Low-Fat Dietary Pattern and Breast Cancer Mortality in the Women’s Health Initiative (WHI) Randomized Controlled Trial

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I have the following financial relationships to disclose:

Consultant for: Novartis, Genentech, Amgen, Genomic Health, Novo Nordisk
Speaker’s Bureau for: Novartis, Genentech

- and -

I will not discuss off label use and/or investigational use in my presentation.
Background
Dietary Fat Intake and Breast Cancer

The Women’s Health Initiative Dietary Modification (DM) Trial
Study Design and Implementation
Primary Breast Cancer Incidence Results (2006)

Rationale for Secondary Analyses
Current Results
Deaths After Breast Cancer
Deaths From Breast Cancer
Breast Cancer Overall Survival
Country-by-Country Breast Cancer Death Rate by Estimated Dietary Fat Intake

The Women’s Health Initiative Dietary Modification (DM) Trial

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Current Results
- Deaths After Breast Cancer
- Deaths From Breast Cancer
- Breast Cancer Overall Survival
WHI DIETARY MODIFICATION (DM) CLINICAL TRIAL

- **Objective:** To determine whether adoption of a low fat dietary pattern would reduce invasive breast cancer incidence

- **Design and Setting:** A randomized, controlled primary prevention trial conducted at 40 US clinical centers entering participants from 1993-1998

- **Participants:** 48,835 postmenopausal women,
  - aged 50 to 79 years,
  - without prior breast cancer,
  - baseline dietary intake > 32% of total calories from fat
  - mammogram not suspicious for cancer
WHI: Dietary Intervention

- Dietary Intervention Goals:
  - Reduce dietary fat intake (target 20% calories from fat)
  - Increase vegetables and fruit servings (target 5/day)
  - Increase grains servings (target 6/day)

- Weight loss not an intervention target

- Diet Group: women given a fat gram goal by centrally trained, registered dieticians implementing a low fat eating plan \(^1, \, 2\)

- Monitoring for all: 4-day food record (baseline), food frequency questionnaire (FFQ) (baseline, year 1 and q 3 years on rotation)

- Control Group: women received dietary guideline report and were not asked to make dietary changes

Structure of the WHI Dietary Intervention

18 group sessions
Year 1

Quarterly maintenance sessions
Year 2 and beyond

Baseline

End of DM Trial

CORE AUGMENTATIONS

• Motivational Interviewing – 3 personal contacts
  • Targeted Messaging – Mailing
  • Tailored Feedback: Personal Evaluation of Fat Intake – Group sessions
    • Tailored Feedback: Personal Evaluation of Fat Intake – Mailing
  • Clinical Center augmentations

Outcome Ascertainment

- Mammogram every 2 years (annually if also in a WHI hormone therapy trial)
- Breast cancer verified by medical record and pathology report review by WHI physician adjudicators at clinical centers with final adjudication and coding at the Clinical Coordinating Center (CCC)
- Cause of death determined at CCC by medical record or death certificate review
- Serial National Death Index queries, last 31 DEC 2011
Women’s Health Initiative
WHI Dietary Modification Trial

373,092 completed the eligibility screening form

56,139 eligible

48,835 randomized

Intervention 19,541
Comparison 29,294

Baseline Demographics of Participants in the WHI DM Trial did not differ by Randomization

<table>
<thead>
<tr>
<th>Age</th>
<th>Body Mass Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td>Mammogram within 2 years</td>
</tr>
<tr>
<td>Breast cancer family history</td>
<td>History of estrogen plus progestin use</td>
</tr>
<tr>
<td>Gail 5y breast cancer risk</td>
<td>History of estrogen alone use</td>
</tr>
<tr>
<td>Reproductive history</td>
<td>Treated diabetes</td>
</tr>
</tbody>
</table>
### Baseline Intakes by Randomization Group

<table>
<thead>
<tr>
<th>Category</th>
<th>Diet Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories from Fat (percent of total/d)</td>
<td>37.6% (4.96)</td>
<td>37.8% (5.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Fruit and vegetable (servings/d, median)</td>
<td>3.8 (1.8)</td>
<td>3.6 (1.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Grains (servings/d, median)</td>
<td>4.7 (2.5)</td>
<td>4.7 (2.4)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Similar intakes in randomization groups at baseline.
### Change in Dietary Intake and Body Weight (Baseline minus Year 1) by Randomization Group

<table>
<thead>
<tr>
<th>Change in Intake (Baseline – Year 1)</th>
<th>Diet mean (SD)</th>
<th>Control mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories from fat (percent of total/d)</td>
<td>-13.9% (7.5)</td>
<td>-2.5% (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fruit and vegetable (servings/d, median)</td>
<td>1.5 (2.1)</td>
<td>0.2 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grains (servings/d, median)</td>
<td>0.4 (2.7)</td>
<td>-0.5 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-3.2 (9.2)</td>
<td>-0.1 (7.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All target intakes significantly changed.
At protocol defined end date, after 8.3 years follow-up (mean)
WHI Dietary Modification Trial: Breast Cancer Incidence by Treatment Group

HR 0.91 (0.83-1.01)
1,727 total diagnoses, p=.07
3.5% of all DM participants

For breast cancer mortality
27 vs 53, HR 0.77 (0.48-1.22)

Prentice RL, Caan B, Chlebowski RT et al. JAMA 2006;395:629-42
Breast Cancer Characteristics of 1767 Cases by Randomization Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diet [N=672] N (%)</th>
<th>Control [N=1095] N (%)</th>
<th>P-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Ductal</td>
<td>435 (64.9)</td>
<td>711 (65.2)</td>
<td></td>
</tr>
<tr>
<td>Lobular</td>
<td>64 (9.6)</td>
<td>98 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Ductal and lobular</td>
<td>84 (12.5)</td>
<td>151 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>87 (13.0)</td>
<td>130 (11.9)</td>
<td></td>
</tr>
</tbody>
</table>

* P-values based on chi-squared tests of association
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<th>P-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>493 (74.8)</td>
<td>814 (75.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Regional or distant</td>
<td>166 (25.2)</td>
<td>264 (24.5)</td>
<td></td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>170 (28.0)</td>
<td>305 (30.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>1-&lt;2</td>
<td>287 (47.3)</td>
<td>405 (41.0)</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>150 (24.7)</td>
<td>278 (28.1)</td>
<td></td>
</tr>
<tr>
<td>Lymph node positive</td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>None</td>
<td>450 (75.0)</td>
<td>170 (75.8)</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>112 (18.7)</td>
<td>167 (17.1)</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>38 (6.3)</td>
<td>69 (7.1)</td>
<td></td>
</tr>
</tbody>
</table>

Breast Cancer Characteristics by Randomization Group

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<th>Control [N=1095] N (%)</th>
<th>P-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Estrogen Receptor</td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Positive</td>
<td>521 (83.9)</td>
<td>851 (83.9)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>100 (16.1)</td>
<td>163 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Progesterone Receptor</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Positive</td>
<td>439 (71.6)</td>
<td>669 (67.0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>174 (28.4)</td>
<td>329 (33.0)</td>
<td></td>
</tr>
<tr>
<td>HER2 positive</td>
<td>90 (18.8)</td>
<td>134 (17.6)</td>
<td>0.61</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>40 (8.5)</td>
<td>74 (9.9)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

- P-values based on chi-squared tests of association.

- Somewhat fewer PR negative cancers in the Diet group.

Background
Dietary Fat Intake and Breast Cancer

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Primary Breast Cancer Incidence Results (2006)

Rationale for Secondary Analyses
Current Results
Deaths After Breast Cancer
Deaths From Breast Cancer
Breast Cancer Overall Survival
Low-Fat Dietary Pattern and Breast Cancer Mortality: Rationale for Secondary Analyses

- At the end of dietary intervention after 8.3 years, of 1767 invasive breast cancers, there were 8% fewer cases in the dietary group (HR 0.92, 95% CI 0.84-1.01, P=0.09) but no suggestion of a reduced incidence during post-intervention follow-up.

- In addition, during dietary intervention, deaths from breast cancer were non-significantly lower in the dietary group (HR 0.77 95% CI 0.48-1.22).

- These findings suggested that dietary modification may reduce breast cancers associated with greater mortality and sustained dietary intervention is needed to maintain effect.

Outcome Measures

- **Deaths from breast cancer**
  (breast cancer followed by death attributed to the cancer)
  and

- **Deaths after breast cancer**
  (breast cancer followed by death from any cause)

- **Breast cancer overall survival**
  (survival from diagnosis with death from any cause)

- All outcomes based on breast cancers diagnosed during dietary intervention

Statistical Considerations

- Analyses of deaths from and after breast cancer during the dietary intervention period, includes all 48,835 study women measured from randomization.

- Analyses of breast cancer overall survival includes the 1767 women with breast cancer diagnosed during dietary intervention with follow-up through August 2014 measured from diagnosis.

- ITT analyses, stratified by age and WHI Hormone Therapy trial randomization status.

48,835 randomized

Intervention

19,541

663 withdrew
254 lost

672 breast cancer cases

40 deaths after Dx

19,541 included in analysis

Comparison

29,294

890 withdrew
273 lost

1095 breast cancer cases

94 deaths after Dx

29,294 included in analysis

Chlebowski, Aragaki, Anderson, et al. AACR 2016 Abst CT043
Low-Fat Dietary Pattern and Deaths from and after Breast Cancer During the Intervention Period

Deaths from Breast Cancer

HR(95% CI) = 0.68 (0.43, 1.07)  
P-value = 0.09  
N = 88 total deaths

Deaths after Breast Cancer

HR(95% CI) = 0.65 (0.45, 0.94)  
P-value = 0.02  
N = 134 total deaths

## Death after Breast Cancer: Exploratory Analyses
### PR Status and Weight Change

<table>
<thead>
<tr>
<th>Adjustment Variable</th>
<th>Death after Breast Cancer HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-dependent variables for PR negative and unknown</td>
<td>0.70 (0.48-1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline weight and subsequent weight change</td>
<td>0.65 (0.45-0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

PR status between randomization groups and diet group weight loss do not explain the death after breast cancer results.

Chlebowski, Aragaki, Anderson, et al. AACR 2016 Abst CT043
Flow of 1,767 Women with Incident Breast Cancer for Analysis of Breast Cancer Overall Survival (1993-2014)

48,835 randomized

Intervention 19,541

Comparison 29,294

672 Breast Cancers

1095 Breast Cancers

Extended Follow-up to Sept 2014

168 deaths after Dx

319 deaths after Dx

672 included in analysis

1095 included in analysis

### Breast Cancer Therapy by Randomization Group

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Diet</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Therapy</td>
<td>79%</td>
<td>75%</td>
</tr>
<tr>
<td>Endocrine Adjuvant</td>
<td>71%</td>
<td>68%</td>
</tr>
<tr>
<td>Chemotherapy Adjuvant</td>
<td>32%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Breast cancer therapy directed by participants’ Health Care providers

Self reported information available in a subset (675 of 1767)

Therapy reflects relatively low stage disease found in this regularly screened population

### Intake Change (Baseline minus after Breast Cancer) by Randomization Group

<table>
<thead>
<tr>
<th>Intake 1.6 years (mean) after breast cancer</th>
<th>Diet</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories from fat (percent of total)</td>
<td>-9.5%</td>
<td>-1.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fruit and vegetable (servings/d, median)</td>
<td>1.5</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grains (servings/d, median)</td>
<td>-0.5</td>
<td>-1.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FFQ after breast cancer diagnosis available in subset (n=1202) of 1767 women with breast cancer

**Dietary Group Participation Continued After Diagnosis**

Breast Cancer Overall Survival for 1767 Women Diagnosed During the Dietary Intervention Period

10 year survival
82% vs. 78%

HR (95% CI)
0.80(0.66-0.97)
P-value = 0.02
N = 487 total deaths
## Cause of Death in Women with Breast Cancer by Randomization Group

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Diet</th>
<th>Control</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause</td>
<td>168</td>
<td>319</td>
<td>0.80 (0.66-0.77)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>65</td>
<td>111</td>
<td>0.89 (0.67-1.11)</td>
</tr>
<tr>
<td>Other Cancer</td>
<td>31</td>
<td>51</td>
<td>0.83 (0.52-1.33)</td>
</tr>
<tr>
<td>CVD</td>
<td>19</td>
<td>55</td>
<td>0.49 (0.29-0.83)</td>
</tr>
<tr>
<td>Other*</td>
<td>51</td>
<td>97</td>
<td>0.87 (0.61-1.25)</td>
</tr>
</tbody>
</table>

* Includes all cause vs other plus unknown

Cause of death available in 400 of 487 breast cancer cases

- All cause mortality, \( P = 0.02 \)
- Interaction P-value, \( P = 0.14 \)
Linear Time Varying Hazard Ratio
Breast Cancer Overall Survival

Intervention Period
HR(95% CI)=0.67(0.48-0.97)

Post-intervention
HR(95% CI)=0.85(0.68-1.07)

The Grambsch and Therneau test provided evidence against proportionality during the intervention period.

**Intervention Period**

HR(95% CI) = 0.67 (0.48-0.97)

**Post-intervention**

HR(95% CI) = 0.85 (0.68-1.07)

Chlebowski, Aragaki, Anderson, et al. AACR 2016 Abst CT043
Linear Time Varying Hazard Ratio
Breast Cancer Overall Survival

Intervention Period
HR(95% CI)=0.67(0.48-0.97)

Post-intervention
HR(95% CI)=0.85(0.68-1.07)
Interactive:


Intervention Period

HR(95% CI)=0.67(0.48-0.97)

Post-intervention

HR(95% CI)=0.85(0.68-1.07)

P-value for trend=0.02

P-value for trend=0.45
Conclusions

- In a breast cancer prevention trial, adoption of a low-fat dietary pattern,
  - Reduced deaths after breast cancer
  and
  - Increased breast cancer overall survival
- Time-trend analyses suggest continued dietary intervention may be needed to maintain benefit.