

Percent

DM
HRT
### WHI CT: Adherence Monitoring

#### DM Trial: C-I Difference

<table>
<thead>
<tr>
<th></th>
<th>% Fat</th>
<th>Calories</th>
<th>#F&amp;V</th>
<th>Wt (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV1</td>
<td>10.9</td>
<td>1.2</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>AV2</td>
<td>9.9</td>
<td>1.2</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>AV3</td>
<td>9.8</td>
<td>1.3</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>AV4</td>
<td>9.5</td>
<td>1.4</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approx N</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV1</td>
<td>26,500</td>
<td>18,000</td>
</tr>
<tr>
<td>AV2</td>
<td>8,600</td>
<td>6,000</td>
</tr>
<tr>
<td>AV3</td>
<td>4,600</td>
<td>3,100</td>
</tr>
<tr>
<td>AV4</td>
<td>5,000</td>
<td>3,200</td>
</tr>
</tbody>
</table>

#### HRT Trial: Adherence

<table>
<thead>
<tr>
<th></th>
<th>Stopped</th>
<th>&lt; 80% Pills</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV1-B</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>AV2-AV1</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>AV3-AV2</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>AV4-AV3</td>
<td>6%</td>
<td>13%</td>
</tr>
</tbody>
</table>

#### CaD Trial: Adherence

<table>
<thead>
<tr>
<th></th>
<th>Stopped</th>
<th>&lt; 80% Pills</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV2-AV1</td>
<td>10%</td>
<td>28%</td>
</tr>
<tr>
<td>AV3-AV2</td>
<td>6%</td>
<td>26%</td>
</tr>
<tr>
<td>AV4-AV3</td>
<td>5%</td>
<td>23%</td>
</tr>
</tbody>
</table>
The Observational Study (OS) serves as a complement to the Clinical Trial.

Women screened for the DM or HRT CT could enroll in the OS, if they were ineligible for the CT, or chose not to join either DM or HRT.
WHI: Purpose of Observational Study

- Purpose of OS
  - To improve risk prediction of cardiovascular disease, cancers, fractures, and all-cause mortality in postmenopausal women
  - To create a resource of data and biological samples which can be used to identify new risk factors and/or disease biomarkers
  - To examine the impact of changes in lifestyle and risk factors on disease and mortality
WHI CT + OS: Baseline Diet (from FFQ)  
(DM Criteria Initial Diet ≥ 32% calories from fat)
WHI CT + OS: Baseline Age Distribution

Mean ± SD: DM = 62.3 ± 6.9; HRT = 63.4 ± 7.2; OS = 63.6 ± 7.4
WHI: Minority Distribution in CT and OS

Total CT = 68,133      Total OS = 93,676

Percent Minority Women in Total CT and OS

<table>
<thead>
<tr>
<th></th>
<th>CT (18.3%)</th>
<th>OS (16.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>10.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Asian/PI</td>
<td>2.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Native American</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Other</td>
<td>1.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>
WHI OS: Education Level

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 0-8</td>
<td>1.7%</td>
</tr>
<tr>
<td>Gr 9-11</td>
<td>3.5%</td>
</tr>
<tr>
<td>HS Grad</td>
<td>16.3%</td>
</tr>
<tr>
<td>Voc/Tech</td>
<td>9.8%</td>
</tr>
<tr>
<td>Some College</td>
<td>26.7%</td>
</tr>
<tr>
<td>BS equiv</td>
<td>11.5%</td>
</tr>
<tr>
<td>Post-Grad</td>
<td>11.9%</td>
</tr>
<tr>
<td>Masters</td>
<td>15.9%</td>
</tr>
<tr>
<td>Doctorate</td>
<td>2.8%</td>
</tr>
<tr>
<td>Total</td>
<td>68.7%</td>
</tr>
<tr>
<td>Some college</td>
<td>42.0%</td>
</tr>
<tr>
<td>HS Grad</td>
<td>5.2%</td>
</tr>
</tbody>
</table>
WHI CT + OS: Baseline Body Mass Index (kg/m²)
Mean BMI: DM = 29.1 ± 6.0; HRT = 29.1 ± 6.1; OS = 27.3 ± 5.9

Percent Normal Weight, Overweight and Obese

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese I</th>
<th>Obese II</th>
<th>Obese III</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>19-24.9</td>
<td></td>
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<td></td>
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<tr>
<td>25-29.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-34.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

% Overwt or Obese
DM: 74.0  HRT: 73.3  OS: 59.2
WHI CT+ OS: Hormone Use & Uterine Status

History of Hormone Use

- Never
- Former
- Current

Hysterectomy Status

- Uterus
- HysterX

Percent

Legend:
- DM
- HRT
- OS