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

WHI Program Office

WHI Steering Committee (SC)

[40 Clinical Center (CC) PIs + CCC PI + PO rep.]

Executive Committee (8 members)

4 Regional Groups of 9-12 CCs
CC PIs; Lead Staff Groups (5/Reg)

Working Group (NHLB Advisory Council)

Performance Monitoring Committee (PMC)

Coordinating Center (CCC)
FHCRC

Data & Safety Monitoring Board
Consortium of NIH Directors

Advisory Committees
DM, HRT, CaD, OS
Special Pop., Behavioral
D&A, P&P, M&M
WHI CT Sample Size, Outcomes, Follow-up
Women, aged 50-79  Total CT = 68,133

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
### Background for Diet/Cancer hypotheses

<table>
<thead>
<tr>
<th>Source</th>
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<tbody>
<tr>
<td><strong>USA National Cancer Act of 1971</strong></td>
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<tr>
<td><strong>Symposium on Nutrition and Causes of Cancer</strong> (AACR, 1975)**</td>
</tr>
<tr>
<td>National Cancer Institute &amp; American Cancer Society</td>
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<tr>
<td><strong>Diet, Nutrition, and Cancer, 1982</strong></td>
</tr>
<tr>
<td>National Academy of Science</td>
</tr>
<tr>
<td><strong>Food, Nutrition, and the Prevention of Cancer: a global perspective</strong></td>
</tr>
<tr>
<td><strong>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:</strong> decreases risk, increases risk, or no relationship</td>
</tr>
</tbody>
</table>
WHI Diet Trial: Intervention Goals
40% of DM Sample (N=19,542)

- Total Fat Intake $\leq 20\%$ of Daily Calories
  - Saturated Fat $\leq 7\%$ of Daily Calories
- Vegetable+Fruit intake $\geq 5$ servings/day
- Grains,Cereals, Legumes $\geq 6$ servings/day
- Maintain these dietary changes for 9 years
## Background for HRT/CHD hypothesis

### Observational Studies
- LRC Prevalence Study (1983, 1987)
- Nurses’ Health Study (1985, 91)
- Framingham Study (1985)-reversed
- Nurses’ Health Study (1997) PERT
- > 20 other Observational Studies
  - HRT users vs nonusers (generally): fewer smokers, more physically active, leaner, healthier, at lower risk, more educated, higher SES

### Clinical Trials
- PEPI (1995) post-m. women, aged 45-64. HRT improved HDL (ERT > PERT), LDL, and fibrinogen, but increased TG.
- 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
- WHI (2005)
WHI HRT Trial (N=27,347): Treatments

Adherence < 80% initiates Intensive Adherence Program

Women with a Uterus (55% by design): Actual = 60.7% (N=16,608)

- Estrogen with Progestin (50%)
  - Conjugated Equine Estrogen (CEE) - 0.625 mg/day +
  - Medroxyprogesterone Acetate - 2.5 mg/day (daily MPA)

  or

  - Placebo (50%)

Women with a Hysterectomy (45%): Actual = 39.3% (N=10,739)

- Estrogen only (50%)
  - Conjugated Equine Estrogen (CEE) - 0.625 mg/day

  or

  - Placebo (50%)
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%
WHI CT (DM+HRT): Minority Distribution

Total CT = 68,133  Minorities = 12,462 (18.3%)

![Bar chart showing minority distribution in WHI CT:]

- Blacks: 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 (DM+HRT): Education Level
**WHI CT: Baseline Body Mass Index (kg/m²)**

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

![Percent Normal Weight, Overweight and Obese](chart)

- DM: 74.0
- HRT: 73.3

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

History of Hormone Use

Hysterectomy Status

Percent

Never | Former | Current | Uterus | HysterX

DM | HRT

Never | Former | Current | Uterus | HysterX

DM | HRT
**WHI CaD: Outcomes, Relationship to CT**

**Total CT = 68,133**

- **DM** 48,836
- **HRT** 27,347

**CaD** 36,282 at 1st (or 2nd) Annual Visit

**Calcium + Vitamin D (CaD)**
- Primary Outcome: Hip Fracture
- Secondary Outcomes: Other Fractures, Colorectal Cancer
WHI CaD Trial (N = 36,282): Treatments
Adherence < 80% initiates Intensive Adherence Program

Supplement* (50%)
Calcium carbonate 1000 mg/day + Vitamin D 400 IUs/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 Normal Weight, Overweight and Obese**

- **DM**: 74.0%
- **HRT**: 73.3%
- **CaD**: 73.5%

The graph shows the distribution of body mass index categories with different colors representing DM, HRT, and CaD.
WHI CT: Hormone Use & Uterine Status

History of Hormone Use

Percent

Never  Former  Current

Hysterectomy Status

Uterus  HysterX

DM  HRT  CaD
Recruitment of 165,000 Women aged 50-79* within 3-4 Yrs

* Age-Specific Goals; CT Goal = 20% Minorities
DM: Initial Diet ≥ 32% calories from fat; CT: medical, willingness

Screening & Baseline (Data Collection & Management)

Randomization to CT or Enrollment into OS
DM: 40% Diet Change; 60% Diet Comparison (Control)
HRT: 50% Active Hormone Pills*; 50% Placebo
*with Uterus: Estrogen+Progestin; Hysterectomy: Estrogen only
CaD: 50% Active Supplements; 50% Placebo [1st Ann. Visit]

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
### WHI Diet Trial: Intervention Goals

#### 40% of DM Sample (N=19,542)

**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

- **ATTENDED**
- **COMPLETED**
- **SUBMITTED FAT SCORES**

First Year Maintenance
Submitted Fat gram Scores in DM Change

Average Goal = 25 grams
WHI DM Change Group: Food Scores

Submitted Vegetable/Fruit and Grain Scores

Number Daily Servings

Goal

≥ 6 grains/day
≥ 5 V&F/day

Year 1

Maintenance

Vegetables + Fruits
Grains
WHI HRT: 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
### 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>
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<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>
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</table>

<table>
<thead>
<tr>
<th>Approx N</th>
<th>Control</th>
<th>Intervention</th>
</tr>
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<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>
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### HRT Trial: Adherence Stopped < 80% Pills

<table>
<thead>
<tr>
<th></th>
<th>Stopped</th>
<th>&lt; 80% Pills</th>
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</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 $\geq 32\%$ 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>Blacks</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>
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</table>
WHI OS: Education Level

- Gr 0-8: 1.7%
- Gr 9-11: 3.5%
- HS Grad: 16.3%
- VocTech: 9.8%
- Some College: 26.7%
- BS equiv: 11.5%
- Post-Grad: 11.9%
- Masters: 15.9%
- Doctorate: 2.8%

- 5.2% total for Gr 0-11
- 26.1% total for HS Grad and VocTech
- 68.7% total for Some College and BS equiv
- 42.0% total for Post-Grad, Masters, and Doctorate

Percentages are approximate and may vary slightly.
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

Percent

<19 Normal DM: 74.0
19-24.9 Overweight HRT: 73.3
25-29.9 Obese I OS: 59.2
30-34.9 Obese II
35-39.9 Obese III
≥40

DM
HRT
OS

% 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